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Layer 3 patchy recurrent excitatory connections may determine the spatial organization of sustained activity in the primate prefrontal cortex

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Abstract

Anatomical studies of primate prefrontal cortex show strong and spatially modulated lateral excitatory connections among pyramidal neurons in the supra-granular layers. We study the role of patchy lateral excitatory connections in generating spatially localized pulses of sustained activity. When the patchy connections drive the firing no spatially localized sustained activity is possible. When the local connectivity is strong enough to produce sustained activity, a localized standing pulses are possible. Additional punctate stimuli boost, or extinguish the standing pulse-system depending on their spacing. When the patchy lateral connections form distinct sub-systems, spatially restricted systems of multiple pulses of sustained activity are observed over a wide range of connection strength parameters.

Keywords: Prefrontal cortex; Sustained activity; Recurrent excitation; Bistability; Working memory

1. Introduction

Neurons located in the dorsolateral prefrontal cortex (PFC) in primates fire topically during the delayed response tasks that require the animal to hold

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information about the stimulus “on-line” [1,2]. A number of investigators have proposed this sustained activity as a cellular correlate of working memory. At the same time, anatomical studies have found extensive and spatially modulated lateral excitatory connections among pyramidal neurons in the supra-granular layers of the primate PFC. In this work we explore the local prefrontal cortical circuit and study the role of patchy lateral excitatory connections in generating spatially localized pulses of sustained activity.

In contrast to previous proposals about the mechanism by which sustained activity is generated (e.g. see Refs. [3–6]), we assume that PFC neurons are mono-stable, and propose that the bi-stability is a network property. That is, by themselves, the constituent neurons cannot sustain activity in absence of a stimulus, but the sustained activity arises as a result of local and lateral recurrent excitatory connections. We thus study the local PFC network using network models made up of mono-stable firing rate units with a sigmoid non-linearity. Our network represents local populations of excitatory and inhibitory cells, approximately at the level of a mini-column. The spatial connectivity of the network, which is a variant of the Amari neural network, is modeled explicitly.

2. The network model

The connection structure is based on the anatomical organization of layer 3 recurrent connectivity found in the primate prefrontal cortex (see Fig. 1A), area 46 and 9 in particular, where labeling studies showed an extensive network of recurrent excitatory connectivity [7]. The connections are laid out in systems of elongated spatially periodic stripes. At the ultra-structural level constituent pyramidal neurons show periodically spaced tufts of axonal collaterals that synapse primarily on pyramidal neurons. These periodically modulated processes are spaced approx. 500 mm, center to center. There is some evidence that the stripes form distinct systems, as opposed to being a part of a translation invariant cortical sheet. There is also evidence that a class of GABA ergic interneurons specific to the PFC provides inhibition on spatial extent consistent with inter-stripe distance [8]. A representative proposed recurrent local circuit is shown in Fig. 1B.

We investigate a network representing excitatory and inhibitory populations in the PFC patch with connectivity reflecting the features discussed above. That is, in addition to the local Mexican hat connectivity, a further, periodically modulated excitatory–excitatory connection is added, see Fig. 2A. The network equations that describe the spatio-temporal evolution of a “firing rate” at a location x, $U(x, t)$ are given by

$$\frac{\partial U(x)}{\partial t} = -U(x) + \int W(x-y) S[U(x)]\, dy. \tag{1}$$

Here $W(x-y)$ gives the spatial structure of the weights, and $S[\,]$ is the sigmoid non-linearity whose slope can be adjusted.

