

Persistent Cortical Activity: Mechanisms of Generation and Effects on Neuronal Excitability

David A. McCormick¹, Yousheng Shu¹, Andrea Hasenstaub¹, Mavi Sanchez-Vives², Mathilde Badoual³ and Thierry Bal³

¹Department of Neurobiology, Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06510, USA, ²Instituto de Neurociencias, Universidad Miguel Hernández-CSIC, Apartado 18, 03550, San Juan de Alicante, Spain and ³Unité de Neurosciences Intégrative et Computationnelles, CNRS UPR 2191, Institut de Neurobiologie Alfred Fessard, 1 avenue de la Terrasse, Bat. 33, 91198 Gif-sur-Yvette Cedex, France

Local cortical networks in the prefrontal cortex and visual cortex are capable of spontaneously generating sustained activity for periods of seconds or longer. This sustained activity is generated through recurrent excitation between pyramidal cells that is controlled by feedback inhibition and can have both a rapid onset and a rapid offset. The period of activity is associated with a marked increase in neuronal responsiveness to the intracellular injection of current pulses, especially those of smaller amplitude. Independently mimicking the depolarization, increase in membrane conductance and increase in noise associated with sustained activity revealed that the depolarization is largely responsible for the increase in neuronal responsiveness, although an increase in membrane noise also facilitates responses to small inputs. These results indicate that the persistent activity associated with the performance of working memory tasks may be generated largely through recurrent networks. They also suggest that feedback pathways, such as those involved in selective attention, may exert a powerful influence on neuronal responsiveness through synaptic bombardment.

Introduction

Neuronal activity in the monkey prefrontal cortex can exhibit a persistent discharge during the ‘memory’ or delay period of a task that requires the animal to remember specific features, such as location, of a target (Funahashi *et al.*, 1989; Fuster, 1995; Goldman-Rakic, 1995; Miller *et al.*, 1996). The occurrence of persistent activity during working memory tasks is not unique to the prefrontal cortex, and indeed is found in multiple cortical, and even subcortical, areas (Fuster and Alexander, 1973; Fuster and Jervey, 1981; Miyashita and Chang, 1988; Hikosaka *et al.*, 1989; Fuster, 1995; Pesaran *et al.*, 2002). Computational models of this persistent activity typically rely upon the operation of recurrent excitatory networks that are controlled by the activation of inhibitory interneurons (Amit and Brunel, 1997; Lisman *et al.*, 1998; Wang, 1999, 2001; Compte *et al.*, 2000, 2003a; Durstewitz *et al.*, 2000b; Timofeev *et al.*, 2000), although it is also possible that intrinsic membrane properties contribute significantly (Marder *et al.*, 1996; Camperi and Wang, 1998; Haj-Dahmane and Andrade, 1998; Egorov *et al.*, 2002). While computational studies have examined the possible role of different components of neuronal networks in the generation of persistent activity, it has been difficult to examine the cellular mechanisms *in vivo*, owing in part to the problems of performing intracellular recordings in awake, behaving animals.

Recently, we reported that slices of the ferret prefrontal and occipital cortex generate recurring periods of sustained (persistent) activity when maintained *in vitro* in an ionic solution that more closely mimics normal cerebrospinal fluid than is traditionally used for maintaining slices (Sanchez-Vives and McCormick, 2000; Shu *et al.*, 2003). This recurrent activity is

composed of so-called ‘UP’ and ‘DOWN’ states and appears nearly identical to that underlying the generation of the cortical slow oscillation *in vivo* during anesthesia or sleep (Steriade *et al.*, 1993a, 2001; Contreras and Steriade, 1995; Contreras *et al.*, 1996). We propose that the mechanisms involved in the generation of this form of recurring sustained activity may have important implications regarding those underlying the generation of persistent activity during working memory tasks in the same neuronal circuits.

Changes in background synaptic activity may not only underlie the generation of persistent neuronal discharge, but also may have strong influences on neuronal excitability and responsiveness to other synaptic inputs (Bernander *et al.*, 1991; Timofeev *et al.*, 1996; Destexhe and Paré, 1999; Anderson *et al.*, 2000a,b; Destexhe *et al.*, 2001; Chance *et al.*, 2002; Fellous *et al.*, 2003; Mitchell and Silver, 2003). Increases or decreases in background synaptic activity may mediate the influence of feedback pathways or local networks on the responsiveness of single neurons. Thus, rapid changes in barrages of fast excitatory and inhibitory postsynaptic potentials may provide a mechanism for neuronal ‘context’ such as the position of gaze in visual-motor transformations (Andersen and Mountcastle, 1983; Andersen *et al.*, 1985; Salinas and Abbott, 1996), selective attention (McAdams and Maunsell, 1999a,b; Treue and Martínez-Trujillo, 1999; Reynolds *et al.*, 2000; Chance *et al.*, 2002), long-range receptive field influences (Carandini and Heeger, 1994; Angelucci *et al.*, 2002; Stettler *et al.*, 2002) and feedback from higher cortical areas (Hupé *et al.*, 1998).

Here we use intracellular and extracellular recordings from ferret prefrontal cortical slices to examine the cellular mechanisms underlying the generation of local sustained activity and how this may influence the neuronal responsiveness of cortical neurons to afferent inputs. These results are relevant to the possible mechanisms of persistent activity during short term memory tasks and may shed light on the mechanisms by which network activity influences neuronal processing.

Methods

Slices (0.4 mm thick) were prepared on a DSK microslicer from the medial prefrontal cortex (anterior to the presylvian fissure) of 2- to 4-month-old ferrets of either sex. The ferrets were deeply anesthetized with sodium pentobarbital (40 mg/kg) and killed by decapitation. The entire forebrain was rapidly removed and the hemispheres were separated with a midline incision. A modification of the sucrose-substitution technique developed by Aghajanian and Rasmussen (1989) was used to increase tissue viability. During preparation of slices, the tissue was placed in a solution in which NaCl was replaced with sucrose while maintaining an osmolarity of 307 mOsm. After preparation, slices were placed in an interface style recording chamber (Fine Sciences Tools, Foster City, CA). For the first 10 min cortical slices were superfused with an equal mixture in volume of the normal bathing medium and the

sucrose-substituted solution. Following this, normal bathing medium was switched into the chamber and superfused the slices for ~1 h, then modified slice solution was used through out the remained of the experiment. Bath temperature was maintained at 34.5–36°C.

Simultaneous extracellular multiple unit and intracellular recordings were performed in layer 5 after at least 2 h of recovery. The normal bathing medium contained (in mM): NaCl, 126; KCl, 3.5; MgSO₄, 1; NaH₂PO₄, 1.25; CaCl₂, 1–1.2; NaHCO₃, 26; dextrose, 10, and was aerated with 95% O₂/5% CO₂ to a final pH of 7.4. Sharp intracellular recording electrodes were formed on a Sutter Instruments (Novato, CA) P-80 micropipette puller from medium-walled glass (1B100F-4, WPI Sarasota, FL) and beveled on a Sutter Instruments beveler to final resistances of 60–100 MOhms. Micropipettes were filled with 2 M KAc.

Dynamic Clamp and Data Analysis Techniques

After obtaining a stable intracellular recording from a layer 5 neuron, a number of experiments were performed with a dynamic clamp technique using a DAP-5216a board (Microstar Laboratory; Dorval *et al.*, 2001). To test the responsiveness of cortical neurons in different states, different amplitude current pulses (typically 400 ms duration) were injected into the intracellularly recorded neurons. The effects of various manipulations on the resulting *f-I* plots, as well as in spike timing, were then examined. The dynamic clamp system operated at 10 000 Hz in standard current clamp (bridge) mode or ~3000 Hz in discontinuous current clamp (DCC) mode using an Axon Instruments Axoclamp-2B amplifier. In current clamp mode, the bridge was carefully balanced with the periodic injection of current pulses. In DCC mode, the headstage output was continuously monitored to ensure adequate settling time during the injection of current. The large majority of experiments were performed in DCC mode, since this was less sensitive to changes in bridge balance. Data collected were carefully monitored for problems with the dynamic clamp technique, which typically appear as breaks or discontinuities in the current injected. Data containing problems with the dynamic clamp technique were discarded.

The extracellular and intracellular data were collected using Spike-2 software (Cambridge Electronic Design; Cambridge, UK). The data was segregated into three periods, UP, DOWN, and in between states, according to activity in the multiple unit recording. The multiple unit recording was rectified and smoothed to yield an outline of the increase and decrease in activity associated with the onset and offset of the UP state. Two thresholds were positioned and the multiple unit activity was required to rise above the highest threshold to be counted as an UP state. The onset and offset of the UP state were then determined by the crossings of the lower threshold, which was set ~2× baseline. Only UP states that were at least 0.5 s in duration were considered. DOWN states were defined as those periods for which the activity level stayed below the lower limit for a period of >0.5 s. Periods that were neither classified as UP nor DOWN were not analyzed.

