Selecting circuits: do neurogliaform cells route information flow through the hippocampus?

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The hippocampus is a brain region that has long been associated with memory, due in large part to the classic study of patient HM, who was unable to form new declarative memories after undergoing bilateral hippocampectomy to treat epilepsy(*1*). However, the hippocampus does not function alone, but operates within a wider network of brain regions (the 'extended memory network') including, amongst other areas, the prefrontal and entorhinal cortices and midline thalamic nuclei such as nucleus reuniens (*2*). Communication between these brain regions is important for many aspects of memory acquisition and consolidation, as well as spatial navigation and decision-making. There are multiple routes through which information can flow through this extended memory network, with direct and indirect pathways converging upon the hippocampus. The mechanisms by which information flow through these different pathways is prioritised has remained largely unknown, but a study in this edition by Sakalar and colleagues provides exciting new insights into the cellular basis of information routing through the hippocampus <ref>.

Communication between neurons is thought to be enabled by neural oscillations: waves of rhythmic electrical activity that facilitate neural dialogue by creating temporal windows in which neuronal firing can be synchronised (*3*). By convention, neural oscillations are grouped into different frequency bands, with each band associated with specific cognitive processes. For example, theta oscillations occur at around 5 to 12 Hz, while gamma oscillations occur between approximately 30 to 140 Hz (*4*). Gamma oscillations, often occurring alongside theta oscillations, can be further parsed into distinct sub-bands mediated by different circuit mechanisms (*4*). This occurs in the CA1 region of the hippocampus, where different types of gamma oscillation are observed: specifically, a slow gamma oscillation ($gamma_S$, ~40 Hz) driven by input from neighbouring CA3, and a faster mid-frequency gamma oscillation ($gamma_M$, ~75 Hz) driven by input from the entorhinal cortex (*5*). CA1 afferents from CA3 arborise in stratum radiatum while those from entorhinal cortex terminate in stratum lacunosum-moleculare, providing an anatomical segregation of these different information streams (see figure 1). There is also a functional segregation of CA3- and entorhinal-driven gamma oscillations, as these different types of oscillation occur at different phases of the CA1 theta oscillation, potentially presenting a circuit-level mechanism that prevents these different information streams from interfering with each other (*5*). One hitherto unanswered question is whether there is a mechanism by which the inputs to an individual pyramidal cell in CA1 can be 'switched' between these different information streams. The study by Sakalar and colleagues provides evidence of a cellular mechanism through which this can occur <ref>.

Within the hippocampus, GABAergic inhibitory interneurons comprise a diverse family of neurons, with multiple subtypes providing exquisite temporal control over the spiking of

pyramidal cells and other inhibitory interneurons (see *6* for our recent review). The importance of inhibitory interneurons in coordinating neuronal oscillations has been well established in recent decades. For analogy, if one considers neuronal oscillations to be akin to music, then excitatory glutamatergic neurons provide the notes while inhibitory interneurons create the intervals between the notes. Thus, neuronal oscillations are generated through a precisely coordinated balance between excitation and inhibition: without appropriately timed pauses between notes, even the most exquisite symphony would degenerate into a cacophony. (*6*)

