Local Field Potential Oscillations as a Cortical Soliloquy

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Synchronized network activity can be recorded as fluctuations in the local field potential (LFP). In this issue of *Neuron*, Fröhlich and McCormick suggest that cortical LFPs themselves contribute to synchronization of the very network that generates them. Thus, in monitoring these brain waves, we may be listening to the cortex talking to itself.

Neurons in the cortex display sparse activity, and the coordination of spike timing across anatomically dispersed neuronal assemblies may provide an effective means for information encoding and communication (Buzsaki, 2006). The synchronous nature of neuronal activity has been explored for well over a century using extracellular electrophysiological recordings, which, even in the modern era of functional imaging techniques, remain key tools for studying cortical network dynamics. The extracellular voltage signals are due to transmembrane currents, which establish varying electric fields around each neuron. Sampling the high-frequency changes in these electric fields can reveal single- and multiunit spiking, while recording the lower-frequency components, termed the local field potential (LFP), detects the superposition of fields generated by synchronous synaptic and action potential activity. It is clear that neurons not only generate electric fields but are in turn sensitive to them (Jefferys, 1995; Weiss and Faber, 2010). However, whether the weak electric fields that are generated endogenously by physiological network activity have a significant effect on the constituent neurons has been an unanswered question. By applying a sophisticated combination of conventional electrophysiological and computational modeling techniques and developing an innovative "field-clamp" method for activity-dependent LFP modulation, in this issue of *Neuron*, Fröhlich and McCormick show that endogenous electric fields can indeed influence neuronal activity in the network that generates them, by providing a feedback mechanism that sharpens network synchrony (Fröhlich and McCormick, 2010).

In order to explore the possible reciprocal interactions between the LFP and neuronal activity, Fröhlich and McCormick focused on slow cortical network oscillations (<1 Hz) recorded in the visual cortex. These brain rhythms are observed during slow-wave sleep, anesthesia, and quiet wakefulness, during which cortical neurons display slow synchronous fluctuations between depolarized Up states and hyperpolarized Down states (Steriade et al., 1993) (Figure 1A). Their first approach was to use multielectrode probes to carefully measure the strength of the endogenous electric fields generated during Up states in vivo. This analysis revealed that Up states are associated with current sinks in deep cortical layers, and corresponding current sources close to the pial surface, with absolute electric field strengths reaching $\sim$2 Vm^{-1} at these dipoles. To test the effects of such electric fields on network activity, the authors then turned to a slice model of Up/Down states previously developed in their laboratory (Sanchez-Vives and McCormick, 2000). This preparation enabled the use of parallel bath electrodes to apply uniform electric fields across the slice, with a similar amplitude and polarity to those recorded in vivo, while the effects on neuronal activity were monitored using intra- and extracellular recordings. The key findings were that (1) static electric fields of 2 Vm^{-1} could depolarize deep-layer pyramidal neurons by $\sim$0.5 mV, (2) the same stimulus accelerated the frequency of slow oscillations, by reducing the time spent in the Down state, and (3) sine wave fields enhanced the periodicity of Up states at even lower thresholds of $\sim$1 Vm^{-1}. Moreover, the exogenous application of more naturalistic field waveforms, derived from LFPs observed in vivo, could modulate the temporal pattern of Up/Down states at amplitudes below 0.5 Vm^{-1}, due to the more rapid onset dynamics of the imposed Up state-like electric field. Together, these results provide evidence that natural neocortical network activity can generate electric fields of sufficient strength to influence itself.

To explore whether changes in somatic membrane potential induced by electric fields could explain their effects on network synchronization, Fröhlich and McCormick employed a computational network model that displays spontaneous Up/Down states. When the applied fields were mimicked by current injection across all neurons in the network, calibrated to induce realistic constant depolarization, they indeed found an acceleration of the slow oscillation. Sinusoidal current injections, within the intrinsic frequency range of spontaneous slow oscillations, were also found to increase Up state regularity. However, the reported changes in membrane potential may not explain all of the results. The applied fields were found to slightly reduce multiunit activity during spontaneous Up states in vitro, but intracellular current injection increased UP state firing rates in the slice and computational model, and imposed electric fields

