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Turning On and Off with Excitation: The Role of Spike-Timing Asynchrony and Synchrony in Sustained Neural Activity

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Abstract. Delay-related sustained activity in the prefrontal cortex of primates, a neurological analogue of working memory, has been proposed to arise from synaptic interactions in local cortical circuits. The implication is that memories are coded by spatially localized foci of sustained activity. We investigate the mechanisms by which sustained foci are initiated, maintained, and extinguished by excitation in networks of Hodgkin-Huxley neurons coupled with biophysical spatially structured synaptic connections. For networks with a balance between excitation and inhibition, a localized transient stimulus robustly initiates a localized focus of activity. The activity is then maintained by recurrent excitatory AMPA-like synapses. We find that to maintain the focus, the firing must be asynchronous. Consequently, inducing transient synchrony through an excitatory stimulus extinguishes the sustained activity. Such a monosynaptic excitatory turn-off mechanism is compatible with the working memory being wiped clean by an efferent copy of the motor command. The activity that codes working memories may be structured so that the motor command is both the read-out and a direct clearing signal. We show examples of data that is compatible with our theory.

Keywords: working memory, asynchrony, synchrony, sustained activity, prefrontal cortex

1. Introduction

Local cortical circuits with reverberating activity have long been viewed as a basis for cortical control of behavior and cognition (Hebb, 1949). Such neural activity has been recorded during working memory tasks, where a memory trace must be held for a specific delay before a behavioral response is required. The animals were required to perform working memory tasks, while recordings were made in the dorsolateral portion of

their PFC (Rosenkilde et al., 1981; Funahashi et al., 1989; Funahashi et al., 1993; Miller and Desimone, 1994; Fuster, 1995).

One version of this experiment is the occulomotor visual memory experiment. Here the task is for the animal to remember the spatial location of the test cue, rapidly flashed on the screen. During a delay the animal is required to fixate on the center of the screen and hold the information about the stimulus location "on-line." When the response cue is flashed (the go signal), the monkey is required to saccade to the remembered position (in the occulomotor delay to response (ODR) task) or to a position 180 degrees from the remembered position (the ODR antisaccade task). At the same time activity of neurons located in area 46 of the PFC, on the banks of the principle sulcus, is recorded. Neurons show activity transients associated with the visual stimulus and the motor response, they also sustain firing during the delay and shut off abruptly at the response initiation (Funashi et al., 1989; Miller and Desimore, 1994; Romo et al., 1999; Rao et al., 1999). Furthermore, each neuron responds with sustained activity when the "memory" cue is presented in a selected part of the visual field, and therefore each neuron has a memory field. The delay activity of such neurons is influenced also by behavioral relevance of the stimulus and is unrelated to the specifics of the response movement. These delay (or "memory") cells constitute nearly 80% of neurons that show spatially related responses (Funahashi et al., 1990; Goldman-Rakic, 1995; Rosenkilde et al., 1981). Delay related activity has been identified in a number of other cortical areas, with which area 46 has reciprocal connections (Goldman-Rakic, 1995; Friedman and Goldman-Rakic, 1988; Fuster, 1989; Floresco et al., 1997).

Proposals have been made that the delay activity may be supported by the long range loops between the PFC and these areas (Goldman-Rakic, 1995). However, recent studies indicate that delay activity in those areas is "distracted" by intervening, behaviorally irrelevant stimuli, while neurons in the PFC preserve their delay firing in the presence of such stimuli. Based on such observations we propose that working memory (i.e., the ability to hold relevant information on-line in spite of intervening sensory stimuli) is a local PFC phenomenon. The delay activity, which is the neural trace of working memory, is then a consequence of reverberation in the cortical circuit.

Nearby neurons have overlapping or adjacent memory fields. This holds true for both pyramidal cells as well as putatively identified inhibitory interneurons (Goldman-Rakic, 1995). Based on this evidence, it has been proposed (notably by Goldman-Rakic, 1995) that the circuit for the generation of sustained activity consists of localized clusters of neurons with similar tuning that are reciprocally excitatorily connected. Cross-cluster connections are then inhibitory. This implies that a localized memory stimulus should evoke a localized focus of delay-related sustained activity.

Thus sustained firing has been proposed to be a result of spatially localized recurrent activity in the prefrontal cortex (Rao et al., 1999) and is the manifestation of network attractors (Zipser et al., 1993; Amit and Brunel, 1997). Here we investigate the mechanisms by which these attractors are initiated, maintained, and extinguished in cortical circuits composed of networks of spiking neurons. We show that a transient excitatory stimulus robustly initiates a localized focus or "bump" of activity. The focus is then maintained by recurrent excitatory synapses provided the firing within the activated assembly is asynchronous. A later transient excitatory input turns off the focus. The effect of this excitation is activity dependent; it must extend over all the neurons that have participated in the bump and uniformly induce transient synchrony. Our results lead to specific biological predictions, and we furnish experimental examples that are consistent with our predictions. Thus we demonstrate a novel "switching-off" effect of synchronization in addition to its role in cognitive concept formation (Engel et al., 1991; Gray et al., 1989; Singer, 1999) and the possible recruitment or *turning on* of neurons across cortical networks (Diesmann et al., 1999).

We consider the sustained activity during the delayed memory task to be due to recurrent excitatory reverberations within the local cortical circuit of the PFC. The substrate for this local circuit is the elaborate supragranular network of recurrent excitatory connections that appear to be organized into reciprocal patches (Lewitt et al., 1993) where pyramidal neurons make synapses locally onto other pyramidals and inhibitory interneurons.

In this report we focus on sustained activity in spatially structured networks of biophysical spiking neurons coupled together with dynamic synapses and specifically on the conditions regarding the relative spike timing necessary for the maintenance and the turn-off of such activity. This differs from previous work on networks for working memory that either

did not consider the spatial component (Zipser et al., 1993; Amit and Brunel, 1997) or employed networks with firing-rate elements with tonic nonsynaptic coupling (e.g., Camperi and Wang, 1999). The dynamics of bump states in spiking integrate-and-fire neurons have been considered recently (Laing and Chow, 2001; Compte et al., 2000). We do not explicitly provide our network with high gain at the single-cell level, which trivially yields memory storage, but rather require the network bistability to arise from the synaptic interactions. We show that the activity bumps are stably maintained in the spiking networks by recurrent AMPA-like synapses without requiring intrinsic cell bistability (as in Guigon et al., 1995; Wang, 1999; Lisman et al., 1998). We also do not require slow state-dependent NMDA synapses to achieve robust sustained activity at low firing rates as reported elsewhere (Wang, 1999; Compte et al., 2000). This is a direct consequence of including a spatial structure in the network and the use of models faithful to the biophysics of cortical neurons, instead of integrate-and-fire neurons, which lack crucial properties (see below). Furthermore, the firing rates we obtain for the sustained activity arise neither from rapid saturation of the synapses (e.g., due to synaptic adaptation or other mechanism leading to sublinear summation of synapses beyond the simple consequence of modeling the synapses as conductances instead of currents) nor from saturating the firing in the cells that are active. In fact, both the excitatory and inhibitory populations have extremely wide dynamic range, with the saturation firing rate well above the observed activity.

