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Transition to seizure: From ''macro''- to ''micro''-mysteries

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Summary One of the most terrifying aspects of epilepsy is the sudden and apparently unpredictable transition of the brain into the pathological state of an epileptic seizure. The pathophysiology of the transition to seizure still remains mysterious. Herein we review some of the key concepts and relevant literatures dealing with this enigmatic transitioning of brain states. At the ''MACRO'' level, electroencephalographic (EEG) recordings at time display preictal phenomena followed by pathological high-frequency oscillations at the seizure onset. Numerous seizure prediction algorithms predicated on identifying changes prior to seizure onset have met with little success, underscoring our lack of understanding of the dynamics of transition to seizure, amongst other inherent limitation. We then discuss the concept of synchronized hyperexcited oscillatory networks underlying seizure generation. We consider these networks as weakly coupled oscillators, a concept which forms the basis of some relevant mathematical modeling of seizure transitions. Next, the underlying ''MICRO'' processes involved in seizure generation are discussed. The depolarization of the $GABA_A$ chloride reversal potential is a major concept, facilitating epileptogenesis, particularly in immature brain. Also the balance of inhibitory and excitatory local neuronal networks plays an important role in the process of transitioning to seizure. Gap junctional communication, including that which occurs between glia, as well as ephaptic interactions are increasingly recognized as critical for seizure generation. In brief, this review examines the evidence regarding the characterization of the transition to seizure at both the ''MACRO'' and ''MICRO'' levels, trying to characterize this mysterious yet critical problem of the brain state transitioning into a seizure.

Introduction

Seizures are classically identified by electroencephalographic (EEG) criteria, which reflect underlying cellular (assumed mainly neuronal) electrophysiological dynamics.

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The transition to seizure is a spontaneous and usually extremely difficult event to predict. Those with epilepsy live in fear of these unpredictable events. Both at the MACRO (EEG) and the MICRO levels (cellular electrophysiology), the underlying dynamics of what constitutes and underlies a transition to the seizure state is poorly understood. For example, at the MACRO level, which deals with the EEG measures and dynamics for seizure identification and prediction, we assume that the ''gold standard'' for seizure identification is electrographic activity. However, often seizure-like semiology or sensations precede EEG changes (not always explainable by remote EEG electrode placement), which could be related to biochemical events, as reported in fMRI studies. For example, Federico et al. (2005) demonstrated a significant change of the blood oxygen level dependent (BOLD) signal several minutes before the seizure. At the MICRO level, most functions as related to the transition to seizure remain a mystery, including synaptic, presynaptic, and postsynaptic changes, gap junctions, glia, extracellular space and ionic changes, a myriad of relevant biochemical changes, and ephaptic transmission. How all these factors are integrated to cause the transition to seizure in epileptic tissue is still quite unclear. This review will focus on the EEG and cellular electrophysiological correlates of the transition to seizure, outlining some of the issues regarding this mysterious change of the brain into a seizure-like state.

The MACROSCOPIC level

Seizure prediction and identification

Seizure prediction, the ability to anticipate when a seizure will occur prior to its onset, remains one of the ''holy grails'' in epilepsy research, with entire scientific meetings dedicated to such pursuits (Frei et al., 2010). The ultimate goal of seizure prediction is to be able to either abort a seizure, through some type of electrical or chemical perturbation, or to warn the individual of an impending seizure (Osorio et al., 2001). Early work in this area by Viglione and Walsh (1975) motivated a very rich and varied literature with more failure than success (Mormann et al., 2007). The concept of seizure prediction necessarily implies that there is some identifiable ''signature'' of a brain state that is not quite ''normal'' but not yet fully transitioned to cause clinical manifestations. This signature is most often sought from electrical recordings either from scalp, or more commonly from intracranially implanted electrodes. What if this transition is not identifiable in some, or most forms of epilepsy? The fact that seizure prediction algorithms to date have met with little success, would seem to bolster this sense of nihilism (Mormann et al., 2007). Furthermore, it has been shown that in a system that is bi-stable, a situation in which a specific parameter of the system need not change for the system's behavior to change, then the transition may not be predictable or identifiable, and the time between seizures is a random process (Suffczynski et al., 2005, 2006). This was elegantly demonstrated, using animal and human data, as well as computational models, that sought to characterize the probability distribution of both interictal time periods and ictal durations. The authors found that for most types of clinical seizures, be they focal or generalized, human or animal, the time between seizures could be modeled by a gamma distribution with the exponent close to or less than one, suggesting a Poisson process, implying a random distribution of the time between seizures. An exponent less than one, would suggest that a seizure is more likely to recur immediately following a seizure, and the longer the time between seizures, the less likely a seizure would be — resulting in clustering of seizures. Conversely, the distribution of the length of the seizures was shown to be quite different to that of the interictal times, with an exponent greater than one, suggesting a deterministic aspect to seizure termination — the longer a seizure continues, the more likely it is to stop. Although bistable systems appear to preclude prediction, they nonetheless possess a unique dynamical property that makes them susceptible to being terminated by stimulation paradigms delivered at the right time and place. As well, the ictal state that is characterized by deterministic features, suggests there is a ''control parameter'' that if modified appropriately, can shorten the duration of the seizure. One may try to identify these control parameters from models, either biological or computational. These control parameters may be myriad, including ionic, synaptic, ephaptic, gap-junctional, field effects, and metabolic, ''causes'' of the transition to and from the seizure state. Thus one potentially realizable approach, in contrast to seizure prediction or anticipation, is early seizure identification, and termination. The emphasis would thus be on developing an understanding of how to terminate various forms of seizures, which is likely only to come from understanding the various microscopic mechanisms that underly the determinism in ictal termination.

Macroscopic recordings have inherent spatial limitations — one can only implant so many electrodes as clinically indicated. This sampling error results in being unable, or unlikely to record directly from the ''ictal onset zone'' (Lüders and Awad, 1992), precluding the capture of the early features of the transition. Nonetheless, the features often ascribed to transition to seizure, are those that are derived from more microscopic and spatially restricted recordings — the limit being isolated brain tissue slices perfused with pro-convulsants (see following sections).

Recently however, large scale ''microscopic'' recordings are being acquired from human subjects (Worrell et al., 2008), as technological advancements have allowed relatively safe, and low cost micro-electrode recordings in the clinical setting. With advancements in computer technologies and storage, acquiring data at high-sampling rates is a prerequisite when examining high frequency oscillations (HFOs), which have been proposed to be markers for epileptogenic brain (Bragin et al., 1999a,b). Although these techniques suffer from the spatial sampling problems mentioned above, they allow the analysis of ''macro''-microelectrode recordings and multi-unit recordings that can help bridge the animal and human literature regarding ictal transitions. Recently it has been shown that single units recorded distant to the epileptogenic region, display alterations in their activity well in advance of the macroscopically recorded seizure (Truccolo et al., 2011), suggesting that much information at a distance, at least in the context of a pathological process like epilepsy may be carried in the activity of a single neuron. Thus a more mechanistic approach to seizure detection, driven