The Future of Intracranial EEG Recording in Epilepsy: a Technological Issue?

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Summary

Intracranial EEG information used for epilepsy surgery has been provided from large widely spaced electrodes over a narrow bandwidth. However, over the last decades, research on animal and more recently on human, promoted by increased interest in developing high-density microelectrode arrays (MEA), has opened new windows for the comprehension of seizure origin and propagation at a submillimeter scale. From an electrophysiological perspective MEA demonstrate to be able to record local field potentials recordings and possibly single units in the mouse cortex. The limitations on the number of channels that can be recorded simultaneously may limit the number of microelectrodes that can be considered and consequently the extent of brain coverage. Thanks to improving microfabrication techniques, several prototypes of MEA are under development and investigation. They will certainly play an important role in the improvement of the understanding of the complicated and evolving concept of epileptogenesis and provide the development of new strategies regarding neurosurgical therapeutic issues.

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Key words: EEG, microrecording, epilepsy, surgery, microfabrication, micro-electrode array

Die Zukunft der intrakraniellen EEG-Ableitung bei Epilepsie: eine Frage der Technologie?

Intrakranielle EEG-Signale wurden bisher mit Elektroden aufgezeichnet, die eine relativ grosse räumliche Distanz zueinander hatten und nur eine stark begrenzte Frequenzbandbreite erfassten. In den letzten Jahren hat aber die Entwicklung von sogenannten Mikro-Elektroden-Arrays (MEA), welche im Tierversuch und auch bereits beim Menschen zum Einsatz kommen, die Möglichkeit eröffnet, Anfallsentstehung und Anfallsausbreitung auch auf einer Grössenskala <1mm zu analysieren. So wurde zum Beispiel in Mäusen gezeigt, dass mit MEA sowohl die lokalen elektrischen Feldpotenziale als auch Aktionspotenziale einzelner Nervenzellen aufgezeichnet werden können. Die begrenzte Anzahl von Signalen, die gleichzeitig registriert werden können, stellt eine Einschränkung insofern dar, als deshalb aktuell nur ein kleines Hirnareal mit MEA exploriert werden kann. Dank der stetigen Verbesserung der Mikrofabrikationstechnologie werden aber mehrere neue Prototypen von MEA entwickelt und bereits getestet. Diese neuen MEA werden mit Sicherheit in Zukunft eine wichtige Rolle für ein verbessertes Verständnis der Ikto- und Epileptogenese spielen und wesentlich dazu beitragen, neue therapeutische Strategien in der Epilepsiechirurgie zu entwickeln.

Schlüsselwörter: EEG, Mikro-Ableitung, Epilepsie, Chirurgie, Mikro-Fabrikation, micro-electrode array

Le futur de l'enregistrement EEG intracrânien pour l'épilepsie : une question technologique ?

Les informations concernant l'EEG intracrânien utilisées pour la chirurgie d'épilepsie ont été obtenues avec des grandes électrodes largement espacées sur une bande passante étroite. Cependant, au cours des dernières décennies, la recherche sur l'animal et plus récemment sur l'homme, motivée par l'intérêt accru pour le développement de microelectrode arrays (MEA), a ouvert de nouvelles fenêtres concernant la compréhension l'origine et la propagation des crises épileptiques à une échelle sous-millimétrique. D'un point de vue électrophysiologique, les MEA ont montré qu'elles étaient capable d'enregistrer des potentiels de champ proche, voire même des enregistrements monocellulaires dans

le cortex de souris. Le nombre limité de canaux d'enregistrement limite le nombre d'électrode simultanément utilisables et, par conséquent, l'étendue de la surface cérébrale à explorer. Grâce à l'amélioration des techniques de microfabrication, plusieurs prototypes de MEA sont en cours de développement et d'essai. Ils joueront certainement un rôle important dans l'amélioration de la compréhension de ce concept compliqué et en évolution qu'est l'épileptogenèse et permettront de développer de nouvelles stratégies thérapeutiques neurochirurgicales.

