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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.

Keywords: epilepsy; micro-electrode; multi-electrode array; human; intracranial; single unit recording

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 analagous 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.

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 Figure 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 40-50μm. 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 150μm 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 40-150kΩ (Prasad and Sanchez, 2012).

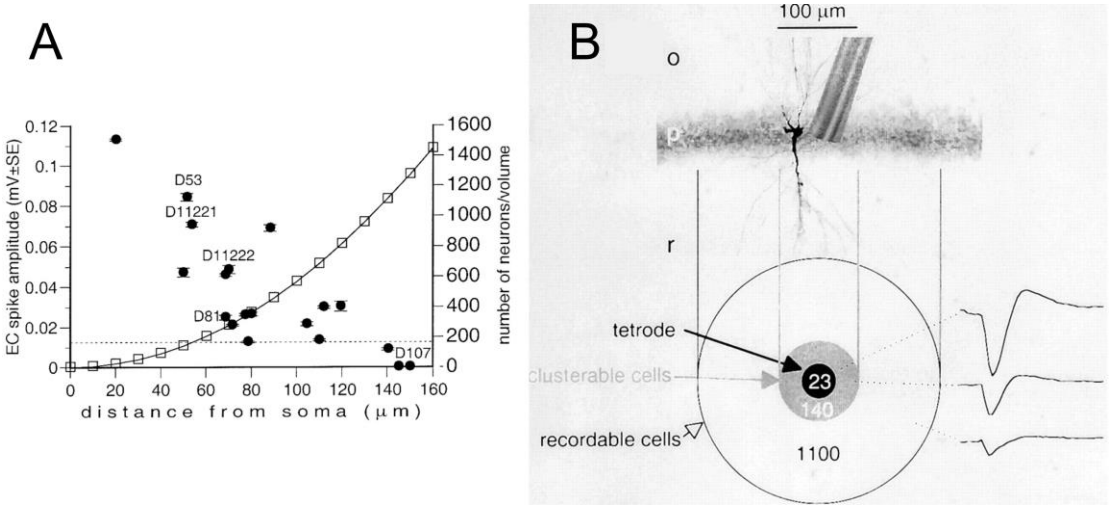

Figure 1: Fig 6 in (Henze *et al.*, 2000): *A*: black dots: average extracellular spike amplitude (±SE) vs. tetrode tip distance from 19 labeled pyramidal cells. White squares: estimated number of CA1 pyramidal cells (based on data from (Aika *et al.*, 1994)). *B*, *top*: CA1 pyramidal cell next to a tetrode (12.5μm wires). *Bottom*: gray area: single unit can be separated (extracellular spikes exceeds 60 μV).

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.

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.*). In the 1950s, simpler metal wire electrodes insulated with platinum, iridium, stainless steel, or tungsten were developed and used as bundles. Table 1 contains the materials commonly used in contact with neuronal tissue, and Table 2 contains the typical insulator coverings. Currently, the most popular electrode metals are platinum-iridium alloy (Pt/Ir), stainless steel and tungsten. These are corrosion resistant, mechanically durable metals (Merrill, 2014). The impedance of the electrode depends on the surface area that comes into contact with the biological tissue, but for the typical 12.5-200μm diameter the impedance of Pt/Ir electrodes are in the 0.1-5MΩ range (Prasad, 2014) and tungsten electrodes in the 30–400kΩ range (Prasad and Sanchez, 2012).

Advanced electrode materials and techniques

Recently research is directed toward reducing the electrode impedance with different contact coatings (S. Zhang *et al.*, 2014), (H. Zhang *et al.*, 2012) in order to eliminate electrode-dependent long term tissue irritation (Nemani *et al.*, 2013; Yoshida Kozai *et al.*, 2012),(Fadiga, 2014; Forcelli *et al.*, 2012) and decrease damage of the tissue due to the implant (Kozai *et al.*, 2014)

Typical electrode contact materials
Platinum
Platinum/Iridium (Pt/Ir)
Pure Iridium
Iridium oxide
Stainless steel
Tungsten
Carbon fiber
Electrolyte - glass micropipette

Table 1. A summary of the typical electrode contact materials, commonly used by the manufacturers.

