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How Can We Identify Ictal and Interictal Abnormal Activity?

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Abstract

The International League Against Epilepsy (ILAE) defined a seizure as “a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.” This definition has been used since the era of Hughlings Jackson, and does not take into account subsequent advances made in epilepsy and neuroscience research. The clinical diagnosis of a seizure is empirical, based upon constellations of certain signs and symptoms, while simultaneously ruling out a list of potential imitators of seizures. Seizures should be delimited in time, but the borders of ictal (during a seizure), interictal (between seizures) and postictal (after a seizure) often are indistinct. EEG recording is potentially very helpful for confirmation, classification and localization. About a half-dozen common EEG patterns are encountered during seizures. Clinicians rely on researchers to answer such questions as why seizures start, spread and stop, whether seizures involve increased synchrony, the extent to which extra-cortical structures are involved, and how to identify the seizure network and at what points interventions are likely to be helpful. Basic scientists have different challenges in use of the word ‘seizure,’ such as distinguishing seizures from normal behavior, which would seem easy but can be very difficult because some rodents have EEG activity during normal behavior that resembles spike-wave discharge or bursts of rhythmic spiking. It is also important to define when a seizure begins and stops so that seizures can be quantified accurately for pre-clinical studies. When asking what causes seizures, the transition to a seizure and differentiating the pre-ictal, ictal and post-ictal state is also important because what occurs before a seizure could be causal and may warrant further investigation for that reason. These and other issues are discussed by three epilepsy researchers with clinical and basic science expertise.

Keywords

Convulsion; Convulsive; Electroencephalogram; Epilepsy; Epileptic; Focal seizure; Epileptiform; Seizure-like; Spike-wave discharge; Theta; Sharp wave; Behavioral arrest; Interictal spike; Ictal; Pre-ictal; Transition to seizure

1.1 Introduction

Seizures are common and important neurological symptoms that may require treatment. Seizures can signal underlying disease. In addition, many research laboratories study mechanisms of seizures. Therefore, a commonly accepted definition of “seizure” is needed for both clinical and research purposes. Some events may obviously be seizures, but others might comprise imitators of seizures [62], epileptiform non-seizure events, or variants of normal laboratory animal behavior.

1.1.1 Clinical Perspective

1.1.1.1 Definition of a Seizure—Webster says that a definition should capture the “essence” of an entity. What then is the essence of a seizure? Table 1.1 highlights definitions from various authorities, dating back to Johns Hughlings Jackson in 1870 [58].

Terms that recur in the various definitions include excessive, disorderly discharge, synchronous, self-limited, abnormal, paroxysmal, neurons, central nervous system (CNS) and cortex. Corresponding symptoms are listed as alteration or loss of consciousness, involuntary movements, sensory, psychic or autonomic disturbances and other clinical manifestations. These terms cover a lot of territory. Delineating the possible clinical manifestations of seizures is beyond the scope of this chapter, but an overview may be found in [73]. In 2005, a task force of the International League Against Epilepsy [37] provided a parsimonious definition of a seizure as “a transient occurrence of signs and symptoms due to abnormal or synchronous neuronal activity in the brain.”

In clinical practice, a clinician rarely sees the abnormal electrical discharge, with the exception of successful video-EEG monitoring, so this discharge is inferred on the basis of a typical constellation of clinical symptoms. Application of the definition also requires ruling out other conditions. For example, abnormal and synchronous firing of thalamic neurons in a patient with Parkinson’s disease [17] represents a transient symptom correlated to tremor, but it is not a seizure. Therefore, a definition of seizures must include an implied qualifier: “and not due to other known conditions producing a similar picture.”

Some writers use the modifying term “epileptic seizures” to distinguish them from common usage of terms such as heart seizures, psychogenic seizures or other non-epileptic paroxysmal events. However, not all seizures imply epilepsy, particularly for single seizures with low likelihood of recurrence or for provoked seizures. Hence, the phrase “epileptic seizures” tends to be either misleading or redundant.

The seizure definition of excessive neuronal discharges derived from Hughlings Jackson’s time, is 144 years old, when awareness of brain electrical activity was new. This mindset has

led generations of clinicians and researchers to think of a seizure as an electrical disorder. Abnormal electrical discharges are just one manifestation of seizures, not necessarily more important than metabolic, blood flow, receptor, gene activation, network connectivity and many other changes that are intrinsic to seizures. A contemporary definition of seizures would likely be less electrocentric and focus more on excessive and sustained activation of specific brain networks. The research community should be challenged to invent a better definition for seizures.

1.1.1.2 EEG Manifestations of Seizures—Clinicians rely heavily on electroencephalographic patterns to identify, classify, quantify and localize seizures [7]. Figure 1.1 illustrates common epileptiform EEG patterns. The term epileptiform is used to connote EEG patterns believed to be associated with a relatively high risk for having seizures. Gloor [43] defined spikes as potentials that stand above the background, have a “pointy” shape, duration between 30 and 70–80 ms, asymmetric rise and fall, and followed by a slow wave. The potential should have a sensible field, meaning that it should be reflected in physically adjacent electrodes and perhaps in synaptically linked regions such as the contralateral hemisphere. “Sharp waves” have durations of 70–200 ms. The distinction between spikes and sharp waves is arbitrary in the clinical arena and is discussed further below (see also [28]).

Spikes may be focal or apparently generalized across widespread regions of brain bilaterally. Rhythmic recurrence of spikes followed by slow waves is referred to as spike-waves. Focal spikes tend to be associated with focal seizures with or without secondary generalization. In contrast, generalized spikes tend to be associated with seizures that are nonfocal at their onset. Generalized spike-waves are associated with absence (previously called petit mal) seizures.

The right panel of Fig. 1.1 illustrates the onset of a focal seizure in the top four channels, which are in the left temporal region. The local rhythm can be seen evolving in amplitude, frequency and degree of sharpness. Other channels also reflect the seizure activity, but it is best formed and earliest in the top four channels. Where the potential becomes sharp, there is a phase reversal (down in one channel and up in the next channel) between the top and the second from the top channel. Polarity conventions of the EEG indicate that the electrode common to both these channels is the site of maximum negativity compared to neighbors on either side. Active (discharging) seizure foci are extracellularly negative, since positive ions flow from the extracellular space into the neuron during excitation. Therefore, the phase reversal of a spike or seizure onset can be used to approximately localize the region of seizure origin.

