Synaptic Background Activity Enhances the Responsiveness of Neocortical Pyramidal Neurons

NICOLAS HÔ[1,2] AND ALAIN DESTEXHE[1,3]
[1]*Department of Physiology and* [2]*Department of Physics, Laval University, Quebec G1K 7P4, Canada; and* [3]*Unité de Neurosciences Intégratives et Computatìonnelles, UPR 2191, Centre National de la Recherche Scientifique, 91198 Gif-sur-Yvette, France*

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Hô, Nicolas and Alain Destexhe. Synaptic background activity enhances the responsiveness of neocortical pyramidal neurons. *J Neurophysiol* 84: 1488–1496, 2000. Neocortical pyramidal neurons in vivo are subject to an intense synaptic background activity but little is known of how this activity affects cellular responsiveness and what function it may serve. These issues were examined in morphologically reconstructed neocortical pyramidal neurons in which synaptic background activity was simulated based on recent measurements in cat parietal cortex. We show that background activity can be decomposed into two components: a tonically active conductance and voltage fluctuations. Previous studies have mostly focused on the conductance effect, revealing that background activity is responsible for a decrease in responsiveness, which imposes severe conditions of coincidence of inputs necessary to discharge the cell. It is shown here, in contrast, that responsiveness is enhanced if voltage fluctuations are taken into account; in this case the model can produce responses to inputs that would normally be subthreshold. This effect is analyzed by dissecting and comparing the different components of background activity, as well as by evaluating the contribution of parameters such as the dendritic morphology, the distribution of leak currents, the value of axial resistivity, the densities of voltage-dependent currents, and the release parameters underlying background activity. Interestingly, the model's optimal responsiveness was obtained when voltage fluctuations were of the same order as those measured intracellularly in vivo. Possible consequences were also investigated at the population level, where the presence of background activity allowed networks of pyramidal neurons to instantaneously detect inputs that are small compared with the classical detection threshold. These results suggest, at the single-cell level, that the presence of voltage fluctuations has a determining influence on cellular responsiveness and that these should be taken into account in models of background activity. At the network level, we predict that background activity provides the necessary drive for detecting events that would normally be undetectable. Experiments are suggested to explore this possible functional role for background activity.

INTRODUCTION

The membrane potential (V_m) of neocortical neurons in vivo is continuously fluctuating due to the presence of synaptic background activity (Azouz and Gray 1999; Contreras et al. 1996; Lampl et al. 1999; Matsumara et al. 1988; Nowak et al. 1997; Paré et al. 1998b), which reflects ongoing activity in the cortical network. This activity may influence dendritic integration due to tonically activated synaptic conductances in dendrites. This theme was explored by modeling studies (Barrett 1975; Bernander et al. 1991; Destexhe and Paré 1999; Holmes and Woody 1989; Rapp et al. 1992), which have suggested that these conductances indeed affect dendritic integration and impose strict conditions concerning the convergence or coincidence of synaptic inputs necessary to discharge the cell.

The electrophysiological properties of synaptic background activity were characterized recently in cat parietal cortex by comparing intracellularly recorded pyramidal neurons in vivo before and after application of tetrodotoxin (TTX) (Destexhe and Paré 1999; Paré et al. 1998b). It was found that background activity accounts for up to 80% of the input conductance, depending on the type and depth of the anesthesia. A significant conductance increase due to background activity has also been demonstrated in cerebellar Purkinje cells (Hausser and Clark 1997).

Another component of background activity is the presence of high-amplitude V_m fluctuations, which is a consistent feature of intracellular recordings in vivo, although paradoxically these are rarely taken into account. In this paper, we have used computational models to investigate the responsiveness of neocortical pyramidal neurons in the presence of synaptic background activity with V_m fluctuations. Possible consequences at the network level were also investigated. Some of these results have appeared previously in a congress abstract (Destexhe and Hô 1999).

METHODS

Computational models were designed based on four morphologically reconstructed neocortical pyramidal cells from cats (1 from layer II-III, 2 from layer V, and 1 from layer VI), which were obtained from two previous studies (Contreras et al. 1997; Douglas et al. 1991). The layer VI pyramidal cell (Fig. 1*A*) was used primarily, and the results were checked using the three other geometries (see RESULTS). The cellular geometries were incorporated into the NEURON simulation environment (Hines and Carnevale 1997). The dendritic surface was corrected for spines, assuming that spines represent about 45% of the dendritic membrane area (DeFelipe and Fariñas 1992). Passive parameters, such as the membrane resistance, capacitance and axial resistivity were estimated by matching the models to passive re-

Address for reprint requests: A. Destexhe, Unité de Neurosciences Intégratives et Computationnelles, CNRS, 1 Avenue de la Terrasse, Bat. 32–33, 91198 Gif-sur-Yvette, France (E-mail: Alain.Destexhe@iaf.cnrs-gif.fr).

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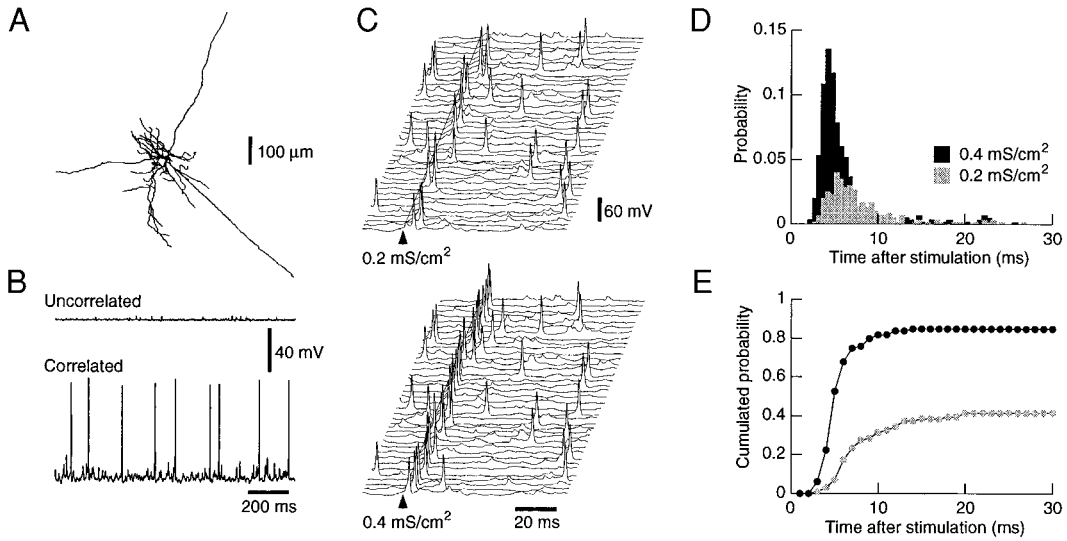

