

Synchronization and desynchronization in epilepsy: controversies and hypotheses

Premysl Jiruska^{1,2,3}, Marco de Curtis⁴, John G. R. Jefferys³, Catherine A. Schevon⁵, Steven J. Schiff⁶ and Kaspar Schindler⁷

¹Department of Developmental Epileptology, Institute of Physiology, Academy of Sciences of Czech Republic, Prague, CZ-14220, Czech Republic

²Department of Neurology, Charles University, 2nd School of Medicine, University Hospital Motol Prague, CZ-15006, Czech Republic

³Neuronal Networks Group, School of Clinical and Experimental Medicine, University of Birmingham, Birmingham B15 2TT, UK

⁴Unit of Experimental Neurophysiology and Epileptology, Fondazione Istituto Neurologico Carlo Besta, Milan, Italy

⁵Department of Neurology, Columbia University, New York, NY, USA

⁶Center for Neural Engineering, Departments of Engineering Science and Mechanics, Neurosurgery, and Physics, The Pennsylvania State University, University Park, PA 16802 USA

⁷Department of Neurology, Bern University Hospital, Bern, Switzerland

Abstract Epilepsy has been historically seen as a functional brain disorder associated with excessive synchronization of large neuronal populations leading to a hypersynchronous state. Recent evidence showed that epileptiform phenomena, particularly seizures, result from complex interactions between neuronal networks characterized by heterogeneity of neuronal firing and dynamical evolution of synchronization. Desynchronization is often observed preceding seizures or during their early stages; in contrast, high levels of synchronization observed towards the end of seizures may facilitate termination. In this review we discuss cellular and network mechanisms responsible for such complex changes in synchronization. Recent work has identified cell-type-specific inhibitory and excitatory interactions, the dichotomy between neuronal firing and the non-local measurement of local field potentials distant to that firing, and the reflection of the neuronal dark matter problem in non-firing neurons active in seizures. These recent advances have challenged long-established views and are leading to a more rigorous and realistic understanding of the pathophysiology of epilepsy.

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Corresponding author P. Jiruska: Department of Developmental Epileptology, Institute of Physiology, Academy of Sciences of Czech Republic, Videnska 1083, Prague 4-Krc, Czech Republic, CZ-14220. Email: jiruskapremysl@gmail.com

Premysl Jiruska is former Epilepsy Research UK fellow. Currently, he works at Institute of Physiology, Academy of Sciences of Czech Republic. In his research he focuses on mechanisms of ictogenesis and functional organization of epileptic foci. **Marco de Curtis** is Head of Pre-clinical Neuroscience Laboratories at Fondazione Istituto Neurologico Carlo Besta and **John G. R. Jefferys** is Professor of Neuroscience at University of Birmingham. Both share common interest in function of neuronal networks in health and disease. **Catherine A. Schevon** is a clinical neurophysiologist and her major research interests are the cellular and network mechanisms of seizure generation and spread, and how these relate to clinical diagnostic studies. **Steven J. Schiff** is Director of the Penn State Center for Neural Engineering and focuses on mechanisms of control of epilepsy, migraines, and Parkinson's disease. **Kaspar Schindler** is a clinical neurologist and works at Bern University Hospital and his main research interest is ictal dynamics and synchronization in human epilepsy.



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Introduction

Coordinated neuronal activity and interactions between neurons and neuronal populations are the basic features of brain function. In the healthy brain, cognitive processes require precise integration of neural activity at specific spatiotemporal scales (Varela *et al.* 2001; Uhlhaas & Singer 2006). Such synchronization occurs at time scales ranging from milliseconds to hours, and over short and long intracerebral distances. Alteration of synchronization can be observed in several neurological and psychiatric disorders (Uhlhaas & Singer 2006).

One of the main disorders in which altered neuronal interactions play a crucial role is epilepsy. Historically, it has been seen as a disorder whose hallmark, spontaneous seizures, consists of high-amplitude, often rhythmic, activity. This has been interpreted as abnormally enhanced neuronal excitability and synchronization. Indeed, the term *hypersynchrony* was coined to describe this distinctive high-amplitude pathological behaviour (Penfield & Jasper 1954; Westbrook 1991; Margineanu 2010). In this review, we discuss the existing literature on seizure synchronization in light of our emerging knowledge of interactions between neuronal populations during seizures.

Synchronization and how it is measured

Synchrony implies that two systems, $x(t)$ and $y(t)$, will asymptotically converge so that their trajectories become identical, $x(t) = y(t)$ (Brown & Rulkov 1997), and that such dynamics are structurally stable (Pecora & Carroll 1990). In practice, one admits the interposition of a function, f , that transforms the values from one system to the other $x(t) = f(y(t))$ (Rulkov *et al.* 1995), and typically this function f is the identity – a straight line with slope equal to 1. For non-identical systems, they can come close, but never exactly synchronize, and neurons and their populations are never identical (for review see Schiff 2012). Synchrony is traditionally inferred from linear correlation (in the time domain) or coherence (in the frequency domain; Fig. 1). Since synchrony reflects a stable functional relationship, perturbing neural systems to probe stability can be very useful when pushing the threshold of subtle synchronization (Francis *et al.* 2003), although this is rarely done in testing whether measures of correlation in epilepsy reflect true synchronization.

Synchronization in epilepsy and seizures is conceptually complex and both decreases and increases in synchrony are integral features. As there are several valid methods of computation, and measurements can be taken on different types of signals and across different spatial scales, the results should be always interpreted with appropriate attention to context (Varela *et al.* 2001; Pikovsky *et al.* 2003). At the cellular level, synchronization

is typically inferred from a linear measure of correlated firing between neurons and can be examined between various neuronal subtypes, e.g. between principal neurons or distinct interneuronal subclasses (Salinas & Sejnowski 2001; Ziburkus *et al.* 2006). Interactions between neuronal populations are often examined indirectly using field potentials, which are presumed to reflect the synaptic currents arising locally from the collective activity of each of these neuronal populations. During seizures important exceptions to this assumption can occur due, for instance, to the distance between the neuronal somata and their synaptic terminals. Spatially, synchronization can be investigated on a local (micro) scale, between adjacent neurons or cortical columns, or across many centimeters of cortex. Synchronization can also be measured on different time scales. Neural firing and high-frequency oscillations are best examined on a millisecond time scale, while low-frequency synchronization requires data samples extending over tens of seconds, hours or even days (Welsh *et al.* 1995).

When interpreting synchronization data, it is essential to know if the synchronization is expressed as a single absolute value, or as a relative value demonstrating a rate of change. In the first case, synchronization (or desynchronization) can be determined by a measure exceeding (or falling below, respectively) a defined threshold. In the second case, synchronization is examined in terms of how it changes in time: an increasing trend in coupling can be interpreted as synchronization, while a decreasing trend can be described as desynchronization.

Rulkov *et al.* (1995) defined the term *generalized synchronization* for non-identical coupled non-linear systems. While linear correlation assesses a linear functional relationship, generalized synchronization detects a non-linear functional relationship between the dynamics of two systems. It was readily apparent that methods to detect non-linear synchronization could reveal relationships in neuronal systems to which linear methods were blind (Schiff *et al.* 1996). But how much functional importance lies within the hard-to-detect non-linear regime remains an open question (Netoff *et al.* 2006). There are a range of metrics of neuronal systems that are used to assess the degree of synchrony – time lags, phase relationships between oscillating signals, mutual information, mathematical continuity – and none has proved a clear winner for different systems and different types of coupling. The non-linear techniques tend to be more sensitive to noise than the linear ones, and noise appears to represent an important factor along with the degree of non-linearity in choosing a detection technique (Netoff *et al.* 2004). The role of non-linear techniques to detect synchronization in epilepsy remains an active and open area for investigation.

