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Making Waves in the Neocortex

Minireview

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Neural oscillators are ubiquitous. Sometimes their functions are obvious: they generate rhythmic movements or synchronize an organism's behavior with its periodic environment. Ironically, the cerebral cortex is one of the most versatile oscillators in the brain, yet the functions of its rhythms are universally obscure. Its dominant frequencies span several orders of magnitude, from $<$1 Hz to $>$200 Hz. Neocortical oscillations and the synchronous firing associated with them are regionally specific, highly dynamic, often involve widely spaced groups of neurons, and can be temporally correlated with the most captivating features of perception, motor control, cognition, and states of arousal (e.g., Singer and Gray, 1995, and references therein). But correlations do not prove causality. The natural history of oscillations has inspired many proposals for their functions, ranging from none (oscillations as epiphenomena) to oscillations as a central substrate for cognition in the brain (for eclectic reviews, see Gray, 1994; Buzsáki et al., 1994). Theoreticians might take solace from the large variety of cortical oscillations; it sometimes seems that there is enough phenomenology to accommodate almost all proposals. But this nut is proving tough to crack experimentally. The evidence supporting specific functions is indirect at best but indisputably tantalizing.

The premise of this review is that understanding the mechanisms of oscillations may help to illuminate their function. We focus here on a few recent studies of the neocortex and its oscillations within two distinct frequency ranges: those between about 5–10 Hz, and the faster (gamma) rhythms of 30–70 Hz. We do not have space to discuss the functions of rhythms nor their generation by subcortical structures such as the thalamus. Synchronous oscillations necessarily require neuronal interactions, and we first describe work on networks of neurons that subserve rhythmic activity. Some neural oscillators include individual neurons that act as intrinsic pacemakers or cells that have selective membrane resonance in either sub- or suprathreshold domains. As we summarize here, some of these features have been observed in neocortical neurons.

Subnetworks of Neurons as Rhythm Generators

The most direct way to demonstrate the local origin of a synchronous rhythm is to record it in an isolated bit of cortex in vitro. Rhythms rarely occur spontaneously in slices of cortex, but they can be induced by appropriate stimuli or drugs. Results from recent studies suggest that distinct subpopulations of excitatory or inhibitory neocortical cells, facilitated by modulation of specific neurotransmitter systems, can mediate a variety of organized rhythms.

Flint and Connors (1996) showed that a network of excitatory cells in layer 5, in the absence of $GABA_A$ receptor-mediated inhibition, can generate spontaneous 8–12 Hz oscillations when the function of NMDA-type glutamate receptors is enhanced by low extracellular magnesium. In contrast, a distinct and much slower (1–5 Hz) synchronized activity is generated by excitatory cells in layer 2/3 when kainate-type glutamate receptors are activated. Intrinsically rhythmic pyramidal cells are suspected as the generators of the layer 5 oscillations (Silva et al., 1991), but the specific instigators of the layer 2/3 activity are unknown.

A series of intriguing studies by Traub, Jefferys, and colleagues suggests that networks of inhibitory neurons alone can generate synchronized gamma oscillations in cerebral cortex. Activating slices of hippocampus with an agonist of metabotropic glutamate receptors or with tetanic stimulation elicits synchronous synaptic events at frequencies of about 40 Hz (Whittington et al., 1995; Traub et al., 1996a). Inhibitory circuits are implicated because: blocking fast excitatory synapses reveals synchronous 40 Hz inhibitory postsynaptic potentials (IPSPs), all oscillations are eliminated by blocking $GABA_A$ receptors, and the frequency of the oscillations is decreased by prolonging inhibitory $GABA_A$ currents with barbiturates. A computer model suggests that oscillations depend on a tonically excited, mutually inhibitory network of interneurons. With intact circuitry, pyramidal cells are presumably synchronized by an oscillating inhibitory drive. Whittington et al. (1995) also briefly report that 40 Hz inhibitory events occur in pyramidal neurons of neocortex, when metabotropic glutamate receptors are activated while ionotropic glutamate receptors and $GABA_B$ receptors are blocked. Neither the phenomenology nor mechanisms of the fast neocortical rhythms were further explored, but a close comparison with hippocampal rhythms would be of great interest. As the authors point out, "it is possible that gamma oscillations arise by different mechanisms in different parts of the brain" (Jefferys et al., 1996).

