Synaptic Noise and Physiological Coupling Generate High-Frequency Oscillations in a Hippocampal Computational Model

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INTRODUCTION

High-frequency oscillations

Since the early 1990s, several groups have evaluated fast coherent oscillations in the brain (Allen et al. 1992; Bragin et al. 1999; Buzsáki et al. 1992; Chrobak and Buzsáki 1996; Csicsvári et al. 1999a; Fisher et al. 1992; Huang and White 1989; Ylinen et al. 1995). There are several patterns of these high-frequency oscillations (HFOs) seen in different regions of the brain. The term “HFOs” is used to describe a number of possibly disparate phenomena, seen in both normal and pathologic circumstances. Even less standardized is what frequency range actually constitutes an HFO—the term has been used to describe activity anywhere from 60 Hz (Worrell et al. 2004) to 700 Hz (Amassian and Stewart 2003). From a clinical neurophysiology perspective, the term refers to activity beyond the typical range of EEG recordings, which historically have a 70-Hz cutoff frequency. HFOs have been recorded in normal human neocortex, both on somatosensory evoked potentials (Coppola et al. 2005) and on electroencephalograms (EEGs; Gonzalez et al. 2006). HFOs in the fast gamma range (60–100 Hz) have been associated with epilepsy, particularly in the preictal period (Traub 2003; Worrell et al. 2004), although they are also seen in normal conditions (Whittington et al. 1997). Because the exact boundaries are not standardized, it is necessary to clarify the usage of these terms in the present work: “gamma” will refer to frequencies from 26 to 100 Hz; “ripples” from 100 to 200 Hz; and “fast ripples” >200 Hz. Gamma oscillations that have been associated with epilepsy are further subdivided into the “fast gamma” range (60–100 Hz), whereas those <60 Hz are likely normal. “HFO” refers collectively to any frequency >60 Hz (fast gamma, ripples, and fast ripples), which may or may not be pathological.

There has been considerable work describing how the physiological network of pyramidal cells and interneurons interact to form coherent oscillations. Basket cell inhibition is a well-known phenomenon in both hippocampus and neocortex and is a key component of many theories of HFO generation (Amitai et al. 2002; Bibbig et al. 2002; Klausberger et al. 2003; Le Van Quyen et al. 2008; Traub et al. 2005a). Coherent oscillations in neuronal networks are produced when coupled interneurons generate rhythmic inhibition to large numbers of pyramidal cells, which in turn send feedback to the interneurons (Bürgers et al. 2005; Traub et al. 1996b, 1997). This phenomenon, known as pyramidal interneuron network gamma (PING), forms a periodic oscillation with a frequency that is dependent not only on the feedback delay but also on the drive to the pyramidal cells (Traub et al. 2000). Computational models of gamma oscillations often use DC injection into pyramidal cells as the driving force (Tort et al. 2007; Traub et al. 1996b). However, it has been difficult to reproduce higher-frequency oscillations (>100 Hz) with those PING mechanisms, which has led to other theories such as driving from ectopic spikes generated in pyramidal cell axons that are coupled to form an axonal network by axoaxonic gap junctions (Draguhn et al. 1998; Traub et al. 2005b).

One subgroup of HFOs, known as ripples, generally refers to oscillations occurring at about 100–200 Hz (Bragin et al. 1999). Ripples have been used to describe both abnormal activity associated with epileptiform sharp waves (Bragin et al. 2004) and normal behaviors such as physiological sharp waves...
(Ylinen et al. 1995) and memory consolidation (Buzsáki et al. 1992; Csicsvári et al. 1999a; Foster and Wilson 2006; O’Neill et al. 2006). In some areas, such as the hippocampal dentate gyrus, they are a marker of epileptic tissue and may be formed in a different manner (Engel Jr et al. 2009) than “normal” brain oscillations (Sejnowski and Paulsen 2006). Ripples appear to require fast coupling between pyramidal cells, such as axonal gap junctions or ephaptic connections (Draguhn et al. 1998; Fox et al. 2004; Traub et al. 2005b). Another subset of HFOs, named “fast ripples” by Bragin et al. (1999), are comprised of oscillations from 250 to 500 Hz and are proposed as a biomarker of epileptic tissue (Bragin et al. 1999; Jacobs et al. 2009a,b; Staba et al. 2007). Fast ripples are only recently being mechanistically classified (Foffani et al. 2007) and there is much interest in describing how they are formed, specifically in epileptic tissue (Engel Jr et al. 2009). The mechanisms that generate HFOs are less understood for ripples and fast ripples, attributed in part to the difficulty posed by recording them and distinguishing HFOs from ensembles of individual neurons firing at such high frequency. In the following text we explore a method by which HFOs can be generated using conventional coupling mechanisms with the only driving force being random synaptic activity. We relate these findings with changes seen in epilepsy, showing in particular that ripples can be produced when the model has pathological changes that are similar to those in epileptic tissue.

**Stochastic resonance and coherence resonance**

Stochastic resonance (SR) was first described over 20 years ago as a method of explaining how detection of a subthreshold signal can be improved by the presence of random noise (Benzi et al. 1983; Fauve and Heslot 1983; Moss et al. 2004). Originally described in nonlinear systems from geology and physics, it was later noted to play a role in neural signal detection, in both peripheral and central systems (Bulsara et al. 1991; Collins et al. 1996; Douglass et al. 1993; Gluckman et al. 1996; Levin and Miller 1996; Stacey and Durand 2000, 2001, 2002). Later studies further established the potential uses of this method in physiological signal detection (Fallon and Morgan 2005; Fallon et al. 2004; Hong et al. 2006; Lugo et al. 2008) and information processing in the hippocampus (Yoshida et al. 2002). These studies demonstrated that certain levels of noise are able to improve detection of subthreshold signals in the nervous system, which has intriguing biological implications both for the role of noise and for the mechanics of neural signal detection.

Further SR research explored the effects of having multiple detectors, known as array-enhanced SR (AESR; Lindner et al. 1995), which predicted that the signal-to-noise ratio (SNR) of a single detector would improve proportionally with the number of neighbors to which it was coupled. This latter system is more suitable to describe physiological neural systems—individual neurons nearly always exist in arrays, especially in the CNS, and there are varying degrees of direct and indirect coupling within the array. Once neurons become coupled in their output behavior, however, another related effect of noise is formed, coherence resonance (CR, also known as stochastic coherence). CR is a phenomenon from the field of physics that describes how a network of coupled detectors can produce a coherent, nearly periodic output when presented with random noise inputs (Hu and Zhou 2000; Neiman et al. 1997; Pham et al. 1998; Pradines et al. 1999; Rappel and Karma 1996; Wang et al. 2000). Computational models of neural networks have been shown to produce this activity as well (Balenzuela and García-Ojalvo 2005; Chiu and Bardakjian 2004; Lindner and Schimansky-Geier 1999; Stacey and Durand 2002).

