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OSCILLATORY ACTIVITY

Contents

Cellular and Network Oscillations in Epilepsy

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Introduction

The traditional hallmark of epileptiform discharge is entrained electrical oscillatory activity in a large enough volume of cerebral tissue to be measurable in the context of a possible seizure disorder and cerebral dysfunction. This oscillatory activity seen in seizures is usually characterized by reduced complexity and increased widespread synchrony as compared with 'normal' brain activity. We are trying to understand the mechanisms underlying the various forms of oscillatory activity and their transitions. As such, the big questions are as follows:

1. How do we measure and characterize these oscillatory activities and their transitions?
2. What are the sources of these oscillations: subcellular, cellular (which cells?), local clusters, small or large neural networks? Are there multiple sources of seizure activity? Do seizures tend to arise from a single focus or is a seizure largely an emergent property of a distributed network?
3. How do transitions from interictal to ictal modes occur? Are seizures a manifestation of coupled oscillators? Are transitions to seizure due to internal or external factors?
4. How can one intervene to change these oscillatory modes from an epileptic to a nonepileptic mode?

To answer these questions, we approach the neuronal system as a nonlinear dynamical system where, conceptually, epileptiform seizures are modes of the system's oscillatory activities. Our research includes both *in vitro* and *in vivo* measurements, as well as modeling and analyses of the system dynamics. Understanding the mechanisms of complex oscillations and transitions will be critical for diagnosing and ameliorating the negative effects of seizures. Insight into these mechanisms may also enhance our understanding of the manner in which other transitions in brain activity take place during nonseizure phases and cognitive processing.

Background

Sources and Scales of Oscillatory Activity

Brain oscillations emanate from many sources at many different levels. Although one often thinks of cellular-level sources, in fact there is a rich supply of oscillatory activity within the cell itself (both biochemical and electrical), as well as multiple sources at the whole network level.

Subcellular oscillations

Oscillations are seen within the nucleus and also within subcellular organelles such as mitochondria. Oscillations

of intracellular ionic concentrations such as calcium and pH have been measured, and there are rhythms of molecular processes and intracellular protein cycling at a range of frequencies.

Cellular oscillations

From an electrical perspective, measures of the neuronal membrane potential have shown a wide range of spontaneous oscillatory frequencies (sometimes called 'noise'). These oscillatory activities arise from several sources, including afferent synaptic inputs (both action potential-evoked and spontaneous), intrinsic ionic current fluctuations, and ephaptic (electric field) effects (which are frequently ignored). These spontaneous membrane fluctuations are as yet little studied and their contributions to the extracellularly-measured field fluctuations are not well understood. Furthermore, the contribution of the more numerous non-neuronal cells, such as glia, are even less well-studied, but could be of greater importance than heretofore realized. Cell types, each type with its signature oscillatory activity, make their own specific contribution to the measures of oscillatory activity.

Intercellular connectivity

The interconnectedness of neurons to each other, and to other cell types, is a further factor contributing to the overall measures of brain oscillations. The more a group of cells oscillates together at specific frequencies, the higher are the expected amplitudes of the emanating common signals. There are several factors that will unite a group of cells. The most obvious are chemical synapses. However, direct intercellular connections via gap junctions are particularly evident in cortical and hippocampal interneurons, and there is a growing literature showing a role for gap junctional communication in the genesis of seizures. Another means of synchronizing groups of cells is via synchronous afferent synaptic input, be it excitatory or inhibitory. For example, synchronous inhibitory input into thalamocortical and cortical–thalamic neurons plays a large role in the generation of thalamocortical oscillations in absence seizures. Ephaptic (field) effects can also be a powerful entrainment force, as can be demonstrated by the application of an electrical field to neural tissue via direct or transcranial brain stimulation. Less recognized but of significant importance are the synchronizing actions of changes in extracellular chemical elements such as potassium, pH, glucose, oxygen, and various hormones.

Clusters

An important emerging concept is that of cellular clusters, a group of synchronized cells (usually thought of as neurons, but glia could also be involved), which oscillate together at the same frequency or frequencies. A cluster provides local synchrony for a period of time in a spatial context. The cells involved in a cluster could be coupled together by various mechanisms for brief to prolonged periods, following which individual cellular units of this cluster could become attached to another spatially contiguous cluster. Thus, there might be an ongoing rearrangement of these cellular clusters, giving rise to a constantly changing source of local oscillatory activity. Finally, we conceive that these clusters are physically interdigitated or intermingled.

Networks

From the local clusters of synchronized cellular elements, the next conceptual level is that of the network. Networks may range from connectivity between 'local' units to connectivity across larger brain regions, to the coupling of brain regions (e.g., the limbic system), to connections between distal sites in opposite brain hemispheres. Whatever the scale, the concept of a network is important for the understanding of brain oscillatory activity and its propagation. Brain networks not only comprise several levels of size and complexity but are also likely to be constantly and dynamically re-arranging and regrouping themselves. Moreover, the various subcellular, cellular, and network sources of oscillations are undoubtedly interacting simultaneously across different levels in an ongoing and dynamic manner.