Electrode insulating materials
Silicon
Ceramic
Teflon
Silicone
Polyurethane
Silicone/polyurethane copolymer
Polyethylene
Polypropylene
Parylene, Parylene-C
Polyether ether ketone
Polyimide
Silicon carbide
SU-8
Borosilicate glass
Epoxy

Table 2. Electrode insulating materials table (Merrill, 2014).

Electrode arrays (probes) to record neuronal ensembles

Local neuronal ensembles can be recorded using one electrode contact; however, limited information can be obtained this way. Larger numbers of units can be separated by increasing the number of recording contacts (Buzsáki, 2004). Since the 1960s, this understanding has resulted in different types of multielectrode wire-array layouts, termed *electrophysiological probes*. These probes are fabricated from different types of wires with insulating and encapsulating materials (Moxon, 1999).

Figure 2 summarizes the typical arrangement of the electrodes in different probes. We grouped the existing electrode configurations in the Table 3 regarding their spatial arrangements. Table 4 contains the electrode manufacturer list, with their electrode types, and applicability area.

The desire for more and more precise multi-electrode probes pushed the manufacturing technology to its limits. Difficulties of the fabricating in the μm range required another solution, and with the improvement of the microelectromechanical systems (MEMS) the expectations were met. MEMS technology is analogue to the microprocessor fabricating silicon technology (Prohaska *et al.*, 1977) (Figure 2F). MEMS based probes have been available since the 1980s (Drake *et al.*, 1988; Prohaska *et al.*, 1986) however, until recently wire probes were used because of their better availability. These types of probes contain a higher number of electrodes with the ability to co-register more than 100 units (Csicsvari *et al.*, 2003).

