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Interaction of synaptic modification rules within populations of neurons

(neuronal networks/ion channels/selection theories/memory)

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ABSTRACT **A theoretical account is given for long- and short-term changes in populations of neurons subject to independent rules for pre- and postsynaptic modification. The postsynaptic rule proposes that coactivated heterosynaptic inputs to a neuron alter the states of ion channels at a given synapse, thereby changing the susceptibility of these channels to local biochemical alterations. The resultant change in the population distribution of local channel states affects the postsynaptic potential produced at the synapse by subsequent inputs. This postsynaptic rule applies, in general, to short-term changes at specific individual synapses. In contrast, the presynaptic rule applies in general to long-term changes in the whole neuron, resulting in an altered probability of transmitter release. Because of neuroanatomical constraints, the presynaptic rule affects large numbers of synapses defined by the connectivity of that neuron and distributed nonspecifically over the population. We show that the combined action of the two independent rules upon populations of neurons arrayed in interconnected neuronal groups leads to consistent alterations of the probability of firing of certain circuits while maintaining variability in the response of the population to novel input. This "dual rules" model fulfills the requirements of the theory of neuronal group selection.**

In this paper, we propose to apply rules for both pre- and postsynaptic modifications to populations of neurons. Our aim is to account for alterations in synaptic strength consistent with the theory of neuronal group selection (1–4). This theory is based on the idea that the nervous system operates as a selective system (akin to natural selection in evolution)—i.e., during somatic time, particular groups of interconnected neurons are selected over other groups. Groups are delineated by the strengths of their synaptic connections; neurons within a group are more tightly coupled than neurons in different groups and tend to share functional properties such as receptive fields. Modification of synaptic efficacy serves as the principal mechanism for the selection of groups and for their competitive interactions.

According to the present proposal, postsynaptic modifications introduce specificity and context-dependence to short-term changes within a network, whereas presynaptic modifications effect long-term changes in the distribution of subsequent short-term modifications. We demonstrate that independent presynaptic and postsynaptic mechanisms acting together over the same period can account for (*i*) the existence of heterosynaptic as well as homosynaptic modifications; (*ii*) the occurrence of stable network changes over several different time scales; (*iii*) the coexistence of long- and short-term changes based upon synaptic modifications distributed within the same network; (*iv*) the requirement that long- and short-term modifications be related to each other despite independent biochemical mechanisms of pre- and postsynaptic change. The fundamental aspect of the present proposal is the analysis of the interaction of the two rules within a specified network. This analysis suggests that the two interacting mechanisms can only function adequately if the network is organized into neuronal groups.

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Postsynaptic Modifications

In discussing modifications of postsynaptic efficacy—i.e., changes in the potential generated at a particular synapse in response to a fixed quantity of transmitter—we consider both the contributions of the presynaptic inputs to the given synapse (homosynaptic inputs) and the contributions of the inputs to other synapses on the neuron (heterosynaptic inputs). The postsynaptic rule involves a family of local biochemical alterations of postsynaptic structures triggered by modifying substances or enzymes. In its most general form, this rule states that it is the positional pattern and timing of heterosynaptic inputs with respect to the homosynaptic inputs to a given synapse that governs the change in postsynaptic efficacy induced by a modifying substance at that synapse. Various mechanisms may be responsible for communication of heterosynaptic effects: intracellular diffusion of modifying substances or messengers, paracrine diffusion, cell surface modulation, and active or electrotonic conduction. Any one or more of these mechanisms are compatible with the postsynaptic rule and with our combined model of interactions of different rules within a network. Here we discuss only the last mechanism in detail because it is exemplary; its plausibility depends most critically on temporal and morphological constraints and many of these constraints apply to the other mechanisms.

In this specific example, homosynaptic inputs give rise to a substance that modifies local voltage-sensitive channels, but the susceptibility of these channels to modification is altered by heterosynaptic inputs (Fig. 1). We assume that the result of the biochemical modification is a change in the voltage-dependent probability of the channel switching between functional states—e.g., open, closed, inactivated. Such a modification would alter the PSP evoked by subsequent homosynaptic inputs, as well as the sensitivity to heterosynaptic inputs. The main assumption is that the local biochemical modifications are *state-dependent*: the probability of modifying a channel depends upon its functional state. Conducted voltages from other synapses will transiently alter the ratio of voltage-sensitive channels in the different possible functional states (hereinafter referred to as the channel population distribution) and thereby alter the number of channels susceptible to modification.

