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What Are the Local Circuit Design Features Concerned with Coordinating Rhythms?

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Abstract

This chapter outlines some of the basic features of neuronal circuits that underlie the rich diversity of population rhythms that can be generated in very small regions of cortex. Areas of cortex less than a millimeter square can generate rhythms from slow waves up to very fast oscillations using combinations of intrinsic neuronal properties combined with chemical and electrical synaptic connectivity profiles. Multiple concurrently generated rhythms can display many different forms of coordination: While mechanisms underlying coordination within individual frequency bands may play a role across frequencies, it is becoming clear that novel modes of coordination, such as concatenation, may also take place. The number of different neocortical rhythms capable of being generated so far shows a fixed relationship in the spectral domain. Building lower frequencies through concatenation of coexistent higher frequencies, across the EEG frequency range, provides a putative way to reconcile the existence of discrete frequency bands with the power law continuum observed in long-term EEG recordings.

Rhythm Generation in Cortex

The mammalian cortex *in situ* generates rhythmic activity over a very broad range of frequencies. The majority of these frequencies are capable of being replicated *in vitro* in small slices of tissue containing all layers of cortex with dimensions down to less than 1 mm. Rhythmic bistability in neuronal membrane potential, corresponding to repetitive periods of population activity and quiescence, occurs at frequencies around and below 0.1 Hz spontaneously in the absence of external excitation or neuromodulation. At the other end of the spectrum, neocortical tissue excited with glutamatergic or cholinergic receptor

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activation generates transient population frequencies up to 400 Hz. Analysis of long-term local field potential, far-field potential, and extracranial EEG recordings suggest a continuum of spectral activity between these extremes, typically with a power law relationship between spectral energy and frequency. However, carefully controlled cognitive and motor-behavioral tasks, and specific patterns of cortical activation and neuromodulation, reveal a range of discrete frequency bands *in vivo* and *in vitro* respectively. In older cortex, with one main layer of principal cells, these discrete rhythms exhibit an interrelationship such that modal frequencies have a ratio approximating to the natural log (e, c.2.7; Buzsáki and Draguhn 2004). In polymodal areas of neocortex, with at least two main principal cell layers (crudely, deep and superficial pyramidal cells), approximately twice as many peaks per spectral band are seen with ratio near $e^{0.5}$ (c.1.6; Roopun, Kramer et al. 2008). In the latter case, combination of such sets of frequencies can produce spectra that approximate very well to the power law relationships seen in long-term *in vivo* recordings (Figure 8.1).

The apparent correlation between the number of different populations of principal cells and the number of discrete frequency bands seen, and the ability to reproduce a huge range of these frequency bands in very small sections of cortex, suggests that the majority of basic rhythm-generating properties of neuronal populations may be held within local circuits. This counters the notion that slower and slower frequencies are generated as emergent properties of larger and larger networks. Instead, it supports the idea proposed by Mountcastle (1978) that the neocortex is functionally and anatomically modular, down to the scale of individual columns. Is this, however, feasible? Columns, of which there are many functional subtypes, each contain neurons of many different types based on morphology, spiking patterns, synaptic targets, and immunocytochemical signature. There are over seven different types of principal cells and many more different subtypes of inhibitory interneurons (the primary coordinators of local circuit behavior). Thus, if specific rhythms emerge as a property of specific local circuits containing different, interconnected principal cells and interneurons, then a great many different rhythms are possible in such a small region. Next we discuss some of the better-understood properties of local circuits and their member neurons that influence network rhythm generation and coordination.

Which Features of Local Circuits Generate Rhythms?

Even the simplest local circuits have many properties that favor rhythm generation. While many of these are often found to operate synergistically, it is worth considering them separately to get a sense of why rhythms are so ubiquitous a feature of electrical activity in cortical resting state and response to input. In addition, the local circuit mechanisms that generate rhythms are often

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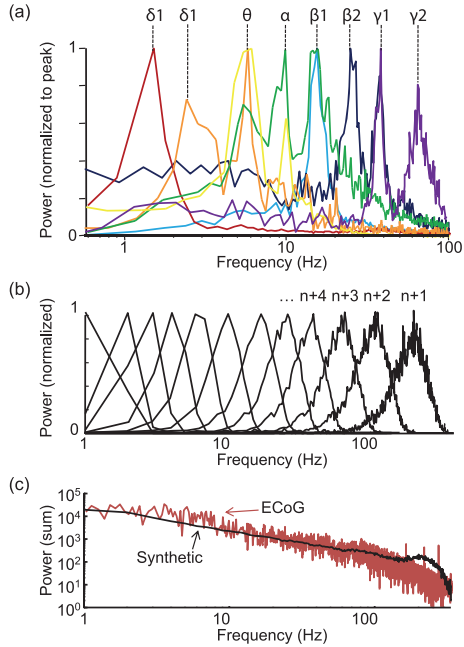