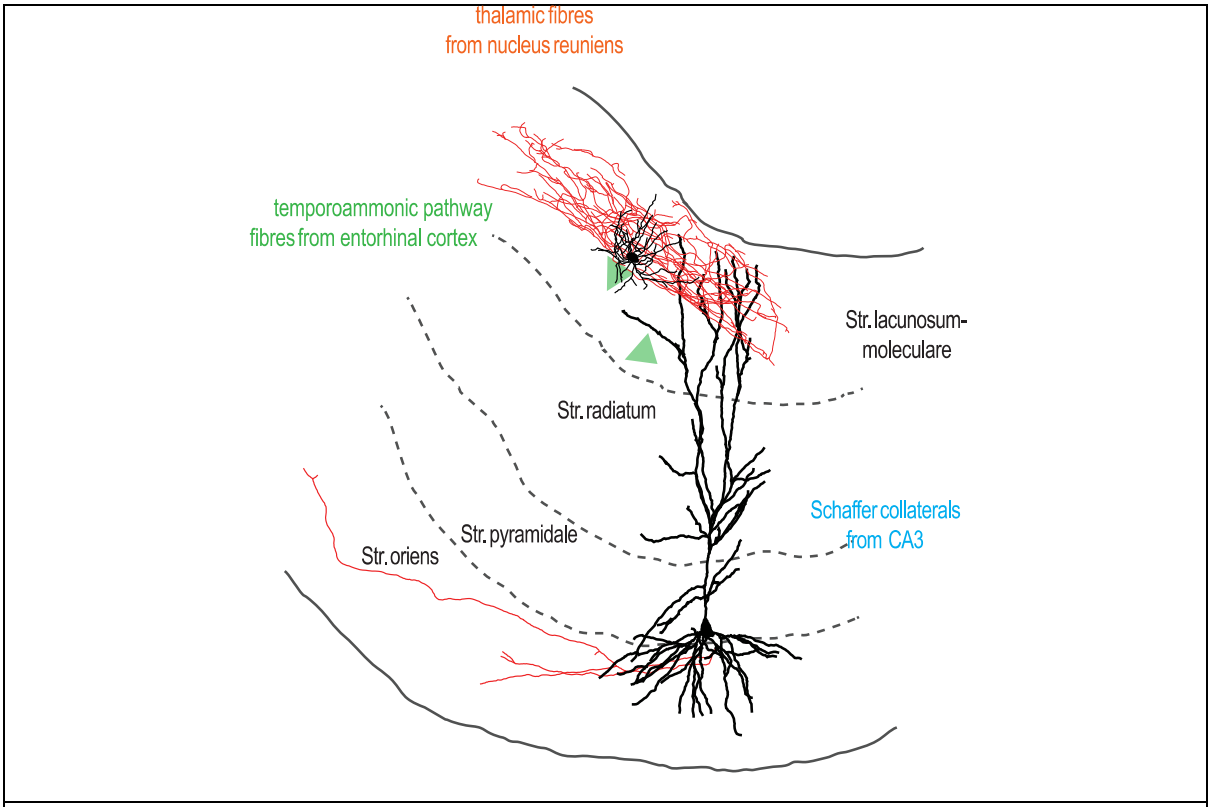

Figure 1: Information flow through the hippocampal region CA1. Representation of different layers within hippocampal region CA1 and routes of information flow from intrahippocampal projections (from CA3, in stratum radiatum) and external inputs arising from entorhinal cortex and nucleus reuniens (in stratum lacunosum-moleculare, or SLM), with pyramidal cell in stratum pyramidale and a neurogliaform cell in SLM. Do inputs to neurogliaform cells from reuniens and entorhinal cortex act synergistically to 'switch' off information streams converging on distal dendrites to allow pyramidal cells to be driven by information arriving via CA3?

Neurogliaform cells are an abundant class of inhibitory interneurons that reside in and project dense axonal arbors throughout stratum lacunosum-moleculare of the hippocampus. They are therefore well placed to inhibit the distal apical dendrites of CA1 pyramidal cells (*7*), but understanding their role in hippocampal information processing has remained elusive. In this issue, Sakalar and colleagues provide compelling evidence that neurogliaform cells play an important role in routing information flow through CA1 <ref>. Using mice running in a virtual reality environment, the authors performed simultaneous *in vivo* extracellular recordings of

spiking and neuronal oscillations across CA1, alongside juxtacellular recordings of putative and anatomically verified neurogliaform cells. They report that neurogliaform cells are strongly driven by $gamma_M$ and that neurogliaform cell firing can uncouple CA1 pyramidal cells from $gamma_M$ oscillations, indicating temporary disconnection of pyramidal cells from entorhinal input. Neurophysiologists tend to view GABAergic inhibition as leading to a decrease in cellular excitability but, remarkably, neurogliaform cells appear to supress $gamma_M$ modulation of CA1 pyramidal cell activity without changing the overall firing rate of the pyramidal cells, suggesting a mechanism that is restricted to the most distal compartments of the pyramidal cell's apical dendrites (figure 1). This study raises intriguing questions about how this neurogliaform-driven uncoupling of CA1 pyramidal cells from entorhinal cortex inputs relates to information processing in the hippocampus.

Numerous aspects of cognition, such as memory and decision making, require information to be communicated between the hippocampus, prefrontal cortex, and entorhinal cortex. This communication is thought to be facilitated by the synchronisation of neuronal oscillations across brain regions. For example, temporal coupling between CA1 and prefrontal theta and gamma oscillations (e.g. *8*, *9*) and between CA1 and entorhinal gamma oscillations (*10*) occurs during decision making in spatial working memory tasks. Remarkably, although synchrony between prefrontal cortex and CA1 is important for memory and decision making, no direct excitatory connection exists between these areas (although *11* recently described an inhibitory PFC projection to hippocampus that only targets interneurons). Rather, glutamatergic prefrontal input to CA1 is relayed through thalamic nucleus reuniens (NRe), which also projects to the entorhinal cortex. Axons from NRe terminate in CA1 in stratum lacunosum-moleculare alongside those from entorhinal cortex (*12*; see figure 1B). We previously reported that neurogliaform cells receive inputs from both NRe and entorhinal cortex (*13*) and preliminary data from our group suggest that NRe preferentially targets neurogliaform cells in CA1 while largely or entirely avoiding pyramidal cells (*14*). Although AMPA receptor-mediated synaptic currents from NRe are small, they have a much larger NMDA receptor-mediated component (*13*, *14*), implying that NRe provides a stronger drive to neurogliaform cells when they are simultaneously activated by another input, such as that arising from entorhinal cortex.

Could the function of NRe input to CA1 neurogliaform cells be to assist prefrontal cortex in selectively disconnecting pyramidal cells from entorhinal input, thereby filtering entorhinal signalling such that specific CA1 pyramids are recruited? This is tentatively supported by evidence that prefrontal relay of different internal context signals, such as contrasting task

demands, instates distinct representations of identical places in CA1, thereby minimising interference between behaviourally similar but contextually disparate events (*15*). Alternatively, could NRe and entorhinal cortex act synergistically through neurogliaform cells to shut down entorhinal input to CA1, thereby creating a permissive state for CA1 pyramidal cells to be driven by the trisynaptic entorhinal–dentate gyrus–CA3 pathway that arrives in the Schaffer collaterals in stratum radiatum? Additionally, preliminary data from our group show that neurons in entorhinal cortex receive synaptic input from NRe of a much larger amplitude than neurons that receive NRe input in CA1 or subiculum (*14*), so neurogliaform cells could support top-down prefrontal inhibition of ongoing entorhinal-CA1 communication in preparation for new information to be transmitted to CA1 via entorhinal-to-dentate gyrus or entorhinal-to-CA1 projections. Such a hypothetical function could provide a cellular substate for the cognitive flexibility required to allow rapid changes of behaviour whilst executing a task.

Like all exciting discoveries, the study by Sakalar and colleagues poses many intriguing questions. Determining the functional role for this neurogliaform cell-mediated suppression of entorhinal modulation of CA1 pyramidal cell activity will present exciting challenges for those investigating hippocampus-dependent cognition, from synaptic physiologists through to those studying oscillations and behaviour.

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