FIG. 1. Method to calculate the response to synaptic stimulation in neocortical pyramidal neurons in the presence of synaptic background activity. *A*: layer VI pyramidal neuron reconstructed and incorporated in simulations. *B*: voltage fluctuations due to synaptic background activity. Random inputs without correlations (*Uncorrelated*) led to small-amplitude V_m fluctuations. Introducing correlations between release events (*Correlated*) led to large-amplitude V_m fluctuations and spontaneous firing in the 5–20 Hz range, consistent with experimental measurements. *C*: evoked responses in the presence of synaptic background activity. Response to a uniform AMPA-mediated synaptic stimulation is shown for 2 values of maximum conductance density (0.2 and 0.4 mS/cm^2). The arrow indicates the onset of the stimulus and each graph shows 40 successive trials in the presence of correlated background activity. *D*: probability of evoking a spike. The spikes specifically evoked by the stimulation were detected and the corresponding probability of evoking a spike in successive 0.5 ms bins was calculated over 600 trials. *E*: cumulative probability obtained from *D*.

sponses obtained intracellularly after application of TTX and synaptic blockers (Destexhe and Paré 1999). Different combinations of passive parameters were used, such as a supplementary shunt conductance of 10 nS in the soma due to electrode impalement, different values of the axial resistivity (80–250 Ωcm) and different distributions of leak conductances in soma and dendrites (nonuniform distributions taken from Stuart and Spruston 1998).

Voltage-dependent conductances were inserted in soma, dendrites, and axon. Na^+ and K^+ currents were simulated using Hodgkin and Huxley (1952) type models and had the following densities (in mS/cm^2): Na^+, 12 in soma, 12 in dendrites, 120 in axon; K^+, 10 in soma, 10 in dendrites, 100 in axon. Kinetics of the currents were taken from a model of hippocampal pyramidal cells (Traub and Miles 1991) in which inactivation was shifted by 10 mV toward hyperpolarized values to match voltage-clamp data of cortical pyramidal cells (Huguenard et al. 1988). Action potential threshold was set to about −55 mV at the soma. In some simulations, a high-threshold Ca^{2+} current and a voltage-dependent and Ca^{2+}-dependent K^+ current were inserted in soma and dendrites with densities and kinetics identical to previous studies (Paré et al. 1998a; Yamada et al. 1998). The model was based on neocortical neurons from cat association cortex, which show few or no evidence for the hyperpolarization-activated current I_h or for low-threshold calcium currents (Paré et al. 1998a,b). These currents were therefore not included in the simulations.

Synaptic currents were simulated by kinetic models of glutamatergic and GABAergic receptors: glutamate α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), glutamate *N*-methyl-D-aspartate (NMDA), and γ-aminobutyric acid type-A ($GABA_A$) receptor types were simulated according to two-state kinetic models (Destexhe et al. 1994, 1998). NMDA receptors were only included in some simulations (see RESULTS) and were modeled with a maximal conductance of 25% as that of AMPA receptors, and the voltage-dependent block was modeled assuming an extracellular Mg^{2+} concentration of 1 mM (see details in Destexhe et al. 1998). Quantal conductances were estimated from miniature synaptic events and were 1200 pS for AMPA and 600 pS for $GABA_A$ (Destexhe and Paré 1999). Metabotropic receptors were not included. Equations for voltage-dependent and synaptic currents were identical to a previous model (Destexhe and Paré 1999).

The densities of synapses in different regions of the cell were estimated from morphological studies in neocortical pyramidal cells (DeFelipe and Fariñas 1992; Fariñas and DeFelipe 1991a,b; Larkman 1991; Mungai 1967; White 1989). The number of synapses per 100 μm^2 of membrane were: 10–20 ($GABA_A$, soma), 40–80 ($GABA_A$, axon initial segment), 8–12 ($GABA_A$, dendrites), and 55–65 (AMPA-NMDA, dendrites), leading to a total of 16563 glutamatergic and 3376 GABAergic synapses for the layer VI cell shown in Fig. 1*A*.

The release conditions corresponding to synaptic background activity were estimated based on recent data from intracellular recordings of pyramidal neurons before and after application of TTX (Destexhe and Paré 1999; Paré et al. 1998b). To match in vivo recordings, high-frequency release conditions with a significant correlation had to be introduced, such that the model displayed V_m fluctuations, low input resistance and depolarized V_m consistent with in vivo measurements (Fig. 1*B*, *Correlated*). These conditions correspond to all presynaptic terminals releasing randomly according to Poisson processes (average rates of 1 Hz at glutamatergic and 5.5 Hz at GABAergic synapses).

The correlation between release events was obtained by forcing some of the synapses to release simultaneously while keeping the random nature of the release at each synapse. This was achieved by generating N_2 Poisson-distributed random presynaptic trains and by redistributing these trains among the N synaptic sites in the model. If $N_2 < N$, all synapses still released randomly with identical statistical properties, but at any given instant some of the N synapses released simultaneously, and were therefore "correlated." The N_2 inputs were redistributed randomly among the N synapses at every time step, such that the average correlation was the same for every pair of synapses irrespective of their location in the dendritic tree. An advantage of this procedure is that the correlation can be controlled independently, by changing N_2, without affecting the average release frequency at each synapse and therefore with no change in the overall synaptic conductance due to background activity. The conductance and correlation

parameters can therefore be adjusted independently. Details of this algorithm were given in Destexhe and Paré (1999).