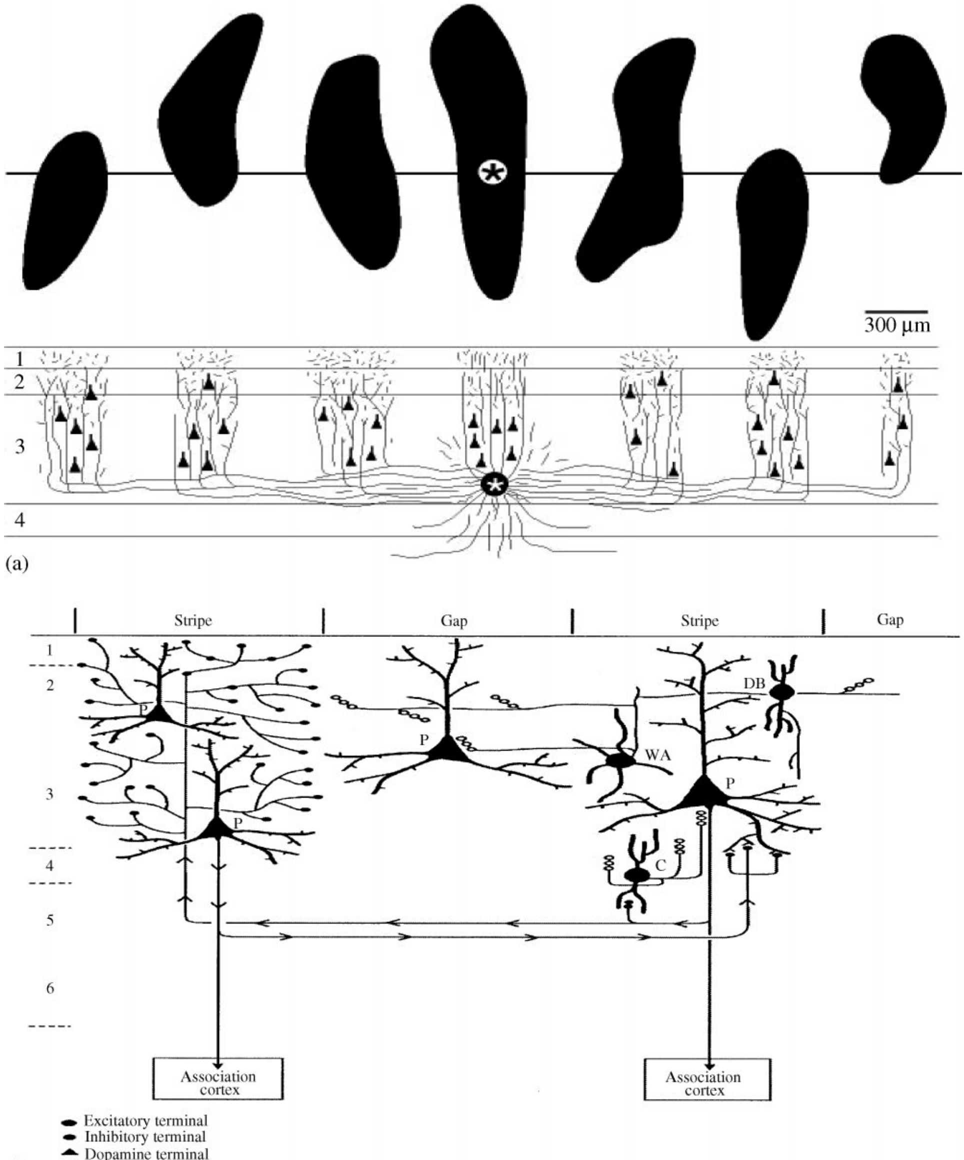


Fig. 1. The anatomy of PC local circuitry. (A) A local injection of anterograde label into layer 3 of the monkey dorsolateral pre-frontal cortex results in a lattice system of labeled stripes. The underlying pyramidal axonal processes are indicated in the diagram (lower half). The dark patches, or stripes show the locations of neurons contacted by the injected population, marked by the star. The cells in the label-free regions do not receive mono-synaptic connections from the injected population. Reproduced with permission from D.A. Lewis. (B) A proposed local circuit underlying the anatomical lattice. Note that the layer 3 pyramidal neurons connect both locally (to other pyramidals and interneurons) and send distant tufted collaterals to the next stripe over, connecting mostly to pyramidals. The inter-stripe gap receives di-synaptic inhibition from the wide arbor inter-neurons (WA). The number on the left indicated cortical layers. Reproduced with permission from D.A. Lewis.

