Synchronization and desynchronization in epilepsy: controversies and hypotheses

Premysl Jiruska¹,²,³, 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 Neuropysiology 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.

(Received 17 July 2012; accepted after revision 21 November 2012; first published online 26 November 2012)

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.

The report was presented at the symposium Why do some brains seize? Molecular, cellular and network mechanisms, which took place at the Epilepsy Research UK Expert International Workshop, Oxford, UK on 15–16 March 2012.
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 intra-cerebral 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 & Yaaari 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*](image)

*A*, signals recorded from CA1 area with nine microelectrodes separated by ∼300 μm. *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-Mg\(^{2+}\) 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 subthreshold inputs) may be dissociated from spike synchronization (reflecting local suprathreshold neural 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
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](image-url)
at the onset of seizures. As the seizure progresses, adjacent clusters (~150 μm diameter separation) demonstrate increased synchronization (Jiruska et al. 2010a). In contrast, synchronization between more widely separated clusters (~300 μm) 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) inter-neurons 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 toward 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 depolarization-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 ‘hypsersynchrony’ 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 hyper-synchrony 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


© 2013 The Authors. *The Journal of Physiology* © 2013 The Physiological Society


**Acknowledgement**

This work was supported by a Czech Ministry of Health Grant IGA NT/11460-4, Epilepsy Research UK grant (P1102), MRC Grant G0802162, Swiss National Science Foundation (project no. SNF 320030_J22010), NIH grant 1R01EB014641-01 US-German Collaborative Research in Computational Neuroscience (CRCNS), and Medical Research Council grant (G0802162). The authors declare no conflict of interest.