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Runaway Synaptic Modification in Models of Cortex: Implications for Alzheimer's Disease

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Abstract—*In models of cortex, the spread of activity along previously strengthened synapses during synaptic modification can result in an exponential growth of a large number of synaptic connections, here termed runaway synaptic modification Analysis of this phenomenon may provide a theoretical framework for describing the initiation and progression of the cortical neuronal degeneration found in Alzheimer's disease Here, the dynamics of learning in a cortical model are described, focusing on the exponential growth produced by allowing synaptic transmission at previously modified synapses during learning of a new pattern It is shown that suppression of synaptic transmission during learning can prevent the strengthening of undesired connections, while allowing desired connections to grow rapidly However, an imbalance of cortical parameters, or storage of overlapping patterns in excess of capacity, can lead to interference during learning and runaway synaptic modification This runaway synaptic modification can progress between different regions These phenomena are discussed with reference to the neuropathological evidence on the initiation and progression of neuronal degeneration in Alzheimer's disease and the behavioral evidence on associated memory deficits*

Keywords—Associative memory, Stability, Hippocampus, Learning, Alzheimer's disease, Interference.

1. INTRODUCTION

In models of cortex, synaptic transmission during synaptic modification can lead to instability in the form of exponential growth of synaptic strength (Grossberg, 1987; Kohonen, 1988; von der Malsburg, 1973). This instability is referred to as runaway synaptic modification. If modifiable synapses can influence their own growth in real cortical networks, then physiological mechanisms for preventing this instability must exist. Here the phenomenon of runaway synaptic modification and possible physiological mechanisms for preventing this instability will be described analytically and in simulations of cortical function. This phenomenon will be discussed in relation to the neuropathological features of Alzheimer's disease.

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Different strategies for maintaining stability during learning have been used in different cortical models. In models with associative memory function, the most common technique consists of suppressing normal activation dynamics within the network during learning (Amit, 1988; Anderson, 1972, 1983; Hopfield, 1984; Kohonen, 1972, 1988). Although the spread of activity within these models forms the basis of memory function during the recall phase, this spread of activity is not permitted during the learning of new memories. More sophisticated approaches were used to maintain stability without suppression of activation dynamics in early models with associative memory function (Grossberg, 1967, 1970, 1972a). These models used modifications of the learning rule such as normalization and the decay of synaptic strength.

Associative memory models that suppress normal activation dynamics during learning do so in a variety of ways. In linear associative memory models, the activity of units within the model is clamped to the input pattern during learning, ignoring intrinsic synaptic transmission (Amari, 1977; Anderson, 1972; McClelland & Rumelhart, 1988), or the spread of activation is assumed slow relative to the speed of learning (Kohonen et al., 1977; Kohonen, 1988). In most attractor neural network models, the learning rule is

computed for the patterns separately from the network (Amit, 1988; Amit, Evan, & Abeles, 1990; Hopfield, 1984), or during application of a "strong external field" (Amit, 1988).

Previously, no biological justification has been provided for this difference in the spread of activation during recall and learning. In fact, most biological theories of synaptic modification depend upon synaptic transmission at the synapse being modified (Brown, Kairiss, & Keenan, 1990; Gustafsson and Wigstrom, 1988). Therefore, biologically realistic associative memories must allow for some synaptic transmission during learning. Although most associative memory models have focused on the dynamics of recall (Amit, 1988; Hertz, Krogh, & Palmer, 1991; Hopfield, 1984), the dynamics of learning must also be considered (Grossberg, 1970, 1972a). As described here, synaptic transmission during learning can enhance the growth of desired connections, but it can also lead to interference between patterns during learning, which may result in runaway synaptic modification.

Recent work has suggested a new neurophysiological mechanism for the suppression of activation dynamics during learning (Hasselmo, Anderson, & Bower, 1991, 1992; Hasselmo, 1993). The cortical neuromodulator acetylcholine has been shown to selectively suppress excitatory synaptic transmission at intrinsic synapses (i.e., synapses between pyramidal cells within one cortical region), while allowing afferent fiber synaptic transmission (i.e., transmission at axons entering the cortex) to operate at full strength (Hasselmo & Bower, 1992). Here this effect is analyzed in terms of learning dynamics, and it is shown that it can completely prevent interference during learning when coupled with intrinsic inhibition, a threshold of synaptic modification, or decay of synaptic strength. This effect of acetylcholine is consistent with behavioral evidence suggesting a role of acetylcholine in memory function (Ghonheim & Mewaldt, 1975; Hagan & Morris, 1989; Kopelman, 1986). However, this mechanism can break down at a certain capacity determined by the overlap between stored patterns, beyond which runaway synaptic modification will occur.

Runaway synaptic modification can also occur at modifiable synapses undergoing self-organization (von der Malsburg, 1973; Grossberg, 1976, 1987; Linsker, 1988; Miller, Keller, & Stryker, 1989). Associative memory function and self-organization are distinguished here on a single basis: the extent to which postsynaptic activity depends upon the modifiable synapses. Modifiable synapses with associative memory function are not the predominant influence on postsynaptic activity during learning, which is separately influenced by other input often referred to as a UCS (Amari, 1977; Anderson, 1972; Grossberg, 1967, 1970, 1972a; Kohonen, 1972, 1988). Associative memory synapses store associations between the presynaptic and postsynaptic activity elicited by elements of external (afferent) input patterns. In contrast, modifiable synapses undergoing self-organization are the predominant influence on postsynaptic activity during learning (von der Malsburg, 1973; Grossberg, 1976, 1987; Linsker, 1988; Miller et al., 1989). Thus, rather than storing an association between elements of externally presented patterns, these synapses form new representations of the presynaptic activity. Instability of self-organizing synapses is usually prevented by placing various constraints on synaptic weight through normalization that ensures the sum of synaptic weights or the sum of squares of synaptic weights remains constant (von der Malsburg, 1973; Linkser, 1988; Miller et al., 1989; Oja, 1989), or by relying upon gated decay of synaptic strength coupled with inhibitory competition between neurons (Grossberg, 1976; Carpenter & Grossberg, 1987)

The phenomenon of runaway synaptic modification may prove relevant to describing the initiation and progression of the neuronal degeneration associated with Alzheimer's disease. Alzheimer's disease has been the focus of clinical research for many years, with a wide range of evidence showing it is associated with a severe impairment of memory function in a range of tasks (Corkin, 1982; Kopelman, 1985; Morris & Kopelman, 1986). Neuropathological research shows that the disease involves neuronal degeneration selective to certain cortical structures (Arnold et al., 1991; Ball, 1972; Braak & Braak, 1991; Brun & Gustafson, 1976; Hyman et al , 1984). One of the main markers for this degeneration is the development of neurofibrillary tangles, which are associated with a breakdown in the normal neurofilament structure of neurons and are often left as remnants of cells that have died. Evidence suggests that the neurofibrillary tangles first appear and attain the highest density in cortical regions associated with memory function, including layer II of the entorhinal cortex, region CA1 of the hippocampus, and the subiculum (Arriagada & Hyman, 1990; Arriagada, Marzloff, & Hyman, 1992; Braak & Braak, 1991; Hyman et al., 1984; Ulrich, 1982). In later stages of the disease, neuronal degeneration appears to progress into regions of association cortex, following the established patterns of intracortical connectivity (Arnold et al., 1991; Pearson et al., 1985). While a vast range of competing theories of the etiology of the syndrome have been proposed, few of them have focused on accounting for the striking initial anatomical specificity of the neuronal degeneration for regions implicated in memory function, and the subsequent progression along anatomical pathways. The analysis of the breakdown of the essential mechanisms of cortical memory function presented here suggests a possible framework for describing the initiation and progression of neuronal degeneration in Alzheimer's disease.

2. ASSOCIATIVE MEMORY FUNCTION

Runaway synaptic modification can occur in a range of associative memory architectures. Here I describe interference during learning for a simple linear associative memory, using a Hebbian learning rule. The network described here is presented in Figure 1. This is a linear heteroassociative memory with the input unit activity in region 1 represented by the activity vector ${}_1\boldsymbol{a}(t)$, output unit activity in region 2 represented by the activity vector ${}_2\boldsymbol{a}(t)$, and connections from units in region 1 to units in region 2 with strengths represented by the matrix $\boldsymbol{W}$. Neither the afferent input nor the strength of connections goes below zero.

The network stores associations between input and output patterns. For each association q, the input pattern presented to region 1 is represented by ${}_1\boldsymbol{a}^{(q)}$ and the output pattern presented to region 2 is represented by ${}_2\boldsymbol{a}^{(q)}$. (Each pattern consists of n active lines where $a_i^{(q)} = 1$, and all other lines with $a_i^{(q)} = 0$.)

The activation rule for the network describes the activity ${}_2\boldsymbol{a}$ as a sum of the input to this region ${}_2\boldsymbol{a}^{(q)}$ and the spread of activity from ${}_1\boldsymbol{a}$ along the connections $\boldsymbol{W}$

$$ {}_2\boldsymbol{a}(t+1) = {}_2\boldsymbol{a}^{(p)} + \boldsymbol{W}\,{}_1\boldsymbol{a}(t). \tag{1} $$

Note that this is a system with a single synchronous cycle of update, rather than the long-term asynchronous settling of models based on the spin-glass analogy. Previous work shows that associative memory models are sensitive to the spread of activation during learning with asynchronous dynamics as well (Hasselmo et al., 1991).

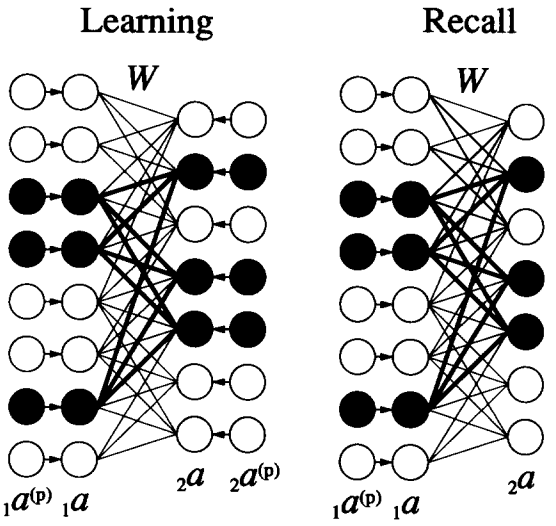

FIGURE 1. A schematic representation of the simple heteroassociative network presented here, with a set of connections $\boldsymbol{W}$ between region 1 neurons (with activity ${}_1\boldsymbol{a}$) and region 2 neurons (with activity ${}_2\boldsymbol{a}$). During learning, afferent patterns of activity influence the activity of region 1 (input ${}_1\boldsymbol{a}^{(p)}$) and region 2 (input ${}_2\boldsymbol{a}^{(p)}$), and the connections $\boldsymbol{W}$ are modified according to a Hebbian learning rule. During recall, only the input to region 1 (${}_1\boldsymbol{a}^{(p)}$) is presented. Activity spreads along the connections to result in region 2 activity closely resembling the previously associated pattern (${}_2\boldsymbol{a}^{(p)}$).

For simple Hebbian learning within this network, the connections are strengthened in proportion to the outer product of the presynaptic activity ${}_1\boldsymbol{a}$ and postsynaptic activity ${}_2\boldsymbol{a}$. If we assume synaptic modification depends upon the presynaptic activity reaching the presynaptic terminal, which is assumed in most theories of long-term potentiation (Brown et al., 1990; Gustafsson & Wigstrom, 1988), then we must use a learning rule incorporating postsynaptic activity at time $t + 1$, with presynaptic activity at time t.

$$ \Delta\boldsymbol{W}(t+1) = \frac{1}{n}\,{}_2\boldsymbol{a}(t+1)\,{}_1\boldsymbol{a}(t)^T \tag{2} $$

where n is the number of active lines, and the superscript T represents the transpose of the vector. In most associative memory models, recall dynamics are suppressed during learning. Thus, the connection strengths in these models are modified based on the activities ${}_1\boldsymbol{a}$ and ${}_2\boldsymbol{a}$ being clamped to the specific desired patterns. That is, if the effect of synaptic transmission is ignored, for each association an input pattern will be clamped on the input units $[{}_1\boldsymbol{a}(t) = {}_1\boldsymbol{a}^{(q)}]$ and a specific output pattern will be clamped on the output units $[{}_2\boldsymbol{a}(t) = {}_2\boldsymbol{a}(t+1) = {}_2\boldsymbol{a}^{(q)}]$. In this case, over m different associations, the final pattern of connectivity will take the form:

$$ \boldsymbol{W} = \frac{1}{n}\sum_{q=1}^{m} {}_2\boldsymbol{a}^{(q)}\,{}_1\boldsymbol{a}^{(q)T}. \tag{3} $$

This is a familiar form of the Hebbian learning rule (Hertz et al., 1991; Kohonen, 1988), and is approximated by the simulation results shown on the right in Figure 2.

3. INTERFERENCE DURING RECALL

Interference during recall occurs when overlapping patterns have been stored in the network. Consider a case during recall, when the input pattern p to region 1 is presented $[{}_1\boldsymbol{a}(t) = {}_1\boldsymbol{a}^{(p)}]$, but the associated output pattern p to region 2 has not been presented. In this case, the activation rule for region 2 from equation 1 takes the form

$$ {}_2\boldsymbol{a}(t+1) = \boldsymbol{W}\,{}_1\boldsymbol{a}(t) = \left(\frac{1}{n}\sum_{q=1}^{m} {}_2\boldsymbol{a}^{(q)}\,{}_1\boldsymbol{a}^{(q)T}\right){}_1\boldsymbol{a}^{(p)} $$

$$ = \frac{1}{n}({}_1\boldsymbol{a}^{(p)T}\,{}_1\boldsymbol{a}^{(p)})\,{}_2\boldsymbol{a}^{(p)} + \frac{1}{n}\sum_{q\neq p}^{m}({}_1\boldsymbol{a}^{(q)T}\,{}_1\boldsymbol{a}^{(p)})\,{}_2\boldsymbol{a}^{(q)}. \tag{4} $$

Since $(1/n)({}_1\boldsymbol{a}^{(p)T}\,{}_1\boldsymbol{a}^{(p)}) = 1$, the first term gives the proper recall of the associated output pattern ${}_2\boldsymbol{a}^{(p)}$. However, the second term shows the interference from other stored patterns, proportional to the dot product between the input pattern p and every other input pat-

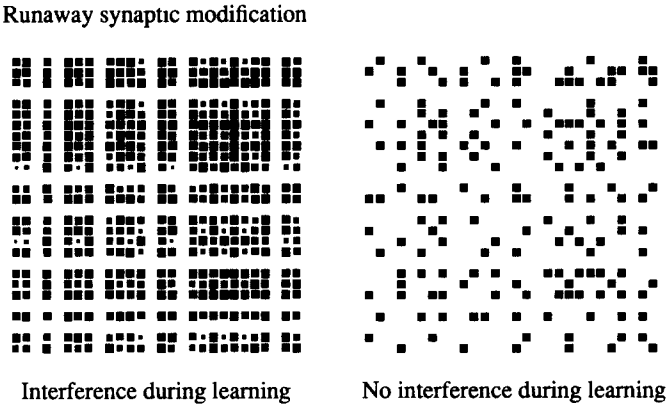

FIGURE 2. Runaway synaptic modification. Final connectivity of the simulation shown in Figure 3 is presented with size of black squares representing the strength of individual connections. Note that runaway synaptic modification due to interference during learning in the network causes strengthening of a large number of connections [resulting in connectivity similar to that described in eqn (14)]. By comparison, far fewer connections are strengthened in a simulation without interference during learning (Figure 6), with connectivity similar to that described in eqn (3).

tern q. This interference term has been described previously in associative memory models with the term "crosstalk" (Kohonen, 1972; Hertz et al., 1991). I will refer to this effect as interference during recall. Note that it depends only on the direct overlap between the stored patterns.