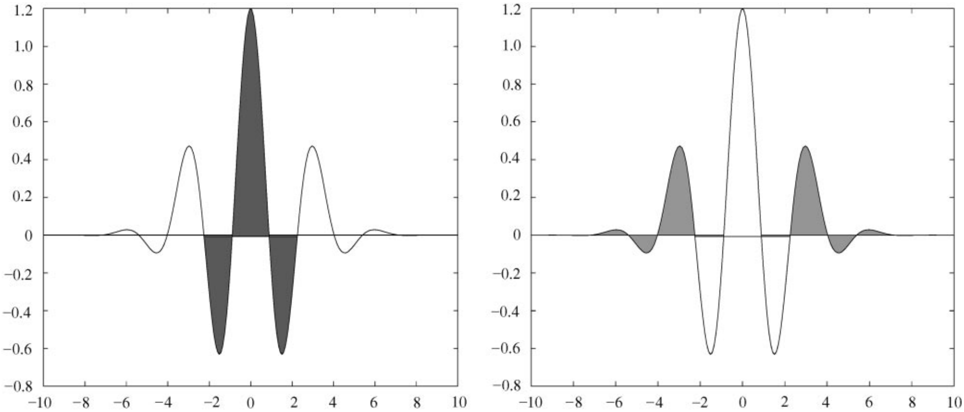


Fig. 2. A representative connection pattern for the network. Note the central "Mexican hat" connections (left) and the lateral excitatory connections modelling the stripe connectivity (right plot).

For the simulations we actually use a discretized, time coarse-grained version of (1)

$$U_i(t+\Delta t) = (1-\Delta t)U_i(t) + \Delta t \sum_j W_{ij} S[U_j(t)], \quad i = 1, \ldots, N \tag{2}$$

Here $U_j(t)$ is the activity of the neural unit at location j, Δt gives the time step, $W_{ij} = W(|i-j|)$ is the weight from unit i to unit j. Note that here the weights depend only on the distance between the two nodes, thus this network is said to be *spatially translation invariant.*

In the case where we want to model the partial discreteness of the patch stripes, we allow the distant "patchy" connections to be spatially modular:

$$U_i(t+\Delta t) = (1-\Delta t)U_i(t) + \Delta t \sum_j [W^{\text{local}}(|i-j|) + W^{\text{patch}}(i,j)] S[U_j(t)],$$
$$i = 1, \ldots, N. \tag{3}$$

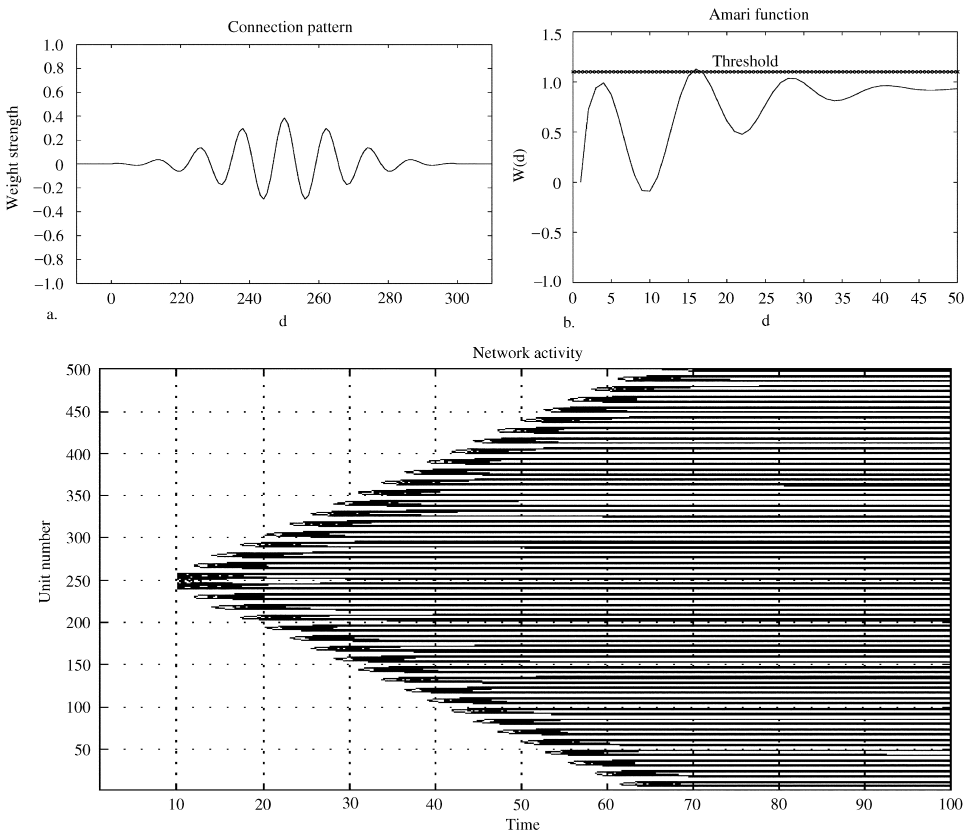
Here we have two classes of connections:

$W^{\text{local}}(|i-j|)$ are the local translation invariant connections or the Mexican hat, producing the basic local center on excitation and lateral inhibition.

$W^{\text{patch}}(i,j)$ are the patchy connections that depend explicitly on i (the physical location of the "postsynaptic" population) and j (the physical location of the "presynaptic" population).

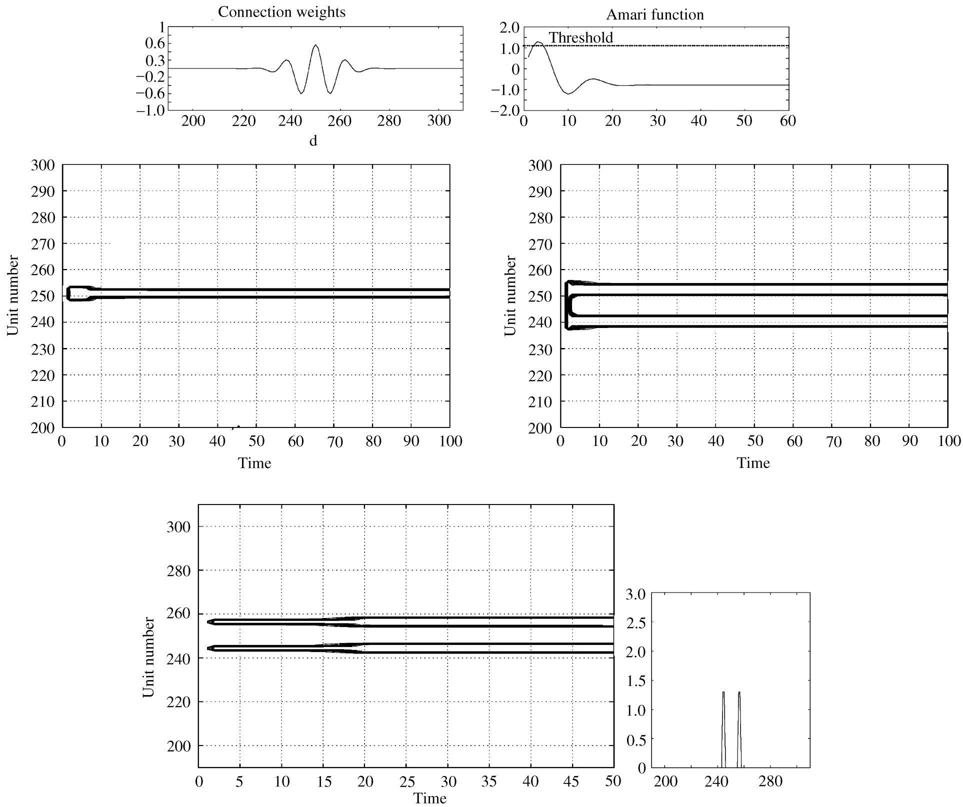
These model the systems of recurrent excitatory connections between the neural units within the same patch system.

Thus, we study two cases of the network: the translation invariant case, where every neural unit has an identical pattern of connections, and the modularized case, where the local Mexican hat connections are translation invariant, but the patchy connections are restricted to distinct mutually connected groups of neurons. For the translation invariant case we study a one-dimensional network, while a two-dimensional version is simulated for the modular case. Simulations were performed using Matlab (the 1-D model) or coded in C (the 2-D netowork). Code with exact parameter setting is available upon request, however, we did not carryout a systematic parameter space search, rather we were concerned with possible patterns of behavior of the network under qualitatively different connection and stimulation schemes.