A particularly interesting feature of gamma oscillations in the visual neocortex in vivo is that they can synchronize widely separated neuronal populations, often with nearly zero phase difference (Singer and Gray, 1995). A surprising mechanism for this is suggested by the modeling and experiments of Traub et al. (1996b) on hippocampal networks. Tight long-range synchrony occurs when the excitation of inhibitory interneurons reaches a level high enough to fire them with spike doublets rather than singlets; the interspike intervals of 4–5 ms during doublets effectively prolongs the "local circuit time constant," so that firing in the local population of neurons is more closely synchronous with firing in a more distant population that has been delayed by long axonal conduction times. Again, the applicability of this model to the neocortex (Jefferys et al., 1996) is unclear. Synchronization in vivo can occur across very

distant neocortical areas (Steriade et al., 1996) and even across the corpus callosum (Engel et al., 1991). The Traub model apparently requires a substantial number of inhibitory connections between synchronized groups; while most long-range connections in neocortex use excitatory synapses, there are indeed subsets of inhibitory cells with long axons that interconnect different visual areas (McDonald and Burkhalter, 1993). But are these connections dense enough, and do they contact inhibitory cells? Can the model account for close synchrony despite the wide range of distances (and thus conduction times) between oscillating neuronal groups in vivo? Do spike doublets actually occur in interneurons of oscillating neocortex? Answers will be difficult to obtain, but the Traub model provides specific and testable predictions.

Rhythmic Burst Firing in Single Neurons

One of the simplest ways to drive a group of neurons rhythmically is to endow some or all of them with membranes that can oscillate intrinsically. Cellular pacemakers are essential components of organized rhythms in oscillators as diverse as the heart and the thalamus. The large majority of neocortical neurons do not generate rhythmic firing patterns on their own, but two groups of candidate pacemaking cells, each with a different range of preferred frequencies, have been identified in the neocortex.

The first group of rhythmic cells generates repetitive bursts of spikes at frequencies of 5–15 Hz (Agmon and Connors, 1991), depending on stimulus intensity. These have been observed in primary somatosensory and visual cortical areas of several species (Amitai and Connors, 1994, and references therein). Bursts consist of 2–5 spikes firing at about 150–300 Hz. Rhythmically bursting pyramidal neurons are morphologically distinctive: they have a relatively large soma and apical dendrite, and they are projection cells, sending their axons to subcortical structures such as the superior colliculus, pontine nuclei, and spinal cord. Their axons also make local and long-distance excitatory connections within the cortex. Evidence that the rhythmically bursting cells of layer 5 may serve as pacemakers comes from studies of two experimental conditions in vitro: reduced GABAergic inhibition and enhanced NMDA receptor activity (Amitai and Connors, 1994, and references therein).

Gray and McCormick (1996) recently described a second, faster set of intrinsically rhythmic neurons in the cat visual cortex in vivo. Their onomatopoeically named "chattering cells" are distinguished by exceptionally fast action potentials that fire in intraburst frequencies up to 800 Hz. Depending on stimulus intensity, they can produce rhythmic bursts at rates from 20–80 Hz. Interestingly, the membrane potentials of chattering cells show no signs of intrinsic oscillations when stimulated at subthreshold levels. Staining shows that chattering cells are a subset of pyramidal neurons in layers 2 and 3. It is not clear whether they are morphologically distinct from other superficial pyramidal cells, and their detailed axonal patterns have not yet been described. The most salient feature of the chattering cells is their oscillatory response during visual stimulation. Characterization of their receptive fields revealed that, by classical criteria, chattering cells are simple cells. When presented with optimally oriented drifting light bars, they respond with rhythmic spike bursts of 20–80 Hz. Rhythmic spiking does not occur spontaneously. Compared to other physiological classes of cortical neurons during visual stimulation, chattering cells have the highest overall rates of firing, the greatest likelihood of high frequency bursting, and the largest subthreshold (presumably synapse-driven) membrane fluctuations in the gamma-frequency band.

The firing behavior of chattering cells is strikingly similar to the rhythmic, often synchronous firing of visually driven cells recorded extracellularly (Gray, 1994). This similarity, along with the cells' physiological and anatomical properties, suggest to Gray and McCormick (1996) that "a major component of visually evoked cortical gamma-band oscillations may be controlled by...CH [chattering] cells." This is certainly plausible, but the evidence so far is circumstantial. In their study, rhythms were evident in other physiologically defined cell types, including intrinsically bursting cells, but they were not as intense as in chattering cells. As usual in intracellular studies of cortex, recordings were particularly sparse from "fast-spiking cells"—those with the physiological signature of GABAergic inhibitory interneurons. Extensive analysis of these would be of particular interest, considering the proposal that inhibitory cells are necessary and sufficient to generate collective 40 Hz rhythms in both hippocampus and neocortex and that their doublet firing might account for long-distance synchrony (Jefferys et al., 1996, and discussion above).