A synaptic input was simulated in addition to the background activity. For this purpose, an additional set of AMPA-mediated synapses was considered such that the conductance density of these additional synapses was uniform in dendrites. The range considered (0–1.5 mS/cm^2) represents a small fraction of the total AMPA conductance available in dendrites (72 mS/cm^2 assuming 1200 pS per synapse and 0.6 synapse per μm^2, as in Larkman 1991). Stimuli consisting of single shocks were used here, but the results were also checked with bursts of stimuli consisting of several shocks (2–5) at high frequency (100–300 Hz) and similar results were obtained (not shown).

All computational models were run on Sparc 20 and Ultra 1 workstations (Sun Microsystems, Mountain View, CA).

RESULTS

We start by illustrating the procedure to calculate the response of pyramidal neurons in the presence of background activity. We investigate the properties of responsiveness and which parameters are critical to explain them. Finally, we illustrate a possible consequence of these properties at the network level.

Measuring responsiveness in neocortical pyramidal neurons

In the layer VI pyramidal cell shown in Fig. 1*A*, synaptic background activity was simulated by Poisson-distributed random release events at glutamatergic and GABAergic synapses (see METHODS). The model was constrained by intracellular measurements of the V_m and input resistance before and after application of TTX (Destexhe and Paré 1999; Paré et al. 1998b). A random release rate of about 1 Hz for excitatory synapses and 5.5 Hz for inhibitory synapses was necessary to reproduce the correct V_m and input resistance. In addition, it was necessary to include a correlation between release events to reproduce the amplitude of V_m fluctuations observed experimentally (Fig. 1*B*, *Correlated*). This model thus reproduces the electrophysiological parameters measured intracellularly in vivo: a depolarized V_m, a reduced input resistance and high-amplitude V_m fluctuations.

To investigate the response of the modeled cell in these conditions, a set of excitatory synapses was activated in dendrites, in addition to the synapses involved in generating background activity (see METHODS). Simultaneous activation of these additional synapses, in the presence of background activity, evoked action potentials with considerable variability in successive trials (Fig. 1*C*), as expected from the random nature of the background activity. A similar high variability of synaptic responses is typically observed in vivo (Arieli et al. 1996; Azouz and Gray 1999; Contreras et al. 1996; Lampl et al. 1999; Nowak et al. 1997; Paré et al. 1998b). The evoked response, expressed as a probability of evoking a spike in successive 0.5 ms intervals, is shown in Fig. 1*D* (cumulative probability shown in Fig. 1*E*). The variability of responses depended on the strength of synaptic stimuli, with stronger stimuli leading to narrower probabilities of evoking a spike (Fig. 1*D*).

Thus the most appropriate measure of synaptic response in the presence of highly fluctuating background activity is to compute probabilities of evoking a spike. In the following, we use this measure to characterize the responsiveness of pyramidal neurons in different conditions.

Enhanced responsiveness in the presence of background activity

To characterize responsiveness, the cumulative firing probability was computed for increasing input strength. In quiescent conditions, the cell responded in an all-or-none manner (Fig. 2*A*), reflecting the threshold for action potentials. Additional conductances were included by calculating the total conductance due to synaptic background activity in each compartment of the neuron. In the presence of this additional dendritic shunt, the response curve was shifted to higher input strength (Fig. 2*A*, dashed line). Thus consistent with the overall gain decrease evidenced in previous studies (Barrett 1975; Bernander et al. 1991; Holmes and Woody 1989), the conductance of background activity decreased responsiveness and imposed strict conditions of convergence to discharge the cell.

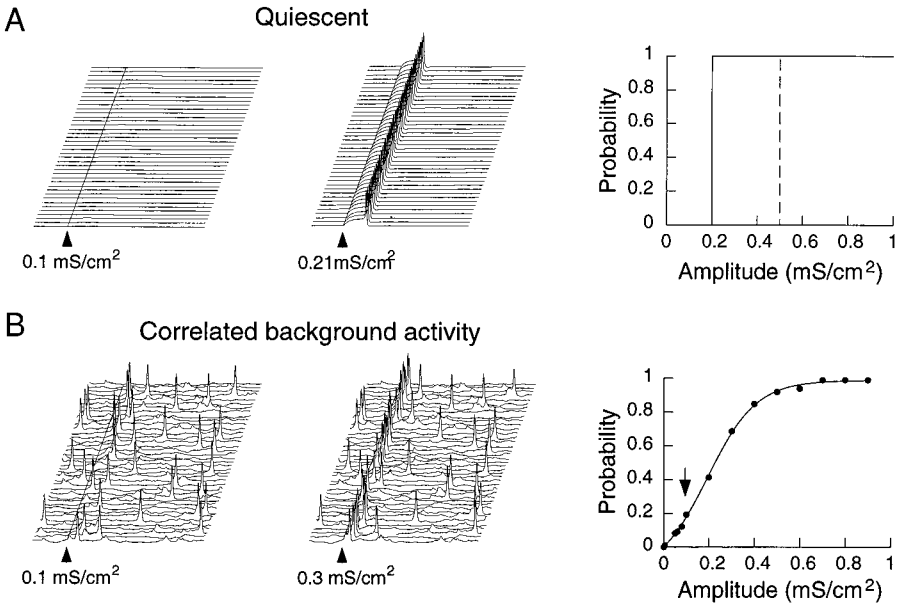

FIG. 2. Synaptic background activity enhances the responsiveness to synaptic inputs. *Left*: successive trials of synaptic stimulation for 2 different stimulus amplitudes (curves arranged similarly to Fig. 1*C*). *Right*: response curve expressed as the cumulative probability of evoking a spike (calculated over 100 trials) as a function of stimulation amplitude (in mS/cm^2; same procedures as in Fig. 1). *A*: response to synaptic stimulation in the absence of background activity (*Quiescent*). The neuron had a relatively high input resistance (R_{in} = 46.5 MΩ) and produced an all-or-none response. The response is compared with the same model in the presence of shunt conductances equivalent to background activity (dashed line; R_{in} = 11.1 MΩ). *B*: response in the presence of correlated synaptic background activity. In this case, the neuron had a relatively low input resistance (R_{in} = 11.2 MΩ) but produced a different response over a wide range of input strengths. In particular, the probability of evoked spikes was significant for inputs that were subthreshold in the quiescent model (arrow). All simulations were done at the same average resting V_m of −65 mV.