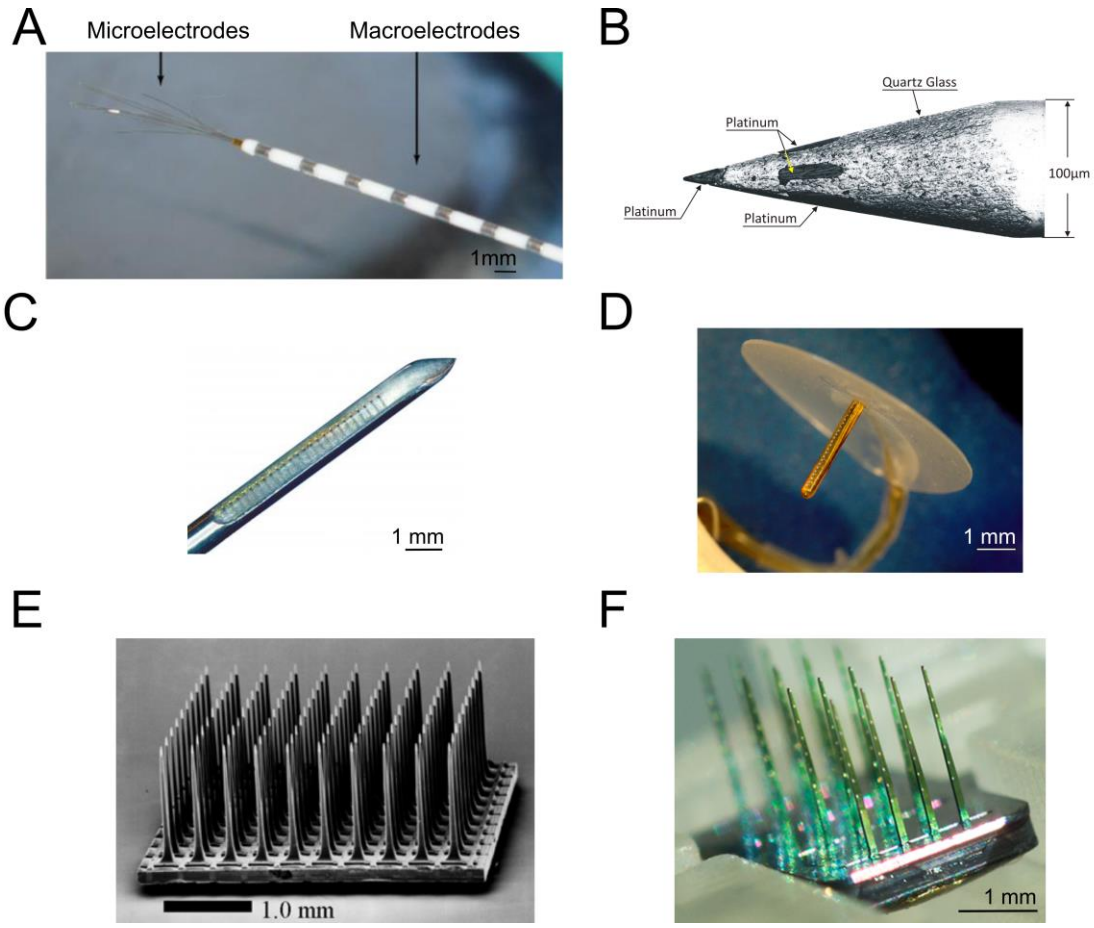

Figure 2. Typical probe configurations.

A) Behnke-Fried- deep brain electrode microwires. Picture from (Misra *et al.*, 2014),

B) Tetrode (picture from Thomas Recordings web; http://www.thomasrecording.com/neuroscience-products/metal-microelectrodes/tetrodes/)

C-D) Laminar (pictures from Plexon and Neuronelektrod; http://www.plexon.com/products/plexon-electrodes-probes-and-arrays; http://www.neuronelektrod.hu/elektrod-tipusok/thumbtack-elektrodok.html),

E) Utah (pictures from Blackrock web; http://www.blackrockmicro.com/content.aspx?id=50)

F) MEMS (picture from NeuroNexus web; http://neuronexus.com/products/neural-probes)

Microelectrode types	µm surface	Example
1	point	wire, capillary
2	1D vertical	laminar
3	2D planar	Utah
4	Multi-point (high density local)	tetrode
5	micro mixture	layer technology, MEMS
Macroelectrode type	mm surface	
6	1D linear	deep brain
7	2D planar	surface electrodes
8	micro-macro mixture	Behnke-Fried in DB, micro between macro grid

Table 3. Typical micro,- and macroelectrode spatial arrangements considering the neuron cell-contact.

Microelectrode manufacturer	Microelectrode types	Research or clinical usage	CE mark
Alpha Omega	1,2,5,6,8	both	have
NeuroNexus	2,5	research	none
Kation Scientific	1	research	none
FHC	1,2,3,6,8?	both	N/A
Blackrock Microsystems	3	both	have
BASi	1	research	none
inomed	1,8,7?	both	have
World Precision Instruments	1,7	research	N/A
MicroProbes	1,3	research	N/A
Science Products GmbH	1	research	N/A

A-M SYSTEMS	1,7	research	none
ripple	1,3	both	have
Stoelting	1	research	none
AD-TECH	6,7,8	both	have
INTEGRA	6,7	both	N/A
IN VIVO	1,7	research	N/A
Thomas RECORDING	1,4,5	research	none
Warner Instruments	1,7	both	have
Technomed Europe	1	clinical	have
Plexon	2,3	both	have
Neuro Biological Laboratories	1,3	research	N/A
DIXI medical	6,7	clinical	have
Medtronic	6,7,8	clinical	have
Tucker-Davies Technologies	1,3	research	N/A
BrainGate	1,3	research	N/A
PMT Corporation	6,7,8	both	have
Neuronelektród	1,2,4,5	both	N/A

Table 4. Currently online available microelectrode manufacturers without exhaustive claim, their microelectrode types (details in table 3.) and CE mark providing features. N/A – information not available.

Probes to record unit ensembles in humans

Table 5 summarizes the most commonly used microprobes in the literature.

Tetrode

Microelectrode probes are most commonly designed in the tetrode configuration. This technique allows the separation of units based on the different appearance on neighboring electrodes (Harris *et al.*, 2000). Originally, the tetrode configuration consisted of twisted isolated wires (M. Wilson and McNaughton, 1993), while with the new MEMS-based tetrode configurations precisely planed 3D coverage can be obtained.

