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Rogue Waves: A Unifying Model of Human Seizure Propagation

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Multiple Sources of Fast Traveling Waves During Human Seizures: Resolving a Controversy

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During human seizures organized waves of voltage activity rapidly sweep across the cortex. Two contradictory theories describe the source of these fast traveling waves: either a slowly advancing narrow region of multiunit activity (an ictal wavefront) or a fixed cortical location. Limited observations and different analyses prevent resolution of these incompatible theories. Here we address this disagreement by combining the methods and microelectrode array recordings (N = 11 patients, 2 females, N = 31 seizures) from previous human studies to analyze the traveling wave source. We find—inconsistent with both existing theories—a transient relationship between the ictal wavefront and traveling waves, and multiple stable directions of traveling waves in many seizures. Using a computational model that combines elements of both existing theories, we show that interactions between an ictal wavefront and fixed source reproduce the traveling wave dynamics observed in vivo. We conclude that combining both existing theories can generate the diversity of ictal traveling waves.

Significance Statement:: The source of voltage discharges that propagate across cortex during human seizures remains unknown. Two candidate theories exist, each proposing a different discharge source. Support for each theory consists of observations from a small number of human subject recordings, analyzed with separately developed methods. How the different, limited data and different analysis methods impact the evidence for each theory is unclear. To resolve these differences, we combine the unique, human microelectrode array recordings collected separately for each theory and analyze these combined data with a unified approach. We show that neither existing theory adequately describes the data. We then propose a new theory that unifies existing proposals and successfully reproduces the voltage discharge dynamics observed in vivo.

Commentary

The nature of seizure activity in the human brain remains relatively poorly understood. In part, this is due to the low-resolution technologies clinically available for recording epileptiform activity. Electrographic recordings such as electroencephalogram (EEG) and electrocorticography (ECoG) are high temporal resolution measurements, which can be recorded continuously, making it feasible to capture seizures and interictal spikes. However, both EEG and ECoG have low spatial resolution and incomplete coverage of the brain, particularly for deep structures. Clinical imaging modalities such as magnetic resonance imaging (fMRI) and ictal single photon emission computed tomography (SPECT) are both capable of recording the entire brain volume and have somewhat higher spatial resolution (though still orders of magnitude lower spatial resolution than would be required to record at the level of individual neurons). But, both MRI and SPECT provide, at best, a delayed snapshot of the blood flow changes associated with seizure activity.[1,2]

The recent development of high density microelectrode arrays (MEAs, 4 × 4 mm grids with 96 1 mm penetrating electrodes) for human implant[3] has made it possible to record activity from individual neurons in the human brain. Unlike EEG and ECoG recordings which record primarily synaptic dipoles,[4] MEA electrode tips are sufficiently small and proximal to neuronal somata to record single action potentials in individual neurons.[5] Over the past 10 years, in small samples of patients with epilepsy, MEAs have been implanted in the putative seizure onset zone during presurgical planning ECoG recordings. Together, these 2 electrode configurations provided large scale, low-resolution (ECoG) and small scale, high-resolution (MEA) sampling of electrical activity in the cortex during seizure onset and propagation. As expected, low-frequency (<50 Hz) local field potential (LFP) signal recorded

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from the MEA electrodes approximately matched that recorded from neighboring ECoG electrodes, while high-frequency (500-3000 Hz) signal recorded from MEA electrodes picked up single-unit activity.[6,7] Two groups used the MEA data to extract unit activity during seizure, which revealed a previously uncharacterized ictal wavefront, evident as a narrow band of spiking activity that is distinct from the LFP signal. Specifically, the LFP signal reflects *traveling waves*, which rapidly propagate across the cortex during spike-and-wave discharges of focal onset seizures.[8,9] As observed during physiological stimuli in the mammalian visual cortex, these traveling waves propagate at a rate of $\sim$100 mm/s and are thought to represent synaptic potentials driven by long-range horizontal connections.[10] The unit recordings reveal a slowly propagating *ictal wavefront*, a $\sim$2 mm band of neuronal spiking that slowly traverses a portion of the cortex at a rate of $\sim$1mm/s.