Since pyramidal cells in the brain have a tremendous number of synaptic inputs, they experience a broad range of synaptic activity. This activity is a combination of random release of neurotransmitter (minis) and the summation of sometimes thousands of independent synaptic signals from various brain areas. At times the synaptic activity can become very intense, such as during active cortical states (see DISCUSSION), and can produce a significant amount of postsynaptic activity. SR and CR allow the researcher to designate a specific input as the “signal” (in the case of SR), whereas all other independent inputs can be treated as “noise” (Stacey and Durand 2002). Using this approach, Stacey and Durand demonstrated that oscillatory neural activity can be produced by physiologically feasible levels of noise and coupling. In the present study we use a more detailed computational model of hippocampus to explore parameters necessary to produce HFOs and to quantify the response using the tools of SR and CR. To facilitate this analysis, throughout this study all random synaptic activity is classified and referred to as “noise.” Using this method, the coherence, frequency, and SNR can be quantified and compared across trials. The results are compared with other physiological models of SR and CR and the parameters are compared with experimental data. Using this analysis, we demonstrate a method by which physiological inputs and coupling can produce coherent oscillations and create pathologic changes similar to epilepsy.

**METHODS**

**Computer model**

A reduced physiological model of the hippocampus was adapted from (Tort et al. 2007). All simulations were performed in NEURON 6.1 on a PC computer (Hines and Carnevale 1997). Our adaptation was performed to evaluate transient high-frequency events, rather than slow theta oscillations, so oriens lacunosum-moleculare (OLM) cells were removed and only one module was simulated (the previous model contained four modules connected by OLM cells). Each module contained 80 pyramidal cells and 20 basket cells (Fig. 1). Pyramidal cells had five compartments (basal dendrite, soma, and three-segment apical dendrite) and contained current sources from the following ion channels: sodium $I_{	ext{Na}}$, A-type potassium $I_{	ext{KATP}}$, delayed rectifier potassium $I_{	ext{KDR}}$, and noninactivating, nonspecific cation $I_C$. Basket cells contained one compartment with $I_{	ext{Na}}$ and $I_{	ext{KATP}}$ (with different parameters from pyramidal cells, as described in Tort et al. 2007). The basket cells were connected entirely all-to-all with the pyramidal cells using inhibitory $\gamma$-aminobutyric acid (GABA) synapses. Each basket cell also receivedafferent excitatory (α-amino-3-hydroxy-5-methyl-4-isozaxolepropionic acid [AMPA]) synapses from 10 randomly selected pyramidal cells. One simulation was performed in which these pyramidal-to-basket cell AMPA synapses had a component of $N$-methyl-$D$-aspartate (NMDA) current. For all synapses, synaptic strength was modulated by changing the conductance, which in the model represents the density of channels and affects the amplitude of the postsynaptic current. Thus a doubling of the conductance doubled the amplitude of the current function and a connection could be “removed” by setting conductance to 0. When NMDA current was added, it was an additional current with peak conductance...
specified as a ratio of the peak AMPA conductance \[ G_{\text{max(AMPA)}} = \text{ratio} \times G_{\text{max(NMDA)}} \]. All synaptic, channel, and membrane parameters were essentially unchanged from the published model and are also similar to another physiologically based hippocampal model (Traub et al. 1997). Additional alterations to the model were: 1) addition of independent, excitatory AMPA synapses on each basket cell and on midpoint of the proximal apical dendrite of each pyramidal cell as “noise synapses”; 2) optional gap junctions between pyramidal cells or between basket cells based on the implementation in Traub et al. (2005a); 3) addition of optional recurrent AMPA synapses in pyramidal cells (see following text). For simulations testing detection of subthreshold signals, a 16-Hz signal was input at the first apical dendrite segment (A1) of the pyramidal cells. Noise synapses were used to introduce independent synaptic “noise” events by determining at each 0.5-ms time step whether a random number generator (uniform distribution) was above a threshold. The threshold was the same for each cell of the same type and was varied to produce the different noise intensities. The quantal size of the synaptic event was further each cell of the same type and was varied to produce the different distribution) was above a threshold. The threshold was the same for all 80 pyramidal cells. Each pyramidal cell has an independent noise synapse. Each basket cell (20) synapses with all 80 pyramidal cells and receives synapses from 10 pyramidal cells. AMPA, \( \alpha \)-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; GABA, \( \gamma \)-aminobutyric acid; NMDA, N-methyl-D-aspartate.

**Data processing**

The output of the network was generated as the average of all pyramidal cell somatic voltages. Thus in the output an AP in one cell generated a waveform that was 1/80 the amplitude of a single AP, making a waveform that was roughly 1 mV. Coincident APs produced higher-amplitude output, whereas slight differences in onset time resulted in widening of the output waveform due to jitter. The summed output was then analyzed by computing the power spectral density (PSD) using the PWELCH function in Matlab (The MathWorks 2008). Note that this function inherently averages the result over multiple time windows. Most data were generated for 1-s duration, to provide a large number of sample windows for averaging.

**SR ANALYSIS.** The SNR was calculated by dividing the power at the input frequency by the average power near that frequency, in the manner commonly used for SR (Moss et al. 2004) (see Fig. 2B). The SNR at each noise intensity was then plotted and compared with a representative SR curve \((\nu = \text{signal strength}; \Delta U = \text{barrier height}, D = \text{noise intensity})\) as follows

\[
\text{SNR} = \left( \frac{\nu \Delta U}{D} \right)^2 e^{-\Delta U/D} \quad (1)
\]

**CR ANALYSIS.** Coherence (\(\beta\)) is based on the same SNR calculation used in SR, adjusted for frequency and peak width. It is computed as shown in Eq. 2 \((\omega_p, \text{frequency producing maximum spectral power}, \Delta \omega = \text{the width at half-peak height}, \bar{D} = \text{SNR of peak as described for SR})\). The coherence was then plotted as a function of both input noise intensity and coupling

\[
\beta = \frac{\bar{D}^2}{\Delta \omega} \quad (2)
\]

**NOISE ANALYSIS.** Noise intensity was calculated by recording the input noise current at the AMPA noise synapse for each noise threshold level (see earlier text). The second moment of this current about its baseline was then calculated. Since the baseline current was 0 before noise began, the value was the expected value of the current squared \((\text{Eq} \. 3)\). This method is similar to calculating the variance but includes the DC offset of the current and is thus more plausible as the total physiological synaptic input

\[
\text{Noise intensity} = \text{mean}(I_{\text{noise synapse}})^2 \quad (3)
\]

**RESULTS**

**Stochastic resonance: noise improves detection of subthreshold signal**

The network was first configured to evaluate how stochastic resonance (SR) affected its signal detection. This model incorporated inhibitory interneurons, a physiological system element that has not been included in previous models of SR. The input signal was configured as a subthreshold synapse that contacted pyramidal cells on the A1 segment. When contacting multiple cells, the signal arrived simultaneously on each postsynaptic cell, simulating a single branched afferent axon contacting the apical dendrite with multiple synaptic contacts. The signal was generated as a 16-Hz periodic synaptic event, a frequency chosen to avoid complex dynamics caused by the cells’ natural resonance near 20 and 40 Hz. Noise was gener-
ated as random AMPA synaptic events at the noise synapses described earlier. For the remainder of this work, “noise” will refer to these random excitatory synaptic events.