Our chief task in this section is to show that the magnitude of electrotonically conducted voltages can be sufficient to affect local modifications. Consider first the constraints on

Abbreviation: PSP, postsynaptic potential.

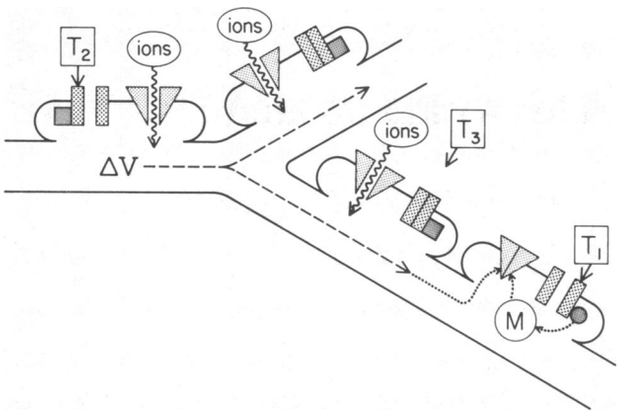

FIG. 1. Operation of one possible mechanism for the postsynaptic rule. Schematic of four synapses on a bifurcating dendritic arbor. Shaded rectangles represent open or closed receptor-operated channels (ROCs); shaded triangles represent voltage-sensitive channels (VSCs). Transmitter (T_1) binding to the lower right synapse activates the receptor-associated structure (shaded square = inactivated; shaded circle = activated) and begins a biochemical cascade producing modifying substance, M. M modifies local VSCs in the appropriate voltage-dependent state. Binding of transmitter, T_2, at the leftmost synapse leads to a local postsynaptic potential (PSP) (ΔV), which is electronically conducted to other synapses (dashed line), changing the state of their VSCs. The voltage change reaches the lower right synapse (dotted line) at a time when the concentration of modifying substance is high, leading to increased modification of the VSCs and a change in the channel population distribution. The other synapses are not modified because the relative timing of local transmitter binding (e.g., T_3 has not yet bound) and heterosynaptic inputs do not meet the permissive conditions.

the relative timing of inputs. Suppose that homosynaptic inputs lead to production of modifying substance persisting for a time t_p after a lag time of t_l and that conducted heterosynaptic inputs produce a local change in membrane potential persisting for a time t_v after a conduction delay of t_d. Then a necessary constraint on modification is that heterosynaptic inputs occur within a time window starting ($t_d + t_v - t_l$) before the homosynaptic inputs and ending at a time ($t_l + t_p - t_d$) after them. If either of these quantities is negative for a given synapse, then presentation of the inputs in that particular order will not lead to a modification.

The state-dependent aspect of the biochemical modification can be represented by the simple two-state model shown in Fig. 2, in which M is the concentration of modifying substance. A represents the active state and I is the inactive state of a channel; we suppose that only channels in the inactive state can be modified. Decay of the modification may

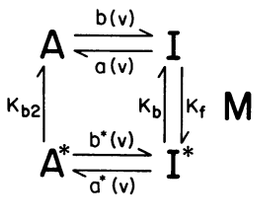

FIG. 2. Reaction scheme for biochemical modification. The diagram represents a simplified case in which channels are in one of only two states: an active state, A, or an inactive state, I. State-specific modification is illustrated by the conversion of I to I^* (but not A to A^*) in the presence of modifying substance, M. Modification changes the voltage-dependent opening and closing parameters, $a(V)$ and $b(V)$, to $a^*(V)$ and $b^*(V)$, respectively. The forward and backward rate constants for the modification step are K_f and K_b. Decay of modification can also occur from state A^* with rate constant K_{b2}, which may be assumed equal to K_b, implying that decay of modification is not state-dependent.

also be state-specific, but for simplicity we assume that it is not: thus, $k_{b2} = k_b$. We assume that the time constants for state transitions, $(a + b)^{-1}$, are small with respect to the time constant for biochemical modification, $(k_f + k_b)^{-1}$. We also assume that the channels are at their equilibrium distribution during the modification. Thus,

$$dN^*(t)/dt = K_f \cdot [I(t) \cdot M(t)] - K_b \cdot [I^*(t) + A^*(t)] \quad [1]$$

$$= K_f \cdot [(N - N^*) \cdot (b(V)/(a(V) + b(V))] \cdot M(t) - K_b \cdot N^*, \quad [2]$$

in which N is the total number of channels, N^* of which are modified. To find the steady-state fraction of modified channels we let $dN^*/dt = 0$ and get a Michaelis–Menten-like equation:

$$N^*/N = M \cdot (b/a + b) \,/\, (M \cdot (b/a + b) + K_b/K_f). \quad [3]$$

The plausibility of this particular postsynaptic mechanism rests upon the magnitude of the change in the PSP resulting from channel modifications. Consider the case in which a single species, k, of voltage-sensitive channels undergoes modification and suppose that N_k^* out of the total number, N_k, of channels of species k are modified. Then, assuming the change in capacitative currents can be neglected, the change in local current due to the modification is approximately given by

$$\Delta I_L = N_k^* \cdot (g_k^*(V) - g_k(V)) \cdot (V - E_k), \quad [4]$$

in which g_k is the voltage-dependent conductance; g_k^* is the modified conductance; and E_k is the reversal potential. Modification of the conductance will alter the local input impedance. However, since the resistance of the nonsynaptic region is unchanged, the impedance change is small compared to the change in the local current. To a first approximation, the relative change in the PSP is given by

$$\Delta V/V = (N_k^*/N_k) \cdot (\Delta g_k/g_k). \quad [5]$$

Values of N^*/N can be estimated from Eq. 3. By using values of $b(V)$ and $a(V)$ from the Hodgkin–Huxley model (5) and assuming that $M \approx 0.1(K_b/K_f)$, a depolarization of 20 mV gives a change in the value of N^*/N on the order of 0.05 for the inactivated state of the regenerative sodium channels. We can estimate $\Delta g/g$ to be between 1 and about 20, based on reports regarding shifts in current–voltage curves due to biochemical modification (6, 7) and therefore the change in the PSP might be as little as 5% and as much as 100% of its original magnitude.

These considerations suggest that postsynaptic modification depends upon (*i*) the number and intensity of heterosynaptic inputs occurring during the modification period, (*ii*) the timing of the heterosynaptic inputs relative to the homosynaptic inputs, (*iii*) the spatial distribution of synapses on the postsynaptic cell (attenuations and conduction delays), and (*iv*) the types of transmitters, receptors, and ion channels present. These factors apply not only to the particular electrotonic mechanisms detailed here but also to the other mechanisms (diffusion of modifier, cell surface modulation) through which the postsynaptic rule might also operate.

Presynaptic Modifications

We now consider changes in presynaptic efficacy, the amount of neurotransmitter released in response to depolarization of a presynaptic terminal. The key feature of the presynaptic rule is a long-term shift in the level of transmitter

release at all presynaptic terminals of a neuron as a result of large fluctuations in the time-averaged instantaneous values of presynaptic efficacy (4). The regulation of transmitter release depends upon a number of incompletely understood complex cell-biological processes and therefore the present model will be pitched at the level of the macroscopic observables—facilitation and depression. We have considered certain aspects of the molecular processes elsewhere (4).

Several separate macroscopic components of increased transmitter release (8), and of decreased transmitter release (9), have been reported. To simplify the model, we make use of only a single component of increased release, a generic "facilitation," and a single component of "depression." We use the same formalism employed by Magleby and Zengel (8) to model facilitation,

$$dF_i/dt = \varepsilon \cdot S_i(t) - \lambda \cdot F_i(t), \quad [6]$$

in which $F_i(t)$ is the degree of facilitation in a presynaptic terminal, i; λ is the decay time constant; $S_i(t)$ is the firing rate of the neuron at time t; and ε is the increase in facilitation per spike.

Synaptic depression is described by a similar equation,

$$dD_i(t)/dt = \kappa \cdot \xi_i(t) \cdot S_i(t) - \beta \cdot D_i(t), \quad [7]$$

in which $D_i(t)$ is the degree of depression in the presynaptic terminal; β is the decay time constant; $\xi_i(t)$ is the presynaptic efficacy of neuron i; and κ is the constant of proportionality between release and depression. The first term indicates that depression increases linearly with the amount of release and that substantial levels of evoked release can only occur at times when significant depolarization has occurred, presumably due to diffusion of calcium away from the release site during the inter-spike interval. The second term represents the decay of depression due to replenishment of depleted transmitter, reactivation of release sites, or return to equilibrium of whatever molecular process is actually involved.