4. INTERFERENCE DURING LEARNING

The recall of other stored patterns can interfere with learning, based on the same activation equation presented above. However, by occurring during learning, this type of interference can enhance subsequent interference and have an even more serious effect on the accuracy of learning within the network. As noted above, with certain exceptions (Grossberg, 1970, 1972a; Kohonen, 1988) this problem has been prevented in most models by ignoring the activation rule during learning, that is, ignoring the effect of synaptic transmission during synaptic modification. However, no physiological justification for ignoring the spread of activity during learning has been presented previously. Interference during learning can be seen quite clearly if we combine the equations for recall and learning [eqns (1) and (2)] with ${}_1\boldsymbol{a}(t) = {}_1\boldsymbol{a}^{(p)}$.

$$\Delta \boldsymbol{W}(t+1) = {}_2\boldsymbol{a}(t+1)\,{}_1\boldsymbol{a}(t)^T = ({}_2\boldsymbol{a}^{(p)} + \boldsymbol{W}\,{}_1\boldsymbol{a}^{(p)})\,{}_1\boldsymbol{a}^{(p)T} \quad (5)$$

In this case, assuming $\boldsymbol{W}^{(1)} = {}_2\boldsymbol{a}^{(1)}\,{}_1\boldsymbol{a}^{(1)T}$, association 1 will interfere with the learning of association 2 as follows

$$\Delta \boldsymbol{W}^{(2)} = [{}_2\boldsymbol{a}^{(2)} + ({}_1\boldsymbol{a}^{(1)T}\,{}_1\boldsymbol{a}^{(2)})\,{}_2\boldsymbol{a}^{(1)}]\,{}_1\boldsymbol{a}^{(2)T}. \quad (6)$$

Thus, the amount of interference is proportional to the overlap between the input patterns being learned, as represented by the scalar product (dot product) ${}_1\boldsymbol{a}^{(1)T}\,{}_1\boldsymbol{a}^{(2)}$. I will refer to this form of interference during learning as first-order interference because it is due to the direct overlap between two input patterns. However, once the interference during learning term has been added to the connection matrix, subsequent learning can involve higher-order interference. For instance, for a third pattern stored, both first- and second-order interference can appear, as represented here

$$\Delta \boldsymbol{W}^{(3)} = [{}_2\boldsymbol{a}^{(3)} + ({}_1\boldsymbol{a}^{(2)T}\,{}_1\boldsymbol{a}^{(3)})\,{}_2\boldsymbol{a}^{(2)} + ({}_1\boldsymbol{a}^{(1)T}\,{}_1\boldsymbol{a}^{(2)})({}_1\boldsymbol{a}^{(2)T}\,{}_1\boldsymbol{a}^{(3)})\,{}_2\boldsymbol{a}^{(1)}]\,{}_1\boldsymbol{a}^{(3)T}. \quad (7)$$

In this case, patterns 1 and 3 may be orthogonal, but as long as they both overlap with pattern 2, higher-order interference during learning will occur. Ultimately, learning of each new pattern can suffer from interference during learning with any previously learned pattern either by direct first-order interference, or through higher-order interference, resulting in the final connectivity matrix

$$\boldsymbol{W} = \sum_{p=1}^{m} \Big[{}_2\boldsymbol{a}^{(p)} + \sum_{q_1<q_2<q_3<\;<q_m<p}^{p-1} ({}_1\boldsymbol{a}^{(q_1)T}\,{}_1\boldsymbol{a}^{(q_2)}) \times ({}_1\boldsymbol{a}^{(q_2)T}\,{}_1\boldsymbol{a}^{(q_3)}) \;\ldots ({}_1\boldsymbol{a}^{(q_m)T}\,{}_1\boldsymbol{a}^{(p)})\,{}_2\boldsymbol{a}^{(q_1)} \Big]\,{}_1\boldsymbol{a}^{(p)T}, \quad (8)$$

where m is the order of interference. This suggests that, when higher-order interactions are taken into account, interference can spread to all patterns stored within the network as long as there is no group of patterns that is entirely orthogonal to other patterns being stored. This effect can be seen quite readily in simulations of cortical associative memory function (see Appendix for description of model). If synaptic transmission is allowed during learning, the network rapidly displays runaway synaptic modification of all connections between units activated by at least one pattern, resulting in confounding of all patterns during recall, as shown in Figure 3.

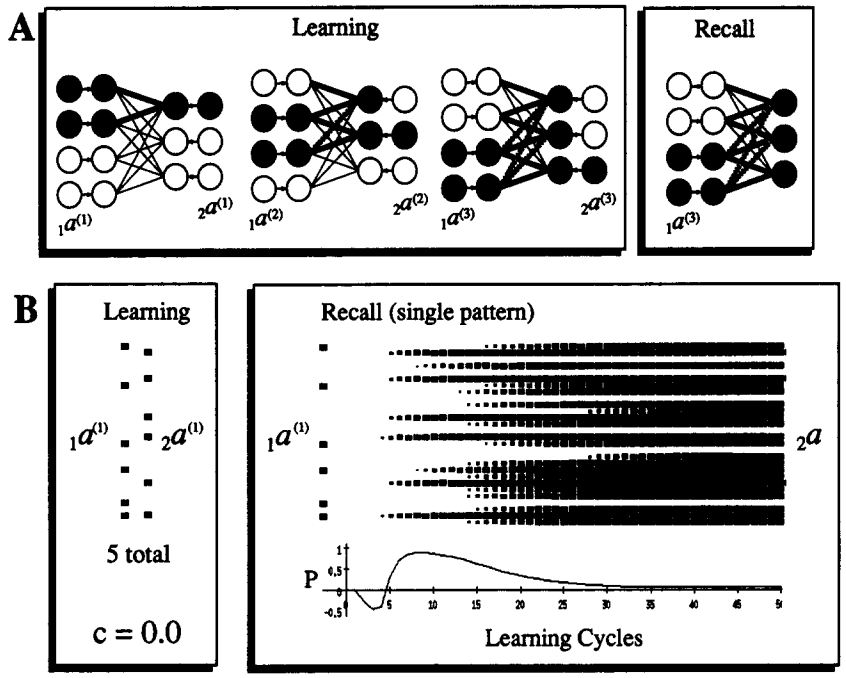

FIGURE 3. (A) Schematic diagram of interference during learning in associative memory function. During learning of the first association, no interference occurs. However, during learning of a second and third association, the spread of activity along previously strengthened connections results in strengthening of additional, undesired connections, shown with broken lines. (B) Interference during learning in a simulation of cortical associative memory function. On the left, the afferent patterns presented to regions 1 and 2 during learning of association 1 are shown. Learning is alternated between this and four other associations stored in the network. On the right, the recall of the network in response to the input pattern in region 1 is shown after each cycle of learning. Note that as learning progresses, interference causes the network to respond to the input to region 1 with components of all patterns stored in region 2. Accompanying graph shows the performance measure *P* that was used to evaluate the recall of all five memories after each cycle of learning (see Appendix). This shows an early increase followed by a decrease to values below 0 due to interference.

5. EXPONENTIAL GROWTH OF SYNAPTIC CONNECTIONS

The effect of synaptic transmission during synaptic modification can also be described by solving the learning rule as a differential equation. This shows that when connections can enhance their own growth, the result is an exponential strengthening of synapses unless other factors in the learning rule such as decay (Grossberg, 1970; Kohonen, 1988) or constraints on total synaptic strength (Grossberg, 1967, 1969; Linsker, 1988; von der Malsburg, 1973; Miller et al., 1989; Oja, 1989) are sufficient to overcome this effect. In the notation provided here, application of a Hebbian learning rule will allow the connection W_{ij} to grow based on a differential equation combining the activation rule [see eqn (1)] and the learning rule [see eqn (2)]:

$$\frac{dW_{ij}}{dt} = \eta\left({}_2a_i^{(p)} + \sum_{k=1}^{n} W_{ik}{}_1a_k^{(p)}\right){}_1a_j^{(p)} \qquad (9)$$

where η is the learning gain and n is the number of units in the network. For learning of a single stored pattern with initial values $W_{ik}(0)$, this is a system of nonhomogeneous linear differential equations with constant coefficients that can be solved on a row-by-row basis. The coefficient matrix ${}_1a_k^{(p)}\,{}_1a_j^{(p)}$ is the outer product of the input patterns. Thus, the matrix has rank 1, and the system has one nonzero eigenvalue equal to the trace of the outer product matrix (Strang, 1988). The system has the following solution

$$W_{ij} = Z_{ij}(e^{t/\tau_j} - 1) + W_{ij}(0) \qquad (10)$$

where

$$Z_{ij} = \left[{}_2a_i^{(p)} + \sum_k^n W_{ik}(0){}_1a_k^{(p)}\right] \Big/ \left(\sum_k^n {}_1a_k^{(p)}\right)$$

and

$$\tau_j = \left[\eta_1 a_j^{(p)}\left(\sum_k^n {}_1a_k^{(p)}\right)\right]^{-1}.$$

Note that the effect of connections on their own growth is to cause exponential strengthening with a time constant reciprocal to the eigenvalue, which is proportional to the sum of the active input lines $\sum_k {}_1a_k^{(p)}$. Thus, patterns with more active elements will more rapidly strengthen connections. Each new pattern learned by the network will have as the initial conditions for this equation the pattern of connectivity associated with storage of previous patterns. The interaction be-

tween the new pattern p and initial conditions set by previously learned patterns takes the form

$$\sum_k W_{ik}(0)\,{}_1a_k^{(p)} \cong \sum_k \left(\sum_{q=1}^{M} {}_2a_i^{(q)}\,{}_1a_k^{(q)} \right) {}_1a_k^{(p)}$$

$$= \sum_{q=1}^{M} \left[{}_2a_i^{(q)} \sum_k^n ({}_1a_k^{(q)}\,{}_1a_k^{(p)}) \right] \quad (11)$$

For learning of the first pattern, or learning of orthogonal input patterns, eqn (11) is equal to zero. In this case, eqn (10) takes the form:

$$W_{ij} = \frac{{}_2a_i^{(p)}}{(\sum_k {}_1a_k^{(p)})} \left\{ \exp\left[\eta\, {}_1a_j^{(p)} \left(\sum_k {}_1a_k^{(p)} \right) t \right] - 1 \right\} + W_{ij}(0) \quad (12)$$

Thus, for the first pattern, or for orthogonal patterns, learning only occurs at synapses on neurons in region 2 that are directly activated by the afferent input pattern (${}_2a_i \neq 0$).

However, for nonorthogonal patterns, eqn (11) is nonzero. In this case, previously learned patterns interfere with the learning of new patterns, allowing strengthening of undesired connections onto neurons not receiving direct postsynaptic afferent input ${}_2a_i = 0$. In this case, strengthening of these undesired connections takes the form:

$$W_{ij} = \frac{[\sum_k^n W_{ik}(0)\,{}_1a_k^{(p)}]}{(\sum_k {}_1a_k^{(p)})} \left\{ \exp\left[\eta\, {}_1a_j^{(p)} \left(\sum_k {}_1a_k^{(p)} \right) t \right] - 1 \right\} + W_{ij}(0) \quad (13)$$

In these equations, as in eqns (7) and (8), interference during learning progresses in proportion to the overlap between input patterns in region 1. It is shown explicitly that the positive feedback due to connections enhancing their own growth causes these additional connections to grow exponentially. In real cortical networks and in nonlinear simulations, the growth of undesired connections may be limited at some saturating value equal to the saturating value of desired connections. However, higher-order relationships between patterns spreads interference more widely, as shown in eqn (8), and the positive feedback due to connections enhancing their own growth causes these connections to grow to their saturating value. Thus, even when the interference due to higher-order overlap is initially very small, this effect causes the interference due to higher-order overlap to grow exponentially, until the network suffers from very severe interference.

6. RUNAWAY SYNAPTIC MODIFICATION AND ALZHEIMER'S DISEASE

The results in the previous two sections show that when higher-order interactions are taken into account, interference during learning can gradually spread to all patterns stored within the network, as long as there is no group of patterns that is entirely orthogonal to other patterns being stored. Once undesired connections are first strengthened, they can grow exponentially to their saturating value. The combination of these two effects will be referred to as runaway synaptic modification. Ultimately, with repeated learning of interfering patterns, as shown in Figure 2, the final connectivity of the network can approximate:

$$\boldsymbol{W} = \sum_{p=1}^{m} \sum_{q=1}^{m} {}_2\boldsymbol{a}^{(q)}\,{}_1\boldsymbol{a}^{(p)T}. \quad (14)$$

Thus, after runaway synaptic modification, presentation of any one pattern p to region 1 recalls all patterns q stored in region 2, as shown in Figure 3. The connectivity becomes very dense, as seen on the left side of Figure 2, which shows simulation results approximating eqn (14) versus eqn (3). With runaway synaptic modification, the total number of connections modified in the network is on the order of n^2m^2 (where n is the average number of neurons activated in each region by each pattern, and m is the number of patterns stored in the network). The number of connections modified during learning without interference [eqn (3)] is on the order of n^2m. Thus, runaway synaptic modification results in an increase in the number of synapses being strengthened that is proportional to the number of patterns stored in the network, m. This difference in connectivity can be seen in Figure 2, which shows the connectivity of the network trained in Figure 3 [eqn (14)], versus a network trained without any interference during learning [eqn (3)].

This large increase in the number of connections modified would place considerable demands on the mechanisms of synaptic modification within a cortical associative memory. These increased demands might have serious effects on the function of the network. A breakdown in function of this type may even be involved in the neuronal degeneration found in Alzheimer's disease. For example, the excessive strengthening of excitatory synaptic connections may result in excitotoxic effects on neurons. The neuronal degeneration in Alzheimer's disease has been suggested to arise from excitotoxic effects (Beal, 1992; Lawlor & Davis, 1992; Pomara et al., 1992)

Alternately, runaway synaptic modification would place considerable additional demands on both presynaptic and postsynaptic mechanisms of synaptic enhancement, including the production of new proteins, the transport of structural components along axons and dendrites, and the overall metabolism of the cells. This might account for some of the characteristics of neuronal degeneration found in Alzheimer's disease. The build-up of amyloid precursor protein (Tanzi, George–Hyslop, & Gusella, 1991; Selkoe, 1991) might reflect excessive production of a protein for maintaining synaptic contacts. Many forms of this protein contain an

extracellular protease inhibitor domain (Hyman et al., 1992) that could play a role in maintaining synaptic connections, and there is evidence that increased expression of this protein occurs in regions undergoing the initial degeneration of Alzheimer's disease (Roberts et al., 1993). In addition, the abnormal phosphorylation of tau protein (Grundkeiqbal et al., 1986; Harrington et al., 1991) and the development of neurofibrillary tangles might reflect a breakdown in axonal transport mechanisms under the excessive demands of runaway synaptic modification. In particular, this latter framework could explain the fact that development of neuritic plaques is not necessarily associated with development of tangles in the same region, but in several cases appears associated with development of tangles in afferent regions (Arnold et al., 1991; Hof & Morrison, 1990). That is, in some areas, the primary neuronal degeneration appears to be presynaptic. The excessive demands on presynaptic neurons to strengthen additional connections due to runaway synaptic modification might explain this characteristic of Alzheimer's disease neuropathology.