SINGLE CELL. A single pyramidal cell was presented with a subthreshold AMPA signal and synaptic noise (Fig. 2). When the subthreshold signal was presented alone (Fig. 2A, top), the cell had subthreshold depolarizations but never fired an AP. Random synaptic activity alone caused the baseline membrane voltage to fluctuate (Fig. 2A, bottom). Each level of noise produced a mean depolarization of the cell, which could produce spontaneous APs. For lower levels of noise, there were only rare, lone APs: Poisson firing. As noise intensity increased, the mean depolarization increased asymptotically. At 0.008 nA², the depolarization was 12 mV, with a variance of 149 mV², and the cell fired frequent APs at random intervals (mean firing rate <10 Hz). At 0.01 nA² and beyond, the noise produced spontaneous, nearly periodic APs. The periodicity became more pronounced as the noise intensity increased. This activity will henceforth be referred to as “noise oscillations.”

When both noise and signal were presented to the cell, the cell exhibited SR. The simulation was performed for a noise intensity ranging from 0 to 0.03 nA². By definition, the SNR is zero for zero noise (subthreshold signal), the SNR is zero for zero noise. For low noise (<0.005 nA²), signal detection was improved as the cell began to fire in response to the signal input, as seen in Fig. 2A (second line). For higher noise, the cell began to fire in response to the noise itself, producing extraneous APs (Fig. 2A, line 3). SR analysis of the raw data quantified this response: the SNR rose for low noise levels then decayed as the noise increased (Fig. 2B). The full response to the noise range is shown in Fig. 2D. In this case, the data have lower SNR than expected by SR at higher noise levels due to the noise oscillations, which are not addressed in SR theory (Stacey and Durand 2002). The sample SR curve generated from Eq. 1 is included (fits only the first 2 data points for “20 baskets”). It does not fit the data well for high levels of noise (see text).

FIG. 2. Stochastic resonance (SR) in a single neuron. A: raw voltage data from a single cell with varying amounts of noise, with and without a subthreshold 16-Hz signal. Shaded lines are added to visualize alignment and are aligned with data in C. All data are 1 s long. B: power spectral density (PSD) of data in lines 2–5 of A. By definition, the PSD is zero with noise = 0 nA² because there is no output (action potentials) from the cell. Signal-to-noise ratio (SNR) is calculated as the ratio of PSD power at 16 Hz and the average baseline power around that point. Note that for the second line the SNR is <1 because the signal power is less than the nearby baseline. (Box, diamond: corresponds to data points in D.) Bottom 2 PSD plots show the response to noise alone without the 16-Hz signal for comparative purposes. C: a basket cell is added as in Fig. 1B. Synaptic strength is that of 20 basket cells. Raw data show reduction in noise (compare with line 3 in A). Dashed line below the voltage tracing indicates signal frequency for both A and C. Bottom: PSD of these data, generating the circle indicated in D. D: plot of SNR vs. noise intensity with and without basket cells. Sample data from B and C are indicated by their corresponding shapes. In general, SNR >10 corresponded good signal detection. Without basket cells the SNR is much lower due to increased random firing. For comparison, a sample SR curve generated from Eq. 1 is included (fits only the first 2 data points for “20 baskets”). It does not fit the data well for high levels of noise (see text).
each pyramidal cell. Adding basket cell inhibition actually improved signal detection: the basket cell effectively inhibited many of the noise-induced APs (Fig. 2C), which led to a significantly higher SNR (Fig. 2D). Beyond 0.01 nA², however, the noise oscillations again disrupted SNR despite the basket cell inhibition.

ENTIRE NETWORK. All 80 pyramidal cells and 20 basket cells were then implemented to test signal detection in the full network. The 16-Hz input signal was input to 20 pyramidal cells, with each cell receiving the synaptic event at the same time. These 20 “signaled” cells had no direct connections with any of the other pyramidal cells, only the indirect feedback provided through the basket cell connections. As with a single cell (Fig. 2), noise was able to improve detection of the subthreshold signal. To demonstrate the network activity, spike raster plots are presented in Fig. 3A. These plots show firing times of all basket and pyramidal cells. The SNR analysis (Fig. 3, B and C) is identical to that of the previous figure, although the range of noise tested was much larger. The 20 signaled cells were arranged as four groups of 5 cells and are the only cells firing with low noise (Fig. 3A, left). As the noise increased, many other cells began to fire and the SNR decreased. For many intermediate amounts of noise (Fig. 3A, middle), the SNR was low because the network fired at harmonics of the signal (see next paragraph). With very high noise levels (Fig. 3A, right), the noise was high enough to overwhelm the 16-Hz signal and the network was extremely active, tending to oscillate coherently at a separate frequency (see next section). The SNR plot (Fig. 3C) again demonstrates that signal detection was improved at low noise, as predicted by SR, but deviated at higher noise levels due to noise oscillations, which led to the unusually shaped SR curve.

The network output was then compared with simulations in which there were no basket cells (Fig. 4). Without basket cells, there was increased, uninhibited noise from the pyramidal cells not receiving the signal and the total noise was increased. Therefore despite the input signal being visible in the raw voltage, the SNR of the 16-Hz signal was greatly reduced. As seen in the spike rastergrams in Fig. 4A, the basket cells reduced the total amount of noise and also produced periods of relative inhibition immediately after each signal event. The basket cells clearly improved the SNR of the subthreshold signal.

**FIG. 3.** SR in hippocampal network. *A:* raw output of network when 20 pyramidal cells received subthreshold signal plus noise at 3 different intensities. Spike raster plots (top) show response of basket cells (top 20 cells) and pyramidal cells (bottom 80 cells). Network output (bottom) is the average membrane voltage of all pyramidal cells. Five groups of 4 pyramidal cells receive the subthreshold signal (duration 1 s). *Left:* only the 20 signaled cells fire with 0.0014 nA² noise. *Middle:* at 0.03 nA², the network oscillates at twice the input frequency (32 Hz). The 16-Hz signal is still present. *Right:* at high noise, the network oscillates at faster frequencies, ignoring the input signal. *B:* PSD for the 3 noise levels, with calculated SNR as shown. Arrows indicate signal frequency of 16 Hz. *C:* SNR plot for the network. Oscillations produced at noise levels above 0.01 nA² corrupt detection of the input signal, leading to unusual SR curve fit (see same curve in different scale in Fig. 4B). Boxes: data for 3 examples in A.
signal in the presence of noise. In addition, they produced a global periodic synchronizing feedback, which often promoted firing of the unsignaled cells at the same frequency (although often with phase delay). The result was that, through basket cell connections, aperiodic signal received by some members of the network was able to tune the output of the entire network. This entrainment to the input signal frequency or its harmonics is demonstrated in Fig. 4C, in which the addition of a periodic input effectively quantized the output frequency of the network containing basket cells (20 signaled cells, intact basket cells; conditions identical to those in Fig. 3 and solid triangles in Fig. 4B). Both the improved SNR and frequency entrainment were more pronounced with larger numbers of signaled cells. Additional simulations in which there was only a single signaled cell (Fig. 4B, hollow squares) and 4 signaled cells (not shown) demonstrated a dose response, in which SNR was higher with increased numbers of signaled cells. The overall result was improved SNR with basket cells present, showing that inhibitory feedback was able to improve signal detection.