In addition to the injection of current pulses, we also manipulated the level of membrane potential, conductance, and variance (noise) occurring within the cell at the recording (injection) site. Membrane potential was manipulated through the intracellular injection of steady current. Changing membrane conductance was achieved with the dynamic clamp system with the reversal potential of the conductance set to the measured resting membrane potential of the cell. Noise was modeled according to Destexhe *et al.* (2001). The total synaptic current, I_{syn} , was composed of two independent conductances according to the following:

$$I_{\text{syn}} = g_c(t)(V - E_c) + g_i(t)(V - E_i)$$

where $g_c(t)$ and $g_i(t)$ are the time-dependent conductances calculated as a one-variable stochastic process similar to the Ornstein-Uhlenbeck process (Uhlenbeck and Ornstein, 1930; Destexhe *et al.*, 2001). In our model E_c is 0 mV and E_i is -75 mV and mean g_c was typically equal to mean g_i . The tau for correlations within G_c was typically 30 ms for both excitation and inhibition.

Results

Intracellular recordings were obtained from layer 5 regular spiking cells in the ferret medial prefrontal ($n = 51$ cells) cortex

maintained *in vitro*. Maintaining these cortical slices in an ionic medium that more closely mimicked that of *in vivo* (see methods) resulted in the spontaneous occurrence of so-called UP and DOWN states (Fig. 1; Sanchez-Vives and McCormick, 2000). UP states, which were typically from 0.5 to 3 s in duration, were associated with an increase in multiunit activity (Fig. 1A; 0.5 s was the shortest acceptable duration to be considered an UP state) and a 4–10 mV depolarization mediated by synaptic potentials (see Table 1). Multiple unit recordings revealed that the start and stop of the UP state was synchronized between neighboring neurons (Fig. 1). Examining the onset and offset of the changes in membrane potential associated with the transitions between the UP and DOWN states revealed that they

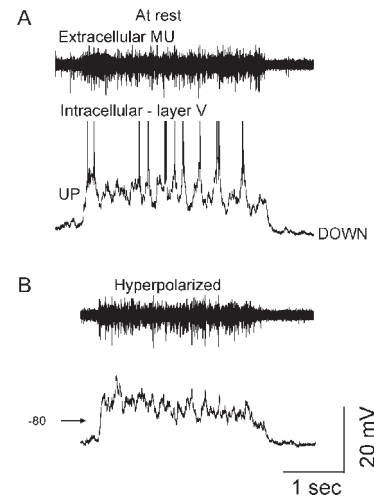


Figure 1. The prefrontal cortical slice *in vitro* spontaneously generates prolonged periods of activity through synaptic bombardments. (A) Simultaneous intracellular and extracellular recordings in layer 5 of the ferret prefrontal cortex. The network enters into the ‘UP’ state for ~3 s prior to a rapid transition to the DOWN state. (B) Hyperpolarization of the intracellularly recorded pyramidal cell reveals the barrage of PSPs arriving during the UP state and the reduction of PSPs during the DOWN state. Note that hyperpolarization or depolarization does not affect the duration of the UP state, which is the same as the average duration of action potential discharge in the local network.

Table 1

Intracellular measurements

Duration of UP state at rest V_m	1.7 ± 0.3 s ($n = 16$)
Duration of UP state after hyperpolarization	1.7 ± 0.4 s ($n = 16$)
Rate of recurrence of UP state at rest V_m	0.2 ± 0.1 Hz ($n = 16$)
Rate of recurrence of UP state after hyperpolarization	0.2 ± 0.1 Hz ($n = 16$)
Single unit firing rate of UP state	17.1 ± 11.1 Hz ($n = 32$)
Single unit firing rate of DOWN state	3.6 ± 3.0 Hz (14/32) 0 Hz (silent, 18/32)
UP–DOWN change in membrane potential	7.6 ± 2.1 mV ($n = 8$)
Increase in membrane conductance during UP state	4–32 nS ($n = 15$)
Increase in membrane variance during UP state	2.6 ± 0.4 mV; $n = 9$
Depolarization induced shift in input–output curve	0.062 ± 0.049 nA/mV
Conductance induced shift in input–output curve	0.016 ± 0.0033 nA/nS

were relatively rapid, often occurring within a time frame of <0.2 s (Fig. 1). Extracellular single unit recordings ($n = 32$ cells), performed in conjunction with multiple unit recordings, revealed that single layer 5 cortical cells discharge during the UP state at a rate that ranged from 2 to 47 Hz (mean \pm SD = 17.1 ± 11.1 Hz). In the DOWN state, 18 of these cells did not spontaneously generate action potentials, while the remaining 14 cells discharged at a low rate that averaged 3.6 ± 3.0 Hz ($n = 14$ cells). Recordings in supragranular layers revealed relatively little spontaneous activity during the down state (Sanchez-Vives and McCormick, 2000). Thus, the recurring sustained activity generated in prefrontal slices was associated with a low level of discharge in layer 5 during the DOWN period, intermixed with up to several seconds of maintained discharge of ~ 10 –20 Hz during the UP period.

Intracellular recordings and manipulation of the membrane potential with the intracellular injection of current revealed that the UP state is generated by the arrival of barrages of EPSPs and IPSPs, and did not provide any evidence for the involvement of persistent inward currents. If the UP state was generated through mechanisms intrinsic to the cell recorded, then hyperpolarization of the cell should have a significant effect on the duration or rate of recurrence of the UP state. However, hyperpolarization of cortical neurons by 10–25 mV, sufficient to prevent action potential discharge during all periods of the activity, did not affect the duration (1.7 ± 0.3 s control; 1.7 ± 0.4 s hyperpolarized) or the rate of recurrence (0.2 ± 0.1 Hz control; 0.2 ± 0.1 Hz hyperpolarized; $n = 16$ cells) of the UP state (see also Sanchez-Vives and McCormick, 2000).

Recording intracellularly with sharp microelectrodes that contained 50 mM QX-314 to block voltage dependent Na^+ currents (e.g. I_{NaT} and I_{NaP}) and 2 M CsAc to reduce K^+ conductances allowed us to directly examine the voltage dependence of PSP barrages underlying the UP state (Sanchez-Vives and McCormick, 2000; Shu *et al.*, 2003). Depolarization or hyperpolarization of pyramidal cells revealed barrages of fast events at all membrane potentials (e.g. Fig. 1B). At resting membrane potentials, these fast events appeared to ride on top of an envelope of depolarization, the amplitude of which depended upon the membrane potential of the cell. Depolarization with the intracellular injection of current reduced the amplitude of the depolarizing envelope associated with the UP state, and if the membrane potential was depolarized with current past -30 to -40 mV, then the PSP barrage associated with the UP state resulted in an overall hyperpolarization rather than a depolarization (Shu *et al.*, 2003). This activity therefore behaved as a roughly balanced mix of EPSPs and IPSPs, with a reversal potential approximately half way between the reversal potential of GABA_A mediated inhibition (-75 mV) and glutamatergic excitation (0 mV) (Shu *et al.*, 2003). Indeed, minimizing the contribution from GABA_A -mediated inhibition (by keeping the cell near E_{Cl}) revealed strong barrages of excitatory postsynaptic potentials during the UP state. Similarly, depolarizing the cell to 0 mV, and thus minimizing the contribution from glutamatergic excitation, revealed the UP state to be associated with strong barrages of IPSPs throughout its entire duration (not shown). The presence of a strong mixture of EPSPs and IPSPs in the membrane depolarization of the UP state is consistent with the fact that the spike rates of both pyramidal neurons and fast spiking interneurons greatly increase during persistent network activity (Sanchez-Vives and McCormick, 2000; Shu *et al.*, 2003).

The critical involvement of recurrent excitation in the generation of sustained activity of the UP state was also demonstrated by examining the effects of bath application of the non-NMDA glutamate receptor antagonist CNQX (10 μM) and the NMDA receptor antagonist dl-APV (25 μM). Bath application of CNQX resulted in a rapid and complete abolition of UP states in both visual and prefrontal cortical slices ($n = 6$ visual; $n = 4$ prefrontal). Interestingly, block of NMDA receptors also resulted in a block of the UP state in the prefrontal cortical slices ($n = 5$), and a block or strong reduction of this activity in the visual cortical slices (Sanchez-Vives and McCormick, 2000). Thus the generation of the UP state depends critically upon the activation of both NMDA and non-NMDA receptors at fast, glutamatergic synapses. In the presence of both CNQX and APV, a subset of layer 5 neurons remained spontaneously active (Compte *et al.*, 2003a), presumably through intrinsic ionic mechanisms. We assume that these spontaneously active layer 5 cells may be involved in the initiation of spontaneously occurring UP states (Fig. 2B).