Finally, dynamical synchronization in noisy systems is a statistical phenomenon, and employing strict

statistical null hypotheses to establish the significance of synchronization should be applied to any of the above strategies. Even determining whether systems are *not* coupled, given noisy electrode data with shared frequencies, can be a difficult albeit necessary question to address (Netoff *et al.* 2006). Recent work invoking methods from random matrix theory (Fig. 2; Li *et al.* 2007; Muller *et al.* 2008) and random networks (Zhao *et al.* 2011) demonstrate that our conceptual understanding of statistical synchrony continues to advance, and will further change our concept of synchrony in epileptic seizures.

Cellular activity during seizures

Penfield and Jasper hypothesized that seizures are an extreme form of synchronous brain activity, characterized by decreased inhibition and enhanced excitation, leading to a transient condition of intense, hypersynchronous neuronal activity (Penfield & Jasper 1954). Electroencephalographic (EEG) recordings during such episodes reveal high-amplitude ictal (seizure) discharges in the Berger (1–25 Hz) frequency bands (Penfield & Jasper, 1954).

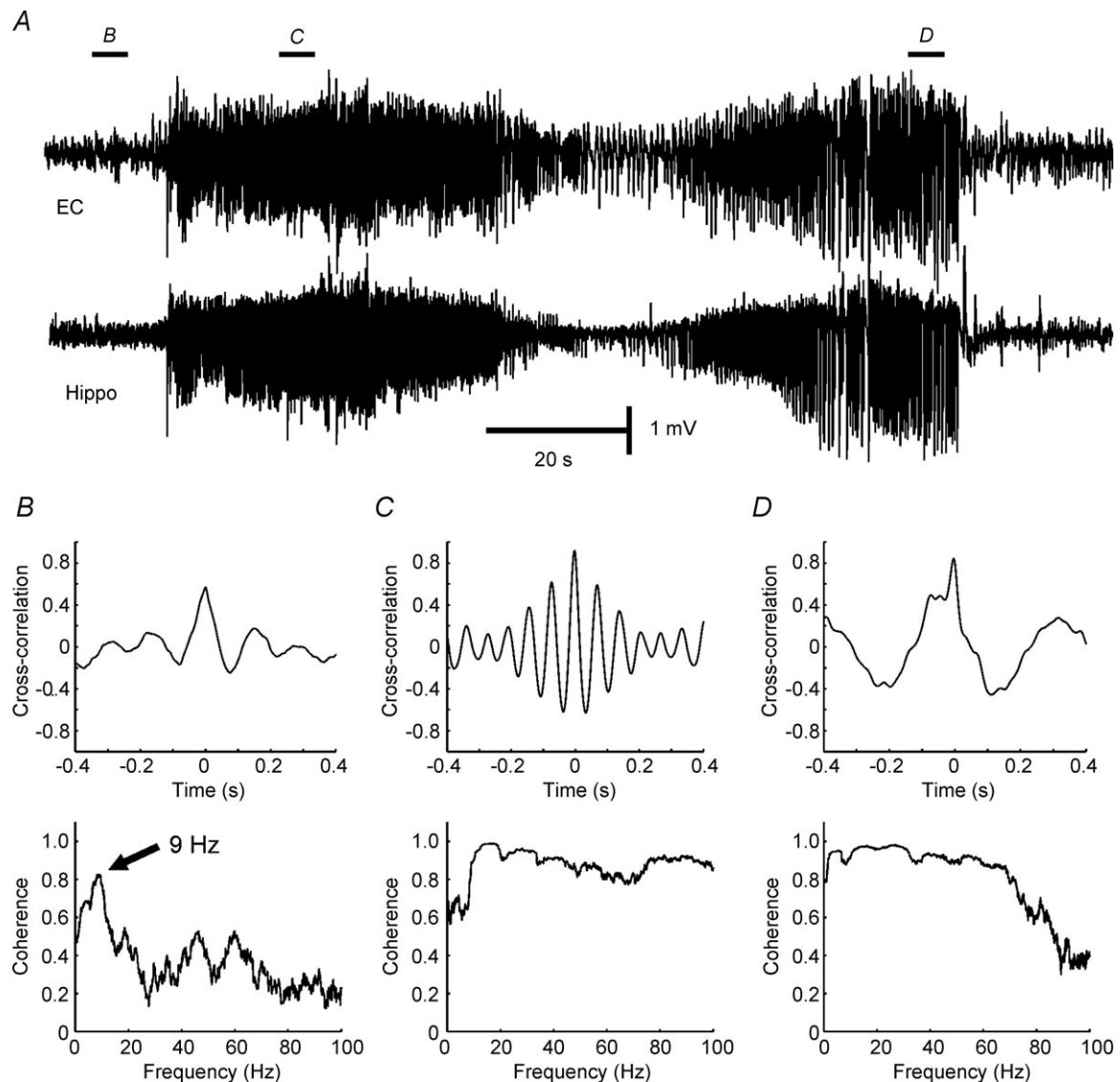


Figure 1. Application of linear correlation and coherence to measure synchronization

A, synchronization between the hippocampus (Hippo) and entorhinal cortex (EC) was examined before and during seizure in a tetanus toxin model of temporal lobe epilepsy (Jiruska *et al.* unpublished results). B, correlation of 0.5 was observed between signals from hippocampus and entorhinal cortex recorded before onset of the seizure. Coherence, often interpreted as a correlation at each frequency, shows an obvious peak in coherence at frequency 9 Hz. C, cross-correlation and coherence during early and final parts of seizure (D) (Jiruska P & Jefferys JGR; unpublished results).

It has long been assumed that sites where the EEG shows high amplitude ictal discharges are participating in the seizure; i.e. that high-amplitude waveforms and intense neural firing are spatially tightly coupled. This concept was first advanced in the 1930s (Bishop 1932), and was further supported by simultaneous intracellular and extracellular recordings from *in vitro* models (Jefferys & Haas 1982; Konnerth *et al.* 1984; Jensen & Yaari 1997).