Oscillations and Complexity

Early investigations into chaotic and epileptic brain activity provided convincing evidence that the dynamics seen during various cognitive conditions were significantly more complex than those seen during a seizure. For example, Babloyantz and Destexhe. reported that electroencephalogram (EEG) recordings of human absence seizures showed simple attractor dynamics as compared with sleep brain activity. In general, most such studies have provided strong evidence in favor of the suggestion that epileptic seizures corresponded to a lowering of complexity in brain electrical activity.

Synchrony and the Unbinding Problem

In contrast to these findings indicating the lowering of complexity during seizures, researchers such as Netoff and Schiff have argued that certain types of seizures may actually be associated with an *increase* in complexity in the form of a reduction in synchrony. Moreover, reductions in complexity have been found in response to ordinary sensory stimulation during cognitive processing. For example, by studying the EEG recorded from the olfactory bulb and the prepyriform cortex of the rabbit, Freeman reported that when the rabbit is presented with a familiar odor, the normally high-dimensional chaotic activity suddenly bursts in a regularized pattern. Singer and many other researchers have also suggested that synchrony and other forms of reduction in complexity can explain how the brain might generate coherent representation by spatio-temporal 'binding' of neural activity.

Although transient reductions in complexity may indeed be observed across cognitive conditions, epilepsy has taught us that, in most cases, it is precisely the strong entrainment of activity and reduction in complexity that is most likely to interfere with cognitive processing. It is a defining feature of neural systems that they avoid prolonged simple and entrained activity and that they tend toward complexity. With the exception of conditions such as status epilepticus, even the entrainment seen during seizures is transitory. Although a great deal of the current literature has focused on synchrony and binding, the study of epilepsy suggests that we need to understand how the brain *avoids* binding and urges us to ask what brain anatomical and physiological principles enable complexity?

Even if one assumes that synchrony and the lowering of complexity may be necessary for cognition, the question remains as to what mechanisms ensure the escape from this entrainment. The question is not simple. Ohayon *et al.* have suggested that the tendency toward synchrony and limit-cycle activity is ubiquitous in certain network models and that this problem of locked-in periodic oscillations may worsen in the presence of some forms of plasticity. How does the brain solve this unbinding problem? What are the mechanisms of transition between the various modes of oscillatory activity that avoid 'lockup?'

Transitions, Intermittency, and Modulation

Although the specific nature of the transitions into and out of seizures is a central question in the field, the basic mechanisms of transition and the triggering factors – if any – are often unknown. Lopes da Silva *et al.* have outlined several potential routes to seizures. One possibility is the switching between two pre-existing 'attractor' brain states via a perturbation or noise. In this scenario, the brain might switch from interictal oscillatory activity to seizures following a stimulus, as in the case of certain photosensitive epilepsies. Another potential route involves an increase in susceptibility to seizure brought about by a parametric change in the system, as might happen over time with a hormonal shift or hypoglycemia.

Beyond these two routes there also exists another possibility in which the shift into and out of seizures may occur autonomously of any external stimulus or change in the system. Specifically, *intermittency* is a form of activity wherein a dynamical system may continually alternate between two modes of activity independently of an external perturbation. Velazquez *et al.* have reported intermittency in human partial epilepsy. There are various known forms of intermittency, and various statistical techniques may help identify the type of transition that precedes a given seizure.

The identification of alternate transition categories and an understanding of the mechanisms underlying brain dynamics could play an important role in clinical treatment. In particular, seizures may be modulated or altogether avoided by carefully applying small perturbations to a system, thereby eliminating low-complexity activity. For example, Schiff *et al.* were able to use small electrical brain stimulations to induce a change from lower complexity 'periodic' behavior to high-complexity 'chaotic' responses, suggesting that the technique might be applied to activity in epileptic foci. Other studies have since followed, demonstrating the feasibility of using various forms of stimulation to modulate ictal activity both in models and in vivo.

Methods

Human EEG and Biological Models of Epilepsy

The conventional and still current standard for measuring epileptiform phenomena is extracranial electrographic field recordings – the EEG. In humans, the primary measure is the scalp EEG, which, in cases where the site(s) of origin of the epileptic activity is unclear, is augmented by intracranial recordings. Because seizures are usually spontaneous events, prolonged (days to weeks) recordings are often required before enough seizure activity has been observed for appropriate diagnosis and localization. Until recently, human EEG recordings, including intracranial EEG, were almost always done with filtering of all high-frequency activity above 70 Hz, thus ignoring important data relevant to our understanding of the brain oscillatory activity associated with epilepsy.

There are in vivo and in vitro models of epilepsy and seizures, too numerous to mention. In in vivo models, extra-cranial and/or intracranial EEGs are generally recorded in association with a stimulus (e.g., repetitive subthreshold intracranial stimulation – 'kindling'), introduction of a chemical (e.g., kainic acid, pilocarpine, cobalt, tetanus toxin), or an insult (e.g., cerebral trauma) given to elicit seizures. These seizures can directly follow stimulation, or occur spontaneously, which is more akin to the human situation. In vitro models provide direct access to cerebral tissue for local electrical field recordings, whole-cell or intracellular recording, cellular or local network imaging of ionic changes (e.g., calcium), or electrical changes monitored by voltage sensitive dyes. In vitro models also provide control of the extracellular environment. However, the relation of these in vivo and in vitro models to the oscillations and basic mechanisms of clinical epilepsy is not always clear.