The intracellular injection of depolarizing current pulses alone never resulted in action potential activity that outlasted the duration of the current pulse, whether the current pulse was injected during the DOWN or UP state (e.g. Fig. 3A; $n = 10$ cells; see, however, Timofeev *et al.*, 2000). In addition, the depolarization and action potential activity occurring in single neurons

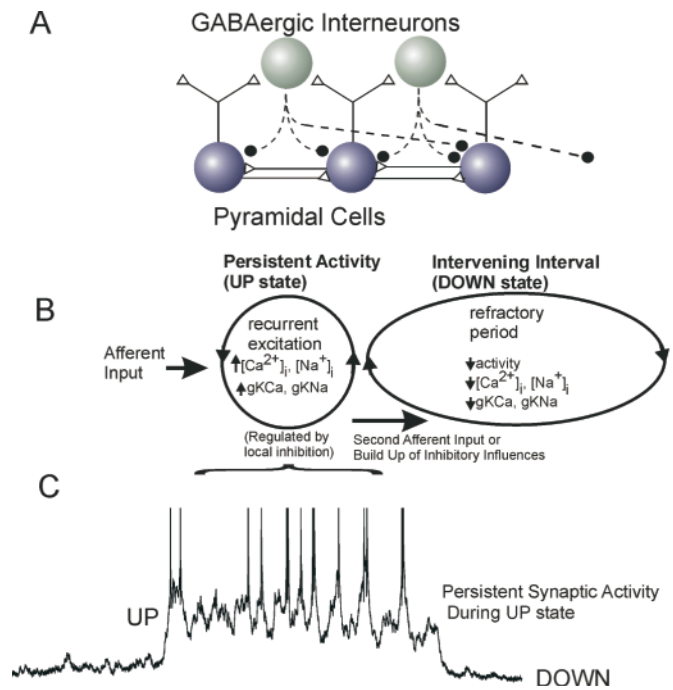


Figure 2. Summary diagram of the proposed mechanisms for the spontaneous generation of the UP and DOWN states in cortical networks. Cortical pyramidal and local GABAergic interneurons are highly interconnected through local axonal connections such that activity in pyramidal cells excites both other pyramidal cells as well as local interneurons. The inhibitory feedback from the local interneurons controls the level of the UP state. Activation of an afferent input can trigger the transition from the DOWN to the UP state. Build up of intracellular levels of Ca^{2+} and Na^+ can activate K^+ currents, which eventually tip the balance back to the DOWN state, during which time the levels of Ca^{2+} and Na^+ inside the cell decrease, thus allowing the network to spontaneously generate another UP state. Another mechanism for making the transition from the UP to the DOWN state is the activation of afferent inputs (Shu *et al.*, 2003).

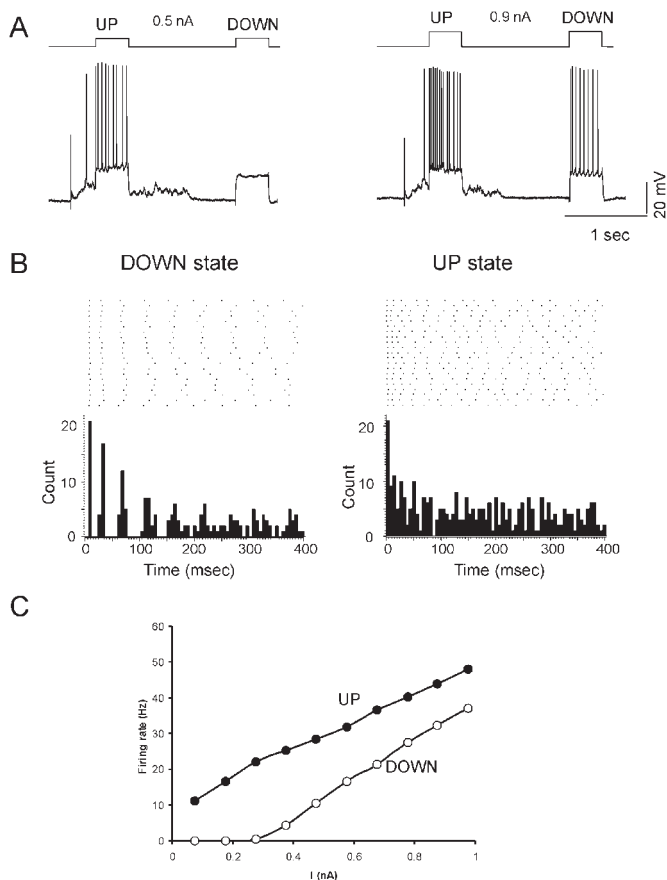


Figure 3. The UP state is associated with a marked increase in neuronal excitability. (A) Intracellular injection of depolarizing current pulses during the UP and DOWN states reveal a marked increase in neuronal responsiveness during the UP in comparison to the DOWN state. Two different amplitudes of current pulses are illustrated. (B) Stimulus histograms of the action potential response of the cell to repeated injections of the same current pulse (0.7 nA) in the DOWN and UP states. The cell responds with more action potentials in the UP state, and the timing of these action potentials varies from pulse to pulse. (C) Response of the neuron to different amplitude current pulses in the UP and DOWN states. Note the marked increase in neuronal responses, especially to smaller amplitude inputs.

never significantly outlasted the activity occurring in local networks, as indicated by nearby multiple unit recordings (e.g. Fig. 1). In other words, we found no evidence for the natural generation of plateau potentials or the ability to normally generate persistent depolarizations through intrinsic cellular mechanisms in our intracellularly recorded cortical neurons. The action potential activity occurring in each cell that we recorded could be explained simply by the barrage of synaptic activity arriving from the local network.

In contrast to the effects of glutamate ionotropic receptor antagonists, local or bath application of GABA_A receptor antagonists (e.g. picrotoxin, bicuculline) resulted in a transition of the UP states into epileptiform activities including paroxysmal bursts of spikes and excitatory postsynaptic potentials (Sanchez-Vives and McCormick, 2000). Together these results indicate that the UP state is generated through recurrent excitation between neighboring pyramidal cells within the cerebral cortex. This recurrent excitation is rapidly and precisely controlled by the activation of local inhibitory interneurons such that a balance is achieved allowing for the generation of a relatively stable membrane potential with a discharge rate (Shu *et al.*,

2003) that is within the range observed *in vivo* in awake, behaving monkeys performing delayed response memory tasks (Funahashi *et al.*, 1989; Miller *et al.*, 1996).

Impact of Sustained Activity on Neuronal Responsiveness

Neurons in the nervous system are constantly bombarded with synaptic activity (e.g. Destexhe and Paré, 1999; Steriade *et al.*, 2001). The level of this ongoing activity is not static: it dynamically changes, resulting in significant changes in the input-output properties of cortical neurons. Presumably, for example, the generation of sustained activity in prefrontal and other cortical areas modulates the response properties of these cells to the arrival of other synaptic inputs (e.g. Chance *et al.*, 2002). Here we examined how barrages of synaptic activity during the UP state modulate neuronal responsiveness to the intracellular injection of current pulses and sine wave currents of varying frequencies.

The intracellular injection of depolarizing current pulses during the UP and DOWN states ($n = 10$ cells) revealed that the UP state, and the barrages of synaptic activity that underlie it, are associated with a substantial increase in neuronal responsiveness (Fig. 3). Indeed, this effect was so powerful that current pulses that were completely subthreshold for the generation of action potentials in the DOWN state could generate a strong train of action potentials during the UP state (Fig. 3). The facilitation of responsiveness depended in part on the amplitude of the current pulse. Larger amplitude pulses were less facilitated than smaller amplitude pulses. This amplitude-dependent facilitation resulted in a decrease in slope of the input-output relationship during the UP state (Fig. 3C; see also Chance *et al.*, 2002).

The intracellular injection of constant current pulses in an otherwise quiescent neuron results in stereotyped trains of action potentials, the interspike intervals of which are relatively repeatable from pulse to pulse (Fig. 3B; Nowak *et al.*, 1997). Injection of the same pulses during the UP state, however, resulted in a considerable increase in variation in the interspike interval (Fig. 3B, UP state) such that the cumulative peristimulus histogram gave a much smoother appearance than that obtained in the DOWN state. In this way, the UP state was associated with an increase in variation in spike timing during constant current pulses.