However, coupling between neuronal firing and field potentials is more complex than this. In early studies, it became obvious that not all sampled neurons participated in the tonic and clonic ictal patterns. Matsumoto & Ajmone-Marsan (1964) reported in a cat model of focal epilepsy the observed increase in neuronal firing in only one third of recorded neurons, which they termed 'active', describing the remaining neurons as 'passive'. An

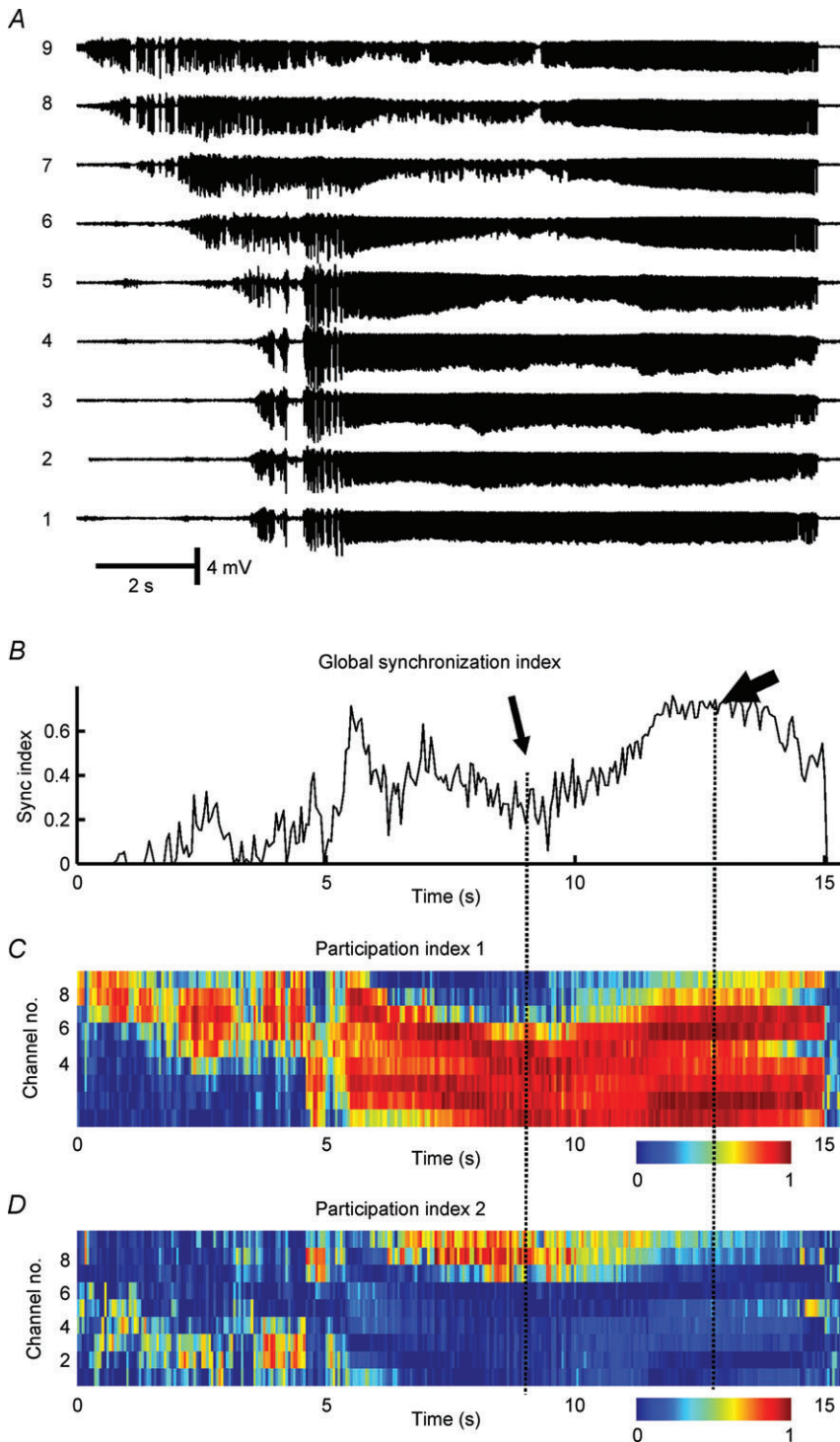


Figure 2. Synchronization profile of seizure activity in the low-calcium model in hippocampal slices *in vitro*

A, signals recorded from CA1 area with nine microelectrodes separated by $\sim 300 \mu\text{m}$. *B*, wavelet phase synchronization was used to calculate the temporal profile of a global synchronization index and shows a progressive increase in synchronization which reaches maximal values towards the end of the seizure. *C*, random matrix analysis was applied to determine the temporal profile of the first participation index. This index identifies the largest synchronization cluster and its components. Colours indicate how much each channel contributes to the cluster at each time. Cold colours indicate a low contribution while hot colours mean a high contribution. *D*, the second largest cluster of synchronization. The drop in global synchronization index (thin arrow) is due to the development of two independent clusters of synchrony. During the final part of the seizure, when synchronization reaches its maximal value, ictal activity is generated by a single large cluster of synchronous activity (thick arrow) to which nearly all channels contribute (Jiruska P & Jefferys JGR; unpublished results; random matrix analysis was described in detail in Li *et al.* 2007).

even higher proportion of passive neurons was found in recordings from humans, using depth electrodes with microwire bundles (Wyler *et al.* 1982; Wyler & Ward, 1986, Babb *et al.* 1987), or the 96-electrode Utah array (Truccolo *et al.* 2011). The latter study found that neuronal firing rates across the territory sampled by the array became much more heterogeneous at the start of seizures than in the preictal period, probably contributed to by passive neurons. Using similar recording techniques but a different site selection strategy, Schevon *et al.* (2012) showed that core areas within the seizure onset zone demonstrate the tonic/clonic ictal patterns predicted by the animal studies. Very highly synchronous firing was detected in the clonic phase, with action potential spike timing that was tightly locked to the phase of ictal discharges in the Berger bands (Fig. 3). Yet ahead of the ictal wavefront, firing appeared heterogeneous, similar to that reported by the Truccolo *et al.* study (Fig. 3).

Calcium imaging studies permitted detailed analysis of seizure propagation *in vitro*. Working with a zero-Mg²⁺ mouse model, Trevelyan *et al.* found that the tonic firing phase is compressed into a narrow ictal wavefront that spreads outward from the origin and progressively recruits additional sites to the seizure (Trevelyan *et al.* 2006, 2007). Behind the wavefront, neuronal burst firing becomes nearly perfectly aligned across sites, due to rapid multidirectional synaptic propagation within the recruited area (Trevelyan *et al.* 2007). Strong postsynaptic barrages emanating from recruited sites invade the non-recruited regions ahead of the wavefront, triggering a strong, rapid feedforward inhibitory response. This response, termed 'surround inhibition', has previously been documented in both *in vitro* and *in vivo* seizure models (Prince & Wilder 1967, Schwartz & Bonhoeffer 2001). Because of surround inhibition, pyramidal cell firing ahead of the ictal wavefront is restrained, and a mismatch arises between firing and the postsynaptic potentials that contribute to EEG.

Because of the rapid and extensive distribution of the powerful synaptic currents generated during a seizure, the size of the penumbra (region in which local field potentials

and neural firing are dissociated) can be arbitrarily large and even multilobar (Schevon *et al.* 2012). Spatial extension of penumbras that are large relative to the seizure focus can explain why many microelectrode studies in humans (Wyler *et al.* 1982; Babb *et al.* 1987; Truccolo *et al.* 2011; Bower *et al.* 2012) failed to record the expected neural signature of a seizure.

These studies highlight that EEG and local field potential synchronization (reflecting non-local sub-threshold inputs) may be dissociated from spike synchronization (reflecting local suprathreshold neuronal outputs). This context is important to keep in mind when investigating the spatial heterogeneity of seizure activity, and for interpreting observed synchronization of EEG signals between sites at differing spatial scales. This phenomenon is analogous to the neuronal dark matter problem, as eloquently discussed by Shoham *et al.* (2006). In seizures, however, we now have evidence that such dark matter regions, where neurons are receiving synaptic inputs but not necessarily producing output spikes, is a spatiotemporal process. Seizing neurons spend much of their time listening and the level of neuronal participation during seizures is regulated by the level of inhibitory tone and surround inhibition. Metrics of synchrony, depending upon whether they measure spikes or local field potentials, will bear complex spatiotemporal relationships to such seizure evolution, as we now discuss.