Figure 8.1 Multiple discrete frequencies of local circuit rhythm: relation to long-term EEG spectra. (a) Multiple modal peak frequencies of persistent rhythms generated in isolated neocortex *in vitro*. All rhythms were generated in secondary somatosensory (parietal) cortical slices maintained in artificial cerebrospinal fluid (aCSF). Rhythms were recorded as local field potentials (LFPs); resulting spectra (from 60 s epochs of data) are plotted with powers normalized to modal peak. In control slices, δ1 (~1.5 Hz) rhythms were generated spontaneously after > 1 h incubation in normal aCSF; δ2 (2–3 Hz) rhythms were generated by bath application of cholinergic agonist carbachol (2 μM). Both delta rhythms had maximal amplitudes in layer 5. In the presence of the glutamatergic receptor agonist kainate (10 nM), θ (6–8 Hz) rhythms were recorded in layers 2/3 and occurred concurrently with δ2 rhythms in layer 5. Following transient activation of cortex by pressure ejection of glutamate, α (~10 Hz) rhythms were generated. Peak amplitude was in layer 5 and was present concurrently with θ and β1 rhythms in layers 2/3 and layer 4, respectively. Following tonic activation by kainate (400 nM), β1 (13–17 Hz) rhythms were generated alone by partial blockade of AMPA/kainate receptors; β2 (22–27 Hz) rhythms were generated in layer 5 by kainate (400 nM) and always occurred concurrently with γ1 (30–50 Hz) rhythms in layers 2/3 in this brain region. Also generated by kainate (400 nM) were γ2 (50–80 Hz) rhythms, but these occurred in layer 5 in aCSF with reduced chloride ion concentration. Additional peak frequencies at ≥ 100 Hz are generated by brief, intense periods of excitation but rarely met the criteria for persistence and thus are not considered here. (b) Similar ratios of adjacent frequency bands can be generated by concatenation of an initial Gaussian white noise source with mean frequency 200 Hz and standard deviation 10% of mean. Lower frequencies were generated from this source by iterating period n = period n–1 + period n–2. (c) By transforming the initial noisy signal into a set of periods (1000 consecutive period widths) iterative concatenation of this set, keeping all previous iteration sums, a power law spectrum ("synthetic," black line) results which closely resembles that from 10 minutes of human temporal cortical ECoG data ("ECoG," red line).

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also those mechanisms manipulated in larger-scale networks to coordinate rhythms spatially and spectrally.

Intrinsic Properties

Individual neurons often show subthreshold membrane potential oscillations. In some cases, these oscillations occur over a narrow range of frequencies, such as for inferior olivary neurons, but more often the frequency is determined, to some extent, by background mean membrane potential (Hutcheon and Yarom 2000). Subthreshold oscillations occur mainly at the lower end of the EEG spectrum. Frequencies around delta, theta, and alpha are most common but oscillations within the beta band are also seen in neocortical pyramidal cells. While these rhythms occur in the absence of action potential generation, they can precipitate spiking when neurons are close to sodium spike threshold. The resulting interaction between a subthreshold rhythm and all-or-none spike generation results in mixed-mode oscillations that may lead to very robust, regular outputs from neurons in the absence of patterned input, or more complex oscillations on multiple timescales with exquisite sensitivity to individual intrinsic conductances (Krupa et al. 2008). They are also closely related to the phenomenon of resonance in neurons (Hutcheon and Yarom 2000). Here, intrinsic properties produce a highly selective frequency filter for neuronal inputs, effectively dictating in which local circuit rhythm a neuron may actively participate.

The intrinsic conductances that give rise to subthreshold oscillations are manyfold. In general at least two conductances are required, with at least partially overlapping, but opposing membrane voltage sensitivities. If such pairs of conductances were instantaneously active, or both constantly active, then a stable equilibrium for membrane potential would be reached. However, with a temporal component—essentially the activation and inactivation/deactivation kinetics of the channels involved—the system "hunts" constantly for, but never reaches, a stable equilibrium state. The resulting oscillation, therefore, has a frequency related to the kinetics of the component conductances. Most commonly involved conductances include those generated by persistent sodium channels, low-threshold activated calcium channels, HCN channels, and a wide range of potassium channels. Of the latter, it is worth noting the m-current, which can "tune" frequencies of axonally generated rhythms (Roopun et al. 2006) and potassium channels, which are sensitive to the ATP content of neurons, allowing network rhythm generation to be linked to the metabolic state of the cortex (Cunningham et al. 2006).

Synaptic Excitation

In cortex, a proportion of principal neurons are locally coupled by excitatory synapses. While it is theoretically possible for such networks to generate local

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rhythms alone, the occurrence of these excitatory connections locally is rather sparse. Estimates from paired principal cell recordings put connectivity probabilities between ca. 1:400 and ca. 1:40 per randomly sampled local cell pair. In addition, the pre- and postsynaptic properties of local excitatory synapses indicate this form of local communication is, for the most part, rather weak. Action potential-initiated presynaptic glutamate release probability is very low for single action potentials (but grows markedly for rapid trains), and postsynaptic unitary events generate target neuron membrane potential changes of a fraction of a millivolt. Excitatory synapses are usually compartmentally localized on dendrites, with sometimes considerable electrotonic distances between synapse and cell soma, again making such activity a rather weak driver of local network rhythms. However, in certain situations the properties above can combine to produce strong local activity. In models of epiletiform activity, a preponderance for burst discharge generation favors glutamate release and temporal summation of dendritic excitatory postsynaptic events. This, coupled with lowered levels of inhibition to reduce postsynaptic voltage shunt can lead to overt, locally synchronous network bursting rhythms in the theta to low beta frequency ranges (Traub et al. 1987). Combinations of recurrent excitation and intrinsic conductances (above) are seen to generate very low (>1 Hz) frequency rhythms in more physiological conditions. For example, temporal summation of background kainate receptor-mediated recurrent excitatory events can combine with intrinsic conductances to generate slow-wave oscillations in some cortical areas (Cunningham et al. 2006), a phenomenon recently termed "group pacemaking" when seen in central pattern-generating circuits.