(A)

Fig. 3. Sustained activity in a network with translation invariance. Here time is plotted in number of iterations, and $d = |i - j|$. (A) Network where bistability is due to the lateral connections: (a) The connection pattern used in this simulation; (b) The Amari function indicating the spatial location of the weights that ensure the bistability. Here the function crosses the threshold at the second peak, which means that the bistability is due to the lateral "stripe" connections; (c) Time plot of sustained activity. Note that the activity spreads in this translation invariant case. (B) A network where the central, local recurrent excitatory connections are sufficiently strong to induce bistability. A number of different patterns of spatially restricted sustained activity are possible, depending on the intial "kindling" stimulus. (C) Intervening excitatory stimuli turn off and/or shift the sustained activity mostly due to lateral inhibition.



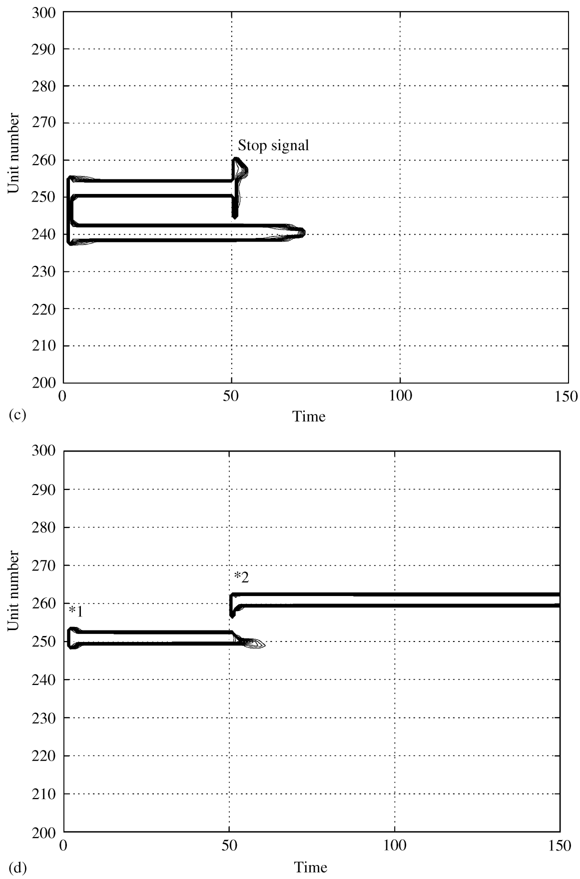
(B)

Fig. 3. (*continued*).

3. Results

Simulation results in the one-dimensional model show that under certain conditions[1] the network exhibits spatially structured sustained activity given a short duration kindling stimulus. The spatial organization of the sustained activity depends on the location and the size of the stimulus and the characteristics of the patchy lateral connections. In the case where the local connectivity is not strong enough to yield

[1] The conditions are can be easily defined by the total strength of connections converging on a unit from all units up to a certain distance away. We call this function the Amari function [9], it is given by for a given unit: $W(x) = \int_0^d w(x)\,\mathrm{d}x$, or for a unit at location i in a discretized network this is just the sum: $W(d) = \sum_0^d w(d), d = |i - j|$. When the connections are such that this function crosses the threshold, the network is bistable and can sustain activity. In the case where $W(d) >$ threshold for d small (less than the distance to the edge of the Mexican hat) the bistability is due to the local connections, when d is large (on the order of the distance to the first lateral excitatory "patch") the bistability is due to the lateral "patchy" connections.



(C)

Fig. 3. (*continued*).

sustained activity, but the patchy lateral connections are, a kindling stimulus that involves at least two excitatory-patch regions is necessary to evoke sustained activity. Our simulations show that in this case, no spatially localized bumps of sustained activity are possible. Activity spreads throughout the network (for an example see Fig. 3A). Thus, the information about the spatial location of the initial stimulus (that needs to be remembered by the network) is lost.

On the other hand, when the local connectivity is strong enough to produce sustained activity, a localized system of standing pulses is possible (Fig. 3B), with a strong central pulse and weaker side bands. It is also possible to observe arbitrarily low firing rates in these side bands.

