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IN MEMORIAM

In Memoriam: Richard Miles: Neuroscience network has lost a key synapse

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On 12 January 2024, we received the sad news that our friend, colleague, and former editor of *The Journal of Physiology*, Richard Miles, had passed away in Guadeloupe. For many neuroscientists, particularly those working in the hippocampus since the 1990s, his name will forever be remembered.

Richard Miles (Fig. 1) earned a degree in Physics from University College London in 1972, followed by an MSc and a PhD in Physiology from the University of Bristol in 1981. His thesis, supervised by Michael J. Purves, investigated the fundamental basis of chemosensitivity. Afterwards, he worked as a research associate at the University of Texas Medical Branch in Galveston and later became an assistant professor at Columbia University in New York. During this time, Richard collaborated with Robert K.S. Wong on various aspects of hippocampal synaptic communication, including its connectivity patterns and potential contribution to epileptiform activity. Additionally, he developed a long-lasting collaboration with Roger Traub, combining experimental and modelling approaches to test new ideas. These formative years greatly influenced Richard's strategies and ambitions for the future. In Richard's own words:

> *This combination of modelling and dual recordings has allowed the generation of simple neuronal network activity to be dissected. The key has been the synthetic nature of the work. A knowledge of single synapses has predicted properties of synaptic circuits which in turn, with simulations, has led to an understanding of the generation of synchrony.*
>
> *(Titres et travaux scientifiques, 1990)*

In July 1989, Richard joined the Department of Biotechnologies at the Pasteur Institute in Paris as a CNRS Research Director. A room of barely 30 m^2, wedged between the laboratories of Henri Korn and Jean-Pierre Changeux, where the footsteps of Eric Kandel, Bert Sakmann and others regularly echoed; in this cramped space, a historic double intracellular

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recording rig with manual micromanipulators, a pipette puller and a microelectrode beveller covered with KCl and alumina concretions were later joined by a patch-clamp rig mounted on a rusty steel plate resting on four tennis balls. In this minimalist environment, many seminal discoveries about the organization and physiology of hippocampal circuits were made. The properties of unitary synapses in the hippocampus were carefully studied using recordings from pairs of synaptically connected neurons. Concepts inherited from quantal analysis at the neuromuscular junction were confronted with the morphological complexity of hippocampal neurons in work combining electrophysiological recordings and anatomical reconstruction, in collaboration with the laboratory of Tamás Freund in Budapest, Hungary. Simple but cleverly designed experimental paradigms were used to explore the functional and anatomical diversity of hippocampal interneurons. While unravelling the properties of synapses and hippocampal circuits, Richard remained fascinated by their synchronization properties. A paroxysmal form of synchronization is obviously epileptic activity. Richard therefore gradually developed close links with local clinical teams, in particular with the neurologist Michel Baulac and the neurosurgeon Stéphane Clémenceau at the Pitié-Salpêtrière Hospital. Inspired by the pioneering work of Massimo Avoli and René Pumain, he began in the late 1990s to record *in vitro* human epileptic brain tissue from postoperative resections for therapeutic purposes. This work added a new dimension to Richard's research and paved the way for a series of studies on the pathophysiology of epilepsy.

Figure 1.
Richard Miles (credit: Stephanie Traub).

Meanwhile, the closure of Henri Korn's laboratory at the Pasteur Institute in 2000 led Richard to move his team first to the Saints-Pères Faculty of Medicine in Saint-Germain-des-Prés and then, in 2003, to the Pitié-Salpêtrière Hospital. There, collaboration with the Epileptology Unit and epilepsy geneticists led to the creation of a new laboratory called 'Cortex and Epilepsy', which combined expertise in clinical and basic research approaches. Richard led this translational team at the Faculty of Medicine of the Pierre & Marie Curie University (now Sorbonne University), and integrated the newly created *Institut du Cerveau et de la Moelle Épinière* (ICM) in 2010. This was an active period – with more than 60 articles published since 2003 – in which Richard's research built on previous work on network activity and synaptic signalling in the hippocampus, but also explored new projects on brain lipids, microglia and inflammation in epilepsy. During this time, Richard did not travel much, arriving in the lab late but leaving in the middle of the night almost every day. He organized his lab a bit like he organized his research: a niche in which he felt comfortable. He received an advanced ERC grant for his last years before his retirement in Guadeloupe in 2019. His last years were peaceful, surrounded by a flourishing nature. His last paper published in 2023 was a review asking how to reconcile human material and animal models to better understand and treat epilepsy (Milior et al., 2023).

Richard's perspective was influential in early studies of microcircuit synchronization and in establishing critical concepts for understanding the emergence of population activity. Together with Roger Traub and Robert Wong, Richard combined theory, simulation and experiments to transform our view. He was one of the first to record simultaneously from two neurons using the hippocampal slice preparation, from which he derived strong intuitions about how large-scale neural circuits operate. At the synaptic level, he characterized monosynaptic connections between pairs of cells and showed how a presynaptic CA3 pyramidal cell can directly activate GABAergic inhibitory cells (Fig. 2*A*). At the circuit level, he showed how such a single pyramidal cell can also initiate di-synaptic inhibitory potentials in another pyramidal cell intermediate interneurons as a basis for controlling sequential firing (Fig. 2*B*). Elaborating on these observations, he reasoned that when inhibition is compromised, polysynaptic excitation can be released in the microcircuit, leading to the emergence of firing synchronization and epileptiform discharges (Fig. 2*C*).

Richard was shy and brilliant and would probably never want us to talk about his legacy. But the foundations he laid have strongly influenced the work of many and shaped our current view of hippocampal function and dysfunction. Below, some of his closest collaborators and friends have summarized how his work has influenced their own perspectives. We hope this testimony can serve as a humble tribute to Richard's contributions, honouring his quiet brilliance and the lasting imprint he has left on our understanding of the hippocampus.

Richard: An honest critic, by György Buzsáki

Attributes of scientists, like many interesting things in the brain, are distributed on a wide, typically lognormal, scale. Richard Miles was surely at one of the tails of this distribution. A shy person with a sharp mind, he expressed his disagreement with his characteristic Miles-style of polite quarrelling. He first smiled, then his eyes deviated to some distant focal point and he uttered a few seemingly irrelevant words. At this point, I began to worry about what would come next, based on the many similar interactions we had with Richard. If I or someone else interrupted, he just gave up and ended the discourse. On the rare occasions, when this did not happen, Richard came up with a well-composed killer punchline, followed by an almost apologetic comment. He was a master of embedding his serious disagreement into English expressions that made him appear like an innocent bystander even though deep inside he was a ferocious attacker (i.e. when the Emperor's missing clothes had to be revealed).

