

Dynamical relaying can yield zero time lag neuronal synchrony despite long conduction delays

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Multielectrode recordings have revealed zero time lag synchronization among remote cerebral cortical areas. However, the axonal conduction delays among such distant regions can amount to several tens of milliseconds. It is still unclear which mechanism is giving rise to isochronous discharge of widely distributed neurons, despite such latencies. Here, we investigate the synchronization properties of a simple network motif and found that, even in the presence of large axonal conduction delays, distant neuronal populations self-organize into lag-free oscillations. According to our results, cortico-cortical association fibers and certain cortico-thalamo-cortical loops represent ideal circuits to circumvent the phase shifts and time lags associated with conduction delays.

thalamocortical system | isochronous oscillations | phase locking | long-range synchronization | axonal latency

Cells in the visual cortex of mammals tend to fire simultaneously when activated by related features of a visual stimulus (1–4). This observation provided some of the early evidence that the nervous system may use an internal temporal code to process information. Since then, multicell electrophysiological studies have revealed the synchronous discharge of neurons distributed in different structures of the cerebral cortex, hippocampal formation, and thalamus (5, 6). Its biological significance derives from the observation that such precise and coordinated spike timing correlates with perception and behavioral performance (7–10). Remarkably, synchrony of neuronal activity is not limited to short-range interactions within a cortical patch. Interareal synchronization across cortical regions including interhemispheric areas has been observed in several tasks (7, 9, 11–14). The topological specificity and temporal unfolding of the synchrony reported in such studies are in agreement with its assumed role of subserving the effective “coupling” of the neuronal dynamics of the respective regions (9, 15).

Beyond its functional relevance, the zero time lag synchrony among such distant neuronal ensembles must be established by mechanisms that are able to compensate for the delays involved in the neuronal communication. Latencies in conducting nerve impulses down axonal processes can amount to delays of several tens of milliseconds between the generation of a spike in a presynaptic cell and the elicitation of a postsynaptic potential (16). The question is how, despite such temporal delays, the reciprocal interactions between two brain regions can lead to the associated neural populations to fire in unison.

Direct cortico-cortical fibers are major pathways of transareal communication and thus one principal substrate for the establishment of long-range synchrony. For instance, severing the corpus callosum was observed to disrupt the interhemispheric synchrony among homotopic cortical areas 17 in the cat (17). However, it is not clear whether direct excitatory cortico-cortical connections alone can mediate the zero phase synchronization of reciprocally coupled neurons for long transmission

delays (18, 19). Several mechanisms have been pointed out as partially responsible for the enhancement of such synchrony. Inhibitory synapses and gap junctions have been proposed to stabilize the synchronous firing of cells under some specific conditions and for a limited range of delays (20, 21). In the case of the hippocampus, a canonical circuit of excitatory and inhibitory neurons have been shown to reproduce successfully the experimental findings of long-range synchrony among hippocampal neurons (5, 22, 23). Synaptic plasticity mechanisms have also been shown to stabilize synchronous γ oscillations between distant cortical areas by reinforcing the connections the delay of which matches the period of the oscillatory activity (24).

Nevertheless, significant long-range synchronization is observed across different species with different brain sizes and at different stages of the developmental growth of brain structures. This requires that any generic mechanism for generating zero time lag long-distance cortical synchrony maintains its functionality for a wide range of axonal lengths. Although it is possible that developmental mechanisms compensate for the resulting delay variations (25), it is still difficult to explain all of the phenomenology of long-distance synchronization without a mechanism that inherently allows for zero lag synchronization for a broad range of conduction delays and cell types.