Furthermore, any additional punctate stimulus that occurs later in the simulation can boost, or extinguish the standing pulse-system depending on its spacing. For example, if the second pulse occurs out of register with the "patches", the two pulses

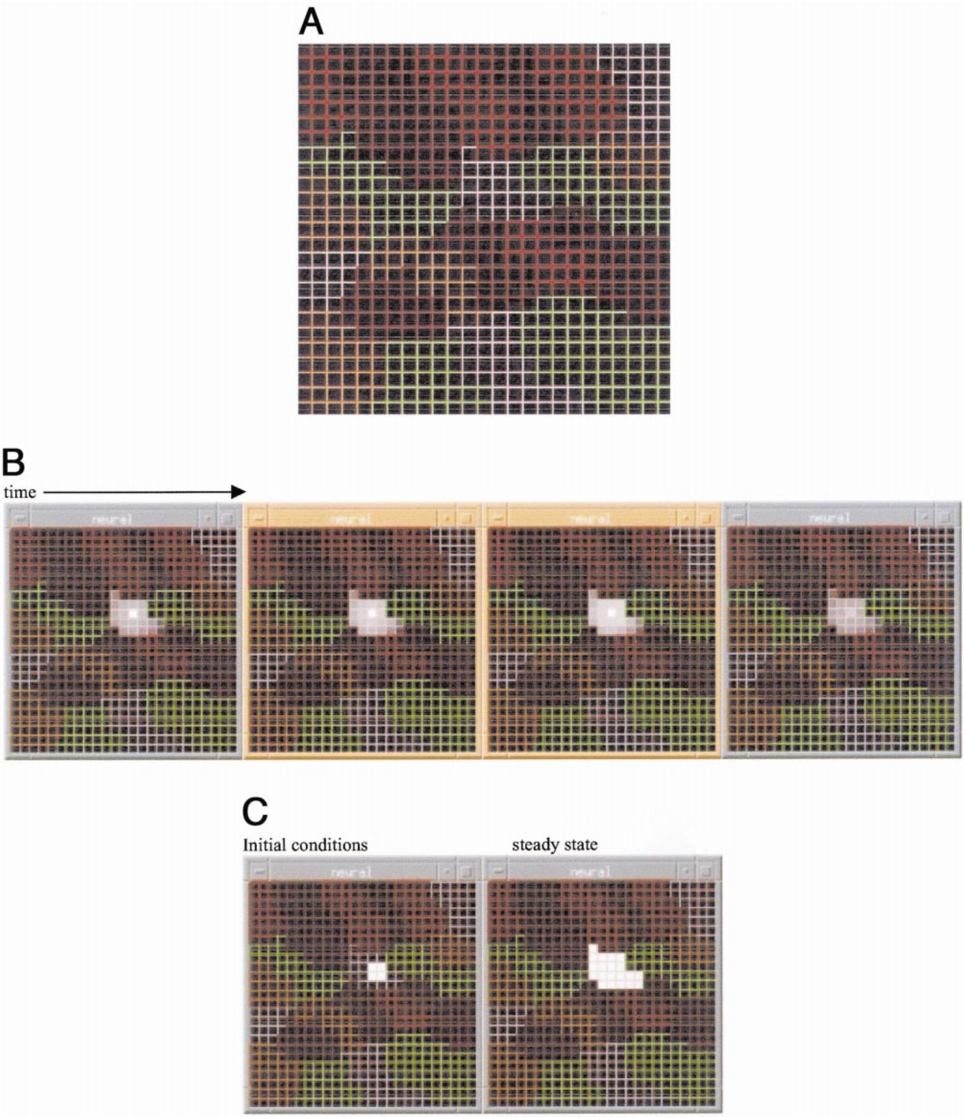


Fig. 4. Network with lateral patches with spatial modularity in two dimensions: (A) 25×25 network; colors indicate the modular systems of interconnected patches, patchy connections also depend on the relative distance between units, local connections are "Mexican hat". (B) Network responds to small punctate stimulus with an activity transient. (C) A larger punctate stimulus leads to sustained local response. Note that activity is restricted to one module. (D) Activating several units in the same patch-system leads to activation of that system, with progressive recruitment of units. (E) Now, we add an intervening stimulus in a competing patch: the previously activated sustained activity is robust, and inhibits the intervening stimulus.