7. SUPPRESSION OF SYNAPTIC TRANSMISSION AND RUNAWAY SYNAPTIC MODIFICATION

The cortex must have some mechanism for preventing interference during learning and runaway synaptic modification. As noted above, many previous associative memory models have avoided interference during learning by preventing the spread of activation during learning, but no physiological mechanism has been described for this widely used modeling feature.

Recent work (Hasselmo et al., 1991, 1992; Hasselmo, 1993) has described a possible neurophysiological mechanism for preventing the development of interference during learning. Experimental evidence from brain slice preparations of the olfactory cortex (Figure 4) show that the neuromodulator acetylcholine selectively suppresses synaptic transmission between pyramidal cells within the cortex, and has almost no effect on the afferent input to the region (Hasselmo & Bower, 1992). Other neuromodulators may have a similar effect on synaptic transmission. If applied selectively during learning but not recall, this suppression can prevent interference during learning. Runaway synaptic modification can also be prevented by incorporating strong decay of synaptic strength coupled with a threshold linear output function (Grossberg, 1970, 1972).

To analyze the effect of suppression and of other cortical parameters on learning, we can modify eqn (9) to include the suppression of synaptic transmission ($1 - c_{sup}$), a homogeneous level of postsynaptic inhibition (H), a threshold of synaptic modification (Ω), and a decay term (γ) gated by presynaptic activity. In addition, because this simplified network has a feedforward, heteroassociative structure, we can include the effect of an output function $g(a)$ for presynaptic neurons, that could include a threshold for output. All of these parameters are reasonable within the scope of existing physiological evidence, and the value of cholinergic suppression of synaptic transmission has been directly derived from experimental data (Hasselmo & Bower, 1992).

When combined with the activation equation, the learning equation takes the form:

$$\frac{dW_{ij}}{dt} = \eta\Big[{}_2a_i^{(p)} + (1 - c_{sup}) \sum_{k=1}^{n} W_{ik} g({}_1a_k^{(p)}) - H - \Omega - \gamma W_{ij}\Big] g({}_1a_j^{(p)}). \quad (15)$$

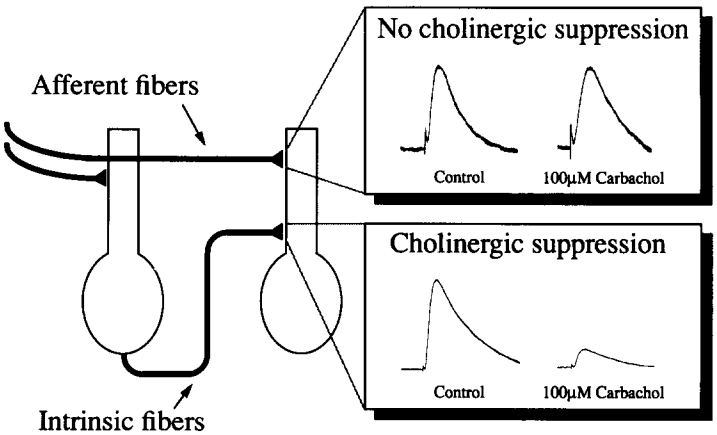

FIGURE 4. Cholinergic suppression of synaptic transmission. Experimental results from brain slice preparations of olfactory cortex show selective suppression of intrinsic and associational fiber synaptic transmission but not afferent fiber synaptic transmission by cholinergic agonists (Hasselmo & Bower, 1992). Synaptic potentials elicited by stimulation of fibers arising from the olfactory bulb and terminating in the superficial layer of piriform cortex do not change in the presence of the cholinergic agonist carbachol (100 μM). However, synaptic potentials elicited by stimulation of fibers arising from within piriform cortex or adjacent cortical regions show over 70% suppression in the presence of carbachol (100 μM).

This yields the solution

$$W_{ij} = Z_{ij}(e^{t/\tau_j} - 1) + W_{ij}(0) \quad (16)$$

where

$$Z_{ij} = \frac{{}_2a_i^{(p)} + (1 - c_{\text{sup}}) \sum_k^n W_{ik}(0) g({}_1a_k^{(p)}) - \gamma W_{ij}(0) - (H + \Omega)}{(1 - c_{\text{sup}}) \sum_k^n g({}_1a_k^{(p)}) - \gamma}$$

and

$$\tau_j = \left(\eta\left\{(1 - c_{\text{sup}})\left[\sum_k^n g({}_1a_k^{(p)})\right] - \gamma\right\} g({}_1a_j^{(p)})\right)^{-1}$$

Note that for the desired connections, as c_{sup} goes to 1 with $\gamma = 0$, the equation approaches the linear growth of W dependent on the strength of afferent input to region 1 and region 2

$$W_{ij} = \eta[{}_2a_i^{(p)} - (H + \Omega)]{}_1a_j^{(p)}t. \quad (17)$$

In contrast, for undesired connections [where ${}_2a_i^{(p)} = 0$], as c_{sup} goes to 1 and $\gamma = 0$, $\tau \to \infty$ and the equation will maintain a steady state at the starting point of $W(0)$. However, setting c_{sup} to 1 is physiologically unrealistic for two reasons. First, experimental evidence shows that suppression of synaptic transmission does not go above an average maximum of about 70% (Hasselmo & Bower, 1992). Second, most theories of synaptic modification depend upon synaptic transmission at the synapse being modified (Gustafsson & Wigstrom, 1988; Brown et al., 1990); thus, the learning rule should have a gain factor containing the term for suppression. In this case, setting c_{sup} to 1 would completely shut off learning.

However, due to the additional terms H and Ω in the equation, it is not necessary to completely suppress synaptic transmission in order to prevent interference during learning. This can be seen if we consider eqn (16) for modification of undesired connections [where ${}_2a_i^{(p)} = 0$].

$$W_{ij} = \frac{[(1 - c_{\text{sup}}) \sum_k^n W_{ik}(0) g({}_1a_k^{(p)}) - \gamma W_{ij}(0) - (H + \Omega)]}{(1 - c_{\text{sup}}) \sum_k g({}_1a_k^{(p)}) - \gamma} \times \left(\exp \eta\left\{\left[(1 - c_{\text{sup}}) \sum_k g({}_1a_j^{(p)}) - \gamma\right] g({}_1a_j^{(p)})t\right\} - 1\right) + W_{ij}(0) \quad (18)$$

As can be seen from this equation, the additional postsynaptic terms H and Ω allow interference during learning to be prevented with only partial suppression of synaptic transmission. Here, H and Ω do not differ in their mathematical features because inhibition is represented as a constant. However, inhibition H will normally vary depending upon input activity (feedforward inhibition) and activity within the network (feedback inhibition). A full consideration of these effects is beyond the scope of the present treatment.

The postsynaptic threshold of synaptic modification was motivated by evidence from physiological studies of long-term potentiation suggesting a difference between the threshold for neuronal output and the threshold for synaptic modification (Gustafsson & Wigstrom, 1988). However, previous analytical work (Grossberg, 1970; Grossberg & Pepe, 1971) suggests that a postsynaptic threshold of synaptic modification causes some inaccuracies in the stored representation of afferent input, particularly for analog valued input. As an alternative to a postsynaptic threshold, cholinergic suppression can also completely prevent the growth of undesired connections when combined with either gated or ungated decay of synaptic strength, which have been used to maintain stability during learning in previous associative memory models (Grossberg, 1970, 1972a)

Equation 18 and simulations show that the decay of synaptic strength gated by presynaptic activity can maintain stability if it is sufficiently strong to cause τ to take a negative value. In this case, desired connections grow with an asymptotic value determined by the afferent input, and undesired connections decay exponentially to zero, as shown in Figure 7. A similar effect is seen with ungated decay of synaptic strength, which causes exponential decay of all synapses not receiving postsynaptic afferent input (Grossberg, 1970, 1972a). Mathematically, cholinergic suppression of synaptic transmission is analogous to a decay gated by both pre- and postsynaptic activity and restricted to values less than 1. In fact, cholinergic suppression (c) decreases the values of decay (γ) necessary to obtain exponential decreases in the strength of undesired connections and asymptotic growth of desired connections. Because the network being analyzed in this section is a single-layer heteroassociative (feedforward) network, the output threshold only affects the values of the afferent input to neurons in region 2, not the subsequent spread of activity within the network. However, in networks with autoassociative or multilayer structure, having a nonzero output threshold also helps to restrict the spread of interference (Grossberg & Pepe, 1970, 1971; Hasselmo et al., 1992; Hasselmo, 1993). In fact, a decrease in this parameter allows greater interference between stored patterns, and has been suggested as a possible model for behavioral features of schizophrenia such as the loosening of associations (Grossberg & Pepe, 1970)

For the network being discussed here, the proper combination of parameters necessary to prevent the spread of interference into undesired connections (and runaway synaptic modification) can be determined by setting the coefficient Z or the reciprocal of the time constant τ of eqn (16) to zero or less

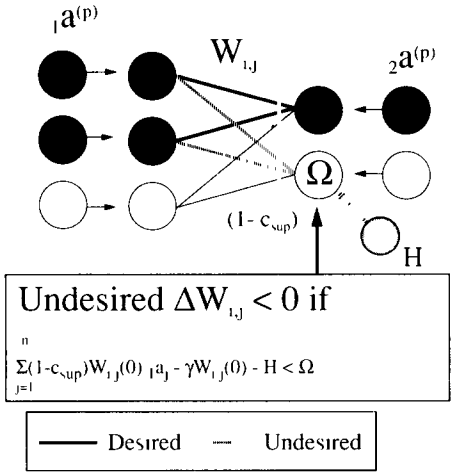

FIGURE 5. Schematic representation of the conditions necessary to prevent interference during learning [eqns (19) and (20)]. Interference during learning involves strengthening of connections to units in region 2 that do not receive direct afferent input (undesired connections shown with dashes). Interference during learning can be prevented if the total excitatory input to these units along previously strengthened connections [$W_{ij}(0)_1a_j$] is suppressed ($1 - c_{sup}$) sufficiently to bring the postsynaptic activity below the level of postsynaptic inhibition (H), the threshold of synaptic modification (Ω), and the decay of synaptic strength (γW_{ij}).

$$\left[(1 - c_{sup}) \sum_k^n W_{ik}(0) g({}_1a_k^{(p)}) - \gamma W_{ij}(0) - (H + \Omega)\right] \leq 0 \quad (19)$$

or,

$$\left(\eta\left\{(1 - c_{sup})\left[\sum_k^n g({}_1a_k^{(p)})\right] - \gamma\right\} g({}_1a_j^{(p)})\right) \leq 0. \quad (20)$$

Thus, as shown in Figure 5, with sufficient suppression of synaptic transmission to bring the spread of activity within the network below the level of inhibition, the threshold of synaptic modification or the decay of synaptic strength, interference during learning can be prevented. In simulations, it can be shown that incomplete suppression of synaptic transmission can prevent the progression of runaway synaptic modification, as shown in Figure 6 (see Appendix for description of model). Thus, for $Z \leq 0$ or $1/\tau \leq 0$ when $_2a_i^{(p)} = 0$, interference during learning will not progress.

An important factor in the above equation is the amount of overlap between the stored patterns. If we substitute the relation from eqn (11) into eqn (19) and solve for c_{sup}, we obtain a notion of the condition that

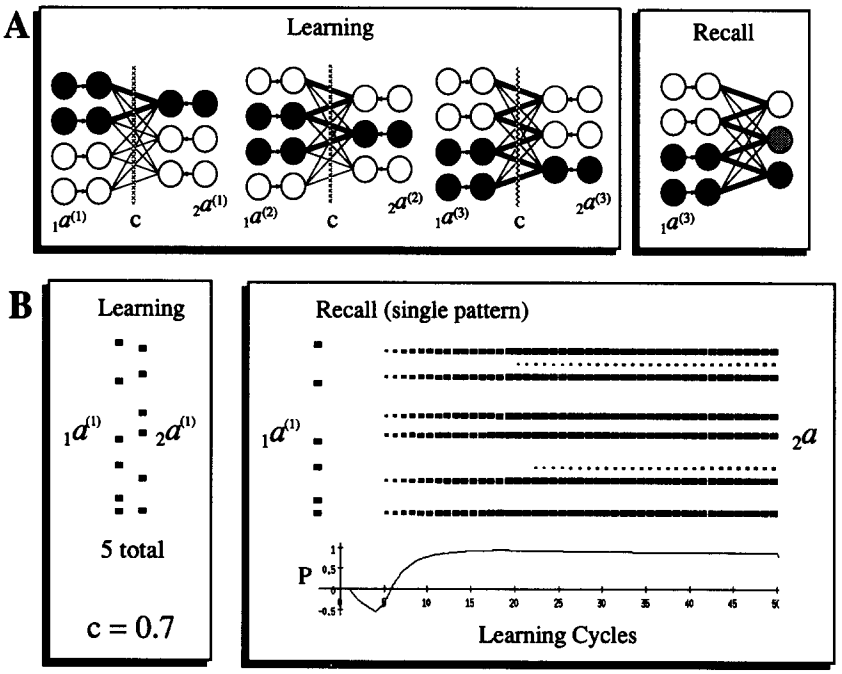

FIGURE 6. (A) Schematic diagram showing that suppression of synaptic transmission during learning prevents the spread of activity along previously strengthened connections. This allows strengthening of only desired connections (connections between neurons receiving direct afferent input). (B) Suppression of synaptic transmission during learning prevents interference in a simulation of cortical associative memory function. On the left, the afferent patterns presented to regions 1 and 2 during learning of association 1 are shown. On the right, the recall of the network in response to the input pattern in region 1 is shown after each cycle of learning. Note that as learning progresses, the network begins to recall the correct associated pattern in region 2, with only slight interference during recall due to first-order overlap with other patterns. The accompanying graph shows that with suppression, the performance measure P increases to a stable level over 0.8.

feedback regulation of cholinergic modulation would need to satisfy for each neuron i:

$$\frac{(H+\Omega)+\gamma\left(\sum_{q=1}^{M} {}_2a_i^{(q)}\,{}_1a_j^{(q)}\right)}{\sum_{q=1}^{M}\left[{}_2a_i^{(q)}\sum_{k}^{n}({}_1a_k^{(q)}\,{}_1a_k^{(p)})\right]} \geq 1-c_{sup}. \quad (21)$$

Note that as the number of patterns stored within the network increases, the sum of the scalar products of the new pattern p with all previously stored patterns q will increase. If the value of c_{sup} is fixed, then this can be seen as a capacity measure for the network, above which interference during learning can result in runaway synaptic modification. In addition, a network with a high correlation between previously stored patterns and new patterns being stored will be more sensitive to runaway synaptic modification. Finally, once a single pattern starts to cause runaway synaptic modification, by strengthening additional undesired connections it enhances the likelihood of additional patterns causing interference during learning.