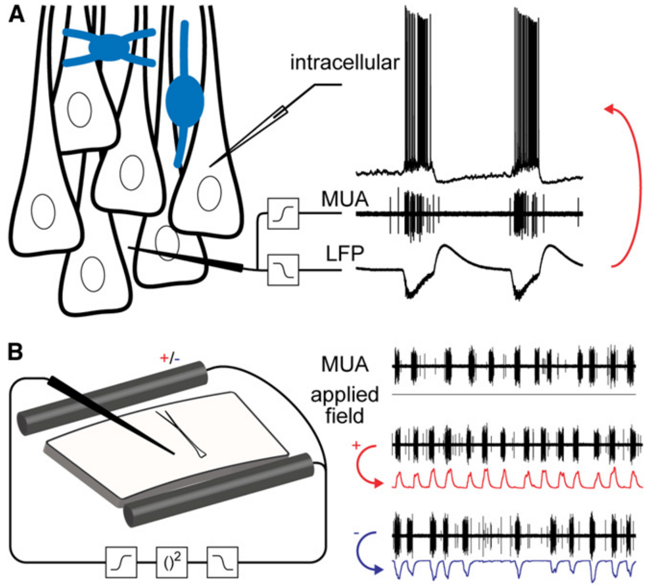

Figure 1. Schematic of the Role of Endogenous Fields in Feedback Network Synchronization

(A) During cortical slow waves, current-clamp recordings (intracellular) reveal that pyramidal neurons alternate between depolarized Up states and hyperpolarized Down states. Simultaneous extracellular recordings in the deep cortical layers show that Up states are associated with bursts of multiunit activity (MUA) and negative deflections in the local field potential (LFP), separated by high- and low-pass filtering, respectively. A possible feedback effect of the LFP on the network activity is indicated by a red arrow.

(B) To determine whether weak endogenous electric fields influence network activity, Fröhlich and McCormick developed a "field-clamp" circuit, in which the strength of electric fields applied across cortical slices was regulated in real time by the recorded multiunit activity (left). During spontaneous cortical slow oscillations, the application of positive-field feedback enhanced Up state rhythmicity, while negative feedback increased Up state variability (right). The depicted effects on the coefficient of variation of the Up state period (±50%) have been exaggerated for illustrative purposes.

also increased neuronal firing elicited by current injection in pharmacologically silenced slices. Electric fields are also likely to affect dendritic conductances, transmitter release, the diffusion of ions and charged neurotransmitters, and the activity of vertically orientated interneurons (Weiss and Faber, 2010). Nevertheless, from their computer model, the changes in somatic membrane potential appear sufficient to explain the effects of weak electric fields on Up state generation and rhythmicity, which might be amplified by circuit interactions (Purpura and McMurtry, 1965; Radman et al., 2007), and reflect the increased probability of recruiting a quorum of neurons to initiate a network phase transition out of the Down state.

The results presented so far, showing effects of weak electric fields on neuronal excitability and network synchronization, are consistent with those from similarly elegant studies performed in the hippocampus (Deans et al., 2007; Fujisawa et al., 2004; Radman et al., 2007). Determining the threshold and mechanisms of such electric field effects is important for assessing the health impact on people exposed to environmental electrical fields and for understanding the experimental and clinical applications of transcranial brain stimulation techniques. However, in extrapolating these effects to support a role for endogenous electric fields in modulating network activity, there could be the nagging doubt that if it is synchronous activity that generates the local field, is its positive effect on synchronization superfluous? In other words, are these field effects actually contributing to the synchronization itself, or do synapses have it all? In order to test this, Fröhlich and McCormick designed a simple version of an electric "field-clamp"—instead of applying the electric field across the slice continuously or at arbitrary time points, the electric field was coupled positively or negatively to the ongoing multiunit activity. Using this method, the authors demonstrate that boosting the endogenous electric field enhances Up state synchrony, while counteracting it increases variability, thus providing the first direct evidence that endogenous electric fields contribute to network synchronization (Figure 1B).