Synaptic Inhibition

Synaptic inhibition is a critical, causal feature of rhythm generation in local networks for frequencies ranging from the theta to gamma range (~ 4–80 Hz). Local circuit interneurons are readily induced to fire by even extremely low levels of excitatory neuronal activity within a network. Differences between excitatory inputs to interneurons and to other principal cells may underlie this. Presynaptically, glutamate release occurs with a high probability, even for single action potentials reaching the terminal. The resulting unitary postsynaptic responses are considerably larger than counterparts in principal cells and have much faster kinetics, which affords a high degree of temporal precision to interneuron activation. Coordinated recruitment of local interneurons is also common, with a high degree of recurrent synaptic inhibition and gap junction-mediated excitation between interneurons of many different types observed. This, coupled with the enormous convergence of excitatory inputs to interneurons and divergence of inhibitory outputs back to principal cells, provides an ideal substrate for the generation of locally synchronous population rhythms.

With synaptic inhibition-based rhythms, the frequency is set predominantly by the kinetics of the inhibitory postsynaptic potentials onto participating

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neurons. For gamma rhythms generated solely by tonic depolarization of interneurons, it is the inhibitory postsynaptic potential between interneurons that sets the frequency. The size and kinetics of these events can support local population rhythms from a frequency of ~30 Hz up to ~80 Hz, but not higher (Traub et al. 1996). Recent reports of cortical activity patterns with frequencies above this have labeled the rhythm "high gamma." This may be slightly misleading as such rhythms cannot be supported by synaptic inhibition and clearly involve different network mechanisms (see below). Inhibition-based rhythms dependent on phasic-synaptic excitation of interneurons are more dependent on the kinetics and amplitude of inhibitory events onto principal cell perisomatic compartments. As such, their frequency range tends to be lower (only going up to ~60 Hz), reflecting the slower kinetics of this form of inhibition compared to recurrent interneuronal inhibition. Lower frequencies than gamma can also be produced by inhibition in a manner that is also dependent on postsynaptic inhibitory event kinetics. Theta rhythms depend on GABAergic inhibition to distal dendrites of principal cells. While the resulting inhibitory postsynaptic event at somata is broadened and slowed by cable properties of dendrites, it has also been shown that the dendritic synaptic current itself has much slower kinetics than those generated by perisomatic targeting interneurons (Banks et al. 2000).

Gap Junctions

Local circuit rhythms occurring at frequencies faster than the conventional gamma band ("high gamma" VFO, "ripples") may occur transiently associated with high frequency discharges in interneurons (Buzsáki et al. 1992), but appear to be generated primarily by nonchemical synaptic communication between neighboring principal cells when studied *in vitro*. In particular, gap junctions between axonal compartments have been shown via dye coupling and electron microscopy (see Hamzei-Sichani et al. 2007) and can support very rapid transmission of action potentials from one axon to another. Sparse (>2 gap junctions per axon) local connectivity of this type generates rhythms up to several hundreds of Hertz, with period duration determined as a statistical property of the "random" network of coupled axons: the mean "path length." These very fast oscillations (VFO) are often seen nested within slower rhythms: In layer 5 neocortical neurons, gap-junctionally coupled axons generate very transient epochs of VFO which are organized into a beta2 frequency population rhythm by the intrinsic properties of individual axons (mainly the m-current). During persistent gamma rhythms, VFO is also seen nested within each gamma period and is the fundamental driving force behind such rhythms (Traub et al. 2003). VFO is also seen accompanying neocortical theta rhythms, alpha rhythms, and even up states, suggesting that gap-junctionally coupled axonal networks may represent the primary source of "noise" used by local cortical circuits to generate rhythms.

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Which Features Are Involved in Dynamic Coordination?

Coordination within a Frequency Band

Synchronization, with near-zero millisecond delay, is a feature of spike generation in populations of neurons responding to patterned sensory input (Gray and Singer 1989). The occurrence of a set of neurons that, at least transiently, generate spikes at the same time is used as a definition of a cell assembly—a subset of all active neurons in a population whose coordinated spike timing represents a central code for features in the sensorium. Zero-phase synchrony among cortical neurons can be readily achieved if each neuron receives a precisely identical pattern of ascending input, but it is difficult to see how such an input can occur, at least for thalamocortical inputs, when the duration and onset kinetics of activation are relatively slow. In such a case the assumption is that synchrony is generated from properties of the cortical neuronal network itself, yet how can this occur when direct connectivity between principal cells is far from 1:1 (see above), kinetics of such connectivity are rather slow, and conduction delays between neurons are finite and distributed over a broad range relative to the temporal precision observed? The key appears to be in the dominance of feedforward inhibitory neuronal activation in corticocortical connections. Here, both local and distal principal cell outputs can converge on single interneuron populations to generate temporally precise postsynaptic events which, in turn, can tightly control the timing of local principal cells. For these reasons it is perhaps not surprising that cortical rhythms during which synchrony is most readily observable are often inhibition-based (e.g., gamma and beta oscillations).