However, in the presence of correlated background activity, the response was qualitatively different (Fig. 2*B*). The cell was more responsive, because small excitatory inputs that were subthreshold in quiescent conditions (e.g., 0.1 mS/cm^2 in Fig. 2, *A* and *B*) could generate action potentials in the presence of background activity (arrow). More importantly, the model cell produced a different response to a wide range of input strength, thus producing a different response to inputs that were indistinguishable in the absence of background activity.

These simulations thus suggest that the presence of background activity at a level similar to in vivo measurements (Destexhe et al. 1999; Paré et al. 1998b) is responsible for a significant effect on the responsiveness of pyramidal neurons. The specific role of the different components of background activity is investigated below.

Enhanced responsiveness is caused by voltage fluctuations

To investigate the role of voltage fluctuations, we compared two models with background activity of equivalent conductance but different V_m fluctuations. By using uncorrelated and correlated background activities (Fig. 1*B*), the neuron received the same amount of random inputs, but combined differently, resulting in equivalent average conductance but different amplitudes of V_m fluctuations. With uncorrelated background activity, small inputs became subthreshold again (e.g., 0.1 mS/cm^2 in Fig. 3*A*). The response curve was steeper (Fig. 3*A*, *right*), closer to the equivalent leak conductance (compare with Fig. 2*A*, dashed line). Thus comparing correlated and uncorrelated activity, it appears that the presence of high-amplitude V_m fluctuations significantly affects cellular responsiveness. The persistence of small-amplitude V_m fluctuations in the uncorrelated case is presumably responsible for the sigmoid shape in Fig. 3*A*.

To dissociate the effect of V_m fluctuations from that of shunting conductance, background activity was replaced by injection of noisy current waveforms at all somatic and dendritic compartments. The total net currents due to background activity were recorded at each compartment and injected in the same locations in a model without background activity. This "replay" procedure led to V_m fluctuations similar to those produced by synaptic background activity (Fig. 3*B*, *left*) but without the important tonically activated synaptic conductance, allowing us to dissociate these two factors. With noisy current injection, the input resistance was comparable to that of quiescent conditions (R_{in} = 45.5 vs. 46.5 MΩ), but the cell was more responsive, with subthreshold inputs in quiescent conditions evoking a significant response in the presence of V_m fluctuations (e.g., 0.05 mS/cm^2 in Fig. 3*B*).

The case of a fluctuating conductance without V_m fluctuations was also tested. The total conductance was recorded in each compartment during correlated background activity and was assigned to the leak conductance in each compartment of a model without background activity. This procedure led to a relatively steep response curve (Fig. 3*B*, dotted curve). Although these conductance fluctuations slightly enhanced re-

