What Is a Seizure?  
Insights From Human Single-Neuron Recordings

Single-Neuron Dynamics in Human Focal Epilepsy.

Epileptic seizures are traditionally characterized as the ultimate expression of monolithic, hypersynchronous neuronal activity arising from unbalanced runaway excitation. Here we report the first examination of spike train patterns in large ensembles of single neurons during seizures in persons with epilepsy. Contrary to the traditional view, neuronal spiking activity during seizure initiation and spread was highly heterogeneous, not hypersynchronous, suggesting complex interactions among different neuronal groups even at the spatial scale of small cortical patches. In contrast to earlier stages, seizure termination is a nearly homogenous phenomenon followed by an almost complete cessation of spiking across recorded neuronal ensembles. Notably, even neurons outside the region of seizure onset showed significant changes in activity minutes before the seizure. These findings suggest a revision of current thinking about seizure mechanisms and point to the possibility of seizure prevention based on spiking activity in neocortical neurons.

Commentary

Countless articles in the field of epilepsy begin with a statement such as: “Epileptic seizures are caused by an imbalance of cerebral excitation and inhibition.” This seems to be a fundamental truth that is rarely questioned. The International League Against Epilepsy (ILAE) defines seizures as “excessive or synchronous neuronal activity”(1). Truccolo et al. report on single-neuron activity in humans before, during, and after seizures by utilizing microelectrode recordings. They find that neuronal firing during seizures is much more heterogeneous than we assumed and can probably not be explained based on a simple model of excitation and inhibition.

They implanted a 96-channel, tightly spaced microelectrode array in the neocortex of four patients (Neuroport, Blackrock Microsystems Inc., Salt Lake City, UT). The array was placed in an area that was likely to be resected in epilepsy surgery. It covered an area of 4 mm² and recorded at a depth of 1 mm. They investigated single-neuron firing during eight seizures by routine intracranial EEG prior to epilepsy surgery. They distinguished between the interictal, preictal, ictal, and postictal periods. They found that neuronal firing during seizures is much more heterogeneous than we assumed and can probably not be explained based on a simple model of excitation and inhibition.

At the onset of the seizure, neuronal firing did not uniformly increase as expected in a purely excitatory event. Heterogeneity of firing patterns increased at seizure onset, as reflected by a measure of variance, the Fano Factor (Figure 1). The authors suggest their findings argue “against homogeneous runaway excitation or widespread paroxysmal depolarization as the primary mechanism underlying seizure initiation.” However, firing patterns within patients seemed reproducible but neuronal recordings over prolonged periods of time are often too unstable to assess with certainty. The authors determine seizure onset as classically defined by intracranial electrocorticography via visual inspection (Figure 1) and show that in the preictal period, there is already a modulation in baseline firing as compared with the interictal state. Preictal firing rate changes are seen less frequently than ictal firing changes. Preictal firing could increase (11.8% of all neurons) or decrease (7.5% of neurons). These findings raise the question of whether there is a clear-cut seizure onset at all. Where does the preictal period end and the seizure start? Seizure onset may not be a single event in time but rather a continuum. The authors propose that the changes in preictal firing may ultimately lead to a viable seizure prediction algorithm. After decades of searching for a reliable seizure prediction algorithm, this may be another venue to pursue. Rightly, the authors caution that their data are too premature to be conclusive. More single-unit recordings of seizures are necessary to test whether this is a workable algorithm.

We may have an easier time with determining the end of a seizure. The authors’ second major observation is the “abrupt
What Is a Seizure?

and widespread suppression of neuronal action potentials at seizure end. This is a very striking and consistent finding (Figure 1). There is neuronal silencing for 20 to 30 seconds after seizure termination. Seizure termination is thought to be a result of depolarization block owing to changing ion concentrations in the extracellular space (2). However, amplitude of action potentials did not decrease towards the end of the seizure as expected if depolarization block had occurred. The authors argue that depolarization block is not the “primary local factor responsible for the observed marked suppression [of neuronal] spiking”; thus introducing another shift in conventional thinking about the generation and termination of seizures.

Which Cells Do What?

A consistent finding in the study is that neurons that are active interictally have increased firing rates during the ictal and preictal period. Neurons were divided into principal neurons and interneurons in one patient. Both types of cells showed modulation of neuronal firing during the ictal and preictal periods, but in the preictal period, interneurons seemed to be more involved. In models of seizures, interneurons and pyramidal cells seem to play very distinct roles (3). As it is difficult to record a sufficient number of interneurons and principal cells, the role of these distinct cells needs further investigation.

At the termination of seizure, both interneurons and principal cells were silenced, and the authors hypothesize that subcortical structures may initiate seizure termination. This hypothesis is certainly not easy to confirm in humans.

The Sampling Error in Human Neurophysiology

Truccolo et al. investigated single neurons in four patients, and in only one patient the recordings were performed in what is traditionally called the seizure-onset zone. This patient had a reduction of seizures but was not seizure free after seizure-onset zone resection. This raises the question of whether recordings performed in the seizure-onset zone would show different results and would be more homogeneous.

Single units were only recorded over a small cortical area, so conclusions about greater seizure dynamics may be premature. Recording from a small cortical patch does not account for the spatial sampling error, which is inherent in human electrophysiology. It was also demonstrated that neuronal recordings can be
What Is a Seizure?

quite diverse depending on the cortical depth of the microelec-
trode (4). This could mean that findings in layer III, which reflects
the depth of the microelectrode array, could be different than in
deeper layers of the cortex such as layer IV or V. Another prob-
lem with single-unit recordings is certainly the problem of sheer
numbers. Of the estimated many billion neurons of the human
brain, recording from 241 cells represents a minuscule amount.
Any conclusions could be over- or underestimating the effect.

Single-Neuron Recordings

Single-neuron recordings are technically difficult to perform.
Artifact contamination and the limited number of neurons that
show any firing pose significant hurdles. In addition, neuronal
firing in humans is not consistent over time, so comparisons even
within patients in recordings days apart are difficult to interpret.
Newer technology on a submillimeter scale may allow for further
insights into seizure dynamics, such as spiral waves during feline
seizures, but may take time to implement in humans (5).

Truccolo et al. certainly made a significant contribution to
understanding human single-neuron dynamics during seizures.
Their investigation during spikes showed similarly interesting
results and also speaks to the heterogeneity of epileptiform activ-
ity (6). Certainly, further investigation of single units in humans
will help us to further investigate the question “What is a seizure?”
with the ultimate goal to find more effective treatments.

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1. Today’s Date: ___06/13/11______________________________

2. First Name _Barbara______________ Last Name _______Jobst__________________ Degree ___MD______

3. Are you the Main Assigned Author? __x__ Yes ____ No
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4. Journal Issue you are submitting for:  ___12.4______________________________________________________

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Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

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__ One of the coauthors (Rod Scott) has since then joined one of basic science research labs at Dartmouth on sabbatical, however he is not involved in clinical care. The study above had absolutely no relationship to research
performed at Dartmouth.

Thank you for your assistance.

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