Epilepsy & Behavior 58 (2016) 11–17

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Review

Exploring human epileptic activity at the single-neuron level

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ARTICLE INFO

Article history:
Received 17 September 2015
Revised 9 February 2016
Accepted 10 February 2016
Available online 16 March 2016

Keywords:
Epilepsy
Interictal activity
Single neurons
Neurophysiology
Seizure prediction
Microelectrode recordings
Postictal state

ABSTRACT

Today, localization of the seizure focus heavily relies on EEG monitoring (scalp or intracranial). However, current technology enables much finer resolutions. The activity of hundreds of single neurons in the human brain can now be simultaneously explored before, during, and after a seizure or in association with an interictal discharge. This technology opens up new horizons to understanding epilepsy at a completely new level. This review therefore begins with a brief description of the basis of the technology, the microelectrodes, and the setup for their implantation in patients with epilepsy. Using these electrodes, recent studies provide novel insights into both the time domain and firing patterns of epileptic activity of single neurons. In the time domain, seizure-related activity may occur even minutes before seizure onset (in its current, EEG-based definition). Seizure-related neuronal interactions exhibit complex heterogeneous dynamics. In the seizure-onset zone, changes in firing patterns correlate with cell loss; in the penumbra, neurons maintain their spike stereotypy during a seizure. Hence, investigation of the extracellular electrical activity is expected to provide a better understanding of the mechanisms underlying the disease; it may, in the future, serve for a more accurate localization of the seizure focus; and it may also be employed to predict the occurrence of seizures prior to their behavioral manifestation in order to administer automatic therapeutic interventions.

1. Introduction

Neurotechnology is the basis for novel insights into epilepsy. In 1934, Fischer and Lowenbach employed the electroencephalogram (EEG) to demonstrate epileptiform spikes for the first time [1]. In the 1950s, Penfield and Jasper utilized electrocorticography (ECoG) to define the epileptogenic zone [2]. Today's technology provides electrical data at a microscale, enabling the simultaneous chronical recording of the activity of multiple, even hundreds of, single neurons in humans.

This type of recording serves in the rare unique neurosurgical treatment of different pathologies, mainly movement disorders such as Parkinson's disease or dystonia and pharmacologically resistant epilepsy [3,4]. Participation of patients with epilepsy, implanted with microelectrodes for clinical reasons, in single-neuron studies has yielded important novel understandings in multiple fields of neuroscience [4,5]. These include, for example, speech encoding [6,7], memory [8–10], auditory encoding [11,12], face identity [13], vision [14], visuomotor coordination [15], motor representation [16], and sleep [17,18]. The same setup can also serve for studying mechanisms of human epilepsy, ictogenesis, at the single-cell level. Nevertheless, literature of this kind of research is currently very limited [19]. Notwithstanding, in recent years, this setup yielded important insights into the microscale of the neurophysiology of human ictogenesis. This article focuses on these seminal studies.

Because microelectrode technology can dramatically affect our understanding of ictogenesis, this review first describes microelectrode implantation in humans. It then focuses on the electrophysiological activity of single neurons during time periods around seizures and interictal discharges and in three zones: the seizure-onset zone, the surrounding penumbra, and outside areas. It also highlights recent advances aimed at prediction of seizure-onset time or the onset zone based on single-unit activity.

2. Microelectrode implantation in humans

2.1. Patient population

A common treatment for patients with pharmacologically resistant epilepsy is neurosurgical: resection of the seizure focus. For this, the seizure focus has to be localized. The patient is therefore clinically monitored for seizures. The basic monitoring records scalp EEG. Patients for whom noninvasive monitoring does not yield concordant data corresponding to a single resectable focus are routinely implanted with invasive electrodes for 1–2 weeks to determine the seizure focus for potential surgical treatment [4,20,21]. The selection of a specific type of intracranial electrodes – depth, subdural grid, subdural strip, or their combinations – is mainly based on earlier indications, obtained by noninvasive monitoring and imaging, of the suspected brain

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http://dx.doi.org/10.1016/j.yebeh.2016.02.014
1525-5050/

area or areas [22–24]. Patient age is also taken into account, even though the successful identification of the ictal onset zone using depth electrodes has been demonstrated in a pediatric population with epilepsy [25] and with no age-related difference in surgical outcome [26]. When clinical criteria indicate the use of depth electrodes, the patient will usually be implanted with 7–13 electrodes.

2.2. The electrodes

In our setup, we use the Behnke–Fried electrode (Adtech Medical Instrument Corporation, Racine, WI) with 8 ring-shaped macro contacts along its shaft, for recording intracranial EEG; the electrode terminates with a set of nine 40-μm platinum–iridium microwires, for recording single-unit activity [20]. A development of the Behnke–Fried electrode, known as the micro–macro electrodes (Adtech Medical Instrument Corporation, Racine, WI), adds 9 radially oriented microwires along the shaft for the 8 macro contacts or 18 radially oriented microwires for a 4-macro-contact version [27].

Single-unit recordings have a unique contribution to the development of brain–machine interfaces [28–32]. Especially common in this field is the Utah intracortical electrode array, also known as the Neuroport array (Blackrock Microsystems, Salt Lake City, UT), which permits the simultaneous implantation of a large number of microelectrodes in a small region of the cortex [33]. A grid of 10-by-10 electrically isolated 1.2-mm-long needles projects out from a 4.2-mm-by-4.2-mm, 0.2-mm-thick silicon substrate. The array has been employed for brain–machine interfaces in patients with tetraplegia [28,32,34] and has also been implanted in patients with epilepsy [35–37]. In the latter population, implantation sites were selected to fall within the putative seizure-onset zone and away from eloquent brain areas, to ensure that the sites would be targeted for subsequent surgical resection.