Synchronization and seizure onset

The large-scale spatial structure of seizure-generating sites is complex. Some evidence suggests that the seizure onset zone is functionally organized into small neuronal clusters. Microelectrode studies of *in vivo* and *in vitro* models of epilepsy and seizures have revealed synchronous firing clustered in tiny (<1 mm diameter) microdomains. Activity in these microdomains was present during epileptogenesis and ictogenesis, and manifested in extracellular recordings as high-frequency signals (Bragin *et al.* 2000; Jiruska *et al.* 2010a). In human surface and

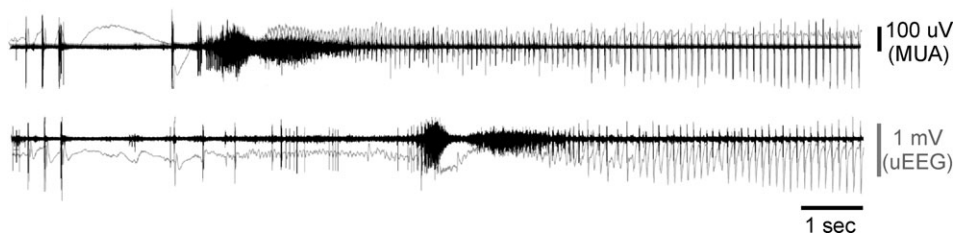


Figure 3. Early parts of a human seizure recording from two Utah array microelectrodes (3 mm apart)
The figure shows simultaneous multi-unit activity (MUA; 300 Hz–3 kHz, 500th order FIR bandpass filter, black traces) and 'micro' EEG (uEEG; <50 Hz low-pass filter, grey trace). The activity in the bottom channel joins the seizure several seconds after the top channel, and shows MUA during the penumbral, tonic and clonic phases of the seizure. Note that the two MUA recordings are highly synchronized during the clonic phase, but at no other time. The penumbral phase clearly demonstrates dissociation between MUA and EEG (Schevon CA, McKhann G, Goodman RR, Yuste R, Emerson RG, Trevelyan AJ unpublished results; for details see Schevon *et al.* 2012).

depth microelectrode recordings, highly localized EEG events termed *microseizures* have been detected, most prominently in the seizure onset zone (Schevon *et al.* 2008, 2010; Stead *et al.* 2010). While microseizures are good candidates for being characteristic markers of the seizure onset zone, their precise role in seizure genesis and propagation has yet to be established. For example, it is possible that instead of expanding outward from a single constrained cortical site, seizures develop from coalescing of spatially separate epileptic microdomains (Bragin *et al.* 2000; Bikson *et al.* 2003; Jiruska *et al.* 2010a). The coalescing of distributed cortical microdomains has been postulated to underlie the transition to higher-amplitude ictal discharges and the emergence of a macroseizure from microseizures (Jiruska *et al.* 2010a; Stead *et al.* 2010). Several mechanisms for this transition have been proposed, including: synchronous excitatory synaptic input, decreased volume of the extracellular space, increased extracellular potassium and loss of inhibitory restraint (Fox *et al.* 2007; Jiruska *et al.* 2010a; Trevelyan *et al.* 2007). Inhibition can promote synchronization through paradoxical mechanisms: by GABAergic depolarization resulting from imbalance of

chloride (reviewed by Pavlov *et al.* 2013, in this issue) or by synchronous recovery from inhibition of a larger population of principal neurons (Klaassen *et al.* 2006).

Desynchronization during seizures

The notion that seizures may arise from multiple, distributed cortical microdomains, and affect cortical regions outside the seizure focus, can explain a finding that at first glance appears to be counterintuitive: desynchronization at the initiation of seizures, followed by increasing large-scale synchronization as the seizure progresses. This desynchronization has been observed in both neural activity and local field potentials *in vitro* and *in vivo* (Netoff & Schiff 2002; Cymerblit-Sabba & Schiller 2012) and has also been well documented in human intracranial and extracranial recordings (Fig. 4; Le van Quyen *et al.* 2001; Chavez *et al.* 2003; Mormann *et al.* 2003; Wendling *et al.* 2003; Schiff *et al.* 2005).

The spatial scale of synchronization between neuronal populations must always be considered. For example, in the low-calcium *in vitro* model, neuronal clusters are associated with high-frequency local field potential signals

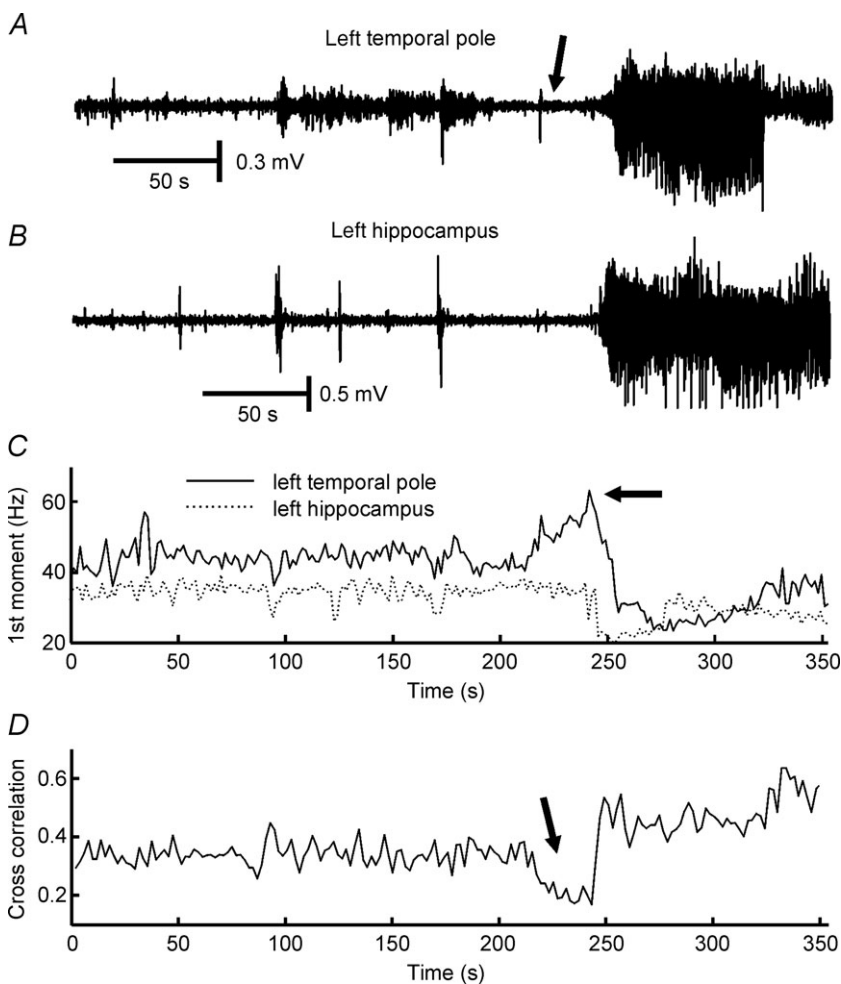


Figure 4. Desynchronization at the onset of a seizure recorded with intracranial electrodes in a patient with temporal lobe epilepsy