Coupled Oscillators Modeling

To further examine the basic mechanisms of oscillations, there has been extensive use of computational models. For example, the mapped clock oscillator (MCO) first described by Bardakjian and Diamant is quantitative in nature and its parameters can be obtained directly from the measured intrinsic transmembrane voltage waveform

in the biological tissue when a segment of the tissue is isolated by partial or complete cuts from its neighborhood. The model thus allows us to explore multiple critical parameters simultaneously at a level of detail not always possible in biological recordings. When such oscillators are coupled together to form networks, they can qualitatively and quantitatively simulate the electrical oscillations recorded in hippocampal neuronal networks. Such models exhibited spontaneous transitions into seizure-like activities and were used to test approaches to predict and then abolish such activities. More details regarding these coupled oscillator models can be found in Further Reading.

Recurrent and Embodied Network Models

To identify the contributions of network structure to oscillations and transitions, we have also modeled activity propagation in more abstract networks, with units governed by probabilistic activation functions (sigmoid, Gaussian) or simple spiking functions with various architectures. For example, we have examined networks with random connections between cells as well as those with spatially organized local connectivity. These models are helping us explore the relation of structure to oscillations in both intact networks as well as in networks with cell deletions (in order to reflect such conditions as posttraumatic epilepsy). There is also active research being done on a range of network architectures, such as small world networks, which may help explain the difference in forms of oscillation (and susceptibility to seizure discharge) across brain structures.

One issue, however, with many of these models is that they are figuratively and literally disconnected from the environment. As such, a recent step has also been the inclusion of 'embodied networks.' These models consist of networks that are connected to external sensors and transducers (robots), and are evolved with genetic algorithms to maneuver in the environment. These embodied models aim at addressing the increasing recognition that behavioral interaction with the environment is critical to brain development, and has an essential role to play in neural oscillations both in epilepsy and other conditions.

Recent Results

Coupled Oscillators – Biological Data

The concept of coupled oscillators is increasingly recognized as useful for the understanding and modeling of brain activity in general and epileptiform activity in particular. We have demonstrated in the isolated mouse hippocampus that recurrent, spontaneous seizures generate bidirectional epileptiform activity along the septotemporal axis (as measured by multiple electrode recordings and optical imaging), indicating a system of coupled network oscillators (see **Figure 1**). Uncoupling the system of oscillators, by partial or complete cuts, resulted in independent bidirectional activity in the separated tissues. Within the same epileptic burst, low- and high-frequency components originated from different locations. A second seizure model (generated by focal tetanic electrical stimulation) also exhibited bidirectional discharges. Clinical data (unpublished), obtained from adjacent intracranial depth electrodes in the hippocampus of epileptic patients, have similarly revealed bidirectional seizure bursting activity, but at a much larger anatomical scale.

Higher Frequencies and Kindling

As mentioned in the Background section, the importance of high-frequency activity has often been overlooked in human EEG and epilepsy. This focus on low frequency at the exclusion of higher ranges has also extended into various seizure models. For example, it has been known for decades that the changes brought about by the repeated stimulations in kindling can have profound long-term effects on low-frequency oscillations. However, changes in high-frequency components were rarely reported, mostly because of limitations in data acquisition equipment and shortcomings in the prevalent approaches to spectral analysis. By increasing the sampling rates and introducing new forms of analysis, we have shown that there are dramatic changes in power and other characteristics of oscillations across all frequencies during kindled seizures. Specifically, we have demonstrated that there is a significant increase in higher frequency events (>80 Hz) during kindled seizures (**Figure 2(a)**). To identify these changes, we recorded the activity at high sampling rates (2–10 kHz) and developed a calibrated amplitude wavelet transform (CAWT) that normalized the power across frequency bands. The normalization of activity by frequency is important because wavelet and other algorithms tend to highlight long period events, thereby drowning out shorter – but likely just as significant – fast events. This application of normalized wavelet analysis across frequency bands could also help elucidate the importance of such events in other models and brain recordings.

Higher Frequencies and Complexity

Although the existence of hippocampal high-frequency electrical activities (greater than 100 Hz) during the progression of seizure episodes in both human and animal experimental models of epilepsy has been previously documented, this information has not been studied between successive seizure episodes or utilized in the application of seizure classification. We examined the dynamical changes of an in vitro low Mg^{2+} rat hippocampal slice model of epilepsy, at different frequency bands, using wavelet transforms and artificial neural