The EEG recorded from the human scalp at the start of the seizure can take at least five different forms, as illustrated in Fig. 1.2. One pattern is rhythmically evolving frequencies in the theta (4–7/s), delta (0–3/s) or alpha (8–12/s) bands. The rhythmical activity can have varying degrees of sharpness, but spikes and sharp waves are not required to be part of the rhythmical pattern of a focal seizure. An evolution of frequency and amplitude over time is needed to distinguish a seizure from many other normal and abnormal rhythmical events encountered in the EEG. The second pattern of seizure origin is rhythmical spiking. This

may be most commonly seen with seizures in hippocampus and neighboring structures. Spike-wave patterns typically occur during generalized absence seizures, but presence of spike-waves cannot be equated with absence epilepsy. Spike-waves also can appear focally during focal seizures or during the course of generalized tonic-clonic seizures. Neocortical seizures often manifest with an electrodecremental pattern, referring to a general flattening of brain rhythms at the start of a seizure. Electrodecremental patterns are commonly seen with tonic, atonic and sometimes tonic-clonic seizures [35]. The apparent disappearance of EEG activity is a consequence of the typical 1–70 Hz bandpass filter used to review EEG. In fact, a very low frequency potential heralds the start of such seizures [57, 92] but is largely filtered out by the low frequency filters commonly utilized during scalp EEG revision. Careful examination of the electrodecremental region shows presence of low voltage, high frequency activity [29, 38]. Considerable study has demonstrated importance of frequencies in the beta (13–30 Hz), gamma range (30–100 Hz), ripple (100–250 Hz) and fast ripple (250–1000 Hz) range. Activity in the fast ripple or higher ranges is sometimes referred to as high-frequency oscillations (HFO's) [32, 98, 100]. HFO's can be useful markers for the region of seizure onset. Epilepsy surgery is more successful when regions generating high frequencies are resected [41]. The fifth electrographic pattern of a seizure onset is no change in the scalp EEG. The presumption here is one of sampling error. Two-thirds of cortex is enfolded in sulci and dipole discharges in sulci do not always project to scalp EEG electrodes. Seizures can originate in mesial temporal, orbitofrontal or inter-hemispheric regions far from scalp electrodes. Negative EEG findings therefore do not rule out underlying focal seizures. The EEG must be correlated with the clinical picture. Of note here is that seizures that begin in the brainstem in experimental animals often lead to convulsions before the forebrain EEG shows any change from normal [42] (personal observations, HES).

1.1.1.3 Ambiguities in EEG Manifestations of Seizures—Electroencephalographers sometimes disagree about whether a particular pattern is epileptiform and representative of associated seizures. Figure 1.3 shows an evolving event over the right mid-temporal region lasting for about 5 s. The EEG technician noted no clinical signs. Such events might be considered too brief to represent a seizure: duration of at least 10 s has occasionally been applied operationally [1], but there is no official minimum time to define a seizure. In animal research, 2–3 s is often used as a minimum time for an electrographic seizure but the length of time that is sufficient to define a seizure is extremely variable [26, 31]. However, discharges accompanied by clinical seizures qualify as electrographic seizures regardless of their duration. In the extreme, a single generalized spike associated with a myoclonic jerk could be considered to be a very brief seizure.

Epileptiform EEG activity has been categorized as ictal, meaning during a seizure, postictal, meaning after a seizure and interictal, meaning between seizures. While ingrained in common usage, these terms may be more confusing than helpful [36]. What sense does it make to designate an interictal spike in cases where there have not been two seizures? Where does the behavioral and EEG pattern of an ictal event merge into the postictal behavioral confusion and EEG slowing? Is postictal slowing always a consequence of the seizure [33]? Delineations between ictal and postictal may not be obvious. Are periodic lateralized epileptiform discharges (PLEDs, Fig. 1.4) interictal, ictal or either depending

upon circumstances [76]? When is a burst of generalized spike-waves interictal and when is it ictal? Behavioral manifestations, such as unresponsiveness and automatisms, tend to occur in direct proportion to the duration of spike-wave discharges [77]. Whether a person is noted to have clinical signs such as limited responsiveness depends upon how carefully they are tested. Meticulous studies [4] show that responsive latency and task accuracy declines even during a period of so-called interictal spikes. Research in animals suggests the same is true for rodents [54], although the assumptions in these studies – that blocking interictal spikes improves behavior and therefore interictal spikes cause behavioral impairment – may not be true. Instead, blocking interictal spikes may only be helpful because of a reduction of other brain abnormalities, not necessarily the spikes *per se*. Clinically, interictal spikes tend to correspond to the zone of origin of a seizure, but not always. Figure 1.5 illustrates interictal spikes from the right temporal region and electrographic seizure onset from the left temporal region in the same patient.

1.1.1.4 Clinical Conclusions—The commonly employed definition of a seizure as a transient occurrence of signs and symptoms due to abnormal or synchronous neuronal activity in the brain is almost a century and a half old, and it does not capture the essential nature of seizures as depicted by modern neuroscience. Seizures are diagnosed clinically, taking into account numerous entities that can imitate seizures, such as syncope, transient ischemic attacks, sleep disorders, confusional migraine, tremor, dystonia, fluctuating delirium and psychological episodes. The scalp EEG is a helpful adjunct to diagnosis of seizure disorders, but it is not clear that an EEG pattern should be intrinsic to a definition of seizures. There is no unifying form; instead at least five different EEG patterns can accompany seizures. EEG correlates of high risk for seizures are categorized as ictal (during a seizure), postictal (after seizure) or interictal (between seizures). These distinctions often are unclear and arbitrary, in that the interictal-ictal boundaries are blurred for many seizures. Even so-called interictal spikes can affect behavior.

We need a better understanding of what constitutes the pathophysiological and behavioral essence of a seizure. Numerous questions arise for basic researchers. Need a seizure always involve an excessive discharge and increased synchrony? Have neurons been given excessive primacy in seizures over glia? Do seizures emerge only in cortex or can they develop in subcortical structures as well? Does it make sense to talk about where seizures start, given the involvement of widespread networks? What brain networks are involved in seizures of different types and which behaviors correlate with seizures in these networks? These questions will only be answered with a collaboration between basic researchers and clinicians.

1.2 Defining Seizure Correlates with Intracranial Electrodes in Patients

The advent of intracranial recordings (with grid and strip electrode arrays) and intracerebral recordings (with depth electrodes) during presurgical evaluation in patients with partial epilepsies resistant to pharmacological treatment changed our view of the electrographic correlate of a seizure. During pre-surgical intracranial monitoring, seizures are recorded with electrodes positioned close to the generators of ictal epileptiform discharges. In particular, depth stereo-EEG electrode implants aim at the epileptogenic area. This is done by

accurately planning electrode insertion on the basis of the analysis of the sequence of localizing clinical features observed during seizures recorded by video monitoring with scalp EEG performed as part of the presurgical examination [23, 85]. Intracerebral recordings are finalized to identify the cortical networks activated during a seizure that should be surgically removed to cure the patient. The areas involved in seizure generation are defined as the seizure-onset zone and the epileptogenic zone, which includes the regions of onset and propagation of the ictal epileptiform discharge. Intracranial recordings contribute to outline a larger area, defined as irritative zone, that generates abnormal interictal events/potentials, but is not directly recruited during a seizure discharges.

A large number of pre-surgical studies focused on the functional interactions between the epileptogenic and the irritative zones have been reported in the last 20 years. These studies demonstrate that (i) the irritative area is not coincident and it is usually larger than the epileptogenic/seizure onset zone, (ii) interictal discharges do not show a coherent relationship with seizure discharges, in terms of location and activation patterns, (iii) the rate of interictal discharges can either increase or decrease just ahead of a seizure and (iv) in most cases the electrographic pattern of seizure onset is completely different from the activity recorded during interictal discharges (for review see [28, 29]; Fig. 1.6).