Mots clés : EEG, micro-enregistrement, épilepsie, chirurgie, microfabrication, micro-electrode array

Introduction

Partial epilepsy is the most common pharmacologically resistant seizure disorder [1]. Although the established electrophysiological signature of partial epilepsy is focal seizures, little is known about the spatial and temporal scales that define the neuronal assemblies underlying this emergent pathological oscillation. For decades, epilepsy surgery has utilized intracranial EEG recorded over a narrow bandwidth (1–100 Hz) from large (~5-10mm diameter), widely spaced (5-10 mm) electrodes [2]. This practice, however, is largely based upon tradition and the limits of sensor technology when intracranial EEG was first recorded, rather than our knowledge of the human brain. These technological limitations often frustrate epileptologists looking for discrete, functional 'lesions' to remove during epilepsy surgery, because seizures arising from the neocortex often appear to start abruptly from large regions of brain [3]. Other applications awaiting better definition of the neurophysiological generators of seizures are seizure prediction [4, 5], whose controversial performance may be due in part to the poor temporal and spatial resolution of clinical intracranial EEG, and implantable anti-epileptic devices [6], whose efficacy might be improved with better targeting and understanding of seizure generators. To date the emergence of spontaneous focal seizures in humans has not been thoroughly investigated at high temporal sampling rates on sub-millimeter spatial scales.

Over the last few years, there has been increased interest in developing high-density arrays of electrodes or microelectrodes incorporating microwires, placed separately or in conjunction with regular macroelectrode grids or depths. In addition to providing denser sampling of cortical activity, these arrays are better suited to recording high-frequency activity. These new recording electrodes have been used mostly for research purposes without established clinical applications, but reports raise the possibility that such high-density arrays with smaller electrodes can record information important for identifying the ictal onset zone and planning surgical resections.

From animal...

Work from Goldensohn et al. [7] in the 1960s describes microepileptiform discharges obtained from a glass pipette electrode on the surface of cat cortex treated with a focal injection of penicillin. They demonstrated focal evolving microepileptiform discharges after penicillin injection on single electrodes in an array of electrodes spaced 2mm apart with no reflection of the discharges on adjacent electrodes. The magnitudes of the recorded potentials were as large as 3mV and were largest in the superficial cortical layers when depth profiles were measured.

More recently, literature about exploration of the content of the EEG in a frequency domain higher than what is permitted by commonly used macroelectrodes emerged. In a rat model of epilepsy created by intrahippocampal kainic acid injection [8], pathological high-frequency oscillations emerged in microdomains ($<1mm^3$) weeks to months before spontaneous seizures developed. Epileptogenesis was proposed to be initiated by local cellular injury, resulting in small clusters of pathologically interconnected neurons. The authors hypothesize that pathologically interconnected neurons generate hypersynchronous discharges that kindle the brain through the creation of new pathological microdomains, and the emergence of an interacting network of pathologically interconnected neuron clusters.

... to human data

Wide-bandwidth local field potential recordings using microelectrodes (diameter<100 µm) in epileptic human hippocampus and neocortex have identified several new classes of electrographic activity localized to sub-millimetre-scale tissue volumes, inaccessible to standard clinical intracranial EEG technology. Pathological high-frequency oscillations have been localized to microdomains ($<1mm^3$) in human epileptic hippocampus [9, 10]. Penetrating microelectrode arrays embedded directly into human epileptic neocortex reveal microperiodic epileptiform discharges [11] and high-frequency oscillations [12] confined to 200-µm-diameter tissue regions. There is debate regarding the significance of microperiodic epileptiform discharges, however, because they have morphology and temporal behaviour similar to what is reported after cortical injury [13], and they have not been established as a specific electrophysiological marker for epileptic tissue.

Stead et al. [14] recorded microseizures and microdischarges, more frequently in the seizure onset zone but also occurring less frequently in control patients. These recordings assess not single-unit activity, but multineuronal activity. Still these studies report the

ability of these new electrodes to assess highly localized activity and, in the case of the microseizures reported by Stead and colleagues, activity that may correlate with region of onset of partial seizures. If that would be the case, those microseizures would be ideal candidates for targeted therapies.