We assume that long-term modification takes the form of a shift in the baseline amount of transmitter release, ξ_i^0. The fundamental presynaptic equation relates the amount of release to this baseline level and the degree of facilitation and depression,

$$\xi_i(t) = \xi_i^0(1 + F_i(t))^3 (1 - D_i(t)). \quad [8]$$

Note that F can range between 0 and an arbitrary maximal value, while D ranges from 0 to 1. It is conceivable that aside from ξ^0, changes in other parameters (ε, λ, κ, or β) could underlie long-term modifications. Eq. **8** resembles those studied by Magleby and Zengel (8) and could be generalized to include products of all components of facilitation and depression. These workers found that raising the facilitatory term to the third power resulted in a better fit to their data. We adopt this nonlinearity, which also agrees with the cubic relationship found by Smith *et al.* (10), for the dependence of PSP magnitude on presynaptic calcium current.

Long-term modification of ξ_i^0 results from biochemical responses to time-averaged fluctuations, both facilitatory and depressive, in the presynaptic strength $\xi_i(t)$; this response could include changes in gene expression with synthesis of controlling proteins, increased transmitter synthesis, or changes in the ultrastructure of release sites. This baseline change alters the dynamical behavior of the neuron in response to subsequent inputs. The system nevertheless has an interesting stability property: stronger synapses will be harder to strengthen and easier to weaken. As ξ_i^0 increases, the degree of facilitation is unchanged (Eq. **6**), but the amount of transmitter released increases, leading to a greater degree of depression (Eq. **7**) for a similar sequence of stimulation. The stability property then follows from the choice that large net facilitatory fluctuations give rise to an *increase* in ξ_i^0, while net depressive fluctuations result in a *decrease* in ξ_i^0.

The main consequence of the presynaptic rule is that all terminals of the presynaptic neuron are influenced, regardless of which correlated inputs (following the postsynaptic rule) were responsible for the change in ξ_i^0. Thus, the consequences of presynaptic changes are temporally stable but are distributed by axonal ramifications over a large number of synapses throughout the network.

Network Interactions of Pre- and Postsynaptic Modifications

The assumption that the mechanisms regulating presynaptic and postsynaptic modifications are independent raises the central issue of this paper: how the two types of change will interact to produce functional changes in network behavior. To explore this question, we examine short-term postsynaptic modifications and long-term presynaptic modifications in order to demonstrate that (*i*) short-term changes in a neuronal group lead to long-term changes primarily within that group; (*ii*) group structure is sufficient to ensure that long-term changes arising from short-term changes in a particular group will differentially affect future short-term changes in that particular group; and (*iii*) long-term changes increase the variability of subsequent short-term changes.

To simplify the analysis, we consider networks consisting of groups of only a single type of neuron with a single type of transmitter and receptor. We assume that the attenuation of voltages between any pair of synapses on a neuron is identical. For postsynaptic modification to occur, we require only a statistical relationship between coactive inputs and ignore the details of timing and voltage attenuation factors—i.e., we consider only the mixed second-order moment between the weighted activities of the heterosynaptic inputs and the time-averaged homosynaptic input. These simplifications will diminish the specificity of the actual postsynaptic rule; nonetheless, the analysis shows that this weaker version is sufficient to address the above three points relating the rules to group structure.

We take for the simplified, formal version of the postsynaptic rule

$$\Delta\eta_{ij} = C_1 \cdot \left\langle \eta_{ij}\xi_j \overline{S}_j(t) \cdot \sum_k \eta_{ik}\xi_k S_k(t) \right\rangle - C_2 \cdot (\eta_{ij} - \eta_{ij}^0), \quad [9]$$

in which $\langle \cdot \rangle$ represents a time average, and η_{ij} is the strength of the postsynaptic connection from neuron j to neuron i, $\Delta\eta_{ij}$ is the change of η_{ij}, and η_{ij}^0 is its baseline value; ξ_j is the presynaptic strength from neuron j, $S_j(t)$ is the activity of neuron j at the time t, and $\overline{S}_j(t)$ is the same activity averaged over some time period; and C_1 and C_2 are constants. The terms in the equation can be appreciated by reference to Fig. 3*A*. The first term is the mixed second-order moment at time (t) between the amount of modifying substance present at the jth synapse and the magnitude of the conducted voltages (depolarizing or hyperpolarizing) from all other synapses on the cell. The second term in Eq. **9** represents the short-term decay of the modification. We have taken the net strength to be the product of post- and presynaptic strengths $\eta \cdot \xi$. This is equivalent to assuming that transmitter and receptors interact with first-order kinetics. We assume that ξ changes slowly with respect to η, and η changes slowly with respect to changes in activity S; thus,

$$\Delta\eta_{ij} = C_1 \cdot \eta_{ij}\xi_j \sum_k \eta_{ik}\xi_k \langle \overline{S}_j(t) \cdot S_k(t) \rangle - C_2 \cdot (\eta_{ij} - \eta_{ij}^0). \quad [10]$$

