COUNTERPOINT TO "WHAT IS AN EPILEPTIC SEIZURE?" BY D'AMBROSIO AND MILLER

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D'Ambrosio and Miller argue that brief (i.e., one to a few seconds), rhythmic electrographic events accompanied by behavioral arrest, which they have observed in rats after lateral fluid percussion (i.e., in an animal model of traumatic brain injury), should be considered seizures in this model of posttraumatic epilepsy (1). A counter argument is that these events are not characteristic of the seizures seen clinically in posttraumatic epilepsy or in other forms of acquired epilepsy. Furthermore, several types of brief, rhythmic activity can be recorded in the electroencephalogram (EEG) of animals and humans without epilepsy. One cannot exclude the possibility that such events represent normal electrical activity, which may (or even may not) occur more often after brain injury. Thus, caution is required. In this counterpoint to "What Is an Epileptic Seizure?" by D'Ambrosio and Miller, the assertion is made that experimental studies on animal models of acquired epilepsy that claim electrographic events to be seizures, when the possibility exists that they may not be seizures characteristic of human acquired epilepsy, could be counterproductive, since research resources could be focused on animal models that may not actually demonstrate acquired epilepsy.

Key Points of D'Ambrosio and Miller's Review

The review by D'Ambrosio and Miller (1) on "What Is an Epileptic Seizure?" develops a series of points that could be summarized as follows:

1) A major issue in experimental epilepsy research continues to be the need to understand how to better treat pharmacoresistant epilepsy.
2) Previous work, particularly research aimed at screening potential antiepileptic drugs (AEDs), has focused more on tonic, clonic, or generalized tonic–clonic seizures, which are difficult to classify.
3) The most prevalent and pharmacoresistant seizures, as frequently seen clinically for resective surgery, are simple and/or complex partial seizures, which generally are associated with subtle behavioral symptoms.
4) Absence seizures also have minimal clinical manifestations, other than behavioral arrest, and characteristically only last a few seconds.
5) Thus, clinical seizures vary considerably in both their electrical and behavioral expression, and many seizure types can be quite short, lasting for only a few seconds.
6) When clinicians are uncertain about what is an epileptic seizure (and not a seizure), then concordance of both behavioral and electrographic data are required.
7) The brief electrographic events described in the lateral fluid percussion model of traumatic brain injury are comparable to posttraumatic epileptic seizures, because similar events have also been seen in humans with posttraumatic epilepsy, and thus, such events should be included within the overall definition of seizures (1,2).

The overall conclusion by D'Ambrosio and Miller is that the electrographic and behavioral events described in their lateral fluid percussion model recapitulate the focal seizures of human posttraumatic epilepsy (i.e., they are simple or complex partial seizures), suggesting that the electrographic events in their model may be useful for studying pharmacoresistant epilepsy. Their points 1 to 6 are well supported in the literature and in their Review, and the clinical observation in point number 7 may well be valid (1). However, it appears that some of their reasoning and the progression of concepts may have logical flaws, potentially leading to spurious conclusions. In particular, while it is accurate that typical electrographic seizures associated with intractable posttraumatic epilepsy are simple and complex partial seizures, which may or may not undergo secondary generalization (3), the electrographic events that are called seizures in the D'Ambrosio and Miller model are quite different in duration, waveform, and frequency of occurrence from the simple and complex partial seizures typically observed with intractable posttraumatic epilepsy (4–9).

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Therefore, in our opinion, the brief electrographic events and behaviors described by D'Ambrosio and Miller (1) are probably not epileptic seizures.