Intracranial pre-surgical studies revealed that the most consistent pattern observed at the onset of a seizure is characterized by fast activity of low amplitude in the *beta-gamma* range ([5, 38, 48]; for review see [29]) that can be preceded by large amplitude spike potentials. The latter events have often been defined as pre-ictal spikes, but their consistent and reproducible occurrence at the very onset of a seizure include them by definition as integral part of a seizure. Experimental studies in animal models and in human post-surgical tissue and intracranial stereo-EEG observations demonstrated that these (pre)ictal population spikes are distinct from interictal potentials [21, 44, 56] and are possibly generated by network mechanisms that are different from those sustaining interictal potentials.

More recent studies demonstrated that the low-voltage pattern associated to the initiation of a seizure correlates with the abolition and possibly the desynchronization of background activity. The substitution of background activity with low-voltage fast activity is the intracranial correlate of the electrodecremental pattern defined as EEG “flattening”, a phenomenon that is commonly pursued to localize the seizure onset area on the scalp EEG (as discussed above). Low-voltage fast activity is also associated with the appearance of large amplitude, very slow potentials lasting several seconds that can be identified on intracranial recordings when low EEG frequencies are not filtered out [9, 57]. These three intracranial electrographic features (fast activity, EEG flattening and very slow potentials) have been proposed as biomarkers of seizure-genesis in the epileptogenic zone [45], since a retrospective evaluation demonstrated that their location on stereo-EEG recordings coincides with the area that has been surgically removed to cure the patient (Fig. 1.7).

The above-mentioned triad of electrographic elements defines seizure networks and the epileptogenic zone in the majority of patients selected for stereo-EEG recordings with intracerebral electrodes. The type of epilepsy referred to surgery could be the reason for the homogeneity of seizure pattern reported in the literature. Most of the patients selected for

pre-surgical studies, indeed, have pharmacoresistant epilepsies due to either focal cortical dysplasia, low-grade epileptogenic tumors (such as gangliogliomas or dysembryogenetic lesions), or mesial temporal lobe epilepsy with hippocampal sclerosis. Seizures in these types of epilepsy may present with similar EEG features. In mesial temporal lobe epilepsy, seizures that initiate with a hypersynchronous spiking pattern have been reported [8, 93]. Fast activity consistently follows the hypersynchronous discharge, suggesting that this pattern represents a variant of the low-voltage fast activity pattern.

Seizure onset patterns different from low-voltage fast activity have been described during intracranial EEG monitoring, for instance in tuberous sclerosis and in cortical malformations such as polymicrogyria [16, 51, 70, 79]. Whether such patterns are the expression of the epileptogenic network specifically caused by the type of lesion or are due to the failure to implant electrodes precisely in the epileptogenic area, is an open question. Moreover, variable seizure onset patterns have been detected with intracranial and extra-cerebral electrode arrays, such as grid and strips, positioned on the cortical surface in the subdural space. The localizing value of subdural electrodes has been questioned (e.g., [47, 90]) and, therefore, their ability to define sources and features of ictal patterns is assumed to be less precise than depth electrodes.

Another crucial issue that emerged from intracranial recording studies and can be confirmed by retrospective analysis of earlier reports on seizure patterns, is the demonstration that focal seizures are characterized by a clear sequence of events that starts with a fast activity pattern and ends with highly synchronous, large amplitude bursting. The striking novel finding in this context is the observation that seizures do not initiate with the explosion of sustained, large amplitude, synchronous potentials, as commonly assumed, but feature low amplitude activity and background activity desynchronization that in several occasions last several tenths of seconds. In between seizure onset and seizure termination, a transition from fast, possibly desynchronized activity [59, 82] into an irregular spiking pattern (referred to as “tonic” in several reports) is observed. During the latter phase synchrony of activity builds up and progressively promotes clustering of highly synchronous discharges separated by periods of post-burst depression (Fig. 1.8). The late-seizure bursting (sometimes defined as “clonic phase”) precedes seizure termination. Interestingly, if seizure onset is restricted to a spatially limited region, seizure termination characterized by synchronous periodic bursting is usually more diffuse and shows the tendency to involve the entire epileptogenic zone. The mechanism for such a widening of the epileptogenic network during the late seizure is still unclear. A synchronizing influence mediated by the involvement of subcortical structures can be proposed. After the end of a focal seizure, post-ictal depression is evident and can be measured as a reduction of background activity in comparison to the pre-ictal condition. These findings can be reproduced in animal models, as discussed in the next section.

In summary, direct evaluation of seizure-generator networks with intracerebral electrodes in focal human epilepsies demonstrates that specific electrographic patterns with a quite reproducible temporal progression define a seizure (typically a focal seizure). De-synchronization of background activity and the appearance of fast low-voltage rhythms characterize seizure initiation and excessive synchronization correlate with termination of

the seizure [59]. Post-ictal depression is typical of focal seizures and should always be verified to identify a seizure.

1.3 Seizures, Seizure-Like Events and Afterdischarges in Animal Models

Based on the intracranial human findings observed in focal epilepsies during pre-surgical monitoring, it is mandatory to re-define the term “seizure” in experimental studies of animal models. We will first address *in vivo* studies performed on animal models of seizures or epilepsy, and then discuss *in vitro* studies carried out on preparations featuring complete or partial preservation of brain networks.

Diverse seizure patterns have been illustrated with *in vivo* intracerebral recordings in animal models of epilepsy obtained with different methods and protocols. In several studies, seizure-like patterns were defined only with EEG, i.e., without the aid of video monitoring. This approach is problematic, because the correspondence of EEG patterns with behavioral symptoms should be verified when seizure events are described. The possibility that the reported EEG potentials are interictal events or even physiological patterns, if not artifacts, should be carefully considered (see Sect. 1.4, below). Incidentally, the lack of a precise definition of a normal EEG in different animal species is a serious limitation to the evaluation of pathological patterns in animal models of seizures and epilepsy. These considerations further support the concept that epileptic phenotypes in animal models should always be carefully analyzed with the aid of video-EEG monitoring, to correlate possible seizure patterns to behavioral/motor changes.

Behavioral seizure correlates are not easy to identify in animals, even when careful electrobehavioral evaluation of the video-EEG is performed, because focal seizures may present with minor symptoms that have little, if any, motor sign. This is a major limitation for seizure identification in animal models: we can only be sure of seizures that correlate with enhanced or decreased motor signs, since other critical non-motor symptoms are difficult to detect. Seizures generated in the hippocampus in animal models (and in patients as well), for instance, can occur during immobility ([8, 15, 80]; see Sect. 1.4, below) and are indistinguishable from normal pauses in behavior unless intracerebral EEG recordings are performed in parallel to video monitoring. In this respect, human EEG studies on the definition of electro-clinical seizure patterns are more standardized and detailed than animal reports. The precise electro-clinical correlation of symptoms during seizures performed in humans demonstrates the finer scientific development of clinical epileptology in comparison to experimental epileptology, and sets an example to improve phenotyping in animal models of epilepsy.