A, recording from the left temporal pole contact located at the seizure onset zone. Ictal onset is characterized by the presence of gamma and fast gamma activity (60–120 Hz; arrow). *B*, simultaneous recording from the left hippocampus. *C*, first spectral moment within the 2–200 Hz frequency band demonstrates a temporal dependence of the spectral content. The presence of a high-frequency onset is characterized by an increase in the first spectral moment (arrow). *D*, temporal evolution of cross-correlation between signals from temporal pole and hippocampus: the initial part of the seizure is characterized by decorrelation (desynchronization; arrow). Unpublished data (Jiruska P, Jefferys JGR, Marusic P) from case reported by Jiruska *et al.* 2008.

at the onset of seizures. As the seizure progresses, adjacent clusters ($\sim 150 \mu\text{m}$ diameter separation) demonstrate increased synchronization (Jiruska *et al.* 2010a). In contrast, synchronization between more widely separated clusters ($> 300 \mu\text{m}$) was low interictally and strengthened and expanded with the progression of each seizure (Jiruska *et al.* 2010a). The interpretation of early ictal desynchronization in human recordings depends strongly on electrode location relative to the recruited seizure territory. If synchrony is measured between two regions at a time when one is generating seizure activity while the second remains unaffected, then the measure will indicate desynchronization (Le van Quyen *et al.* 2001).

Desynchronization has been described during seizure onsets characterized by the presence of signals in the beta and gamma ranges (15–40 Hz) classified as low-amplitude fast activity (Wendling *et al.* 2003; de Curtis & Gnatkovsky 2009) recorded in seizures originating from both neocortex and entorhinal cortex in humans and in an *in vitro* guinea pig model of seizures (Wendling *et al.* 2003; Gnatkovsky *et al.* 2008; de Curtis & Gnatkovsky 2009). They found suppressed action potential firing at seizure initiation, while local (mainly somatic-projecting) interneurons demonstrate sustained and intensive discharges resulting in prominent and fast inhibitory postsynaptic potentials in principal cells (Wendling *et al.* 2002; de Curtis & Gnatkovsky 2009). The most plausible explanation for these findings is the ‘inhibitory veto’ in the area ahead of the ictal wavefront, described above (Trevelyan *et al.* 2006, 2007), i.e. the recordings were penumbral and the seizure focus was located elsewhere.

The concept of spike synchronization needs to be understood within a framework where synaptic conduction pathways have finite conduction velocity and each path is of a different length. Synchrony, the concept of a stable functional relationship where elements do similar things at the same time, needs to be broadened to that of polychronicity in neural networks, when time lags must be incorporated into the firing time of each neuron as population activity is considered (Izhikevich 2006). The epileptic brain possesses myriad of mechanisms that may synchronize the action potential firing on a millisecond time scale, involving both synaptic and non-synaptic mechanisms. There is a large amount of literature reviewing these mechanisms, which are beyond the scope of the present review (Dudek *et al.* 1986; Jefferys, 1995; Carlen *et al.* 2000; Jefferys *et al.* 2012a,b; Zorec *et al.* 2012).

Caution must, however, be observed in extrapolating these results to all types of seizures. Differences exist between experimental models and between epilepsy syndromes. Several distinct and region-specific seizure onset patterns are known and may have different cellular, network and synchronization mechanisms (Bragin *et al.* 2005, 2009; Bertram 2009; de Curtis & Gnatkovsky 2009). Human seizures, as reflected in the complex

and varied clinical semiological findings, coupled with the distinctive electrographic patterns of various seizure types, all bespeak to the likelihood of different dynamical mechanisms in these ictal events.

The impact of spatial scale on synchronization has been well demonstrated in the genesis of interictal pathological high-frequency oscillations (Jefferys *et al.* 2012). In normal brain exposed to pro-epileptic conditions, populations of bursting cells can synchronize their action potential firing (Foffani *et al.* 2007). This collective firing manifests in local field potentials as high-frequency oscillations, with spectral peaks corresponding to the inter-spike frequency of individual neurons firing at 200–300 Hz (Dzhala & Staley 2004). In contrast, in the chronic epileptic brain, interictal high-frequency oscillations with frequencies up to 800 Hz (fast ripples) have been recorded (Staba *et al.* 2002; Bragin *et al.* 2004; Jiruska *et al.* 2010b). It has been suggested that oscillations at frequencies far higher than the maximum firing rate of a pyramidal cell can be explained by an emergent network phenomenon generated by independent (out-of-phase) neuronal populations (Bikson *et al.* 2003; Foffani *et al.* 2007; Ibarz *et al.* 2010). This epileptic phenomenon demonstrates the importance of spatial scale and the nuances of synchronization measures. Although temporally uncorrelated, the out-of-phase firing may still be regarded as synchronized, or at least have a polychronous relationship, in terms of having a stable phase (Rosenblum *et al.* 1996) or temporal lags (Rosenblum *et al.* 1997). Demont-Guignard *et al.* (2012) examined in detail the role of pyramidal cell population sizes, the spatial distribution of hyperexcitable pyramidal cells and the level of synchronization between action potentials in forming interictal high-frequency oscillations. In their combined computational and *in vitro* study they showed that a weak level of synchronization between afferent action potentials can manifest as extracellular fast ripples, while the progressive increase in the synchronization between action potentials resulted in a shift from fast ripple oscillations to an interictal EEG spike discharge.

Synchronization and seizure termination

Synchronization reaches its peak during the final stages of the seizure (Fig. 2). A consistent observation across different *in vitro* and *in vivo* models and human seizures is that they terminate simultaneously over large areas of the brain (Topolnik *et al.* 2003; Timofeev & Steriade 2004; Schindler *et al.* 2007b; Truccolo *et al.* 2011). Therefore, it has been suggested that either enhancing or disrupting synchronization may promote seizure termination and may potentially be used as abortive therapy.

Fires stop when there is nothing left to ignite; epileptic seizures might stop when there is nothing left to excite. Thus, one possible way in which seizures terminate is

the creation of an extended area of hypoexcitable tissue, or a 'zone of relative refractoriness'. An extensive series of *in vivo* experiments used multi-site intracellular and extracellular neuronal recordings and local cortical field potential recordings to investigate initiation, development and cessation of spontaneous spike-wave seizures in cats under ketamine–xylazine anaesthesia (Timofeev & Steriade 2004). Early after seizure onset, the propagation time between field potentials recorded at multiple sites of neocortex progressively decreased while long-range synchrony increased and reached a maximum towards the end of the seizure (Topolnik *et al.* 2003). When all the affected neuronal pools are drawn into highly synchronous paroxysmal activity the seizure terminates. Increasing synchronization towards the end of seizures has not only been noted in animal models, but also in several studies of intracranially recorded seizures in humans (Schiff *et al.* 2005; Schindler *et al.* 2007a,b,c; Kramer *et al.* 2010). In the cat model of spontaneous spike-wave seizures, the synchronous activity towards the end of the seizures was in the form of ~ 1 Hz oscillations synchronized by EPSPs, but paced by intrinsic neuronal oscillations. Each cycle of the oscillation is initiated by hyperpolarization-activated depolarizing current (I_h) and then enhanced by Na^+ and Ca^{2+} currents. These depolarizing currents then activate potassium currents (I_K), which have a hyperpolarizing effect. The idea is that Ca^{2+} -dependent activation of the hyperpolarizing currents eventually overcomes the depolarizing effect of the I_h component of the oscillation. As this effect occurs simultaneously it results in seizure termination across the entire synchronized territory (Timofeev & Steriade, 2004).