8. REGULATION OF CHOLINERGIC MODULATION

Equation 21 shows the level of cholinergic suppression necessary to prevent interference from other stored patterns during learning. If cholinergic modulation maintains this relationship, runaway synaptic modification can be prevented. Therefore, it might be expected that feedback mechanisms regulating the cholinergic innervation of the cortex would keep cholinergic modulation within this range over the long term. In addition, as noted above, this analysis assumes that acetylcholine is primarily released during learning of new stimuli, and not during recall of previously learned information. Thus, there must be some short-term mechanism for regulating the cholinergic modulation of cortical structures depending upon whether the afferent stimulus is novel or familiar.

Cholinergic innervation of cortical structures arises from nuclei of the basal forebrain. The medial septum and vertical limb of the diagonal band of Broca innervate the hippocampus, the horizontal limb of the diagonal band of Broca innervates the olfactory cortex and bulb, and the magnocellular nucleus basalis of Meynert innervates neocortical structures (Mesulam et al., 1983). Among the influences on these nuclei are inhibitory (GABAergic) inputs from the nucleus accumbens, which may serve to downregulate the cholinergic modulation of cortex (Sarter, Bruno, & Dudchenko, 1990). The inhibitory regulation of the basal forebrain may be influenced by output from the hippocampus entering the lateral septum and the nucleus accumbens. It is unlikely that a signal as specific as eqn (21) could be computed by the feedback to the basal forebrain, but an approximation of this term could take the form of a measure of the variance of the activity levels within a cortical region. The response to unfamiliar patterns will cause little activation, while the progression of runaway synaptic modification will cause activity that is too broadly distributed. In both cases, low variance would occur in situations where it would be desirable to increase cholinergic modulation. In contrast, effective recall of specific patterns would be expected to strongly activate a specific subset of neurons, resulting in a higher variance. The neurophysiological and computational characteristics of the feedback mechanisms that modulate cholinergic suppression of synaptic transmission remain an important topic for future research.

9. THE INITIATION AND PROGRESSION OF ALZHEIMER'S DISEASE

If the neuronal degeneration in Alzheimer's disease is due to runaway synaptic modification, then eqn (16) may provide a theoretical framework for describing the initiation and speed of progression of Alzheimer's disease. If $Z > 0$ and $1/\tau > 0$ for $A_i = 0$ in eqn (16), runaway synaptic modification will be initiated. Once runaway synaptic modification occurs, it will progress with a time course determined by the size of the coefficient Z and the time constant of the exponential τ, as shown in eqn (16) and illustrated in Figure 7. Figure 7 shows the growth of undesired connections (${}_2a_i^{(p)} = 0$) with different values of γ, c_{sup}, and H. For larger values of c_{sup}, the growth of desired connections approaches a linear increase, and the growth of undesired connections becomes increasingly slow. If the neuronal degeneration in Alzheimer's disease is due to runaway synaptic modification, then the equation for growth of undesired connections might provide a rough mathematical approximation of the initiation and speed of progression of Alzheimer's disease.

This theoretical framework for describing the neuronal degeneration of Alzheimer's disease is largely neutral with respect to specific etiological factors. Essentially, anything that affects the balance of the different cortical parameters described in eqns (19) and (20) will affect the propensity for initiation of runaway synaptic modification. Thus, runaway synaptic modification could be due to a chronic decrease in the levels of cortical inhibition H, the threshold of synaptic modification Ω, the decay of synaptic strength γ, or the suppression of synaptic transmission c_{sup}. In this framework, the initiation of runaway synaptic modification is also sensitive to the amount of overlap between the input activities, which increases with number of patterns stored or the average overlap between patterns, as shown in eqn (21). Thus, this equation can be seen as a capacity measure for the network, above

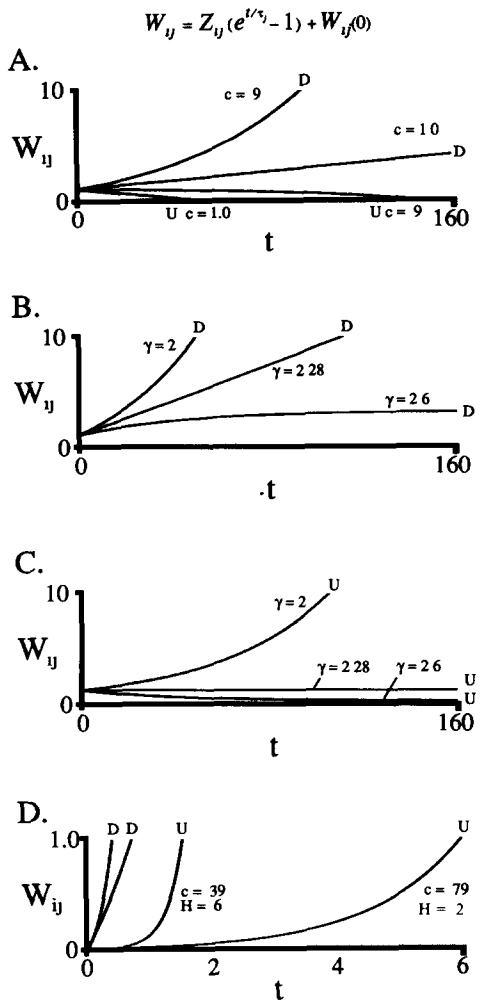

FIGURE 7. (A) Change in strength of desired and undesired connections W_{ij} computed from eqn (16) with $\Sigma_k^n {}_1a_k^{(p)} = 6$, $g({}_1a_k^{(p)}) = \tanh({}_1a_k^{(p)})$, $W(0) = 1.0$, $H = 0.1$, and $\Omega = 0$. With c_{sup} set to 1.0, desired connections (D) grow linearly due to pre- and postsynaptic activity remaining constant, and undesired connections (U) decrease linearly due to postsynaptic activity being below the threshold Ω. With c_{sup} set to 0.9, undesired connections still decay, and desired connections grow exponentially. (B) Change in desired synaptic connections with the same conditions except $c_{sup} = 0.5$, $H = 0.0$, and $\gamma > 0$. The addition of decay allows desired connections to grow asymptotically for values of γ satisfying $(1 - c_{sup}) \Sigma_k^n g({}_1a_k^{(p)}) = 2.28 < \gamma$. Thus, for $\gamma = 2.6$ growth is asymptotic, for $\gamma = 2.28$ growth is linear, and for $\gamma = 2$ growth is exponential. (C) Change in undesired synaptic connections with the same conditions as in (B). For $\gamma = 2.6$ synapses decay exponentially, for $\gamma = 2.28$ synaptic strength remains constant, and for $\gamma = 2$ growth is exponential. Thus, for insufficient decay relative to synaptic suppression, runaway synaptic modification can occur. (D) Growth of desired and undesired connections W_{ij} computed from eqn (16) with $\Sigma_k^n W_{ik}(0) {}_1a_k^{(p)} = 6$, $\Omega = 0$, $\gamma = 0$, and c_{sup} and H set to different values such that $Z = 0.01$ but τ changes value. For larger values of c_{sup}, τ is larger, and growth of undesired connections is slower. For smaller values of c_{sup}, τ is smaller, resulting in a more rapid growth of undesired connections. A greater imbalance of cortical parameters resulting in larger Z also results in a more rapid growth of undesired connections. These differences in the balance of cortical parameters might underlie the earlier appearance and possible faster progression of presenile dementia.

which interference during learning can result in runaway synaptic modification.

Sensitivity to runaway synaptic modification depends upon the capacity for Hebbian modification of synapses. Without Hebbian synaptic modification, eqn (15) depends only upon the presynaptic activity ${}_1a_j^{(p)}$, in which case the solution takes the form $W_{ij}(t) = {}_1a_j^{(p)} t$. In this case, interference during learning does not occur. In addition, the speed of progression of runaway synaptic modification depends upon the gain of the learning rule. Thus, for η that is small, the time constant τ in eqn (16) will be large, and the progression of runaway synaptic modification will be correspondingly slow. Where the gain of the learning rule is large, runaway synaptic modification will progress more rapidly.

These characteristics could explain the selectivity of neuronal degeneration in Alzheimer's disease for those regions that have strong properties of synaptic modification and are implicated in associative memory function. The selectivity of Alzheimer's disease for components of the hippocampal formation is summarized in Figure 8. The earliest and most severe development of neurofibrillary tangles in Alzheimer's disease appears in layer II of the entorhinal cortex, among cells giving rise to the perforant path projection to the molecular layer of the dentate gyrus (Arriagada & Hyman, 1990; Arnold et al., 1991; Braak & Braak, 1991; Arriagada et al., 1992; Hyman et al., 1984). This pathway was the first where experiments demonstrated Hebbian long-term potentiation properties (McNaughton, Douglas, & Goddard, 1978; Levy & Steward, 1979). In contrast, the granule cells of the dentate gyrus show comparatively few neurofibrillary tangles (Arnold et al., 1991; Arriagada et al., 1992; Ball, 1972; Hyman et al., 1984). The mossy fiber projection of these granule cells into region CA3 of the hippocampus shows long-term potentiation that depends only upon presynaptic activity, not a Hebbian conjunction of pre- and postsynaptic activity (Zalutsky & Nicoll, 1990).

Equations (19) and (20) suggest that sensitivity to runaway synaptic modification depends upon the level of suppression of synaptic transmission during learning, c_{sup}. Less suppression of synaptic transmission during learning will allow more chance of Z or $1/\tau$ being greater than zero. In other words, Hebbian synaptic modification without suppression of synaptic transmission will make synapses more sensitive to interference during learning. The perforant pathway projection to the outer molecular layer of the dentate gyrus does not show suppression of synaptic transmission by cholinergic agonists, in contrast to the projection to the middle molecular layer (Yamamoto & Kawai, 1967; Kahle & Cotman, 1989). Thus, it might be expected that the region giving rise to the innervation of the outer molecular layer would be more sensitive to Alzheimer's disease neuropathology. Indeed, the development of

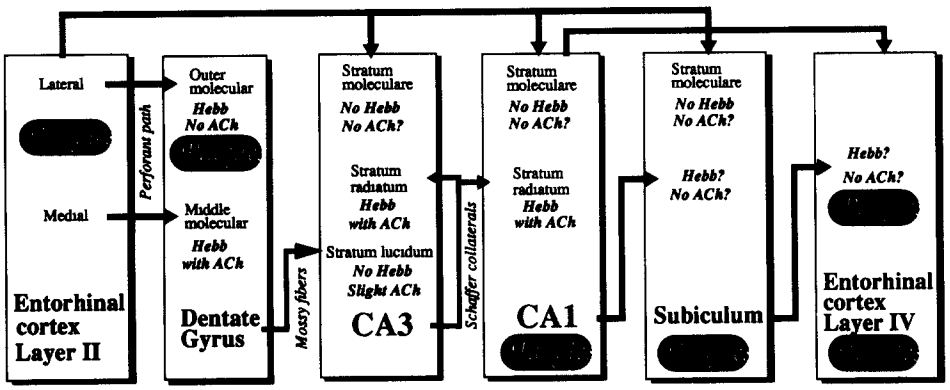

FIGURE 8. Schematic diagram of the major subregions and connections of the hippocampus, showing the distribution of neuronal degeneration associated with Alzheimer's disease in relation to Hebbian synaptic modification and cholinergic suppression of synaptic transmission. Hebbian synaptic modification is represented by the label *Hebb*, and evidence for cholinergic suppression of synaptic transmission is represented by *ACh*. Neuritic plaques (*Plaques*) may be associated with runaway synaptic modification due to Hebbian learning without cholinergic suppression, and neurofibrillary tangles (*Tangles*) may develop in regions giving rise to terminals affected by this runaway synaptic modification. Lack of Hebbian synaptic modification of the mossy fibers may prevent development of tangles in the dentate gyrus, and cholinergic suppression of synaptic transmission at axons arising from region CA3 may prevent development of tangles in this region.

neurofibrillary tangles in entorhinal cortex layer II may show its earliest appearance in the most lateral region (Braak & Braak, 1991), which gives rise to the projection to the outer molecular layer.

In the framework presented here, suppression of synaptic transmission by neuromodulators such as acetylcholine can prevent the initiation and progression of runaway synaptic modification. Thus, it might be expected that once interference during learning starts to occur, the brain would possess a feedback mechanism whereby the cholinergic suppression of synaptic transmission would increase in response to runaway synaptic modification. In Alzheimer's disease, it has been shown that the cholinergic innervation of the molecular layer of the dentate gyrus shows sprouting of cholinergic innervation (Geddes et al., 1985) and increased staining for AChE in some cases (Hyman et al., 1986). This has previously been attributed to the loss of the perforant pathway innervation from entorhinal cortex, but may actually reflect an earlier process in response to the initiation of runaway synaptic modification. A similar effect might underlie the increases of neuronal size in the rostral portion of the medial septum in nonhuman primates showing age-related memory deficits (Rapp & Amaral, 1992). Cholinergic innervation could respond to external messengers released during runaway growth of synaptic connections with a corresponding increase. This might explain regions of dense cholinergic innervation found even in normal cortex (Mesulam et al., 1992). Alternately, a more complex feedback mechanism sensitive to the variance of neuronal activity could trigger increased cholinergic input in response to the greater spread of activity in the network.

In later stages, Alzheimer's disease is characterized by striking decreases in the cortical levels of cholinergic enzymes (Davies & Maloney, 1976; Perry et al., 1977) and a degeneration of the nuclei of the basal forebrain giving rise to this cortical innervation (Whitehouse et al., 1982). The loss of cholinergic innervation could underlie the initiation of runaway synaptic modification in Alzheimer's disease. Alternately, it might be expected that the increased feedback demands on the cholinergic innervation to slow the progression of runaway synaptic modification could caused degeneration of this system.

The effect of acetylcholine on cortical synaptic transmission has been shown to follow a dose–response curve that was fitted with the following equation (Hasselmo & Bower, 1992):

$$f = 0.72\left(1 + \frac{C}{6\ \mu M}\right)^{-1} + 0.28 \qquad (22)$$

where C is the concentration of cholinergic agonist, and f is the percentage of synaptic transmission remaining during cholinergic modulation. This equation shows that on average about 72% of synaptic transmission was sensitive to cholinergic suppression, with a K_d of about 6 μM, while 28% of synaptic transmission was not sensitive, leading to the asymptotic minimum. The portion of synaptic transmission insensitive to cholinergic suppression may be necessary to maintain the capability for synaptic modification.