Seizure Types That Are Characteristic of Posttraumatic Epilepsy

What do models actually model? How similar to the human condition do models of human disease need to be? It is an issue that is regularly and vigorously debated, still without any clear resolution, and a working consensus would be extremely useful. Making progress in the understanding of the pathophysiology of epilepsy (and ultimately in the development of better therapies) involves the development of models that closely parallel the particular type of epilepsy that they simulate, with regard to pathology and physiology. Posttraumatic epilepsy has a variable pathology, from minimal damage to multilobar injury, with the added potential of foreign material from penetrating injuries (3,10,11). The electrophysiological characteristics of the clinical seizures are equally variable, depending on the site of the injury and the location of the seizure onset zone in relation to the injury. In spite of this variability in pathology and electrophysiology, simple and complex partial seizures, when recorded intracranially, generally follow a pattern of regularly occurring electrographic spikes (sometimes referred to as a *tonic* discharge) that are frequently followed by electroencephalogram (EEG) spikes occurring in a bursting mode (sometimes called a *clonic* component). Furthermore, these seizures generally undergo a series of progressive changes during the seizure (12). Their duration typically ranges from 30 seconds to 2 minutes, although they can be as short as several seconds or as long as several minutes (4–9). There is often a postictal phase, with a significant reduction in electrographic activity, which can even be below what was occurring before the seizure (4–10). In undamaged regions, individuals frequently have normal activity that, at times, is quite rhythmic. Even if they do not have seizures, patients with brain trauma will also have bursts of rhythmic activity, which occur in normal tissue and may not imply dysfunction.

Animal Models of Posttraumatic Epilepsy: Events That May *Not* Be Epileptic Seizures

There have been a few studies involving animal models of traumatic brain injury that develop spontaneous seizures (lasting tens of seconds) many months after a fluid percussion (13,14) or controlled cortical impact (15,16) injury. The injury is often extensive and the seizures, which look similar to what is recorded on intracranial monitoring in humans, are clearly defined and have a typical ictal progression and postictal suppression (13,16). In the model described by D'Ambrosio and colleagues, the events reported as seizures appear as nonprogressive, rhythmic trains of activity of waxing, and waning amplitude, which are similar to human sleep spindles or alpha rhythm (1,2). These discharges are associated with behavioral arrest, but the arrest is not always associated with a recorded electrographic event, and the same electrographic events can occur in sham controls (1,2). These three points, plus the extremely brief and innocuous nature of the behavioral events, beg the question of whether this is really a *distinctive* behavioral change. The issue, therefore, is whether these events are seizures or some other type of nonseizure event (17–20), as discussed in a previous *Epilepsy Currents* commentary (21) in regard to this specific model (22). Unanimous agreement on what is or is not a seizure will probably never be achieved, but it is clear that these discharges, which many investigators and clinicians would not consider to be seizures, do not resemble the partial seizures that are usually associated with posttraumatic epilepsy (3–11). Because of the lack of agreement between the clinical condition and the animal model regarding the electrophysiological appearance of the electrographic events, one could question whether this particular model of brain trauma described by D'Ambrosio and Miller is in fact a model of posttraumatic epilepsy (1,2,22).

Absence Seizures

D'Ambrosio and Miller note that the seizures in their model have similarities to absence seizures, which are typically only a few seconds but can be longer than 10 seconds. Although the seizures they describe in their model are frequently only 1 second to a few seconds duration, the investigators emphasize that the seizures were at times greater than 10 seconds. This finding suggests that the recorded rhythmic activity has some similarities to absence seizures; however, unlike absence seizures, 1) the electrographic activity did not occur on all EEG electrodes and 2) these electrographic events were attributed to an injury and not to genetic background. (1,2,22). The possibility that these events are runs of normal rhythmic activity has not been eliminated. Patients with posttraumatic epilepsy have simple and/or complex partial seizures that may generalize, and they do not typically have absence seizures (3). Partial and absence seizures are completely different in etiology, physiology, and therapeutic pharmacology. Whether these recorded events are absence seizures or are a nonseizure run of normal rhythmic activity (17–21) is unimportant, because in either case, they are not typical of the seizures characteristic of posttraumatic epilepsy.

Other Animal Models of Acquired Epilepsy

The review by D'Ambrosio and Miller, including their proposed definition of a seizure, also has relevance for certain electrographic events seen in some of the experimental models