High-density microelectrode arrays

Multiple electrode arrays (microelectrode arrays - MEAs) consist of a substrate on top of which coplanar electrodes are manufactured, concentrating them into a limited area. A first type of MEAs is used for *in-vitro* electrophysiological experiments, aiming at performing multiple parallel measurement of the electrical activity of cell cultures, where the older patch-clamping based technology would typically enable up to six or eight parallel measurements, only. Typically, the electrode pitch is in the range of 200µm [15] down to 60µm for recent developments, with 512 individual recording sites [16]. Electrical connectivity is provided to the borders of the system, translating dimensions one to two higher orders of magnitude. MEAs have gained a wide acceptance in the community of neuroscientists, and are a standard tool for *in-vitro* experiments. Currently used MEAs are purely passive devices, which creates the stringent need to place dedicated amplification devices in the closest vicinity. MEAs using three dimensional microelectrode tips have been demonstrated recently. The use of non-invasive electrodes that do not penetrate the cell membrane presents significant challenges. Fromherz [17] has pioneered this field, first presenting gate-less FET transistors to detect extracellular neuronal electrical activity [18], and more recently extending this work to capacitive sensors. A non-standard CMOS process has been applied in the development by Cohen et al. [19] where floating-gate transistors have their gate-voltage potential affected by cells appropriately placed on them. Silicon post-processing of a chip produced in standard CMOS technology has been demonstrated as a reliable technique to fabricate planar electrodes and connect them with readout electronics [20]. The inter-electrode pitch is usually in the order of several tens of micrometers, leaving significant area for local electronic processing and relatively large electrode plates. The highest density array reported to date has an inter-electrode pitch equal to 7.8µm [21]. Finally, using three-dimensional micromachined microelectrodes to couple to living matter has been attempted [22] where electrodes are 40µm high, only 15µm being exposed, and with a minimal pitch of 170µm, and [23] where electodes are >50µm high, one of the 60 available electrode covering an area of 60µm x 60µm.

An example of current solution for high-density recording of epileptic activity on the human cortical surface consist of hybrid macroelectrodes along with microwire arrays with bundles of wires connected to the electrodes (AD-Tech, Inc.). The microwire arrays contain 40-µm-diameter platinumiridium wire spaced 0.5-1 mm apart. Macrocontacts are 4-mm-diameter platinum-iridium discs spaced 5-10 mm apart, center-to-center (**Figure 1**).

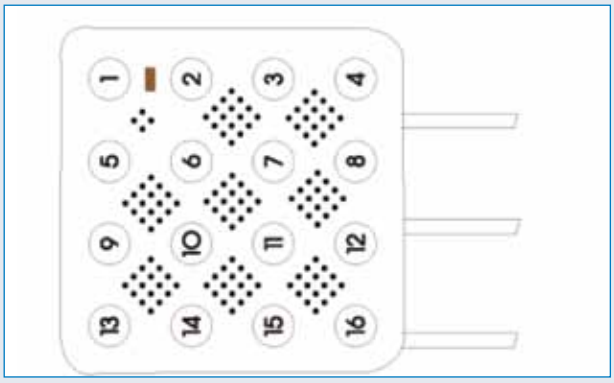

Figure 1: Scheme of a hybrid electrode macroelectrodes along with microwire arrays with bundles of wires connected to the electrodes proposed by AD Tech.

Signals recorded from MEA

From an electrophysiological perspective, the extracellular local field potentials recorded by microwires seem to be primarily a manifestation of the co-operative activity of the local neuronal population. Until recently, the local field potential was thought to exclusively reflect the summation of post-synaptic currents because of their relatively slow dynamics. This is the reason that extracellularly recorded action potentials – with the fast Na+ current being the largest contributor – are detected only if the microwire is close to the cell. The amplitude of the extracellular action potential falls off rapidly with distance, and the events are unlikely to constructively sum because of their brief duration. However, it has been recognized that there are additional sources of local field potentials not associated with synaptic currents and they can be significant [24]. They include Ca++-mediated action potentials generated in dendrites [25], slow long-lasting calcium-mediated potassium currents, voltage-dependent intrinsic oscillations in neurons [26] and currents related to glia-neuron interactions [27].