The main advantage of the tetrode configuration lies in the concentration of recording contacts. The ability to record a single unit on more than one contact allows the reconstruction of the unit in space (Blanche, 2005; Dombovári *et al.*, 2014). This arrangement limits the spatial coverage of neurons by concentrating the microelectrodes to a local region.

Figure 2B illustrates an advanced version of tetrode configuration.

Microwire bundles within Behnke-Fried depth macroelectrode

In humans, wire microelectrodes have been paired with clinical depth macro electrodes for a long time. These microwires consist of isolated tungsten (Fried *et al.*, 1999) or Pt/Ir (Babb *et al.*, 1973) wires that are inserted into the internal lumen of the stereotactically implanted macroelectrode array. Typically 4-8 wires are inserted (Fried *et al.*, 1999; Misra *et al.*, 2014) in the mesial temporal lobe. This approach is advantageous with regard to the ease of implantation and the relatively high success rate to record unit activity. In contrast, the disadvantage of microarrays placed within macroarrays lies in the difficulty to control the implantation depth and therefore the cortical (or subcortical) layer it probes. This type of paired micro/macroelectrode is typically to study activity from deep structures such as the mesial temporal lobe (Jacobs *et al.*, 2007; Kreiman *et al.*, 2002; Ogren *et al.*, 2009; Quiroga *et al.*, 2005) or fronto-parieto-medial surfaces (Halgren *et al.*, 2015). Due to the nature of its design, neocortical sites cannot be approached by this technique.

Laminar recording technique

Laminar multielectrode probes record electrical activity throughout the depth of the cortex and provide layer specific activity. Various types of laminar wire probes have been designed for acute and chronic recordings in humans and animals.

The overall advantage of the laminar multiprobe technique is obtaining measurements from all layers in a cortical column, thus allowing the recording of layer-specific multiple unit activity (MUA) and producing current source density (CSD) plots. CSD analysis provides an approximation of summed transmembrane currents in vertically arranged structures (Freeman and Nicholson, 1975; Nicholson and Freeman, 1975), including the hippocampus and neocortex. The general disadvantage of this approach compared to electrodes with a sharp tip is that the recording contacts are located on the shaft formed by the cut end of the wire electrodes. Thus, only a 180° hemisphere of volume is reached instead of the typical 360° spherical volume from a freestanding tip. Additionally, the laminar multiprove penetrates parallel to the neurons, resulting in a low probability for neurons to remain within the crucial 50μm distance required for unit separation.

Cortical-laminar, "Thumbtack" probe

Chronic neocortical recordings are obtained from a thumb-tack like shape with a short shaft (4mm), ending in a small flat silicone head (Figure 2D). This probe was designed to be implanted beneath subdural grid electrode arrays by a neurosurgeon with microsurgical skills in order to avoid electrode damage. The probe is introduced manually through a small hole on the pia mater, with special care taken to avoid any cortical damage or bleeding in the penetration track, as this could result in a decrement in signal quality. The laminar technique allows for layer-specific representation of the neocortex and is relatively easy to implant; however, this probe is not implantable into sulci or any deep brain structures. See supplementary online material for demonstration of the implantation procedure. Note the needle puncture of pia mater before the electrode penetrates the cortex.

Depth-laminar

To overcome challenges of implanting a laminar probe into deep structures, the depth-laminar electrode was created. This probe consists of a long shaft of the thumbtack without the flat head, designed to insert into the lumen of the depth macro-

electrode, allowing the laminar probe to reach hippocampal, parahippocampal, frontobasal, and cingular surfaces (Halgren *et al.*, 2015).

Hippocampal-laminar

A third type of laminar probe was designed for acute, intraoperative recordings from the hippocampus without the use of additional macroelectrode. This probe combines the depth-laminar technology with a 10cm long, 350µm diameter, stainless steel needle shaft. The 24 contacts near the tip of the needle are formed by the cut ends of linearly arranged 25µm diameter Pt/Ir wires (resistance 500 kOhm at 1 kHz). The first contact is positioned 5 mm above the tip (Figure 2C).