Resolving the spatial origin of these propagating ictal discharges is thought to be important as it may help to refine the ideal target for surgical resection. Two primary studies on this topic have developed seemingly contradictory models of the origin of traveling waves: (1) the "ictal wavefront model"—traveling waves emerge from the slow band of spiking termed the ictal wavefront and (2) the "Fixed source model"—traveling waves emerge from a fixed location in the cortex. In the highlighted study, Schlafly et al[11] sought to resolve this controversy by combining the small samples of patient data from both studies, analyzing the data with a unified processing pipeline, and testing both models of traveling wave propagation. As quantifying the traveling wave direction and stability using data from nearly 100 electrodes is both nontrivial and critical to this study, the authors first validated 2 different approaches to analyzing traveling wave direction using both simulated and real data. Next, traveling wave propagation direction and stability was analyzed for each discharge during the window of time surrounding when the ictal wavefront passed through the MEA. The ictal wavefront model predicts that the traveling wave should always propagate away from the ictal wavefront. As the ictal wavefront approaches, the traveling waves would travel in the same direction as the ictal wavefront. Then, in the wake of the ictal wavefront, traveling waves should reverse direction and propagate in the opposite direction of the ictal wavefront. This prediction proved to be partly true: most recordings showed a distinct change in traveling wave propagation direction immediately after the passage of the ictal wavefront. The traveling wave direction was only roughly orthodromic, then antidromic to the ictal wavefront propagation, but the shift in direction was distinct enough to suggest that the ictal wavefront plays a role in determining traveling wave direction.

Beyond the time window immediately surround the ictal wavefront passage, the traveling wave direction was not consistent with the ictal wavefront model. During this window, the traveling wave direction was often stable for long periods of time, but not well-aligned with the ictal wavefront. Across all seizures recorded in the pooled dataset, there was a median of 3 intervals with stable traveling wave direction estimates, with the longest stable interval occurring after the passage of the ictal wavefront. The authors propose a model in which the traveling wave propagates from both the ictal wavefront and a fixed source. During the window of time that the ictal wavefront traverses a given region, the traveling wave direction is predominantly influenced by the ictal wavefront propagation direction. After the ictal wavefront passes, its influence dwindles, and the traveling wave direction returns to emanating from a fixed source. A simple neural mass model was created to simulate how this might work and to highlight the complexity of determining the origin of traveling waves that are influenced by multiple sources. In particular, the relation of the MEA to the fixed source can substantially alter the apparent influence of the ictal wavefront on traveling wave direction.

The work highlighted here addresses a difficult and important problem in surgical planning: how to define the region of tissue to resect for maximal efficacy and minimal side effect. Presumably in focal epilepsy there is an ideal finite, removable site from which seizures emerge. It remains unclear whether the ideal resection site is the source of traveling waves, the source of the relatively recently discovered ictal wavefronts, or whether ictal wavefronts and traveling waves emanate from the same location. This study focuses on identifying the origin of traveling waves as they are measurable with standard clinical electrodes capable of covering large portions of the cortex, whereas ictal wavefronts can currently only be detected in small discrete regions. Here, Schlafly et al define a model where the traveling wave propagation is defined by both a fixed source and the slow-propagating ictal wavefront. A perfect model of this interaction might be able to predict the traveling wave direction from the ictal wavefront activity when the ictal wavefront is traversing the MEA. However, the traveling wave is largely composed of synaptic activity, which is determined not only by the spiking activity in nearby neurons but also by the (largely unknown) anatomical orientation of their projections. It is possible that the traveling wave propagation during passage of the ictal wavefront is not particularly important, rather the fixed traveling wave source may define the ideal resection site. If this is true, the stable traveling wave discharge direction after the passage of the ictal wavefront should point to the ideal resection target. While the utility of such recordings in surgical planning remains to be seen, the traveling wave propagation model proposed here simplifies interpretation of complex and seemingly conflicting datasets to make testable predictions about the origins of seizure activity in human epilepsy.

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