

High-resolution Electroencephalography Provides New Insights into Epilepsy

a report by

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DOI: 10.17925/USN.2008.04.01.44

Perturbations of the electrical oscillations of the cerebral cortex of epileptics were first demonstrated by Berger,¹ soon after he discovered the existence of recordable brain electrical activity in humans in July 1924. Although interested in electroencephalography (EEG) not as a medical tool but rather as a physical measure of mental processes, Berger's writings provided the initial descriptions of many of the patterns important to the current practice of clinical EEG: the alpha rhythm and alpha blocking with eye opening, sleep patterns, disorganization of the EEG following anoxia, three per second discharges with absence seizures, and post-ictal slowing.

Advances in medicine are often driven by technological developments. The Eithoven string galvanometer allowed Berger to discover the human EEG. Vacuum tube amplification permitted clinical EEG to flourish, remaining the principal brain imaging technique until the 1970s, when it ceded that role to computerized X-ray tomography. Still, EEG remains the principal clinical tool for the diagnosis of epilepsy. During the 1980s, improved amplifiers and video technology, plus advances in digital data acquisition and storage, made it possible for video EEG monitoring and intracranial recording to become standard fare for the evaluation and treatment of certain patients with epilepsy.

Currently, microelectrodes suitable for human use, along with higher-capacity data acquisition and storage systems, are enabling technologies for refining, by orders of magnitude, the temporal and spatial resolution of brain electrical recordings in patients with epilepsy. Early results suggest that data obtained from microelectrodes and microelectrode arrays implanted in the seizure foci of epilepsy patients are likely to inform, in very significant ways, our understanding of the pathophysiological disturbance present in the epileptogenic cortex, as well as the process of seizure generation. These results hold the promise of leading to novel treatments for medically refractory epilepsy, including improvements in surgical brain resection and implantable devices designed to warn patients of impending seizures, or even to stop them from becoming clinically manifest by targeted delivery of drugs or electrical stimulation to affected brain areas.^{2,3}

Recorded through the intact skull, the EEG reflects summated synchronous fluctuations of membrane potentials, primarily of the apical dendrites of millions of neurons spread over several square centimeters.⁴ Brain signals passing through the scalp and skull are blurred and attenuated, especially in the higher frequencies.⁵ A large area of the brain's surface must be active at any one time to generate EEG signals that are recordable at the scalp. Indeed, brain signals involving less than about 6cm² of cortex may be invisible on scalp EEG.⁶ Furthermore, EEG signals from brain areas such as the inferior frontal lobe are difficult to record from surface electrodes; scalp-recorded EEG may detect only propagated activity from distant sources.⁷ Nonetheless, for routine diagnostic purposes scalp recordings are the most practical option and are generally sufficient.

However, for epilepsy patients requiring surgical treatment the data provided by scalp recordings often prove insufficient to adequately localize the part of the brain responsible for generating seizures.⁸ In these cases, the electrical effects of the skull are eliminated by surgically implanting electrodes into the subdural space or into the substance of the brain. Intracranial electrode recordings help to more accurately target tissue for surgical removal by defining the locations of interictal and seizure activity at a resolution of 0.5–1cm—the typical interelectrode spacing used in clinical subdural and depth arrays. Intracranial EEG also extends the scope of brain signals that can be monitored. Scalp EEG recording is best suited to detecting oscillations up to about 40Hz, a consequence of volume conduction and the electrical properties of the coverings of the brain.⁹ With intracranial EEG, higher frequencies in the gamma range (25–~150Hz) can be discerned. These signals often provide important clues as to the location of the epileptogenic zone, and are often prominent at seizure onset.^{10–14}