The Utah array consists of microelectrodes of the same length, thus aimed at recording at the same layer of the cortex. To record from multiple cortical layers simultaneously, a laminar multiple microelectrode has been developed [38]. This thumbtack-like electrode contains a linear array of 22–24 platinum–iridium 40-μm contacts along its shaft, whose length corresponds to the depth of the cortex. The laminar electrode has been implanted in patients with epilepsy [38].

Recently, novel microelectrode technology was developed with bioactive surfaces for chronic neural interfaces [39]. The new type of electrodes is an order of magnitude smaller than current ones and allows for acute and chronic single-neuron recording. For reviews of advanced neurotechnologies for chronic neuronal interfaces, see [40,41].

In parallel to recent developments in depth electrode technology, ECoG grids are also being miniaturized. Ultrathin and flexible silicon nanomembrane transistors, combined into the electrode array, enable new dense arrays of thousands of amplified and multiplexed sensors connected using considerably fewer wires [42]. This technology has been tested on cats and provided new insights into the propagation of seizure waves in their neocortex but is still unavailable for human use because of its "active" nature: the grid internal transistors are constantly being powered. In between today's ECoG grid contacts lying on the surface of the cortex and the microelectrode array that penetrates the cortex lies a new array of electrodes for recording local field potentials (LFPs) and action potentials from superficial cortical neurons without penetrating the brain surface, as was recently implanted in two patients with epilepsy [43].

2.3. The recorded signal

In our setup, the anatomical locations of the electrodes are routinely verified after the implantation by magnetic resonance imaging (MRI) or by computer tomography (CT) coregistered to preoperative MRI. Bandpass filtered signals (0.3–3 kHz) from these microwires are recorded at 30 kHz using a 256-channel acquisition system (Neuroport, Blackrock, Salt Lake City, UT). For comparison, electroencephalography (EEG) and electrocorticography (ECoG) signals are recorded at most at 2 kHz. The recorded signals are then spike sorted (WaveClus [44], SUMU [45]). Because of the ambiguity of the term "spike", in this review, "spike" will refer to the EEG or ECoG waveform characteristic of epileptic seizures, whereas the rapid rise and fall of an electrical membrane potential of a neuron will be named "action potential". Still, the term "spike sorting" means distinguishing between action potentials generated by different neurons recorded on the same electrode.

2.4. Chronic recordings

Microelectrode performance is affected by both abiotic (electrophysiology, impedance, electrode morphology) and biotic (microglial reactivity, blood–brain barrier disruption, biochemical markers of axonal injury) factors [46]. Long-term recording has therefore been an important challenge since the early days of microelectrode recordings of single neuronal action potentials [47,48]. Strumwasser demonstrated the ability to chronically record neural activity using microwires in hibernating squirrels [49]. Recordings of the same neuron in patients with epilepsy for several hours were reported already in the early 1970s [50]. As was recently shown in the monkey using a 96-electrode array, the activity of the same neuron can be recorded chronically, for periods even longer than 100 days, maintaining stable firing properties over time [51]. In humans, microelectrode arrays provided useful data even a few years after implantation [52]. Automatic algorithms were reported to track the activity of the same unit over the span of a few months of recordings [53].

3. Neuronal epileptic activity

The first successful single-unit recording in the human neocortex was carried out by glass micropipettes inserted into the posterior temporal lobe during an operation to locate the epileptogenic area [54]. The early studies of human neuronal activity verified the existence of bursting units in the chronic epileptogenic focus [55], already shown by then in the monkey [56]. Bursting units were also found in the contralateral homotopic of the seizure focus and in ipsilateral, but not contralateral, adjacent regions. During all the clinical seizures, when a seizure spreads bilaterally on the electroencephalogram, more neurons appear to become involved, suggesting increased synchrony between neurons in the participating brain area. As a seizure approaches, the clustering of neuronal action potentials becomes more marked, more regularly periodic, and more frequently associated with the ictal waves, as the latter increase in amplitude and duration [57]. Many neurons in the focus, as well as in the surrounding area, fire synchronously with the surface sharp waves, whereas few neurons in the surrounding area show rhythmic burst without correlation with the surface activity [58]. In monkeys, another primary difference between normal and epilepsy-related neurons is the ability of the former to modify the firing pattern and rate, which is far more limited in the latter [59].

Although an inhibitory surround of the epileptogenic focus was described in the cat at the single-cell level almost fifty years ago [60], only recently was an equivalent inhibitory restraint identified in the human by high-frequency oscillations [61] or by single units [37]. The territories surrounding the "ictal core" are referred to as the "penumbra". In the penumbra, neurons showed a much lower level of firing, no stereotyped firing patterns, heterogeneity of firing across the electrode array, no phase locking, and minimal change in electrode coherence. Their activity seemed identical to that recorded ahead of ictal waves, suggesting these areas were not recruited to the seizure (although affected by it). Although the areas implanted with microelectrode arrays were characterized as "penumbra", the transition between them and the "true" seizure-onset zone, characterized by an abrupt onset of tonic firing at the arrival of the ictal wavefront or an intense hypersynchronous firing accompanying paroxysmal depolarizing shifts, were not observed. The penumbra was demonstrated in single neurons only in 10 seizures of 2 patients, and electrodes were within the clinically identified "seizure-onset zone" [37].