For gamma rhythms, the mechanisms that are perhaps best understood are those involving the coordination of activity in multiple, spatially separated neuronal populations. Consider a local gamma-generating circuit that comprise principal neurons and perisomatic targeting interneurons and provide a source of phasic, $GABA_A$ receptor-mediated synaptic inhibition. Such a circuit controls the timing of principal cell spiking via simple, local feedback inhibition, effectively providing a window of opportunity for principal cell spike generation a few milliseconds wide every gamma period. Many such local circuits may exist independently in cortex in the absence of functional connectivity between them, but such independence implies no fixed phase relationship between spike timings for neurons in different local circuits (Figure 8.2a). However, with connectivity between separate local circuits, coordination of each gamma rhythm is readily observed. The key feature of such coupled networks that provides the mechanism for this coordination is feedforward inhibition. Interneurons in a local circuit receive temporally precise excitatory synaptic input from both local and distal principal cells in such a manner that the phase difference, and conduction delay, between local circuits is effectively coded in the time difference between spike doublets generated in one gamma

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period—the first spike arising from local synaptic excitation, the second coming from the distal feedforward input (Figure 8.2b; Traub et al. 1996).

The consequence of spike doublet generation is a compound inhibitory input to principal cells, which effectively prolongs the gamma period during which spike doublets occur. For such a system to provide a means for principal

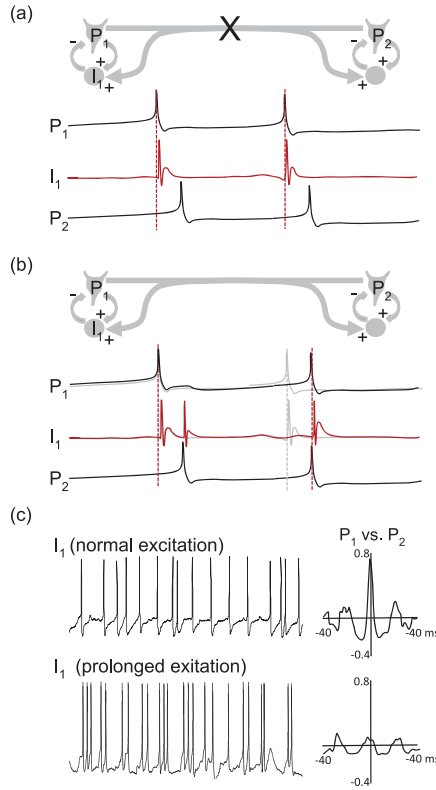

Figure 8.2 Feedforward inhibition provides a substrate for long-range synchrony during gamma rhythms. (a) At its most basic level, the local circuit gamma generator consists of reciprocal synaptic connections between principal neurons and interneurons. Principal neurons also have long-range axon collaterals that preferentially target distal interneurons. Without these, principal cell spiking in two such local circuits is not coordinated. Scheme shows the pattern of interneuron and principal spiking for the left-hand local circuit compared to the principal spiking in the unconnected right hand circuit. (b) With functional long-range feedforward inhibition, interneurons receive excitatory inputs from both local and distal principal cell populations (defined by a common mean delay, illustrated as P_1 and P_2, respectively). This generates spike doublets and prolongs the period of inhibition projected to local principal cells. This prolonged period of inhibition causes phase delay and brings the two principal cell spikes into synchrony. (c) The above mechanism is exquisitely sensitive to the amplitude and kinetics of excitatory input onto fast spiking interneurons. Disruption of this with genetic manipulation of AMPA receptor subunits causes excessive spike generation in interneurons and consequent disruption in long-range synchrony (Fuchs et al. 2001).

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cell spike times to converge on synchrony, the relationship between spike doublet interval and period duration change has to be nonlinear. This nonlinearity is observed both experimentally and in computational models: The shorter the doublet interval, the smaller the second component of the principal cell–inhibitory synaptic event through basic paired pulse depression. If the time difference between distal and local inputs to an interneuron is very short, then the probability of generating the second spike in a doublet decreases owing to the kinetics of spike after hyperpolarizations in interneurons. This latter mechanism is sufficient, alone, to induce synchrony with spike doublets in computational models. In addition, this method of "correction" for spike timing differences can only work when spike delays are less than ca. 20% of the period length. This implies that coordination of rhythms over longer conduction delays requires longer period widths (slower frequencies). A comparison of the synchronizing properties of inhibition-based gamma and beta rhythms has shown that beta rhythms are indeed more effective coordinators of activity across longer conduction delays for this very reason (Kopell et al. 2000). A prediction from this mechanism is that disruption of interneuronal spike doublet generation should have a detrimental effect on coordination of gamma rhythms over distance. Such an effect is observed if the kinetics of excitatory inputs to interneurons is altered genetically (Figure 8.2c; Fuchs et al. 2001).