Through what mechanism(s) is the barrage of synaptic activity during the UP state causing an increase in neuronal responsiveness to the current pulses along with an increase of spike timing variability? The barrages of synaptic potentials that underlie the UP state are associated with three general changes in the post-synaptic cell: depolarization of the membrane potential by an average of 7.6 ± 2.1 mV; increase in membrane conductance, ranging from 4–32 nS ($n = 15$ cells); and an increase in membrane potential variance of 2.6 ± 0.4 mV ($n = 9$ cells; Table 1). These values are similar or a little smaller than those reported during the slow oscillation *in vivo*, where the UP state is on average between 9.6 (Steriade *et al.*, 2001) and 14.5 mV (Stern *et al.*, 1997) depolarized to the DOWN state, the SD of the membrane potential is increased by 2–3 mV (Stern *et al.*, 1997; Steriade *et al.*, 2001) and the membrane conductance is increased by an average of 27 nS (Paré *et al.*, 1998; Steriade *et al.*, 2001). To examine which of these three general changes (depolarization, increase conductance, increase membrane variance) were responsible for the increases in neuronal response during the UP state in our preparation, we manipulated each

independently and examined the effect on the response to the intracellular injection of constant current pulses (Figs 4–7).

Changing the membrane potential of layer 5 pyramidal cells through the intracellular injection of current resulted in marked changes in neuronal responsiveness to the current pulses (Fig. 4). Depolarization resulted in a leftward shift in the input–output curve, without a change in slope, such that a smaller current pulse was needed in order to activate the same number of action potentials ($n = 5$ cells). This is as expected, since depolarization results in a decrease in the distance between the membrane potential and spike threshold. On average, we found a relationship of 0.062 ± 0.049 nA/mV change

in the input–output relation, meaning that an 8 mV depolarization would result in a decrease of 0.5 nA in the current required to inject to yield the same spike response.

To examine the effect of increases in membrane conductance on neuronal responses to current pulses, we used a dynamic clamp system (Dorval *et al.*, 2001). Increases in the apparent ‘leak’ conductance of the membrane (with the reversal potential of the leak set at the resting membrane potential of the cell) resulted in a rightward shift in the input–output relationship (Fig. 5B; $n = 5$ cells). The average shift ($n = 5$ cells) was 0.016 ± 0.0033 nA per nS increase in baseline membrane conductance, meaning that a 10 nS increase in membrane conductance will

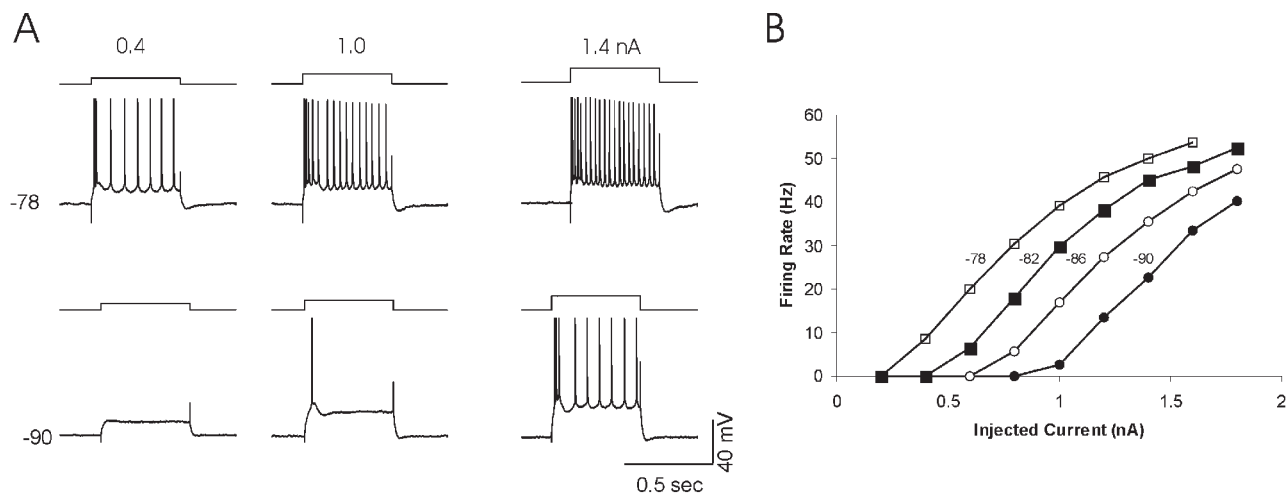


Figure 4. Depolarization increases neuronal responsiveness. (A) Examples of a pyramidal cell’s response to the intracellular injection of three different amplitude current pulses at -78 and -90 mV. (B) Graphical illustration of results revealing that hyperpolarization of the cortical pyramidal cell with the intracellular injection of current shifts the input–output curve to the right, without marked effects on slope.

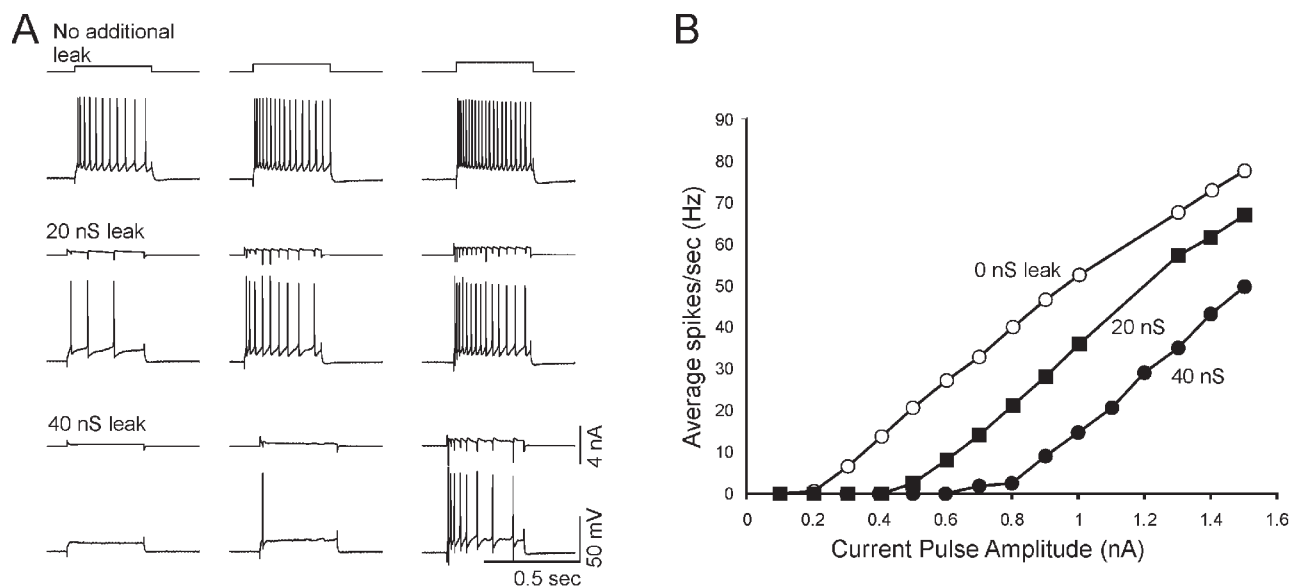


Figure 5. Increases in background membrane conductance with the dynamic clamp system results in a decrease in neuronal responsiveness. (A) Examples of neuronal response to three different current pulse amplitudes at three different levels of added ‘leak conductance’ that reversed at the resting membrane potential. (B) Graphical plot of the data demonstrating that the input–output curve shifts to the right with increases in artificial membrane conductance. The reversal potential of the background leak conductance was set to the resting membrane potential in order to avoid changes in membrane potential with changes in conductance. Points at 1.1 and 1.2 nA for 0 and 20 nS were discarded because the neuron was not in the same adaptive state as for the rest of the data.

result in a requirement of 0.16 nA of additional current to achieve the same spike response. Again, these shifts in the input-output relation occurred without marked changes in slope (Fig. 5B).

Finally, to examine the effects of increases in membrane variance on the input-output relationship, we used the dynamic clamp system to inject noise consisting of both excitatory and inhibitory conductances adjusted to give statistical features similar to that of the synaptic activity associated with natural UP states ($n = 6$ cells; see Methods). Three different levels of injected noise (with SDs of 0, 2 and 4 nS; for both the excitatory and inhibitory components; see Methods) were investigated. For all cases, the average conductance was set to 2–5 nS for the excitatory (reversal potential of 0 mV) and 2–5 nS for the inhibitory (reversal potential of -75 mV) components of the injected background activity. Increasing the average excitatory and inhibitory noise to 2 nS resulted in an increase in the SD of the membrane potential to 2.87 ± 0.34 mV ($n = 7$ cells), which is similar to that occurring during the natural UP state.

Increases in membrane potential 'noise' through this method resulted in an increase in neuronal response to depolarizing current pulses, especially to smaller inputs (Figs 6 and 7). (Note that the average membrane potential does not change in response to the addition of noise since the injected conductance does not change.) The enhancement by noise was dependent upon the amplitude of the current pulse injected, resulting in a change in slope of the input-output relationship (Fig. 6D). Measurements of the action potential response to the smallest current pulse that generated action potentials in the presence of noise revealed an increase in effectiveness equivalent to an increase in the amplitude of the noise-free current pulse by 48 ± 21 pA per nS of increased SD of both G_e and G_i ($n = 4$ cells). The addition of noise-2, which results in a similar increase in SD of the membrane as the natural UP state, should then result in an increase in the number of action potentials generated by the smallest current pulse equivalent to increasing the constant current pulse by ~ 0.1 nA (see also Chance *et al.*, 2002).