In vivo recording of seizures and characterization of seizure patterns have been performed in a relatively small number of studies that describe animal models of epilepsy, largely on temporal lobe epilepsy models developed in rats and mice. Other models in which video-EEG electrobehavioral characterization of focal seizures was analyzed in detail include post-traumatic epilepsy models [25, 65, 66], models of perinatal anoxiaischemia [61] and infantile spasms [81]. These reports confirmed that EEG correlates of seizures are largely characterized by fast activity at onset, followed by irregular spiking; and periodic bursting that develops with time during seizures (and usually represents the last pattern before seizure

termination: [8, 15, 46, 95]). Post-ictal depression ensues and is infrequently characterized in these models.

Other electrographic potentials that supposedly represent the expression of an epileptic brain have been reported and quantified to support the characterization of epilepsy models. The behavioral correlates of these pathological patterns are often not described (and may not be possible to identify), and in some reports the claim is made that a specific pattern that does not respond to the criteria defined above is regarded as seizure. It is frequently assumed that epileptiform discharges that last longer than 2–3 s can be considered as ictal, as mentioned above [26, 31]. The criterion of duration to discriminate between an interictal and ictal discharge is quite subjective and could be misleading when applied to focal epilepsies. Since a consensus on this issue is still missing, more stringent criteria to define a seizure are required and should be identified.

Seizure patterns comparable to those described *in vivo* in animals (and in human focal epilepsies) can be reproduced in preparations of the entire brain or portions of brain tissue maintained *in vitro* in isolation. Obviously, the absence of the peripheral limbs that expresses motor symptoms prevents any definition of seizure in these experimental conditions. Therefore, the identification of interictal and seizure-like patterns on *in vitro* preparations relies exclusively by electrophysiological recordings, and the identification of stringent criteria for seizure definition is quite critical.

Seizure-like events characterized by fast activity at onset, followed by irregular spiking and terminating with periodic bursting discharges are induced by diverse pharmacological manipulations in adult whole guinea pig brain preparation ([44, 89]; Fig. 1.8), in neonatal en bloc preparation of cortical areas/systems, such as the *in toto* hippocampal-parahippocampal structures [30, 64] and in complex tissue slices, in which connectivity between cortical structures is preserved, such as entorhinal-hippocampal slices ([6, 60]; Fig. 1.8).

In several studies performed on slice preparations, prolonged epileptiform events are described, which are characterized either by repeated spikes or by large paroxysmal depolarizing shifts followed by a depolarizing plateau potential on which decrementing discharges occur (see [28]). These types of discharges are often defined as seizure-like, even though their identification as seizures is questionable: similar events, indeed, are never observed during spontaneous seizures recorded *in vivo*, but can be generated by repeated stimulations, as afterdischarges induced by the kindling procedure. In slice studies, the measurement of the duration of “afterdischarges” is usually reported as a criterion to distinguish between interictal and ictal events. This assumption is based on the idea that the mechanisms that generate interictal and ictal events are similar and differ only by the duration and persistence of repetitive spiking or bursting activity. However, this conclusion may not be correct, based on recent findings demonstrating that seizure-like events in complex preparations are initiated with a prominent activation of inhibitory networks, whereas this may not be true for interictal spikes. The analysis of seizure-like discharges in neocortical and hippocampal slices exposed to different pro-epileptic conditions demonstrate that GABAergic networks are active at the very onset of a seizure [30, 39, 40, 67, 99]. These

findings were confirmed in the *in vitro* isolated whole guinea pig brain [29, 44]. In this preparation, pre-ictal (ictal) spikes and fast activity that characterize seizure onset correlate with activation of GABAergic interneurons and with a cessation of neuronal firing in principal excitatory cells that last several seconds. In this model, the progression of seizure activity characterized by the transition to the irregular spiking and periodic bursting phases was sustained by ectopic firing of principal cells driven by changes in extracellular potassium induced by inhibitory network activation at seizure onset [88].

In conclusion, the definition of seizure-like events in *in vitro* preparation should be reconsidered and should rely on the reproduction of seizure patterns observed in humans and in chronic animal models of epilepsy. This “reverse translational” approach might help to focus future *in vitro* studies on the mechanisms of seizure generation that more reliably reproduce human focal epilepsy.

1.4 Defining Seizures in Basic Epilepsy Research: Potential Problems Specific to Rats and Mice

Defining seizures in humans requires consideration of several issues, as discussed above. In basic epilepsy research, conducted mainly in rodents (rat or mouse), there are other issues that are important. In order to quantify seizures for preclinical studies, one would want to be precise about seizure onset and seizure termination. However, not only are seizures hard to define, but the exact time of their onset and termination are also problematic. Other issues are also relevant: if there are brief pauses between seizures, when is the pause sufficient to define the events as two separate seizures? Post-ictal depression is often followed by a series of afterdischarges or spikes that become more and more frequent – when does the repetitive spiking become frequent enough to be called the onset of the next seizure? This issue is not only important in establishing seizure frequency, but it also is important when defining status epilepticus (SE). When examined at high temporal resolution, there are often pauses between seizures during SE. Does this mean it is not SE? If there are no convulsions (non-convulsive SE) how does one determine what is and what is not SE? Similar to humans, defining a seizure in rodents is not as easy as one might think.

1.4.1 Behavioral State—There are several behaviors that make up the vast majority of the lifespan in rats and mice: exploration, sleep, grooming, eating and drinking. In addition, there is a state called “quiet immobility,” “awake rest” or “behavioral arrest” where rodents stop moving, their eyes are open, and they stare blankly into space. Typically the animal is standing at the time, and has just walked across the cage or explored its surroundings. Unlike humans, this behavioral state can be prolonged (over 10 s). It presents problems for the epilepsy researcher because it appears similar to an absence seizure. Therefore, understanding the normal behavioral states of rodents, and their EEG correlates, is important for epilepsy researchers using these species.

1.4.1.1 Hippocampal EEG Associated with Exploration: Theta Rhythm: Associated with exploration, behavioral arrest, and sleep in rodents are distinct EEG rhythms that can be recorded with chronic electrodes implanted in hippocampus [14]. As shown in Fig. 1.9a and originally described by Green and Arduini [50], EEG oscillations at theta frequency

(commonly called theta rhythm) are recorded in hippocampus when an animal explores. Theta oscillations vary in frequency but are typically 6–10 Hz in rats and mice [12, 50, 91].

