Typical epileptic seizures are recorded as large rhythmic electrical activity in the neocortex, hippocampus, and other brain structures. This activity is usually thought to be some form of abnormally synchronized synaptic activity, with or without excessive synchronized local neuronal firing (1). Synaptic models have dominated ideas of the basic mechanisms of epileptic discharges for many decades. Zhang and colleagues revisit the idea that neurons can be synchronized through nonsynaptic mechanisms, in particular by the electric fields their activity generates. The idea that mammalian neurons can be modulated by weak (a few mV/mm) extracellular electric fields is not new (2, 3), nor is the idea that such modulation can synchronize abnormal activity reminiscent of epilepsy under some experimental conditions (4). The challenge that Zhang and colleagues set themselves was to test whether these kinds of mechanisms play important roles in a conventional acute model of epilepsy induced in hippocampal slices by 4-amino-pyridine (4-AP).

Propagation of epileptiform activity can be independent of synaptic transmission, gap junctions, or diffusion and is consistent with electrical field transmission.


The propagation of activity in neural tissue is generally associated with synaptic transmission, but epileptiform activity in the hippocampus can propagate with or without synaptic transmission at a speed of ~0.1 m/s. This suggests an underlying common nonsynaptic mechanism for propagation. To study this mechanism, we developed a novel unfolded hippocampus preparation, from CD1 mice of either sex, which preserves the transverse and longitudinal connections and recorded activity with a penetrating microelectrode array. Experiments using synaptic transmission and gap junction blockers indicated that longitudinal propagation is independent of chemical or electrical synaptic transmission. Propagation speeds of 0.1 m/s are not compatible with ionic diffusion or pure axonal conduction. The only other means of communication between neurons is through electric fields. Computer simulations revealed that activity can indeed propagate from cell to cell solely through field effects. These results point to an unexpected propagation mechanism for neural activity in the hippocampus involving endogenous field effect transmission.

How Does Epileptic Activity Spread?
transmission. The fact that the activity continues to start in CA3 adds some weight to authors’ hypothesis because CA3 does not easily generate low-Ca field bursts, but it would have been informative to see examples of the activity produced by low-Ca in this preparation.

The change to low-Ca caused a modest, but significant, slowing of propagation in the transverse direction (from CA3 to CA1) and acceleration in the longitudinal (septal to temporal) direction. This manipulation resulted in a significant anisotropy of propagation speed—surprising for a mechanism that depends on electric fields, particularly given that in normal Ca (and in intact synaptic transmission) speeds were isotropic, despite known differences in connectivity with direction.

While the speeds in opposite directions changed under low-Ca, the epileptiform bursts still mostly (but not exclusively) started in the septal CA3 region, perhaps due to greater neuronal excitability in the septal CA3 region.

Other plausible propagation mechanisms were considered here. Mediation by diffusion of K, for instance, is much slower (4), leading the authors to conclude this is not how the 4-AP activity propagates. Gap junctions pose a trickier challenge. They are well documented between inhibitory neurons and between glia, and have been suggested between excitatory hippocampal neurons. The fundamental problem is that compounds that block gap junctions are not particularly selective. Zhang and colleagues use the antimalarial drug, mefloquine, which they state blocks gap junctions containing connexin (Cx) 36. A reference cited (7) reports that Cx 43 and 50 are also blocked, and other papers suggest that pannexins may also be blocked. This promiscuity may help the case here. Mefloquine also depresses neuronal excitability (7), which argues against tight specificity for gap junctions. Mefloquine did not affect propagation longitudinally, which can reasonably be interpreted as showing a lack of dependence on gap junctions (and whatever else the drug does). Curiously, there was a significant slowing of transverse propagation, which argues for a significant role for mefloquine in gap junction block or decreased excitability.

Two further investigations supported a role for electric fields: Reducing extracellular osmolarity accelerated propagation, which is consistent with swelling of cells, strengthening coupling through electrical fields. Computer simulations of plausible cell densities were consistent with propagation by electric fields (but see reference (6)).

The carefully worded title of this paper hints at a fundamental problem in making critical tests of the hypothesis of neuronal synchronization through electric fields. It is fairly straightforward to block synapses pharmacologically; it is harder to block gap junctions selectively. Diffusion can be distinguished by much slower propagation, but electric fields still lack effective selective tests. That said, it is likely that electric fields play an important role in seizure propagation, as proposed here.

by John G. R. Jefferys, PhD

References

Instructions
The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

1. Identifying information.
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2. First Name John  Last Name Jefferys  Degree PhD

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