

## MAKING GENERALIZATIONS ABOUT SEIZURE PROPAGATION

**The Source of Afterdischarge Activity in Neocortical Tonic–Clonic Epilepsy.** Trevelyan AJ, Baldeweg T, van Drongelen W, Yuste R, Whittington M. *J Neurosci* 2007;27(49):13513–13519. Tonic–clonic seizures represent a common pattern of epileptic discharges, yet the relationship between the various phases of the seizure remains obscure. Here we contrast propagation of the ictal wavefront with the propagation of individual discharges in the clonic phase of the event. In an in vitro model of tonic–clonic epilepsy, the afterdischarges (clonic phase) propagate with relative uniform speed and are independent of the speed of the ictal wavefront (tonic phase). For slowly propagating ictal wavefronts, the source of the afterdischarges, relative to a given recording electrode, switched as the wavefront passed by, indicating that afterdischarges are seeded from wavefront itself. In tissue that has experienced repeated ictal events, the wavefront generalizes rapidly, and the afterdischarges in this case show a different “flip-flop” pattern, with frequent switches in their direction of propagation. This same flip-flop pattern is also seen in subdural EEG recordings in patients suffering intractable focal seizures caused by cortical dysplasias. Thus, in both slowly and rapidly generalizing ictal events, there is not a single source of afterdischarge activity: rather, the source is continuously changing. Our data suggest a complex view of seizures in which the ictal event and its constituent discharges originate from distinct locations.

## COMMENTARY

Seizure discharges consist of synchronized firing of cortical neurons. When such a discharge occurs focally and is limited to a mere fraction of a second, it is considered an interictal burst—identified on EEG as a spike or sharp wave and intracellularly as a paroxysmal depolarization shift. When the discharge is sustained for a longer period, supports high-frequency firing, and is immediately followed by lower-frequency repetitive bursting over the ensuing seconds, the discharge is considered representative of an ictal event, and in vivo, it is typically accompanied by a clinical seizure.

The term “afterdischarge” has been used by experimental electrophysiologists to describe the secondary and tertiary bursts that may follow the initial paroxysmal depolarization shift and comprise the later part of a synchronized ictal-length discharge recorded in cortical pyramidal cells. In kindling experiments, afterdischarges are induced by tetanic stimulation, and only after repeated stimulation do they become sufficiently long to produce a behavioral correlate. By electroencephalographic standards, one would associate the term afterdischarge with the pattern of low-frequency, repetitive bursting activity that accompanies the clonic phase of a tonic–clonic seizure. So, although the term is not used in a consistent manner, the discharges in each case follow a similar initiating excitatory synchronized event, hence the term “after discharge.”

In the early 1930s, Adrian applied excitatory stimuli to the cortex of mammals and studied the propagation patterns of the evoked activity (1). He described waves of activity traveling outward from the stimulated point and was perhaps the first to use the term “afterdischarge” to describe the delayed series of waves that followed the inciting event at a lower frequency. He observed that these waves sometimes started from the stimulated region but at times originated from distant points and traveled toward, instead of away from, the stimulating electrode. Adrian also reported clonic motor activity accompanying the recorded afterdischarges. The recent report by Trevelyan and colleagues builds on the work of Adrian and many others who have studied the propagation of different phases of seizures. Although the current study is more observational than mechanistic, its strength is in its attempt to correlate in vitro data obtained from young mice with EEG data from children with refractory focal seizures.

In the present study, the low-magnesium model was used to elicit seizure discharges in the neocortex. Reducing extracellular magnesium unblocks channels associated with NMDA receptors, making them more readily excitable. When perfused with artificial CSF that contains a reduced concentration of magnesium ions, the neuronal network in neocortical slices from young mice typically expresses a mixture of epileptiform activities, including ictal length bursts with a classic tonic–clonic pattern (2). The speed of seizure propagation in this model increases over time, allowing for comparison of slowly and rapidly propagating seizure discharges.

The authors performed simultaneous recordings from pairs of layer 5 pyramidal cells in coronal neocortical slices

maintained *in vitro*. They noted that the propagation velocity of afterdischarges from one electrode to the other was highly uniform, but the direction of propagation for afterdischarges was variable. In the case of slowly propagating ictal events, later afterdischarges recorded in a pair of electrodes reversed direction as the ictal wavefront passed by, suggesting the afterdischarges emanated from the ictal wavefront itself, but spread in both directions relative to the wavefront. Direction of propagation is influenced by the relative refractoriness of the neighboring cortical areas, resulting in a reverberation of the activity in the network and later afterdischarges being seeded by newly recruited areas of cortical activity distal to the original site of activation. Occasional failure of an afterdischarge to back-propagate was observed as well and never occurred in the forward direction, further supporting the contention that refractoriness of the region in question would determine whether it could support an incoming afterdischarge. These findings are consistent with those of Adrian (1) and numerous other investigators since (3,4).

Continued exposure to a low-magnesium environment elicited ictal discharges that generalized with increasing ease, presumably as a result of progressive disinhibition in the system (5,6). These rapidly propagating events induce, almost simultaneously, cortical refractoriness in large territories, resulting in frequent reversals of propagation direction in the train of consecutive afterdischarges within an ictal event (i.e., a “flip-flop” pattern). The authors conclude that there can be numerous foci for afterdischarge initiation in cortex exposed to frequently recurring ictal events. They support this conclusion with subdural EEG data from four children with focal neocortical pathology and frequent poorly controlled seizures; in all of these recordings, the propagation of the series of afterdischarges within a given ictal event displayed the same flip-flop phenomenon.

As stated in the abstract, the authors propose that the primary ictal discharge and its afterdischarges “originate from distinct locations.” If true, it would suggest a kindling-like phenomenon that allows for the independent generation of discharges from sites remote from the primary seizure focus; such a phenomenon may well occur and may contribute to the ease by which seizures generalize (7). However, ultimately, afterdischarges by definition cannot exist independent of their primary inciting event. Hence, does it matter whether afterdischarges follow the same propagation pattern as the primary ictal discharge? If the trigger can be aborted, the afterdischarges will be prevented as well. So, it would seem far more important to understand the mechanisms underlying initiation and propagation of the initial ictal depolarization that accompanies the tonic phase than to understand the nature of afterdischarges in the clonic phase. Yet, if the afterdischarge can be eliminated, the seizure will be abbreviated, possibly limiting the discharge to interictal length! Therefore, it might be useful to understand

the underlying mechanisms for afterdischarge generation and propagation, especially if they turn out to be substantially different from the mechanisms for the initial burst, as more and more studies seem to indicate (4,6,8–10). Unfortunately, this particular study does not shed light on the mechanisms underlying afterdischarge production.

What is the take-home message of this study? Perhaps, it could be a cautionary note to those who interpret EEGs, especially in children: focal seizures often rapidly generalize, obscuring the precise localization of the site of seizure onset, and in such instances, it can be tempting to look at the afterdischarges. Through the study of EEGs in children with focal epilepsy, the authors validate the well-documented observation that afterdischarges reverberate in the neuronal network, thereby appearing to emanate from multiple regions and not exclusively from the original site of seizure onset. So, based on this study, EEG studies performed to localize a seizure focus cannot reliably use the apparent afterdischarge source as a reliable factor in assessing seizure site of onset.

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## References

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