Now let us assume that neurons are segregated into groups. Let capital letters—e.g., I, J, K—denote groups,

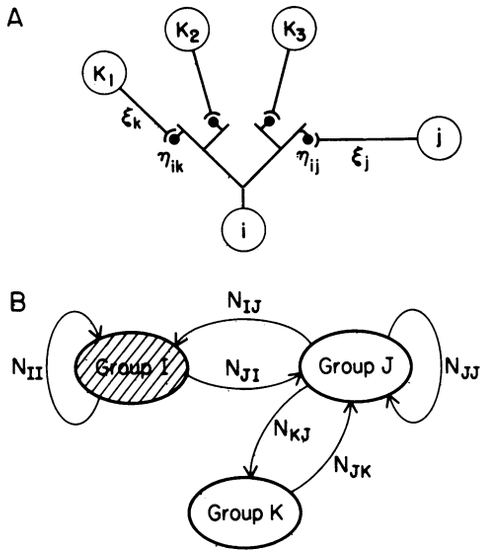

FIG. 3. Schemes for assessing interaction of the two rules. (*A*) Simplified schematic of postsynaptic interactions. Circles represent neurons. Neuron i receives inputs from neuron j and from neurons k_1, k_2, k_3. Change in postsynaptic strength η_{ij} depends on the statistical relationship between the timing of the inputs from j with respect to other inputs to i as given by Eq. **9** in the text. (*B*) Classes of connections among groups. Ellipses represent neuronal groups and arrows represent intra- or inter-group connections. A long-term change in presynaptic strengths of cells in group I differentially affects subsequent short-term changes in the postsynaptic strengths of these various classes of connections (see text).

rather than individual neurons, let N_{IJ} be the number of connections from group J to group I, and let N_{II} be the number of intra-group connections in group I. All connections between the same pair of groups are assumed to have the same pre- and postsynaptic strengths. We are interested in postsynaptic modifications of the connections both within and between various groups as shown in Fig. 3*B*. The modifications of connections from any group M to any group L (where M, L, and H are dummy variables) are given by

$$\Delta\eta_{LM} = C_1 \cdot \eta_{LM}\xi_M \sum_H N_{LH}\eta_{LH}\xi_H\langle\bar{S}_M(t)\cdot S_H(t)\rangle - C_2\cdot(\eta_{LM} - \eta^0_{LM}). \quad [11]$$

Consider that, due to short-term fluctuations, a long-term presynaptic modification has occurred in one group, for example, in group I: $\xi_I \rightarrow \xi_I + \delta_I$, in which δ_I is a constant. Long-term modifications in other groups or in several groups could be treated similarly. We assume that the modification in group I does not significantly affect the statistical relationship between firing of neurons in different groups. Then substituting into Eq. **11** and keeping only first-order terms in δ_I, we find that after a long-term modification in group I, the change in subsequent short-term modifications of the various classes of connections between groups (Fig. 3*B*) is given by:

$$\Delta^2\eta_{LM} \equiv \Delta'\eta_{LM} - \Delta\eta_{LM} = \delta_I C_1[N_{LI}\eta_{LI}\eta_{LM}\xi_M\langle\bar{S}_M(t)\cdot S_I(t)\rangle + \begin{cases} 0 & \text{if } M \neq I \\ \eta_{LI}\sum_H N_{LH}\eta_{LH}\xi_H\langle\bar{S}_I(t)\cdot S_H(t)\rangle] & \text{if } M = I. \end{cases} \quad [12]$$

There are three conditions jointly sufficient to guarantee that η_{II} is the biggest change—i.e., that short-term changes in the group experiencing the long-term modification are maximally affected:

$$(i)\ N_{II}\eta_{II} > N_{JI}\eta_{JI}$$

$$(ii)\ \langle\bar{S}_I(t)\cdot S_I(t)\rangle > \langle\bar{S}_J(t)\cdot S_I(t)\rangle$$

$$(iii)\ \sum_H N_{LH}\eta_{LH}\xi_H\langle\bar{S}_I(t)\cdot S_H(t)\rangle \approx 0.$$

These conditions are (*i*) connectivity within a group is stronger than between groups, (*ii*) neurons in the same group fire together more often than neurons in different groups, and (*iii*) on the average, input from different groups is statistically unrelated. Within the context of this simplified model, these conditions define the necessary attributes of a neuronal group (1–4)—i.e., a set of tightly connected cells that fire predominantly together and constitute the smallest neural unit of selection. Note that these conditions are *not* met if the network is randomly connected.