Feedback mechanisms may increase the amount of cholinergic synaptic transmission ($f = 1 - c$) in proportion to the requirement presented in eqn (21). Initially, increases in concentration (C) will be capable of preventing runaway synaptic modification. But as the level of synaptic transmission during learning approaches the asymptote (0.28 in the equation above), the concentration required to maintain the relationship in eqn 21 goes to infinity. This would occur when the

top part of eqn 21 approaches 1/0.28 times the bottom part. At this point, feedback activation of cholinergic modulation will be unable to prevent the progression of runaway synaptic modification, but the feedback mechanisms may place increasingly greater demands on the cholinergic innervation. The feedback mechanisms could ultimately underlie the development of neuronal degeneration in the basal forebrain cholinergic nuclei. It should be noted that synaptic decay that is proportional to the strength of a synapse (Grossberg, 1970) will help considerably in preventing these increased feedback demands.

10. COMPARISON WITH A NONLINEAR SIMULATION OF CORTICAL PARAMETERS

The results presented here apply to a linear associative memory, and cortical associative memory function has clear nonlinear properties. However, comparison with nonlinear simulations of cortical associative memory function suggests that the analysis of linear function provides a good qualitative description of the effect of interference during learning in a nonlinear network. The simulation presented here is similar to previous autoassociative memory simulations, which were studied with both one-step synchronous dynamics and multi-step asynchronous dynamics (Hasselmo et al., 1991, 1992; Hasselmo, 1993). However, this simulation has a heteroassociative structure intended to resemble associational connections between cortical regions. The details of the simulation are presented in the Appendix, along with a description of a performance measure based on normalized dot products.

As shown in Figure 3, despite the nonlinearities, interference during learning causes runaway synaptic modification in this simulation of cortical heteroassociative memory function. Ultimately, the network responds to an individual input pattern presented to region 1 during recall with elements of all patterns stored in region 2. As shown in Figure 6, 70% suppression of synaptic transmission during learning prevents this runaway synaptic modification. The final synaptic connectivity in these two simulations is illustrated in Figure 2, showing the dramatically increased number of connections modified during runaway synaptic modification.

The simulation allowed testing of suppression of synaptic transmission during learning at a range of values. The time course of change of performance in the simulation can be compared with the results from the analysis of the linear system. To obtain a notion of the relative time course of change of desired and undesired connections for different values of c_{sup}, we can determine the time required to obtain a given connection strength $W(t)$ for both the desired connections and the undesired connections. Rearranging eqn (16), we obtain

$$t = \tau_j \log\left(\frac{[W(t) - W(0)] + (Z_{ij})}{Z_{ij}}\right). \qquad (23)$$

The time required to reach a connection strength of $W_{ij}(t) = 1.0$ from a starting strength of $W_{ij}(0) = 0$ is shown for desired and undesired connections in Figure 9, with the level of cholinergic suppression c_{sup} plotted on the y axis. In this case, the sum of input lines was 6 and $\Omega = 0$. In this graph, the curve was computed for desired connections with ${}_2a_i^{(p)} - 1$ and $\sum_k^n \times W_{ik}(0)_2a_k^{(p)} = 0$. For undesired connections, the curve was computed with ${}_2a_i^{(p)} = 0$ and $\sum_k^n \times W_{ik}(0)_2a_k^{(p)} = 1$. As an approximation for the fact that undesired connections would not grow in the simulations until desired connections had been strengthened, the curve for undesired connections is added to the curve for desired connections.

This analysis gives a good qualitative description of results from the nonlinear simulation of cortical associative memory function. Results from the simulation of cortical associative memory are plotted on the right in Figure 9, with larger black squares representing better performance (higher values of the performance measure P presented in the Appendix). The figure shows that the speed of learning to obtain good recall performance for a desired pattern compared to the speed of interference from other patterns shows qualitatively the same pattern as the curves computed analytically. This is despite the fact that the simulation contains nonlinear input–output relations and nonlinear (saturating) growth of synaptic connections. The qualitative features of the simulation are very close to the characteristics of eqn (23). In addition, very similar patterns of performance were found in simulations of olfactory cortex associative memory function (Hasselmo et al., 1992), even when the simulation utilized asynchronous settling dynamics similar to those of attractor neural networks (Hasselmo et al., 1991).

Figure 9 also displays the curves obtained for different values of H, showing that, with greater inhibition and a higher threshold of synaptic modification, the period of time for growth of undesired connections is larger. Note that in the equation for undesired connections the time to attain a strength of 1 goes to infinity as $H + \Omega$ approaches $(1 - c_{sup}) \sum_k^n W_{ik}(0)_1a_k^{(p)}$. Thus, undesired connections do not grow when synaptic transmission is suppressed below the level of inhibition and the threshold of synaptic modification. This indicates again that there is a proportional relation between the level of cholinergic suppression necessary to prevent interference during learning and the level of inhibition and the threshold of synaptic modification. As shown in Figure 9, results from simulations show a similar relationship between these variables.

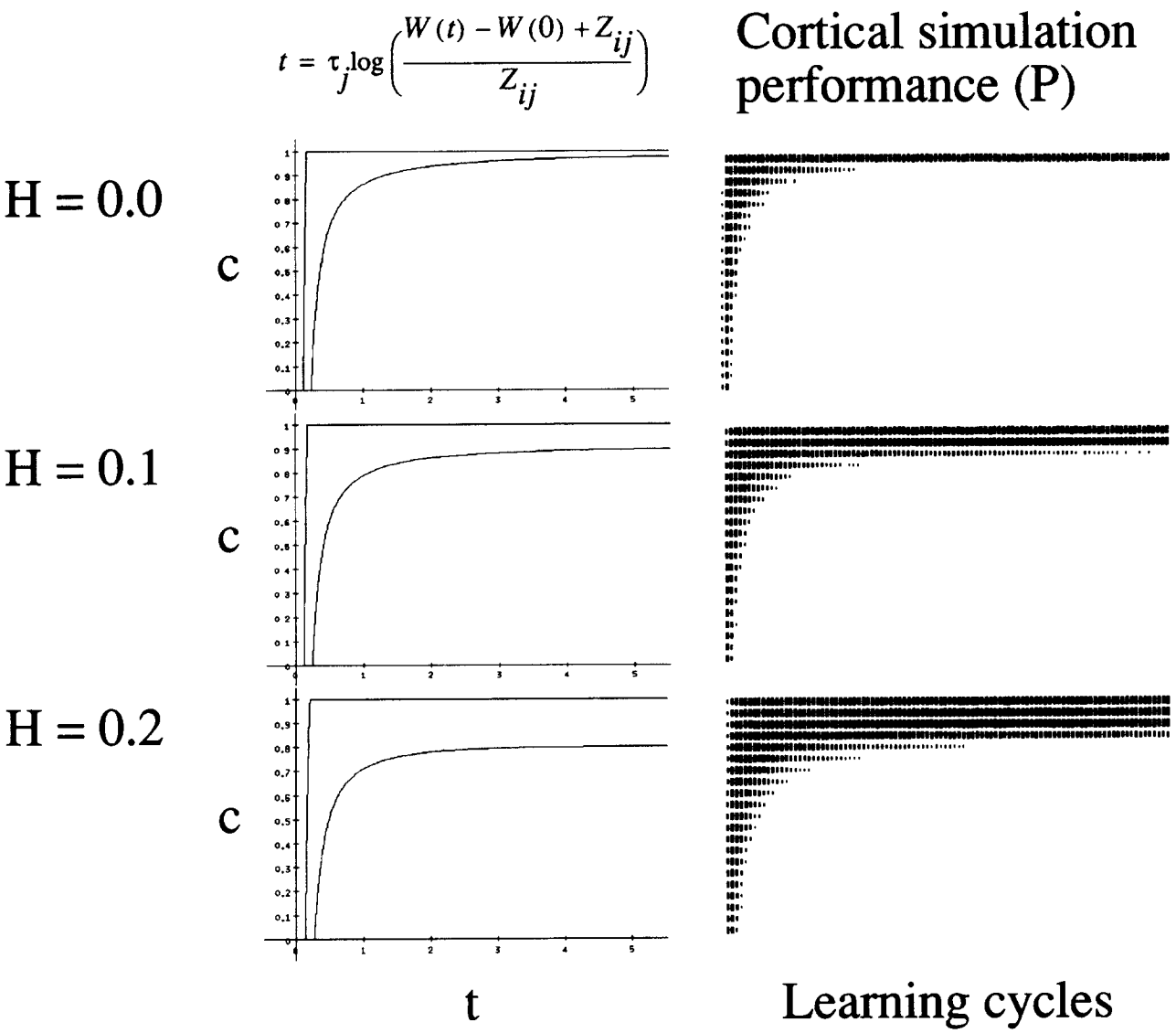

FIGURE 9. Comparison of the results from analysis of the linear system [eqn (23)] with performance results from a nonlinear simulation of cortical associative memory function (Appendix). On the left, the time to attain a connection strength of $W_{ij} = 1$ as computed with eqn (23) is shown for different values of c_{sup} in each graph. On the right, the performance measure computed from the nonlinear simulation of cortical associative memory function is shown across a number of learning cycles for different values of c_{sup} in each graph. Size of black squares represents performance level. The time course of growth of undesired connections in the equation corresponds to the time course of decay of performance in the nonlinear simulation. Different graphs are shown for different values of inhibition. As the level of inhibition (H) increases, less cholinergic suppression (c_{sup}) is necessary to prevent interference during learning. Thus, the growth of undesired connections and the decay in performance measure are delayed for values of ($1 - c_{sup}$) just above H, and are prevented for values of ($1 - c_{sup}$) less than or equal to H.

11. RUNAWAY SYNAPTIC MODIFICATION IN SELF-ORGANIZING SYSTEMS

In contrast to models of associative memory function, synaptic transmission at synapses undergoing Hebbian synaptic modification is a regular feature in models concerned with the self-organizing properties of cortical networks, since these models do not contain a separate input providing the predominant influence on post-synaptic activity. However, these models avoid the exponential growth of a broad population of synapses by implementing various methods for ensuring that total synaptic strength within the network stays within certain bounds. The mechanisms for maintaining stability in many of these networks are difficult to relate to real biological systems, since many of them use afferent synapses which are both excitatory and inhibitory and perform learning on input patterns with a zero mean (Linsker, 1988; Oja, 1989; Xu, 1993). These models differ from real cortical networks in that most inhibitory connections within cortical structures are purely local, and the longer-range afferent and associational connections of cortical structures appear to be primarily excitatory. In some of these networks, synaptic growth

is simply limited at certain positive and negative values (Linsker, 1988), and in others the learning rule is modified to ensure that the sum of squares of synaptic weights remains constant (Oja, 1982, 1989).

In networks using purely excitatory afferent synapses, some methods used to prevent runaway synaptic modification include the normalization of total synaptic strength arising from an individual input neuron (von der Malsburg, 1973; Miller et al., 1989) and decay of synaptic strength dependent upon postsynaptic activity (Grossberg, 1976; Carpenter & Grossberg, 1987). These features allow learning to be directly influenced by synaptic transmission without allowing the exponential growth of synaptic connections. A general notion of the characteristics of runaway synaptic modification in a self-organizing system can be obtained if we consider a modification of eqn (9) in which modifiable connections are the predominant influence on postsynaptic activity (i.e., ${}_2a^{(p)} = 0$), and synaptic decay γ is gated by postsynaptic rather than presynaptic activity. Certain models of cortical self-organization use this type of postsynaptic gating of decay, along with numerous other features not present in these equations (Grossberg, 1972b; Grossberg, 1976; Carpenter & Grossberg, 1987). Here, a very simplified form is presented simply to illustrate basic characteristics. The equation takes the following form:

$$\frac{dW_{ij}}{dt} = \eta\left(\sum_{k=1}^{n} W_{ik1}a_k^{(p)}\right)({}_1a_j^{(p)} - \gamma). \tag{24}$$

In this case, the system has the solution

$$W_{ij} = Z_{ij}(e^{t/\tau_j} - 1) + W_{ij}(0) \tag{25}$$

with

$$Z_{ij} = \left[\sum_{k}^{n} W_{ik}(0){}_1a_k^{(p)}\right] \Big/ \left(\sum_{k}^{n} {}_1a_k^{(p)}\right)$$

and

$$\tau_j = \left[\eta({}_1a_j^{(p)} - \gamma)\left(\sum_{k}^{n} {}_1a_k^{(p)}\right)\right]^{-1}.$$

This form of the equation ensures that synaptic connections with postsynaptic activity but without presynaptic activity will decay exponentially because for ${}_1a^{(p)} = 0$ and $\gamma > 0$, $({}_1a^{(p)} - \gamma) < 0$. Although the exact mathematical features of this learning rule have not been demonstrated experimentally, the qualitative features of this effect resembles heterosynaptic depression, which has been shown in experimental preparations of structures such as the dentate gyrus (Gustafsson & Wigstrom, 1988; Sejnowski & Stanton, 1990). This form of the learning rule allows synapses with presynaptic activity to grow exponentially, as long as $({}_1a^{(p)} - \gamma) > 0$. If decay is scaled to synaptic weight (i.e., γW_{ik} in place of γ), the growth of synapses is asymptotic, as discussed above with reference to decay gated by presynaptic activity.

This learning rule allows the feedforward connections to region 2 to self-organize in response to an input pattern presented to region 1. Depending upon the initial connectivity, sets of individual neurons in region 2 can become strongly tuned to particular input patterns. As discussed further below, this mechanism may underlie the rapid formation of representations of episodic events in the dentate gyrus. If subsequent input activates some of the same neurons in region 2, these neurons will weaken their connections with components of the first pattern (due to the gated decay), and strengthen their connections with components of the second pattern. The weakening of specific connections is vital to maintaining stability in the system.

As can be seen from the equation, insufficient decay strength can allow a breakdown in function, resulting in runaway synaptic modification within the network. In the extreme case, if $\gamma = 0$, each synapse with presynaptic activity will grow exponentially, but excessive growth will occur even with decay if the decay rate is too slow to remove undesired connections during learning, or if partial presynaptic activity exceeds the level of decay. The problem is illustrated here for a network using decay, but would apply to an imbalance in any mechanism for the normalization of synaptic strength (Linsker, 1988; von der Malsburg, 1973; Miller et al., 1989; Oja, 1989), though networks with the more realistic feature of purely excitatory connections between layers will be more sensitive to this effect. Here it is proposed that neuronal degeneration in some regions in Alzheimer's disease may result from runaway synaptic modification due to an imbalance of the mechanisms of normalization of synaptic strength. Such an imbalance might result from flaws in the normal molecular mechanisms regulating the strengthening and weakening of synaptic connections, which could include mutations or overproduction of the amyloid precursor protein, or molecular mechanisms resulting in the improper phosphorylation of the tau protein.

Normalization and decay of synaptic strength can be incorporated in associative memory models without disrupting their function, but in those cases, synaptic transmission must not be the predominant influence on postsynaptic activity during learning. Thus, once feedback connections are incorporated (Grossberg, 1976; Carpenter & Grossberg, 1987) or information in separate processing streams is combined (Carpenter, Grossberg, & Reynolds, 1991), activation dynamics must be controlled in a manner that prevents previously modified connections from interfering with the learning of new associations. In previous simulations, this involves complex activation dynamics resulting in the $\frac{2}{3}$ rule (Carpenter & Grossberg, 1987; Carpenter et al.,

1991), but a similar effect can be obtained with suppression of synaptic transmission during learning.