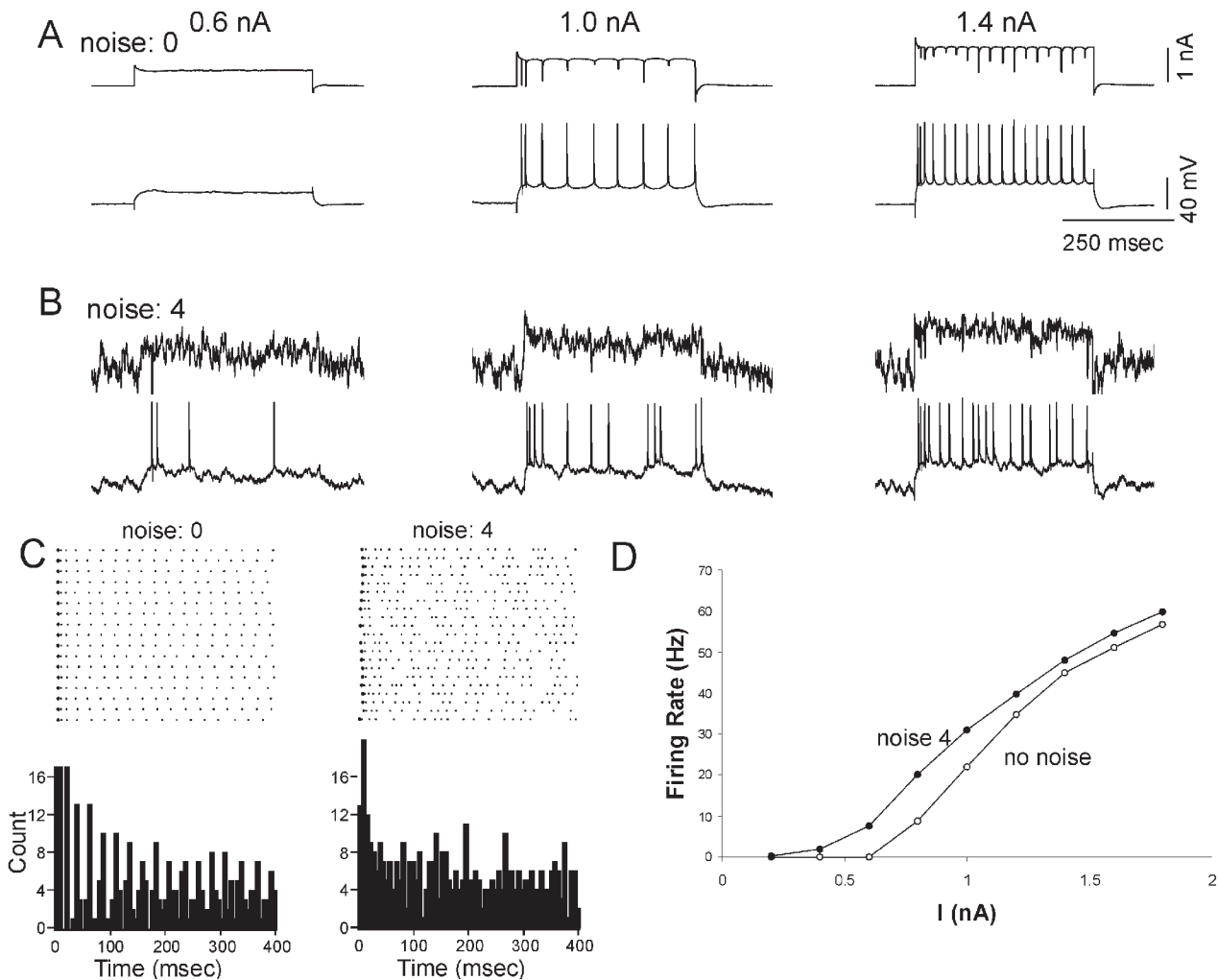


Figure 6. Increases in membrane potential variance result in increases in neuronal responses, especially to smaller inputs. (A) Examples of the response to the intracellular injection of three different amplitude current pulses with no added 'noise' (membrane variance). The membrane conductance was the same with and without noise, so the addition of noise did not result in a change in membrane potential. The difference between (A) and (B) is that the SD of G_e and G_i in (A) was 0 nS, while in (B) it was 4 nS. (B) Examples of the response of the neuron to the same three pulses when the SD of both G_e and G_i was set to 4 nS. (C) Stimulus histograms of the response of the neuron to repeated injections of the same current pulse with and without additional noise injection. There is an increase in spike timing variability to constant current pulses with the addition of noise. (D) Input-output plot of the response of the cell with and without noise. Note that the addition of a noisy conductance results in an increase in action potential response to small inputs.

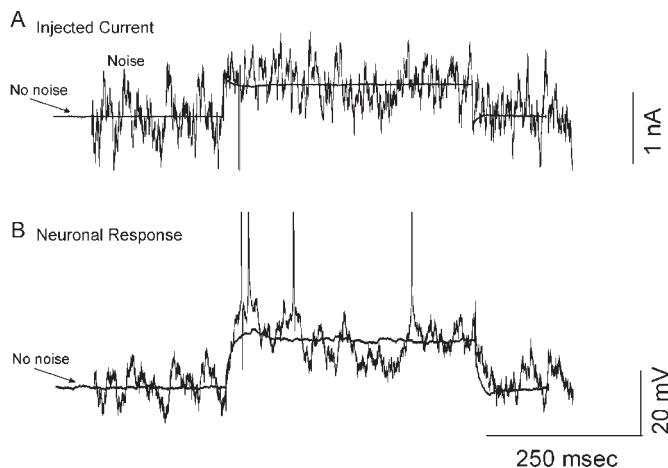


Figure 7. Expansion of the response of the neuron to the same current pulse before and after the addition of noise. (A) Injected current with and without added noise. (B) Response of the neuron to these two current injections. Note that the addition of noise occasionally brings the membrane potential above threshold for action potential generation. Same cell as in Figure 6.

Expansion of the responses to current pulses with and without the addition of membrane potential variance revealed the mechanism of enhancement. The addition of depolarizing current transients on top of the relatively steady depolarization of the constant current pulse resulted in occasional crossings of spike threshold (Fig. 7). Thus, depolarizing current pulses that were normally subthreshold became suprathreshold and generated action potentials. Since the action potentials during the current pulse were generated by the combination of the pulse and the randomly varying noise, the timing of these spikes varied widely from trial to trial, but were confined to the timing of the current pulse. The facilitatory effect on larger current pulses was less marked, since the injected noise adds both depolarizing and hyperpolarizing components. When neurons are spiking rapidly, the addition of noise both increases and decreases spike probability, through these depolarizing and hyperpolarizing components.

Synaptic Activity of the UP State Facilitates the Response to Sine Wave Currents

Prior *in vivo* investigations have suggested that the spontaneous synaptic activity associated with the UP state may contribute to contrast-invariant responses in visual cortical neurons by removing the so-called 'iceberg' effect (Anderson *et al.*, 2000b). Here we investigated this phenomenon by examining the effects of the UP state on the response to the intracellular injection of sine wave currents of varying frequencies and amplitudes ($n = 7$ cells). The UP state increased the response to 4–5 Hz sine waves considerably (Fig. 8). During the DOWN state, the intracellular injection of the sine wave typically yielded action potentials only near the peak of the depolarizing phase of the current injection (Fig. 8B,C). However, during the UP state, action potentials were generated throughout a greater extent of the depolarizing phase, resulting in a better representation by the average action potential discharge of the amplitude-time course of the sine wave input (Fig. 8B,D). To quantify this effect, we examined the peak cross correlation between the injected sinewave current and the spike rate histogram. The UP state resulted in an increase in the peak cross correlation between injected current

and the spike rate of the recorded cell (28% increase from $r = 0.44$ to 0.57 ; $n = 6$; $P < 0.01$). This increase in correlation by the UP state, however, was frequency dependent (see below).

By examining the response of cortical cells to sine waves of different amplitudes, it became evident that the UP state was associated with a decrease in the iceberg effect (Fig. 8E), owing to a decrease in the amount of current needed to elicit an action potential, an increase in the number of action potentials generated with each current level above firing threshold, and an increase in their temporal representation of the sine wave current (e.g. see Fig. 8B). An additional effect of the UP state on the spike response to sinewave currents was a shift in the peak spike rate to earlier times: a phase advance (Fig. 8C,D,G).