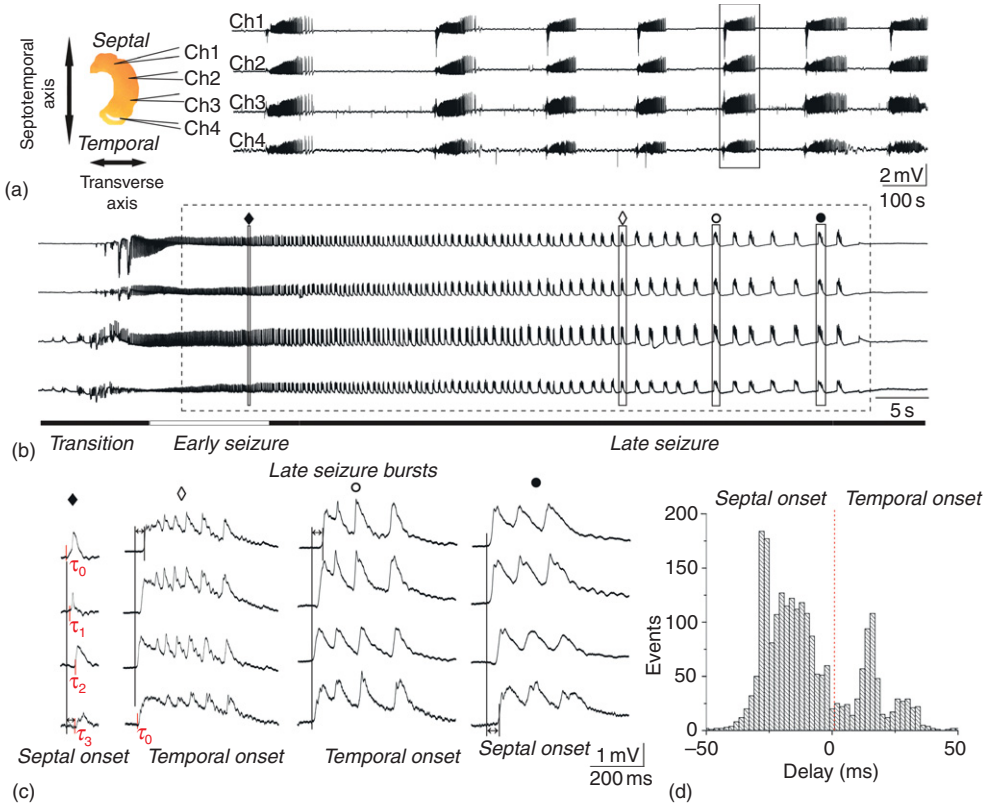

Figure 1 Multisite field recordings illustrate bidirectionality. (a) Four field electrodes in the CA1 subfield (Ch1–Ch4) placed along the septotemporal axis of the hippocampus (left inset-arrows denote direction of two axes) record recurrent, spontaneous seizures from the intact hippocampus. (b) A single seizure (expanded from panel (a)) recorded from all four electrodes shows the three characteristic phases of seizure. The transition phase is characterized by temporal onset during which there is lack of functional coupling, and later during the seizure (early, late phases), epileptiform activity displays bidirectionality and becomes functionally coupled across all four channels. (c) Bidirectionality of single intraseizure bursts (expanded from panel (b)) shows both septal (♦, •) and temporal (◊, ○) onsets. Vertical red lines illustrate beginning of events as represented by their relative times of onset ($\tau_0\tau_0$, τ_1, τ_2, τ_3), and (↔) denotes difference in times between the septal and temporal events. (d) Histogram of the event delays between the two outermost electrodes (Ch1–Ch4) reveals that most epileptic activity in the analysis window is of septal origin, while the average delay between these two channels is irrespective of the site of onset. Adapted from Derchansky M, Rokni D, Rick JT, *et al*. (2006) Bidirectional multisite seizure propagation in the intact isolated hippocampus: The multifocality of the seizure focus. *Neurobiology of Disease* 23: 312–328.

networks (ANNs). By dividing the time–frequency spectrum of each seizure-like event (SLE) into frequency bins, we analyzed their burst-to-burst variations within individual SLEs as well as between successive SLE episodes, using high sampling rates (10 kHz). We demonstrated that the activities of high-frequency oscillations in the 100–400-Hz range increased as the slice approached SLE onsets and in later episodes of SLEs. By examining the time-dependent relationship between different frequency bands, we showed the importance of the higher frequencies for classification of activity. In particular, we demonstrated that activities in the frequency range 100–400 Hz were critical for the accurate classification of electrographic seizure-like episodes – containing interictal, preictal, and ictal states – in brain slices undergoing recurrent spontaneous SLEs. Although preictal activities could be classified with an average accuracy of $77.4\% \pm 6.7\%$ using frequency spectrum in the range 0–400 Hz, we could achieve a similar level of accuracy by using a nonlinear relationship between 100–400-Hz and <4-Hz frequency bands only. We have demonstrated that the decrease in complexity (as measured by the Lyapunov exponent) between interictal and ictal events was significant for the higher frequency bands. These experiments are important in that not only do they examine the change in power across frequencies but also quantify changes in the system's dynamical properties, including complexity (**Figure 2(b)**).