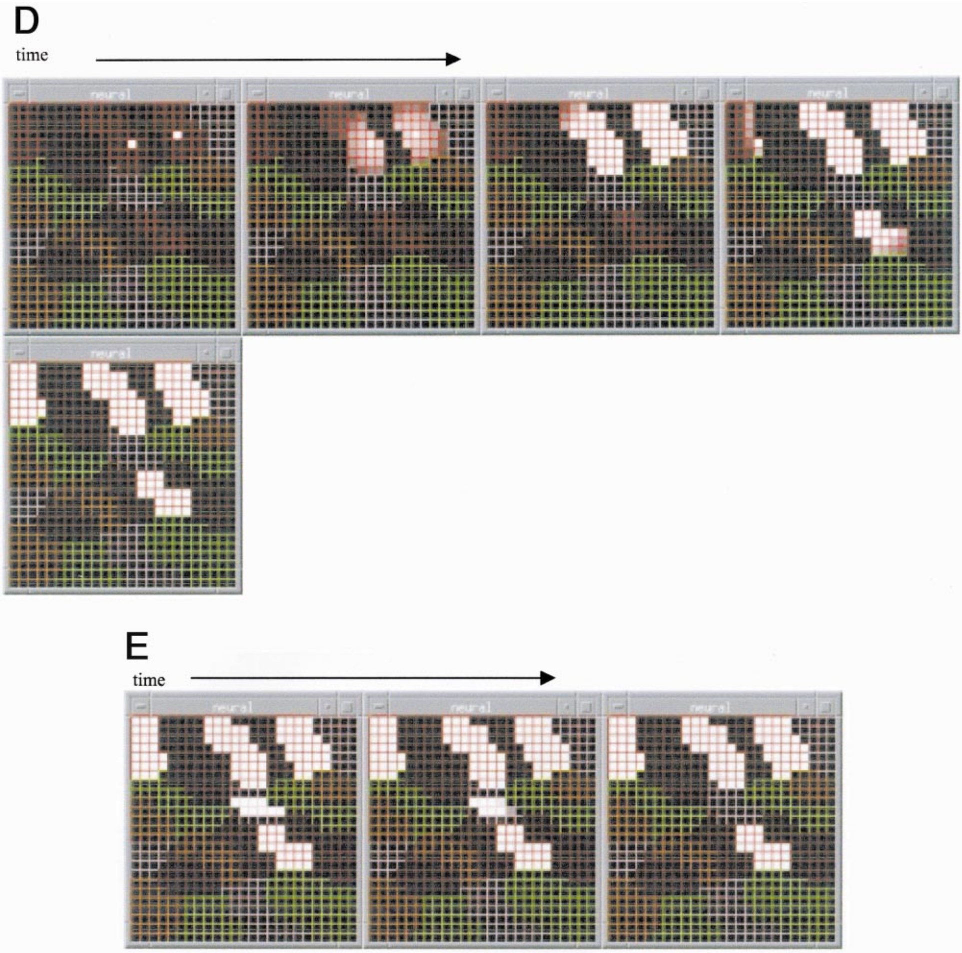


Fig. 4. (*continued*).

interact in a negative fashion and both pulses extinguish (Fig. 3C). If the second pulse is spaced farther from the focus of sustained activity, the original can be extinguished, by lateral inhibition, and a new bump appears (Fig. 3D).

In the case where the patchy lateral connections form distinct sub-systems, spatially restricted systems of multiple pulses of sustained activity are observed over a wide range of connection strength parameters (see Fig. 4). These include systems with a strong central pulse and side-bands restricted to the patch system, or activation of all patches within the patch system. The translation invariant local connectivity acts to restrict the spread of activity to other patch systems through lateral inhibition, while the local excitation partially recruits the immediate adjoining neurons. In fact, the behavior of the network with two or more initial stimuli can be quite complicated and may depend on the relative position, strength of the two stimuli, as well as the spatial characteristics of the lattice system.

In summary, we propose that the spatial organization of the patchy excitatory connections as well as the relative spatial organization of the afferents may have a significant effect on the spatial and temporal organization of sustained activity in the PFC. That is a single or spatially extended punctate excitatory stimulus may ignite bumps of sustained activity, as well as boost or extinguish previously occurring bumps depending on its size and position in relation to the connection patches.

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