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Epileptic seizures from abnormal networks: Why some seizures defy predictability

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Summary Seizure prediction has proven to be difficult in clinically realistic environments. Is it possible that fluctuations in cortical firing could influence the onset of seizures in an ictal zone? To test this, we have now used neural network simulations in a computational model of cortex having a total of 65,536 neurons with intercellular wiring patterned after histological data. A spatially distributed Poisson driven background input representing the activity of neighboring cortex affected 1% of the neurons. Gamma distributions were fit to the interbursting phase intervals, a non-parametric test for randomness was applied, and a dynamical systems analysis was performed to search for period-1 orbits in the intervals. The non-parametric analysis suggests that intervals are being drawn at random from their underlying joint distribution and the dynamical systems analysis is consistent with a nondeterministic dynamical interpretation of the generation of bursting phases. These results imply that in a region of cortex with abnormal

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connectivity analogous to a seizure focus, it is possible to initiate seizure activity with fluctuations of input from the surrounding cortical regions. These findings suggest one possibility for ictal generation from abnormal focal epileptic networks. This mechanism additionally could help explain the difficulty in predicting partial seizures in some patients.

Introduction

Epileptic seizures are brief, episodic phenomena. Partial seizures, the most common seizure type, arise from focal brain regions (e.g. temporal, parietal) (Niedermeyer, 2005).

While in some instances there may be an identifiable cause for the seizures (e.g. tumor, cavernoma, hippocampal sclerosis), in other instances no clear pathology is determined. The hallmark of an epileptic seizure is the involvement of local or regional neural networks; repetitive firing of a single neuron does not produce symptoms without this network involvement. What causes the interictal to ictal transition? A typical partial seizure lasts less than 2 min plus any postictal state (Afra et al., 2008). Therefore, even if a patient has very frequent seizures, the majority of time is spent in the interictal state. While some seizures can be provoked or are more likely to occur under certain situations (e.g. sleep deprivation, photic stimulation), the majority of seizures appear to occur spontaneously without known association with definable influences.

There has been considerable interest in seizure prediction in recent years. Obviously if seizures could be reliably predicted, then the option for targeted therapy exists (e.g. stimulation), or at least the patient could remove themselves from potentially dangerous situations. The underlying hypothesis for seizure prediction is that there are changes in cerebral dynamics that may precede the clinical seizure by minutes to hours (reviewed in Sackellares, 2008). These changes may be local (i.e. near the seizure focus) or remote. These changes are not apparent with visual analysis of the EEG, even with intracranial recording arrays. Some groups have identified high frequency activity that may signal the onset of neocortical partial seizures, but this is an example of improved seizure detection, not prediction (Worrell et al., 2004, 2008; Bragin et al., 2010). Reliable seizure predication has been challenging and even the most enthusiastic proponents of the prediction hypothesis acknowledge the difficulties with current algorithms (Lehnertz et al., 2007; Mormann et al., 2007; Andrzejak et al., 2009).

Seizure prediction may be difficult due to rapid bistable state changes at the time of ictal onset in the neocortex (Suffczynski et al., 2006; Lopes da Silva et al., 2003).

The mechanisms underlying a bistable state change may be quite different between primary generalized (e.g. absence) and partial epileptic seizures. A bistable state change may be more applicable to these primary generalized seizures which have abrupt bilateral cerebral onset. In this paper, a different possible mechanism is presented under which seizure prediction would be difficult in some patients with focal seizure onset.

Knowing, as we do, that partial seizures are a reflection of transient abnormal regional network activity, it is reasonable to postulate that these seizures in at least some (perhaps many) patients result from abnormal neural networks (e.g. the epileptogenic zone) (Jacobs et al., 2000). We describe here a model of the epileptogenic zone where the epileptic focus is represented by an abnormal neural network that has very slightly altered connectivity so that, while seizures only occur infrequently, they can be triggered by normal background activity originating from outside the epileptogenic zone. This background activity could be influenced by various physiologic factors (e.g. sleep), but nevertheless this background activity would not result in seizure activity in the non-epileptic brain. This does not discount the possibility that some changes in neural network synchrony may occur in the ''normal'' brain since the cumulative lifetime incidence of unprovoked seizures approaches 4% (Hauser et al., 1993). Often these seizures are provoked (e.g. medications and alcohol) and less than half of these patients have recurrent seizures. The lifetime cumulative risk of developing epilepsy only ranges from 1.4% to 3.3% (Krumholz et al., 2007; Berg and Shinnar, 1991). In this model, however, where normal background activity, occasionally or rarely produces a seizure in abnormal regional networks, seizure prediction would be difficult since detectable preictal changes would not be present; the first changes would in fact be seizure initiation.

Epileptic networks in neocortex or the hippocampus show anatomical changes compared to normal tissue (Jacobs et al., 2000; Sallin et al., 1995). These changes can progress with time (Sallin et al., 1995; Arellano et al., 2004). This could result in neuronal networks more amenable to seizure generation (electrical or clinical) over large regional areas. There is a complex interrelationship, much of it not well understood, between neurons which are dysfunctional and the neural networks which can promote seizures (Leussis and Heinrichs, 2007; Kumar et al., 2007; Swann et al., 2007). Even in the non-epileptic brain, excitatory connections predominate with 80—90% of synapses being excitatory (Braitenberg and Schüz, 1998).

With neuronal network simulations it is possible to control, study, and quickly change the various influences on network behavior. Recently, we presented the results of computational simulation studies examining the role of external field stimulation on ongoing bursting activity in a neural network (Anderson et al., 2007, 2009). The cortical model used in these studies consists of discrete single compartment Hodgkin—Huxley type cells which are spatially arranged in a realistic fashion having both a layered and columnar structure. Since neural network behavior reflects the aggregate output of the component neurons, single compartment neurons allow greater computational efficiency and the ability to model larger networks in studies of network behavior. Arrangements of connected simulated neurons in this manner can demonstrate spontaneous bursting phases and have spatial characteristics similar to seizures recorded from humans (Anderson et al., 2007, 2009; Kudela et al., 1997, 2003a,b, 2005; Franaszczuk et al.,