The mechanism described above links principal cell spike generation causally to the generation of coordinated gamma rhythms themselves. However, more recent evidence using powerful and elegant analysis of relative spike times has revealed that stable sequences of spikes can occur within the duration of the window of activity afforded by gamma rhythms (about 5 ms maximum). In the visual cortex, stable phase differences between spike times and the ongoing gamma rhythm correspond to the "goodness of fit" between stimulus presented and the orientation preference for individual cells (Fries et al. 2007). It is difficult to consider how such small but robust interspike intervals can be maintained using conventional models of rhythm generation which involve orthodromic neuronal spike generation: Combinations of a stable population of rhythm and spike rate differences around the population frequency would lead to phase precession rather than stable phase differences, and heterogeneity in neuronal excitation amplitude and timing do not generate stable, non-zero phase differences—at least during gamma rhythms in hippocampus.

To generate robust phase differences in the order of a few milliseconds, a system is needed with network time constant of equivalent order or less. Such a system exists when considering gap junctional connectivity between principal cell axons (see above). Networks of interconnected axons generate rhythms with periods dictated by the network structure itself. Activity percolating through a randomly connected network has a mean path length: the average number of intermediate axons an action potential needs to "jump" across to travel from any given axon to another. Each "jump" takes a finite time, ca. 0.25 ms. The period of oscillation in such a system is therefore the mean path length

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multiplied by this time constant. Types of slower population rhythm exist in which such activity underlies the pattern of synaptic events observed (e.g., persistent gamma rhythms and beta2 rhythms in association cortex). During persistent gamma rhythms, principal cell spikes are predominantly antidromic, with activity originating directly in axons. The temporal structure generated by such axonal network activity is directly observable in the compound excitatory synaptic events that recruit interneurons (Figure 8.3; Traub et al. 2003). An

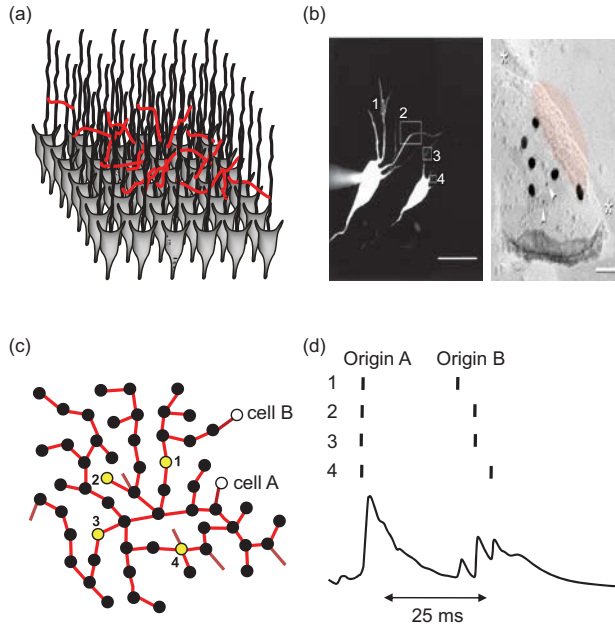

Figure 8.3 Evidence for nonsynaptic axo-axonic connectivity underlying persistent gamma rhythms. (a) The underlying feature of local circuits that supports persistent oscillations in the gamma and also beta2 band appears to involve direct, gap-junctional connectivity between axonal compartments of principal cells. Local axonal collaterals form a sparsely interconnected network that allows action potentials to pass from one principal cell to another. (b) Anatomical evidence for this is far from equivocal. Time-lapsed dye-coupling images, however, show passage of dye from one axonal compartment to another in a nearby cell (left), and FRIL electronmicroscopy shows small-diameter gap junctions between hippocampal principal cell axons (right). At least some of the connections involved in these gap junctions are of the type cx36, shown by the anti-Cx36 immunogold beads (Hamzei-Sichani et al. 2007). (c) Computational modeling of random, locally connected axons from regular spiking pyramidal cells reproduces many of the features of nonsynaptic communication underlying VFO and gamma rhythms. Scheme shows a small part of a large network of axons demonstrating the profile of connectivity needed. (d) Such connectivity allows activity to percolate through the network, generating sequences of action potentials with short, but finite, phase delays when seeded from the same source. Changing sources of initial action potentials also changes the pattern of phase delays, as observed in compound synaptic potentials to local circuit interneurons during gamma rhythms.

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additional consequence of such a mechanism is that stable, though brief, relative spike delays are readily generated, with the sequence of spike generation dictated by the network structure and the origin of the first spike in a sequence (Figure 8.3)—a simple, nonsynaptic analog of synfire chains. While such a mechanism provides an attractive working hypothesis for very rapid spike sequences, during a slower rhythm it is not without problems. Spike propagation through axonal plexi is exquisitely sensitive to well-characterized synaptic excitatory and inhibitory events, but requires that somatic action potentials be predominantly antidromically generated—something that runs counter to the conventional neuronal doctrine.