In this paper, we investigate a simple network motif (26) that naturally accounts for the zero lag synchrony among two arbitrarily separated neuronal populations. We want to stress the separation of processes generating local rhythms or oscillations in a brain structure from the mechanisms responsible for their mutual synchronization. The model that we present below provides a proof of principle for a synchronizing mechanism among remote neuronal resources despite long axonal delays. The basic idea is that when two neuronal populations relay their activities to a third mediating population, the redistribution of the dynamics performed by this unit leads to a robust and self-organized zero lag synchrony among the outer populations (27, 28). Even if no particular brain structure or physiological condition is intended to be faithfully reproduced, this type of connectivity pattern is characteristic for the reciprocal interaction of different cortical areas and the associative thalamic nuclei, such as the pulvinar (29, 30), and as we shall show below it can give rise to isochronous dynamics in remote cortical populations. To demonstrate this effect, we conducted extensive simula-

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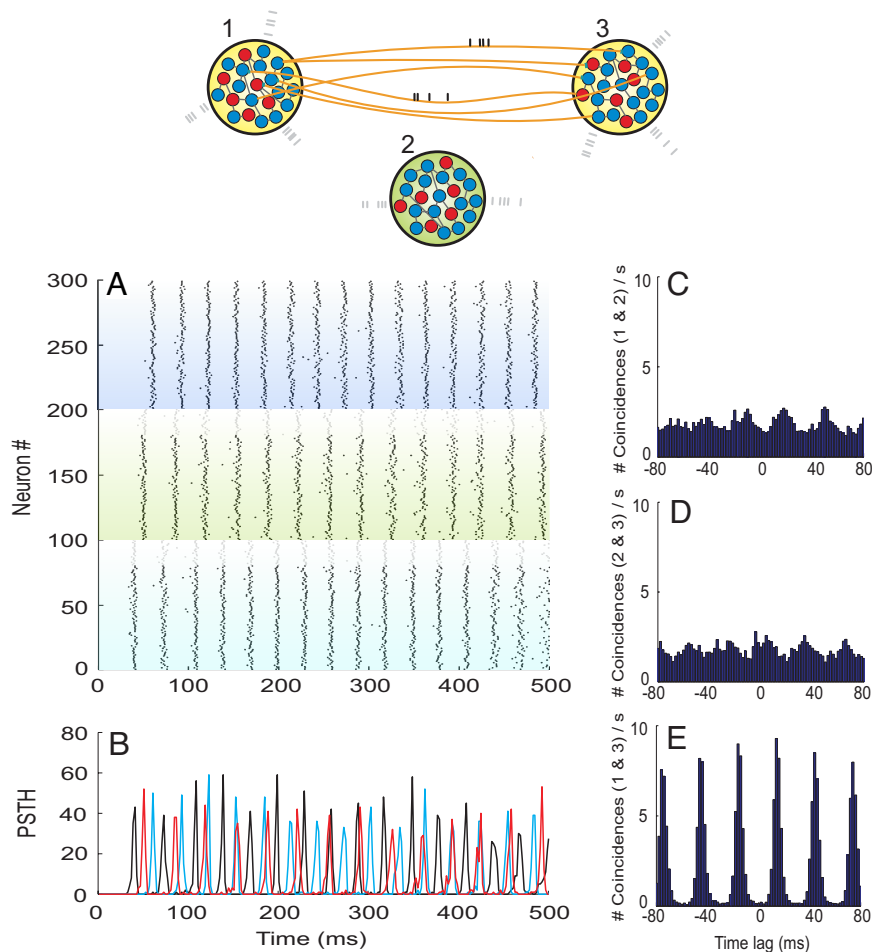


Fig. 6. Dynamics of 2 large-scale networks interacting directly. Population 2 is disconnected from other populations. Structure of the panels and parameters are otherwise as in Fig. 5.

for cortical activity is performed. However, the principal message of our results is not the identification of the physiological structures potentially responsible for long-range cortical synchrony but to show that the long latencies associated with cortico–thalamo–cortical loops are compatible with synchronization across large distances. Coherent oscillations between remote cortical populations can of course be generated also by reciprocally coupling these areas to other cortical areas or other subcortical structures. In fact, the aggregation of several of such motifs around a putative hub (forming a star-like network with the center unit playing the role of the relay element) also favors satellite nodes to spike in zero lag synchrony (41).

The most important requirement for zero phase lag synchronization is that the relay population of cells occupies a temporally equidistant location from the pools of neurons to be synchronized. It is significant to point out that recent studies have identified a constant temporal latency between thalamic nuclei and almost any area in the mammalian neocortex (42). Thus, in this scheme, thalamic nuclei occupy a central position for the mediation of zero phase solutions.

