

Glossary

Labelled lines theories: Physiological theories according to which a sensation is generated by the activation of a specific coding and transmitting system. Defenders of a labelled lines theory of pain propose that pain is a specific modality with its own receptors and fibres.

Pattern theories: Physiological theories according to which the different sensations result from distinct spatiotemporal patterns of activation of nerve impulses, rather than from the activation of distinct and specific afferents. Defenders of a pattern theory propose that pain results from the intense activation of receptors and pathways that are unspecific to pain.

hypothesized to shape motor planning (Rizzolatti *et al.*, 1997), the perceptual disabilities of patients with CRPS may be relevant to the disturbances in using the pathological limb that are particularly characteristic of these patients. Such studies offer a new theoretical framework for the investigation of cognitive rehabilitation as a potentially effective technique to treat clinical pain. To summarize, the study of Bultitude *et al.* illustrates the current dynamics of pain research, reflecting recent contributions from the theories and methods of cognitive neuropsychology.

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Stereotypical activation of hippocampal ensembles during seizures

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

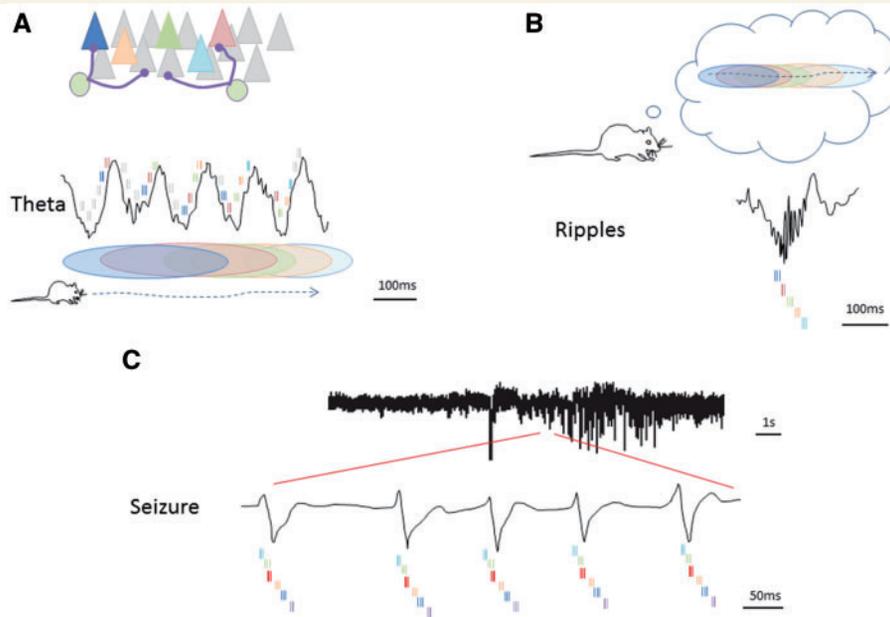


Figure 1 Temporal sequences in the hippocampus. (A) As a rat moves from left to right, it successively crosses the firing field of individual place cells (coloured ellipses). The firing activity of each neuron and its relationship to theta rhythm (black trace) is represented above. Action potentials 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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Uncovering hidden integrative cerebral function in the intensive care unit

This scientific commentary refers to ‘Early detection of consciousness in patients with acute severe traumatic brain injury’, by Edlow *et al.* (doi:10.1093/brain/awx176).

Over the past two decades a wide range of hidden integrative cerebral function has been identified in some behaviourally unresponsive or minimally responsive patients (see Laureys and Schiff, 2012 for a review). Modern neuroimaging tools and sophisticated electrophysiological methods have provided an increasingly clear picture of brain function following severe injuries. To date, however, the investigation of graded cerebral function has largely focused on chronic recovery long after the period of acute injury (with exceptions, e.g. Claassen *et al.*, 2016). In this context, a study by Edlow *et al.* in this issue of *Brain* breaks considerable new ground (Edlow *et al.*, 2017). The investigators provide the first prospective study combining neuroimaging and electrophysiological assessment of the level of consciousness in severely brain-injured patients in the first 2 weeks of an intensive care period.

Edlow and colleagues enrolled 16 patients with acute severe traumatic brain injuries and carried out a series of structured experimental paradigms using functional MRI and quantitative EEG combined with sophisticated multivariate pattern recognition algorithms. Their work was based on two *a priori* hypotheses: (i) that direct brain measurements with functional MRI or quantitative EEG would reveal

evidence of language comprehension or cortical processing in patients without behavioural evidence of language function; and (ii) if present, such evidence would provide predictive information about 6-month outcomes. The major success of this study is the identification of cognitive motor dissociation (CMD) in half of the subjects without behavioural evidence of language function. CMD has been proposed as a term to categorize patients with no, or only very limited, behavioural evidence of awareness who nonetheless demonstrate unequivocal empirical evidence of command-following via functional MRI, quantitative EEG or similar indirect measurements of brain response to spoken language (Schiff, 2015) (Fig. 1). In the present study, four of eight patients without behavioural evidence of language function were identified as CMD patients by the functional MRI method; this observation, though made in a small sample, suggests that such dissociations are likely to be common in the ICU.

The investigators also examined evidence for higher-order cortical processing of language and musical stimuli at the acute stage using functional MRI and quantitative EEG. They introduce a new term, higher-order cortex motor dissociation (HMD), to label the presence of contingent brain responses to these stimuli in patients without evidence of language function. Patients with statistical evidence of a contingent functional MRI or quantitative EEG response to either language or musical stimuli when compared to control or

rest periods were identified as having HMD. Earlier studies have assessed similar isolated evidence of higher-order responses from association cortices (e.g. Menon *et al.*, 1998 demonstrated isolated and selective processing within visual association cortex) but, as Edlow *et al.* note, whether such responses are evidence of awareness is more ambiguous. Although patient outcomes were not statistically linked to functional MRI or quantitative EEG responses across the group of subjects, the use of HMD and CMD designations to augment the best behavioural assessment of highest level of consciousness improved sensitivity to detect recovery beyond post-traumatic confusion at 6 months after injury.

As shown in Fig. 1, CMD represents a sharp recategorization of patients from measurements available using quantitative behavioural assessment tools (Schiff, 2015). The Edlow *et al.* study validates the direct translation to the ICU of the functional MRI strategies employed in earlier work with patients in the later stages of recovery. Collectively, both the HMD and CMD findings in the study highlight an often neglected third dimension of recovery that is critical in thinking carefully about the severely injured brain—the functional integrity of the cerebrum or corticothalamic system *per se* (Fig. 1). Several studies have now provided evidence that CMD is associated with broad preservation of the dynamic structure of wake and sleep cerebral network physiology