12. OVERVIEW OF CORTICAL FUNCTION

A full characterization of the behavioral deficits of Alzheimer's disease will ultimately require a full working model of human memory function. This is beyond the scope of the present article, but a general framework will be provided for discussing the spread of neuropathology and the neuropsychological implications of these ideas. Already, considerable research on amnesics has indicated a heterogeneity of memory phenomena, with different aspects of memory function having different anatomical localization (Squire, 1992). The memory deficits associated with the anatomical specificity of Alzheimer's disease fit the general framework of this anatomical localization. In this framework, the behavioral symptoms of the disease can be characterized in terms of the initial progression of interference within the hippocampal formation, causing a breakdown in memory function placing high demands on contextual and relational representations with an intermediate time course. This accounts for the fact that in early stages of Alzheimer's disease, remote memory and implicit memory are retained—factors also retained in amnesics. In the model, the gradual spread of interference into neocortical areas eventually perturbs semantic representations and implicit memory, causing phenomena such as a broadening of semantic categories and hyperpriming phenomena. Ultimately, the model suggests that the spread of interference phenomena into the long-term semantic representations of neocortical structures causes severe language and perceptual impairments such as those noted in late stages of Alzheimer's disease. Note that dependent upon the progression of runaway synaptic modification relative to the nature of cognitive representations, the impairment could show greater relative severity for language or for visuospatial function.

The overview of cortical function is presented in Figure 10. In this framework, the primary visual, sensory, auditory, and motor cortices would be the lowest layer of the hierarchy, with association areas of progressively higher order being represented by higher levels in the hierarchy (naturally, a more sophisticated representation will allow connections crossing levels of the hierarchy). The entorhinal cortex would be analogous to the highest level of the neocortical regions. This area then projects into the dentate gyrus of the hippocampal formation, which projects onward to region CA3 and CA1. CA1 projects back to entorhinal cortex either directly or via the subiculum (Amaral & Witter, 1989). In addition, the hippocampal formation may influence the cholinergic modulation of cortical structures arising from the nuclei of the basal forebrain. This would include regulation of the cholinergic modulation of the hippocampal formation arising from the medial septum via output to the lateral septum, as well

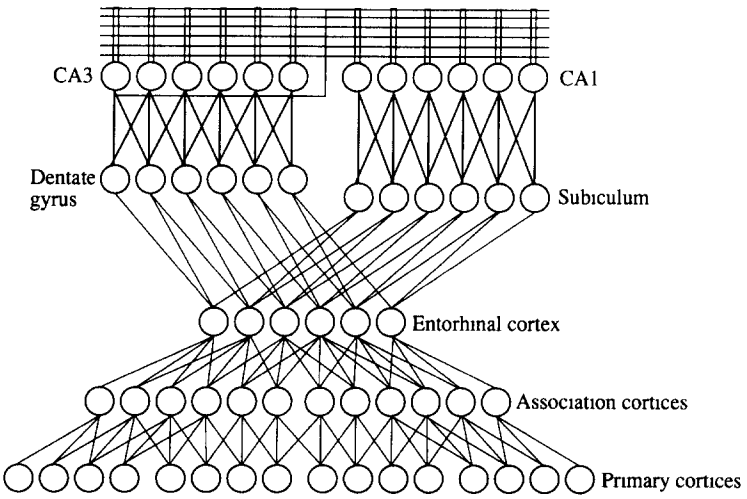

FIGURE 10. Schematic diagram of the overview of cortical function. The three bottom layers are neocortical structures characterized by self-organizing feedforward and associative feedback connections between layers. Activity in primary cortical areas is associated with specific sensory stimuli and particular motor responses, association cortical regions form stable higher-order representations of this activity, and parahippocampal and entorhinal cortices form representations of information from different modalities. Layer II of entorhinal cortex projects to the dentate gyrus, which is here assumed to form rapid representations of episodic events. Dentate gyrus projects onward to region CA3, which has autoassociative connections providing completion of missing elements of dentate gyrus activity. The Schaffer collaterals linking region CA3 to region CA1 are assumed to store associations between CA3 activity and direct entorhinal input to CA1. Region CA1 projects to layer IV of entorhinal cortex (here layers II and IV are represented by a single set of neurons) either directly or via the subiculum, allowing the hippocampal representation to activate components of neocortical representations. The direct projection from entorhinal cortex to regions CA1 and CA3 is not shown.

as regulation of the cholinergic modulation of other cortical structures.

The neocortical components of this framework consist of functional modules with self-organizing feedforward connections and associative feedback connections. In this framework, cholinergic modulation plays an important role in setting the proper dynamics for learning and recall. During learning, modulation shuts down the associative feedback connections sufficiently such that feedforward connections are the predominant influence on neuronal activity at each level. This allows the hierarchy to develop a self-organized representation of the afferent information with progressively higher levels of representational sophistication, as in other models of self-organizing systems (Carpenter & Grossberg, 1987; Linsker, 1988). Depending upon the learning rule, the normalization of synaptic weights and the neuronal input–output functions, these self-organizing feedforward connections can form representations of specific input patterns or features of these patterns (Carpenter & Grossberg, 1987), or they can form principal component or subspace representations of the input covariance matrix (Oja, 1989; Xu, 1993).

At the same time as these feedforward self-organized representations are being formed, the feedback connections will function as associative memory synapses. They will not be the predominant influence on postsynaptic activity, but they will be strengthened in a pattern such that they form an association between the higher-order representation and the representation at a lower level. The ultimate result is a network with essentially symmetric connections in which the feedback connection matrix is the transpose of the feedforward connection matrix. This resembles the types of representations formed by autoassociative back propagation (Baldi & Hornik, 1989), counter-propagation networks (Hecht–Nielsen, 1987), and instar–outstar networks (Grossberg, 1972b). However, in this case the network is folded back on itself such that the input layer and output layer are the same, as in adaptive resonance networks (Carpenter & Grossberg, 1987).

During recall, removal of cholinergic modulation allows this network to show the essential characteristics of an associative memory, but in contrast to a single layer associative memory, this structure has a greater capacity and responds to input according to the higher-order representation of the input covariance matrix in different cortical layers. Specific behavioral tasks can be modeled in this framework as involving afferent input to particular primary cortical areas, and requiring motor responses based on specific representations activated by the afferent input. For example, naming of a hammer would involve visual input of a hammer coupled with a question "What is it?" Within the model cortex, a higher order representation will be activated by the input activity, and a response, "hammer," will be generated in cortical areas mediating speech. Note that this response does not require activation of the hippocampal formation. Aspects of implicit memory such as priming can also be described within this framework without involving activation of the hippocampal formation. For instance, if subtle changes in weight due to Hebbian synaptic modification occur during the response to the hammer, subsequent stem completion of "ham—" will more rapidly converge to the word "hammer" than to other words such as "hamper."

This framework also attempts to account for the relative necessity of the hippocampus, entorhinal cortex and parahippocampal gyrus for explicit memory or relational memory. For example, if on the following day the subject is asked "What did I show you during testing yesterday?", the afferent input will not converge to a specific response based only on the representations existing in neocortical structures. Instead, this type of representation is presumed to depend upon the highest levels of the cortical model—the subregions of the hippocampus. This relative segregation of the rapidly formed representations of explicit or relational memory might be required to provide greater stability for the neocortical representations. If neocortical representations are constantly being updated by new information, this will cause instability of semantic representations (Gluck & Myers, 1992; McClelland et al., 1992; Rueckl, 1992). This instability can be prevented if explicit or relational information initially has its strongest influence within the hippocampus, and only gradually influences cortical representations through the influence of feedback connections activated during subsequent behavior or possibly during sleep. Naturally, the more rapid modification of connections within the hippocampus would make it more sensitive to runaway synaptic modification. Thus, the increased gain of the learning rules in the hippocampus would have to be accompanied by very strong normalization mechanisms, or very strong decay of previously formed representations.

In this framework, the hippocampus forms rapid representations that underlie the intermediate component of explicit memory, before the feedback from the hippocampus sufficiently alters neocortical processing to constitute *consolidation* of the new information. The strictly feedforward input to the dentate gyrus probably performs a major part of this process, forming representations similar to the self-organizing feedforward connections of other cortical layers, but forming them more rapidly, and drawing on broader relations received from the high-order representations of a variety of modalities. The output from these rapid representation neurons then projects via the mossy fibers to region CA3, where autoassociative mechanisms will ultimately provide completion capabilities. Finally, the representation is passed on to region CA1 and the subiculum, which form associative connections with

the entorhinal cortex. This framework resembles previous theoretical frameworks for hippocampal function (Marr, 1971; McNaughton & Morris, 1987; Rolls, 1990).

In terms of the specific example presented above, the question "What did I show you in the test yesterday?" will activate a general representation of the experimenter and the concept of testing. In a subject with an intact hippocampus, this activation should be sufficient to activate at least a component of the rapid representation formed in the feedforward connections to the dentate gyrus on the previous day, possibly based primarily on the appearance of the experimenter and the room itself. Within region CA3, this activity will undergo completion, activating the components associated with the hammer. This activity will propagate back through region CA1 and the subiculum to the entorhinal cortex, and on to visual areas encoding the appearance of the hammer and the language areas that constitute the response "a hammer." Within this general framework, the spread of neuropathological features, and the neuropsychological symptoms of Alzheimer's disease will be discussed. Obviously, this is only an initial sketch. More detailed computational treatments are in preparation.

13. SPREAD OF INTERFERENCE DURING LEARNING IN MULTISTAGE MODELS

Interference during learning and runaway synaptic modification has the capacity to spread between different regions of a cortical model such as the one proposed in the previous section. In particular, the associative feedback connections can provide the basis for the spread of runaway synaptic modification from the hippocampus back into neocortical structures. This spread occurs more easily if the patterns being associated at each level are overlapping. However, interference can spread to a region in which orthogonal patterns are being stored if the patterns are presented more than once out of sequence. Consider, for example, a network with three regions, with activity of the units in each region designated by ${}_1\boldsymbol{a}$, ${}_2\boldsymbol{a}$, and ${}_3\boldsymbol{a}$. The activity between regions 1 and 2 shows the first-order interference described previously in eqn (6). The learning rule for the connections between region 2 and region 3 will then have as its presynaptic component the activity in region 2 [that was presented as postsynaptic activity in eqn (6)]. The focus of this section is to show that interference will spread between regions, not to fully characterize that interference. For simplicity, the equations will include only a portion of the effects of synaptic transmission at each stage. For considering the effects of first-order interference, the equations will ignore the component of learning due to synaptic transmission from region 2 to region 3, leaving us with only the postsynaptic activity due to direct afferent input (${}_3\boldsymbol{a}^{(p)}$).

Thus, for learning of patterns q_2, analogous to eqn (6), the learning rule will take the form

$$\Delta_{32}\boldsymbol{W}(t+2) = {}_3\boldsymbol{a}(t+2)_2\boldsymbol{a}(t+1)^T$$
$$= [{}_3\boldsymbol{a}^{(q_2)}][{}_2\boldsymbol{a}^{(q_2)} + ({}_1\boldsymbol{a}^{(q_1)T}{}_1\boldsymbol{a}^{(q_2)})_2\boldsymbol{a}^{(q_1)}]^T. \quad (26)$$

For considering the spread of interference into the next set of connections during learning of patterns p, we consider the effect of synaptic transmission between region 2 and region 3, but not between region 1 and 2, and obtain for the learning rule

$$\Delta_{32}\boldsymbol{W} = ({}_3\boldsymbol{a}^{(p)} + {}_{32}\boldsymbol{W}_2\boldsymbol{a}^{(p)})_2\boldsymbol{a}^{(p)I}$$
$$= \left\{{}_3\boldsymbol{a}^{(p)} + \sum_{q_2=1}^{p-1} {}_3\boldsymbol{a}^{(q_2)}{}_2\boldsymbol{a}^{(q_2)I}{}_2\boldsymbol{a}^{(p)} + {}_3\boldsymbol{a}^{(q_2)}\right.$$
$$\left.\times\left[\sum_{q_1=1}^{p-2}({}_1\boldsymbol{a}^{(q_1)T}{}_1\boldsymbol{a}^{(q_2)})_2\boldsymbol{a}^{(q_1)}\right]^T{}_2\boldsymbol{a}^{(p)}\right\}_2\boldsymbol{a}^{(p)I}$$
$$= \left\{{}_3\boldsymbol{a}^{(p)} + \left[\sum_{q_2=1}^{p-1}{}_2\boldsymbol{a}^{(q_2)I}{}_2\boldsymbol{a}^{(p)} + \sum_{q_1=1}^{p-2}({}_1\boldsymbol{a}^{(q_1)T}{}_1\boldsymbol{a}^{(q_2)})\right.\right.$$
$$\left.\left.\times({}_2\boldsymbol{a}^{(q_1)I}{}_2\boldsymbol{a}^{(p)})\right]{}_3\boldsymbol{a}^{(q_2)}\right\}_2\boldsymbol{a}^{(p)T} \quad (27)$$

This equation shows that interference developing in the set of connections from region 1 to region 2, dependent on the overlap between patterns in region 1 (${}_1\boldsymbol{a}^{(q_1)T}{}_1\boldsymbol{a}^{(q_2)}$), can influence the interference during learning in the connections from region 2 to region 3. However, the interference can only spread to region 3 in proportion to the overlap between patterns in region 2 (${}_2\boldsymbol{a}^{(q_1)T}{}_2\boldsymbol{a}^{(p)}$). Thus, orthogonal patterns in region 2 will allow no spread of interference into the connections beyond region 3 if each pattern is learned only once. However, repeated learning of the same patterns in region 2 will result in a spread of interference because the scalar (dot) product of pattern q_1 with pattern p is nonzero if $q_1 = p$

These effects can be observed in simulations of a multilayer associative memory, as shown in Figure 11. Here, a three-region network has been trained with overlapping patterns in region 1, and orthogonal patterns in regions 2 and 3. Note that interference develops initially on the connections between region 1 and 2, but with repeated learning of patterns in region 2, interference spreads into region 3. Associative learning between 2 and 3, without activity in region 1, does not develop interference during learning because the patterns are orthogonal.