As expected for AESR, the response of the ensemble improved with an increasing number of signaled elements. These results, however, are quite different from previously reported examples of SR and AESR. First, noise oscillations disrupted signal detection for higher noise levels, deviating from the
predictions of SR. Second, signal detection was improved with purely inhibitory feedback, which effectively decreased the noise content at low noise levels and raised SNR. Last, the basket cells entrained the network to fire at specific frequencies, which were often strongly influenced by the subthreshold periodic signal. These last two effects of basket cells exerted a powerful influence on the network output. At very high noise levels, the basket cells also had a role in synchronizing the network to noise oscillations, as seen in Fig. 3 for 0.06 nA². The generation of network oscillations is explored in further detail in the next section, but for purposes of SR it produced “noise” that quickly overwhelmed detection of the deterministic signal input.

Coherence resonance

The ability of a noisy input to produce coherent, nearly periodic oscillations in a coupled network is the basis of coherence resonance (CR). As in previous simulations evaluating SR in pyramidal cell networks (Stacey and Durand 2002), noise oscillations were prominent in the current model and disrupted the expected SR curve, even for small amounts of noise. That effect is best seen in Fig. 3 for 0.06-nA² noise, in which the noise oscillations completely overwhelmed the input signal. The network effectively produced a coherent, periodic signal with no input other than random noise. The rest of the simulations were performed with noise as the only inputs to explore the role of CR in this model.

Oscillations in a single cell. The network oscillations result from coupling of individual oscillating neurons. The model was first tested with a single neuron to compare it with the network response. High noise levels presented to a single pyramidal cell produced noise oscillations that reached a maximum of 190 Hz (Supplemental Fig. S1).1 Connecting the single neuron to a basket cell slightly lowered the peak frequency in proportion to the synaptic strength. These results in a single cell reinforce two important concepts: that random noise can produce a nearly periodic output in a neuron and that basket cells can modulate the frequency response.

Network oscillations with basket cell coupling. In a network of oscillating uncoupled cells, each oscillates independently and the output is not coherent (e.g., see Fig. 4A, right, when basket cell coupling is removed). With sufficient coupling, oscillating neurons can become synchronized. CR provides a method for quantifying and analyzing this effect. The network was first connected in its baseline configuration, with no coupling except for the basket cells. Figure 5 demonstrates that noise and coupling synergistically generated coherent oscillations in the network. CR is typically characterized by low coherence at lower noise levels, a “resonant” peak of coherence as noise increases, followed by a drop at very high noise levels as the network desynchronizes (Stacey and Durand 2002). Furthermore, coherence increases as coupling strength

1 The online version of this article contains supplemental data.

FIG. 5. Coherence resonance. A: response of the network to three levels of noise, without any periodic signal input. Power spectrum for each (bottom) shows peak power at 20, 36, and 69 Hz, respectively. Data are for the baseline basket conductance of 0.275 nS. The coherence for 0.06 nA² noise was much greater than the other two. Illustrations of $h$ and $\Delta \omega$ are indicated by dashed and dotted lines on each PSD plot, and produce the indicated coherence. B: $\beta$: coherence as a function of noise and basket cell conductance. Data in A are marked with circles. Increasing coupling raised the coherence. Increasing noise improved coherence at lower levels, then degraded it. For very high noise, coherence returned to high levels. Note lack of resonant peak without any basket cells (far right). C: frequency response of the network. Increased coupling lowered peak frequency; noise increased the frequency.
is increased. CR analysis thus computes the coherence as both noise and coupling are modulated. Figure 5A shows raw data (spike rasters and voltage output) for the network with basket cell coupling of 0.275 nS and three noise levels. This coupling corresponds to the baseline conductance of the GABA synapse from the basket cells to pyramidal cells. For each noise level, the network oscillated at different frequencies (20, 36, and 69 Hz, respectively). When the cells fired very synchronously, as for 0.06 nA², the PSD peak was very sharp and the coherence was higher. That the peak coherence occurred at 36 Hz is not surprising because it corresponds to the frequency expected with the PING mechanism involving GABA synaptic feedback from the basket cells.

The coherence for a broad range of noise and coupling intensities is shown in Fig. 5B. Coherence rose with increased coupling and the resonant peak was present as noise intensity increased. There were, however, two important differences from standard CR theory. First, unlike typical CR systems, the coupling herein is purely inhibitory, through GABAergic synapses, whereas CR is normally described in positive feedback systems. Second, the data differ significantly from the expected CR curve at high noise levels: after an initial drop in coherence at high noise, the coherence increases relentlessly thereafter. This deviation from CR theory is attributed to the characteristics of this neural system. The pyramidal cell firing rate is much slower than the maximum basket cell firing rate, so even at high noise levels the inhibitory coupling on the pyramidal cells is sustained, whereas in typical CR the noise would overcome the coupling at high levels and lower the coherence. In addition, the postsynaptic membrane effectively filters high-frequency signals and, at very high levels, noise resembles a DC current. For comparison, the response of the network without any basket cell connections is also shown in Fig. 5, B and C (0 nS), demonstrating that without coupling there is some inherent synchrony generated at high noise when all the cells fire at nearly the same rate, even though at low noise there is no CR peak. These high levels of noise, however, are likely at the extreme of normal physiology (mean rate of noise events for noise above 0.2 nA² is >4,000 Hz).

The frequency of the coherent oscillations is of particular interest (Fig. 5C). This model was originally designed to simulate activity of the hippocampus, specifically how basket cell feedback can produce gamma oscillations when the pyramidal cells received DC current injection (Tort et al. 2007). These results show that random synaptic inputs can also generate gamma oscillations (>30 Hz), reaching up to the HFO range (110 Hz with the baseline 0.275-nS coupling). The oscillation frequency rose proportionally higher as synaptic strength from the basket cells decreased. With very low basket cell input (0.075 nS), the frequency reached nearly 150 Hz. These frequencies are significantly lower than those in a single cell (190 Hz), even one with feedback from 20 basket cells (175 Hz, Supplemental Fig. S1). Thus the oscillation frequency decreased when there were more pyramidal cells and more basket cell input.