I first met Richard at an SFN meeting in New Orleans. He was a member of the successful trio of Wong–Traub–Miles, the most unusual combination of three humans, each with idiosyncratic characters, working together at Columbia University. Opposites attract each other, as the wisdom says, but these excellent scientists were more orthogonal to each other in their thinking, lifestyle and social traits than opposites. Yet, their love of science, curiosity and complementarity held them together. While walking from the convention centre back to their hotel, the trio was interrogating me about the poster I had presented. I learned more during this 15 minute walk than during the entire meeting.

My path crossed with Richard again soon; this time I was the facilitator. The key player was Nobuaki Tamamaki, who visited me in San Diego and told me about a new funding source, HFSP, whose noble mandate was to support international collaborations. I immediately called Richard in Paris and Tamás Freund in Budapest and agreed to submit a grant on hippocampal interneurons. Since HFSP was not well-advertised initially, we had good luck obtaining and getting support for 6 years (with renewal). In our effort, we were joined by Helmut Haas and Roger Traub. I think all partners of our group agree that those years were perhaps the most rewarding epoch of our scientific lives. We visited each other's labs, exchanged students, postdocs, mailed (brain-transplanted) live rats and brain tissue across

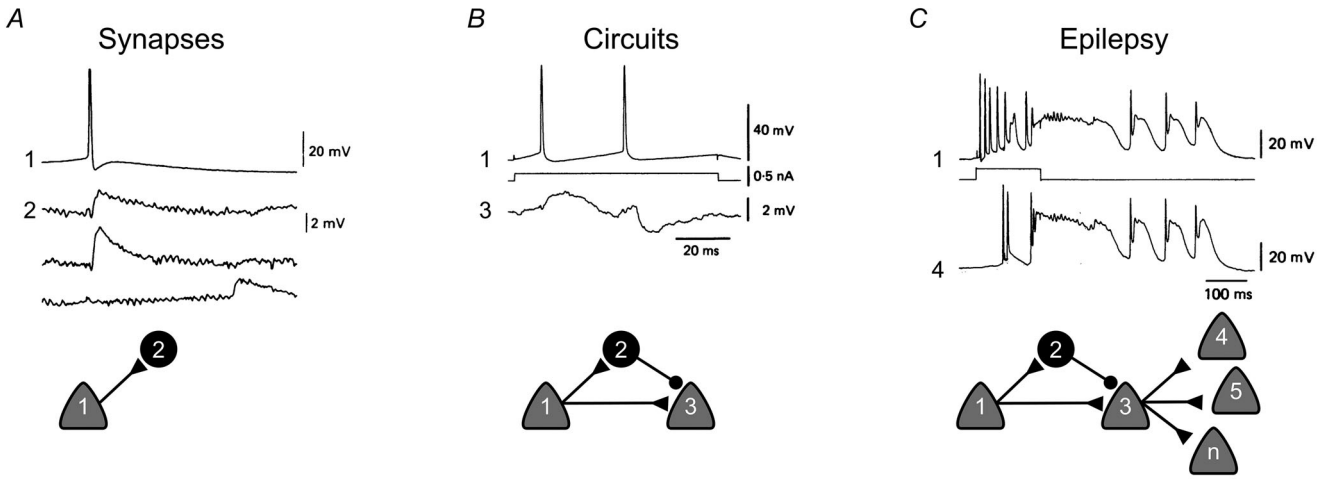

Figure 2. Main concepts derived from dual intracellular recordings in hippocampal slices
A, monosynaptic connections from a CA3 pyramidal cell and a GABAergic interneuron. Modified from Miles R. Synaptic excitation of inhibitory cells by single CA3 hippocampal pyramidal cells of the guinea pig *in vitro*. *The Journal of Physiology* 428:61–77 (1990). *B*, hippocampal microcircuit inferred from dual recordings from two monosynaptically connected pyramidal cells. Modified from R Miles, RK Wong. Excitatory synaptic interactions between CA3 neurones in the guinea-pig hippocampus. *The Journal of Physiology* 373 (1), 397—418 (1986). *C*, suppression of inhibition by picrotoxin caused pyramidal cell firing in the microcircuit to propagate and synchronize, resulting in epileptiform discharges. Modified from R Miles, RK Wong Inhibitory control of local excitatory circuits in the guinea pig hippocampus. *The Journal of Physiology* 388 (1), 611—629 (1987).

continents, and wrote our progress reports at our annual meetings (typically on Grand Cayman Island in the Caribbean – n.b., I bet these visits primed Richard's mind to eventually settle on Guadeloupe). Our last meeting was on the island of Corsica (organized by Y. Ben-Ari), where Richard, Tamás and I outlined the main ideas about a hippocampal interneuron review. We felt that the time was right for such a piece. Eventually, Richard bailed out due to our time pressure but many of his thoughts were incorporated in our published review (Freund & Buzsaki, 1996).

Richard Miles' contributions are felt in many areas of neuroscience, from epilepsy to inhibition. Although his most celebrated work is the demonstration of the distinction between dendritic and somatic inhibition (Miles et al., 1996), I think his most important insight was a question that he formulated first: 'How many subtypes of inhibitory cells in the hippocampus?' (Parra et al., 1998). This work was conceived a long time before molecular classification of neuron types became possible and the paper's modest conclusion that 'expression of different combinations of transmitter receptors by different groups of hippocampal interneurons may permit a very subtle matching of inhibitory cell activity to the computational needs of different behavioral states, resulting in a high flexibility of response' has remained as important today as it was then. Our beloved Richard has made his legacy in neuroscience. Richard, I keep my precious memories of you in my heart (more precisely in my hippocampus).

Joint ventures with Richard in unravelling synaptic communication in hippocampal networks, by Tamás F. Freund

Being an anatomist by training, I have always been searching for the functional correlate of the structural features identified in cortical/hippocampal networks. This correlation has been a central dogma in the Szentágothai school of anatomists, where I received my basic training, mostly under the supervision of Peter Somogyi. Somogyi initiated collaborations with electrophysiologists and pharmacologists in Oxford to provide direct evidence for the predictive power of anatomy in functional studies. My group in Budapest with similar plans in mind joined forces with Gyuri Buzsáki at Rutgers, Newark, and Richard Miles at the Pasteur Institute, Paris. Both collaborations turned out to be extremely fruitful and resulted in a highly productive joint HFSP grant that continued for 10 years, with the involvement of two additional labs. Besides its considerable professional benefits, another invaluable outcome of this grant was a lasting friendship between the members of the group.