In animal models of epilepsy, theta rhythm is interesting because epileptic animals are less likely to exhibit seizure activity during exploratory behavior, when theta oscillations occur in hippocampus [69]. This “anticonvulsant” nature of exploration and theta rhythm in hippocampus has been attributed to many potential mechanisms but has not been defined conclusively [22]. It is useful to record theta oscillations *in vivo* because large theta rhythm is found in hippocampus but it is much smaller or not observed elsewhere. Therefore, theta oscillations can be used to confirm the recording is in hippocampus. Theta oscillations are also useful to record because their amplitude can be used to define the specific layer within hippocampus where the recording electrode is located. For example, if a stimulating electrode is used to evoke field EPSPs in area CA1 from the Schaffer collateral input, the field EPSP should be recorded in the layer where theta is relatively small, stratum radiatum. In contrast, where theta is larger, the adjacent stratum lacunosum-moleculare, the field EPSP evoked by the same stimulus would be small or have a positive polarity. Because the entorhinal cortex is a source of theta rhythm (the other major source originates in the septum; [12]), theta oscillations are very large in stratum lacunosum-moleculare and the outer two-thirds of the molecular layer of the dentate gyrus, where the entorhinal cortical projection (the perforant path) to hippocampus terminates.

1.4.1.2 Hippocampal EEG Associated with Behavioral Arrest: Sharp Wave-Ripples:

The hippocampal EEG shown in Fig. 1.9b is taken from a rat that explored and then paused – entering a period of behavioral arrest. As described by Buzsaki originally [10, 11], the hippocampal EEG changes dramatically when an animal stops exploring and pauses in a frozen stance, with eyes still open. Theta oscillations decrease and the EEG becomes irregular. In addition, sharp waves (SPWs) occur intermittently. SPWs are ~100 msec duration spikes that reflect synchronous firing in a subset of area CA3 neurons, which in turn activate area CA1 apical dendrites by the Schaffer collateral axons and the dentate gyrus, most likely by backprojecting axons of CA3 pyramidal cells. Therefore, SPWs can be recorded in many locations within hippocampus [10, 11].

The term SPW is important to discuss in the context of epilepsy, because it is sometimes used interchangeably with the term interictal spikes (IIS). Hippocampal SPWs are distinct from interictal spikes because hippocampal SPWs occur without seizures, i.e., they are not interictal (between ictal events). Hippocampal SPWs are recorded only in hippocampus- if one moves a recording electrode just outside the hippocampus, SPWs are not observed (Pearce and Scharfman, unpublished). IIS in an epileptic rodent can be typically recorded from multiple cortical electrodes simultaneously at many sites in the brain. However, SPWs can be generated by circuits outside hippocampus, i.e., other types of SPWs besides those generated in area CA3. For example, SPWs are generated in entorhinal cortex and piriform cortex [68]. Notably, the underlying mechanisms for an IIS may or may not be the same mechanisms for a SPW, although they do seem related. For example, GABAergic mechanisms may trigger interictal spikes (as discussed in the previous section); GABAergic network oscillations (ripples) are also involved in SPWs. The classic view of the IIS is that it is generated by a giant paroxysmal depolarization shift (see previous section); a synchronous

depolarization in pyramidal cells also drives SPWs. Regardless, if SPWs and IIS are terms that are used synonymously, there may be differences in the underlying cellular processes/mechanisms that are overlooked, so it is important to consider the terms carefully.

When recording electrodes are positioned near the CA1 pyramidal cell layer, fast oscillations called ripples [84] can be detected at about the same time as the SPW (Fig. 1.9f). Therefore, the term “SPW-R” (sharp wave-ripple) is now used instead of the original term, sharp wave. Ripples in the hippocampal EEG correspond to synchronous oscillations of pyramidal cells that are caused by rhythmic IPSPs that are initiated by action potentials in a subset of hippocampal GABAergic interneurons that innervate pyramidal cell somata and initial axon segments. As synchronous release of GABA from these peri-somatic targeting interneurons hyperpolarize pyramidal cell somata that are in close proximity, chloride ions enter the pyramidal cells in a repetitive manner and cause a series of extracellular positivities. The positivities wax and wane as the pyramidal cell IPSPs start and stop, leading to an oscillation [19].

1.4.1.3 The Hippocampal EEG Becomes Active During Sleep: The hippocampal EEG becomes extremely active during sleep in the rodent, and is irregular, called large irregular activity (LIA: Fig. 1.9c). The increase in the hippocampal EEG is often simplified as a type of disinhibitory state that coincides with a ‘switch’ from sensitivity to sensory input to a state where intrinsic circuitry is active [52]. A similar idea has been proposed for piriform cortex during slow-wave sleep; odor input is reduced in favor of processing between piriform cortex and other forebrain sites [97]. For the epileptologist, it is important to recognize that comparing the hippocampal EEG between animals without considering the behavioral state may make one animal seem normal (if it is exploring) compared to seizure like activity in the other if it is asleep (Fig. 1.9). Compressing the EEG can make this more difficult; for example, if the EEG is compressed it is hard to distinguish a noisy baseline from theta oscillations, so the EEG may look inactive when an animal is exploring. For these reasons, expansion and compression of the EEG should be varied during examination of the EEG for seizures. In addition, the type of electrode and recording system should stay the same for any given set of experiments.

1.4.1.4 When Normal Activity Appears To Be Epileptic: One of the implications of the discussion above for epilepsy research is the possibility that normal EEG activity may be mistaken for seizures. For example, an investigator may think that the animal is freezing because it is having a seizure, but actually exhibiting normal behavioral arrest. This interpretation is based on the limbic seizure stage scale of Racine, who based the scale on behaviors of rats during electrical stimulation of the amygdala during kindling. He suggested that there was initially a period of immobility with small mouth or face movements with small mouth or head movements, and called this a stage 1 or 2 in his scale of limbic seizure severity [78]. The only problem with this idea is that it can be confused with behavioral arrest.

During behavioral arrest, investigators could interpret the irregular activity and repetitive SPW-Rs to be a seizure (Fig. 1.9). Likewise, the transition from behavioral arrest back to exploration may seem like the termination of a seizure, particularly when the EEG is

compressed (Fig. 1.9). In light of these potential problems, describing stage 1 seizures without a hippocampal electrode is problematic. An animal that suddenly stops and appears unresponsive could be interpreted to have a stage 1 seizure when it actually is pausing between episodes of exploration.

Another problem arises in studies of seizure frequency evaluated over time. For example, studies of epileptogenesis often record animals over weeks. There is typically no consideration of behavioral state when the results are quantified. If there is less exploration because an animal is sleeping more, EEG power in the theta band may decrease. EEG power in high frequency bands may increase if there are more SPW-Rs because the animal is pausing more, or sleeping more.

1.4.2 Spike-Wave Discharge—In many strains of rats, the state of behavioral arrest is accompanied by spike-wave discharge in thalamocortical networks [20, 27, 96]. These discharges have been noted in almost every strain of rat, such as Long-Evans [83], where approximately 90 % of female rats exhibited spike-wave discharges spontaneously by 4 months of age. In Wistar rats, Gralewicz [49] reported that 73 % of male rats showed spike-wave discharges by 6 months of age and 93 % of males at 24 months of age. Kelly [63] reported spike-wave discharges in female Fischer 344 rats at 4 and 20 months of age. In rats that are genetic models of absence epilepsy (GAERS, Wag Rij) spike-wave discharges are a characteristic of the strain, and used to gain insight into mechanisms of absence epilepsy [20, 27]. Numerous genetic models of absence epilepsy also exist based on spontaneous mutations in mice (*e.g.*, *lethargic*; [18, 74]). As shown in Fig. 1.10, spike-wave discharges accompany behavioral arrest in naïve Sprague-Dawley rats. These discharges vary according to the sex, age, environment and other factors [13] but are not always observed [96], making control recordings critical to any study of rats in an animal model of epilepsy.