The analysis and simulations in this section suggest a framework for describing the progression of neuronal degeneration between different cortical regions in Alzheimer's disease. Neuronal degeneration appears to spread along well-established intracortical connections in Alzheimer's disease (Pearson et al., 1985; Arnold et al., 1991). This has previously been attributed to the spread of a specific external pathogen, but if runaway synaptic modification underlies the neuronal degen-

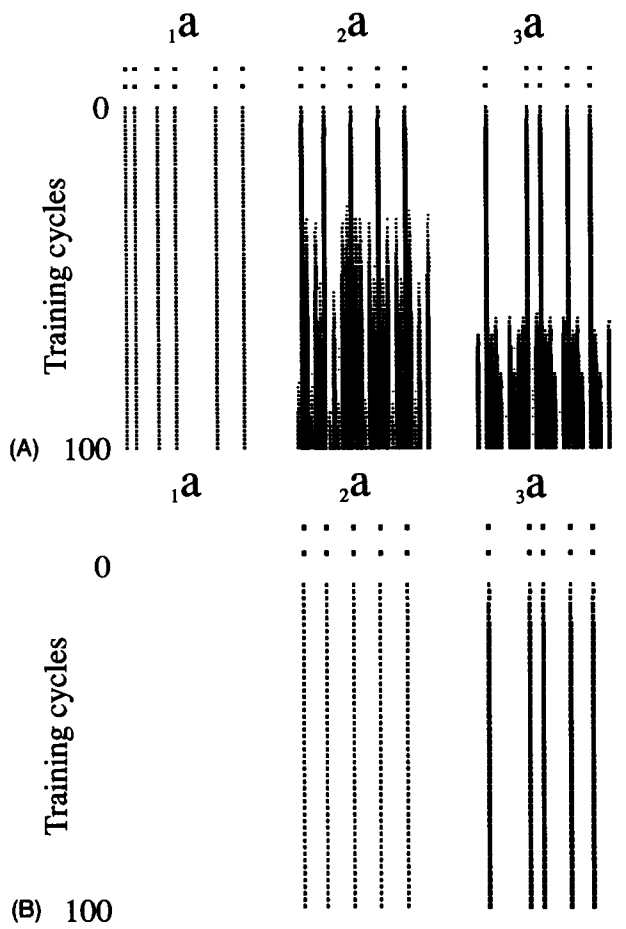

FIGURE 11. (A) Spread of interference between different layers of a multilayer associative memory. Region 1 receives five overlapping input patterns, while regions 2 and 3 receive five nonoverlapping (orthogonal) input patterns. The recall of the entire network in response to afferent input patterns comprising elements of a single association is shown for different stages of learning. Results show that interference during learning in the connections between regions 1 and 2 gradually causes runaway synaptic modification and more intrusions from other patterns during recall. Eventually, the interference during learning spreads to the connections between regions 2 and 3, causing runaway synaptic modification and a decay of recall in region 3 as well. (B) Learning in regions 2 and 3 without input to region 1 does not show interference during learning because the input patterns to regions 2 and 3 are orthogonal, preventing any development of interference.

eration of Alzheimer's disease, the spread of progression between different regions may follow a mechanism such as that described in eqn (26).

14. RELATION TO NEUROPSYCHOLOGICAL EVIDENCE

The theoretical framework of cortical function described here can be used to model some of the neuropsychological symptoms of patients with senile dementia of the Alzheimer type (SDAT). A schematic representation of the development and spread of runaway synaptic modification in different stages of the cortical model is shown in Figure 12. In this schematic representation, runaway synaptic modification initially appears in the projection from the entorhinal cortex to the dentate gyrus, subsequently influencing the projection from CA1 to the entorhinal cortex, and finally spreading along feedback connections to progressively lower-order neocortical structures. This matches the description of the progression of degeneration based on neuropathological evidence (Braak & Braak, 1991). The figure also gives a very simplified overview of how this breakdown in function might be able to account for some of the following experimental data.

1. Patients with SDAT show evidence for increased intrusions in a number of different tasks (Fuld et al., 1982; Troster et al., 1989; Jacobs et al., 1990; Delis et al., 1991). In the Visual Reproduction Test of the Wechsler Memory Scale-Revised (WMS-R), SDAT patients show increased numbers of intrusions, adding components of previously learned visual patterns during free recall of single patterns (Troster et al., 1989; Jacobs et al., 1990). In the California Verbal Learning Test, SDAT patients show high levels of free-recall and cued-recall intrusions, similar to Korsakoff 's patients (Delis et al., 1991).

In the framework presented here, these effects are attributed in initial stages of the disease to runaway synaptic modification in the innervation of the molecular layer of the dentate gyrus by neurons of layer II of entorhinal cortex. These connections have a strong capacity for synaptic modification, as shown in studies of long-term potentiation (McNaughton, et al., 1978). Although cholinergic suppression of synaptic transmission in the middle molecular layer (Kahle & Cotman, 1989) may give these synapses associative memory function and greater stability, the synapses of the outer molecular layer presumably have a significant influence on postsynaptic activity during learning, giving them self-organizing characteristics. Thus, these connections might be more sensitive to the runaway synaptic modification described in eqn (25). If this region provides the basis for immediate retention of a wide range of episodic information, then it would have to deal with a buildup of considerable overlap between stored information [as illustrated in eqn (21)] due to the constant storage of information and the fact that episodic memories frequently consist of rearrangements of previously stored information.

The synapses of the dentate gyrus could avoid runaway growth by a number of mechanisms. As noted above, the outer molecular layer does not show suppression of synaptic transmission. However, gated or ungated decay of synaptic strength could help reduce the pressure on the capacity of this system by gradually removing initial conditions due to previously stored information. Phenomena of heterosynaptic and homo-

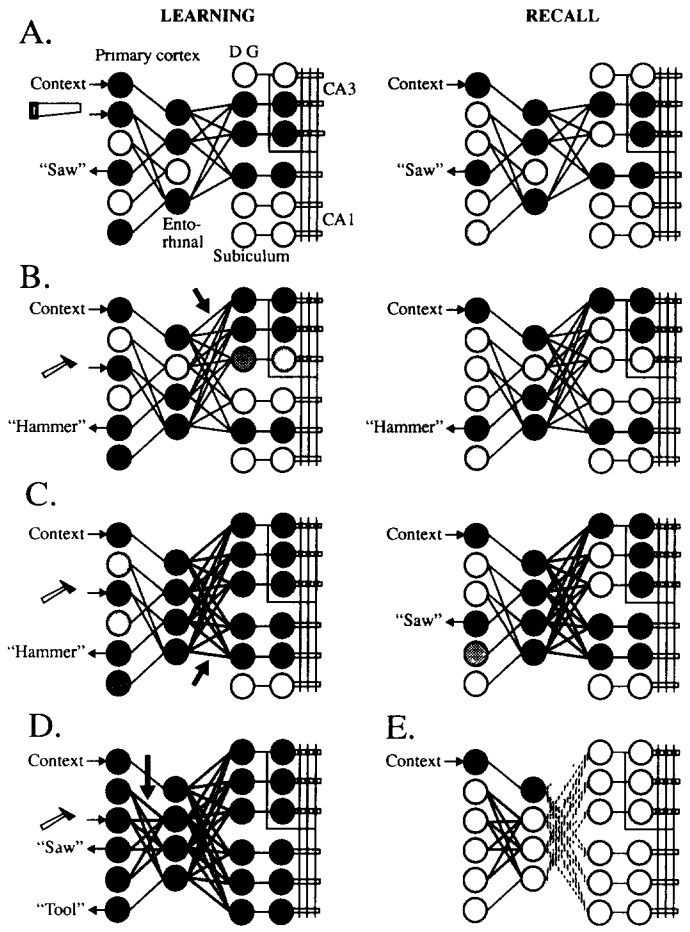

FIGURE 12. A simplified representation of how runaway synaptic modification might progress in cortical regions, and the effect of this progression on memory function. Populations of neurons in different areas are represented by circles, with darker shading representing greater activity. Only connectivity strengthened during particular learning episodes is shown. In the column on the left, cortical activity is shown during learning of new stimuli, while the column on the right shows the recall in response to a context cue. Rows A–E show different stages of the spread of runaway synaptic modification. (A) Normal function during exposure to the visual image of a saw presented in a specific context. Neocortical representations of the visual image of the saw and the corresponding name have been formed previously, allowing presentation of the stimulus to activate higher-order representations that allow the response "saw." Activity in association cortices activates a particular pattern of neurons in the entorhinal cortex. Spread of activity from the entorhinal cortex to the dentate gyrus activates two neurons, and connections between these two neurons and the active entorhinal neurons are strengthened, rapidly forming a new representation of the episodic memory. Activity spreads along the mossy fibers to region CA3, where autoassociative synapses are strengthened. In addition, activity spreads along the Schaffer collaterals into region CA1, activating a sparser representation of the episodic memory. Finally, connections between neurons in CA1 and the subiculum and active neurons in entorhinal cortex are strengthened (layers II and IV of entorhinal cortex are represented by the same set of circles). During recall, presentation of only the context directly activates only one neuron in entorhinal cortex. This neuron weakly activates a dentate gyrus neuron. In region CA3, autoassociative recall allows the weak input from the dentate gyrus to activate the full representation of the episode, with activity spreading on to CA1 and the subiculum. The spread of activity back to entorhinal cortex activates other components of the episode, allowing recall of the visual image of the saw and the proper response "saw." (B) Early stage of runaway synaptic modification during learning and recall of a second item. A visual image of a hammer is presented, activating neocortical representations that result in a pattern of activity in entorhinal cortex sharing components with the previous activity due to the context and the category of the item as a tool. This activates a subset of dentate gyrus neurons overlapping with the previous subset. With insufficient normalization or decay of synaptic connections, the perforant pathway from entorhinal cortex to the dentate gyrus (arrow) shows the initiation of runaway synaptic modification due to partial recall of the saw episode (see Figure 13 for more detail). However, the activity in the additional neuron is not sufficient to perturb the representation of the hammer episode in region CA3, and a separate, orthogonal representation is formed in region CA1 and the subiculum. Thus, during recall, presentation of the context activates the hippocampal circuit in such a manner that the item hammer can be recalled correctly. (C) Progression of runaway synaptic modification into back projections from region CA1 and subiculum to entorhinal cortex (arrow). If runaway synaptic modification has caused a greater overlap in the representation formed in the dentate gyrus, or the imbalance of cortical parameters is larger, the presentation of the hammer might cause a greater spread of activity into dentate gyrus neurons previously activated by the saw episode. In this case, the CA3 representation links components of both episodes, and neurons in CA1 and the subiculum representing both episodes are activated. Activity spreads back to entorhinal neurons involved in encoding both episodes, resulting in runaway synaptic modification of the back projections (note that excess activity spreads into neocortical areas, but these more stable representations are not yet perturbed, allowing proper identification

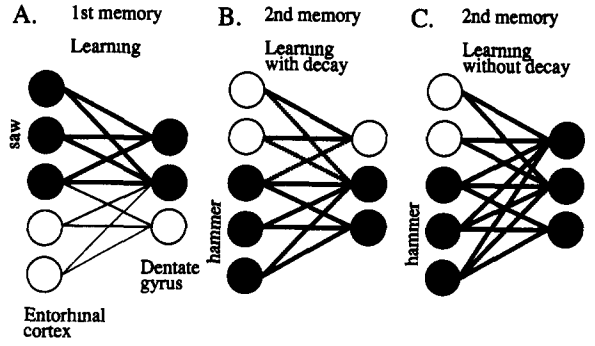

FIGURE 13. Schematic representation of runaway synaptic modification in the perforant path. (A) Presentation of the saw in a particular context activates a subset of three entorhinal cortex neurons. Two dentate gyrus neurons receiving input from all three of these neurons are activated and those connections are strengthened. (B) Learning with decay. During presentation of the hammer in a similar context, two dentate gyrus neurons are activated, including one activated during presentation of the saw. Connections between active neurons are strengthened, while postsynaptic normalization or gated decay allows weakening of connections from inactive entorhinal neurons. If a postsynaptic threshold of synaptic modification is assumed, presynaptic normalization or gated decay can cause weakening of connections to the less active dentate gyrus neuron (connections decreasing in strength are shown with dashed lines.) (C) Learning without decay. With the second input, runaway synaptic modification can occur if gated decay is not sufficiently strong. In this case, the spread of activity representing the recall of the previous event (learning of the saw) activates the top dentate gyrus neuron, leading to strengthening of input to this neuron, and growth of additional connections between entorhinal neurons encoding the hammer episode and the dentate gyrus neuron previously representing the saw episode. In addition, the connections from the inactive entorhinal cortex neurons are retained, which will exacerbate later runaway synaptic modification.

synaptic long-term depression (Sejnowski & Stanton, 1989) suggest that pre- or postsynaptic activity alone can lead to weakening of synaptic connections, supporting the possibility of postsynaptic and presynaptic gated decay. Mechanisms involving axonal transport may allow for a rapid reallocation of presynaptic resources, allowing normalization of synaptic strength due to newly strengthened synapses removing resources from previously strengthened synapses. [Synapses that show long-term potentiation also show considerable posttetanic potentiation (PTP) (McNaughton, 1982), a rapidly decaying form of synaptic modification ($\tau <$ 100 s) that might be the basis of some immediate or iconic memory function.]

In the framework presented here, recall of previously learned information during storage of new information could cause a mingling of representations of the information in the dentate gyrus, as shown in Figures 12 and 13. For example, these figures show a highly simplified representation of cortical activity during learning and recall of a particular stimulus. In a trial in which the subject is presented with a saw, a subset of dentate gyrus granule cells might be activated. Synapses between active entorhinal cortex neurons and active granule cells will be strengthened.

Subsequently, during the trial in which the subject views a hammer, neurons in the entorhinal cortex activated during the viewing of a saw might be activated due to some shared feature of the stimulus or the context. That is, the entorhinal representation of the episode in which the saw was presented might overlap with the entorhinal cortex activity generated during presentation of the hammer. In this case, some of the dentate gyrus granule cells activated by the hammer episode might also have been activated by the saw episode. In a normal subject, decay gated by postsynaptic activity or the postsynaptic reallocation of synaptic strength would weaken the synapses between any inactive entorhinal neurons that previously represented the saw and the dentate gyrus granule cells that are active during presentation of the hammer. Connections undergoing decay are shown as dotted lines in Figures 12 and 13. In this manner, the granule cells representing the hammer episode weaken their connection with most components of the saw episode, and strengthen their connection with entorhinal neurons active during the hammer episode. During recall, this will decrease the likelihood of components of the previous saw episode activating granule cells representing the hammer episode. At the same time, decay gated by presynaptic

of the hammer during its presentation). In this case, during recall, presentation of the context may activate only a subset of dentate gyrus neurons, but region CA3 will recall elements of both stored patterns, causing activation of neurons representing both events in region CA1, the subiculum and entorhinal cortex. This could result in the erroneous response of "saw" rather than "hammer," or an inability for neocortical structures to settle into any response. Note that the likelihood of intrusions or interference should be greater for more similar events. (D) Frequent coactivation of cortical representations causes runaway synaptic modification to spread to the more slowly modified neocortical representations (arrow). Frequent interference during learning such as that shown in (C) has led to consistent coactivation of neurons in entorhinal cortex associated with both tools during presentation of either the hammer or the saw. This has led to strengthening of feedforward and feedback connections between the visual and verbal representations of the saw and the semantic representation of the hammer, and vice versa, representing the spread of runaway synaptic modification into neocortical structures. Thus, in response to presentation of the visual image of the hammer, the subject has all representations activated, and may respond with "saw" or "tool," instead of "hammer." (E) Recall is shown at an even later stage of degeneration, when runaway synaptic modification has led to neuronal death, destroying input and output from the hippocampus. In this case, presentation of the context does not activate any component of the hippocampus, and episodic memory is severely impaired.

activity or the presynaptic normalization of synaptic connections between entorhinal neurons activated by the hammer episode and inactive granule cells that represented the saw episode. During recall, this will decrease the likelihood of components of the hammer episode activating granule cells representing the saw episode.