Coordination between Frequency Bands

In addition to coordination of rhythms of the same frequency, generated in spatially separate cortical regions, coordination of rhythms of different frequencies is also seen. This can occur in a single brain region or in multiple, interconnected regions, and takes a variety of forms. One of the most commonly observed interactions between frequencies is the amplitude modulation of a higher frequency coordinated with the phase of a lower frequency—nesting. This is seen for multiple rhythms nested within neocortical delta activity (Lakatos et al. 2005; Figure 8.4) but is currently best studied in hippocampus, where VFO is seen nested within gamma rhythms which are, in turn, nested within theta rhythms.

The local circuit features required for nesting of gamma within theta rhythms are understood at a basic level. Gamma rhythms are generated by reciprocal interaction between principal cells and fast-spiking, perisomatic-targeting interneurons, whereas theta rhythms may occur from the coordinated output of a different subset of interneurons providing slower inhibition to distal dendritic compartments of principal cells. This compartmental separation of two inhibitory inputs allows a division of labor such that theta rhythms organize dendritic excitatory inputs in "packets" during a broad window of opportunity around 50–100 ms wide. Perisomatic gamma frequency inhibition then coordinates the output from these excitatory epochs at a finer timescale. Evidence suggests that appropriate nesting of gamma and theta inputs, and thus timing bursts of gamma frequency input with excitatory input, is done by mutual interaction between the two interneuron subtypes: Theta frequency outputs from oriens-lacunosum molecular interneurons organize basket cell outputs into packets of spikes coincident with the period of maximal dendritic principal cell excitation. In turn, output from basket cells provides trains of inhibition to oriens-lacunosum molecular interneurons to activate an intrinsic h-current and thus time rebound spiking in these cells (Rotstein et al. 2005).

Other forms of interaction can be seen in phase synchrony measures across frequency bands in cortex. Here synchrony is seen when the period length of one locally generated rhythm is an integer multiple of another locally

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generated rhythm (Figure 8.4). Such a situation requires that outputs from at least one neuron be critical to both rhythm-generating circuits. Paired neuronal recordings in human cortex suggest that this is entirely feasible, with multiple delay times evident for a single neuron activation of a number of different, interconnected local neurons (Molnar et al. 2008). When period lengths for two or more local rhythms are closely—but not exactly—matched, variable phase relationships may occur. Rhythmic changes in phase relationship are seen between superficial and deep neocortical laminae-generating gamma and beta2 frequency rhythms, respectively. Here, the pattern of phase change is determined by the trigonometric identity relating the two coexistent frequencies (Roopun, Cunningham et al. 2008; Figure 8.4).

This latter example of coordination of rhythms between different local cortical laminae reveals some aspects of the dynamic complexity inherent in a system with discrete sequences of rhythm, illustrated in Figure 8.1. In particular, with the ratio of adjacent frequencies seen in neocortex (ca. 1.6), the rate of phase change seen between two adjacent rhythms in the sequence corresponds to the frequency of the next rhythm in the sequence. For example, superficial gamma rhythms and deep beta2 rhythms in parietal cortex generate a phase relationship that cycles at beta1 frequencies (Figure 8.5a). What is also apparent

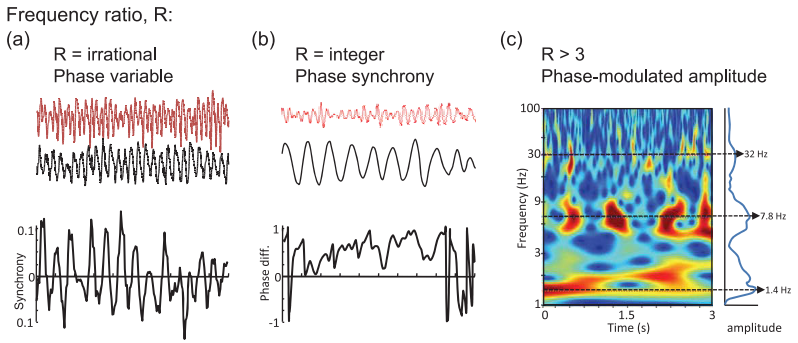

Figure 8.4 Common signatures for cross-frequency coordination. (a) When frequency ratio (R) is irrational, the phase relationship between two concurrently generated frequencies is nonstationary. Traces show LFP activity in superficial and deep cortical laminae during concurrent γ1 and β2 rhythm expression (Roopun, Cunningham et al. 2008). In this case, average synchrony between oscillators is near zero, with a periodic change in instantaneous phase corresponding to the sum of the periods of the two rhythms shown. (b) When R is an integer, a stable phase difference can be seen between the two rhythms recorded from single or pairs of brain regions. The figure shows bandpass filtered activity within the γ1 and α bands in MEG recordings, and the corresponding plot of phase difference between the bands (modified and reproduced with permission from Palva et al. 2005). (c) When R is relatively large, "nesting" of coexpressed frequencies may occur. The phenomenon is observed as an amplitude modulation of one frequency relative to the phase of a lower frequency. The figure shows the nesting of spontaneous γ1 rhythms within a concurrent θ rhythm, and the concurrent amplitude modulation of the θ rhythm by a coexistent δ1 rhythm in macaque supragranular cortex. (Figure modified and reproduced with permission from Lakatos et al. 2005).