**EFFECT OF NMDA CURRENT ON GAMMA POWER.** Recent experimental work has demonstrated that NMDA blockade (with ketamine or MK-801) results in increased gamma frequencies in rat neocortex (Pinault 2008) and hippocampus (Lazarewicz et al. 2009). The preceding simulations were repeated with varying levels of NMDA current added to the pyramidal-to-basket cell “AMPA synapse” to test this effect. All other parameters were unchanged: the simulations were performed using the same range of pyramidal cell noise as in Fig. 5, with the baseline level of GABA conductance (0.275 nS). Several levels of NMDA current were tested, generated with a peak conductance that was a specified ratio of the AMPA current ranging from zero to 0.5. The results, shown in Supplemental Fig. S2, demonstrate that increasing amounts of NMDA current decreased the coherence, the peak oscillation frequency, and the total gamma (30–100 Hz) power in the network. Peak oscillation frequency was more sensitive to NMDA current at high noise levels (>0.11 nA²; Supplemental Fig. S2D). The difference in gamma power was very pronounced for all levels of noise (Supplemental Fig. S2E). With high NMDA current (ratio ≥0.1), the network was suppressed and did not produce oscillations. These results agree with the experimental finding that increasing NMDA blockade increases the gamma power. They also provide a possible explanation for this phenomenon: the additional NMDA current caused the basket cells to fire more frequently and produced increased inhibitory feedback on the pyramidal cells that lowered their firing rate. Effectively, increasing NMDA current alters the dynamics of PING and decreases the gamma power. The remainder of the simulations did not include any NMDA current.

**COHERENT OSCILLATIONS WITH GAP JUNCTIONS.** Gap junctions provide an alternative method for generating coherent oscillations. Gap junction current was generated according to Eq. 4, where \( I_{\text{gap}} \) is in nA, voltages in mV, and \( V_{\text{m}} \) is assigned as the \( V_{\text{m}} \) of the connected cell. The conductances were tested within a broad range, from a “low” level causing minimal change to a “high” level where connected cells always fired synchronously

\[
I_{\text{gap}} = (V_{\text{gap}} - V_{\text{m}})g_{\text{gap}} \tag{4}
\]

All of the previous CR simulations were repeated with gap junctions between basket cells, using low (1e-5 µS) and high (1e-4 µS) conductances. Basket cells can be highly coupled by gap junctions (Fukuda et al. 2006), forming wide-ranging connections (Sik et al. 1995), which was an important part of the results of the original implementation of this model in Tort et al. (2007). When measuring the output of the network (pyramidal cell membrane voltage), there was no appreciable change in either the coherence or the frequency response when the gap junctions were present in the basket cells (data not shown). However, when noise was added directly to the basket cells, gap junctions had significant effects on the network (see later section).

Gap junctions were then placed between pyramidal cells. Unlike the basket cells, pyramidal cells are not so tightly coupled as basket cells in vivo, as evidenced by their independent firing. Few data are available concerning the prevalence and strength of these connections, although they are present to varying degrees. The simulation was performed for several levels of coupling between 0.001 and 0.05 µS (which produced the low and high levels as before), with the connection in the A1 dendrite segment of each cell. Two protocols were tested. First, a total of 39 scattered connections were made between the 80 cells. This left many of the cells without any connections and created several clusters of coupled cells. The coherence was reduced in this situation from when there were no gap
junctons. This happened because the clusters and the uninvolved cells were all independent, often oscillating at different frequency or phase. An example is shown in Fig. 6A, which shows that even with very high coupling (0.05 \( \mu \text{S} \)) the overall coherence was actually lower than the corresponding simulation without any gap junctions (2,200 vs. 13,800 in Fig. 5). Although the cells connected by gap junctions were synchronized, the overall ensemble was not, and the output was disrupted by the uncoupled cells. This low number of gap junction connections never produced greater coherence than when basket cells were the only coupling mechanism. When basket cells were removed, the coherence was very poor due to increased noise (not shown).

For gap junctions to have a significant effect in this model, they had to be widely distributed. At the extreme, all cells would be connected in a syncytium. To simulate this, all pyramidal cells were coupled in a linear “inline” chain with 79 gap junctions (1–2–3–...–78–79–80). These gap junctions had strong effects on the coherent oscillations. One interesting change was the loss of the “resonant peak”: there was no drop in coherence for noise 0.1–0.15 nA\(^2\) with higher levels of coupling (Fig. 6B, solid line is baseline data from Fig. 5 for comparison). Another major difference was the increased oscillation frequency (Fig. 6C). These effects were present with the gap junctions added to the baseline network containing basket cells (dashed lines, Fig. 6, B and C) and were even more prominent when the basket cells were removed. For low coupling (0.001 \( \mu \text{S} \), no basket cells), coherence was not as high as that in the basket cell case, although the oscillation frequency was much higher. Similar results were found for 0.005-\( \mu \text{S} \) coupling (not shown). For higher coupling levels (0.01, 0.05 \( \mu \text{S} \), no basket cells), coherence was much higher than that with basket cells alone (Fig. 6B), as was the oscillation frequency (Fig. 6C). In fact, for all values of gap junction conductance, the oscillation frequency was identical for a given level of noise and was also identical to that of a single cell at the same noise level. These results show that, through the effects of CR, gap junctions can produce fast coherent oscillations in the ripple range, but require extensive connectivity and/or loss of basket cells to be effective.

COHERENT OSCILLATIONS WITH RECURRENT CONNECTIONS. The last method of coupling simulated was recurrent synaptic connections. These connections are quite common in the hippocampal CA3 region—over 25% of connections can be recurrent axons (Wittner et al. 2007)—but much less so in CA1 (around 1/130 cells are connected with recurrent axons; Bernard and Wheal 1994). Two levels of recurrent connections were simulated. In the first, a total of 4 pyramidal cells (5% of cells) were connected via AMPA synapses to the A1 dendrites of 3–6 other pyramidal cells, for a total of 18 synapses. With basket cells present, there was no appreciable difference in output (data not shown). As with the sparse gap junctions, the oscillations produced by the basket cells were more powerful.

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**FIG. 6.** Coherent oscillations with gap junctions. **A**, left: with 39 gaps scattered randomly, there are clusters of neurons firing together near bottom of raster, but the overall network coherence is less than without gaps (see Fig. 5). **Middle**: in the extreme case of having all neurons connected together by 79 inline gaps, the cells all fire together, but coherence is not very high due to frequency jitter. **Right**: without basket cells, the inline network coherence is very high. All plots are 1 s long. **B**: with inline gaps and baskets removed, coherence for 3 levels of coupling strength are all greater than that produced by basket coupling alone as in Fig. 5. Addition of the basket cells to the inline gaps (dashed line, “+B”) also reduces coherence. **Box**: data indicates in A and Fig. 5. **C**: Frequency response of network with inline gaps and no basket cells is identical to that of a single cell, even at very low conductance, and is in the ripple range. Addition of basket cells lowers frequency to gamma range (dashed line). Frequency was faster in all cases than for the basket cell coupling alone.
than any effect of the recurrent connections. A more extreme case of recurrent connections was then implemented, consisting of 10 pyramidal cells each connected to 8 others via recurrent connections, for a total of 80 connections distributed over 50 cells. This represented significant axonal sprouting and is shown in Fig. 7. There was strong coupling between the connected cells, but the network response did not oscillate very well and was generally worse than if there were no recurrent connections. Similar results have been found previously (Traub et al. 2000). The network contained a population of cells oscillating due to the basket cell coupling described in Fig. 5 and a separate population oscillating at a faster frequency due to the recurrent feedback. The two populations were asynchronous, so the output had lower coherence. When basket cells were removed, the recurrent connections were able to produce coherent oscillations at high frequency (>120 Hz). This effect occurred at almost all noise levels, but there was significant frequency jitter so the coherence was low at many points (Fig. 7B). The oscillation frequency was much faster with the recurrent connections even at low levels of noise, even faster than a single cell’s response to the same noise level (Fig. 7C). Although the response was different from the predictions of CR, recurrent connections produced oscillations in response to noise that were in the ripple range. When basket cell coupling was removed, the network output was a coherent ripple-frequency oscillation.