Increasing the frequency of the sine wave current from 10 to 100 Hz resulted in variations of this general finding. Increasing the frequency of current injection into neurons is well known to decrease the amplitude of the membrane deviation, owing to the low-pass filtering characteristics of neuronal membranes (e.g. Nowak *et al.*, 1997). Owing to this decrease in response, the cell was depolarized with the intracellular injection of current at higher frequencies (40–100 Hz) so that sinewave input generated action potentials, typically in both the DOWN and UP state. The UP state facilitated spike responses to all inputs up to the higher frequencies tested (50, 100 Hz; Fig. 9). The increase in peak cross correlation caused by the UP state, as well as the phase advance, both decreased with increasing frequencies of the sinewave current (Fig. 8F,G). These results indicate that although the UP state results in a general increase in responsiveness to a broad range of frequencies, the amplitude of this effect is frequency dependent.

Discussion

Our results demonstrate that slices of the prefrontal cortex maintained *in vitro* can generate prolonged periods of sustained activity when maintained in a slice solution that more closely resembles the ionic composition of cerebrospinal fluid than is typically used. We utilized this spontaneous network activity to address the mechanisms by which sustained activity may be generated within local circuits within the prefrontal cortex and how it may influence the responsiveness of single cortical cells to other inputs.

Mechanisms of Generation of UP and DOWN states

Our results demonstrate that sustained activity *in vitro* is generated by barrages of EPSPs and IPSPs, owing to activity in pyramidal and non-pyramidal neurons (Sanchez-Vives and McCormick, 2000; Shu *et al.*, 2003; see also Steriade *et al.*, 1993a). In both of these cell types the PSP barrages bring the cells close to firing threshold and in at least pyramidal cells the intermixed PSPs exhibit an average reversal potential of between -20 and -40 mV (Sanchez-Vives and McCormick, 2000; Shu *et al.*, 2003). The influence of inhibitory interneurons is critical in the generation of relatively stable periods of activity, since blocking GABA_A-receptor mediated inhibition results in the transformation of recurring persistent activity into paroxysmal discharges (Sanchez-Vives and McCormick, 2000).

The cyclical generation of UP and DOWN states, which occurs through all areas of the cerebral cortex so far recorded, appears to occur naturally as a result of the recurrent connectivity of the cerebral cortex and the membrane and synaptic properties of

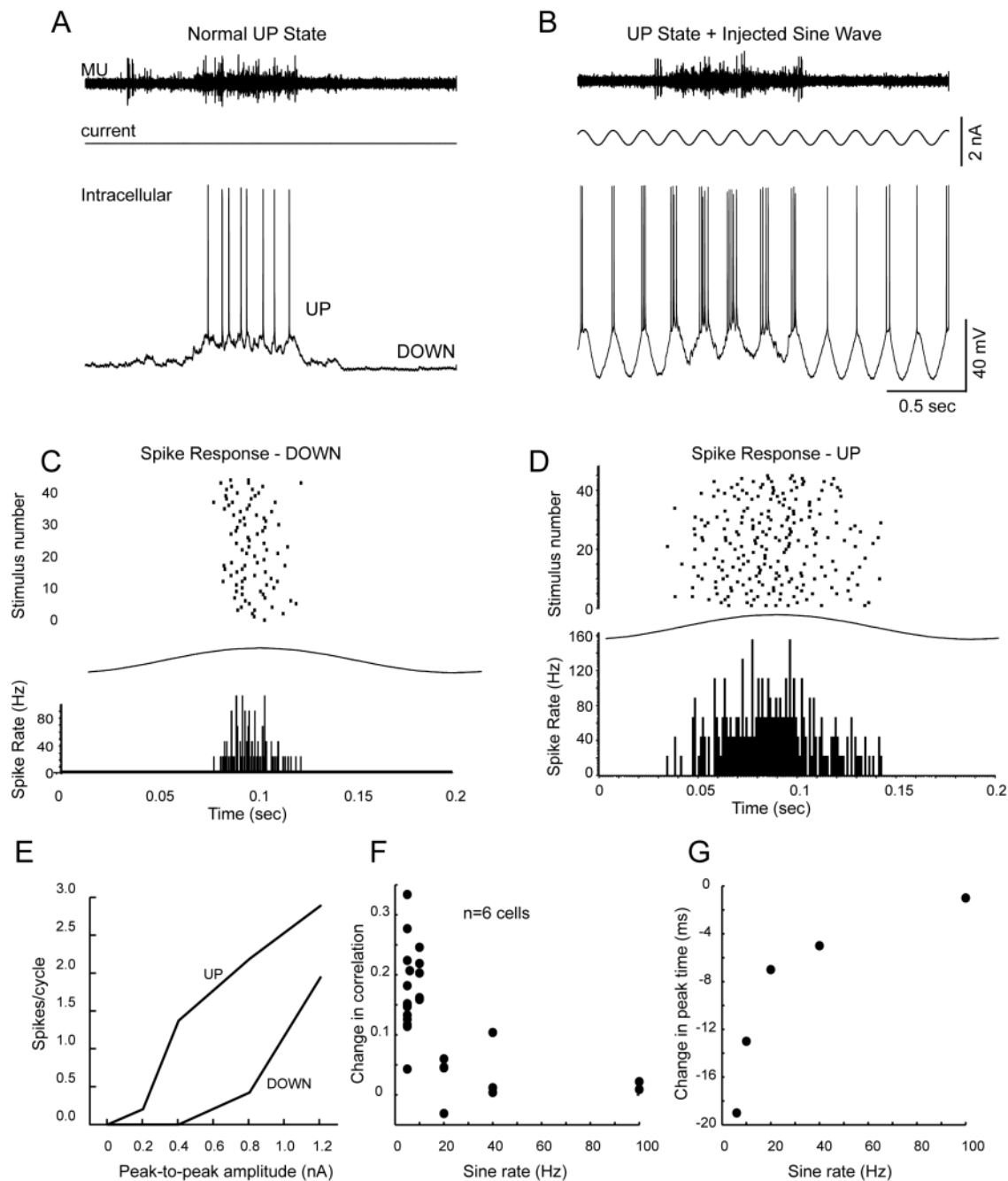


Figure 8. The UP state enhances the neuronal response to the injection of a low frequency (5 Hz) sine wave. (A) Simultaneous intracellular and extracellular recordings of the UP state in this layer 5 pyramidal cell. (B) Example of the response of the neuron to the continuous injection of a 5 Hz sine wave before, during, and after the UP state. (C, D) Peristimulus histograms and raster plots of the action potential response to the sine wave injection during the DOWN (C) and UP (D) states for the same number of trials. (E) The UP state facilitates the responsiveness to various amplitude sine wave currents (4 Hz), thereby reducing the 'iceberg' effect. (F) Absolute increase (from the DOWN to UP state) in peak cross correlation between the injected sinewave current and the spike rate histogram for several cells ($n = 6$) versus the frequency of the injected sinewave. Note that the increase in correlation by the UP state diminishes as the frequency of the sinewave increases. (G) Advance in the time of peak firing rate by the UP state versus frequency of the injected current. With low frequency inputs, there is a strong advance in neuronal discharge by the UP state and this effect diminishes with increases in frequency. Cells in (A–D) and (E) are different. Data in (F) are from six cells, while in (G) they are from one cell.

the constituent elements (Metherate and Ashe, 1993; Steriade *et al.*, 1993a; Cowan and Wilson, 1994; Contreras *et al.*, 1996; Stern *et al.*, 1997; Sanchez-Vives and McCormick, 2000; Shu *et al.*, 2003). A basic feature of the cerebral cortex is strong, local recurrent excitatory connections between pyramidal cells (see White, 1989; Braitenberg and Shuz, 1998). These recurrent

excitatory connections also contact local inhibitory interneurons, which, in turn, inhibit neighboring pyramidal cells. Neuronal models indicate that this type of neuronal network architecture (recurrent excitation tempered by inhibition) can readily generate at least two states of activity, in similarity to those shown here (Amit and Brunel, 1997; Wang, 1999; Compte

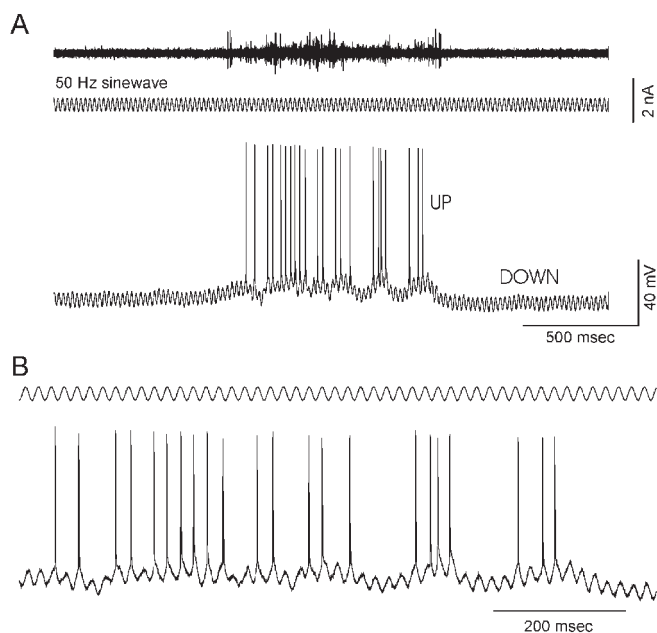


Figure 9. The UP state facilitates the response to the intracellularly injected 50 Hz sine wave current. (A) During the UP state, the cell generates single action potentials that are phase locked to near the peak of the 50 Hz sine wave. (B) Expansion of part of the response in (A) for illustration.

et al., 2000; Durstewitz *et al.*, 2000a; Timofeev *et al.*, 2000; Brunel and Wang, 2001).