Richard's discoveries with Bob Wong were truly stimulating for us because using the most sophisticated electrophysiological methods, they analysed precisely those connections that we were interested in from the connectivity side (Miles & Wong, 1987a,b). Our lab had great traditions in studying inhibitory circuits. For us, seeing those interneurons in action in the hippocampal slice when Richard was using paired intracellular recording to study their interactions was simply a dream come true. His work cried out for the anatomical correlate, as did our anatomical findings for the direct identification of the physiological features of the inhibitory connections. This mutual interest and trust, as well as the complementary technical skills, evolved into a long-lasting collaboration that resulted in a *Nature* paper right at the beginning. For the first time in the history of brain research, single, anatomically identified synapses could be characterized electrophysiologically (Gulyas et al., 1993). Our seminal joint discoveries also included the demonstration of disinhibition in the septohippocampal slice (Toth et al., 1997), and the functional characterization of various interneuron types (Miles et al., 1996). Several PhD students and postdocs from my lab went to work with Richard for a year or two to learn his techniques and concepts, as well as to develop a functional understanding of cortical networks. Our group and I personally owe Richard a great debt of gratitude and respect for shaping our thinking and understanding of cortical network operations, both under physiological conditions, and during epileptiform activity.

If you got to design the system, how would you build it? By Desdemona Fricker

I remember drawings of metre-long axonal arbors on big sheets of paper, glued together, on the walls of Richard's office at the Pasteur Institute. He, Tamás Freund and Attila Gulyás had been counting synapses made by the axons of single CA3 pyramidal cells. Structure as the basis for function. Richard's questions about divergence and convergence never left me. The transmission came over many years.

During my thesis, Richard let me examine 'factors' that govern neuronal excitability. We investigated what controls EPSP-to-spike coupling. Accurate measurements of membrane potential could be obtained in cell-attached recordings, leaving the cell membrane intact (Fricker et al., 1999). We found that the balance of subthreshold intrinsic currents and interactions between interneurons and pyramidal cells assures the precision of action potential timing (Fricker & Miles, 2000, 2001). Slice work is rather remote from behaviour and cognition, and it seemed difficult to understand place cells or memory. Richard's work emphasized the network aspect; the general principles of collective behaviours of neurons.

This was Richard's approach: find a brain region with a well-defined function, accessible for feasible experiments; 'A region that can be studied both as a network and a computational system' (Traub & Miles, 1991). Experiments should provide information on intrinsic, synaptic and circuit properties, and be combined with computational modelling. Inspired by Richard's logic, I was looking for new territory, moving out of the hippocampus. Not too far away lies the presubicular head direction cortex. The pre- (also called post-) subiculum is a periarchicortex, between the old and the new brain structures. It is the thalamorecipient area for the brain's compass signal, and it functions as an attractor network. It is more closely linked to sensory inputs, and as such may be a bit easier to understand. Richard's questions keep coming back. How do excitatory and inhibitory neurons interact, and may this support head directional firing (Nassar et al., 2018; Simonnet et al., 2017)? Optogenetics let us examine converging inputs (Richevaux et al., 2023), but how do these signals stabilize or flexibly reset the attractor? More work is needed, he would say.

Richard insisted on asking careful questions; he embraced uncertainty. His scientific engagement felt right and genuine. People liked him because he was brilliant and kind. He also was an outsider, a stranger. Of British origin.

Recurrent ideas, by Attila I. Gulyás

As a scientist, I grew up in the János Szentágotai Functional Anatomy school. As a student, and later colleague of Tamás Freund, first I studied the types and connectivity of hippocampal inhibitory neurons, as an anatomist. However, to reveal function, one needs to know not only the structure, but also the behaviour and the interactions of neurons. When the Buzsáki, Freund, Haas, Miles, Traub and Tamammaki labs started a collaboration with the help of an HFSP grant, I had the good fortune to visit Richard's lab on several occasions. At first, I brought my anatomist's knowledge to support Richard's physiology. We identified many cell types, and published a *Nature* paper (Gulyas et al., 1993), which demonstrated that hippocampal pyramidal cells excite inhibitory neurons through a single release site.

During the long night shifts, we had endless conversations about science, life, and everything else. I really enjoyed working with Richard, so I returned a few years later to study electrophysiology. During a year of struggles, discussions, fights, world-changing ideas, and the background music of FIP radio and cigarette smoke, I learned a lot about electrophysiology, the insane promiscuity of hippocampal inhibitory neuron properties, my limitations, and the precise way Richard did science. We published a *Neuron* paper in which we unorthodoxly argued that the anatomical, physiological and pharmacological properties of inhibitory neurons are combined rather freely (Parra et al., 1998). After the Zen of anatomy, the battlefield of electrophysiology was so intense that when I left, I swore I would never touch a recording pipette again.

Yet, to pursue my driving question – How does the interaction of excitatory and inhibitory neurons result in different types of network activities? – I turned out to be an electrophysiologist in Budapest some years later, and with Norber Hájos, we set out to decipher the generation of *in vitro* hippocampal gamma and sharp-wave ripple (SWR) activity.

Two of my papers that I am most proud of were influenced by Richard's works and ideas on the build-up of activity in the recurrent excitatory network of the hippocampus, and by the skills I had learned in his lab.

By analysing the build-up of EPSCs and IPSCs recorded from pyramidal cells and inhibitory neurons in a slice generating SWRs, as well as the distribution of SWR interevent distribution we concluded that SWR initiation is a Poisson process. When the spontaneous activity of PCs reaches a threshold, the activity starts to build up exponentially, until parvalbumin containing inhibitory cells are recruited. The reciprocal inhibition of these cells will then generate high-frequency phase-locked inhibition and pyramidal cell firing that result in the observed ripple oscillations (Schlingloff et al., 2014).

We then turned to Richard's favourite, epilepsy. Inducing epileptiform activity in hippocampal slices, we found that interictal events are generated in a similar way. Here, the runaway excitation of the PCs results in the depolarization block of parvalbumin containing basket cells, that are thus not able to limit the spread of synchrony, and all PCs will fire together, until the activity stops due to refractory mechanisms. Interictal events can be thus considered pathological SWRs (Karlócai et al., 2014).

I kept in contact with Richard since then, in the forms of monthly reading lists and idea exchange emails. Like Science, I will miss him too.

The smartness of reducing of the system to a synapse, by Gilles Huberfeld

Being fascinated by the control provided by interneurons on neuronal networks, Richard Miles unavoidably turned his physiology research to epilepsy. Most of his previous research addressed how phasic GABAergic inhibition would control synchronization of local pyramidal cells and how, when inhibition was blocked, the process of recruitment, tremendously abrupt as pyramidal cells enrolled those they were connected to, quickly ended up with a global discharge, even if triggered by a single cell.