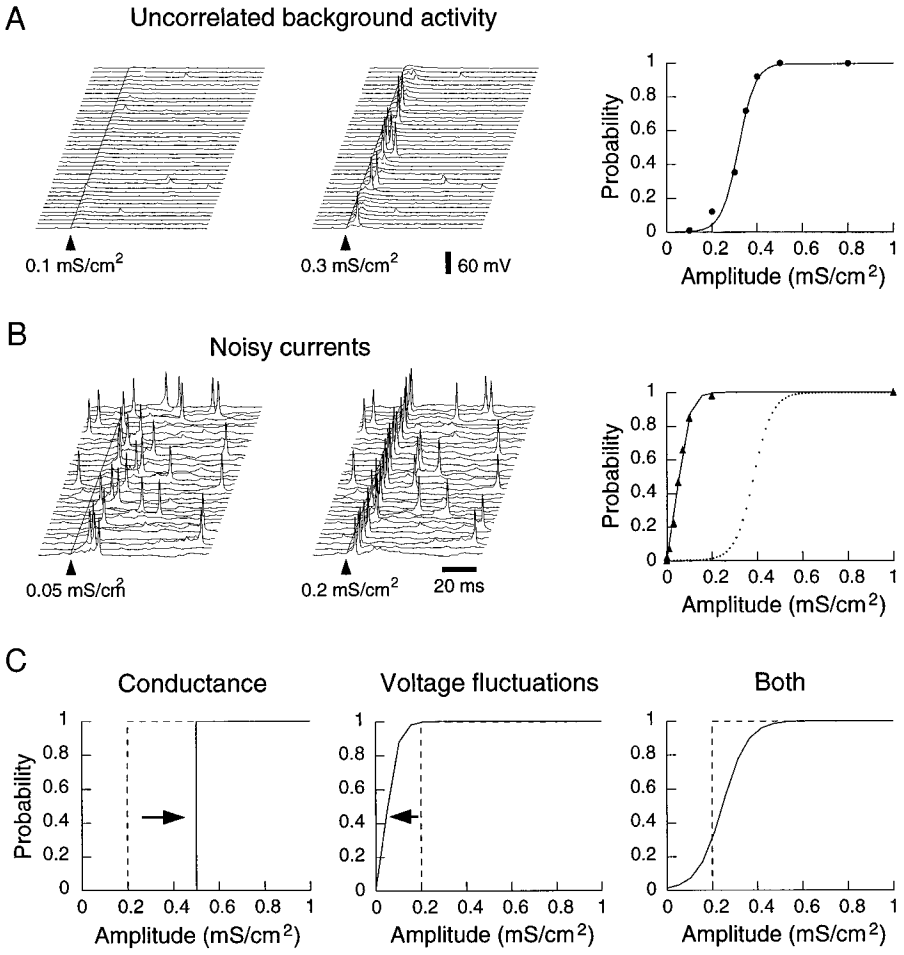

FIG. 3. Enhanced responsiveness is due to voltage fluctuations. *A*: synaptic responses in the presence of uncorrelated background activity. This simulation was the same as in Fig. 2*B* but without correlations in background activity, resulting in similar input resistance (R_{in} = 10.0 MΩ) but smaller amplitude V_m fluctuations (see Fig. 1*B*). The response curve was steeper. *B*: simulation in the presence of fluctuations only. Noisy current waveforms were injected in soma and dendrites, leading to similar V_m fluctuations as in Fig. 2*B* but with a high input resistance (R_{in} = 45.5 MΩ). The response curve (continuous line) showed enhanced responsiveness. Fluctuating leak conductances without V_m fluctuations did not display a significant enhancement in responsiveness (dotted curve; R_{in} = 11 MΩ). *Panels* in *A* and *B* were arranged similarly to those in Fig. 2. *C*: reconstruction of the response curve. *Conductance:* effect of adding a leak conductance equivalent to synaptic bombardment (continuous line; R_{in} = 11.1 MΩ) compared with a quiescent model (dashed line; R_{in} = 46.5 MΩ). *Voltage fluctuations:* effect of adding noisy current waveforms (continuous line; R_{in} = 45.5 MΩ) compared with the quiescent model (dashed line; R_{in} = 46.5 MΩ). *Both:* combination of noisy current waveforms and the equivalent shunt (continuous line; R_{in} = 11.1 MΩ) compared with the quiescent model (dashed line). The response curve was qualitatively similar to that in the presence of correlated background activity (Fig. 2*B*). All simulations correspond to the same average resting V_m of −65 mV.

sponsiveness, this effect was small compared with that of V_m fluctuations.

To assess the importance of these different factors, their effect was compared in Fig. 3*C*. The effect of conductance is to decrease responsiveness, as shown by the shift of the response curve toward larger input strength (Fig. 3*C*, *Conductance*). The effect of voltage fluctuations is to increase responsiveness by shifting the curve to the opposite direction (Fig. 3*C*, *Voltage fluctuations*). Combining these two factors led to a response curve (Fig. 3*C*, *Both*) which was qualitatively similar to the correlated background activity (compare with Fig. 2*B*, *right*).

We therefore conclude that the behavior of the neocortical cell in the presence of correlated background activity can be understood qualitatively by a combination of two opposite influences: a tonically active conductance, which decreases responsiveness, and voltage fluctuations, which increase responsiveness.

Robustness of enhanced responsiveness

The robustness of this finding was examined by performing variations in the configuration of the model. Simulations using four different reconstructed pyramidal cells from cat neocortex, including a layer II-III cell and two layer V cells, showed a similar enhancement in responsiveness for all cases (Fig. 4). For each cell, correlated background activity (continuous curves) was compared with the equivalent shunt conductance (dashed curves), showing that the presence of background activity significantly enhanced responsiveness for the four cellular morphologies considered.

To test the influence of dendritic excitability, the density of Na^+ and K^+ channels were varied in dendrites, soma, and axon. Rescaling these densities by the same factor resulted in a different global excitability of the cell and gave rise to a shift in the response curves, as expected (Fig. 5*A*). However, in all cases, comparing correlated background activity (continuous curves) to models with equivalent shunt (dashed curves), revealed an enhancement in responsiveness irrespective of the exact position of the response curves.

The same phenomenon was also present for various other parameters, such as the distribution of leak currents (Fig. 5*B*), different axial resistivities (Fig. 5*B*), different sets and densities of voltage-dependent currents (Fig. 5*C*), different combinations of synaptic receptors, and different release frequencies (Fig. 5*D*). For all cases, variations of parameters had an expected effect of shifting the response curve, but the presence of background activity always led to a significant enhancement in responsiveness similar to Fig. 5*A*.

We also tested whether the enhancement in responsiveness was sensitive to the proximity of the excitatory inputs to the somatic region. We calculated the synchronized stimulation of increasing densities of AMPA-mediated synapses located exclusively in the distal region of dendrites (>200 μm from soma; see Fig. 6*A*). The response curve following stimulation of distally located AMPA-mediated inputs was computed sim-

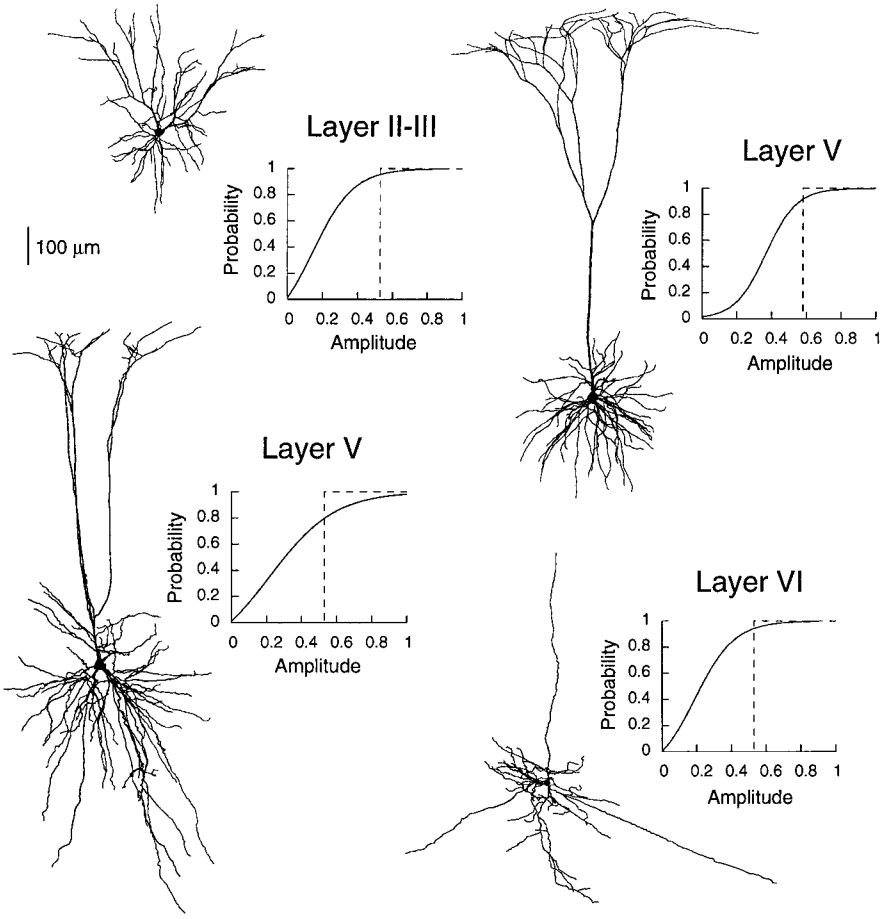

FIG. 4. Enhancement in responsiveness for different dendritic morphologies. Four different reconstructed neocortical pyramidal neurons are shown with their respective response curves (*insets*), comparing background activity (continuous lines) with equivalent dendritic shunt (dashed lines). The response curves varied slightly in different cells, but the enhancement in responsiveness was present in all cases. Each cell was simulated with identical densities of voltage-dependent and synaptic conductances and identical average resting V_m of -65 mV.

ilarly as for uniform stimulation. Here again, the presence of background activity led to an enhancement of the responsiveness of the cell (Fig. 6*B*), showing that the mechanisms described above also apply to distally located inputs.