**EFFECTS OF ADDING NOISE TO BASKET CELLS.** Several simulations were then performed in which the basket cells received noise inputs as well as the pyramidal cells. In these simulations, the noise intensity for basket cells and pyramidal cells was independent. Thus for each given basket cell noise intensity, a full range of pyramidal cell noise was simulated. The results, shown in Fig. 8, show several important effects. Because noise caused basket cells to fire more frequently, they suppressed the pyramidal cells and made them less prone to fire in response to their own noise sources. This lowered the coherence (Eq. 2) of the network because the pyramidal cells fired more sparsely and coherence was designed to measure only the pyramidal cell output. The result was a loss of the resonant coherence peak near 0.06 nA² (Fig. 8C—compare with Fig. 5B). The coherence was high when pyramidal noise was >0.25 nA², regardless of basket noise intensity. The frequency of coherent firing, however, was strongly dependent on basket cell noise, dropping almost linearly as basket noise increased (Fig. 8D). There were some minor irregularities when pyramidal cell noise was low and basket cell noise was high—the pyramidal cells were very suppressed and the network output was not a coherent oscillation, so measuring the peak frequency was somewhat unreliable (e.g., the nonoscillating pyramidal cell output in Fig. 8B, which generates very low coherence in Fig. 8C). Overall, increased basket cell activity due to noise reduced the frequency of pyramidal cell oscillations proportionally and decreased the pyramidal cell coherence when pyramidal cells had low to medium noise levels.

Another important effect of basket cell noise is that, when the basket cells were coupled with gap junctions, they formed their own coherent oscillations. The basket cell oscillations had two key differences from those in pyramidal cells: they were not modulated by any inhibitory feedback and they were faster. As seen in Fig. 8B, when connected by gap junctions, the basket cells formed coherent 200-Hz oscillations in response to noise. There were only minor changes in the pyramidal cell output, similar to the earlier section with gap junctions between basket cells that did not have noise inputs. Although the pyramidal cell coherence did not change appreciably, the output of the basket

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**FIG. 7.** Recurrent axons generate fast oscillations. A: raw voltage and PSD for network with 80 recurrent axons with (“+”B”) and without (“−”B”) basket cells. Bottom: the network oscillated much faster without basket cells (70 vs. 176 Hz). All data shown are for 0.15 nA² noise. B: coherence for the network with recurrent axons is generally lower than the data in Fig. 5 (in which basket cells are the only coupling mechanism). C: frequency response of data in A, compared with that of a single cell and the data in Fig. 5. Basket cells maintained the network output in the gamma range, despite the recurrent axons. When basket cells were removed, the network oscillated faster than even a single neuron, and well into the ripple range. Figure legend in C applies also to B.
cells was a coherent 200-Hz oscillation (composed of GABA inhibitory postsynaptic currents [IPSCs]) that produced sparse firing in pyramidal cells. When the pyramidal cells received no noise, the basket cells still produced coherent nearly 200-Hz oscillations, but the pyramidal cells never fired any APs (not shown). This simulation therefore demonstrates that increased synaptic noise and gap junctions in the basket cells produce characteristics similar to a sharp-wave–associated physiological ripple (Ylinen et al. 1995): 200-Hz IPSC output with sparse or absent firing of pyramidal cells. Later work will explore the relationship between these findings and experimental recordings of typical ripple oscillations.

**DISCUSSION**

**On the physiological relevance of model parameters**

Although the basic model used in this study has been presented and validated previously (Tort et al. 2007), the current configuration contains new noise inputs and coupling that need to be justified physiologically.

**NOISE INPUTS.** The neurons in this model received noise inputs in the form of random excitatory synaptic events. This is in contrast to the original configuration of the model, in which DC current was used to generate oscillatory activity (Tort et al. 2007). A key finding of this work is that periodic oscillations can also be generated with synaptic inputs, which are the primary physiological input to these cells. For the basis of the analyses used herein, any synaptic event is included as noise. This not only facilitates quantifying the response of the network through SR or CR, but also allows for analysis of each cell in terms of the sum of all its inputs (Rudolph and Destexhe 2004). Thus these simulated neurons can be compared with physiological recordings in terms of the variance and DC shift generated by all inputs. Recordings of quiescent CA1
pyramidal cells in slices have somatic voltage variance of 0.01 to 0.04 mV^2 (Wahl et al. 1997). Those figures were obtained under conditions that are vastly different from those seen by these cells in vivo. As described previously (Stacey and Durand 2001, 2002), there are numerous input sources that can significantly change this level. In particular, there are obviously input levels high enough to produce APs, which in this model corresponded to the threshold of 149 mV^2. Beyond that level, another form of quantification is needed because it becomes difficult to interpret variance with frequent APs. The rate of APs and mean depolarization are more appropriate measures. In vivo recordings of neocortex in awake animals demonstrate a high conductance state, characterized by a highly variable depolarization of ≤20 mV (Destexhe et al. 2003). This state stems from a large amount of inputs into the cells, the majority of which are likely synaptic. During this period cortical neurons have lower input resistance and AP discharges of ≤40 Hz. Recent work has also shown that pyramidal neurons function more like oscillators in vivo, when all synaptic inputs are present (Prescott et al. 2008), and that signal detection is improved when the cells are in the depolarized state (Wolfart et al. 2005). Those physiological data were not obtained during seizures, but rather represent a normal, active behavioral state. Obviously, the inputs during a seizure can be significantly higher. Recordings in cat neocortex during seizures demonstrate parameters very similar to those described herein (Grenier et al. 2003).

