Stereotypical activation of hippocampal ensembles during seizures

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This scientific commentary refers to 'Involvement of fast-spiking cells in ictal sequences during spontaneous seizures in rats with chronic temporal lobe epilepsy', by Neumann *et al.* (doi:10.1093/brain/awx179).

In addition to affecting a person's behaviour and risk of accidents, seizures are believed to result in various neurophysiological changes that disrupt nervous system integrity. Although anti-epileptic treatments exist, they are not always effective and in some epilepsy syndromes, such as temporal lobe epilepsy, a large proportion of patients are pharmacologically resistant. In order to develop seizure-preventing treatments, researchers have been trying to identify the neurological processes leading to seizures. In this issue of *Brain*, Neumann and co-workers use extracellular electrophysiological recordings to determine the temporal evolution of neuronal activity preceding and during spontaneous temporal lobe seizures in rats (Neumann *et al.*, 2017). They provide evidence that ictal discharges preferentially recruit specific cell ensembles firing in stereotypical sequences. In contrast to the classic view that seizures result from excessive runaway excitation, they show that the predominant cell types activated during ictal discharges are fast-spiking, putative inhibitory interneurons.

Two concepts have traditionally been put forward as fundamental to epilepsy pathology: excitation–inhibition balance and hypersynchrony. The concept of excitation–inhibition balance is based on the assumption that normal brain function depends on the perfect balance between

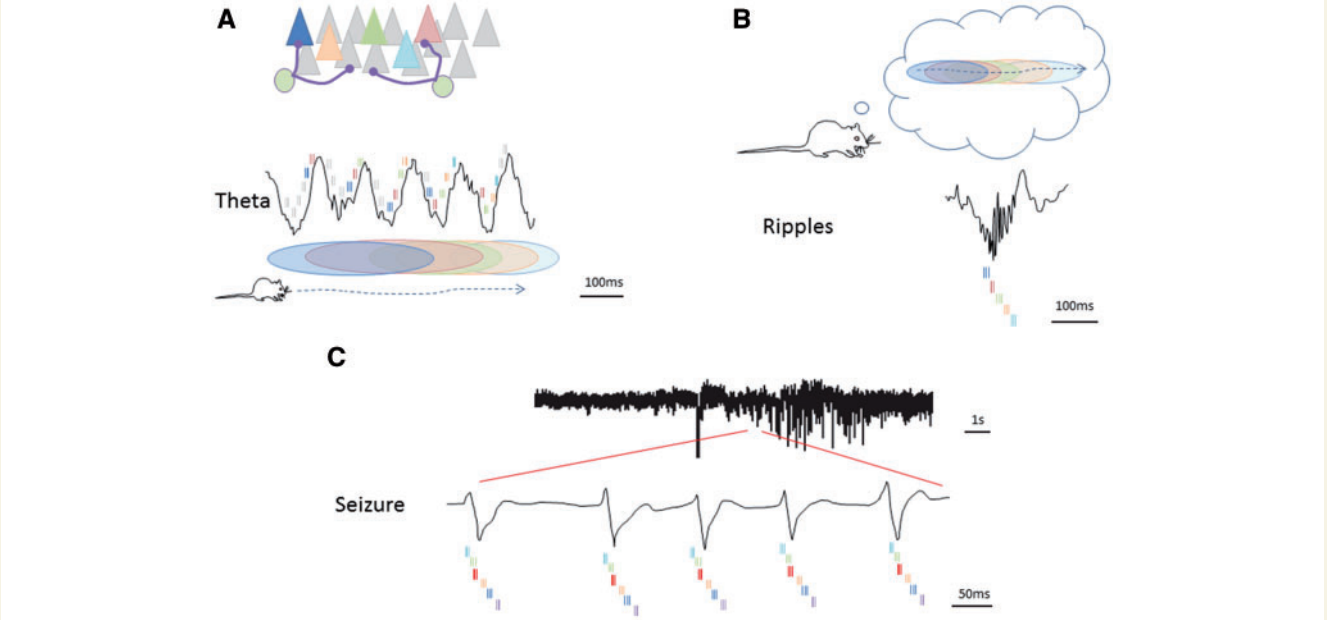

Figure 1 Temporal sequences in the hippocampus. (**A**) As a rat moves from left to right, it successively crosses the firing field of individual place cells (coloured ellipses). The firing activity of each neuron and its relationship to theta rhythm (black trace) is represented above. Action potentials of each cell are represented as vertical lines in the corresponding colour. The location of recorded place cells (coloured triangles) in the pyramidal cell layer is shown in the *upper* schematic (green disks correspond to interneurons). In each theta cycle, place cells fire in a sequence that recapitulates the ongoing trajectory of the rat. (**B**) When rats are immobile or at rest, the hippocampal local field potential is characterized by sharp-wave ripples. During these events, place cells also fire in sequences that represent past or future trajectories of the rat. (**C**) Pathological sequences of pyramidal cell firing are repeatedly activated during each ictal discharge (Neumann *et al.*, 2017). The sequences are similar from one ictal discharge to another and are also repeated from seizure to seizure. Scales, traces and drawings are not real data but are shown for illustration purposes.

excitatory and inhibitory inputs to principal cells. Too much excitation or too little inhibition causes hyperexcitability of the network, in turn leading to seizures. While the excitation–inhibition balance concept was appropriate to describe static, continuous network states, it fails to address the fine-tuned temporal structure of spiking activity that occurs at various timescales (Fig. 1). Indeed accumulating evidence suggests that the processes leading to and driving seizures are more complex than previously proposed (see Jiruska *et al.*, 2013 for a comprehensive review).