Optimal conditions for enhanced responsiveness

To evaluate the range of voltage fluctuations at which responsiveness is optimally enhanced, the response probability was computed for subthreshold inputs at different conditions of V_m fluctuations. These different conditions were obtained by varying the value of the correlation, leading to background activities of identical conditions of conductance and average V_m but different amplitudes of V_m fluctuations (see Destexhe and Paré 1999). The probability of spikes specifically evoked by subthreshold stimuli was represented as a function of the amplitude of V_m fluctuations in Fig. 7 (symbols). This figure shows that there are no spikes evoked without background activity or with background activity with fluctuations of too small-amplitude. However, for V_m fluctuations larger than about $\sigma_v = 2$ mV (as measured by the standard deviation of V_m), the response probability shows a steep increase and stays above zero for background activities with larger fluctuation amplitudes.[1] The responsiveness is therefore enhanced for a range of V_m fluctuations of σ_v between 2 and 6 mV and more. Interestingly, this optimal range approximately matches the level of V_m fluctuations measured intracellularly in cat parietal cortex in vivo ($\sigma_v = 4.0 \pm 2.0$ mV in Destexhe and Paré 1999; indicated by a gray area in Fig. 7).

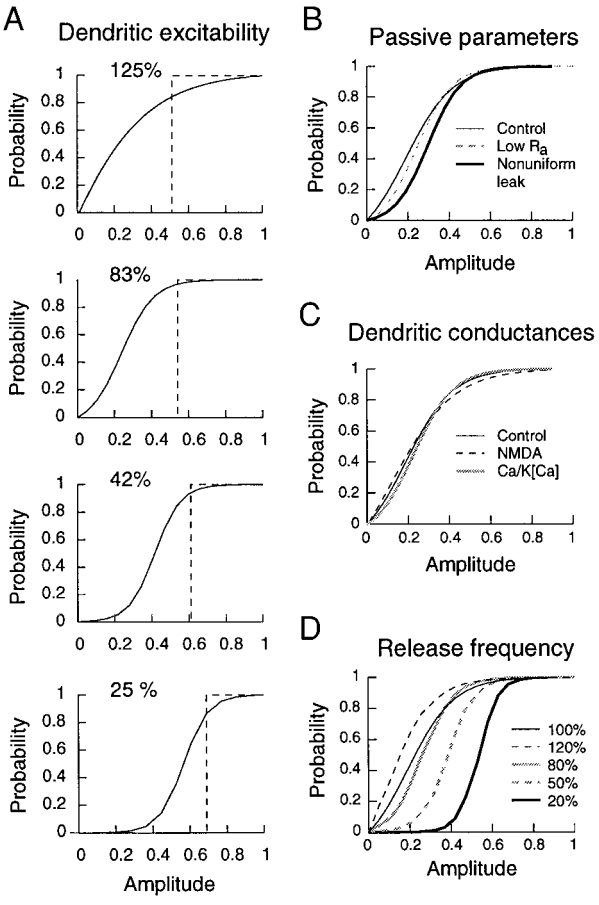

FIG. 5. Enhancement in responsiveness for different distributions of conductances. *A*: modulating dendritic excitability by using different densities of Na^+/K^+ conductances shifts the response curve, but the enhancement in responsiveness was present in all cases (the relative Na^+/K^+ conductance densities are indicated with respect to control values). *B*: effect of different variations of the passive parameters (low axial resistivity of $R_a = 80$ Ωcm; nonuniform leak conductances; from Stuart and Spruston 1998). *C*: addition of NMDA receptors or dendritic Ca^{2+} currents and Ca^{2+}-dependent K^+ currents. *D*: modulation of the intensity of background activity (values indicate the excitatory release frequency relative to control). Similar to *A*, the parameters in *B–D* affected the position of the response curve, but the enhancement in responsiveness was present in all cases. All simulations were obtained with the layer VI cell and correspond to the same average resting V_m of −65 mV.

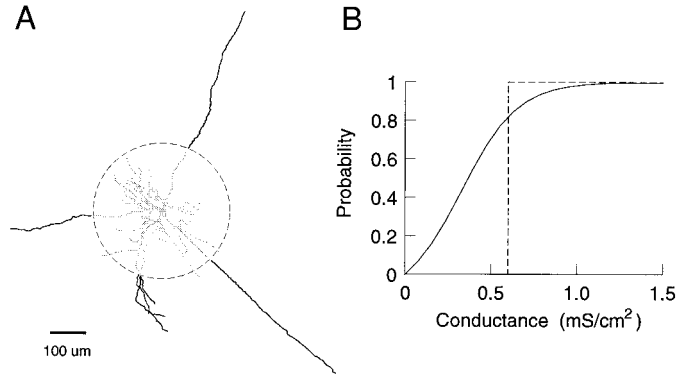

FIG. 6. Enhancement in responsiveness for inputs localized in distal dendrites. *A*: subdivision of the distal dendrites in the layer VI cell. The distal dendrites (shown in black) were defined as the ensemble of dendritic segments laying outside 200 μm from the soma (dashed line). The unstimulated dendrites are shown in light gray. *B*: probability of evoking a spike as a function of the strength of synaptic stimulation in distal dendrites. The response obtained in the presence of correlated background activity (continuous line) is compared with that of a model including the equivalent dendritic shunt (dashed line). Background activity enhanced the responsiveness in a way similar to uniform stimulation.