Much of the data presented herein lie within the parameters recorded in vivo during these activated states. In our computer model, with baseline physiological parameters, basket cell connections, and no gap junctions, output similar to the physiological high conductance state (16-mV depolarization, oscillations around 40 Hz) occurred with noise intensity about 0.1 nA^2 (second moment about zero, or variance plus the square of the mean). The depolarization with high noise levels increased asymptotically—a single cell had a 13-mV depolarization with 0.01-nA^2 noise (Supplemental Fig. S1B), whereas increasing the noise to 0.1 nA^2 produced about 16-mV depolarization (not shown). However, the firing rates for those two noise levels were very different: a single cell had Poisson firing with 0.01 nA^2 (second moment about zero, or variance plus the square of the mean). The response was similar in the full network, except that the oscillations were coherent and slower (~40 Hz) with 0.1-nA^2 noise (Fig. 5). Most simulations increased the noise further to a maximum of 0.33 nA^2. At that maximal level, the network cells fired at about 110 Hz and were depolarized at about 18 mV. Therefore by increasing the noise intensity by less than fourfold above the physiological high conductance state, the network produced oscillations similar to fast gamma or ripples. This increase in noise level is easily reconciled in epilepsy, and is similar to parameters found in cat neocortex (Grenier et al. 2003). There is already evidence from human EEG recordings that high-frequency power (and thus variance) increases prior to seizures (Worrell et al. 2004, 2008). Previous work in hippocampal slices and computer models has demonstrated similar findings, that synaptic events occur prior to epileptiform activity (Chamberlin et al. 1990; Traub and Dingledine 1990). It is not unreasonable to assume that synaptic noise before or during a seizure could reach fourfold its normal baseline. Physiological ripples also occur under non-epileptic conditions, but rely on the synaptic barrage of large sharp-wave inputs to trigger them (Ylinen et al. 1995), which also increases the synaptic activity for a brief period.

**RECURRENT SYNAPTIC CONNECTIONS.** Coupling in this network took the form of recurrent synaptic connections, gap junctions, and basket cell inhibition. Recurrent axons are uncommon in CA1 (Bernard and Wheal 1994), but in CA3 are more common, can play a prominent role in neural firing (Jones et al. 2007; Li et al. 1994; Wittner et al. 2007), and can be increased in epilepsy (Siddiqui and Joseph 2005). In epilepsy, there is evidence of increased synaptic inputs to CA1 from the entorhinal cortex (Shetty 2002). Under baseline conditions, with no recurrent connections, our model was similar to the CA1 region. We simulated two levels of recurrent synaptic connections, one with 5% of neurons connected and another with 50/80 cells connected. The 5% case is a conservative estimate to simulate the effects of a process similar to axonal sprouting in CA1, but would not be pathological in CA3. The latter case simulates a very large number of recurrent axons, applicable to pathological sprouting in either CA1 or CA3.

**GAP JUNCTIONS.** The study of gap junctions is an emerging field. They have been difficult to classify and quantify, but they clearly play a role in signal detection. Gap junctions between interneurons are known to play a major role in HFO generation (Fukuda et al. 2006; Saraga et al. 2006; Simon et al. 2005). Additionally, axoaxonic gap junctions between pyramidal cells were predicted in computer simulations of HFOs (Traub et al. 1999) and both in vitro and microscopic work have shown evidence to corroborate this (Draguhn et al. 1998; Hamzei-Sichani et al. 2007). These two forms of gap junctions are well-known hypotheses for oscillatory behavior in the hippocampus (Traub et al. 2003). The current model did not include axoaxonic gap junctions. The effect of interneuron gap junctions was not noticeable in the current CR analysis due to the connectivity and coherence measurement of this network—the basket cells were already strongly coupled due to the synaptic connections and the coherence output did not directly monitor basket cells. This does not imply that basket cell gap junctions are not important, but rather that the tuning of this computer model had already produced the synchronizing effect of the basket cell syncytium that is generated by gap junctions in vitro/in vivo (Amitai et al. 2002).

The gap junctions that produced ripple frequencies in these simulations were dendrodendritic connections between pyramidal cells. This form of gap junction has not been widely studied in hippocampal HFOs. Gap junctions between principal neurons are well known in other areas of the CNS: they are found in areas such as olfactory neurons (Migliore et al. 2005), spindles bursts in the barrel cortex (Minkleaev et al. 2007), and oculopalatal tremor (Hong et al. 2008) and have been tested with combined computer simulation/in vitro preparations (Tseng et al. 2008). Dye-injection studies in hippocampal CA1 pyramidal demonstrate 1.6 neurons coupled per injection with normal pH and 3.25 at 7.9 pH when bursting activity arises, indicating that a high level of gap junction connectivity is associated with synchronized bursting activity (Church and Baimbridge 1991). Within epilepsy research, there is much evidence suggesting gap junction formation or dysfunction plays important roles in seizure formation (He et al. 2009; Talhouk et al. 2008; Thompson et al. 2008). There are, however, no standard quantitative parameters to describe the range of gap junction connectivity in vivo, either norm 1 or pathological conditions. To address this, our simulations used...
a broad range of gap junction coupling. In one extreme (0.001 μS), there was negligible voltage change in the targeted cell, yet clear differences in signal output. At the other extreme, the conductance was high enough (0.05 μS) that most APs were likely to be duplicated in the coupled cell. Physiological systems likely lie between these extremes, although the precise parameters depend on cellular structure and dynamics. Previous modeling work used parameters similar to those used herein: 25 nS to 1 μS for dendrodendritic connections (Tseng et al. 2008) or about 2 nS for axoaxonal connections (Traub et al. 1999).

**Comparison with Ephaptic Interactions.** The implementation of gap junctions in the model (current injection through a resistor) is also quite similar to the effects that would be seen with ephaptic interactions (Fox et al. 2004). The main difference is that the input resistance lowers when a gap junction is inserted, whereas an ephaptic effect produces a simple DC injection. However, conditions that produce increased ephaptic interactions, such as cellular swelling, also lower the input resistance (Fox et al. 2004). Therefore although ephaptic interactions were not specifically included in this model, they are likely to be quite similar to the results for these dendrodendritic gap junctions. The primary difference would be connection with more neighboring cells than that in the gap junction case.

**Basket Cells.** The role of inhibitory interneurons is difficult to quantify, but is an inherent and critical part of computer models of brain activity (Cunningham et al. 2004; Dyhrfjeld-Johnsen et al. 2007; Netoff et al. 2005; Tiesinga et al. 2004; Tort et al. 2007; Traub and Bibbig 2000; Traub et al. 2005a). The parameters for the basket cells were identical to those used and justified previously (Tort et al. 2007) and the conductance of the GABA synapse onto pyramidal cells (0–0.775 nS) is comparable to that of previous simulations (Traub et al. 2000).

**Basket cells and noise improve signal detection**

The ability of noise to improve detection of a subthreshold signal, or SR, has been described previously in neural models (Chiu and Bardakjian 2004; Kawaguchi et al. 2008), with excitatory and inhibitory noise sources (Rudolph and Destexhe 2003), in vitro hippocampal slices (Guckman et al. 1996; Stacey and Durand 2001), and a visual-stimulus in vivo study (Funke et al. 2007). To our knowledge, this is the first rigorous demonstration of SR in a physiological model of neocortex or hippocampus that includes inhibitory interneurons. A possible concern about the inclusion of inhibitory basket cells is that they could diminish the SR effect. However, the results show quite the opposite: for low noise levels the SNR was improved when the basket cells were present, both in a single cell and in the network. The inhibitory feedback occurs after a spike, which allows low events to occur but inhibits secondary events that follow. The overall effect was a reduction in the background noise over a wide range of noise, similar to that seen in prior work with inhibitory noise sources (Rudolph and Destexhe 2003). At higher noise levels, the basket cells promoted synchronized periodic firing, which disrupted signal detection and diverged from the SR curve. These two effects are important factors in evaluating cortical networks for SR because they likely play a role in any experimental preparation that contains inhibitory interneurons.