2. Methods

2.1. Biophysical Conductance-Based Network

For the purposes of this study we use a one-dimensional network of conductance-based single compartment neurons. Both excitatory and inhibitory neurons are included. The connections between the neurons depend on spatial separation between the cells and cell type. Excitatory connections from the pyramidal neurons to other pyramidal neurons and to the interneurons follow a Gaussian synaptic footprint. The inhibitory connections (to the pyramidal neurons and other interneurons) also follow a Gaussian footprint but with a larger extent. This inhibitory connection pattern is consistent with the anatomy of a specialized population of interneurons that are present in the layers II/III of the prefrontal cortex. These interneurons, the wide-arbor cells, have axonal arbors extending over 300 microns and furnishing pericolumnar inhibition (Lund and Lewis, 1993). The functional effect of such connectivity is lateral inhibition.

The excitatory synapses are parameterized to model fast AMPA-type and the inhibitory synapses model GABA-A type. The strength of connection, the maximal synaptic conductance, is adjusted to obtain stable maintenance of a localized focus of activity. In addition, a portion of the neurons in the network are targeted by extrinsic inputs (see below), and all neurons in the network have a small noisy current added to yield a low irregular basal firing rate. The network boundary conditions are periodic. In general we chose the size of the connectivity so that each cell contacted roughly half the neurons in the network; however, if we simulated more neurons, keeping the connections the same, our results would not change.

Parameter values for the basic simulations (e.g., Fig. 2) are indicated below. We have also varied the parameters and the size of the network and found that the phenomena we observe (the asynchrony, the bump maintenance, and the turn-off by synchrony) are largely independent of the individual parameter choices (see Fig. 3 and the discussion in Results).

The equations for the network are as follows. The equations for each of the N excitatory neurons are

$$
\begin{aligned}
C\frac{dV_e}{dt} &= I^e_{\text{mem}} + I^e_{\text{syn}} + I^e_{\text{ext}} + I^e_{\text{rand}} \\
\frac{dn_e}{dt} &= \phi[\alpha_n(V_e)(1-n_e) - \beta_n(V_e)n_e] \\
\frac{dh_e}{dt} &= \phi[\alpha_h(V_e)(1-h_e) - \beta_h(V_e)h_e] \\
\tau_e\frac{ds_e}{dt} &= A\sigma(V_e)(1-s_e) - s_e \\
\frac{d[Ca]}{dt} &= -0.002 g_{Ca}(V_e - V_{Ca})/ \\
&\qquad \{1+\exp(-(V_e+25)/2.5)\} - [Ca]/80,
\end{aligned}
$$

where

$$
\begin{aligned}
I^e_{\text{mem}} = &-g_L(V_e - V_L) - g_{Na}[m_\infty(V_e)]^3 h_e(V_e - V_{Na}) \\
&- \left(g_K n_e^4 + \frac{g_{AHP}[Ca]}{1+[Ca]}\right)(V_e - V_K).
\end{aligned}
$$

Those for the N inhibitory neurons are

$$\begin{aligned} C\frac{dV_i}{dt} &= I^i_{\text{mem}} + I^i_{\text{syn}} + I^i_{\text{ext}} + I^i_{\text{rand}} \\ \frac{dn_i}{dt} &= \phi[\alpha_n(V_i)(1-n_i) - \beta_n(V_i)n_i] \\ \frac{dh_i}{dt} &= \phi[\alpha_h(V_i)(1-h_i) - \beta_h(V_i)h_i] \\ \tau_i\frac{ds_i}{dt} &= A\sigma(V_i)(1-s_i) - s_i, \end{aligned}$$

where

$$\begin{aligned} I^i_{\text{mem}} = &- g_L(V_i - V_L) - g_{Na}[m_\infty(V_i)]^3 h_i(V_i - V_{Na}) \\ &- g_K n_i^4(V_i - V_K). \end{aligned}$$

Other functions are $m_\infty(V) = \alpha_m(V)/(\alpha_m(V) + \beta_m(V))$, $\beta_m(V) = 4\exp(-(V+55)/18)$, $\alpha_m(V) = 0.1(V+30)/[1-\exp(-0.1(V+30))]$, $\alpha_n(V) = 0.01(V+34)/[1-\exp(-0.1(V+34))]$, $\beta_n(V) = 0.125\exp(-(V+44)/80)$, $\alpha_h(V) = 0.07\exp(-(V+44)/20)$, $\beta_h(V) = 1/[1+\exp(-0.1(V+14))]$, $\sigma(V) = 1/[1+\exp(-(V+20)/4)]$. Parameter values are $C = 1$, $\phi = 3$, $\tau_e = 4$, $A = 20$, $g_{Ca} = 0.1$, $V_{Ca} = 120$, $g_L = 0.05$, $V_L = -65$, $g_{Na} = 100$, $V_{Na} = 55$, $g_K = 40$, $g_{AHP} = 0.01$, $V_K = -80$, $\tau_i = 8$. The synaptic current entering the jth excitatory neuron is

$$\begin{aligned} I^e_{\text{syn}} = &- \frac{\left(V_e^j - V_{ee}\right)}{N}\sum_{k=1}^{N} g_{ee}^{jk}\, s_e^k \\ &- \frac{\left(V_e^j - V_{ie}\right)}{N}\sum_{k=1}^{N} g_{ie}^{jk}\, s_i^k, \end{aligned}$$

where $V_{ee} = 0$, $V_{ie} = -80$, V_e^j is the voltage of the jth excitatory neuron, $s^k_{e/i}$ is the variable giving the temporal evolution of the synapse emanating from the kth excitatory/inhibitory neuron (modeled with first-order kinetics), and