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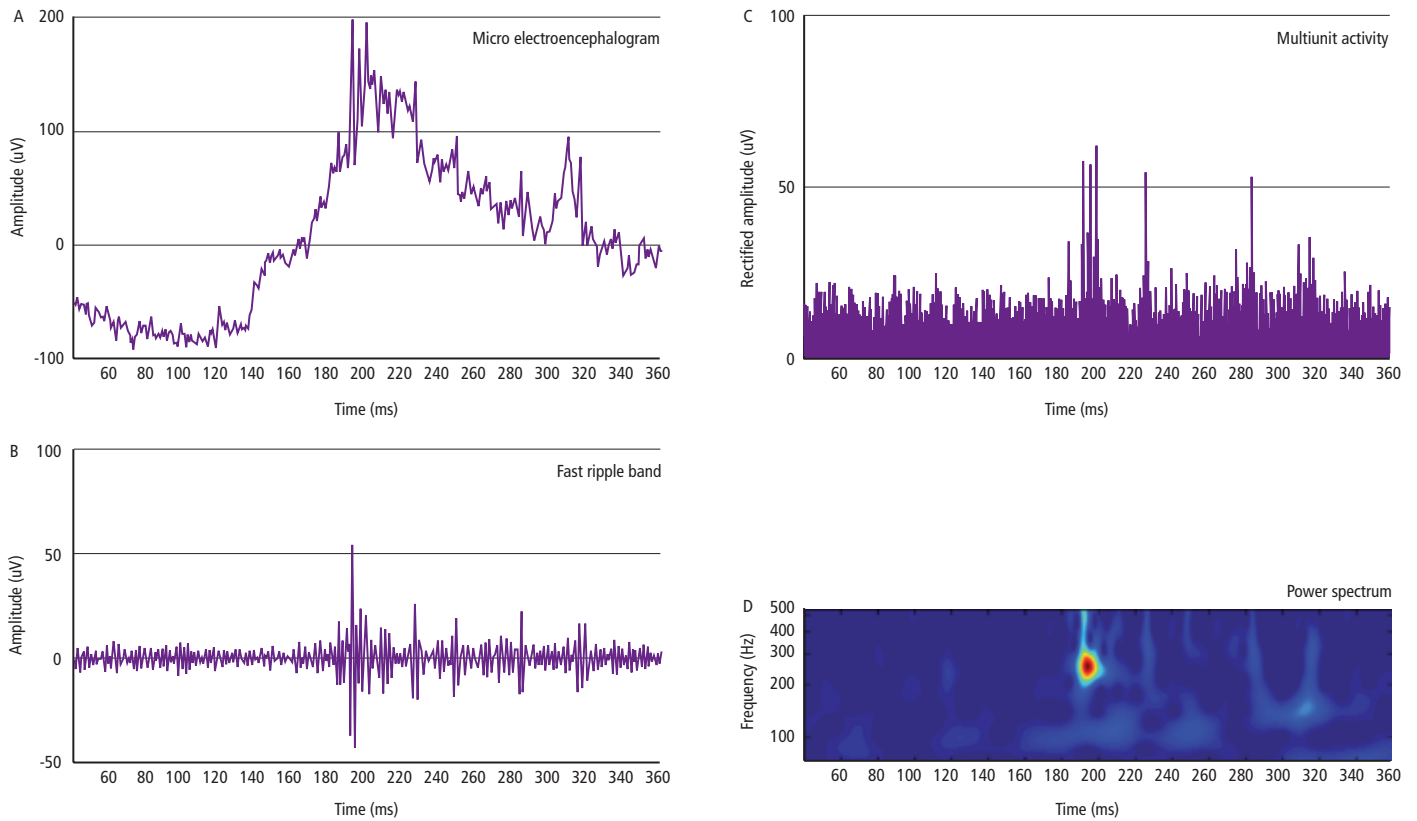
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California, Los Angeles and Columbia University. She has extensive prior experience in signal processing and systems engineering, both as a Member of Technical Staff at AT&T Bell Laboratories and through training in electrical engineering and computer science at the Johns Hopkins University, receiving her PhD in computer science.

Figure 1: Interictal Epileptiform Discharge with a Superimposed Fast Ripple Recorded from a Microelectrode Implanted in Layer IV of the Lateral Temporal Neocortex