Subthreshold Membrane Resonance in Single Neurons

Many neocortical neurons display subthreshold fluctuations of their membrane potential when depolarized to just below spike threshold. These oscillations are generated by intrinsic, nonsynaptic membrane conductances. Subthreshold oscillations occur in less than half of sampled pyramidal cells in vitro, where they generally have peak-to-peak amplitudes under 10 mV and vary in frequency from about 5–20 Hz (Silva et al., 1991; Amitai, 1994; Gutfreund et al., 1995). Oscillation frequency increases with membrane depolarization. In one report of neocortical neurons recorded in vivo, about 20% of projection neurons (presumably pyramidal cells, including transcallosal cells) displayed subthreshold oscillations of 20–40 Hz (Nuñez et al., 1992). Overall, the frequency range of intrinsic subthreshold oscillations in most pyramidal cells is lower than that of synchronized gamma-range oscillations. One report of recordings from smooth stellate neurons (presumed to be inhibitory interneurons) revealed subthreshold oscillations with a mean frequency of about 45 Hz (Llinás et al., 1991). Subthreshold oscillations in all neocortical cell types seem to depend on voltage-gated Na^+ and K^+ conductances (Llinás et al., 1991; Amitai, 1994; Gutfreund et al., 1995).

The functional significance of subthreshold oscillations in neocortical neurons is unknown. Presumably, subthreshold events are not communicated between neurons in the neocortex. How might subthreshold oscillations influence spike firing? Paradoxically, neocortical neurons with the most rhythmic intrinsic firing tendencies are also the cells with the least conspicuous

subthreshold oscillations (Amitai, 1994; Gray and McCormick, 1996). Moreover, as membrane oscillations exceed spike threshold, repetitive spikes are not simply triggered by oscillation peaks; spiking changes the timing of subsequent membrane events (Amitai, 1994).

Subthreshold resonance could affect spike-encoding properties by operating as a band-pass filter, preventing a cell (and consequently the network in which it is embedded) from encoding certain frequencies, while promoting others. Indeed, Carandini et al. (1996) recently demonstrated band-pass spiking properties by stimulating pyramidal cells with suprathreshold sinusoidal currents; spike generation was most probable on the depolarizing parts of the stimulus cycle, and the neurons' preferred frequency range was 8–30 Hz. However, when the stimulus current was switched to a pattern of broadband noise, frequency tuning widened considerably, becoming essentially flat from 0.1–130 Hz. The authors suggest that one function of gamma frequency cortical rhythms might be to broaden and linearize neurons' spiking responses to stimulus-related frequencies.

Riding the Waves

Our current understanding of cortical oscillators is decidedly weak. Their phenomenology needs closer study. For example, how much do the various specific subclasses of neurons participate during various oscillations, how do excitatory and inhibitory neurons interact, how large are synchronous rhythmic cell assemblies, and how and when do they alter their size? Studies of mechanisms are impeded by a classic experimental dilemma: even a local cortical network is too complex to analyze and understand fully when intact but reducing it also fundamentally changes it. Apparent insights from drugged models in vitro must somehow be tested in vivo and au naturel. Local neocortical oscillators also need to be understood within their larger context. In the thinking brain, they may rarely operate uncoupled from subcortical oscillators, in particular those of the thalamus, and it is clear that oscillations in connected regions interact (e.g., Nicolelis et al., 1995; Contreras et al., 1996; Steriade et al., 1996). The age-old observation that cerebral rhythms vary with functional states of the brain (Adrian and Matthews, 1934) implies that oscillators are dynamically regulated. Key mechanistic questions include: how do sets of local oscillators rapidly and specifically couple and uncouple within the cortex, and how are cortical oscillators controlled by the subcortical regulatory systems associated with arousal and sleep? Understanding the ultimate problem, the behavioral functions of neocortical oscillations, would benefit immensely from methods that disrupt synchronous oscillations while doing minimal damage to all other cortical processes. Pessimists will scoff that this can never be done selectively, but recent success with a remarkably analogous problem in the locust brain (MacLeod and Laurent, 1996) should give hope to those who investigate waves in the cerebral cortex of vertebrates.

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