$$g_{ee}^{jk} = \alpha_{ee}\sqrt{\frac{100}{\pi}}\exp(-100[(j-k)/N]^2)$$

and

$$g_{ie}^{jk} = \alpha_{ie}\sqrt{\frac{30}{\pi}}\exp(-30[(j-k)/N]^2).$$

Similarly, the synaptic current entering the jth inhibitory neuron is

$$\begin{aligned} I^i_{\text{syn}} = &- \frac{\left(V_i^j - V_{ei}\right)}{N}\sum_{k=1}^{N} g_{ei}^{jk}\, s_e^k \\ &- \frac{\left(V_i^j - V_{ii}\right)}{N}\sum_{k=1}^{N} g_{ii}^{jk}\, s_i^k, \end{aligned}$$

where $V_{ei} = 0$, $V_{ii} = -80$, V_i^j is the voltage of the jth inhibitory neuron and

$$g_{ei}^{jk} = \alpha_{ei}\sqrt{\frac{30}{\pi}}\exp(-30[(j-k)/N]^2)$$

and

$$g_{ii}^{jk} = \alpha_{ii}\sqrt{\frac{30}{\pi}}\exp(-30[(j-k)/N]^2).$$

$I^i_{\text{ext}} = 0.5.I^{i/e}_{\text{rand}}$ consists of pulses of the form $\pm 5e^{-2t}$, where positive and negative pulses have equal probability of arriving, and the times of arrival are chosen from a Poisson distribution with mean rate 20 Hz. Parameter values are $\alpha_{ee} = 0.14$, $\alpha_{ei} = 0.1$, $\alpha_{ie} = 0.06$, $\alpha_{ii} = 0.02$. For the purposes of this report the number of neurons N was set at 100 for most of the simulations. Figure 2 has a stimulus of a Gaussian of the form $1.5\exp(-60[(j-N/2)/N]^2)$ for $12 < t < 42$ and a 1ms stimulus of strength 50 at $t = 522$ for neurons 21-79. Figure 3B has stimulus of a Gaussian of the form $1.5\exp(-60[(j-N/2)/N]^2)$ for $30 < t < 60$ and a 1ms stimulus of strength 50 at $t = 480$ for neurons 1 to 9 and 41 to 100. Fixed currents are randomly chosen from uniform distribution over $[-0.2, 0.2]$. Figure 3C has a stimulus of a Gaussian of the form $1.5\exp(-260[(j-N/2)/N]^2)$ for $30 < t < 60$ and a 1ms stimulus of strength 50 at $t = 480$ for neurons 21-79.

We checked the robustness of our results by varying parameters (see Fig. 3) and changing the packing density of the neurons. For the second case we simulated 500 neurons with connectivity re-adjusted so that each neurons would contact roughly half the domain. Our results remained the same as for the original network.

2.2. *A Simple Excitatory Circuit Used in the Appendix*

As a basic computational unit for the two-neuron circuit we used the θ-neuron, which results from a mathematical reduction of biophysical models of cortical neurons (see Gutkin and Ermentrout, 1998). The dynamical evolution of the voltage and the currents is translated into dynamics of a phase variable θ. The phase tracks the membrane voltage from rest ($\theta = \theta_{\text{rest}}$) through the action potential ($\theta = \pi$) and then back to rest.

We studied a circuit of two synaptically interconnected θ-neurons:

$$\frac{d\theta_1}{dt} = (1 - \cos\theta_1) + (1 + \cos\theta_1)(\beta + g_{s_{12}} s_2), \quad \theta \in [0, 2\pi]$$

$$\frac{d\theta_1}{dt} = (1 - \cos\theta_2) + (1 + \cos\theta_2)(\beta + g_{s_{21}} s_1), \quad \theta \in [0, 2\pi]$$

$$\frac{ds_i}{dt} = \alpha(\theta_{\text{pre}})(1 - s_i) - \frac{s_I}{\gamma}$$

$$\alpha(\theta_{\text{pre}}) = \kappa \exp[-\rho(1 - \cos(\theta_{\text{pre}} - \theta_{\text{thresh}}))],$$

where θ_1 and θ_2 are the phases of the two neurons, β is a bias, and $g_{s_{12}}$ and $g_{s_{21}}$ are the synaptic coupling strengths (taken to be symmetric in our study). s_i $(i = 1, 2)$ gives the time-evolution of the synaptic conductance for each neuron, $\theta_{\text{thresh}} = 3$, $\kappa = 1$, $\rho = 20$, $\gamma = 2$. Both neurons are parameterized to be excitable (bias is below zero). Synaptic strengths are adjusted to produce circuit bistability. All simulations were performed using XPPAUT (G.B. Ermentrout 1999, www.pitt.edu/~phase).

2.3. *Synaptic Efficiency*

Ermentrout (1996) showed that the phase response curve (PRC), which defines how incoming inputs affect the next firing time, can be readily computed from a given neural model. The convolution of the synapse function and the PRC defines the synaptic efficiency (SE) and gives the net ability of the synapse to influence the firing of the post-synaptic neuron. For a neuron with an interspike interval of T, we can compute the SE in real time by first computing the PRC and then multiplying by the excitatory synaptic inputs to obtain

$$SE_i(t) = g_s\, s_j(t)(\text{PRC}(t, \text{mod}(T))), \qquad (1)$$

where T is the firing period of the neuron studied. For further discussion, see Ermentrout (1996). In this article we use the SE in the Appendix to show precisely the biophysical mechanism by which synchrony turns off sustained activity without requiring direct inhibitory action.

3. Results

Our network is constructed of two populations of neurons: 100 excitatory and 100 inhibitory. Both neuron types are modeled as single compartment conductance-based cells using the Hodgkin-Huxley formalism (see Methods and Fig. 1). The parameters for the cell

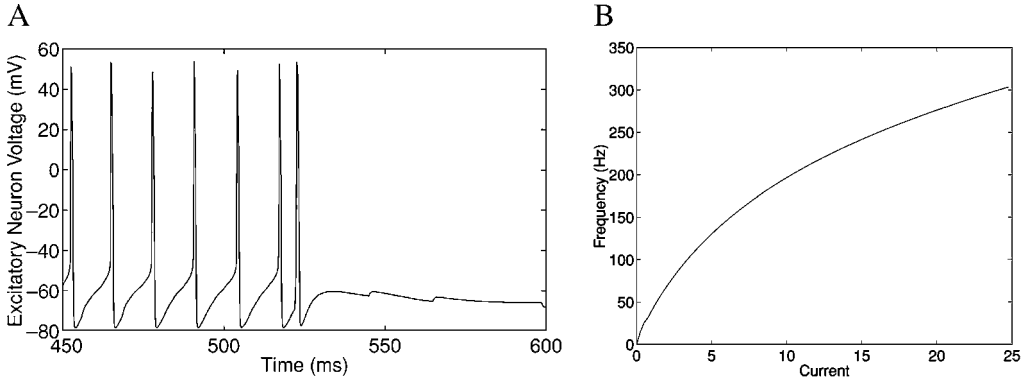


Figure 1. We use conductance based neurons in our simulations. Here we show an example of a pyramidal cell firing in the focus and its f/i curve. **A:** Representative voltage trace for a cell in the excitatory population at the switch-off. Here the cell we show is undergoing firing since it participates in the focus of activity shown in Fig. 2. The cell stops firing as the focus is stopped by synchrony. **B:** Frequency/current (FI) curve of a representative neuron in the excitatory population. Here, unlike in the rest of the article, the stimulus is a prolonged current step. The y-axis gives the amplitude of injected current step; the x-axis is the steady-state response frequency.