Computer modelling of neuronal networks supports the counterintuitive theory that ongoing network activity can be both initiated and terminated by synchronous excitatory synaptic input. Membrane impedance shunting, due to massively increased membrane conductance, disrupts synaptic integration and results in decreased efficacy of excitatory transmission that can promote termination of synchronized neural bursting (Gutkin *et al.* 2001). Another candidate mechanism for seizure termination is inhibitory transmission. Inhibition mediated by interneurons, their mutual interconnectivity and their connectivity with principal cells may provide a mechanism by which synchronized excitation may cause potent synchronization of inhibition (Pavlov *et al.* 2013, in this issue). This phenomenon has been reported during interictal spikes (Lebovitz 1979; de Curtis *et al.* 2001) and ictal discharges (Lado & Moshe 2008), possibly contributing to their synchronous post-excitatory depression. Most recently, a framework to unify the dynamics of seizure termination has been offered characterizing termination as a discontinuous critical transition or bifurcation (Kramer *et al.* 2012).

Post-excitatory depression is also mediated by non-synaptic mechanisms, particularly by changes in the extracellular environment that may outlast the recurrent synaptic inhibition. In the piriform cortex of the isolated guinea pig brain preparation, rhythmic interictal spikes are followed by a prolonged extracellular alkaline shift that closely correlates with inter-spike periodicity (de Curtis *et al.* 1998). Such pH changes induced by synchronous discharging of neurons during an interictal spike may promote synchronous post-spike depression of principal cell activity via decoupling of gap junctions. A similar phenomenon may, in principle, occur during the periodic bursting typical of the clonic (late) seizure phase, and could eventually contribute to seizure termination via synchronization of inhibition.

These diverse mechanisms all share the involvement of progressively greater large-scale synchronization of neuronal activity as seizures progress, which may be considered as an emergent self-regulatory mechanism for seizure termination.

Epilepsy and hypersynchrony

The term 'hypersynchrony' appeared to originate from early studies on human electroencephalogram and epilepsy, and was initially used to describe the diffuse spatial distribution of a normal monomorphic 3–5 Hz rhythm occurring (hypnagogic hypersynchrony) in children during drowsiness (Kellaway & Fox 1952). The term hypersynchrony seemed to be first applied to seizures by Penfield & Jasper (1954), and referred to an underlying mechanism of excessive synchronization of activity in a large population of neurons manifesting as high-amplitude rhythmic epileptic discharges. It has since been extrapolated to indicate synchronization of both field potentials and neuronal activity at larger spatial scales. This review demonstrates that synchronization in epilepsy is very complex, and may appear different depending on the spatial scale, the definition of synchrony and the signals being measured (i.e. neuronal spikes *vs.* low-frequency field potentials). As this review demonstrates, seizures are far more complex, dynamical phenomena than they were postulated to be when hypersynchrony was first suggested to be an adequate organizing principle to account for seizures. Although the term hypersynchrony has embedded itself within the accepted professional knowledge base of epilepsy, the accumulating evidence now suggests that a simple metric of increased synchronization is inadequate to account for seizures.

Conclusions

Synchronization in epilepsy is a much more complex phenomenon than often presented in the literature. The study of ictal synchronization is a rapidly evolving

field, which benefited from introduction of more sophisticated statistical methods of synchronization characterization. Recent advances and observations on ictal synchronizations/desynchronizations have substantially contributed to our understanding of its pathophysiology, creating novel insights into the organization of epileptic networks and ictogenesis. Further, these observations may open new therapeutic methods for promoting seizure termination.

References

- Babb TL, Wilson CL & Isokawa-Akesson M (1987). Firing patterns of human limbic neurons during stereoencephalography (SEEG) and clinical temporal lobe seizures. *Electroencephalogr Clin Neurophysiol* **66**, 467–482.
- Bertram EH (2009). Temporal lobe epilepsy: where do the seizures really begin? *Epilepsy Behav* **14**, 32–37.
- Bikson M, Fox JE & Jefferys JGR (2003). Neuronal aggregate formation underlies spatiotemporal dynamics of nonsynaptic seizure initiation. *J Neurophysiol* **89**, 2330–2333.
- Bishop G (1932). Cyclic changes in excitability of the optic pathway of the rabbit. *American Journal of Physiology-Legacy* **103**, 213–224.
- Bower MR, Stead M, Meyer FB, Marsh WR & Worrell GA (2012). Spatiotemporal neuronal correlates of seizure generation in focal epilepsy. *Epilepsia* **53**, 807–816.
- Bragin A, Azizyan A, Almajano J & Engel J Jr (2009). The cause of the imbalance in the neuronal network leading to seizure activity can be predicted by the electrographic pattern of the seizure onset. *J Neurosci* **29**, 3660–3671.
- Bragin A, Wilson CL, Almajano J, Mody I & Engel J Jr (2004). High-frequency oscillations after status epilepticus: epileptogenesis and seizure genesis. *Epilepsia* **45**, 1017–1023.
- Bragin A, Wilson CL & Engel J Jr (2000). Chronic epileptogenesis requires development of a network of pathologically interconnected neuron clusters: a hypothesis. *Epilepsia* **41**, S144–S152.
- Bragin A, Wilson CL, Fields T, Fried I & Engel J Jr (2005). Analysis of seizure onset on the basis of wideband EEG recordings. *Epilepsia* **46**, 59–63.
- Brown R & Rulkov NF (1997). Designing a coupling that guarantees synchronization between identical chaotic systems. *Phys Rev Lett* **78**, 4189–4192.
- Carlen PL, Skinner F, Zhang L, Naus C, Kushnir M & Perez Velazquez JL (2000). The role of gap junctions in seizures. *Brain Res Brain Res Rev* **32**, 235–241.
- Chavez M, Le Van Quyen M, Navarro V, Baulac M & Martinerie J (2003). Spatio-temporal dynamics prior to neocortical seizures: amplitude versus phase couplings. *IEEE Trans Biomed Eng* **50**, 571–583.
- Cymerblit-Sabba A & Schiller Y (2012). Development of hypersynchrony in the cortical network during chemoconvulsant-induced epileptic seizures *in vivo*. *J Neurophysiol* **107**, 1718–1730.
- de Curtis M & Gnatkovsky V (2009). Reevaluating the mechanisms of focal ictogenesis: the role of low-voltage fast activity. *Epilepsia* **50**, 2514–2525.
- de Curtis M, Librizzi L & Biella G (2001). Discharge threshold is enhanced for several seconds after a single interictal spike in a model of focal epileptogenesis. *Eur J Neurosci* **14**, 174–178.
- de Curtis M, Manfredi A & Biella G (1998). Activity-dependent pH shifts and periodic recurrence of spontaneous interictal spikes in a model of focal epileptogenesis. *J Neurosci* **18**, 7543–7551.
- Demont-Guignard S, Benquet P, Gerber U, Biraben A, Martin B & Wendling F (2012). Distinct hyperexcitability mechanisms underlie fast ripples and epileptic spikes. *Ann Neurol* **71**, 342–352.
- Dudek FE, Snow RW & Taylor CP (1986). Role of electrical interactions in synchronization of epileptiform bursts. *Adv Neurol* **44**, 593–617.
- Dzhala VI & Staley KJ (2004). Mechanisms of fast ripples in the hippocampus. *J Neurosci* **24**, 8896–8906.
- Foffani G, Uzcatogui YG, Gal B & Menendez de la PL (2007). Reduced spike-timing reliability correlates with the emergence of fast ripples in the rat epileptic hippocampus. *Neuron* **55**, 930–941.
- Fox JE, Bikson M & Jefferys JGR (2007). The effect of neuronal population size on the development of epileptiform discharges in the low calcium model of epilepsy. *Neurosci Lett* **411**, 158–161.
- Francis, JT, Gluckman, BJ & Schiff, SJ (2003). Sensitivity of Neurons to Weak Electric Fields. *J Neurosci* **23**, 7255–7261.
- Gnatkovsky V, Librizzi L, Trombin F & de Curtis M (2008). Fast activity at seizure onset is mediated by inhibitory circuits in the entorhinal cortex *in vitro*. *Ann Neurol* **64**, 674–686.
- Gutkin BS, Laing CR, Colby CL, Chow CC & Ermentrout GB (2001). Turning on and off with excitation: the role of spike-timing asynchrony and synchrony in sustained neural activity. *J Comput Neurosci* **11**, 121–134.
- Ibarz JM, Foffani G, Cid E, Inostroza M & Menendez de la PL (2010). Emergent dynamics of fast ripples in the epileptic hippocampus. *J Neurosci* **30**, 16249–16261.
- Izhikevich EM (2006). Polychronization: computation with spikes. *Neural Comput* **18**, 245–282.
- Jefferys JGR (1995). Nonsynaptic modulation of neuronal activity in the brain: electric currents and extracellular ions. *Physiol Rev* **75**, 689–723.
- Jefferys JGR, de la Prida LM, Wendling F, Bragin A, Avoli M, Timofeev I & Lopes da Silva FH (2012). Mechanisms of physiological and epileptic HFO generation. *Prog Neurobiol* **98**, 250–264.
- Jefferys JGR & Haas HL (1982). Synchronized bursting of CA1 hippocampal pyramidal cells in the absence of synaptic transmission. *Nature* **300**, 448–450.
- Jefferys JGR, Jiruska P, de Curtis M & Avoli M (2012). Limbic network synchronization and temporal lobe epilepsy. In *Jasper's Basic Mechanisms of the Epilepsies*, eds. Noebels JL, Avoli M, Rogawski MA, Olsen RW & Delgado-Escueta AV, pp. 176–189. Oxford University Press.
- Jensen MS & Yaari Y (1997). Role of intrinsic burst firing, potassium accumulation, and electrical coupling in the elevated potassium model of hippocampal epilepsy. *J Neurophysiol* **77**, 1224–1233.