These observations raise several questions: are spike-wave discharges in rodents normal? It has been suggested that they could serve important purposes related to sensory processing [71, 86, 94] or aging and excitability [71]. If this is true in rodents, is human spike-wave discharge normal too? One possibility is that spike-wave discharges and behavioral arrest were present in early stages of evolution and then reduced because behavioral arrests (without complete attention) would be dangerous in the presence of predators – vigilance would be advantageous. In humans, the spike-wave discharges that do arise may be vestiges of rodent circuitry that have not completely been removed by evolution. Photic stimulation can trigger spike-wave discharges in humans [24, 87], and may be a method to trigger these ‘vestigial’ oscillations.

Another implication of the observations in rats in Fig. 1.10 is relevant to the detection of seizures in hippocampal electrodes in rodent studies of epilepsy. In Fig. 1.10, the hippocampal electrode appears to show rhythmic spiking when spikewave discharges occur in the frontal and occipital leads. The rhythmic spiking in hippocampus could be volume conducted from thalamus, or it could reflect hippocampal neural activity. In light of the fact that the frontal cortical lead shows spike-wave oscillations, one would know that volume conduction in the hippocampal lead is a possibility. However, if there were only an electrode in hippocampus, which is a common recording arrangement in epilepsy research, the

rhythmic activity in hippocampal electrodes might be interpreted to be a seizure generated in hippocampus. Because it is accompanied by a frozen, ‘absence’ behavior, it could be concluded that there was a Racine stage 1 seizure. Importantly, some of the normal rodents with spike wave discharges also have head nodding or mastications, which could make an investigator more convinced of seizure activity – because these movements were also noted by Racine in his classification of stage 1–2 behaviors. Importantly, most of the spike-wave discharges occur at approximately 7–9 Hz and are stable (in frequency) within a spike-wave episode or across episodes (Fig. 1.10; [13, 20, 27, 96]). Therefore, rhythms at this frequency (e.g., theta rhythm) that occur in hippocampus can be a signal to investigators to interpret their EEG data cautiously.

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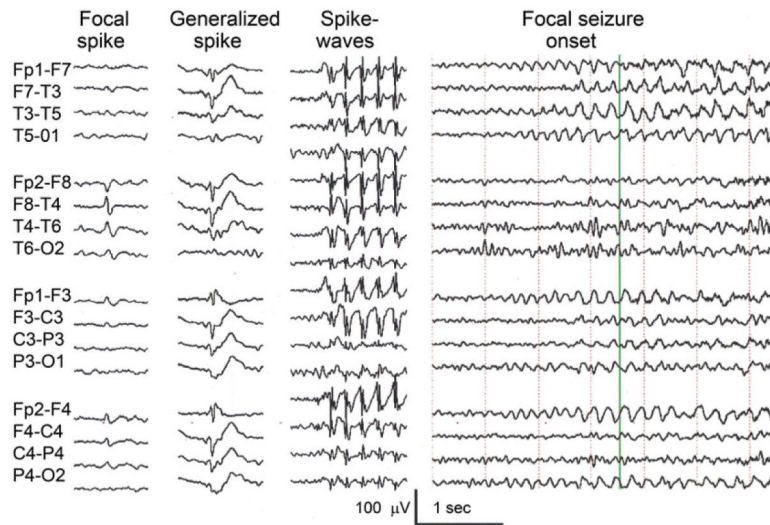


Fig. 1.1. Common epileptiform EEG patterns. Common patterns are shown for individuals with focal spikes, generalized spikes, spike-waves, and a seizure with focal onset (From Fisher, unpublished)

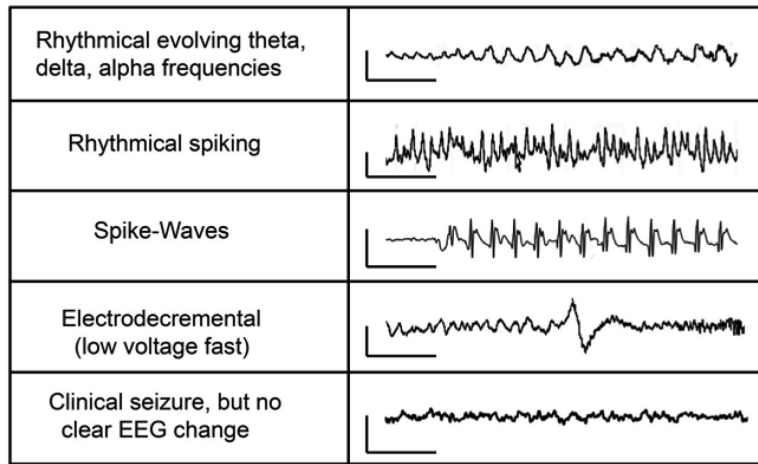


Fig. 1.2. Common EEG patterns at the start of seizures in patients with epilepsy (From Fisher, unpublished)

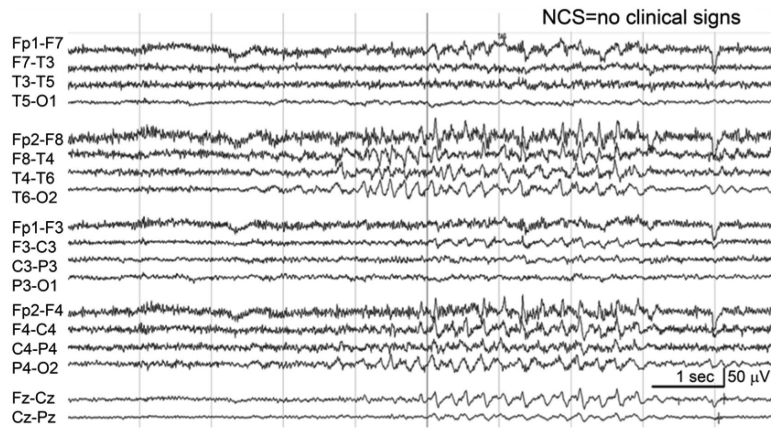


Fig. 1.3. Is this a seizure? Rhythmical brief epileptiform activity, illustrating the ambiguity involved in deciding whether an EEG event corresponds to interictal activity or a seizure (From Fisher, unpublished)