This design allowed intraoperative hippocampus recordings (Ulbert, Maglóczky, *et al.*, 2004) with accurate histological reconstruction of the electrode trajectory (Fabó *et al.*, 2008). Recordings from this probe can be linked off-line to specific layers of the hippocampus based on histological verification of the penetration track following en block resection of the hippocampus. Future improvements to the laminar electrode probe includes the incorporation of MEMS technology, allowing simultaneous vertical and horizontal recordings (Berényi *et al.*, 2014).

Utah array, Neuroport

The other widely used electrode system, the Utah array, consists of 96 silicon electrode shafts arranged horizontally in a grid (Jones *et al.*, 1992; Maynard *et al.*, 1997; Nordhausen *et al.*, 1994). (Figure 2E) This array records on average 178 units (1.85 units / contact). This 2D arrangement samples a larger number of cortical columns. Furthermore, as the electrode consists of sharp tips (in contrast with the mid-shaft contact), there is a high probability of measuring single unit activity. On the other hand, this recording approach lacks laminar information and the sampled layer depends partly on the design of the probe. As for the Utah array, histology following resection confirmed the electrode tips to be located in the lower portion of layer III in 66% of recordings (Truccolo *et al.*, 2011). However, due to incomplete penetration, the probe reached the cortical layers in a variable manner. Additionally, implanting these arrays are not trivial. A designated pneumatic device is inserted in order to "shoot" the probe into the cortex for the densely placed needles to penetrate the pia mater (Rousche and Normann, 1992). This procedure may cause additional damage to the tissue during implantation. Moreover the implantation device containing a rod hitting the surface of

the electrode is heavy and may cause additional severe injuries if used in an inappropriate way.

electrode arrays probe type	**wire type**	**impedance**	**contact diameter [µm]**	**contact spacig [µm]**	**contact number**	**shank length**	**shank diameter [µm]**	**isolation**
Laminar **; cortical, depth	Pt/Ir	1 MOhm ±10% at 100 Hz	40	75-200	22-24	5mm-20cm	350	Polyimide
Laminar **; hippocampus	Pt/Ir	500 kΩ at 1 kHz	25	100-200	24	10 cm	350	Polyimide
Tetrode	Pt/Ir, nickel-chromium	0.5-2 MΩ at 1 kHz	12.7	4*-10	4	variable	wire type dependent	Polyimide
Utah	Titanium, tungsten, platinum	80-150 kΩ (80 to 800 kΩ) at 1 kHz	Sharp (80 at the base)	400	96	0.5-1.5 mm	80	Polyimide prolene, glass
Wires in Behnke-Fried depth macroelectrode	Pt/Ir	50-500 kΩ +20-30 kΩ at 1 kHz in vivo	40	random	8	1-5 mm	N/A	teflon

Table 5. Probe types, Pt/Ir – platinum-iridium alloy, N/A – information not available.

* only the insulation around wires; **manufactured by Laszlo Papp (Neuronelektród Kft, Budapest, Hungary).

Neuronal firing patterns in epileptic cortex

According to the early reports, the paroxysmal depolarizing shift (PDS) consists of a 200 – 500Hz high frequency burst of action potentials superimposed on a slow intracellular depolarizing potential. This phenomenon was validated using various experimental models including acute and subacute slice and whole brain preparations (de Curtis and Avanzini, 2001; Steriade and Amzica, 1999),(de Curtis *et al.*, 2012; Matsumoto and Ajmone-Marsan, 1964), (de Curtis and Avanzini, 2001; Karlócai *et al.*, 2014).

Recent studies from slice preparations demonstrated that various hippocampal cell types exhibit different firing patterns during PDS events. The authors of these studies postulated a dynamic change in the network behavior during the transition from normal to epileptic states (Karlócai *et al.*, 2014). In this hypothesis, increasing excitation in the hippocampus results in increasing activity in inhibitory circuitry, leading to acute and selective breakdown of the parvalbuminergic perisomatic inhibition. As a result, pyramidal cells become dysinhibited, resulting in abundant, burst-type firing that leads to a depolarization blockade and cessation of the paroxysmal event.

Based on field potential synchronization in *in vivo* human studies hypersynchronous unit activity was hypothesized (Chatrian *et al.*, 1974). Several early studies using microelectrodes indeed showed increased multi - (Altafullah *et al.*, 1986; Ulbert, Heit, *et al.*, 2004), and single unit activity (Babb and Crandall, 1976; Isokawa-Akesson *et al.*, 1989; Wyler *et al.*, 1982) during IID generation. Other studies however, found no or limited correlation (Babb *et al.*, 1973; Rayport and Waller, 1967; Thomas *et al.*, 1955; Wyler *et al.*, 1982).