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is that, following a period of concurrent gamma and beta2 rhythm generation, reduction in excitation to the cortex stabilizes the phase relationship between deep and superficial layers, with the beta1 frequency now manifest directly in

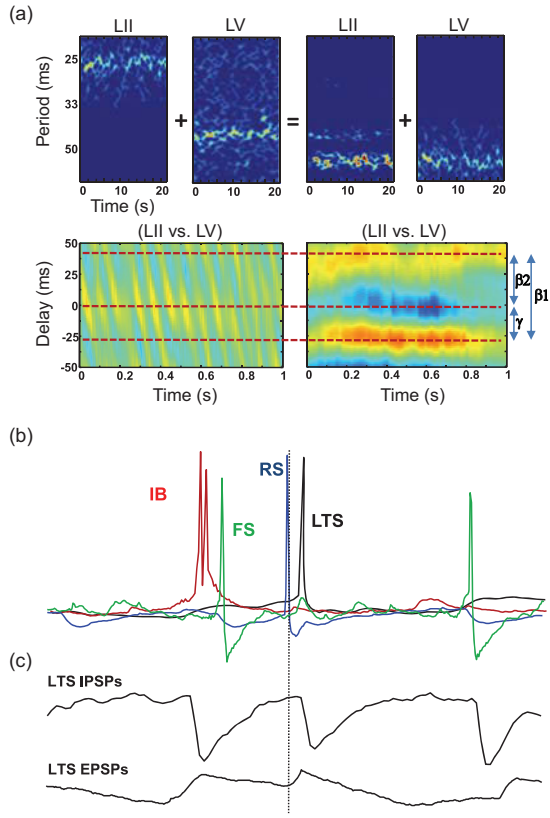

Figure 8.5 Local circuit features underlying period concatenation. (a) Somatosensory cortical slices generate concurrent γ and β2 rhythms in superficial (LII) and deep (LV) laminae, respectively. Reduction in excitation to cortex translates these two rhythms into a single β1 frequency rhythm seen in all laminae. Generation of a β1 rhythm from two preceding rhythms changes the phase relationship between laminae. With γ and β2 rhythms, interlaminar phase difference is nonstable showing rapid, rhythmic phase precession repeating every ~60 ms. Emergence of β1 oscillations stabilizes interlaminar phase relationship, with lag and lead times corresponding to the original γ and β2 period lengths (b) The β1 rhythm is accompanied by a pattern of spike generation in neurons suggesting concatenation: LV intrinsically bursting (IB) cells activate fast spiking (FS) interneurons with short latency. Superficial pyramids (RS) spike on the rebound of an inhibitory postsynaptic potential (IPSP) from these FS cells and proceed to activate low threshold spiking (LTS) interneurons with short latency. Following a slow inhibitory synaptic event from LTS cells, IB cells rebound to spike again. (c) The sequence of concatenated spiking of FS and LTS cells can be seen in the inhibitory synaptic potential generation in individual LTS cells. In addition, the concatenation sequence of IB and RS cell spiking is also visible in this cell type.

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the raw local field potential in both layers (Figure 8.5b). Clues as to how this occurs come from the nature of this stable phase relationship: The periods of the original two rhythms (gamma and beta2 frequency) are observed in the cross correlation, suggesting that one period of the observed field potential beta1 rhythm is composed of sequential periods of the original gamma and beta2 oscillations. In other words, the two rhythms now have concatenated periods, with the simple sum of the two original periods corresponding to the new beta1 rhythm generated by reduced excitatory drive.

Two features of the local neocortical network appear vital in facilitating this concatenation process. First, as the degree of excitation of cortical neurons needs to be reduced to see this phenomenon, there is insufficient tonic drive to principal cells to sustain spontaneous action potential generation. Instead, spikes are generated through rebound excitation mediated by activation of an intrinsic conductance, Ih (Kramer et al. 2008). Second, interneurons must still be active to provide the hyperpolarization required to bring membrane potential of principal cells down to levels where Ih can participate in rebound depolarizations. Two subtypes of interneuron are required for the coordination of superficial and deep layer local circuits to generate the concatenation sequence. First, burst firing in layer 5 principal cells activates superficial fast-spiking interneurons. These interneurons provide a brief inhibitory postsynaptic potential to superficial principal cells (as they would do during gamma rhythms) inducing a rebound action potential thereafter. This superficial principal cell output is sufficient to activate the second interneuron subtype involved: low threshold spiking cells. Output from these interneurons target dendrites of principal cells, producing a slower inhibitory postsynaptic potential which causes rebound spiking approximately one beta2 period later (Figure 8.5c). Thus, as seen for coordination of gamma rhythms alone, both interneurons and intrinsic neuronal properties also combine to provide a mechanism for coordination of rhythms at different frequencies.

Why Have Dynamic Coordination of Rhythms?