Recently, we performed acute in-vivo recordings in mice with a novel, flexible, polyimide neural probe with two layers of platinum electrodes [28]. The devices were packaged ensuring robustness and biocompatibility. Using electrical modeling and impedance testing the device has shown to be adequate for neural recording experiments. Single and multiple units were identified. Principal Component Analysis is used to quantify the quality of the recordings. **Figure 2** demonstrates local field recordings identifying two single units in the

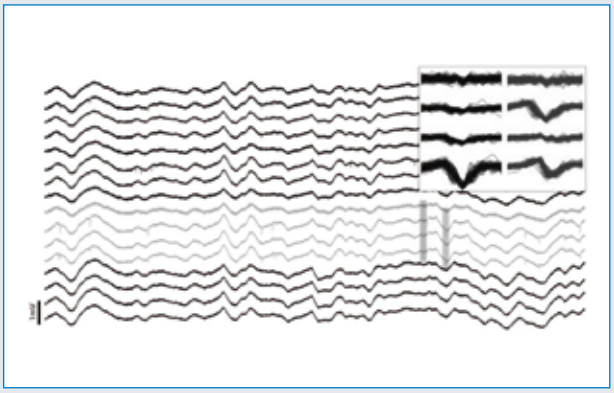

Figure 2: Recordings from of a 16 MEA polyimide neural probe with two layers of platinum electrodes on mouse cortex, Adapted from Mercanzini A et al. Sensors and Actuators A, 2008.

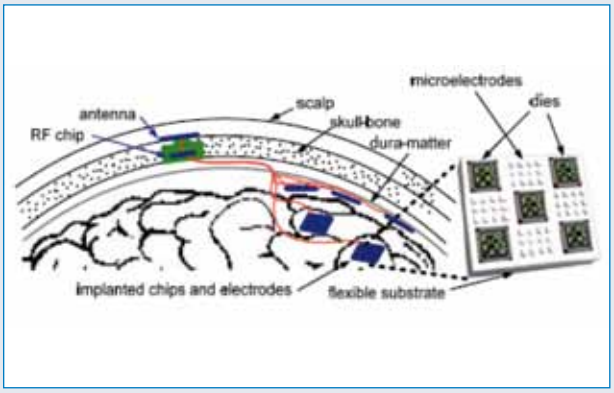

Figure 3: Schematic representation of the proposed Wireless MEA.

mouse cortex. All 16 electrode sites were active. Histological study of the limited tissue reaction around the implant showed the long term implant stability [29].

Extent of coverage

The extent of coverage by recording arrays is in part dependent on the knowledge of the localization of the ictal onset zone. The ictal onset zone may be much more localized than the epileptogenic zone (the region targeted for resection for optimal surgical outcome) or the irritative zone (corresponding to interictal discharges), but even experts acknowledge that these zones are often overlapping and often not clearly defined [30]. For the purposes of early seizure detection, one would want to be as close as possible to the ictal onset zone. In some patients this is a discrete region; in other patients (e.g., patient with nonlesional neocortical partial epilepsy), the ictal onset zone may be broad or regional. Although it is not uncommon to incorporate 100-200 intracranial contacts into macroelectrode recording arrays, there are some limits on the size and extent of the arrays posed by the extent of the craniotomy and inherent risks of larger arrays. The use of high-density electroencephalography employing larger arrays of electrodes for scalp recordings is oriented toward dipole source localization. These larger arrays have been shown to provide improvements in effective spatial resolution up to 512 electrodes if the noise level remains low [31]. In intracranial recording, the incorporation of microelectrode arrays placed within the space of traditional grid arrays offers an increased density of points of measure which can provide a superior understanding of the local network dynamic involved in the early stages of the seizure [14]. Still, the limitations on the number of channels that can be recorded simultaneously may limit the number of microelectrodes that can be considered. The use of macroelectrodes may remain a valid compromise between size of the electrodes and area of the brain covered, especially in the context of the presurgical evaluation where the location of the seizure focus is not yet clearly identified. Thereafter, the use of MEA could be used for a further refinement of the ictal/epileptogenic zone.