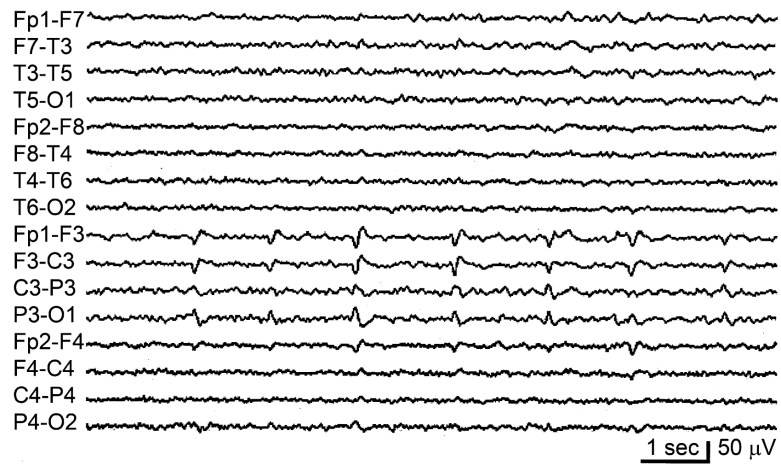


Fig. 1.4. Periodic lateralized epileptiform discharges (PLEDs) – are they ictal or interictal? PLEDs over the left central (C3) region are shown. Some electroencephalographers consider this pattern to be interictal and others ictal, while still others believe it depends upon particular circumstances (From Fisher, unpublished)

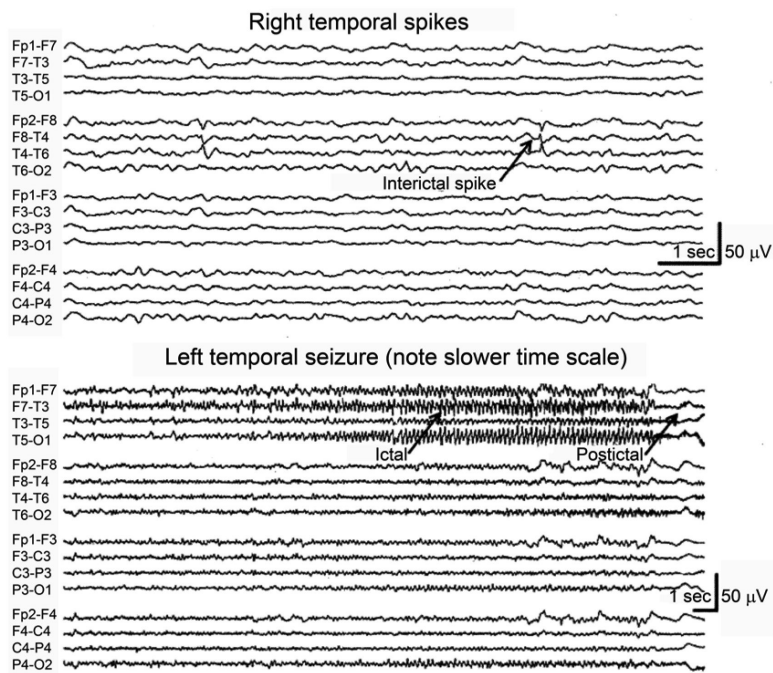


Fig. 1.5. Interictal-ictal disparity with spikes in the right hemisphere and seizures on the left. Interictal-ictal disparity in the same patient as Fig. 1.5, with interictal spikes over the right temporal region, but seizure onset from the left temporal region. Note different time scales for each segment (From Fisher, unpublished)

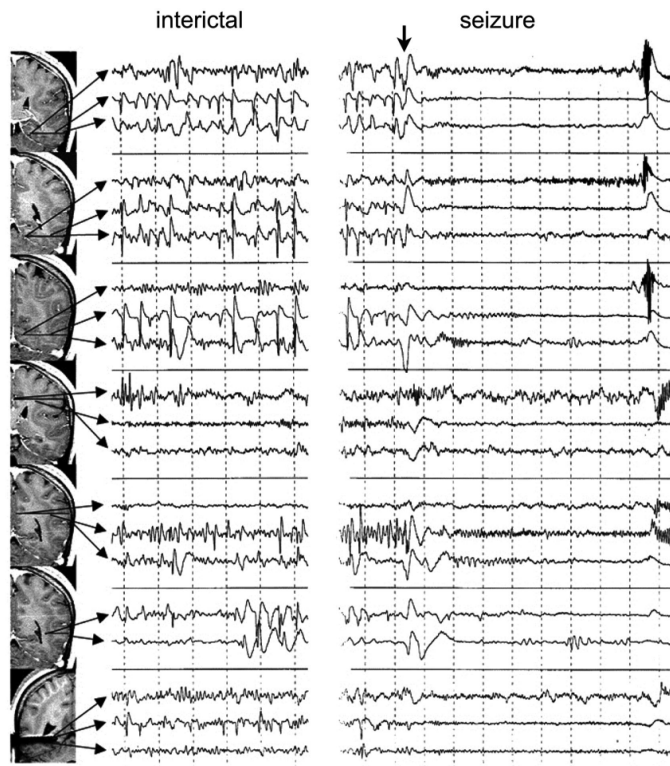


Fig. 1.6. Recordings with intracerebral stereo-EEG electrodes in a patient with focal epilepsy secondary to focal cortical dysplasia. *Far left:* The position of the recording electrodes is illustrated. *Left:* Interictal discharges recorded with intracerebral stereo-EEG electrodes in a patient with focal epilepsy secondary to focal cortical dysplasia. *Right:* Seizure onset is marked by the *arrow*. The *slow spikes* that precede the ictal low-voltage fast activity are different in location and morphology from the interictal spikes (Courtesy of Francione, Tassi and LoRusso of *Claudio Munari Epilepsy Surgery Center, Niguarda Hospital, Milano*)

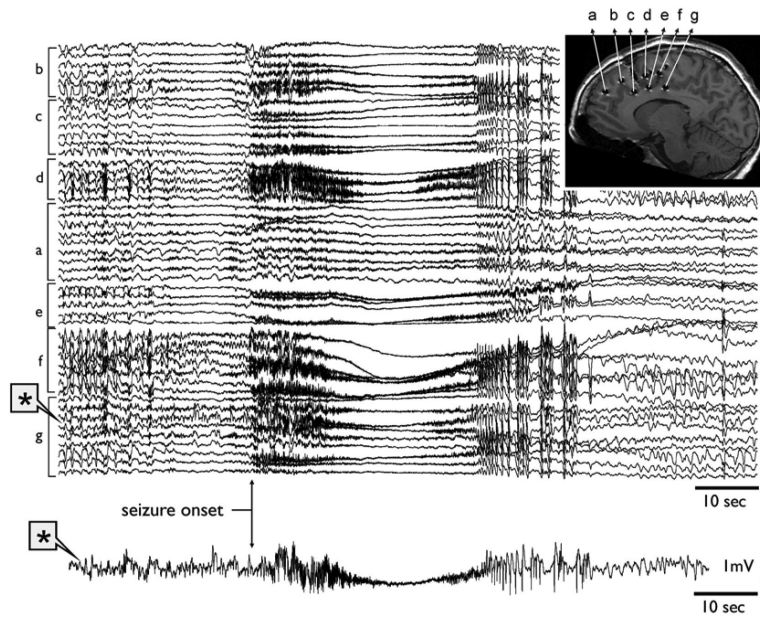


Fig. 1.7. Intracerebral recording of a focal seizure with stereo-EEG electrodes (as shown in the *upper right inset*) in a patient with cryptogenic focal epilepsy during presurgical evaluation. Multi-contact electrodes are identified by *letters*. The EEG marked by an *asterisk* is expanded at the *bottom*. When the seizure begins (*seizure onset, arrow*) there is a reduction of background activity, appearance of fast activity, and subsequently there is a very slow potential (From Gnatkovsky, Francione, Tassi and de Curtis, unpublished)