of acquired pediatric epilepsy. Most notably, animal models of acquired epilepsy—based either on behaviorally assessed hyperthermic convulsions, as a potential model of complex febrile seizures of childhood (23), or on behaviorally monitored prolonged periods of hypoxia, as a model of neonatal hypoxic–ischemic encephalopathy (24) in immature rats—are associated with subsequent electrographic events that have been reported to be nonconvulsive seizures, using video-EEG (23,24). The electrographic events typically ranged from a few seconds to about 10 seconds. The concern, once again, is that these events may represent forms of electrographic activity other than seizures, such as theta rhythm or other types of normal rhythmic activity that are not commonly associated with temporal lobe or posttraumatic epilepsy. As with the posttraumatic epilepsy model (1,2), consensus on whether these EEG findings are seizures may never be achieved; however, it is apparent that the electrographic events shown for these models are not typical of the simple and complex seizures recorded in humans during clinical seizures that occur following complex febrile seizures or hypoxic–ischemic encephalopathy. For these reasons, it may be better to consider the animal models as simulating the effects of prolonged hyperthermia or hypoxia in the young animal (as opposed to complex febrile seizures or hypoxic–ischemic encephalopathy), but *not* as correlates of subsequent acquired epilepsy, such as temporal lobe epilepsy.

The Potential Consequences of Being Too Broad or Restrictive in Classification of What Is an Epileptic Seizure?

On the surface, the questions: "What is a seizure?" and "Is this event (EEG or behavioral) a seizure?" are simple and clear. Thus, one might expect a simple and clear response, however, as the review by D'Ambrosio and Miller points out, there are times when the decision of whether an event is or is not a seizure is anything but simple (1). Clinical experience has demonstrated that people can have seizures with EEG changes (at least on scalp recordings) that are minimal or do not have an epileptiform morphology at all. To confuse the issue, there are EEG patterns that look like seizures but that are never associated with clinical changes. D'Ambrosio and Miller rightly note that in some cases the diagnostic certainty, even after recording many events, is not high (1). Diagnostic uncertainty is commonplace in the clinical world. The fundamental question, however, is whether the same degree of uncertainty is appropriate and to be tolerated in the laboratory world of strictly defined classifications and categorizations as in clinical diagnosis. If a population of experimental animals in a model of acquired epilepsy does not actually have spontaneous recurrent epileptic seizures, then interpretation of the results will be seriously flawed. It is important that the epilepsy research community decide whether or not to be as broadly inclusive as possible when defining classifications of epilepsy models. A broad classification carries with it the risk that some models may be included that do not actually represent the specified disorder (i.e., epilepsy). Yet, a classification of an epileptic seizure that is too strictly and narrowly delineated (such that all designated models are defined as having epilepsy only on the basis of the clear presence of spontaneous recurrent seizures) risks the exclusion of some models that have epilepsy as well. Misclassification is *not* a small problem, because appropriate classification of the models will have a profound impact on whether the mechanisms of epilepsy and epileptogenesis will ever truly be understood.

Conclusions

The review by D'Ambrosio and Miller generally argues that human epilepsy is variable in pathology and physiology and, therefore, the experimental research community should be more inclusive in what is accepted as an epileptic seizure in animal models of posttraumatic epilepsy and other forms of acquired epilepsy. The authors encourage the inclusion of a wider range of electrographic events than are considered now, including events that have shorter durations and simpler waveforms than is typically seen for simple and complex partial seizures in human posttraumatic epilepsy (1). Their rationale is that many types of brief rhythmic events in the EEG—even with a subtle clinical manifestation (e.g., a behavioral arrest lasting <1 second to a few seconds)—should be considered an epileptic seizure. If, however, one takes the position that the seizures in an animal model of posttraumatic epilepsy should be as similar as possible to the seizures in the human clinical syndrome upon which it is based (i.e., display electrographic events characteristic of simple and complex partial seizures), the approach described by D'Ambrosio and Miller (1,2) is seen as flawed. This interpretation of the clinical data and its application to their model could potentially cause researchers to misclassify an electrographic event as an epileptic seizure (i.e., we are concerned that the events in question may not actually be relevant to the seizures that characterize human posttraumatic epilepsy), which may lead to incorrect conclusions regarding relevant mechanistic principles (and erroneous therapies derived from them) that, in reality, are unrelated to the epilepsy. A position of wanting to limit classification of electrographic events as seizures does not mean that *only* models with the characteristic spontaneous recurrent seizures normally thought to define a particular epilepsy syndrome should be studied, as there is much to be learned from other models and experimental systems that do not precisely mimic human epilepsy. In these situations, however, one must acknowledge the limitations of the system and what one can conclude from it in terms of translational research on epilepsy. It may be time for

the epilepsy community to have an in-depth discussion about different animal models, how they are used, and what relevant information can be derived from them.

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