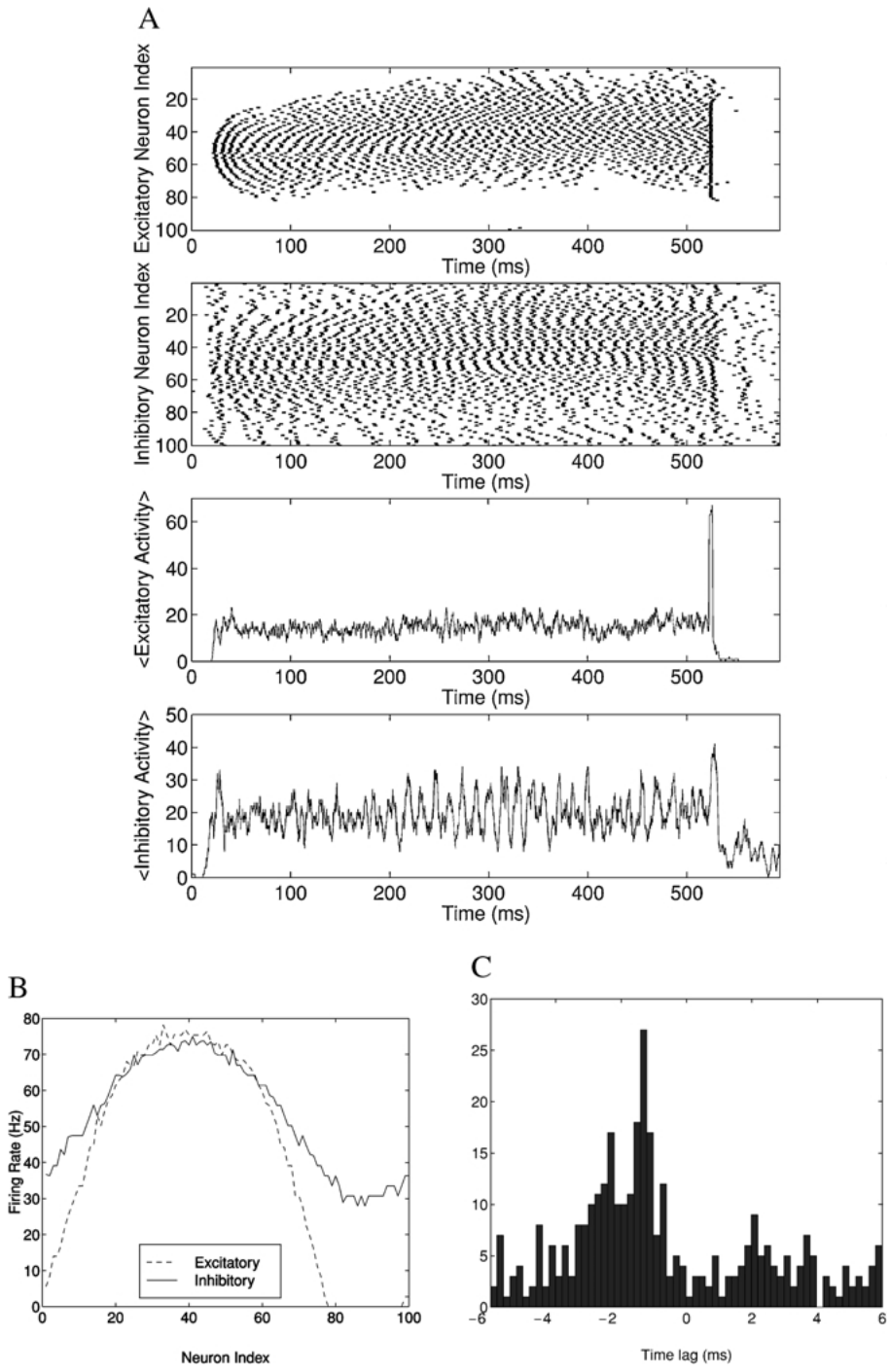
models were chosen to correspond to physiologically realistic values. The excitatory neurons included spike-frequency adapting currents; the inhibitory neurons did not. The synapses by which the neurons were coupled have physiologically realistic time-constants (see Methods). In our network, both cell types made recurrent connections onto other cells (excitatory and inhibitory) with spatially dependent synaptic footprints (see Methods). The absolute strength of the connections was adjusted to ensure recurrent excitation sufficient to maintain the activity, while the inhibition was strong enough to ensure that this activity was spatially localized.

A spatially localized transient excitatory stimulus induces stable persistent firing in cells that initially fire at a low (random) base rate (Fig. 2). We generally used a transient set of currents with a Gaussian spatial profile centered on the middle of the network as an initial stimulus (see Methods). The timing and the synchronization of these inputs is not critical: we were able to initiate activity generically with square pulses as well as stimuli with a certain amount of asynchrony (simulations not shown). These "kindled" neurons then recruit their neighbors, both excitatory and inhibitory, as determined by the profile of their connectivity. The entire ensemble keeps firing after the stimulus is removed, maintaining a "focus" of activity. This firing persists due to the input from the recurrent monosynaptic excitatory connections. The cells outside the focus are inhibited from firing through the disynaptic lateral inhibition. The structure of the recurrent connectivity determines the spatial profile of the activity focus. To obtain a spatially restricted focus, the recurrent excitation and inhibition impinging on a given cell should be in balance (Fig. 3A). If inhibition dominates, only a transient response is observed; if excitation dominates, the activity spreads through the whole network. The requirements for the initial stimulus transient are generic; a small stimulus may initiate a larger structure, or a large stimulus may shrink down to a smaller focus. The basic profile of the focus is determined by the spatial envelope of the connections.