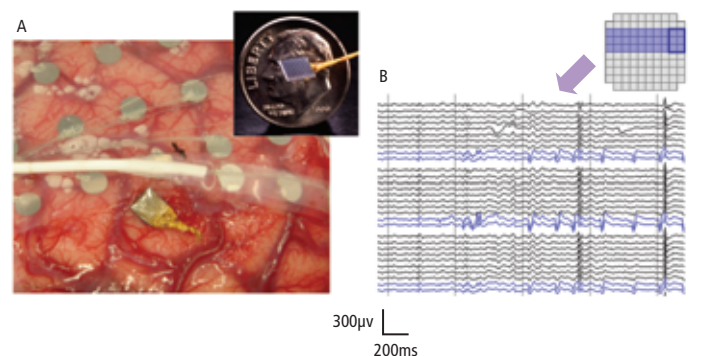


A: Local field potentials recorded by the microelectrode and bandpass filtered from 1 to 500Hz, showing a fast ripple superimposed on the negative peak of the discharge. B: The same time-slice bandpass filtered from 100 to 500Hz reveals the components of the fast ripple oscillation, with initial higher amplitude followed by a stuttering pattern corresponding with the downslope of the epileptiform discharge. C: Multiunit activity, reflecting action potentials within the 180 micron listening sphere of the microelectrode, obtained by bandpass filtering from 800Hz to 3kHz and rectifying the signal. Note the strong correspondence between unit activity and the high-amplitude peaks of the fast ripple oscillation. D: Time–frequency power spectrum computed using Morlet wavelet decomposition reveals the maximum power of the fast ripple at 250–300Hz.

Using microwire electrodes implanted into the mesial temporal structures of patients undergoing surgery for temporal lobe epilepsy, a team at the University of California, Los Angeles (UCLA) discovered ‘fast ripples’—brief and highly spatially restricted oscillations in the 250–600Hz range.¹⁵ Fast ripples have been found to be most prominent in the location of seizure onset in human mesial temporal lobe epilepsy,^{15–18} as well as in animal models of epilepsy.^{19–21} Similar oscillations have been detected in both mesial temporal structures and the neocortex^{14,18,22} in recordings of high temporal resolution from standard subdural electrodes. As signals in this frequency range can represent a mixture of membrane potentials and action potentials, there is an ongoing debate about the physiology underlying fast ripples. Fast ripples correlate strongly with bursts of action potentials from very small populations of neurons and may be seen in conjunction with epileptic sharp wave discharges (see *Figure 1*).^{23,24}

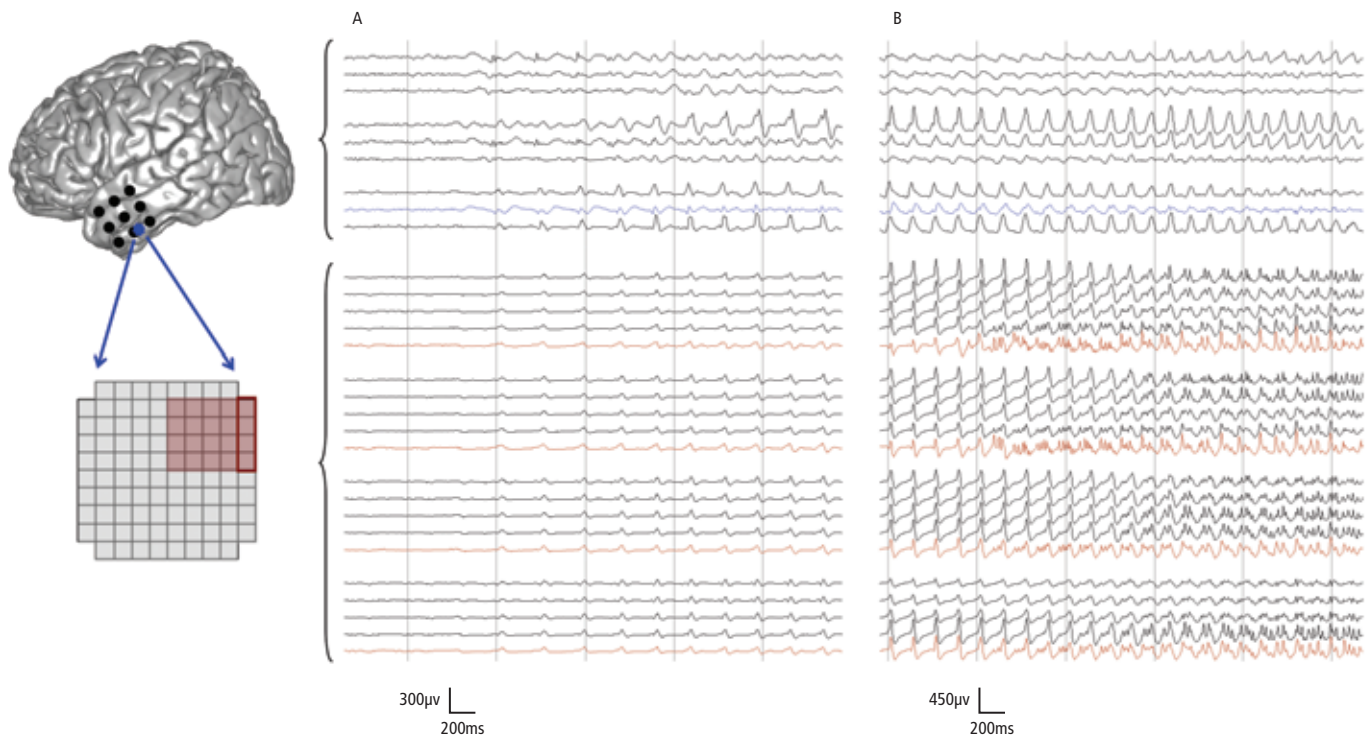
It is unclear whether these oscillations are the result of fast-spiking, tightly interconnected interneurons, augmented by currents cycling through gap junctions,²⁵ or clusters of neurons firing out of phase.²⁴ Despite their strong spatial correlation with the epileptogenic zone, the role that fast ripples play in epilepsy is not known. Trevelyan and colleagues have proposed that they may be related to an inhibitory feedback mechanism, serving to dampen the spread of ictal discharges