Similarly, improved coherent oscillations with basket cells is a rather novel method of coupling within CR literature, but well described in neurophysiology, such as with PING. In CR literature, the coupling is normally excitatory (Balenzuela and García-Ojalvo 2005; Chiu and Bardakjian 2004; Wang et al. 2000), which is typically represented as gap junctions, ephaptic connections, or excitatory synaptic connections in physiological computational models (Stacey and Durand 2002). This work demonstrates that CR is also present in this physiological case of basket cell inhibition.

**Noise oscillations and epileptiform activity**

The network model was able to generate periodic oscillations in response to random synaptic activity. These oscillations have many similarities, both in character and etiology, with epileptiform HFOs. Of particular interest was the finding that an increase in either intrapyramidal gap junctions (Drauguh et al. 1998) or recurrent axons (Jefferys and Traub 1998) could increase the frequency of the oscillations to the ripple range (100–190 Hz), especially when fewer basket cells were present. This configuration is very similar to the pathologic changes seen in epileptic tissue and suggests a method by which pathologic ripples could be generated within such tissue. HFOs in these ranges are often correlated with seizures (Bragin et al. 2004; Dudek 2003; Fisher et al. 1992; Jirsch et al. 2006; Rampp and Stefan 2006; Worrell et al. 2004). Ripples are often considered abnormal in hippocampal tissue (Bragin et al. 1999, 2004), although the characteristics that separate them from physiological ripples (Ylinen et al. 1995) are still unknown (Engel Jr et al. 2003). In addition, these results produce the HFOs with pyramidal cell APs, which has been hypothesized as a way of identifying epileptiform ripples (Engel Jr et al. 2009). These results were similar to recent work demonstrating that pyramidal cells fire during the ripple peaks, with interneurons firing just afterward once the ripple begins (Le Van Quyen et al. 2008). There were two important limitations of this model. First, at high frequencies the pyramidal cells in this model fire very fast and experimental work to date shows sparse pyramidal cell firing in ripples (Csicsvari et al. 1999a,b). Second, this network was not able to produce oscillations in the fast ripple (>250 Hz) range. Further work will evaluate the pathologic changes necessary to produce such frequencies.

The coherent noise oscillations described herein are a form of CR, which is typically described in other physical systems or in neural models that have more abstract physiological correlation (Balenzuela and García-Ojalvo 2005; Chiu and Bardakjian 2004; Wang et al. 2000). Although the current model is an arbitrary and reduced structure, it is founded on physiologic channel dynamics and synapse functions and the input and output characteristics can be compared with true physiology. The oscillations were present under many different configurations and parameters and appeared to be an inherent characteristic of the network. When presented with enough input, any neuron is capable of repetitive firing. In a network, some form of coupling is required to synchronize constituent cells and, in this case, the basket cells provided ample coupling. In our model, the firing frequency was determined by the interaction of the input, the refractory period of the cell, the rate of firing and synaptic characteristics of basket cells, and other complex network and channel dynamics. This hippocam-
pal network had a propensity to fire from 40 to 100 Hz, the gamma range, when the background was highly active. These results were similar to the generation of gamma oscillations in Traub’s model (Traub et al. 1997). The model also reproduces the effect of NMDA blockade increasing gamma power, which is a model of schizophrenia (Lazarowicz et al. 2009; Pinault 2008). Our model predicts that this latter effect may be ascribed to modulation of the interneuron activity, effectively altering the network frequency through the PING effect. There are various theories about the generation of fast neural oscillations and, at times, they appear to be mutually exclusive. For example, normal gamma oscillations and physiological ripples appear to be produced by similar mechanisms: IPSP oscillations with sparse pyramidal cell firing (Bragin et al. 1999; Chrobak and Buzsáki 1996; Tort et al. 2007; Traub et al. 1996a; Ylinen et al. 1995). However, others have shown HFOs that are formed by bursts of pyramidal cell population spikes (Bragin et al. 2007) and can occur when IPSPs are blocked by bicuculline (Behrens et al. 2007). In addition, HFOs are described to be dependent on either axoaxonic gap junctions (Traub et al. 2000), ephaptic connections (Fox et al. 2004), or recurrent excitatory axons (Dzhala and Staley 2004). Recognizing these different conditions is difficult, but may provide insight into the pathology of epilepsy, particularly if one assumes there are two populations of HFOs—normal and pathological (Engel Jr et al. 2009). This study describes a method that may link the two forms of HFOs: CR predicts and describes that various levels of noise and coupling can produce oscillations similar to both “normal” and “abnormal” oscillations. Under normal conditions, physiological levels of noise can generate network gamma oscillations through the PING mechanism as well as 200-Hz oscillations in the basket cells similar to physiological IPSP ripples. When noise and/or coupling are abnormally high, the network generates fast oscillations (fast gamma and population-spike ripples) in the pyramidal cells that are similar to epileptiform activity, even when basket cells are removed. The effects demonstrated herein occurred with inputs that are very plausible physiologically and were not dependent on any specific or ordered coupling configurations. This work suggests that noise oscillations are an inherent property of hippocampal networks. In addition, this network is only subtly different from neocortex and these same principles also are likely to apply to neocortical oscillations.

Conclusion

This work demonstrates how synaptic noise and coupling can improve signal detection and generate coherent oscillations in a hippocampal computer network. The parameters that generated these effects are physiologically feasible. We propose that SR and CR are tools that can quantify inherent properties of neural systems when noise and coupling are favorable and that both the high conductance state (Destexhe et al. 2003) and seizures provide such conditions. Noise clearly plays an important role in signal processing and may be an important factor in the generation of epileptiform oscillations. There is tremendous clinical activity involved in treating people with epilepsy, but there are fundamental gaps in our understanding that hinder this mission. Several such gaps are our lack of understanding of what distinguishes epileptic networks from normal brain, what constitutes a seizure, and what generates individual epileptic events, both “pathological” interictal oscillations and ictal phenomena. More specific questions arise from recent work identifying HFOs, especially ripples and fast ripples, as potential markers for epileptogenic regions. The mechanisms generating these events are still unclear. Computer simulations, provided they are grounded on physiological constraints, provide powerful tools for exploring the mechanisms of such phenomena that are currently beyond electrophysiologic technology. Our study suggests that synaptic activity quantified as “noise” and network coupling generate both normal and abnormal coherent oscillations. Furthermore, it predicts that changes in the noise and/or the coupling similar to those seen in epilepsy can generate pathological HFOs. As technology becomes able to monitor and modulate noise and coupling in physiological networks, these principles can be explored in vitro and in vivo on the network scale.

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