In general, it is quite probable that a variety of mechanisms are responsible for bringing synchrony at different levels (distinguishing for example, among local and long-distance synchrony) and different cerebral structures. The fact that each thalamus projects almost exclusively ipsilaterally (the massa intermedia is clearly inadequate for supporting the required interthalamic communication) is already an indication that the callosal commissure should play a prominent role in facilitating interhemispheric coherence. Lesion studies have since long confirmed this view (17). However, within a single hemisphere the disruption of

intracortical connectivity by a deep coronal cut through the suprasylvian gyrus was observed not to disturb the synchrony of spindle oscillations across regions of cortex located at both sides of the lesion (6). This finding suggests that subcortical, and in particular cortico–thalamic interactions, could be responsible for maintaining both the long-range cortical and thalamic coherence found in such a regime. It is likely that subcortical loops with widespread connectivity such as the associative or nonspecific cortico–thalamo–cortical circuits could run in parallel as an alternative pathway for the large-scale integration of cortical activity within a single hemisphere (30, 35, 40, 43). As we have shown here, with such connectivity pattern even large axonal conduction delays represent no detriment to the observation of zero time lag synchronization. It is also important to remark that connectivity studies in primate cortex have identified the pattern of connections studied here as the most frequently repeated motif at the level of cortico–cortical connections in the visual cortex (44–46). The functional relevance of this topology of cortical network is unclear but according to our results is ideally suited to sustain coherent activity.

In summary, the network motif highlighted here has the property of naturally inducing zero lag synchrony among the firing of 2 separated neuronal populations. The associative thalamic nuclei have the cortex as their main input and output sources and seem to represent active relay centers of cortical activity with properties well suitable for enhancing cortical coherence (30). From the experimental side, the relatively well-controlled conditions of brain slice experiments, allowing for the identification of synaptically coupled neurons and cell type, might be a first step for testing whether the topology

investigated here provides a significant substrate for coherent spiking activity. Another important issue is how the dynamic selection of the areas that engage and disengage into synchrony is achieved. It has been hypothesized that a dynamically changing coherent activity pattern may ride on top of the anatomical structure to provide flexible neuronal communication pathways (47). Based on the properties formerly reviewed, subcortical structures such as some thalamic nuclei might be promising candidates to play a role in regulating such coherence and contribute to the large-scale cortical communication.

Materials and Methods

Two neuronal models were numerically simulated to test the synchronization properties of the neuronal circuits investigated here.

In the most simplified version of the neuronal motif we focused on the dynamics of 2 single-compartment neurons that interact with each other via reciprocal synaptic connections with an intermediate third neuron of the same type (see Fig. 1 *Top*). The dynamics of the membrane potential of each neuron was modeled by the classical HH equations (48) plus the inclusion of appropriate delayed synaptic currents that mimic the chemical interaction between nerve cells.

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The second class of models we have considered consists of 3 large balanced populations of IAF neurons (49). Fig. 5 *Upper* is a sketch of the connectivity. Each network consisted of 4,175 IAF neurons of which 80% were excitatory. The internal synaptic connectivity was chosen to be random, i.e., each neuron synapsed with 10% of randomly selected neurons within the same population, such that the total number of synapses in each network amounted to $\approx 1,700,000$ contacts. In addition to model background noise, each neuron was subjected to the influence of an external train of spikes with a Poissonian profile. The interpopulation synaptic links were arranged such that each neuron in any population receives input from 0.25% of the excitatory neurons in the neighboring population. Note that the interpopulation links remained small in number compared with the local coupling that allows to consider the system as 3 weakly interacting networks of neurons rather than a single homogeneous network. Intrapopulation axonal delays were set to 1.5 ms, whereas the fibers connecting different populations were assumed to involve much longer latencies to mimic the long-range character of such links.

Parameters, evolution equations, simulation schemes, and data analysis for these 2 models are detailed in the *SI Materials and Methods*.

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