The stability of the spatial structure of the focus is also dependent on the relative firing times of the neurons within the focus. In Fig. 2A (3rd trace from top) we see that the instantaneous firing rate of the focus does not show persistent coherent oscillations. The key is that the firing is globally asynchronous in the excitatory population. This asynchrony is a direct consequence of two effects. The first is that the neurons in the focus receive heterogeneous input due to the spatial structure of the focus: neurons in center of the focus receive more synaptic input than those at the edges. The second is that the intrinsic synaptic kinetics tend to destabilize synchrony (Ermentrout and Kopell, 1998). The asynchrony provides a temporal spread of synaptic inputs to a given neuron within the focus, which ensures that it receives sufficient depolarization to fire again after it has recovered from spiking.

Although the network activity is asynchronous, the firing times of neighboring neurons may appear correlated because they share many inputs and fire at similar rates (e.g., as in Brody, 1998). Thus even though the total EEG can show very low coherence, the pairwise cross-correlograms of cells in the focus may show peaks. Furthermore, the inhibitory population can show partial synchrony under various parameter choices, which does not affect the structure of the focus. This may explain the seemingly paradoxical experimental observations of synchronous coherence (Funahashi, 1998) and nonsynchronized firing rate variations (Brody, 1999). Recently Funahashi and Inoue (2000) recorded from pairs of neurons in the PFC and observed peaked correlograms (at various delay shifts).

Figure 2. Turning on and off a focus with brief transient excitation in a network of spiking neurons. Here we see the behavior of a one-dimensional network. The spatial spread of the connections and the biophysical properties of the cells are described in Methods. The strength of connections was in general adjusted to respect excitation/inhibition balance impinging on each neuron. A small amount of random noise was added to the network to produce random firing of approximately 5 Hz (however the asynchrony did not depend on this noise, as the noise-free network gives essentially the same results). **A:** The space-time rastergrams of the excitatory (upper) and inhibitory (lower) populations clearly show a spatially restricted focus of activity. The initial stimulus is a transient focus of afferent excitation to the excitatory neurons only (see Methods). The focus develops due to the recurrent connectivity: the recurrent excitation supports the activity, while the disynaptic inhibition constrains it spatially. The focus persists and the firing of neurons within the focus is asynchronous, with neurons near the focus edges firing at lower rates than those at the center. A transient excitatory current terminates the focus. The activity of the excitatory population (here a sum of spikes across the excitatory (upper) and inhibitory (lower) populations giving the overall firing rates, or spike time histograms) clearly shows no sustained coherent oscillations in the excitatory network. **B:** The mean frequency profile of the focus is determined by the spatial profile of the connections. The dashed graph is the excitatory population and the slightly wider solid graph is the inhibitory population. **C:** Adjacent neurons can show peaks in cross-correlograms. Here we show a cross-correlograms for excitatory neurons 50 and 51. Note that the peak is slightly shifted.



These correlograms appear to have a similar shape to the ones we observe in our simulations (e.g., Fig. 2C). A common interpretation of peaked correlograms is the the two neurons fire synchronously and therefore are involved in a synchronously oscillating network (e.g. Engel et al., 1991; Singer, 1999). Brody (1998), on the other hand, showed that peaked cross-correlograms can appear due to slow covariations in the firing rate of two neurons. Our findings are compatible with this latter picture since pairs of nearby neurons in our network