Figure 2: The Microelectrode Array (Cyberkinetics Neurotechnology Systems Inc., Foxboro, MA) Alongside Standard Subdural Electrodes Implanted on the Surface of the Right Parietal Lobe in a Patient with Epilepsy



A: The 96-microelectrode array (inset) is 4mm square, covering approximately the same surface area as a standard 4.5mm-diameter disk electrode. The microelectrode grid is laid out as 10x10 regularly (400-micron) spaced microelectrodes, with empty corners. The tips are positioned in the cortical layer IV. B: Microseizure (blue traces), depicted for clarity in a selected subgroup of microelectrode channels as indicated by the solid blue region in the schematic of the microelectrode array. The electrode sites recording the microseizure are indicated by the dark-blue-lined box. The microseizure involves a group of six channels covering a 1.2x0.8mm area, and is not evident in the adjacent microelectrodes, only 400 microns away. Electroencephalography spikes seen in adjacent standard electrodes appear in the microelectrode array recording as nearly identical waveforms occurring simultaneously in all channels (e.g. arrow).

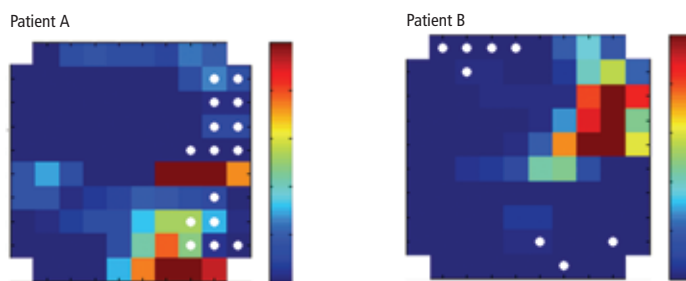
Figure 3: Involvement of a 'Microepileptic Focus' in Secondary Recruitment, Recorded Simultaneously by Both Standard Electrodes and the Microelectrode Array in the Left Anterolateral Temporal Lobe



In A and B, the top channel group (bracket) shows recordings from selected subdural electrodes, arranged in three rows from anterior to posterior and superior to inferior order, as depicted on the accompanying brain image. The location of the microelectrode array is shown as a blue star in the brain image, and the nearest subdural electrode is indicated by a blue trace in the electroencephalogram. The bottom set of traces shows recordings from a subgroup of microelectrodes corresponding to the solid red box on the schematic microelectrode grid.

