



## Better Resolution and Fewer Wires Discover Epileptic Spiral Waves

### Flexible, Foldable, Actively Multiplexed, High-Density Electrode Array for Mapping Brain Activity *in Vivo*.

Viventi J, Kim D-H, Vigeland L, Frechette ES, Blanco JA, Kim Y-S, Avrin AE, Tiruvadi VR, Hwang S-W, Vanleer AC, Wulsin DF, Davis K, Gelber CE, Palmer L, Van der Spiegel J, Wu J, Xiao J, Huang Y, Contreras D, Rogers JA, Litt B. *Nat Neurosci* 2011;14:1599–1605.

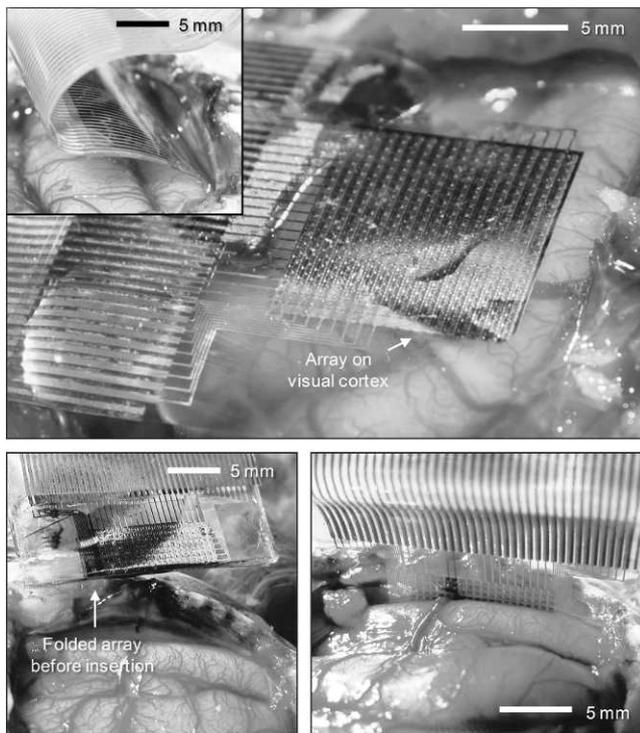
Arrays of electrodes for recording and stimulating the brain are used throughout clinical medicine and basic neuroscience research, yet are unable to sample large areas of the brain while maintaining high spatial resolution because of the need to individually wire each passive sensor at the electrode-tissue interface. To overcome this constraint, we developed new devices that integrate ultrathin and flexible silicon nanomembrane transistors into the electrode array, enabling new dense arrays of thousands of amplified and multiplexed sensors that are connected using fewer wires. We used this system to record spatial properties of cat brain activity *in vivo*, including sleep spindles, single-trial visual evoked responses and electrographic seizures. We found that seizures may manifest as recurrent spiral waves that propagate in the neocortex. The developments reported here herald a new generation of diagnostic and therapeutic brain-machine interface devices.

### Commentary

“So what exactly *is* a seizure?” Teaching physicians have faced this question for more than 50 years with a measure of frustration. The classical teaching that follows—about how to recognize a seizure—tends to ignore the spirit of the original question. Yes, we can identify a seizure when we see it, but understanding the underlying network dynamics has been elusive. The normal and abnormal patterns that form the basis of clinical electrophysiology are primarily based upon years of observation. Traditional EEG uses established norms for sampling rate, electrode size, and interelectrode distance. The best resolution available has been intracranial grid and depth electrodes, containing ~3-mm electrodes spaced 10 mm apart. Those norms were chosen to maximize surface area coverage with a feasible number of wire connections. For half a century, the state of the art did not change: clinical epilepsy focused on localizing the seizure to a region of brain, which is ideal for this wide distribution. But it is clear that such a macroscopic scale is inadequate to resolve the eloquent details of seizures and other brain phenomena. Within the unsatisfying answer to “What is a seizure?” is an implied apology for past technological limitations.