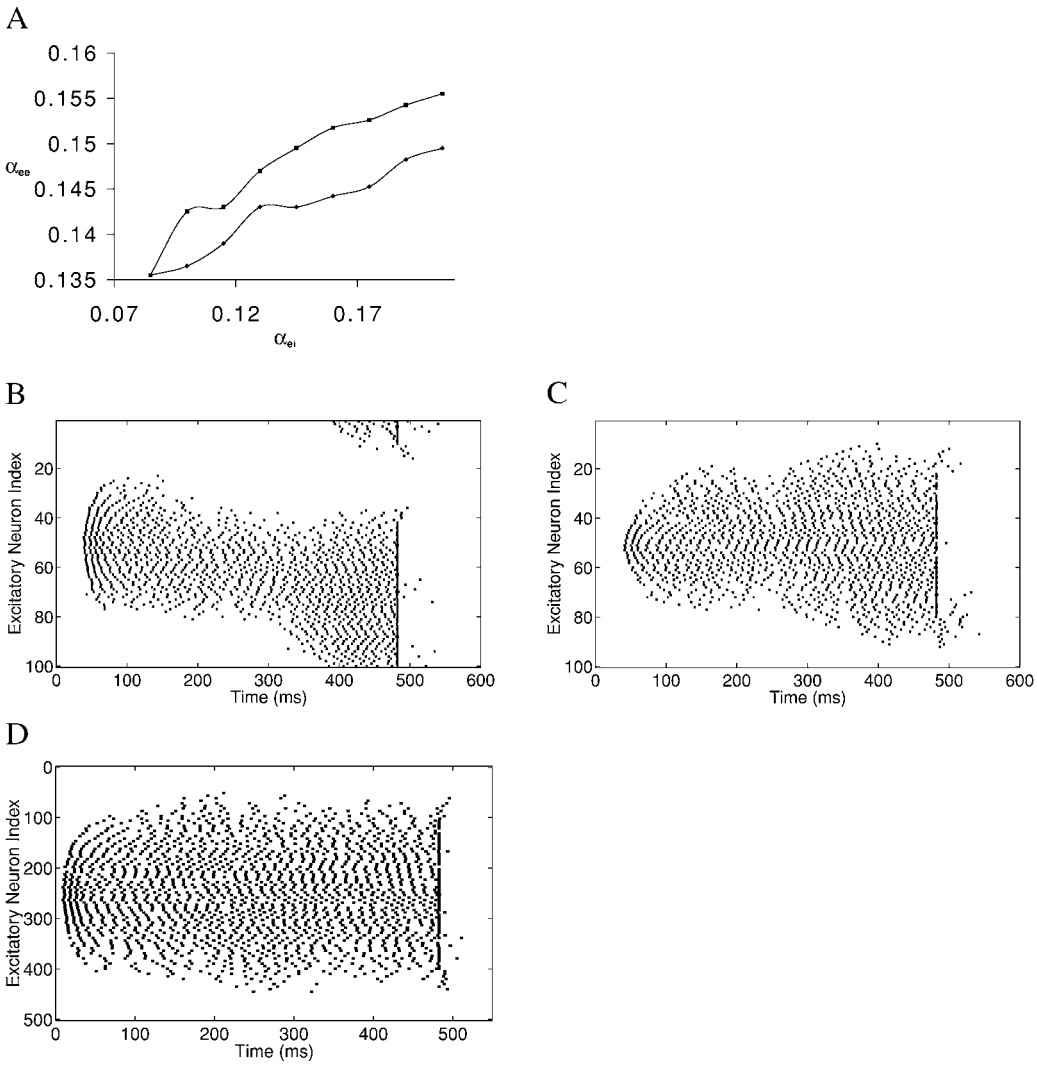


Figure 3. Asynchrony and the termination effect of synchronisation by excitatory input is robust under various network parameter choices. Here we give some examples for various parameters. **A:** The existence and stability of the spatially restricted focus depends on the relative balance between excitation and inhibition. When the two are roughly balanced (region between the two curves), the focus is stable and is turned off by synchrony. Outside this region the focus either does not exist (inhibition is too strong) or is not spatially stable (the excitation is too strong and the activity spreads throughout the whole network). **B:** The effects are robust under randomized cell parameters (see Methods). **C:** The activity focus is independent of the size of the initial stimulus, here the spread of the Guassian was decreased by a factor of 4-1/3 from the stimulus in Fig. 2. **D:** The results are independent of the packing density of the neurons. Here we keep the "physical" size of the network the same, as determined by the spatial extent of the connection profiles, but simulate the network with 1000 neurons.

do show peaked cross-correlograms but no synchrony is seen on the network level.

The necessity of asynchrony to maintain the focus activity leads to a novel way of using synchrony to extinguish the focus (Fig. 2A). If the spikes of the excitatory neurons within the focus are momentarily aligned by transient excitation, the activity shuts off. When synchronized, the synaptic inputs arrive during the refractory period in which the neurons are unable to fire. Thus activity in the focus cannot be maintained and the focus extinguishes. This effect is model independent. For conductance-based neurons, during asynchronous firing, the synaptic efficiency of the recurrent excitation is high because the synaptic inputs are continuously integrated by the neural membrane. Under a brief strong stimulus, the total excitatory

synaptic current to a given cell does not change, but the net influence of the synapses on the postsynaptic cell (i.e., the synaptic efficiency (SE); see Methods and Appendix) decreases dramatically. The synaptic input arrives right after the spike, when the fast sodium channels are inactivated and the active conductances that underlie the spike and after-hyperpolarization, such as the slow K-currents, are still open. This dramatically increases the total cross-membrane conductance of the cell or equivalently decreases the integration time constant of the cell. The synapses are shunted and cannot depolarize the cell to threshold. This effect is also seen in simple integrate-and-fire neurons, provided that the integration time constant of the neurons is shorter than the synaptic time-course (simulations not shown). For conductance-based neurons this requirement is relaxed: the time constant of the cells can be quite long at rest, but the synchronous synapses will still be "shunted" due to the spike-dependent decrease in the input resistance as discussed above. In simple terms, if the inputs are all synchronized, then by the time the neuron has recovered from firing, the synaptic current will have disappeared.

The switch-off by synchronizing excitation is preserved under varying network parameters (Fig. 3B–C), provided that the excitation/inhibition balance condition is satisfied (Fig. 3A). Furthermore random synaptic noise that we include in the network does not disturb the focus or the effect of synchronizing stop signal significantly. We thus propose that this role of synchrony is generic to networks where sustained firing is maintained by recurrent connectivity. We have also demonstrated our effect in two-dimensional networks of spiking neurons (simulations not shown). Based on our simulations, asynchrony in the synaptic events relative to the spike times in the postsynaptic neuron is a basic requirement for the recurrent connections to keep the activity going with AMPA-like fast excitatory synapses.

4. Discussion

In our simulations, we have not considered the possible role of synaptic dynamics (such as synaptic depression) (Markram and Tsodyks, 1996), but we expect that such would only strengthen our prediction about asynchrony. We view the requirement for asynchrony as a direct consequence of the role of recurrent connectivity. Our results are not contradictory to the results of Diesmann et al. (1999), which show that that synchrony

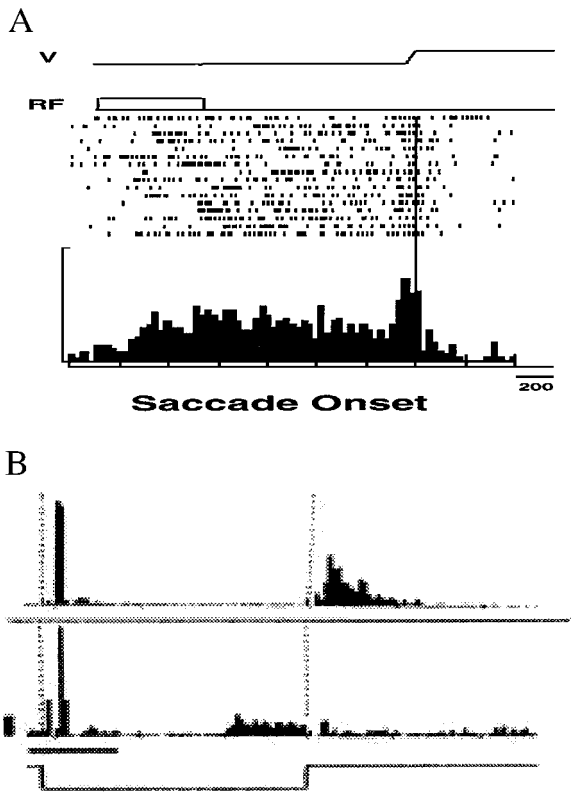


Figure 4. Experimental correlates of effects predicted from theory: transient spike in the firing at response initiation and activity dependent suppression of response to synchronising excitatory stimulus. **A:** Representative cell activity over many trials from lateral interparietal area (LIP) shows a sharp increase and fall in the firing rate at response initiation. Note that in single trial histograms activity terminates abruptly, while in the cross-trial histogram activity appears to ramp down rapidly. This effect is predicted for a massive synchronous burst in the PFC, which is conveyed to this LIP neuron. The same synchronous burst terminates the activity in the PFC and consequently in the LIP neuron, thus we actually see a suppression of activity below the steady state level. Data adapted with permission from Colby and Duhamel (1991). **B:** Activity dependent depression of response to synchronizing excitatory stimulus in the visual cortex. Sensory responses were evoked for both on and off transitions of a light bar positioned along the border between the on and off regions of the receptive field of a simple cell. Here in control condition (upper trace) the cell shows a strong response to the onset of the stimulus. The circuit is conditioned to show sustained activity for 1 sec preceding the stimulus by K iontophoresis (lower trace). After the conditioning (and an appropriate delay to ensure wash out of potassium), the circuit is retested (Debanne et al., 1998). The sustained activity is still present, presumably due to strengthened intracortical connections, but the on response is wiped out. Here the visual stimulus provides a synchronous afferent discharge to the cortical network. In the neuron that is previously quiescent the synchronizing stimulus evokes a strong response. However, for an *a priori* active neuron that persists in firing due to recurrent connections, the same stimulus turns off the neuron due to synchronization. Data adapted with permission from Debanne et al., (1998).

leads to stable propagation of neural activity since recurrent connections were not considered.