A: Electrographic seizure onset, with initial low-amplitude, fast activity, and slow repetitive discharges, progressively involving more electrode sites and evolving in amplitude in the standard channels. The microelectrode recording reflects propagated activity (i.e. not volume-conducted signals) from the seizure source, evidenced by small channel-to-channel variations in latency and morphology. B: Seven seconds after seizure onset in the microelectrode channels, shown in red, the pattern abruptly shifts from the propagated sharp waves to repetitive bursts of sharp beta activity that is quite distinct from activity in the surrounding channels. This activity spreads rapidly to nearby channels and eventually to the entire microelectrode array, and then becomes evident in the subdural recording over the subsequent one to two seconds. Perhaps reflecting a 'microepileptic focus,' the same channels in which a 'secondary seizure' appears to have been ignited here are notable for abundant interictal microseizure activity (not shown).

Figure 4: Quantification of Fast Ripple Detections in Two Patients Implanted in the Left Lateral Frontal Lobe and Comparison with Microseizure Foci



In each diagram, square colored pixels correspond to channel location in the microelectrode array; the number of detections per channel is encoded by a red-blue color spectrum. Fast ripples were detected in fewer than half of the recorded channels, and the majority clustered in fewer than 10 channels, covering only about 10% of the recording area. These locations were generally not coincident with channels in which microseizures were recorded, suggesting that fast ripples and microseizures likely reflect distinct neurophysiological processes.

and constituting a natural defense against seizures.²⁶ Using a 4mm-square penetrating array of 96 1mm-long microelectrodes with recording tips 3–5 microns in diameter implanted into the epileptogenic cortex, we recorded electrical patterns resembling seizures restricted to a small number or even a single microelectrode (see Figure 2).²⁷ These tiny

discharges are lost in recordings from standard subdural electrodes, as these electrodes effectively average the electrical signals from the area of cortex that they cover. Since the array's interelectrode spacing of 400 microns corresponds roughly to the scale of cortical macrocolumns—architectural elements ranging from 300 to 500 microns in diameter²⁸—it is possible that these 'microseizures' are limited to one or several macrocolumns. Similar discharges have also been observed by researchers at Mayo Clinic using 40-micron-diameter microwire surface electrodes with 1mm spacing embedded in subdural grids.²⁹

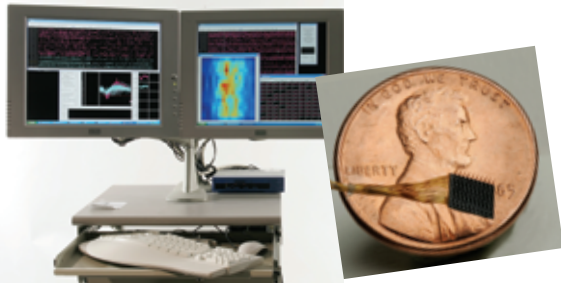
The significance of microseizures and their potential role in the generation of clinical seizures are matters of speculation. Although they are most frequently seen within the epileptogenic zone, the majority of microseizures that we have observed have had not a clear relationship to larger, clinically evident seizures. Most microseizures appeared to start and stop on their own. In a few cases in both our series and the Mayo Clinic study, however, microseizures were observed to be involved in seizure initiation and evolution. Figure 3 shows the recruitment of cortex, sampled by the microelectrode array, into an ongoing seizure beginning with a series of propagated ictal discharges that appear to incite local microseizure activity at a small number of microelectrode sites. This secondary microseizure rapidly spreads to adjacent electrodes, then to the entire array, and is later picked up by the nearby subdural intracranial EEG.

Any formulation of the respective roles of fast ripples and microseizures in the process of seizure development is strictly speculative. While it appears that they may both be signatures of epileptogenic cortex, sharing the common property of having tiny, isolated generating areas, they appear to represent distinct phenomena. We only rarely observed fast ripples and microseizures to be temporally coincident. Furthermore, they are generally found at different locations within the cortex sampled

by the microelectrode array, sometimes adjacent to one another and sometimes completely separate (see *Figure 4*). Still, we find it tempting to speculate that perhaps clinical seizures occur when microseizures, beginning in tiny cortical domains surrounded by non-epileptogenic tissue but possibly functionally interconnected, spread to involve adjacent regions; fast ripples reflect a defensive system that acts to contain their spread. ■

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