The ability of cortical neurons to maintain activity while discharging at a relatively low rate presumably results from the large degree of convergence and divergence of activity within the cerebral cortex. Each cortical pyramidal cell receives ~10 000 synapses, of which ~2/3 to 3/4 are excitatory (see White, 1989; Abeles, 1991; Braitenberg and Shuz, 1998). The fact that connections between any two pyramidal cells involve only a small number of synapses (<5) indicates that each neuron receives input from over one thousand other excitatory cells. Even a low firing rate among this multitude of neuronal inputs may yield, depending upon the strength of inhibitory mechanisms, sufficient depolarization of the postsynaptic neuron to result in maintained action potential discharge. The strong regulation of this activity through the activation of local inhibitory interneurons, as well as intrinsic hyperpolarizing currents (e.g. K⁺ currents) in pyramidal cells, keeps the firing rate low (see Contreras *et al.*, 1997b).

In our cortical slices, and during slow wave sleep or anesthesia *in vivo*, this neuronal activity can be expressed as a synchronized depolarization and hyperpolarization of nearly all cortical neurons, leading to so-called 'UP' and 'DOWN' states (Metherate and Ashe, 1993; Steriade *et al.*, 1993a; Cowan and Wilson, 1994; Contreras *et al.*, 1996; Stern *et al.*, 1997; Sanchez-Vives and McCormick, 2000). We propose that the UP state is initiated by the generation of a burst of activity in a critical number of pyramidal cells (either through intrinsic ionic mechanisms or through recurrent excitation in a subgroup of cells) at a time in which the network has recovered from the refractory period that followed the previous UP state (Sanchez-Vives and McCormick, 2000; Compte *et al.*, 2003a). The spontaneous transition to the DOWN state then may occur owing to the build up of intrinsic K⁺ currents in pyramidal neurons owing to

the activity generated by the UP state (Sanchez-Vives and McCormick, 2000; Compte *et al.*, 2003a). Otherwise the transition to the DOWN state may result in response to the strong activation of inhibitory neurons (Brunel and Wang, 2001; Shu *et al.*, 2003) or perhaps in response to synchronized activation of a large fraction of the neurons in the network, thereby leading to a synchronized refractory period (Gutkin *et al.*, 2001; Shu *et al.*, 2003). In slices, the UP state of the slow oscillation propagates across the slice as it sequentially recruits neighboring regions of tissue into the activity (Sanchez-Vives and McCormick, 2000). The propagation of UP states *in vivo* should occur in considerably more complicated patterns, given the three dimensional structure of the brain and cortical connectivity.

Is the UP state of the slow oscillation equivalent to the maintained membrane potential and low firing rate of the cortex in the waking, but resting state? The answer to this question is not yet known. On the positive side, stimulation of the brainstem that results in activation of the EEG or the natural transition to waking both result in a loss of the DOWN state, with a maintained membrane potential of cortical cells that is similar to that of the UP state (Steriade *et al.*, 1993b, 2001), suggesting that the UP state and the 'waking' membrane potential have similar mechanisms of generation. However, the apparent input resistance of cortical pyramidal cells is higher during the maintained depolarized membrane potential of waking in comparison to the UP state (Steriade *et al.*, 2001), perhaps owing to the increased release of neuromodulatory agents (e.g. acetylcholine). Thus, the membrane potential of cortical neurons in the waking brain may be maintained in a depolarized state through both recurrent excitation as well as the actions of neuromodulators, while in the sleeping brain, the persistent activity of the UP state may be largely due to the recurrent excitatory activities alone. Either way, it is clear that nearly all or all regions of the cortex possess the intrinsic ability to generate persistent depolarized states with a relatively low firing rate through local recurrent connections – a mechanism that is often used to model the generation of persistent activity in cortical networks.

Implications for the Cellular Mechanisms of Persistent Activity during Working Memory

There are two general hypotheses concerning the mechanisms of persistent activity. The first is that the activity is generated through self-sustained excitation within a neuronal network, mediated by recurrent activity. The second is that the persistent activity is generated through intrinsic membrane mechanisms, such as afterdepolarizations. These two hypotheses are not mutually exclusive, and both mechanisms may, at least theoretically, contribute.

Our results lend strong support to the hypothesis that cortical networks can generate local sustained activity through recurrent excitatory interactions. Indeed, the firing rate of our pyramidal cells during the UP state is within a similar range to that occurring during the delay period of working response memory tasks *in vivo*, namely from a few up to ~40 Hz (Funahashi *et al.*, 1989; Miller *et al.*, 1996). Action potentials during both the UP state and during the delay period *in vivo* often occur in a highly variable manner, consistent with a Poisson-like process (Compte *et al.*, 2003b; A. Hasenstaub, C. Ghandi and D.A. McCormick, unpublished observations). Prefrontal cortical persistent activity *in vivo* can last for periods of seconds in delay response tasks (Fuster, 1995). In normal slice solution, our sustained activity had a maximal duration of ~4 s, although we have recently found

that bath application of the h-channel blocker ZD-7288 results in a marked prolongation of UP states so that they may last for up to 10–12 s (C. Ghandi and D.A. McCormick, unpublished observations). Finally computational approaches successfully model the persistent activity during both the UP state and during the delay period in working memory tasks by using recurrent excitation that is controlled with local inhibition (Wang, 1999, 2001; Compte *et al.*, 2000, 2003a).

However, there are also a number of significant differences between the UP state activity studied here and the properties of persistent activity generated *in vivo*. First, the UP state *in vitro* (and during anesthesia and sleep *in vivo*) is characterized by barrages of synaptic activity in nearly all intracellularly recorded neurons (Metherate and Ashe, 1993; Steriade *et al.*, 1993a; Contreras *et al.*, 1996; Sanchez-Vives and McCormick, 2000), leading to strong increases in extracellularly recorded multiple unit activity. Although intracellular recordings *in vivo* have not yet been performed to examine the synaptic activity underlying delay period activity, extracellular single unit data has demonstrated that only a minority of cells discharge at an increased rate during the delay period, with many neurons not changing their firing rate, or even decreasing their discharge, during this period (Funahashi *et al.*, 1989). Also, in behaving monkeys, although some neighboring cortical neurons may exhibit correlated activities, others may exhibit very different patterns during the behavioral task (Constantinidis *et al.*, 2001). In contrast, during the UP state *in vitro* and *in vivo*, neighboring cells are often correlated in their activities. Finally, in some (but not all) recordings *in vivo*, the discharge rate of the cortical neuron may vary as a function of some feature of the stimulus (e.g. location, frequency) (Funahashi *et al.*, 1989; Romo *et al.*, 1999). Although action potential activity *in vitro* varies in intensity from UP state to UP state, this variation occurs spontaneously. One possible mechanism by which neuronal discharge rate could be continually varied *in vivo* is through changes in network architecture, either through the addition or subtraction of neuronal participation in the network (see Koulakov *et al.*, 2002), or simply through a non-uniform change in the level of activity in participating neurons.

Although there are similarities between persistent activity during working memory tasks *in vivo* and sustained activity generated spontaneously *in vitro*, there are also considerable differences. These similarities and differences indicate that while the *in vitro* activity may yield important information concerning the generation of persistent activity through recurrent excitation, there are important limitations to the *in vitro* system as a model of delay period discharge *in vivo*.

Intrinsic Afterdischarges do not Contribute to Persistent Activity

Another leading hypothesis as to the origin of cortical mnemonic activity is that it is generated through intrinsic membrane mechanisms. For example, cortical pyramidal cells can generate prolonged afterdischarges in the presence of high doses of neuromodulatory agents (such as non-hydrolyzable muscarinic receptor agonists) through a Ca^{2+} -activated cation current (Andrade, 1991; Haj-Dahmane and Andrade, 1996, 1998; Egorov *et al.*, 2002; Fransen *et al.*, 2002) or through persistent Na^+ currents (Timofeev *et al.*, 2000).