An alternative way to switch-off sustained activity in the network would be through a direct inhibitory signal or through the action of disynaptic lateral inhibition. For the first point, we believe that switching off the focus by excitation is much more biologically plausible anatomically and physiologically. Anatomical studies of synaptic targets for intrinsic cortical connections in the monkey prefrontal cortex show that excitatory efferents, afferents and lateral connections in the supragranular layers of the frontal cortex strongly favor excitatory synapses onto pyramidal neurons (Meltchinsky et al., 1998). Furthermore, there is physiological evidence suggesting that long-range connectivity is excitatory, whereas inhibitory effects are local—for example, a monosynaptic EPSP followed by disynaptic IPSPs (Hirsh et al., 1998; Bringuier et al., 1999). Thus a "stop" signal emanating from the motor cortex is likely to be excitatory and impinge preferentially onto the pyramidal neurons.

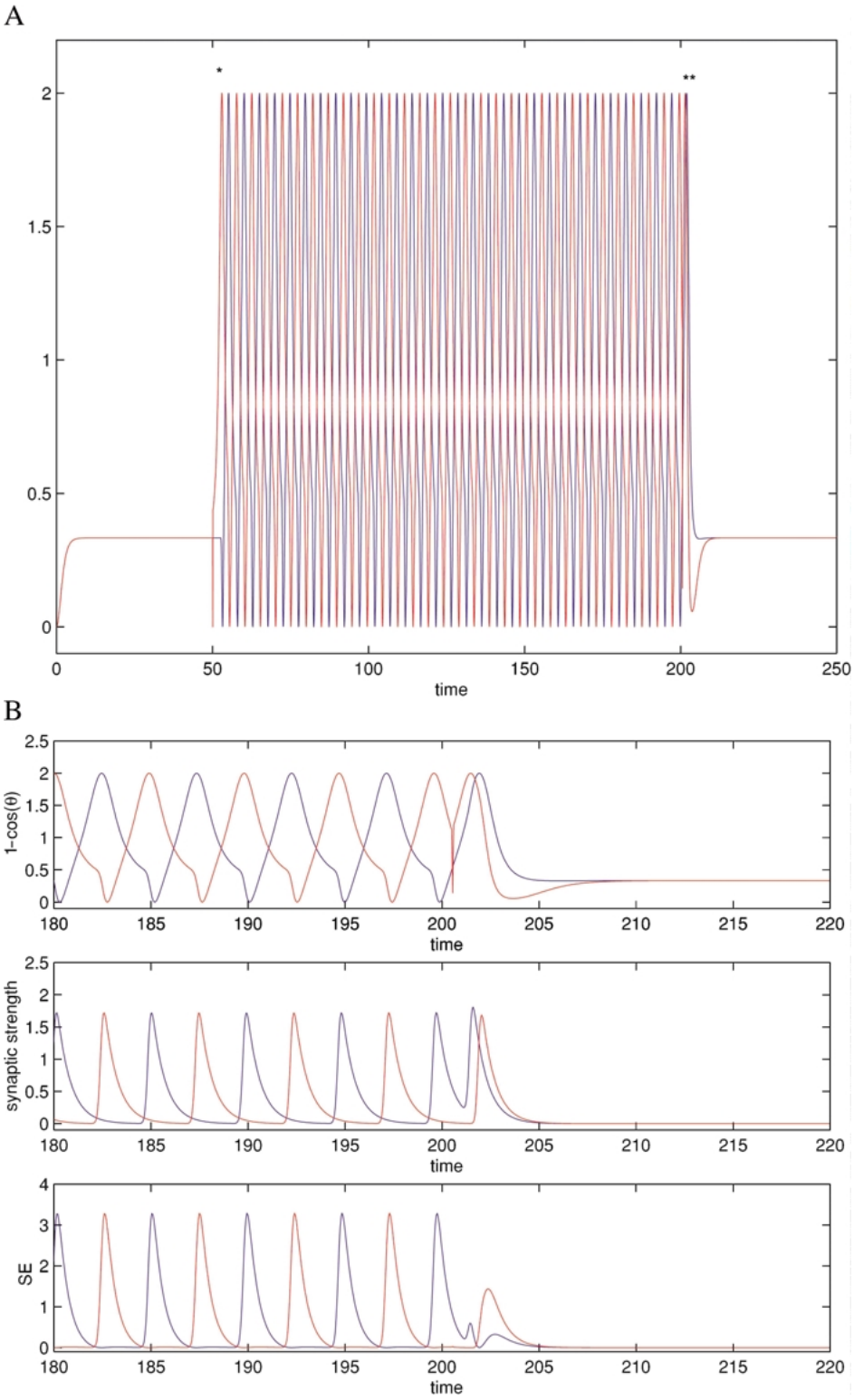
We believe the inhibition-dependent mechanism does not apply to our work since the activity in the network stops immediately after synchronization. Furthermore we use a simple two-cell purely excitatory circuit (see Appendix) to show the same switch-off behavior. Although we cannot rule out completely the role of inhibition in extinguishing the focus, we argue that for the models presented here, inhibition is not required to switch off the sustained activity. Its dominant role is to constrain the activity spatially (certainly in a purely excitatory circuit the bump of activity would spread). Whether this is truly the picture in the PFC remains to be investigated.

Previously, the use of strong recurrent excitation to maintain sustained activity has been criticized for unrealistically high firing rates (Wang, 1999). However, as shown in Fig. 2B, the firing rates in our foci are physiologically reasonable (especially for neurons on the edges of the focus), yet the synapses have modest time constants (5 to 10 ms). We have also been able to obtain sustained foci with lower firing rates with appropriate adjustments in parameters (simulations not shown). Our results differ from Wang (1999), where it was argued that synapses with very long time constants are required for slow firing rates. We believe that this is in part because Wang (1999) uses integrate-and-fire neurons that spike as soon as threshold is crossed. Biophysically based models with ionic channels, which we use, have a delay in time from the moment threshold is crossed to the time that a full action potential develops, especially when the neuron is fired by synaptic inputs that bring the membrane voltage just beyond the threshold. This delay enables recurrently connected neurons that have fast synapses to fire at low rates. Such delays have been observed experimentally (Azouz and Gray, 1999) and theoretical studies have previously shown that these delays persist in noisy perturbed models (Gutkin and Ermentrout, 1998). The key for such delays is that the synapses that push the neuron to fire must fall close to the threshold—that is, they should be balanced just beyond threshold.