More recent studies consisting of larger numbers of recorded units in humans demonstrated that ~50% of units during an interictal discharge demonstrated modulation in their firing rate, and 8% showed an observed decrease in firing rate (Keller *et al.*, 2010). These units showed heterogeneous and complex behavior during interictal discharges than had been predicted from previous experimental settings. SUA activities during ictal events were also less hypersynchronous as was previously hypothesized (Babb *et al.*, 1987; Truccolo *et al.*, 2011). Detailed analysis of ictal unit firing revealed the presence of an inhibitory wave local to the seizure onset zone ,

suggesting that inhibitory input may prevent the spread of the seizure (Schevon *et al.*, 2012). The real high frequency unit response occurred in a delayed manner during seizure spread without apparent change in the low frequency signal, implying that the typical oscillatory phenomena recorded in the classical EEG reflect only the inhibitory synaptic barrages.

The unit response of frontal lobe neurons to single shock electrical stimuli also showed heterogeneous firing patterns (Alarcón *et al.*, 2012).

Ripples and high frequency oscillations

High frequency ripples has recently been established as an essential measure of epileptic cortex (Bragin *et al.*, 1999). In the temporal lobe, slow ripples (central frequency bellow 150 or 200Hz) predominate in the non-epileptic hemisphere while fast ripples (above 200Hz) were observed more frequently in the seizure-generating hemisphere (Staba *et al.*, 2004). Furthermore, evidence of ripples correlate with the epileptogenic or seizure onset zone (Jacobs *et al.*, 2009; Staba, C. L. Wilson, Bragin, Fried and Engel, 2002b; Urrestarazu *et al.*, 2007), histopathological alterations (Staba *et al.*, 2007), and surgical outcome (Jacobs *et al.*, 2010).

Studying hippocampal ripples in animals models and human brain slices provided evidence that fast ripples may emerge from the unreliable burst firing from neuronal ensembles (Alvarado-Rojas *et al.*, 2014; Foffani *et al.*, 2007). It has been suggested that fast ripple oscillations may act as an interference pattern within the brain. This observation was further validated with combined micro-and macroelectrode recordings in humans showing that many of the fast ripple events observed by microwires were missed with macroelectrodes (Worrell *et al.*, 2008). Single unit analysis during ripple oscillation revealed that interneurons fired earlier than pyramidal cells in the hippocampus (Le Van Quyen *et al.*, 2008).

Micro-spike/Macro-spike

Creating a probe that combines several of the discussed techniques may provide complementary and additional information regarding the nature of neuronal ensembles. Using intermediate-size electrodes, microdischarges have been observed, suggesting that that epileptically active microdomains are present in the cortex not visible on macroelectrodes (Stead *et al.*, 2010; Schevon *et al.*, 2008). Interestingly, a similar

observation was made in rodent hippocampal slices (Hofer *et al.*, 2014) where micro-spikes or synchronized discharges were interpreted as normal phenomena of the cortex.

Deep brain stimulation possibilities

Deep brain stimulation (DBS) is an upcoming method targeting various psychiatric and neurological diseases including epilepsy (Temel *et al.*, 2015). During the clinical procedure of therapeutic lead implantation for patients with Parkinson's disease (PD) and other movement disorders, microelectrode recording is routinely performed intraoperatively (Starr, 2002). Analysis of unit activity coregistered with cortical EEG markers could be identified underlying the effect of DBS on PD symptoms (de Hemptinne *et al.*, 2015; Shimamoto *et al.*, 2013). Since DBS therapy is available for epilepsy patients (Fisher *et al.*, 2010), the widespread use of DBS in the clinical setting will provide detailed information about subcortical control of epileptic cortex.