We did not find any evidence that our persistent activity in prefrontal cortex is generated through intrinsic cellular mechanisms. Hyperpolarization or depolarization of recorded

neurons did not affect the duration of the UP states nor did it affect the periodicity of the rhythm, which is matched by the duration and periodicity of activity in the extracellularly recorded network (see also Sanchez-Vives and McCormick, 2000). In addition, the UP state is associated with a substantial increase in membrane noise and conductance, consistent with barrages of synaptic activity. Extracellular multiple unit recordings reveal strong increases in action potential discharge in neighboring neurons, which is consistent with the observed PSP barrages in the intracellularly recorded cells (see Fig. 1). Finally, block of excitatory synaptic transmission completely blocks the generation of persistent activity of the UP state (Sanchez-Vives and McCormick, 2000), and the intracellular injection of depolarizing current pulses did not result in persistent activity in any of our cells.

The generation of afterdischarges through a Ca^{2+} -activated cation current in single neurons *in vitro* is a questionable model of persistent activity generated *in vivo*. First, the afterdischarges generated *in vitro* only occur during the strong and continual stimulation of muscarinic, or other metabotropic, receptors. It is not clear that such receptor stimulation occurs *in vivo*. The intracellular injection of depolarizing currents in awake, sleeping, or anesthetized animals *in vivo* has not yet been found to result in afterdischarges in cortical neurons (e.g. Sanchez-Vives *et al.*, 2000; Steriade, 2001; Steriade *et al.*, 2001), unless K^+ currents are artificially blocked with the intracellular injection of Cs^+ (Contreras *et al.*, 1997a). Secondly, persistent activity *in vivo* during the performance of working memory tasks is associated with a highly variable interspike interval, which is consistent with the generation of this activity through synaptic mechanisms (Brunel and Wang, 2001; Compte *et al.*, 2003b). In contrast, the generation of persistent activity through intrinsic membrane mechanisms typically results in a highly regular discharge rate (Egorov *et al.*, 2002). Finally, the generation of persistent activity through network mechanisms has the distinct advantage that it can be turned on and off quickly (Fig. 1; see also Brunel and Wang, 2001), which does not appear to be the case with afterdischarges generated during constant muscarinic receptor stimulation (see Egorov *et al.*, 2002). At present, the most parsimonious explanation of the available data is that cortical neurons generate persistent activity *in vivo* largely or exclusively through recurrent excitation that is controlled by inhibition – perhaps in a manner similar to that detailed here for UP state activity. We do not rule out, however, the possibility that intrinsic membrane properties also contribute. It is probable that intrinsic ionic currents, such as persistent Na^+ currents (Timofeev *et al.*, 2000) or Ca^{2+} -activated cation currents (Egorov *et al.*, 2002), that facilitate the response to excitatory inputs will also facilitate the generation of persistent recurrent network activity. In this way, we envision intrinsic ionic mechanisms to be facilitatory and regulatory, but not primary sources, of persistent activity *in vivo*.

Implications of Background Synaptic Activity on Gain Modulation and Attention

Cortical neurons are imbedded in a richly interconnected network and receive tens of thousands of synaptic inputs (reviewed in White, 1989; Braitenberg and Shuz, 1998). Although many of these synaptic connections arise from local circuits, they also arise from distal cortical regions, including feedback pathways, and presumably provide a mechanism by which the responsiveness of single cortical cells can be modu-

lated by behavioral and cortical 'context'. Here we have demonstrated that barrages of excitatory and inhibitory synapses can result in significant changes in neuronal excitability and responsiveness. The barrages of synaptic activity associated with the UP state result in a significant increase in the responsiveness of cortical neurons to the intracellular injection of depolarizing current pulses, particularly those that were subthreshold (Fig. 3), resulting in a decrease in the slope of the input-output relation (Fig. 3; see also Chance *et al.*, 2002). This effect is mediated largely through depolarization of the membrane potential, so that inputs are more effective at driving action potentials, and through the increase in membrane noise, which changes the slope of the input-output relation and facilitates responses to small inputs (Chance *et al.*, 2002).

Changes in membrane variance (noise) will not only affect the number of spikes generated, but also spike timing. In response to constant current pulses, cortical neurons generate a relatively stereotyped pattern of action potentials that is repeatable from trial to trial (see Figs 3B and 6C). The addition of noise in this situation can have strong effects on spike timing, since the cell will spike at the peaks of the depolarizing components of the noisy current (Mainen and Sejnowski, 1995; Nowak *et al.*, 1997). If the noise varies from trial to trial in a random manner, then the action potentials generated during the current pulse will be smoothed, owing to a decrease in the repeatability of spike times. An additional effect of the added noise, however, is that the average histogram of the spike response is more representative of the amplitude-time course of the current pulse or low frequency sine wave input (see Figs 6C and 8). For low frequency inputs, therefore, increases in membrane variance in a population of neurons may not only increase their responses to small inputs, but also may yield a more accurate representation of the amplitude-time course of the signal.

How does background activity affect the responses to synaptic inputs? This question has been addressed with computational models (Hô and Destexhe, 2000; Destexhe *et al.*, 2001), through the injection of artificial conductances in cortical neurons *in vitro* (Hasenstaub *et al.*, 2002; Mitchell and Silver, 2003), and through the activation of synaptic potentials *in vivo* (Timofeev *et al.*, 1996). These studies reveal that membrane depolarization and small to moderate increases in membrane variance may facilitate the responsiveness to synaptic inputs, especially those of lower amplitude. Increases in membrane conductance decrease neuronal responsiveness, causing an increase in threshold. For long duration inputs, increases in membrane conductance affect all inputs about equally, leading to a rightward shift in the input-output curve. However, if the inputs are random trains of EPSPs from a small number of cells, then increases in membrane conductance can cause a decrease in slope, or gain, of the frequency of output spike train versus the mean frequency of input EPSP rate (Mitchell and Silver, 2003).

Functional Implications of Background Synaptic Activity

The convergence of a large number of inputs onto each cortical neuron has the functional implication that the cells activity may be strongly influenced by a wide variety of different neural circuits. This broad influence may provide a mechanism to explain diverse effects such as: (i) the ability of sensory context (i.e. far field stimuli) to modulate the response to discrete sensory stimuli (Carandini and Heeger, 1994; Angelucci *et al.*,

2002; Stettler *et al.*, 2002); (ii) the transformation of sensory to motor maps of external space (Salinas and Abbott, 1996); (iii) increases in neuronal responsiveness with attention (McAdams and Maunsell, 1999a,b; Hahnloser *et al.*, 2002); and (iv) the functional operation of feedback pathways, a common and little understood feature of cortical architecture (Hupé *et al.*, 1998; Hahnloser *et al.*, 2002). For example, the spontaneous barrages of synaptic activity associated with the UP state result in an increase in response probability to small inputs, with relatively little change in the response to larger inputs (Hasenstaub *et al.*, 2002). This is similar to the effects of attention on the contrast-response function curves of neurons in V4 (Reynolds *et al.*, 2000). Here attention results in an increase in neuronal response to low contrast (i.e. weak) stimuli, while responses to high contrast (i.e. strong) stimuli are relatively unaffected. This amplitude-dependent enhancement is similar to our findings that synaptic barrages enhance the responsiveness of cortical neurons to current pulses (Fig. 3). This suggests that barrages of synaptic activity may underlie the attentional affects observed by Reynolds *et al.* (2000).

However, in other conditions, attention can result in an enhancement of the response to all stimuli in a multiplicative manner (McAdams and Maunsell, 1999a,b; Treue and Martinez-Trujillo, 1999). This effect of attention may also result from barrages of synaptic activity, since it has been shown that decreases in membrane variance that do not change the average membrane potential of the cell and which are balanced with decreases in membrane conductance can change neuronal 'gain' (Hô and Destexhe, 2000; Chance *et al.*, 2002). Perhaps attentional mechanisms increase neuronal responsiveness both by depolarizing some cells with barrages of synaptic activity, while increasing the 'gain' (slope of the input-output relation) of other cells by decreasing membrane conductance and noise that reverses near resting membrane potential.

Conclusions

A common and pervasive theme of cortical networks is local feedback excitation between pyramidal cells that is controlled and tuned by disinaptic feedback inhibition. This basic architecture, left to its own devices, spontaneously generates two patterns of activity: relative quiescence and persistent activity. The generation of persistent activity in the prefrontal cortex (and other cortical areas) may take advantage of this basic architecture to serve as a mnemonic device, much in the manner of a neuronal 'flip-flop'. These flips in neuronal network activity may not only serve to temporarily store information, but will also have strong influences on neuronal responsiveness and may provide a neuronal mechanism underlying diverse behavioral effects. In all of these behavioral conditions, however, neuronal activities display important features that are yet to be replicated *in vitro* and remain to be investigated in full.

Notes

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Address correspondence to David A. McCormick, Department of Neurobiology, Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06510, USA. Email: David.mccormick@yale.edu.

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