Given these group conditions, we can rank the classes of connections in a hierarchy according to the magnitude of the change in subsequent short-term modifications. The intrinsic connections of group I ($\Delta^2\eta_{II}$) are always affected to the greatest extent; connections between other groups ($\Delta^2\eta_{JK}$) are always affected the least; and the three remaining classes of connections are affected to different relative extents depending upon the relative values of N_{II}/N_{JI}, $\eta_{II}/\eta_{JI}/\eta_{JJ}$, and $\langle\bar{S}_I S_I\rangle/\langle\bar{S}_J S_I\rangle$. We would usually expect $\Delta^2\eta_{JJ}$ to be the smallest of the three, $\Delta^2\eta_{IJ}$ to be the largest for a few select groups J that are highly correlated in input with group I, but $\Delta^2\eta_{JI}$ to be largest for most other groups J.

This analysis indicates that the organization of a network into neuronal groups provides a sufficient condition for long-term changes in group I to give rise to a hierarchy of changes in subsequent short-term modifications among various groups, but with the greatest change occurring in group I itself. It can be shown both formally and by using a computer simulation of the model presented here (unpublished data) that a long-term change in one group increases the variability in subsequent patterns of short-term changes both in that group and in all other groups that receive connections from that group. This leads to competition between groups: the differential enhancement of particular short-term changes in each group due to long-term changes in that group is opposed by nonspecific variation of all short-term changes in that group resulting from long-term changes in other groups. This generation of variability in the population is a requirement that must be met by any selection theory of nervous system function.

Discussion

Several consequences of the present model are worthy of note. The postsynaptic rule, even in its weakened version (see Fig. 3*A*), differs from the Hebb rule (11). In the present rule, the correlated firing of neuron j and neuron i is neither necessary nor sufficient to change the postsynaptic strength, η_{ij}, of the connection from j to i. Rather, η_{ij} is modified when the time-averaged firing of neuron j is temporally associated with the firing of a large number of other neurons, k, which synapse onto neuron i. In this way, synaptic alterations are governed by population effects in the network. Indications of such effects have been reported in several preparations (12, 13).

Our analysis of the postsynaptic mechanism suggests that instead of dividing inputs into only two classes—excitatory and inhibitory—and thinking of neuronal operations in Boolean terms, we might rather consider a kind of "transmitter

logic" in which each transmitter (in association with its postsynaptic partners) can lead to characteristic modifications of synapses receiving only certain other transmitters and located on only certain other parts of the dendritic tree. Such a system would generate within the same network a great diversity of classes of synaptic modifications, all specific, but varying with respect to magnitude, time course, origin, and target.

With regard to the presynaptic mechanism, there are two reasons for postulating that the long-term modification occurs on a total cell basis rather than independently at individual synapses. (*i*) We have assumed that presynaptic modifications are dependent upon the firing of the cell; although a single neuron may have several quasi-independent functional domains both for output as well as for input (14), in general most presynaptic terminals of a neuron fire together. (*ii*) We implicitly assume that certain long-term modifications must involve a change in gene expression (6). Given the inherent time lags in the production and transport of newly synthesized gene products, there is no currently known way to route the new material selectively to individual synapses.

Although both modification rules discussed here can act synchronously (but independently), one or the other may predominate in different regions of the brain depending upon the anatomical or pharmacological differences. Moreover, a more general treatment than the one presented here would allow changes at several overlapping time scales in both pre- and postsynaptic populations.

The critical predictions of the present model are as follows. (*i*) Pre- and postsynaptic modifications occur independently through separate mechanisms and in no case will be found to be contingent only upon correlated firing across individual synapses. (*ii*) Each class of biochemical modifications will primarily affect those channels or receptors that are in a particular functional or conformational state. Such modifications will lead to measurable changes in the magnitude and time course of the PSP. (*iii*) Long-term presynaptic modifications occur on a cell-wide basis. (*iv*) Short- and long-term modifications are differentially distributed over the same neuronal population. (*v*) The presence of neuronal groups guarantees that long-term modifications differentially enhance the short-term changes that led to those modifications. If any of these predictions is not fulfilled, the model is at best inadequate and at worst incorrect.

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