Possible consequences at the network level

The above results show that enhanced responsiveness can be demonstrated at the single-cell level, in which case the high variability of responses makes it necessary to perform averages over a large number of successive stimuli. Because the nervous system does not perform such temporal averaging, the physiological meaning of enhanced responsiveness would therefore be unclear if it relied exclusively on performing a large number of trials. We illustrate below that this averaging can also be performed at the population level (spatial averaging), leading to an instantaneous enhancement in responsiveness for single-trial stimuli.

We have examined the simple case of a feedforward network of pyramidal neurons, whose behavior was compared with and without synaptic background activity. This simple paradigm is illustrated in Fig. 8*A*. One thousand identical presynaptic pyramidal neurons received simultaneous afferent AMPA-mediated inputs with conductance randomized from cell-to-cell and projected to a single postsynaptic cell. The differences in afferent input thus created variations in the amplitude of the

[1] After reaching a peak, the probability of evoking spikes decreased steadily with σ_v in Fig. 7. This decrease was partly attributable to a decrease in R_{in} because states with large σ_v also have a high rate of spontaneous firing, and therefore activate voltage-dependent currents which contribute to lower the R_{in}. Simulations were run in which this R_{in} decrease was compensated, which led to about twice less decrease of the probability (not shown).

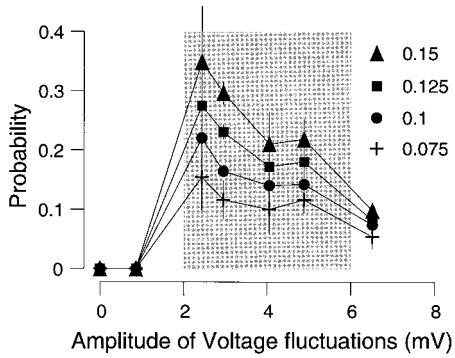

FIG. 7. Enhancement in responsiveness occurs for levels of background activity similar to in vivo measurements. The probability of evoking a spike was computed for subthreshold inputs in the presence of different background activities of equivalent conductance but different amplitudes of voltage fluctuations, indicated by their standard deviation of the V_m (σ_v). These different conditions were obtained by varying the value of the correlation. The different symbols indicate different subthreshold input amplitudes (+ = 0.075 mS/cm^2, circles = 0.1 mS/cm^2, squares = 0.125 mS/cm^2, triangles = 0.15 mS/cm^2; vertical bars = SE). In all cases, the enhanced responsiveness occurred at the same range of voltage fluctuations, which also corresponded to the range measured intracellularly in vivo (gray area; $\sigma_v = 4.0 \pm 2.0$ mV; from Destexhe and Paré 1999). All simulations correspond to the same average V_m of −65 mV.

excitation and on the timing of the resulting spike in the presynaptic cells. The output of this population of cells was monitored through the EPSP evoked in the postsynaptic cell.

In quiescent conditions (absence of background activity), the EPSP evoked in the postsynaptic cell was roughly all-or-none (Fig. 8*B*), reflecting the action potential threshold in the presynaptic cells (similar to Fig. 2*A*). When the presynaptic cells received correlated synaptic background activity (which was different in each cell), the EPSPs were more graded (Fig. 8, *C* and *D*), compatible with the sigmoid response curve in Fig. 2*B* (*left*). Perhaps the most interesting property was that the smallest inputs, which were subthreshold in quiescent conditions, led to a detectable EPSP in the presence of background activity (0.1–0.15 mS/cm^2 in Fig. 8*D*). This shows that the network transmitted some information about these inputs, while this was filtered out in quiescent conditions.

Thus although this paradigm is greatly simplified (identical presynaptic cells, independent background activities), it illustrates the important possibility that the enhanced responsiveness shown in Fig. 2*B* may be used in populations of pyramidal neurons to *instantaneously* detect a single afferent stimulus. In these conditions, the network can detect a remarkably wide range of afferent input amplitudes. Similar to an effect previously reported in neural networks with additive noise (Collins et al. 1995), networks of pyramidal cells with background activity can detect inputs that are very small compared with the threshold for action potentials.

DISCUSSION

In this paper, we have demonstrated using computational models that background activity can significantly enhance the responsiveness of neocortical pyramidal neurons. The significance of this finding is discussed below, as well as possible predictions to test it experimentally.

Background activity enhances synaptic responsiveness

Previous models (Barrett 1975; Bernander et al. 1991; Destexhe and Paré 1999; Holmes and Woody 1989; Rapp et al. 1992) established that the *conductance* of background activity decreases cellular responsiveness and imposes strict conditions of convergence or coincidence. We show here that the *voltage fluctuations* of background activity also have a determining influence on cellular responsiveness. Models in the presence of background activity with voltage fluctuations can produce responses to inputs that would be subthreshold in quiescent conditions (Fig. 2). This result challenges the intuitive view that neurons with low input resistance should also have a low responsiveness.

These different contributions to background activity were evaluated by representing the conductance by an equivalent dendritic shunt, and representing voltage fluctuations by injec-

