

## MICROSEIZURES IN HUMAN NEOCORTEX: A ROLE FOR ULTRA-SMALL SEIZURES?

**Microphysiology of Epileptiform Activity in Human Neocortex.** Schevon CA, Ng SK, Cappell J, Goodman RR, McKhann G Jr, Waziri A, Branner A, Sosunov A, Schroeder CE, Emerson RG. *J Clin Neurophysiol* 2008;25(6):321–330. **SUMMARY:** The authors report the use of dense two-dimensional microelectrode array recordings to characterize fine resolution electrocortical activity (“ $\mu$ EEG”) in epileptogenic human cortex. A 16-mm<sup>2</sup> 96 microelectrode array with 400- $\mu$ m interelectrode spacing was implanted in five patients undergoing invasive EEG monitoring for medically refractory epilepsy. High spatial resolution data from the array were analyzed in conjunction with simultaneously acquired data from standard intracranial electrode grids and strips.  $\mu$ EEG recorded from within the epileptogenic zone demonstrates discharges resembling both interictal epileptiform activity (“microdischarges”) and electrographic seizures (“microseizures”) but confined to cortical regions as small as 200  $\mu$ m<sup>2</sup>. In two patients, this activity appeared to be involved in the initiation or propagation of electrographic seizures. The authors hypothesize that microdischarges and microseizures are generated by small cortical domains that form the substrate of epileptogenic cortex and play important roles in seizure initiation and propagation.

### COMMENTARY

Basic research on the mechanisms underlying the generation of epileptic seizures has technical and conceptual problems when the work is performed at the interface of cells and neuronal networks of the human neocortex. In particular, progress has been hindered by the difficulty of concomitantly recording the electrical activity of single neurons and their surrounding local neuronal network before, during, and after epileptic seizures. Neuronal action potentials have been recorded experimentally from human cortex for several decades using single microelectrodes (1). This technique obviously can reveal the firing patterns of individual neurons in relation to the highly synchronous hyperactivity characteristic of epileptic seizures in the cortex but alone, does not allow determination of epileptiform activity in adjacent small domains of the neocortex. The microelectrode array used in the study by Schevon et al., however, is able to reveal when epileptiform activity occurs in one or more specific sites but not in other nearby sites. Furthermore, the two-dimensional relationship of the array can show when epileptiform activity is on contiguous electrodes or occurs in a more scattered pattern of electrode sites.

Changes in the electrophysiological characteristics of individual human neurons and the functional properties of their local synaptic circuits associated with acquired epilepsy are best studied at a biophysical level with *in vitro* systems. Brain slices prepared from cortical tissue after surgical resections to treat patients with intractable epilepsy are a potentially useful model. These *in vitro* experimental systems, however, obviously lack synaptic input from most of their normal or abnormal connections. More importantly, although brain slices may display some

forms of hyper-excitability and hyper-synchrony, they do not generate spontaneous, recurrent electrographic seizures without the addition of convulsive drugs, even when the tissue is obtained from a human with severe epilepsy (2). The ability to study electrical activity at many adjacent sites in the cortex of an awake human with epilepsy—under the conditions described here—is typically limited by the technical difficulty of recording the activity of many single neurons and/or isolated neuronal populations. The study by Schevon and coworkers uses a microelectrode array to analyze the local field potentials in various areas of the neocortex of patients undergoing invasive EEG monitoring for surgical treatment of intractable epilepsy. This approach has the potential of allowing researchers to obtain data simultaneously from single neurons and their local neuronal networks.

Schevon and colleagues obtained recordings from five patients with microelectrode arrays positioned within the boundaries of an intracranial grid. The microelectrode array could record from up to 96 different sites, with a 400- $\mu$ m interelectrode spacing. The microelectrode array was capable of detecting normal versus abnormal electrical activity at each of the 96 independent, but adjacent, sites. Most of the microelectrodes in the array exhibited synchronous local field potentials, when EEG spikes were observed on the intracranial grid. Other types of rhythmic electrical activity also were observed on the microelectrode arrays, including “microdischarges,” which were defined as localized epileptiform discharges present on one or a few adjacent recording electrodes in the array but not present on the intracranial EEG. When microdischarges occurred in repetitive, evolving patterns, they were defined as “microseizures.” These events were seen in most of the patients and were characterized by a morphology, periodicity, and frequency that is similar to seizure discharges. A comparison of the electrical activity on the microelectrode array with the epileptiform discharges on the

intracranial grid, detected microseizures on the microelectrode array when EEG spikes were not seen on the intracranial grid. Thus, epileptiform activity was recorded within microdomains of epileptogenic neocortex although traditional EEG spikes were not present, suggesting epileptiform activity can occur within extremely small neuronal networks of the neocortex. This finding leads to the hypothesis that microdomains with elementary seizure-like activity are present within seizure-onset zones.

One question is whether these microseizure events represent actual abnormal activity linked mechanistically to seizure onset in an epileptogenic zone or whether they would have otherwise been seen in normal brain. Although the authors intended to position the microelectrode arrays in the tissue that was already identified as epileptogenic, one recording site was subsequently assessed as nonepileptogenic, and microseizures were not recorded in that tissue, which suggests that microseizures are not present in relatively normal or nonepileptogenic brain. Microseizures could build up before and even appeared to trigger frank seizures, supporting the hypothesis that microseizures, localized to only a few cubic millimeters, play a role in the initiation of full epileptic seizures.

A question raised by the authors is whether the highly focal nature of these events makes them similar to high-frequency oscillations or fast ripples that have been seen in human temporal lobe epilepsy with a different type of multi-electrode recording (3,4). Like these local field potentials, high-frequency oscillations are thought to be highly localized, but they are recorded within a much higher frequency band than used in this study. Although microelectrode arrays, such as those used in the study of Schevon et al., are amenable to the recording of electrical signals in a higher frequency band and would allow high-frequency oscillations and single action potentials to be analyzed, these authors focused on local field potentials. Nonetheless, it is intriguing to consider a possible relation between microseizures and high-frequency oscillations.

This paper offers insights into how small regions of human neocortex are active before and during actual epileptic seizures. The authors have proposed that the neocortex of an individual with epilepsy is heterogeneous, with some microdomains that are epileptogenic and other nearby microdomains that are not,

which is similar to the findings of regions with high-frequency oscillations or fast ripples (3,4). It is unclear whether those areas that do not show microseizures, yet are near an area that does, are nonepileptogenic or whether all areas are similar and probabilistic factors determine which neurons participate in microseizures. To demonstrate that specific microdomains are epileptogenic and other immediately adjacent microdomains are not would require evidence that some microdomains repeatedly show microseizures, while other microdomains never show them (4).

The microelectrode array approach offers considerable potential for future research, because these arrays could be used in animal models (i.e., control preparations) as well as human epilepsy. In both cases, an analysis of the electrophysiology of individual neurons within a brain slice preparation that was obtained from a cortical region adjacent to an area previously recorded with a microelectrode array could be performed. Thus, the use of microelectrode arrays provides a novel window through which to observe epileptiform activity of single neurons and nearby small neural networks in human patients with intractable epilepsy. When combined with well-established electrophysiological techniques used for examining the biophysics of seizure discharges in neurons, it may be possible to link molecular and cellular mechanisms to systems level phenomena and thus gain valuable new insights into the pathophysiology of epilepsy.

by F. Edward Dudek, PhD

## References

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