Observing large amplitude, widespread oscillatory discharge in the EEG of patients during seizures, early epileptologists proposed that seizures were the consequence of hypersynchronous activation of large groups of neurons. However, recordings in humans reveal that seizures are immediately preceded by a decrease rather than an increase in synchronization of intracranial EEGs (Mormann *et al.*, 2003). Furthermore, Truccolo *et al.* (2014) showed that the apparent hypersynchrony observed during ictal spikes is a consequence of a global increase in firing rates of all neurons rather than of a local synchronization process between pairs of neurons. Finally, it has been shown that the firing rates of the majority of cells do not change significantly during seizures, even for neurons recorded in the seizure onset zone (Bower *et al.*, 2012).

Similarly, the idea that seizures and epileptiform activity result from a loss of inhibition has been challenged by several discoveries. *In vitro* experiments suggest that interneuron hyperactivity, i.e. excessive inhibition rather than lack thereof, precedes seizure onset (e.g. Ziburkus, 2006). This has been confirmed *in vivo*, in temporal lobe epilepsy models. A series of studies by the groups of Karen Moxon and Paul Buckmaster show that a subgroup of hippocampal interneurons increases its firing rate in the period immediately preceding seizure onset (e.g. Karunakaran *et al.*, 2016).

Given the accumulating evidence, canonical concepts of dysregulation of excitation–inhibition balance or hypersynchronous networks are progressively being replaced by a more complex view where the precise timing of activity between neuronal subtypes is critical. In line with this view, the report from Neumann and colleagues offers exciting new data that nicely complete the seizure generation puzzle.

Neumann and colleagues performed extracellular local field potential (LFP) and single unit recordings in the dorsal CA1 region of the hippocampus in chronically epileptic rats. Like several groups before them, they used the characteristic extracellular waveform shapes to identify putative interneurons and pyramidal cells.

Glossary

Cell assembly: An ensemble of neurons that become activated to form a functional unit. The functional unit can represent a perception, an action or a more abstract concept such as an autobiographical episode. In 1949, in *The Organization of Behavior: A Neuropsychological Theory* Donald O. Hebb postulated that a memory trace was formed during the repetitive activation of neurons in a given sequence (the assembly). The resulting strengthening of synapses amongst members of the assembly would constitute the memory trace. Here, the functional unit is defined by a specific spatiotemporal structure of firing.

Interictal spikes: Abnormal neuronal discharges typically seen on the EEG between seizures. These are high amplitude, brief (<200 ms) short-lasting events that usually occur in or near the seizure focus. Their presence is an important factor in the diagnosis of epilepsy.

Seizures: The International League Against Epilepsy (http://www.ilae.org) provides the following definition: 'An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain'. As of today, the exact mechanisms leading to seizures are not completely understood.

What distinguishes this study from others is the ability to record large number of neurons at the same time, also during seizures. Two major findings can be extracted from this study. The first is that ictal discharges are dominated by the activity of fast-spiking, putative inhibitory neurons rather than pyramidal cells. Importantly, these interneurons displayed unusually strong coupling to oscillations in the LFP, even before seizures. While this observation is reminiscent of previous reports, the exciting part of the current study is that neuronal firing during ictal discharges is organized in stereotypical sequences. During ictal spikes, neurons from the same assembly are activated in a specific temporal order that is not only similar from one ictal spike to another but also between seizures. This strongly suggests that seizures recruit a restricted number of neurons within the network and that this recruitment follows a stereotypical order, reminiscent of Hebbian assemblies.

In healthy animals, hippocampal networks are known to organize neuronal activity in temporal sequences. During exploration of the environment, hippocampal neurons behave as 'place cells' in the sense that they are only active when the rat enters a specific region of the environment called the cell's place field. As the animal moves through the environment, it crosses the place fields of several cells, thereby organizing place cell firing into a sequence corresponding to the ongoing spatial trajectory. Intriguingly, depending on the arousal state of the animal, place cell sequences similar to those experienced during exploration are also observed at different timescales (Fig. 1). During exploration, hippocampal network activity is modulated by theta oscillations (6–12 Hz). In each theta cycle, lasting ~90–160 ms, pyramidal cells fire in sequences that correspond to a compressed version of the ongoing trajectory (Fig. 1A). During immobility or slow wave sleep, sequences of pyramidal cell firing occur during high frequency, 100–250 Hz oscillations (sharp-wave ripple complexes) and recapitulate past or future/planned trajectories. Here, Neumann and colleagues report a new type of sequence, this time entrained by ictal discharges. Therefore, even in a pathological state it appears that sequence organization is the default mode for hippocampal function. While in non-pathological states hippocampal sequences play a role in episodic memory and behavioural planning, it is likely that epileptic sequences are meaningless.

How are normal and pathological sequences generated? Several studies (reviewed in Buzsáki, 2010) suggest that inhibitory interneurons play a critical role in the formation, segregation and temporal organization of cell assemblies. Interneuron loss and/or alteration of GABAergic transmission have been documented in epilepsy. Despite this loss, an increase in interneuron drive is observed both before and during seizures, supporting the idea that in epilepsy, the remaining inhibitory networks still strongly drive network function. Indeed, several studies show that the trajectory and propagation speed of seizures (Trevelyan *et al.*, 2007) and interictal spikes (Sabolek *et al.*, 2012) are restrained by GABAergic inhibition. Alteration of GABAergic function in a network may therefore give rise to a preferred, rigid spatiotemporal pattern of neuronal firing (an attractor state) characteristic of seizures.

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