But studies on human postoperative epileptic tissues stressed a key role for interneurons in an unexpected way. Together with the Pitié-Salpêtrière team, he showed that genesis of interictal activities was not due to a reduction of interneuron activity/loss of inhibition, as expected from his own previous data and from the leading opinion, but rather to the depolarizing/excitatory effects of interneurons due to a defective chloride regulation in subicular pyramidal cells (Cohen et al., 2002).

Such results perfectly fitted with a key aspect of his scientific philosophy: 'play with the system'. Playing with combined extra and intracellular recordings, the human hippocampal system revealed that inhibition was indeed the 'chef d'orchestre' but that it conducted rather than controlled abnormal activities of neuronal ensemble. It also stressed the way Richard Miles tended to reduce complex systems to the behaviour of single or a duo of synapses. This is the way he was facing the science community. One single interaction after another. One paper telling a complete story after the other. And as in CA3, these concepts spread in the neuroscience community.

This seminal research was my entrance into research and guided my translational work in epilepsy. I later contributed to show that this mechanism was at play in various focal epilepsies, such as focal cortical dysplasias (Blauwblomme et al., 2019) and tumours (Pallud et al., 2014), suggesting that this mechanism is common if not universal. Richard Miles passed away before we clearly evidenced the primary cause(s) of chloride dysregulation, the precise subtype of causative interneurons and their network organization. Another element of Richard Miles's personality also deeply tinted my approach. He systematically attempted to address a scientific question or to build new tools by deriving it from another. It was a kind of proximity approach that in fact totally fitted with the 'one synapse after the other' concept.

Finally, Richard Miles' communication occurred not only with who (he was selective and his selectivity criteria remained obscure and sometimes paradoxical to me) but also when he would decide it. Such windows of communication, amazingly florid, rather occurred at night in the lab. Richard would then need to sit on the ground, in the lab but also in a restaurant or in the street, and the magic arose.

One of the key synchronizing synapses of our world has now been made silent.

Beyond memory: The legacy of a mentor, by Jean Christophe Poncer

Let's face it: as a young undergraduate, I had no specific tropism for inhibitory neurons. My main motivation for studying neuroscience was the mirage of understanding the mechanisms of memory. Philippe Ascher, my first mentor in neuroscience (another brilliant scientist and generous person who also sadly left us recently), had welcomed me into his lab for an internship in 1991 and then kindly guided me through several key stages of my budding career. When we were discussing labs for my PhD, Philippe suggested that I visit Richard Miles, 'a very promising kid' who had just started his lab at the Pasteur Institute. After the first impression of a rather unique personality, I was dazzled by Richard's comprehensive vision of cortical circuits, from synaptic properties to network behaviour. I decided to embark with him on a long journey into hippocampal inhibitory circuits, even if it meant – I thought – temporarily distancing myself from the mirage of studying memory. I was proud to become his first graduate student!

Richard's signature approach to the physiology of hippocampal circuits was that of paired recordings from neurons using sharp intracellular microelectrodes in guinea pig hippocampal slices. Although tedious and demanding, this technique became (and still is) the gold standard for several generations of researchers in the study of neural networks (Miles & Poncer, 1996). Using this approach in Bob Wong's lab a few years earlier, Richard had made the intriguing observation that *latent* polysynaptic excitatory circuits in CA3 could be *revealed* by a brief period of tetanic afferent stimulation (Miles & Wong, 1987a). This unmasking of polysynaptic connections was shown to reflect reduced synaptic inhibition, but with a delay of several minutes. Direct recordings from CA3 interneurons showed that this delay could be explained by a transient increase in interneuron excitability that persisted during blockade of glutamatergic synaptic transmission with AMPA and NMDA receptor antagonists (Miles, 1991).

Determined to understand the mechanism involved in this form of interneuron plasticity, and although many neuromodulators could have contributed, Richard had an intuition – as he often did throughout his career – that it might involve metabotropic glutamate receptors (mGluRs). The existence of G-protein-coupled glutamate receptors had been suggested only a few years earlier (Sladeczek et al., 1985; Sugiyama et al., 1987), and the first member was cloned in 1991 (Masu et al., 1991), shortly after the first specific agonist, trans-1-aminocyclopentane-1,3-dicarboxylic acid (tACPD), was identified (Palmer et al., 1989). Using this agonist – and long nights of recording and discussions of all kinds, Richard sitting in lotus position, cigarette in mouth – we were able to test Richard's hypothesis, which was confirmed by showing that mGluR activation transiently increased interneuron excitability (Miles & Poncer, 1993). However, we found that prolonged application instead led to a reduction in IPSP amplitude and frequency. We solved this enigma in a second study

by showing that two different subtypes of mGluRs exert opposite effects on interneurons (which were not yet identified), increasing their excitability while reducing synaptic GABA release (Poncer et al., 1995).

These two studies, published in *The Journal of Physiology* – Richard's favourite journal – not only helped to illustrate the emerging role of mGluRs in synaptic function and plasticity, they also paved the way for my own research, particularly with Beat Gahwiler and Scott Thompson at the Brain Research Institute (HiFo) in Zurich (Poncer et al., 1997, 2000), and that of subsequent lab members. The diversity of hippocampal interneurons was gradually revealed, again with a visionary contribution from Richard (Miles et al., 1996; Parra et al., 1998). Then came the study of postoperative human tissue and the role of chloride transporters in defective inhibition in epilepsy (Cohen et al., 2002). As with mGluRs, Richard's exceptional intuition and curiosity enabled him to make connections between several emerging fields of neurobiology, to formulate original hypotheses, to choose the simplest and best way to test them, and thus to inspire several generations of researchers. So much for memory. And long live inhibition.

The threshold of neuronal storms, by Liset M de la Prida

When I was a physics student in La Habana, I used to spend time in the library where many scientific journals were available. I had already started to be interested in brain activity as a complex system and reading a lot about neurons and circuits. One day, I found an issue of *Nature* from 1983 on the shelf. As I started looking at it, I ran into a paper written by someone called Richard Miles and Robert K.S. Wong (Miles & Wong, 1983). The paper showed that activating single neurons could initiate a cascade of firing in a brain slice. The cascade was not immediate, but lagged the single cell firing by some tens of milliseconds. By that time (and this is poetic licence), there was a tropical storm discharging vertically over the city. The three events made some endurable connections I would only understand several years later.