- Jiruska P, Csicsvari J, Powell AD, Fox JE, Chang WC, Vreugdenhil M, Li X, Palus M, Bujan AF, Dearden RW & Jefferys JGR (2010a). High-frequency network activity, global increase in neuronal activity, and synchrony expansion precede epileptic seizures *in vitro*. *J Neurosci* **30**, 5690–5701.
- Jiruska P, Finnerty GT, Powell AD, Lofti N, Cmejla R & Jefferys JG (2010b). Epileptic high-frequency network activity in a model of non-lesional temporal lobe epilepsy. *Brain* **133**, 1380–1390.
- Jiruska P, Tomasek M, Netuka D, Otahal J, Jefferys JG, Li X & Marusic P (2008). Clinical impact of a high-frequency seizure onset zone in a case of bitemporal epilepsy. *Epileptic Disord* **10**, 231–238.
- Kellaway P & Fox BJ (1952). Electroencephalographic diagnosis of cerebral pathology in infants during sleep. I. Rationale, technique, and the characteristics of normal sleep in infants. *J Pediatr* **41**, 262–287.
- Klaassen A, Glykys J, Maguire J, Labarca C, Mody I & Boulter J (2006). Seizures and enhanced cortical GABAergic inhibition in two mouse models of human autosomal dominant nocturnal frontal lobe epilepsy. *Proc Natl Acad Sci U S A* **103**, 19152–19157.
- Konnerth A, Heinemann U & Yaari Y (1984). Slow transmission of neural activity in hippocampal area CA1 in absence of active chemical synapses. *Nature* **307**, 69–71.
- Kramer MA, Eden UT, Kolaczyk ED, Zepeda R, Eskandar EN & Cash SS (2010). Coalescence and fragmentation of cortical networks during focal seizures. *J Neurosci* **30**, 10076–10085.
- Kramer MA, Truccolo W, Eden UT, Lepage KQ, Hochberg LR, Eskandar EN, Madsen JR, Lee JW, Maheshwari A, Halgren E, Chu CJ & Cash SS (2012). Human seizures self-terminate across spatial scales via a critical transition. *Proc Natl Acad Sci U S A*. in press.
- Lado FA & Moshe SL (2008). How do seizures stop? *Epilepsia* **49**, 1651–1664.
- Le Van Quyen M, Martinerie J, Navarro V, Baulac M & Varela FJ (2001). Characterizing neurodynamic changes before seizures. *J Clin Neurophysiol* **18**, 191–208.
- Lebovitz RM (1979). Autorhythmicity of spontaneous interictal spike discharge at hippocampal penicillin foci. *Brain Res* **172**, 35–55.
- Li X, Cui D, Jiruska P, Fox JE, Yao X & Jefferys JG (2007). Synchronization measurement of multiple neuronal populations. *J Neurophysiol* **98**, 3341–3348.
- Margineanu DG (2010). Epileptic hypersynchrony revisited. *Neuroreport* **21**, 963–967.
- Matsumoto H & Ajmone-Marsan C (1964). Cortical cellular phenomena in experimental epilepsy: ictal manifestations. *Exp Neurol* **9**, 305–326.
- Mormann F, Kreuz T, Andrzejak RG, David P, Lehnertz K & Elger CE (2003). Epileptic seizures are preceded by a decrease in synchronization. *Epilepsy Res* **53**, 173–185.
- Müller M, Baier G, Rummel C & Schindler K (2008). Estimating the strength of genuine and random correlations in non-stationary multivariate time series. *Europhys Lett* **84**, 10009.
- Netoff TI, Carroll TL, Pecora LM & Schiff SJ (2006). Detecting coupling in the presence of noise and nonlinearity, In *Handbook of Time Series Analysis*, eds. Schelter BI, Winterhalder M & Timmer J, pp. 265–282. Wiley-VCH Verlag GmbH & Co. KGaA
- Netoff TI, Pecora LM & Schiff SJ (2004). Analytical coupling detection in the presence of noise and nonlinearity. *Phys Rev E Stat Nonlin Soft Matter Phys* **69**, 017201.
- Netoff TI & Schiff SJ (2002). Decreased neuronal synchronization during experimental seizures. *J Neurosci* **22**, 7297–7307.
- Pavlov I, Kaila K, Kullmann DM & Miles R (2013). Cortical inhibition, pH and cell excitability in epilepsy: what are optimal targets for antiepileptic interventions? *J Physiol* **591**, 765–774.
- Pecora L & Carroll T (1990). Synchronization in chaotic systems. *Phys Rev Lett* **64**, 821–824.
- Penfield W & Jasper H (1954). *Epilepsy and the Functional Anatomy of the Human Brain*. Little Brown, Boston.
- Pikovsky A, Rosenblum M & Kurths J (2003). *Synchronization: A Universal Concept in Nonlinear Sciences*. Cambridge University Press.
- Prince DA & Wilder BJ (1967). Control mechanisms in cortical epileptogenic foci. “Surround” inhibition. *Arch Neurol* **16**, 194–202.
- Rosenblum MG, Pikovsky AS & Kurths J (1996). Phase synchronization of chaotic oscillators. *Phys Rev Lett* **76**, 1804–1807.
- Rosenblum MG, Pikovsky AS & Kurths J (1997). From phase to lag synchronization in coupled chaotic oscillators. *Phys Rev Lett* **78**, 4193–4196.
- Rulkov NF, Sushchik MM, Tsimring LS & Abarbanel HDI (1995). Generalized synchronization of chaos in directionally coupled chaotic systems. *Phys Rev E Stat Phys Plasmas Fluids Relat Interdiscip Topics* **51**, 980–994.
- Salinas E & Sejnowski TJ (2001). Correlated neuronal activity and the flow of neural information. *Nat Rev Neurosci* **2**, 539–550.
- Schevon CA, Goodman RR, McKhann G Jr & Emerson RG (2010). Propagation of epileptiform activity on a submillimeter scale. *J Clin Neurophysiol* **27**, 406–411.
- Schevon CA, Ng SK, Cappell J, Goodman RR, McKhann G Jr, Waziri A, Branner A, Sosunov A, Schroeder CE & Emerson RG (2008). Microphysiology of epileptiform activity in human neocortex. *J Clin Neurophysiol* **25**, 321–330.
- Schevon CA, Weiss SA, McKhann G Jr, Goodman RR, Yuste R, Emerson RG & Trevelyan AJ (2012). Evidence of an inhibitory restraint of seizure activity in humans. *Nat Commun* **3**, 1060.
- Schiff SJ (2012). *Neural Control Engineering: The Emerging Intersection between Control Theory and Neuroscience*. MIT Press, Cambridge.
- Schiff SJ, Sauer T, Kumar R & Weinstein SL (2005). Neuronal spatiotemporal pattern discrimination: the dynamical evolution of seizures. *NeuroImage* **28**, 1043–1055.
- Schiff SJ, So P, Chang T, Burke RE & Sauer T (1996). Detecting dynamical interdependence and generalized synchrony through mutual prediction in a neural ensemble. *Phys Rev E* **54**, 6708–6724.