Testing normal functions in epileptic patients

The need for recording single neuronal activities in epilepsy patients offers a possibility to test physiological processes. Due to the frequent seizure involvement of the temporal lobe, numerous studies have been performed to understand emotional and memory processes. Human hippocampal neurons respond in a highly specific manner to complex stimulus features and categories (Fried *et al.*, 1997), and are selective for the novelty of the stimulus (Rutishauser *et al.*, 2006). In a free recall task, individual neurons are able to reactivate the pattern shown in the preceding learning period (Gelbard-Sagiv *et al.*, 2008). Amygdala neurons do participate mostly in fear processes. For review see (Guillory and Bujarski, 2014).

The observation of strong interactions between different types of epilepsies and sleep processes led to the deeper understanding of sleep rhythms in implanted epilepsy patients. Thalamocortical unit activity underlies the generation of slow oscillation, one of the most important brain processes participating in generation of sleep (Crunelli *et al.*, 2015). Slow wave activity in humans showed alternating neuronal excitation and inhibition patterns identified previously in animal models as upstates and downstates (Cash *et al.*, 2009; Csercsa *et al.*, 2010; Nobili *et al.*, 2012; Peyrache *et al.*, 2012; Staba, C. L. Wilson, Bragin, Fried and Engel, 2002a).

Unit recordings in epileptic patients will be important to develop a deeper

understanding of different kinds of multisensory integration processes such as visual, both in motion detection (Ulbert, Karmos, *et al.*, 2001) or emotional reactions (Kawasaki *et al.*, 2001), and auditory and speech functions (Halgren *et al.*, 2015).

Limitations

While there is much to be learned from unit recordings in human cortex, there exists several limitations to the technique. First, information regarding characteristics of the neuron is missing besides some clues on excitatory or inhibitory nature based on AP morphology and spike repetition rate (Csicsvári *et al.*, 1999; Le Van Quyen *et al.*, 2008; Ylinen *et al.*, 1995). Second, neurons that do not fire or have low firing rate are not likely to be picked up by extracellular recordings. Third, only a small patch of cortex is sampled and information regarding the other units in the ensemble is an important component that is lacking. If the goal is to use single units as a predictor of seizures, it would be difficult with the recording from only one brain region. Finally, wires between the electrodes and amplifiers necessitate computers to be in the vicinity of the recording system. Recent approaches have developed wireless technology with portable preamplifiers (Wise *et al.*, 2004) and biofuel cell applications (Andoralov *et al.*, 2013) reducing the need of recharging the portable amplifier's battery.

Future development

There are several limitations that prevent unit recording from more widespread use in clinical settings. These are the difficulty of microelectrode implantation and the extreme down sampling of the brain in space. To incorporate these methods into clinical diagnostics, clinicians would need more robust, less vulnerable sensors and wider spatial coverage. The invasive nature of the microelectrodes limits the number of recording spots. The future may be the utilization of non-invasive techniques like 2-photon microscopy. This method allows recording of multiple units by a scanning laser light beam. The visible changes during the activity arises from injected (Jay, 1988) or genetically expressed light sensitive proteins (Baratta, 2012; Pastrana, 2010). The usage of light instead of electrodes opens the horizon of wider brain areas without entering the cortex by the sensor. However, the need of special dyes or genetic modification exert another limitation for human application. Injection of labeled proteins may change the behavior of the neuronal network (Peron *et al.*, 2015) and be toxic (Jacobson *et al.*, 2008; Reiners *et al.*, 2014), preventing the translation of the method into clinical work.

Promising alternatives include the intrinsic optical signal (IOS) imaging technique. In this technique, the visible signal arises from the slight refractive index change of firing neurons where the cellular water content changes due to ionic currents during action potentials (Kim and Jun, 2013).

Combination of electrophysiological and imaging data requires special probes with integrated optodes in them (Keller *et al.*, 2009). The formerly mentioned meso-scale electrodes, like brain surface microcontacts may be capable to record unit activites from the surface as shown by the NeuroGrid project (Khodagholy *et al.*, 2014). Finally, when having the activity of hundred thousands of neurons together the problem of analysis will need faster data processing techniques than we have already.

In conclusion unitary activity has been the hallmark of normal and abnormal 'brain function'. The need to record units in both research and clinical realms across multiple specialties will likely persist in the near future. The practical methods fulfilling these criteria are the matter of future research and innovation.

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