One caveat to this story, as acknowledged by the authors, is the simplicity of the applied field, which is linear and one-dimensional, in contrast to the nonuniform and three-dimensional structure of LFPs observed in vivo (Anastassiou et al., 2010). These inadequacies are clearest for the negative feedback experiments, in which it was only possible to suppress the endogenous electric field by <50%, due to the complexity of the endogenous field itself, and the difficulty of predicting its temporal profile from the local multiunit activity. In order to show the full influence of LFPs on network synchronization, it would be necessary to implement a true multidimensional field-clamp based on feedback via multiple LFP recording sites in vivo. It is not clear whether such a method is feasible, but it appears unlikely that the basic biological principle established would be altered.

At the cellular and network level, the endogenous fields appear to have three main effects on the cortical slow oscillation: increased frequency, increased regularity, and thus increased synchrony (Figure 1B). Thus, while the field feedback is not necessary for the slow oscillations to occur, it appears to enhance them. What are the implications for brain function? Very little functional evidence exists, but it has been reported that transcranial electric fields that boost slow oscillations during sleep potentiate subsequent memory recall (Marshall et al., 2006). The impact of endogenous field effects may be more apparent in pathological states. For example, feedback coupling between the LFP and network synchronization could contribute to the progressive intensification of cortical slow oscillations during ictal transition, as has been observed for sleep-related spike-wave seizures, and to the fast synchronization of epileptiform bursts (Jefferys and Haas, 1982; Timofeev and Steriade, 2004). Applying future variations on the "field-clamp" technique will hopefully provide further direct evidence for electric field effects in regulating both cortical function and dysfunction.

In conclusion, Fröhlich and McCormick convincingly demonstrate that the field generated collectively by neurons in a cortical network is of sufficient strength to influence the activity in the very network that generates it. This synchrony-enhancing effect of LFPs generated by physiological activity is a novel and interesting finding, but it should be noted that the significance of synchrony in cortical network function has itself been questioned (Shadlen and Movshon, 1999). Thus, the skeptic might argue that one epiphenomenon merely enhances another and dismiss this "cortical soliloquy" as a meaningless mumble. Nevertheless, these exciting results provide new insight into how cortical networks organize and regulate their own activity, and, by establishing this field effect, Fröhlich and McCormick have opened a new chapter in the exploration of the function of network synchrony.

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A Roadmap to Brain Mapping: Toward a Functional Map of Human Parietal Cortex

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In this issue of *Neuron*, Nelson and colleagues report a novel parcellation of human lateral parietal cortex based on task-induced response profiles and resting-state functional connectivity. Their findings inform current debates about the contributions of parietal cortex to cognition, including the retrieval of episodic memories.

What is the function of the parietal lobe in human cognition? Asking neuroscientists and cognitive psychologists this question would likely generate a wide range of answers. Responses might include such functions as attention, action intention, spatial perception, decision making, numerical cognition, working memory, and even long-term (episodic) memory retrieval. That the functions ascribed to the parietal lobe—more specifically, lateral parietal cortex—are vast and seemingly disparate has motivated efforts to carve the region at its anatomical and functional joints. While considerable progress has been made using architectonic methods in the postmortem human (Figures 1A and 1B) and nonhuman primate, initial functional parcellations of human lateral parietal cortex have been coarse grained. For example, a dorsal/ventral axis of parietal organization has been proposed based on studies of attention (e.g., Corbetta et al., 2008), episodic memory retrieval (e.g., Cabeza et al., 2008; Wagner et al., 2005), and resting-state functional connectivity (e.g., Fox and Raichle, 2007). While these initial functional parcellations have yielded important insights, continued advances in understanding lateral parietal function likely require specification of finer-grained organizational structure. In this issue of *Neuron*, Nelson et al. (2010) take a significant step along the road toward a fine-grained functional parietal map, revealing six functionally distinct regions in human lateral parietal cortex. Their findings may help resolve seemingly conflicting accounts of parietal function, including current debates about how the region supports retrieval of episodic memories (Cabeza et al., 2008; Hutchinson et al., 2009; Vilberg and Rugg, 2008; Wagner et al., 2005).

In their study, Nelson et al. partitioned the left lateral parietal cortex using a sophisticated approach that iterated