The work by Traub, Miles and Wong was inspiring (Traub et al., 1989). I learned about the Hogdking–Huxley differential equations to describe neurons with multiple compartments, and to connect them in a circuit, which could reproduce experimental data (Traub, Miles, & Wong 1987; Traub, Miles, Wong, Schulman et al., 1987). Other papers in journals I found in the library showed me there was a way to connect circuits and models with oscillations in the sleeping and aroused brain (Buzsáki et al., 1992; Steriade et al., 1993). I was fully inoculated when I started my PhD studies in Spain on mechanisms of population discharges along brain development, called giant depolarizing potentials (GDPs) (Cossart & Khazipov, 2022).

The idea of a delayed period following single cell discharges leading to neuronal synchronization has always been influential for me. While studying GDPs emerging spontaneously from the immature hippocampal slices, I noticed a preceding period of increased synaptic activity occurring intracellularly (Menendez de la Prida & Sanchez-Andres, 2000). By combining recordings of cell pairs, it was clear that such a bout of activity was sometimes coordinated across cells but often failed to trigger synchronization (Menendez de la Prida & Sanchez-Andres, 1999a). My idea was that such a preceding build-up period was a nonlinear process with a threshold for activity becoming synchronized in the neural population (Menendez de la Prida & Sanchez-Andres, 1999b). That was precisely what Richard saw while stimulating single cells.

I met Richard at the Institut Pasteur by 1998 and talked to him about my ideas on threshold dynamics controlling the emergence of population bursts. He told me about percolation instead, as a theory to understand how activity propagates in a network through some specific nodes that he and Roger were discussing (Traub & Miles, 1991). It took yet a few more years of encounters and discussions until I finally moved to Paris in 2002 to start working in the threshold project with Richard. Using a combination of extracellular and intracellular recordings in disinhibited slices, we examined the conditions for population discharges to emerge (Menendez de la Prida et al., 2006). We managed to track fluctuations of firing, local field potentials and synaptic activity over time, and observed how they build up before reaching a certain level just before the discharge onset. We promoted population discharges by injecting activity from single cells, while reducing the efficacy of excitatory synapses delayed their occurrence. In all cases, reaching a certain threshold was critical to trigger the event. We proposed that the initiation of hippocampal population discharges, either GDPs, sharp-wave ripples or epileptic discharges, could be explained by a nonlinear build-up period with a threshold to transit from uncoordinated to coordinated neuronal firing.

Over time, Richard and I have exchanged a wealth of ideas. Yet, it was the connection forged by three fundamental things that truly bound us: neurons, circuits and the storms of the Caribbean.

Synaptic puzzles, by Katalin Toth

I met Richard when I was a neuroanatomy student in Tamás Freund's laboratory. We were discussing his 1987 paper with Robert K. Wong (Miles & Wong, 1987a) on a latent synaptic pathway in the hippocampus that could

be revealed by suppressing inhibition. The discussion was like reading a detective story, full of intrigue and mystery, while waiting for the final result to be revealed. I later learned that this was Richard's trademark approach: ask an intriguing question and peel back the functional layers one by one until the underlying mechanism is revealed. As an anatomy student, I understood how to study structure, so when I had the opportunity to work with Richard on function, I jumped at the chance and joined him in Paris at the Pasteur Institute.

It was during this period of my training that I learned to appreciate the beauty of numbers in neuroscience. We were working on a multi-laboratory project that led to the identification of the number of synaptic connections between connected hippocampal cells. This fundamental information about the basic connectivity of neurons is integrated into our current way of analysing, testing and interpreting network behaviour. These experiments required infinite patience, Richard had an amazing ability to persevere and obtain data that provided the first insights into the exact nature of these connections (Gulyas et al., 1993). His determination to find the right answer to his questions was always fuelled by his propensity to identify key questions that moved the field forward.

In a subsequent paper, Richard turned his attention to the functional implications of subcellular specialization within neurons. Richard used a few very clever experimental manipulations to show the striking differences between the functional roles of somatic and dendritic inhibition. This was the first demonstration of differential effects of inhibitory inputs innervating distinct subcellular compartments on the spike outputs of excitatory cells (Miles et al., 1996). This work opened the door to an incredibly exciting new field of research investigating the impact of different types of inhibitory cells on network function, which continues to flourish and grow today.

Interactions between different brain regions were difficult to investigate at the single cell and synapse level in the 1990s. We developed a new slice preparation that allowed us to study inhibition between the medial septum and the hippocampus, and identified a disinhibitory role for septal inputs that was long suspected based on anatomical data from the Freund lab (Toth et al., 1997). Richard's work flourished at the intersection of structural and functional observations, his novel theories could be fully tested using these complementary approaches.

Richard's mentorship went beyond how his thinking and scientific approach later shaped my own research. The impact of his kindness and willingness to help, not only in the realm of science but in all sorts of everyday matters, has stayed with me over the years. Since I left his laboratory, it has been a pleasure to keep in touch with him. Whenever I crossed the Atlantic, I stopped in Paris to spend some time with him, with discussions and dinners like in the 'old days'. During our last conversation I tried to persuade him to write a book, which would undoubtedly have been an exciting read for anyone interested in fundamental neuroscience, epilepsy research and/or scientific puzzles.

A tribute to Richard Miles, electrophysiologist extraordinaire, by Roger D. Traub

Richard Miles and I often disagreed. Never mind that. The man was brilliant; it was a privilege to know and work with him, and he had as much influence on my own thinking and Science as just about anyone. It is a troubled time for me now: he is the second of my few close collaborators to be lost in just a few years (the other was another Englishman, Miles Whittington).

I first met Richard when he was a postdoc with Bob (Robert K.S.) Wong at the University of Texas Medical Branch, Galveston. It was in the mid-1980s. The occasion of the visit was as a follow-up to a paper Bob and I had published in *Science*, 1982, titled 'Cellular mechanisms of neuronal synchronization in epilepsy'. In this paper, Bob and I showed some experimental recordings (of his, naturally) from the disinhibited CA3 region of a guinea pig hippocampal slice, where the most unexpected finding was that a synchronized discharge could be elicited with a minimal stimulus, and after a long latency; and we presented a computer model that could account for the experiments. The model rested on three hypotheses: (a) CA3 pyramidal cells were intrinsically bursting neurons, which had already been established; (b) any one CA3 pyramid synaptically excited more than one other, on average; (c) in the presence of block of (fast) synaptic inhibition, a burst in one pyramid would evoke a burst in a monosynaptically connected pyramid, with a latency of the order of 10 ms. This model, in simulations, produced results that looked real. The model was in no way sophisticated, as judged by the standards of theoretical physicists or various biology Nobel laureates – they were not shy about sharing such opinions. Nevertheless, hypothesis (c) was quite counterintuitive from a biological point of view. Exceedingly powerful excitatory synapses were known in those days – climbing fibre synapses on cerebellar Purkinje cells – but not between pyramidal cells.