Ongoing developments

Another solution consisting of using highly flexible and thin substrates to create active electrode arrays combining a large number of electrodes with integrated circuits distributed over a relatively large area over the cortex is under development in partnership with engineers of the Swiss Federal School of Technology. By placing many of these recording systems on the potentially epileptic parts of the cortex previously detected by the standard non-invasive methods, sufficient information with respect to the localization of the epileptic foci with high spatial resolution quality could be recorded (**Figure 3**). Low-noise amplifiers that operate in an intermediate range of frequency to record low as well as high frequency ripple and/or spiking signals which can be representatives of epilepsy are integrated in the system. Furthermore, subcutaneous implantation is enabled by the presence of an RF chipset located in a burr hole in the skull for remote powering and wireless data transmission (**Figure 3**), avoiding the risk of infection induced by the externalized wires. Finally, long-term recordings could be performed, providing refined information from each patient. Implantation of this device should be performed through a minimally invasive approach and transmission of the patient data could even be performed on an outpatient basis. Verification of the proof of concept of this technology is under investigation on animal.

Future MEA designs for human use could also incorporate several microelectrode elements disposed on an implantable slightly penetrating device, in order to record deeper cortical neuronal layers. **Figure 4**

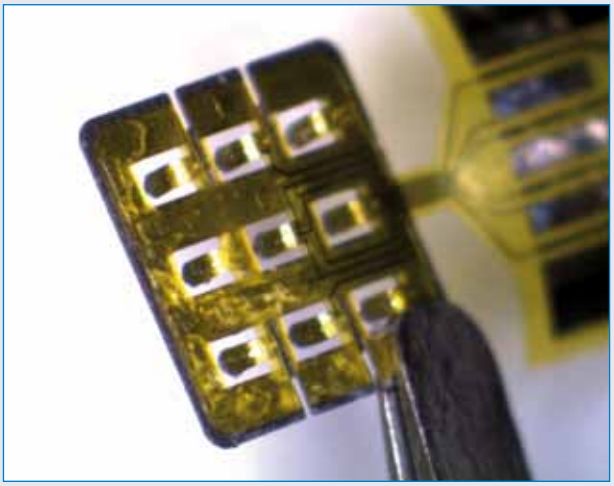

Figure 4: Early prototype of a MEA which is intended to sit on the surface of the brain, with slightly penetrating shanks wearing microelectrodes.

demonstrates an early prototype of the cortSTIM (Aleva Neurotherapeutics SA, Lausanne) which is intended to sit on the surface of the brain, with slightly penetrating shanks and on which microelectrode recordings are disposed. This design offers a truly 3D volume from which to capture single unit and local field potential recordings with higher signal-to-noise ratios than classic EEG electrodes. Furthermore, the 3D natures of the electrode layout offers also novel possibilities in cortical stimulation.

Conclusions

Recent technological developments improving microfabrication techniques have provided new insights in seizure detection at a submillimetric scale. Increasing evidence that microseizures may preceed detectable epileptic events at a standard electrocorticographic scale opens new frontiers not only for the comprehension of seizure origin and propagation, but also regarding neurosurgical therapeutic issues (increasing selectivity of tissue resection, earlier seizure detection and targeted suppression by electrical stimulation before clinical manifestation). In other words, each step of the detection paradigm can be a target of future experiments to bring to fruition a seizure warning mechanism that can significantly improve the quality of life of patients or to optimize closed loop therapy devices. From the choice of electrodes to the decision making algorithm, it is important to take a comprehensive look at the various elements that are part of this complicated and evolving process.

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