- Schindler K, Elger CE & Lehnertz K (2007a). Changes of EEG synchronization during low-frequency electric stimulation of the seizure onset zone. *Epilepsy Res* **77**, 108–119.
- Schindler K, Elger CE & Lehnertz K (2007b). Increasing synchronization may promote seizure termination: evidence from status epilepticus. *Clin Neurophysiol* **118**, 1955–1968.
- Schindler K, Leung H, Elger CE & Lehnertz K (2007c). Assessing seizure dynamics by analysing the correlation structure of multichannel intracranial EEG. *Brain* **130**, 65–77.
- Schwartz TH & Bonhoeffer T (2001). In vivo optical mapping of epileptic foci and surround inhibition in ferret cerebral cortex. *Nat Med* **7**, 1063–1067.
- Shoham S, O'Connor DH & Segev R (2006). How silent is the brain: is there a “darkmatter” problem in neuroscience? *J Comp Physiol A Neuroethol Sens Neural Behav Physiol* **192**, 777–784.
- Staba RJ, Wilson CL, Bragin A, Fried I & Engel J Jr (2002). Quantitative analysis of high-frequency oscillations (80–500 Hz) recorded in human epileptic hippocampus and entorhinal cortex. *J Neurophysiol* **88**, 1743–1752.
- Stead M, Bower M, Brinkmann BH, Lee K, Marsh WR, Meyer FB, Litt B, Van GJ & Worrell GA (2010). Microseizures and the spatiotemporal scales of human partial epilepsy. *Brain* **133**, 2789–2797.
- Timofeev I & Steriade M (2004). Neocortical seizures: initiation, development and cessation. *Neuroscience* **123**, 299–336.
- Topolnik L, Steriade M & Timofeev I (2003). Partial cortical deafferentation promotes development of paroxysmal activity. *Cereb Cortex* **13**, 883–893.
- Trevelyan AJ, Sussillo D, Watson BO & Yuste R (2006). Modular propagation of epileptiform activity: evidence for an inhibitory veto in neocortex. *J Neurosci* **26**, 12447–12455.
- Trevelyan AJ, Sussillo D & Yuste R (2007). Feedforward inhibition contributes to the control of epileptiform propagation speed. *J Neurosci* **27**, 3383–3387.
- Truccolo W, Donoghue JA, Hochberg LR, Eskandar EN, Madsen JR, Anderson WS, Brown EN, Halgren E & Cash SS (2011). Single-neuron dynamics in human focal epilepsy. *Nat Neurosci* **14**, 635–641.
- Uhlhaas PJ & Singer W (2006). Neural synchrony in brain disorders: relevance for cognitive dysfunctions and pathophysiology. *Neuron* **52**, 155–168.
- Varela F, Lachaux JP, Rodriguez E & Martinerie J (2001). The brainweb: phase synchronization and large-scale integration. *Nat Rev Neurosci* **2**, 229–239.
- Welsh DK, Logothetis DE, Meister M & Reppert SM (1995). Individual neurons dissociated from rat suprachiasmatic nucleus express independently phased circadian firing rhythms. *Neuron* **14**, 697–706.
- Wendling F, Bartolomei F, Bellanger JJ, Bourien J & Chauvel P (2003). Epileptic fast intracerebral EEG activity: evidence for spatial decorrelation at seizure onset. *Brain* **126**, 1449–1459.
- Wendling F, Bartolomei F, Bellanger JJ & Chauvel P (2002). Epileptic fast activity can be explained by a model of impaired GABAergic dendritic inhibition. *Eur J Neurosci* **15**, 1499–1508.
- Westbrook GL (1991). Seizures and epilepsy. In *Principles of Neural Science*, eds Kandel ER, Jessel TM & Schwartz JH. McGraw-Hill, New York.
- Wyler AR, Ojemann GA & Ward AA Jr (1982). Neurons in human epileptic cortex: correlation between unit and EEG activity. *Ann Neurol* **11**, 301–308.
- Wyler AR & Ward AA Jr (1986). Neuronal firing patterns from epileptogenic foci of monkey and human. *Adv Neurol* **44**, 967–989.
- Zhao L, Beverlin B, Netoff T & Nykamp DQ (2011). Synchronization from second order network connectivity statistics. *Front Comput Neurosci* **5**, 28.
- Ziburkus J, Cressman JR, Barreto E & Schiff SJ (2006). Interneuron and pyramidal cell interplay during in vitro seizure-like events. *J Neurophysiol* **95**, 3948–3954.
- Zorec R, Araque A, Carmignoto G, Haydon PG, Verkhratsky A & Parpura V (2012). Astroglial excitability and gliotransmission: an appraisal of Ca²⁺ as a signalling route. *ASN Neuro* **4**, e00080.

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