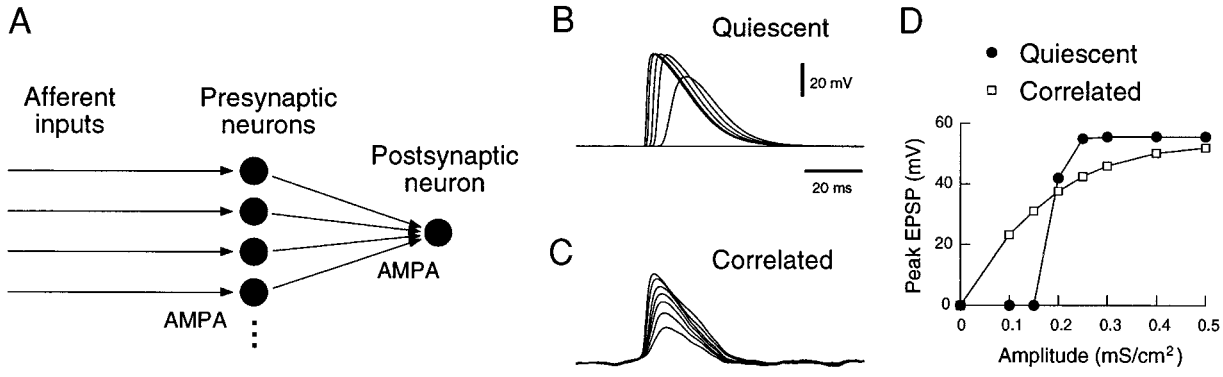

FIG. 8. Synaptic background activity enhances the detection of synaptic inputs at the network level. *A*: feedforward network consisting of 1000 presynaptic neurons identical to Fig. 1*A*. All presynaptic neurons connected the postsynaptic cell using AMPA-mediated glutamatergic synapses. The presynaptic neurons were excited by a simultaneous AMPA-mediated afferent input with randomly distributed conductance (normal distribution with standard deviation of 0.02 mS/cm^2; other parameters as in Fig. 1*B*). *B*: EPSPs evoked in the postsynaptic cell in quiescent conditions (average afferent conductances of 0.1, 0.15, 0.2, 0.25, 0.3, 0.4, and 0.5 mS/cm^2). The EPSP was approximately all-or-none, with smallest inputs evoking no EPSP and strongest inputs leading to EPSPs of constant amplitude. *C*: same simulations in the presence of correlated synaptic background activity. The same conductance densities led to detectable EPSPs of progressively larger amplitude. *D*: peak EPSP from *B* and *C* plotted as a function of the average afferent conductance. The response was all-or-none in control conditions (*Quiescent*) and was graded in the presence of background activity (*Correlated*), showing a better detection of afferent inputs.

tion of noisy current waveforms. Models in which background activity was represented by the equivalent conductance have a clearly different responsiveness (Fig. 2), suggesting that representing background activity only by a shunt conductance is not sufficient. A similar disparity was obtained in models with only voltage fluctuations (Fig. 3*B*), showing that representing background activity by injection of noisy current waveforms is not sufficient either. On the other hand, a good approximation of the cell's responsiveness was obtained when these two factors were combined (Fig. 3*C*). This analysis therefore suggests that noisy current injection together with a shunt conductance should provide an acceptable representation of the effect of background activity.

The model also indicates that the enhancement in responsiveness due to background activity is relatively insensitive to factors such as dendritic morphology, passive parameters, the type of synaptic receptors, and the nature and distribution of voltage-dependent conductances in dendrites (Figs. 4 and 5). Changing these parameters affected the response curve, as expected, but in all cases, the presence of background activity significantly modified the responsiveness. The same conclusions also hold for inputs arising at distal dendritic sites (Fig. 6) or for inputs consisting of high-frequency bursts of stimuli (not shown). Consequently, similar conditions of release at excitatory and inhibitory synapses should result in background activity that affects the responsiveness of a wide range of cell types in cerebral cortex, irrespective of the details of their morphology and biophysical properties.[2]

There is a possibility that the enhancement in responsiveness due to voltage fluctuations stems from mechanisms similar to stochastic resonance, which is an amplification or optimization of weak inputs by the assistance of noise in nonlinear systems (Gammaitoni et al. 1998; Wiesenfeld and Moss 1995). Preliminary results (Rudolph and Destexhe 2000) show that the presence of stochastic resonance can indeed be demonstrated in this model, but that it occurs only for a limited range of parameters. On the other hand, enhanced responsiveness is seen for a remarkably wide range of parameters, even in cases where there is no evidence for stochastic resonance (not shown). More detailed investigations will be necessary to characterize the exact relation between these two phenomena.

Possible functional consequences

An interesting observation was that the enhanced responsiveness was obtained for a range of V_m fluctuations comparable to that measured intracellularly during activated states in vivo (Fig. 7). This suggests that the level of background activity present in vivo represents conditions close to optimal for enhancing the responsiveness of pyramidal neurons. It is possible that the network maintains a level of background activity whose functional role is to keep its cellular elements in a highly responsive state.

In agreement with this view, Fig. 8 illustrated that, in a simple feedforward network of pyramidal neurons, the presence of background activity allowed the network to instantaneously detect synaptic events that would normally be subthreshold (0.1–0.15 mS/cm^2 in Fig. 8*D*). In this case, background activity sets the population of neurons into a state of more efficient and more sensitive detection of afferent inputs, which are transmitted to the postsynaptic cells, while the same inputs would be filtered out in the absence of background activity.

These results should be considered in parallel with the observation that background activity is particularly intense in intracellularly-recorded cortical neurons of awake animals (Matsumara et al. 1988; Steriade et al. 1999). In the light of the present model, we interpret the occurrence of intense background activity as a factor that facilitates information transmission. It is therefore conceivable that background activity is an active component of arousal or attentional mechanisms, which is a possible direction to explore in future models.

Predictions

The general prediction of this model is that neurons with low input resistance can be more responsive if V_m fluctuations are taken into account. This prediction could be tested intracellularly in vivo by considering two different states of background activity in the same cell and comparing the response to synaptic stimuli in these two states. For example, this could be performed under urethane or ketamine-xylazine anesthesia, in which neocortical neurons oscillate synchronously between an active phase and a silent phase (Contreras and Steriade 1995). During the active phase, cortical neurons display intense background activity with high-amplitude V_m fluctuations, whereas the hyperpolarized phase is characterized by a virtual absence of background activity (Paré et al. 1998b). The model predicts that excitatory inputs that are subthreshold or indistinguishable during the silent phase should become detectable and distinguishable if analyzed during the active phase at the same V_m.

This prediction could also be tested in slices by injecting conductances combined with noisy current waveforms, leading to neurons with low input resistance and large-amplitude V_m fluctuations similar to in vivo measurements. The model predicts an increased sensitivity to synaptic stimulation in such conditions.

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[2] Note that the effect of background activity was only considered here for regular-spiking cells and not for the different types of bursting cells present in cerebral cortex (Connors and Gutnick 1990). The characterization of the effect of background activity on the latter type should be done in future studies.

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