Our model also made another unexpected prediction: stimulation of even a single neuron might, in the presence of disinhibition in the CA3 region, evoke a synchronized population discharge. This prediction is far more specific than just an imbalance of excitation and inhibition (to use the common parlance nowadays).

In a beautiful series of papers published in *The Journal of Physiology* and in *Nature*, Richard and Bob Wong verified the model hypotheses and the model prediction concerning stimulation of a single neuron. An example of burst propagation is shown in Fig. 3. Their

experimental data were significant not only for epilepsy mechanisms, but also for demonstrating the usefulness of an experimental/modelling paradigm, one now taken for granted: specifically that one could combine experimental data on single-neuron intrinsic membrane properties with data on unitary monosynaptic connections, in order to construct a network model of collective activity, a model that would make specific testable predictions. Such a paradigm has been of extreme usefulness in the study of central pattern generators, as well as other types of (not-too-complex) neuronal circuits. Of course, things can get messy once the network becomes complicated, but this is not the place to address such matters.

The series of papers by Miles and Wong went further than what is described above. Specifically, they showed, qualitatively, the existence of a 'critical phenomenon' as synaptic inhibition is blocked, a discontinuity in network behaviour. These findings prompted the writing of a monograph (Traub and Miles, *Neuronal Networks of the Hippocampus*, Cambridge, 1991), a book that never would have existed without Richard (or Bob Wong, for that matter). Richard wrote the experimental parts and I wrote the introduction and modelling/theoretical parts. It is gratifying indeed to have heard from some distinguished neuroscientists that our book had a positive influence on them. I like to think Richard would have been pleased.

When I first met Richard in Galveston I was not at all sure what to make of him. He was not afraid of Gulf of Mexico hurricanes. He said what he thought. He was eccentric. I had dealt with brilliant eccentrics before, but Richard was not like them. He was a modest eccentric. It doesn't imply a lack of strong ideas, far from it. Nevertheless, he was modest. It took me a few years to fully realize his genius, but I finally got it.

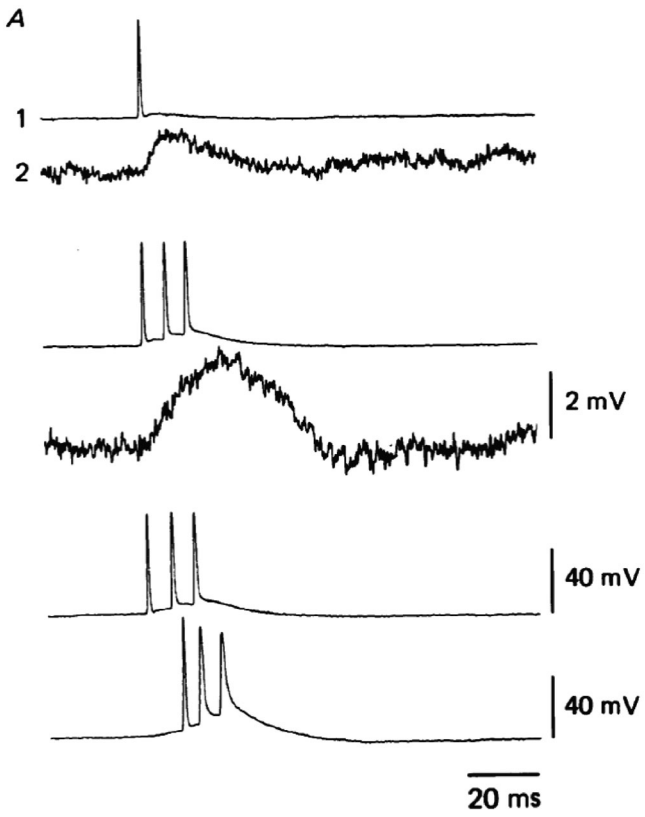

Figure 3. A classic Miles & Wong experiment (part of Fig. 4 in Miles R and Wong RKS (1987b))
Simultaneous intracellular recordings from two CA3 pyramidal neurons in picrotoxin to block $GABA_A$ receptors. The two neurons were monosynaptically connected, and one or more action potentials were induced in cell 1 by current injection. The bottom pair of traces shows that a burst of action potentials can evoke – under these conditions – a burst of action potentials in a synaptically connected neuron.

Human epilepsy research in understanding inter-species differences and physio-pathological processes, by Lucia Wittner

When I started my career as a neuroanatomist in the laboratory of Tamás Freund, in the Institute of Experimental Medicine in Budapest, I was fascinated by the beauty of neurons, and their resemblance to bushes and trees. The hippocampus also seemed to be a beautiful brain region with its special structure. I admired the shape of the hippocampal cell layers outlined by granule cells and pyramidal neurons. Looking at a Golgi-stained human hippocampal section made me feel like I was wandering in a wonderful forest. I knew that the hippocampus was responsible for learning and memory formation, but I could not really imagine how these essential functions could take place in such a small region of the human brain. I tried to understand what makes humans a unique species able to build skyscrapers, vehicles and rockets going to the Moon, and the link between this ability and the learning functions residing in the hippocampus. There were several hippocampus-related research topics I could join in the lab; finally, I chose the one related to the human brain: inhibitory interneurons in the human hippocampus, and their changes in temporal lobe epilepsy. This is how human epilepsy research became part of my life.

During my PhD period, I met someone at a conference telling me that Richard Miles had started to record neurons in the human epileptic hippocampus and found that GABA can be depolarizing (Cohen et al., 2002), and by the way, he was looking for an anatomist. My post-doctoral period with Richard Miles at the Pitié-Salpêtrière hospital was a win–win situation for both of us: I could learn electrophysiology from a world class expert in a laboratory grouping researchers and epileptologists, and he could have a neuroanatomist in his lab, who is specialized in the human epileptic hippocampus.

Beside electrophysiology and physiological/epileptic synchronizations, I learned a lot from Richard about how to ask questions, how to build up a series of experiments to examine a hypothesis, and how to write a scientific article in a comprehensive and interesting way. I admired and tried to catch the crystal clear logic of his thoughts concerning scientific questions. But most importantly, I enjoyed the conversations with him, about life, politics, science, and everything. Most probably during the evenings, and lasting into the night, he might have been sitting on the floor, with a coffee and a cigarette, and the deepest, the most interesting, thought-provoking discussions happened.