The role of dynamic coordination within a frequency band has been highlighted particularly well for gamma and beta rhythms with respect to cognition and motor control, respectively. In each case, the key feature of the rhythm is that it temporally coordinates firing patterns of neurons to provide "windows of opportunity" for coactivation. The phase relationship between a rhythm at two spatially separate sites governs the relative timing of local activity at one site and distal synaptic inputs from the other. Such a relationship powerfully modulates the ability of one site to interact with the other and controls the degree of synaptic plasticity at each site, thus also influencing future interactions. Therefore, the degree of coherence of rhythms (whether field potentials or spike trains) has been shown to signal the degree of "communication" between

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structures: a large-scale network property with documented behavioral correlates (e.g., Baker 2007; Fries 2005). In addition, even small changes in mechanisms underlying such interactions may correlate with underlying pathology in psychiatric illness (e.g., Phillips and Silverstein 2003; Roopun, Cunningham et al. 2008). Whether we can apply that which we have learned from such studies to coordination across different coexistent frequency bands remains to be elucidated.

The observation of multiple discrete frequencies in neocortex suggests a possible general scheme of rhythm generation where different "frequency channels" are used to process different forms of information. However, thus far this has been observed mainly in association cortex, and the *in vitro* experimental models used provided a highly reduced and stable rhythm-generating environment. Transient, as opposed to persistent, cortical drive generates a broad range of frequencies, and thalamic—and external sensory—involvement in cortical function also generates variable frequencies. For example, thalamocortical spindle oscillations may vary in frequency from within the delta band up to beta frequencies, variable whisking frequency (around the theta/alpha bands) can be matched by oscillations in superficial barrel cortex, and cortical theta rhythms may be variably paced by the sniff cycle in rodents. In addition, frequencies of network rhythm can be observed in cortical regions other than association areas that do not fit the concatenation sequence. Gamma rhythms in primary, auditory, and visual cortices have different frequencies which do not directly correspond to that seen in parietal cortex, and entorhinal cortex can generate two gamma rhythms through different local circuits, only one of which is frequency-matched to the gamma rhythms seen in association cortex.

Questions remain: Are different discrete frequencies, and their coordination patterns, of any importance to cortical function? Do they just represent a very specific activity state of cortex whose dynamic signature we can record and recognize? Are they purely epiphenomenal? Do they form the substrate for all higher-order dynamics in brain? Given their overt expression in isolated, persistently oscillating association cortex, concatenated sequences of frequency bands may represent a spectral baseline upon which polymodal sensory and neuromodulatory influences may act. The functional significance of the ratio between multiple frequencies illustrated here for gamma and beta rhythms is not yet understood for neuroscience, though it has been much discussed in the context of other natural systems. In the current context, this ratio fosters minimal interference between coexistent frequencies, something that could not be relied upon in a system composed of multiple, continually variable rhythm generators. It has been proposed that sensory information may be handled more efficiently if it is processed along multiple "channels" with differing temporal scales (Wiskott and Sejnowski 2002). For example, evidence for the segregation of sensory information into different "frequency channels" is apparent from studies examining how different levels of detail in the visual field are processed (Smith et al. 2006). In this study, perception based on processing coarse

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level features occurred at theta frequencies, whereas perception of objects requiring more detailed features was associated with a faster, beta frequency rhythm—an observation which fits with the decrease in precision of tuning curves for visual cortical neurons with decreased spike frequencies. A ratio of ca. 1.6 between coexpressed frequencies may permit many "channels" for information processing to coexist with minimal temporal interference (multiplexing). In addition, a framework of discrete network frequencies, as opposed to a continuum of oscillation states, better matches the discrete anatomical organization of networks in neocortex into hierarchies and clusters (Sporns et al. 2004).

An additional advantage of coordination between discrete frequency bands is that the cortex can perform "simple math" to combine information held in different "frequency channels" (i.e., the concatenation process highlighted above). Successive concatenation steps are feasible with the ratio of discrete frequencies observed in association cortex. Thus information processed at gamma and beta2 frequencies may combine into a beta1 frequency code. This code may coordinate with other regions oscillating at beta2 frequencies to generate an alpha frequency and so on. As the concatenation process required for this implies the generation of specific phase relationships between component local circuits, multiple higher frequencies may then be "packed," albeit crudely, into a single lower frequency rhythm and unpacked for further processing at a later stage. For example, the relationship between delta rhythms and higher frequency components during sensory processing (e.g., Lakatos et al. 2005) suggests that during slow-wave sleep, subsequent delta rhythm generation may provide a substrate to replay coordinated multiple frequencies associated with previous sensory events.

Summary

The association between cortical rhythm generation and cortical function is strong for many aspects of sensory processing (particularly with gamma rhythms) and motor control (beta rhythms). The mechanisms of rhythm generation, per se, not only provide a substrate for temporal control of neuronal spike firing but are also labile to the pattern and degree of spiking of principal cells in local and spatially separate circuits. Thus, a combination of intrinsic, chemical, and electrical synaptic properties of neurons and their resulting local networks provides a powerful but highly labile means by which to translate cortical inputs and outputs into a temporal code based on principal cell spike patterns. What is becoming increasingly clear is that even very small local circuits in cortex have sufficiently diverse features to generate many network rhythms concurrently. The major challenges arising from this are to understand the temporal patterns produced by multiple frequencies, the underlying mechanisms by which they interact, and the consequences for generations of

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principal cell spike codes. Each challenge must be considered if we are to further understand the cortical temporal landscape as it relates to the behavior of the whole organism.

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