Transitions, Noise, and Intermittency in Coupled Oscillator Models

Coupled oscillator models, based on the biological transmembrane voltage recordings from in vitro hippocampal slices, were used to investigate the following:

1. *The stochastic resonance effects.* That is, we examined the relation of noise to the occurrence of coherent

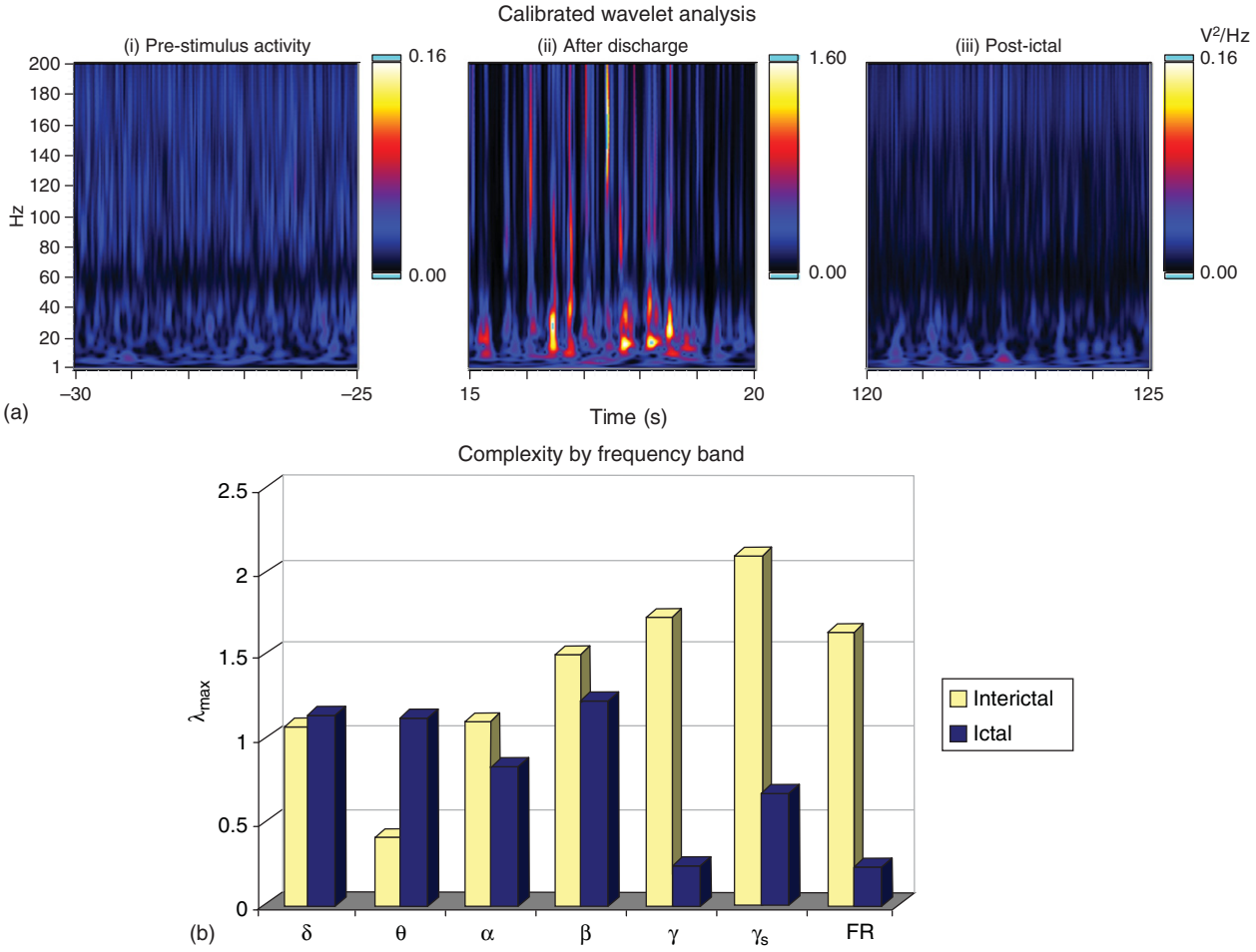

Figure 2 High frequency and complexity. (a) Changes in high-frequency events during kindled seizures. The figure shows the CAWT analysis for 5 s of (i) preictal, (ii) after discharge, and (iii) postictal hippocampal activity in kindled seizures. The kindling stimulus was applied to the perforant path and is indexed here as $t = 0$. This normalized amplitude wavelet analysis confirmed previously reported changes in power at lower frequencies but also demonstrated that changes extended into the high-frequency bands of 80–200 Hz. Note that the *Z* amplitudes are zoomed (10×) for the pre- and postictal events in order to show the activity in these periods. As such, the changes in activity are even more pronounced than the graphs otherwise indicate. The darker banding at 60 Hz is due to a notch filter. Adapted from Ohayon EL (2000) Connectionism and Wavelets in the Modeling and Analysis of Neural System Dynamics. M.Sc. Thesis., Ottawa: National Library of Canada, Ottawa. (b) Complexity measures across frequency bands. The maximum Lyapunov exponents (λ_{max}) were computed for each frequency band in hippocampal recordings in the Mg^{2+} model of epilepsy. A time series at each frequency band was constructed from the average wavelet coefficients in frequency. It is shown that the most significant decrease in complexities occurred in the higher frequency dynamics (>40 Hz). The frequency ranges shown are as follows: delta (δ, <4 Hz), theta (θ, 5–8 Hz), alpha (α, 8–15 Hz), beta (β, 15–40 Hz), gamma (γ; 40–100 Hz), super gamma (γ_s, 100–250 Hz), and fast ripples (FR, 250–400 Hz). Adapted from Chiu AWL, Jahromi SS, Khosravani H, Carlen PL, and Bardakjian BL (2006a) The effects of high-frequency oscillations in hippocampal electrical activities on the classification of epileptiform events using artificial neural networks. *Journal of Neural Engineering* 3: 9–20.

oscillations. We found that field and gap junctional coupling pathways exhibited significant stochastic resonance effects in the 4–8-Hz frequency range, but did not exhibit stochastic or coherence resonance phenomena at 0.5 Hz. This helped explain why reported in vitro seizure control strategies using pulse-trains could be effective at 0.5 Hz.