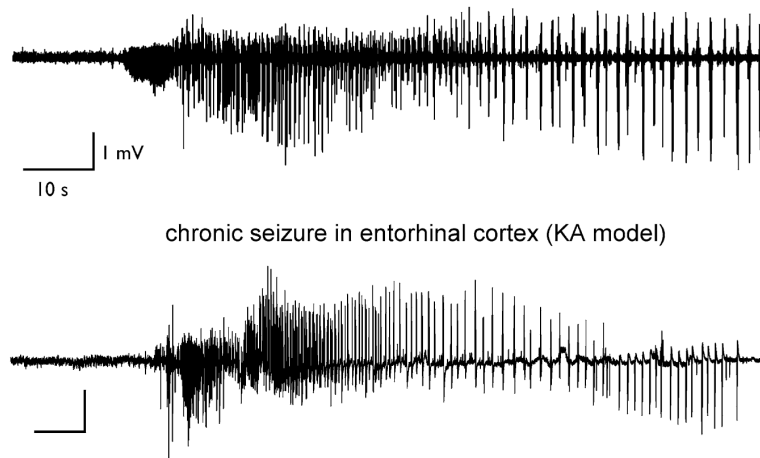


Fig. 1.8. Seizures recorded in guinea pig entorhinal cortex. The *upper trace* was recorded in the *in vitro* isolated guinea pig brain after systemic application of 50 μ M bicuculline. In the *lower panel* a seizure is shown, which was recorded *in vivo* 3 months after injection of kainic acid in the hippocampus. Both seizures are characterized by fast activity at the onset followed by irregular firing and late periodic bursting (From DeCurtis, unpublished)

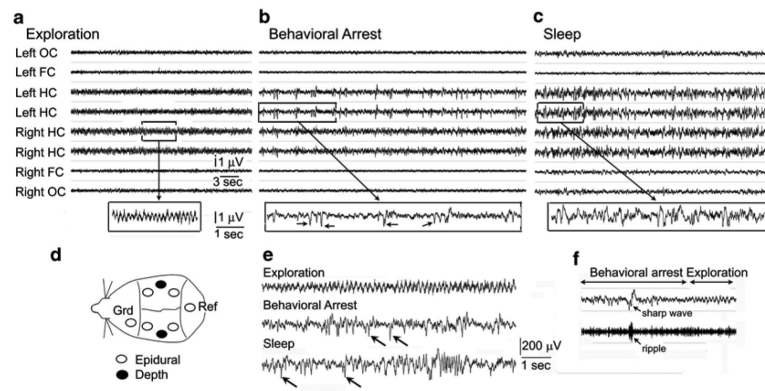


Fig. 1.9. EEG characteristics in the normal adult rat. (a) Using 8 electrodes (shown in d), awake behaving rats were recorded in their home cage. During exploration, hippocampal electrodes exhibited theta oscillations. The area outlined by the *box* is expanded at the *bottom*. (b) During a spontaneous arrest of behavior, sharp waves (*arrows*) occurred regularly in the hippocampal EEG. (c) During sleep, the hippocampal EEG became active. (d) The recording arrangement included 4 epidural electrodes and 2 twisted bipolar electrodes in the dorsal hippocampus, one in each hemisphere. *Grd* ground; *Ref* reference. (e) A summary of a-c is shown. In three behavioral states there are large differences in the hippocampal EEG with sharp waves (*arrows*) in behavioral arrest and sleep. (f) During sharp waves, filtering in the ripple band (100–200 Hz) shows that a ripple occurs at the same time as the sharp wave (From LaFrancois and Scharfman, unpublished)

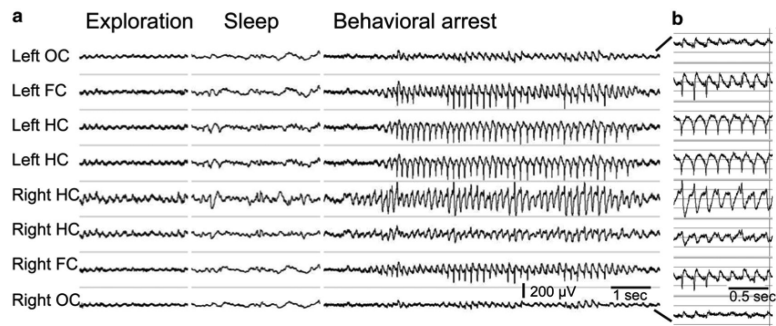


Fig. 1.10.

Spike-wave discharges recorded from the normal adult hippocampus of the rat. (a–b) A recording from an adult Sprague-Dawley rat shows typical EEG activity during exploration and behavioral arrest. In behavioral arrest, there were spike-wave discharges. Animals were monitored during the recordings to be sure that artifacts related to grooming or chewing did not occur during spike-wave discharges. (c) Recordings in b are expanded (From Pearce and Scharfman, unpublished; see also [101])

Table 1

Prior Definitions of Seizure

References	Definitions – Note that several say “epilepsy” in place of “seizure”
Jackson [58]	Epilepsy is a symptom... an occasional, an excessive and a disorderly discharge of nerve tissue (in the highest centers)
Penfield and Jasper [75]	An epileptic seizure is a state produced by an abnormal excessive neural discharge within the central nervous system
Aird et al. [3]	Epilepsy may be defined as a paroxysmal disturbance of central nervous system (CNS) function, which is recurrent, stereotyped in character, and associated with excessive neuronal discharge that is synchronous and self-limited
Engel [34]	Epileptic seizures are the clinical manifestations (symptoms and signs) of excessive and/or hypersynchronous, usually self-limited, abnormal activity of neurons in the cerebral cortex... An epileptic seizure may consist of impaired higher mental function or altered consciousness, involuntary movements or cessation of movement, sensory or psychic experiences, or autonomic disturbances
Hauser and Hesdorffer [53]	A seizure can be defined as a paroxysmal disorder of the central nervous system characterized by abnormal cerebral neuronal discharge with or without loss of consciousness
Hopkins et al. [55]	An epileptic seizure is a clinical manifestation presumed to result from an abnormal and excessive discharge of a set of neurons in the brain. The clinical manifestation consists of sudden and transitory abnormal phenomena, which may include alterations of consciousness, motor, sensory, autonomic, or psychic events, perceived by the patient or an observer
Adams et al. [2]	Epilepsy may be defined as an intermittent derangement of the nervous system due presumably to a sudden, excessive, disorderly discharge of cerebral neurons