Over the past several years, many groups have implemented modern technologies to demonstrate that faster sampling rate (1) and smaller electrode scales (2) can be helpful to

understand seizures. Newly described phenomena such as microseizures (3, 4) and multiunit firing patterns (5) have generated intriguing ideas about seizure generation. This field is now accelerating, helped in part by Brain Computer Interfaces (BCI) research, which is developing similar technology (6) for such endeavors as brain control of prostheses in paralyzed patients (7) and advanced neuropsychological testing (8). Although these strategies take advantage of cutting-edge technology, they are all faced with two large limitations. First, spatial resolution improves with a larger number of electrodes and it is very difficult to manage hundreds of wires. Second, unlike most electrodes, the human brain is neither flat nor straight. Some custom fabrication techniques attempt to account for the curvature of the brain (9), but such electrodes still do not conform to the sulcal surfaces. One alternative is to use optical techniques such as light scattering (10) or voltage sensitive dyes (11), which have high resolution and conform to the brain's surface. In the latter study, Huang et al. demonstrated complex spiral waves across the visual cortex of anesthetized rats during a sleeplike state or infusion of bicuculline or carbachol. They characterize these waves and suggest that such activity may have both normal and pathological consequences. Perhaps their most important conclusion is that new types of data become available when recording from cortex on this “mesoscopic” network scale: such recordings reveal spatiotemporal interactions that add multiple new dimensions to conventional EEG. But these techniques still have limited applicability to humans: they are potentially toxic, they sample at a much slower rate than electrodes, and they require imaging with a flat camera, greatly reducing the advantage of coating



the sulci. Novel recording strategies are necessary to overcome these challenges.

Viventi et al. have developed a microelectrode grid that addresses these concerns with two new technologies. This electrode array is housed on a very supple substrate that can make direct contact with cortex within the sulci or the interhemispheric fissure. The electrodes are flat, platinum-coated contacts placed 500  $\mu\text{m}$  apart, similar to the spatial resolution of the Utah array used in BCI (7) and epilepsy (5) research. There are 360 contacts on the 1  $\text{cm}^2$  array, yet only 39 wires are required because of multiplexing. The multiplexing is accomplished by placing transistors next to each electrode and selecting them with an input current. Thus, the array itself is powered, which is a significant paradigm shift in EEG technology.

The authors present three types of *in vivo* recordings in cats to demonstrate the utility of this device: sleep spindles, visual evoked responses (VER), and picrotoxin-induced focal seizures. Each case demonstrates the power of increased spatial resolution: spindles arise from a small area of the grid and are very synchronous and consistent; VER are able to map the visual field with impressive precision; and picrotoxin-induced seizures contain complex waves moving laterally across the cortex. The seizure recordings are very intriguing—although a normal EEG electrode records merely a train of spikes, this array demonstrates a sequence of wavefronts moving across the cortex in planes and spirals. These epileptic spiral waves in cats are similar to those described in detail in normal rat neocortex (11). The authors classify these waves with machine-learning algorithms and find five ictal patterns. The core of the seizure is 19 identical spiral waves—a pattern very similar to cardiac reentrant rhythms. Then, the seizure terminates abruptly after a planar wave arises in the opposite direction. These results are

preliminary but lead to fascinating questions. Did the planar wave stop the seizure? Are epileptic spikes actually a population average of complex cortical waves? Can we use these data to distinguish normal from epileptic waveforms? These questions represent a new frontier in epilepsy research made possible by this new electrode technology.

Of course, these advances come at a cost. First, the volume and dynamics of the data are much more complex than conventional EEG; visualizing a static snapshot is inadequate to capture the spatiotemporal interactions. New techniques will be required to analyze these data, especially in a clinical setting. Second, there are still major safety concerns with the device. To make the substrate more flexible, the authors greatly reduced its thickness. The clinical norm for intracranial electrodes is to use thick, durable silastic, which has minimal risk of tearing or electrical leakage. These new electrodes are orders of magnitude thinner and thus will invite legitimate scrutiny about durability and electrical integrity. This problem is compounded by having “active” electrodes: they require a potentially dangerous direct current (DC; 5  $\mu\text{A}$  into each of 20 columns) to power the transistors. Epilepsy centers currently take careful precautions to block current flow into intracranial leads; using a grid having constant DC will be a major change in protocol. Before placement in humans, it will be critical to develop and verify reliable safety measures to assure the current never leaks out of the grid. If these challenges can be overcome, this technology may lead to significant changes in our understanding of the nature of seizures.

by William Stacey, MD, PhD

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## *Epilepsy Currents Journal*

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Brian Litt is a co-mentor on my current NIH K08 grant

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