2. *The mode transitions from higher to lower complexity modes.* We were also interested in how the transitions might occur. We found spontaneous intermittent mode transitions, from higher complexity modes (possibly chaotic) to lower complexity (possibly rhythmic) modes, similar to those observed in in vitro hippocampal slice models under low-magnesium conditions. Mode transitions from high to low complexity were also shown to be associated with epileptic seizures in humans and onset of SLE in hippocampal in vitro slice models.

Synchrony, Complexity, and Intermittency in Network Models

In addition to the observations in the coupled oscillator models, the importance of intermittency for understanding autonomous transitions in epilepsy (and the potential therapies based on an understanding of intermittency) was explored in networks with random connectivity. When we tested networks with initial random connectivity and random activity, the vast majority of networks quickly stopped oscillating (**Figure 3(a)**) or settled to limit-cycles with periodic and fully synchronized activity (**Figure 3(b)**). These findings suggest that the inherent propensity of clusters and larger networks to enter into periodic synchronized activity – and, by extension, seizures – may be more prevalent than previously recognized.

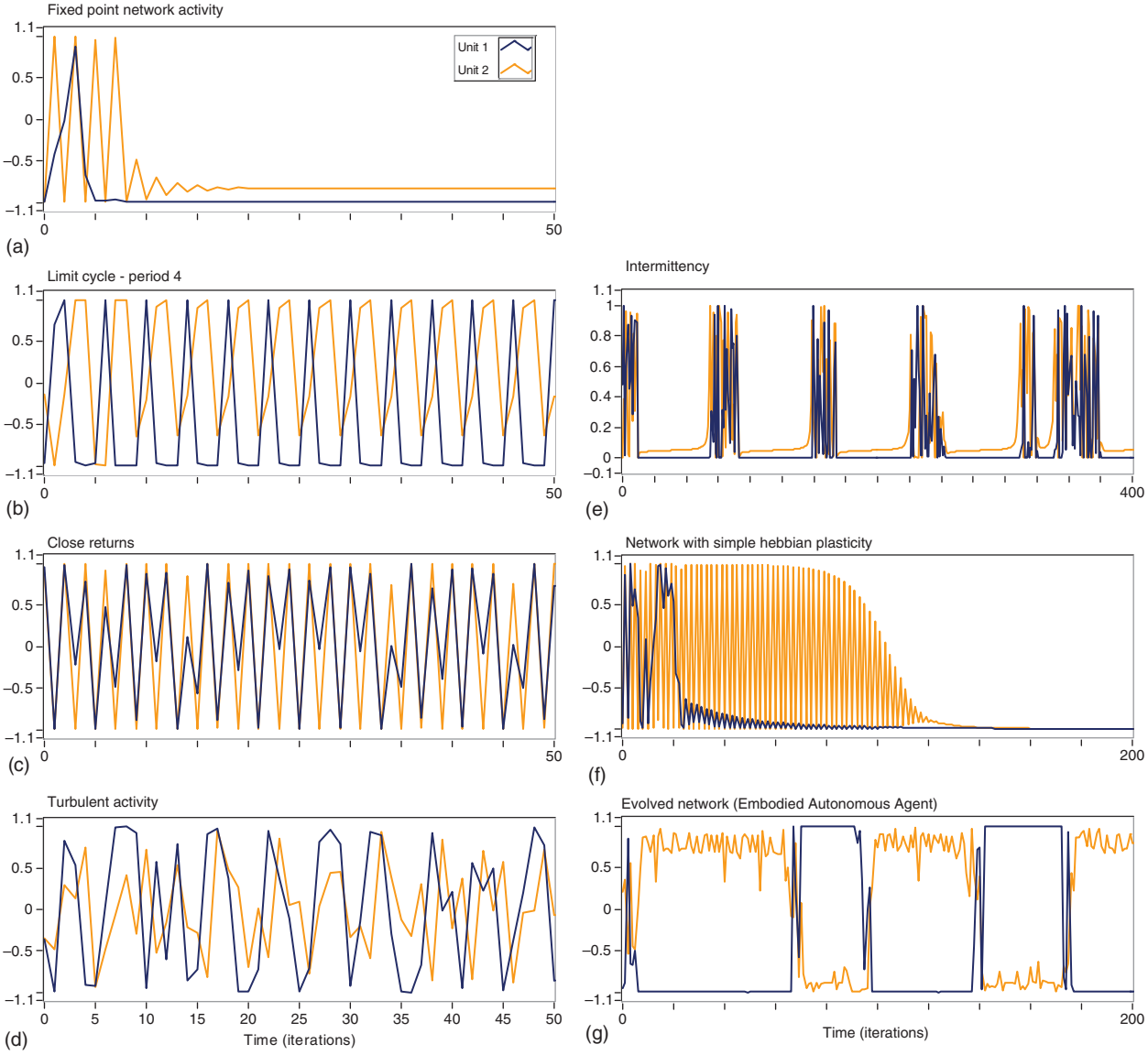

Figure 3 Activity dynamics in random and embodied neural network models. Most random networks settled to (a) fixed point and (b) limit-cycles characterized by periodic, synchronized activity (81% in the sigmoidal random networks). The remaining networks showed activities that were either (c) close to periodic but never precisely repetitive (13%) or were entirely (d) turbulent (6%). A subset of the nonperiodic networks showed (e) intermittent changes in phase reminiscent of transitions seen in epilepsy. The addition of simple Hebbian plasticity reduced complexity in random networks and quickly led to fixed points (f). On the other hand, embodied networks that were evolved to interact with the world showed (g) persistent nonperiodic activity. (Graphs show activity of 2 of 5 units; *y* axis is activity level normalized so that a value of 1 represents full excitation.) Reproduced from Ohayon EL, Kalitzin S, Suffczynski P, *et al*. (2004) Charting epilepsy by searching for intelligence in network space with the help of evolving autonomous agents. *Journal of Physiology-Paris* 98: 507–529.

However, these models have also demonstrated that complex oscillatory patterns can be an emergent property of network structure. For example, some networks were shown to generate complex oscillatory activity even if the constituent units were not themselves oscillators. In these cases, the nonperiodic activity showed either close to periodic but never precisely repetitive activity ('close returns') (**Figure 3(c)**) or highly turbulent activity (**Figure 3(d)**). By further examining these nonperiodic networks, we were able to demonstrate that in certain cases, the activity could switch autonomously between turbulent and quiet phases (**Figure 3(e)**). The change between the two phases of activity in these networks showed a distribution known to be characteristic of intermittency. Given that the units in all of these models were identical, the model demonstrates that intermittency can be the direct result of network structure and need not depend on changes to intrinsic cell properties. The autonomous switching in these models due to network structure thus demonstrates that some transitions into and out of seizures may be occurring in the absence of external perturbation or noise, and possibly without any change to neuronal properties. The continuous nature of these autonomous transitions also suggests that the very notion of a distinct epileptic 'state' may be questionable.