Another difference between our approach and Wang (1999) is that we explicitly include spatial structure in synaptic connectivity. This allows for a balance of excitation and inhibition impinging on a given neuron and brings out the spike delays. Wang (1999), on the other hand, is constrained to balance strong long-lasting excitatory connections with strong inhibition, and when the long lasting excitation is substituted by fast excitation, it has to be very strong to overcome the strong inhibition. We believe that such excitation is well beyond the regime where any spike delays are possible even for conductance-based models and thus result in "pegging" the network at high firing rates. The combination of asynchronous firing, which spreads the effective synaptic current over a long period of time, and the delay to firing of our model system are sufficient to enable persistent recurrent activity at low firing rates with fast synaptic dynamics.

Recently, Compte et al. (2000) have published a model of spatial working memory that includes spatial structure. However, their model operates in a different parameter regime than ours. They use leaky

Figure 5. A simple two-cell circuit of canonical θ-neurons allows us to understand the biophysical mechanism for the synchrony induced switch-off of sustained activity. Neuron 1 is red, and neuron 2 is blue. Both are connected to each other by symmetric excitatory synapses. **A:** With sufficiently strong synapses the network is bistable. A transient excitatory stimulus to one of the neurons (marked by *) turns the sustained activity on. A later excitatory stimulus (**) instantaneously synchronizes both neurons and the activity turns off. **B:** An enlarged view of the activity switch-off. Top trace is a plot of $v = 1 - cos(\theta)$, a normalized "voltage" with spikes occurring when $v = 2$. The middle trace shows the synaptic inputs and the lower trace—the SE. The sustained activity is antisynchronous. Thus the synapses come when the neuron is most excitable and SE is maximum. During the brief excitation the synapses synchronize and arrive when the both neurons are refractory. The SE shows a marked decrease as the two synapses decrease in their efficacy.


A
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time
synaptic strength
2.5
2
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integrate-and-fire neurons that are biased to be tonically active. To sustain localised activity at low firing rates, they use strong nonspecific inhibition together with long-lasting NDMA-like excitation. The stopping mechanism is through multisynaptic inhibition. They find that when strong spatially selective fast synapses are added, the network develops synchrony as previously described in Bush and Sejnowski (1996). Similar to our results, Compte et al. (2000) find that synchrony can destroy the bump state. In our model, the neurons are intrinsically quiescent and the localized bump arises from the fast AMPA recurrent synapses. Inhibition in our model is not strong. It is balanced with excitation and constrains the activity spatially.

Our simulations make a number of predictions for *in vivo* experiments. We predict transient synchrony at the time of the response or at the instant when the animal expects to make a response. An increase in synchrony and a rapid upswing in the firing level at response initiation has been reported in the motor cortex (Riehle et al., 1998). Our model also predicts a sharp transient increase in the rate of sustained firing at the time of the response, followed by a rapid drop in activity. This has been seen in a number of delayed response experiments and has often been interpreted as motor-related activity. We propose here that this signal reflects a corollary discharge of the motor command that directly terminates the sustained firing. Once the command has been issued, the information used to generate it can be cleared. This is the sequence of events that was suggested as a conceptual model by Funahashi and Inoue (2000) based on their experimental results.

For example, neurons in parietal cortex exhibit activity that conforms to this pattern (Colby and Duhamel, 1991; Gnadt and Andersen, 1988). In single neurons in the lateral intraparietal area during a memory-guided saccade task, a transient sensory response is followed by a prolonged period of activation while the animal maintains a representation of the stimulus location. In some neurons this activity commonly increases sharply at the time of the saccade and is then sharply truncated as seen in Fig. 4A (Colby and Duhamel, 1996). Without discounting alternative explanations for this effect, such as local inhibition, we propose that such a transient is compatible with an incoming efferent copy of the eye-movement command. This copy of the command is sent to the parietal cortex to terminate the activity representing the target and then resets the system for the next visual input.

We also predict that the switching off by excitation is activity dependent. This means that the synchronizing trigger needs to impinge on the neurons that are *a priori* firing due to the recurrent synaptic connections. In a network of quiescent neurons this trigger may act as an on switch. Illustrations of this can be found in sensory cortical networks, where the thalamo-cortical afferents provide a synchronising trigger. Figure 4B shows sensory responses evoked by contrast changes in a simple cell in the primary visual cortex (Debanne et al., 1998). In control conditions, the cell shows a transient response to the OFF transition and a robust response to the ON transition. The cell is then conditioned to exhibit prolonged sustained activity following the OFF stimulus. The conditioning is accomplished by a visual stimuli paired with iontophoresing potassium, likely affecting not only the neuron recorded but also the local population of cells. After the removal of the potassium (by wash-out), the sustained response to the OFF stimulus persists. Presumably this is due to strengthened local connectivity. However the response to the ON stimulus, presented during the sustained activity, is suppressed. This effect is consistent with a synchronising afferent excitation switching off cells engaged in reverberating activity.

Finally, we predict that sustained activity in the PFC during working memory tasks should be asynchronous. Any apparent synchrony should be explainable by firing rate covariations. We further propose a new role for transient synchrony in neural activity: in circuits that support working memories through sustained activity, synchronization acts as a way to erase memory traces that are no longer salient for the animal's behavior. This predicts that transient locally synchronizing stimulation of the PFC during a delayed response task should extinguish the active memory trace and significantly degrade the animals performance.

Appendix: Turning On- and Off- with Excitation: The 2-Neuron Circuit and Synaptic Efficiency

Here we show that the turn-off is independent of the inhibition and also of the specific model used (see Fig. 5). We show that in a purely excitatory circuit of two neurons, transient synchrony turn off synaptically sustained activity. We further use the simple model to pin point some of the finer details of the biophysical mechanism by which the turn-off happens.

In the two-neuron circuit the sustained activity is asynchronous, with the firing frequency determined

by the strength of the recurrent synapses as well as their time course. We see that synchronising the two neurons stops the activity. Looking at the SE shows clearly that the activity stops because the synaptic currents are "shunted" by the neuron undergoing its firing cycle. This turn-off is completely independent of inhibition that is present in the spatially structured network above.

Furthermore, since we show the effect with a simple model, whose parameters are rather more general than those used in the conductance based neurons above, we suggest that the effects we exhibit in this report are independent of model choice.

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