That 2-year period in Richard Miles' laboratory profoundly formed my way of thinking about synchronizations, epilepsy and science. It also broadened my point of view on many other topics not related to science: the importance of well-being, enjoying friendships and the happy moments of life. Since then, I have tried to use Richard's philosophy and methods in hypothesis building, experiment planning, data analysis and scientific writing. With his help, and the knowledge he taught me, I could get slightly closer to answering the questions about which properties in humans differ from those of other mammals, and why certain brain regions are prone to generating epileptic synchrony while others are not. However, I still do not know how hippocampal synchronizations provide such a huge advantage to humans over other mammals in their learning and memory functions, and where the border is between physiological and epileptic synchronizations. Without Richard's brilliant ideas and advice, it will be a more difficult task to answer these questions.

Richard Miles: A scientist and a gentleman, by Robert Wong

Richard Miles, Roger Traub and I met at the beginning of our scientific venture in 1980. We collaborated closely for over a decade. It was the most exciting and enjoyable part of my career. We worked on understanding the network properties of the hippocampus; each of us contributed to different aspects of the project.

Richard Miles provided the most comprehensive information on unitary synaptic transmission in the hippocampus. I am fascinated and enthralled by his work. It's an interesting story worth telling and I'll briefly describe it here (Le Duigou et al., 2014).

By using paired intracellular recording, he showed how pyramidal cells communicate with each other and with inhibitory neurons, and how inhibitory neurons in turn regulate mutual excitation between pyramidal cells. Details in the unitary synaptic transmission revealed network communication in the hippocampus which provided a basis for short-term information retention in the hippocampus.

He focused on the CA3 region of the hippocampus. First, he measured the unitary synaptic magnitude between pyramidal cells and demonstrated that suprathreshold excitation can occur. A single burst firing, a common occurrence in CA3 pyramidal cells, has a 30% success rate in triggering action potential bursts in a follower postsynaptic cell. Then using physiological means, he estimated the total number of postsynaptic contacts each pyramidal cell makes with its neighbour.

So how did he estimate the number of postsynaptic contacts each pyramidal cell made? The amplitude of unitary EPSPs was measured directly to be between 1 and 2 mV. Then an estimate of the total number of recurrent synapses each pyramidal cell received was derived from the giant EPSP's underlying interictal spikes produced in a disinhibited hippocampal slice. The amplitude of the giant EPSP was about 50 mV. So it is estimated that each pyramidal cell receives about 30 inputs from neighbouring pyramidal cells. In a symmetrical neuronal network, the amount of synaptic input to a cell is equal to the output of the cell to other neurons.

The above derivation allowed him to estimate that a burst in a pyramidal cell elicits bursts in more than one postsynaptic pyramidal cell. So, activity on one pyramidal in the hippocampal CA3 circuit elicits a chain reaction and causes an exponential growth of excited pyramidal cells in the network. Richard confirmed this prediction by showing that a single active pyramidal cell can trigger burst firing in an entire network of pyramidal cells when inhibition is removed. Recurrent inhibition controls this recruitment process. Again by using paired recording Richard demonstrated the exceptional strength of synaptic recruitment of inhibitory neurons by the recurrent synapses of pyramidal cells – a single action potential in a pyramidal cell has a 40% chance of triggering an action potential in an inhibitory neuron. The output of the inhibitory neuron dampens excitatory spread among pyramidal cells over a large area. The detailed demonstration of the CA3 network complements the prediction by a model proposed by Roger Traub (Traub & Wong, 1982).

Richard's indulgence in scientific pursuit was immense. I think that he loved doing science and assigned high value to scientific accomplishment. I was impressed one time when I dropped by his apartment and found that he had cut the power cord of his television. He had, in his gentle way, tremendous self-discipline.

I am blessed for the extended period I had working with Richard and consider him a most valuable friend. I had planned to visit him in his new location but life moved on and I missed the opportunity. I value his science, and the memory of his distinct, warm and sincere friendship will accompany me for the rest of my journey.

References

Blauwblomme, T., Dossi, E., Pellegrino, C., Goubert, E., Iglesias, B. G., Sainte-Rose, C., Rouach, N., Nabbout, R., & Huberfeld, G. (2019). Gamma-aminobutyric acidergic transmission underlies interictal epileptogenicity in pediatric focal cortical dysplasia. *Annals of Neurology*, **85**(2), 204–217.

Buzsáki, G., Horváth, Z., Urioste, R., Hetke, J., & Wise, K. (1992). High-frequency network oscillation in the hippocampus. *Science*, **256**(5059), 1025–1027.

Cohen, I., Navarro, V., Clemenceau, S., Baulac, M., & Miles, R. (2002). On the origin of interictal activity in human temporal lobe epilepsy in vitro. *Science*, **298**(5597), 1418–1421.

Cossart, R., & Khazipov, R. (2022). How development sculpts hippocampal circuits and function. *Physiological Reviews*, **102**(1), 343–378.

Freund, T. F., & Buzsaki, G. (1996). Interneurons of the hippocampus. *Hippocampus*, **6**(4), 347–470.

Fricker, D., & Miles, R. (2000). EPSP amplification and the precision of spike timing in hippocampal neurons. *Neuron*, **28**(2), 559–569.

Fricker, D., & Miles, R. (2001). Interneurons, spike timing, and perception. *Neuron*, **32**(5), 771–774.

Fricker, D., Verheugen, J. A. H., & Miles, R. (1999). Cell-attached measurements of the firing threshold of rat hippocampal neurones. *The Journal of Physiology*, **517**(Pt 3), 791–804.

Gulyas, A. I., Miles, R., Sik, A., Toth, K., Tamamaki, N., & Freund, T. F. (1993). Hippocampal pyramidal cells excite inhibitory neurons through a single release site. *Nature*, **366**(6456), 683–687.

Karlócai, M. R., Kohus, Z., Káli, S., Ulbert, I., Szabó, G., Máté, Z., Freund, T. F., & Gulyás, A. I. (2014). Physiological sharp wave-ripples and interictal events in vitro: What's the difference? *Brain*, **137**(Pt 2), 463–485.

Le Duigou, C. L., Simonnet, J., Teleñczuk, M. T., Fricker, D., & Miles, R. (2014). Recurrent synapses and circuits in the CA3 region of the hippocampus: An associative network. *Frontiers in Cellular Neuroscience*, **7**, 262.

Masu, M., Tanabe, Y., Tsuchida, K., Shigemoto, R., & Nakanishi, S. (1991). Sequence and expression of a metabotropic glutamate receptor. *Nature*, **349**(6312), 760–765.

Menendez de la Prida, L., Huberfeld, G., Cohen, I., & Miles, R. (2006). Threshold behavior in the initiation of hippocampal population bursts. *Neuron*, **49**(1), 131–142.

Menendez de la Prida, L., & Sanchez-Andres, J. V. (1999a). Nonlinear frequency-dependent synchronization in the developing hippocampus. *Journal of Neurophysiology*, **82**(1), 202–208.