Although ongoing changes to the structure were not *necessary* for intermittency in these models, the activity was shown to exhibit changes in the statistics of transitions as a result of alterations to connectivity. In other words, changes in network structure could modulate the properties of the intermittency. As such, the model illustrates that intermittency mechanisms of transition are in fact compatible with the other mechanisms of seizure transitions enumerated by Lopes da Silva *et al.* (see Transitions, Intermittency, and Modulation in Background), and that the various mechanisms of transition are probably taking place concurrently in an interactive manner.

With regards to changes in connectivity, it is interesting to note that the addition of simple Hebbian plasticity drove even the most complex network activity to synchrony and eventually to the cessation of oscillations (**Figure 3(f)**). This finding suggests that it will be critical to identify the types of plasticity that generate brain structures that can maintain complex persistent activity and avoid seizures.

Interaction with the environment may be another factor important in avoiding periodic oscillations or fixed point activity. To demonstrate this point, the random networks were connected to external sensors and transducers (robot chassis). These embodied networks were then evolved over several generations, using an evolutionary algorithm that selected for continuous movement and the ability to avoid obstacles. As the behavior evolved, so did the dynamics of the activity, going from the largely fixed point and synchronized periodicity of the random networks to more complex multistable activity (**Figure 3(g)**). This demonstration is the first embodied modeling of epilepsy, illustrating the importance of the environment in producing structural changes that avoid seizures.

Future Directions

Technical Considerations

Our research highlights the need to consider multiple sources and scales when studying oscillations and transitions to seizure. Many challenges remain for the future. There are important questions of measurement and other technical issues. For example, the location and method of measurement, the chosen frequencies, and the use of linear versus nonlinear techniques are all ongoing debates in the field. Should we continue to rely primarily on electrical measures or is the better measure of epileptiform activity a reflection of something else, such as magnetic fields or chemical movements?

Autonomous Neurodynamics, Environment, and Embodiment

Our research demonstrates that the analysis must consider events in the higher frequencies, and forms of transition that go beyond simple attractors and parametric changes. In particular, the various intermittent forms of activity seen in the biological and model systems suggest a possible explanation for how certain transitions might occur autonomously, without a triggering stimulus. The research into autonomous neurodynamics is currently a major interest of our group, both in terms of understanding neural activity in epilepsy as well as how transitions in brain dynamics might occur in other cognitive conditions. As such, our research paradigms and models must also increasingly consider the role of bidirectional interactions of the embodied brain and the environment. Many laboratories are now uncovering the importance of enriched environment on development in general and susceptibility to seizures in particular. Our own research has shown that modeling of embodied networks connected to the environment can lead to increased complexity in oscillatory activity and to the escape from seizures. These connections – involving interaction within the environment, plasticity, and resultant oscillatory activity – need to be further explored. The attention to evolutionary sensorimotor modeling is also notable in that it moves away from modeling seizures as the primary goal and turns toward modeling the manner in which biological systems *avoid* pathological synchrony.

