Synchronized spikes prevail in cortical networks, and their modulations are associated with attention, sensory processing and motor behaviors, yet it remained unclear how spikes can synchronize at the millisecond precision in a noisy network. Our new evidence shows that neurons do not easily synchronize; rather, in order to make them generate synchronous spikes, “parent” presynaptic neurons commonly shared by them are required to synchronize in advance. Therefore, the conventional style of neurophysiological research is unable to reach the true origin of synchronization. Neurons transmit spikes through a web of neurites and synaptic junctions, in which segregation and integration of multiple spike flow contribute to information processing. Individual spikes are usually orchestrated into synchronized events consisting of various sizes of neuron populations. The strength of synchronization between any two neurons is often referred to as a ‘functional’ connection, and their large-scale network topology has been examined by graph-theoretic studies. On the other hand, anatomical studies have addressed the ‘structural’ connectivity of synaptic wiring among neurons. A fundamental question, however, is how the functional and structural connectivity are mutually correlated? Unfortunately, due to a lack of appropriate experimental techniques, spiking patterns and synaptic architectures have not been directly compared in identical neuronal networks and information is still lacking about their relationship. The only possible approach is mathematical modeling of “in-silico” neuronal networks. The numerical simulation can infer how patterned activities emerge from specifically structured circuits and how they in turn lead to network reorganization, but this conjecture has to be experimentally verified. To do this, it is essential to record the spatiotemporal pattern of spikes from neuronal networks in which the synaptic connectivity was identified.

In our recent paper, we conducted simultaneous patch-clamp recordings from two or more CA3 pyramidal neurons in organotypic cultures of hippocampal slices. The CA3 region includes an autoassociative network in which pyramidal cells are unidirectionally or bidirectionally synapsed with a connection probability of 20–30%, and thus, we sometimes encountered synaptic coupling between randomly selected pairs of pyramidal cells. Importantly, the connected pairs exhibited higher rates of synchronous firing than uncoupled pairs did; in other words, the functional connectivity becomes stronger when two neurons are anatomically connected. Thus, the functional connectivity is a relatively good reflection of network wiring topology.

Can the presence of synaptic connections fully explain spike synchronization between the two neurons? The answer is, of course, no. In general, cortical excitatory synapses are weak and unreliable, and a single synapse is insufficient to induce a suprathreshold depolarization to emit an action potential of a postsynaptic neuron (Fig. 1A). To make it fire, dozens (or even hundreds) of presynaptic neurons...
synchronized pairs of neurons share more numbers of common presynaptic neurons. Furthermore, targeted patch-clamp recordings from highly synchronized neurons revealed that they received highly correlated synaptic inputs.

Then, are these correlated inputs responsible for synchronized spike output? The story is not straightforward. We found that in silico generated correlated inputs were unable to efficiently elicit synchronized spikes even though their correlation efficiency was increased to a realistic extent. This implies that spontaneously occurring synaptic inputs convey more information that can be used for cross-correlation measurements, thereby efficiently producing synchronized spikes in postsynaptic neurons (Fig. 1B). Then what is the true source of synchronization?

During further careful comparisons between functional and anatomical connectivity, we realized that common parent neurons per se are already synchronized in a power-law scale, sending highly coherent synaptic inputs to postsynaptic neurons. Consistent with this, when silico correlated synaptic inputs were generated from power-law-scaled presynaptic spike trains and injected into two pyramidal neurons, we now found that they exhibited strongly synchronized spikes, as comparable to actual synchronization (Fig. 1C).

Overall, what our study finally unveiled is that synchronized spike outputs require highly correlated synaptic inputs arising from “parent” presynaptic neurons, but also vice versa. Moreover, the synchronized parents naturally require synaptic inputs from highly synchronized spikes of “grandparent” neurons, which must also be synchronized by further upstream synchronized neurons, and so on. Now we must return to the fact that CA3 neurons are densely interconnected through a recurrent network. Our journey for searching the origin of synchronization will eventually come back to the starting point of synchronization. This functional recursive loop, a feature often found in the self-organizing complex system, can be interpreted as a “recurrent network” version of synfire chain.13–15

In the brain, the degree of synchronization is known to vary depending on the behavioral state. Under awake conditions, the network tends to be more asynchronous.16,17 Thus, a next-step study will be required to elucidate the modulation of the synchrony level.

References
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