Menendez de la Prida, L., & Sanchez-Andres, J. V. (1999b). Nonlinear transfer function encodes synchronization in a neural network from the mammalian brain. *Physical Review E*, **60**(3), 3239–3243.

Menendez de la Prida, L., & Sanchez-Andres, J. V. (2000). Heterogeneous populations of cells mediate spontaneous synchronous bursting in the developing hippocampus through a frequency-dependent mechanism. *Neuroscience*, **97**(2), 227–241.

Miles, R. (1991). Tetanic stimuli induce a short-term enhancement of recurrent inhibition in the CA3 region of guinea-pig hippocampus in vitro. *The Journal of Physiology*, **443**, 669–682.

Miles, R., & Poncer, J. C. (1993). Metabotropic glutamate receptors mediate a post-tetanic excitation of guinea-pig hippocampal inhibitory neurones. *The Journal of Physiology*, **463**, 461–473.

Miles, R., & Poncer, J. C. (1996). Paired recordings from neurones. *Current Opinion in Neurobiology*, **6**(3), 387–394.

Miles, R., Toth, K., Gulyas, A., Hajos, N., & Freund, T. (1996). Differences between somatic and dendritic inhibition in the hippocampus. *Neuron*, **16**(4), 815–823.

Miles, R., & Wong, R. (1983). Single neurones can initiate synchronized population discharge in the hippocampus. *Nature*, **306**(5941), 371–373.

Miles, R., & Wong, R. (1987a). Latent synaptic pathways revealed after tetanic stimulation in the hippocampus. *Nature*, **329**, 724–726.

Miles, R., & Wong, R. (1987b). Inhibitory control of local excitatory circuits in the guinea-pig hippocampus. *The Journal of Physiology*., **388**, 611–629.

Milior, G., Morin-Brureau, M., Pallud, J., Miles, R., & Huberfeld, G. (2023). Animal models and human tissue compared to better understand and treat the epilepsies. *Epilepsia*, **64**(5), 1175–1189.

Nassar, M., Simonnet, J., Huang, L.-W., Mathon, B., Cohen, I., Bendels, M. H. K., Beraneck, M., Miles, R., & Fricker, D. (2018). Anterior thalamic excitation and feedforward inhibition of presubicular neurons projecting to medial entorhinal cortex. *Journal of Neuroscience*, **38**(28), 6411–6425.

Pallud, J., Quyen, M. L. V., Bielle, F., Pellegrino, C., Varlet, P., Labussiere, M., Cresto, N., Dieme, M., Baulac, M., Duyckaerts, C., Kourdougli, N., Chazal, G., Devaux, B., Rivera, C., Miles, R., Capelle, L., & Huberfeld, G. (2014). Cortical GABAergic excitation contributes to epileptic activities around human glioma. *Science Translational Medicine*, **6**(244), 244ra89.

Palmer, E., Monaghan, D. T., & Cotman, C. W. (1989). Trans-ACPD, a selective agonist of the phosphoinositide-coupled excitatory amino acid receptor. *European Journal of Pharmacology*, **166**(3), 585–587.

Parra, P., Gulyas, A., & Miles, R. (1998). How many subtypes of inhibitory cells in the hippocampus? *Neuron*, **20**(5), 983–993.

Poncer, J. C., McKinney, R. A., Gähwiler, B. H., & Thompson, S. M. (1997). Either N- or P-type calcium channels mediate GABA release at distinct hippocampal inhibitory synapses. *Neuron*, **18**(3), 463–472.

Poncer, J. C., McKinney, R. A., Gáhwiler, B. H., & Thompson, S. M. (2000). Differential control of GABA release at synapses from distinct interneurons in rat hippocampus. *The Journal of Physiology*, **528**(Pt 1), 123–130.

Poncer, J. C., Shinozaki, H., & Miles, R. (1995). Dual modulation of synaptic inhibition by distinct metabotropic glutamate receptors in the rat hippocampus. *The Journal of Physiology*, **485**(Pt 1), 121–134.

Richevaux, L., Lim, D., Nassar, M., Rodrigues, L. D., Mauthe, C., Cohen, I., Sol-Foulon, N., & Fricker, D. (2023). Projection-specific integration of convergent thalamic and retrosplenial signals in the presubicular head direction cortex. *Elife*, **12**, RP92443.

Schlingloff, D., Káli, S., Freund, T. F., Hájos, N., & Gulyás, A. I. (2014). Mechanisms of sharp wave initiation and ripple generation. *Journal of Neuroscience*, **34**(34), 11385–11398.

Simonnet, J., Nassar, M., Stella, F., Cohen, I., Mathon, B., Boccara, C. N., Miles, R., & Fricker, D. (2017). Activity dependent feedback inhibition may maintain head direction signals in mouse presubiculum. *Nature Communications*, **8**, 16032.

Sladeczek, F., Pin, J.-P., Récasens, M., Bockaert, J., & Weiss, S. (1985). Glutamate stimulates inositol phosphate formation in striatal neurones. *Nature*, **317**(6039), 717–719.

Steriade, M., McCormick, D. A., & Sejnowski, T. J. (1993). Thalamocortical oscillations in the sleeping and aroused brain. *Science*, **262**(5134), 679–685.

Sugiyama, H., Ito, I., & Hirono, C. (1987). A new type of glutamate receptor linked to inositol phospholipid metabolism. *Nature*, **325**(6104), 531–533.

Toth, K., Freund, T., & Miles, R. (1997). Disinhibition of rat hippocampal pyramidal cells by GABAergic afferents from the septum. *The Journal of Physiology*, **500**(Pt 2), 463–474.

Traub, R., & Miles, R. (1991). Multiple modes of neuronal population activity emerge after modifying specific synapses in a model of the CA3 region of the hippocampus. *Annals of the New York Academy of Sciences*, **627**, 277–290.

Traub, R. D., Miles, R., & Wong, R. K. (1987). Models of synchronized hippocampal bursts in the presence of inhibition. I. Single population events. *Journal of Neurophysiology*, **58**(4), 739–751.

Traub, R. D., Miles, R., Wong, R. K., Schulman, L. S., & Schneiderman, J. H. (1987). Models of synchronized hippocampal bursts in the presence of inhibition. II. Ongoing spontaneous population events. *Journal of Neurophysiology*, **58**(4), 752–764.

Traub, R. D., Miles, R., & Wong, R. K. S. (1989). Model of the origin of rhythmic population oscillations in the hippocampal slice. *Science*, **243**(4896), 1319–1325.

Traub, R. D., & Wong, R. K. S. (1982). Cellular mechanism of neuronal synchronization in epilepsy. *Science*, **216**(4547), 745–747.

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