Relation between Network Structure and Oscillatory Activity

Another important frontier is the uncovering of the relation between network structure and the propagation of oscillatory activity. Netoff *et al.* and other groups have demonstrated that small world architectures, for example, can be an important factor in seizure dynamics. Our own work with random networks suggests that many seizure-like phenomena may arise even in the absence of complex architectures or plasticity. Current work is concentrating on modeling the propagation in spatial networks; results to date suggest that heterogeneity in structure (not just unit properties) may play a critical role in the form of oscillations and their propagation. These findings might help explain why the probability of seizures rises following cell damage or cell death in cases of trauma and aging. The most recent findings suggest that architecture may even override factors such as the balance between inhibitory and excitatory components.

Prediction of Seizure Activity

An artificial neural network possesses the ability to learn, generalize, and solve complex problems, and it is ideally suited for biological systems because of its inherent nonlinearity and its capacity to adapt its synaptic weights in response to changes in external environment. Our group's wavelet-based ANN design has been shown to be capable of classifying modes of brain activity and their transitions in an in vitro model of epilepsy from hippocampal extracellular recordings. Such a network was able to predict the onset of the ictal state within *minutes*. This delay provides a feasible time to facilitate appropriate modulatory actions to suppress the ictal state, avoid the 'locked-in' oscillatory low-complexity modes of a seizure, and increase system autonomy. This approach can lead to further success as the investigation is expanded to include both various signal features and the many new decision-making tools available to computer scientists (e.g., support vector machines).

Concluding Remarks

The brain is a complex, dynamic compilation of many interacting systems, which can adopt many oscillatory modes in space and time. To understand seizure modes, we need to consider the intrinsic properties of the multiple elements of the different systems, the network structure, connectivity, and the dynamics of interaction across spatiotemporal scales and with the external environment. This knowledge will provide us with the framework to develop therapeutic tools to measure, anticipate, and prevent (or eradicate) epileptic seizures.

See also: **Networks**: Recurrent Synaptic Actions and the Genesis of Epileptiform activity; **Non-Synaptic Mechanisms**: Non-Synaptic Mechanisms of Neuronal Synchronization: A Possible Role in Fast Oscillations; Role of Gap Junctions in Epileptic Synchronizations; **Oscillatory Activity**: Cellular Mechanisms of Network Oscillations Occurring Prior to, and during, Seizures; High-Frequency Weakly-Synchronized Activity at the Onset Focal Seizures; Neuronal Networks Generating Pathological High Frequency Oscillations.

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Cellular Mechanisms of Network Oscillations Occurring Prior to, and during, Seizures

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Introduction

Epileptiform discharges consist of the synchronized firing of principal neurons, usually in the form of bursts. The discharges, however, may repeat so as to form an oscillating activity pattern, at frequencies ranging from <1 Hz to over 20 Hz. In addition, neuronal network oscillations can occur prior to, during, and following the seizure proper, and there is a wide range of frequencies at which such oscillations can be recorded. Consideration of the oscillation mechanisms is important. An understanding of these mechanisms may allow prediction of an incipient seizure. And if there is a causal relationship between the events generating a pre-seizure oscillation and the events constituting the seizure proper, then that relationship might suggest a specific approach to therapy. Understanding the intricacies of this subject is not straightforward. The relevant oscillations involve a number of distinct mechanisms – synaptic and gap junctional – and the relation between different types of oscillation can be subtle. Furthermore, data are incomplete. We will present several examples illustrating some of the issues, and the interested reader can then delve further into the literature.

Background

In vitro models have been widely used to gain some understanding of the cellular mechanisms underlying epileptic activities in the intact brain. Until about 1999, most of the work with in vitro models employed experimental techniques that were designed to alter the balance between synaptic excitation and inhibition, in accord with what might be called the 'classical' idea of how epilepsy works. For example, synaptic inhibition might be reduced or suppressed completely with bath-applied GABA receptor blockers; recurrent excitation might be enhanced, by increasing NMDA receptor mediated currents in low $[Mg^{2+}]_o$ media (which also suppress synaptic inhibition); or axonal excitability might be enhanced and large depolarizing GABA currents produced with 4-aminopyridine. It is now apparent, however, that the generation of epileptiform activity involves more than a disturbed balance between synaptic excitation and inhibition. There are numerous phenomena associated with epileptiform discharge, including a variety of network oscillations, that can only be understood in terms of electrical coupling via gap junctions. The realization that gap junctions must play a critical role came largely from two experimental observations: first, that very fast oscillations (VFO) can occur without chemical synaptic transmission; and, second, that most experimental models of gamma and beta oscillations were dependent on gap junctions.

Methods

In our studies, we use both physiological experimentation and computer modeling. In vitro slice experiments have been carried out on hippocampus, entorhinal cortex, neocortex, and cerebellum, with tissue from rats, mice, or human patients (obtained, with proper consent, during neurosurgical procedures for medically intractable epilepsy). In parallel, we have generated detailed network models simulated on a supercomputer. In this latter work,