As shown on the right in Figure 13, impairment of these mechanisms of decay or normalization would allow the connections confounding the two events to remain. In addition, these connections and additional undesired connections would be strengthened due to the spread of activity along previously strengthened connections. In this case, upon being presented with the context for viewing the hammer, the entorhinal neurons encoding this episode would activate dentate gyrus neurons encoding both the hammer episode and the saw episode. This might result in a response of "saw," which would be interpreted as an intrusion from previous learning trials. Interference effects within a more complicated cortical model have been used in a similar framework to describe some of the neuropsychological features of schizophrenia (Grossberg & Pepe, 1970, 1971). In particular, the development of spurious associations due to crosstalk in the network was linked to *punning* behavior in schizophrenics. In some cases, SDAT patients show memory deficits without intrusions of previous information (Kopelman, 1985). However, this does not necessarily mean that interference has not occurred because the activation of representations of multiple different episodes might make it impossible for any specific response to be generated, as proposed in discussions of the interference theory of memory function (Postman & Underwood, 1973).

2. Interference effects in tests of short-term retention. Patients with SDAT show deficits in the Brown–Peterson task, which requires free recall of three items presented before a period in which a distractor task is performed (Corkin, 1982; Kopelman, 1985; Morris, 1986). They also show deficits on delayed recall (after 2 min) of 16 stimuli that had been presented repeatedly in a Delayed Recognition Span Test (Moss et al., 1986). Impairments on the Brown–Peterson task have previously been attributed to proactive interference effects from previously learned material because even normal subjects show much better recall on the first few trials (Keppel & Underwood, 1962). In addition, it has been shown that neurological syndromes such as Korsakoff's disease increase the sensitivity to proactive interference from similar stimuli in a preceding trial in this task (Butters & Cermak, 1980). Currently, tests are being performed to determine if subjects with SDAT show a similar increased sensitivity to proactive interference in this task.

Once interference during learning begins to occur, it will lead to increased overlap between new memories and previously stored information [eqn (21)], thereby enhancing interference during subsequent behavior. In this framework, the more rapid loss of information during the first 2 min before free recall in SDAT patients (Moss et al., 1986) is attributed to interference from the intervening information. It is plausible that performance at 15 s depends largely on persistent activity or effects of posttetanic potentiation within neocortical structures. Recall based on these phenomena will not show sensitivity to interference during learning because they do not involve synaptic modification that is Hebbian in nature. In contrast, recall at 2 min may depend upon Hebbian synaptic modification of the input to the dentate gyrus, which is sensitive to interference during learning.

3. Sparing of certain aspects of implicit memory function. In particular, SDAT patients show normal priming in certain tasks such as perceptual priming (Nebes, Martin, & Horn, 1984; Keane et al., 1991) with hyperpriming phenomenon in certain semantic priming tasks (Chertkow & Bub, 1990). In other studies, SDAT patients show priming that does not show differences dependent on semantic-relatedness (Chertkow, Bud, & Seidenberg, 1989), and there is evidence for impaired priming in other tasks (Keane et al., 1991). It is possible that these different effects represent different stages of the breakdown of function in Alzheimer's disease.

In the framework presented here, implicit memory phenomena are presumed to be mediated not by the hippocampal formation, but by neocortical structures. In the model, these structures are assumed to have a smaller gain (η) of synaptic modification. Thus, while presentation of information causes large changes in synaptic strength within the dentate gyrus and hippocampal formation, much smaller changes are caused in neocortical structures. Although long-term potentiation has been described in neocortical structures (Bear, Press, & Connors, 1992), it is more difficult to obtain and generally smaller in amplitude. In the model presented here, these changes are presumed to occur at a representational level below that of episodic events. At this level in the model, specific convergence to a word such as hammer in a very general context (free recall) is more difficult to obtain. However, with cues that partially activate specific connections primed previously, such as "ham—," convergence to "hammer" rather than "hamper" will appear more rapidly and with higher probability. Because this priming involves smaller changes at connections between representations that are modified only very slowly, they will be less sensitive to interference during learning and runaway synaptic modification than the representations formed in the hippocampal formation. However, once runaway synaptic modification spreads along back projections into neocortical structures, the result could be hyper-

priming and priming independent of semantic categories, such as that observed in some studies (Chertkow & Bub, 1990; Chertkow et al., 1989).

4. Eventual deficits in semantic memory. In naming tasks, SDAT patients show frequent reversion to superordinate semantic categories and errors using semantic-associative terms that increases in longitudinal tests (Bayles & Tomoeda, 1983; Hodges, Salmon, & Butters, 1992; Huff, Corkin, & Growdon, 1986; Martin & Fedio, 1983; Nebes, 1989; Ober et al., 1986). This effect would depend upon the spread of runaway synaptic modification along feedback connections from the hippocampal formation and entorhinal cortex to regions of the association cortex, as shown in Figure 12. Within any one cortical region, runaway synaptic modification will tend to follow the boundaries of cognitive representations, lumping together representations of items that share features. Thus, a group of objects with similar attributes will be analogous to binary patterns with a higher dot product between patterns within the set than with patterns from other categories. Patterns of the same type will interfere with each other before interfering with other categories, resulting in an intermediate stage where runaway synaptic modification occurs along category boundaries, lumping individual tools together and individual vegetables together, without lumping tools with vegetables. At this stage, convergence to a single exemplar of a category, such as hammer or saw, is less accurate, but the activity all falls within a single superordinate category such as tool. This phenomenon could account for the semantic associate errors and use of superordinate terms in naming tasks by patients with SDAT (Bayles & Tomoeda, 1983; Hodges et al., 1992; Huff et al., 1986; Martin & Fedio, 1983; Nebes, 1989; Ober et al., 1986).

5. Temporally homogeneous impairments of remote memory function. SDAT patients show consistent evidence for an impairment of remote memory without a temporal gradient, that is, without consistent differences in memory for different decades (Wilson et al., 1981; Corkin et al., 1984). Though the effects of interference during learning will be most marked for new information being stored, the spread of runaway synaptic modification back initially into temporal lobe neocortex and ultimately other cortical areas will gradually cause retroactive interference with the information referred to as remote memory. Thus, the model could account for the consistent evidence for impairments of remote memory function in SDAT (Wilson et al., 1981; Corkin et al., 1984). Because the interference will depend more upon the similarity of the information than upon temporal recency, the effects of Alzheimer's disease on remote memory should be relatively diffuse, rather than showing a consistent temporal gradient. Although the stereotype of senility usually includes a bias toward preserved recall of early memories, experimental data shows relatively even impairment across different decades (Wilson et al., 1981). The apparent preservation of early memories is attributed to frequent recital of well-rehearsed early memories or confabulation (Corkin et al., 1984). In fact, the frequent referral to a few memories is suggestive of a system in which all memory function has become focused on a few stored associations. This could result from the mathematical tendency of a matrix of connections to push postsynaptic activity progressively toward the eigenvectors with the largest eigenvalue. Interference during learning could result in the persistent recall of a few very strong memories.

6. Modular specificity of deficits in SDAT. In different cases, impaired cognitive function can show selectivity for particular modalities, more strongly influencing either language function or visuospatial processing (Albert & Lafleche, 1991). In the framework described here, this can be accounted for by simply extending the phenomenon described for semantic categories. If the initial occurrence of runaway synaptic modification follows the bounds of semantic categories (due to local imbalances of specific parameters or due to the amount of correlation between the different patterns being stored), then further growth will follow the bounds of larger-scale categorical distinctions. If runaway synaptic modification initially occurs within cortical language areas, it will subsequently spread to neurons sharing components with the affected areas, that is, other language areas; if the phenomenon initially occurs in areas subserving visuospatial processing, the subsequent spread will more strongly influence regions involved in visuospatial processing. Although descriptions of the progression of Alzheimer's disease that depend on the spread of an internal pathogen must appeal to the spatial proximity of these pathways, the framework presented here allows for a description of progression that actually links functional cognitive structures to the pattern of progression of pathology.

15. DISCUSSION

The dynamics of learning in a model of cortical associative memory function can be described by solving a system of nonhomogeneous differential equations combining the learning rule and activation rule, as shown in Section 5. This analysis shows that when synaptic transmission is allowed during synaptic modification, previously strengthened connections enhance their own growth, allowing for exponential growth of connections required for associative memory function. However, this same effect can lead to the exponential growth of undesired connections due to interference between patterns. This interference during learning can impair associative memory function by causing runaway synaptic modification within the network, as shown in Figures 2 and 3.

Suppression of synaptic transmission during learning (Figure 4) can slow the progression of runaway synaptic modification, as discussed in Section 7. This suppression can completely prevent the initiation of interference during learning if it brings the activity of neurons not receiving direct afferent input below the threshold of synaptic modification, as shown in Figures 5 and 6. However, as additional associations are stored within the network, eventually a critical capacity will be reached beyond which interference during learning cannot be prevented. The metabolic demands or excitotoxic effects of runaway synaptic modification could be severe enough to cause neuronal degeneration. Thus, the analysis presented here could provide a theoretical framework for describing the initiation and progression of neuronal degeneration found in Alzheimer's disease.

Most previous models of cortical associative memory function have ignored the normal activation dynamics of the network during learning (Amari, 1977; Anderson, 1972; Amit, 1988; Amit et al., 1990; Kohonen et al., 1977; Kohonen, 1972; Hopfield, 1982). These researchers realized that allowing synaptic transmission during synaptic modification in an associative memory would cause the connectivity within the network to "blow up" (Kohonen, 1988). However, most prevailing theories of long-term potentiation depend upon some synaptic transmission at the synapse being modified (Gustafsson & Wigstrom, 1988; Brown et al., 1990). Therefore, it appears biologically unrealistic to completely suppress activation dynamics during learning. As shown here, partial suppression of synaptic transmission during learning coupled with inhibition or decay of synaptic strength (Grossberg, 1970, 1972a) can prevent the development of interference. Thus, evidence for selective cholinergic suppression of intrinsic fiber synaptic transmission (Hasselmo & Bower, 1992) provides a putative neurophysiological mechanism for what has been a standard feature of associative memory models for over 30 years.

As summarized in Sections 6, 8, and 12, this work suggests a theoretical framework for describing the selective distribution of neuronal degeneration in Alzheimer's disease (Ball, 1972; Brun & Gustafson, 1976; Hyman et al., 1984; Arnold et al., 1991; Braak & Braak, 1991). Interference during learning would put demands on an activated neuron to strengthen connections at a considerably greater number of synapses than in normal learning. The metabolic demands or excitotoxic effects of this runaway synaptic modification might result in the type of neuronal degeneration found in Alzheimer's disease. Regions showing Hebbian modification without suppression of synaptic transmission will be particularly vulnerable to the initiation of runaway synaptic modification, as illustrated in Figure 8. This might explain the selective sensitivity to neuronal degeneration of neurons in the lateral entorhinal cortex layer II projecting to the outer molecular layer of the dentate gyrus (Hyman et al., 1984; Arnold et al., 1991; Braak & Braak, 1991). These connections show strong associative long-term potentiation (McNaughton et al., 1978; Levy & Steward, 1979), without suppression of synaptic transmission by acetylcholine (Kahle & Cotman, 1989). This would also predict that projections from the neurons showing neuronal degeneration in region CA1 and the subiculum have a strong capacity for Hebbian synaptic modification, without cholinergic suppression.

This work suggests that the effect of neuromodulatory agents such as acetylcholine may play a vital role in preventing the breakdown of associative memory function. Experimental evidence for selective cholinergic suppression of synaptic transmission was obtained from the primary olfactory cortex (Hasselmo & Bower, 1992). However, cholinergic suppression of synaptic transmission has been found in the hippocampus and neocortex, though its selectivity for afferent versus intrinsic fiber pathways has not been investigated (Yamamoto & Kawai, 1967; Hounsgaard, 1978; Valentino & Dingledine, 1981; Kahle & Cotman, 1989; Sheridan & Sutor, 1990). This cholinergic suppression of synaptic transmission may prevent runaway synaptic modification at sets of synaptic connections such as the Schaffer collaterals, which show long-term potentiation with Hebbian properties (Wigstrom et al., 1986; Kelso, Ganong, & Brown, 1986). Much theoretical work has focused on the possible role of the hippocampus as an associative memory (Marr, 1971; McNaughton & Morris, 1987). Previously, the clamping of activity during learning in this region has been attributed to very strong synaptic inputs referred to as detonator synapses (Marr, 1971; McNaughton & Morris, 1987), but with cholinergic suppression of synaptic transmission during learning, such synapses need not be present.

This theory of the progression of Alzheimer's disease is neutral with respect to specific etiological factors. The initiation of runaway synaptic modification could result from a subtle imbalance of the parameters of cortical function, including but not limited to the threshold of synaptic modification, the level of feedback or feedforward inhibition, the decay of synaptic strength, the strength of activation along previously modified connections, and the cholinergic suppression of synaptic transmission. Other factors that might play a role are the threshold of action potential generation and the cholinergic enhancement of postsynaptic excitability (Hasselmo & Barkai, 1992; ffrench-Mullen et al., 1983). Such an imbalance could be caused by genetic factors, environmental factors, or simply by exceeding the effective capacity of the network. This suggests that features of the molecular biology of Alzheimer's disease, such as the build-up of amyloid protein (Selkoe, 1991; Tanzi et al., 1991; Roberts et al., 1993)

and the development of paired helical filaments (Grundkeiqbal et al., 1986; Harrington et al., 1991), should be associated with excessive demands upon the cellular mechanisms of synaptic modification.

If the neuronal degeneration of Alzheimer's disease results from the effects of runaway synaptic modification, then eqn (16) might provide a mathematical approximation of the time course of initiation and progression of this degeneration. As shown in eqn (16) and Figures 7 and 9, the progression of runaway synaptic modification depends upon the size of the coefficient Z and the time constant τ. For a small imbalance of cortical parameters, the network can function normally for a considerable period. However, when the network starts to reach the limits of its capacity, interference during learning enters a positive feedback cycle, resulting in the exponential progression of runaway synaptic modification. A more severe imbalance of cortical parameters will cause an earlier development of interference during learning, and in this case the progression will be more rapid. This feature of the model would be in keeping with evidence suggesting a more rapid progression of Alzheimer's disease with a presenile onset (Hansen et al., 1988; Seltzer & Sherwin, 1983). However, some clinical evidence does not support this difference in speed of progression (Huff et al., 1987). Interestingly, this analysis suggests that Alzheimer's disease may not be a disorder with a specific time course, but may progress with a continuum of time courses dependent upon the severity of the underlying cortical imbalances. In particular, it suggests that the neuronal degeneration may progress at an unnoticed level for many years prior to the onset of a pathological state. This is supported by evidence showing a similar distribution of neuropathology on a much smaller scale in normal aging (Ulrich, 1982; Berg, 1985; Arriagada & Hyman, 1990; Arriagada et al., 1992).

If cholinergic innervation plays a role in preventing interference during learning, then it might be expected that interference during learning would activate feedback mechanisms to enhance cholinergic modulation, thereby delaying the progression of runaway synaptic modification. Such a mechanism might explain the increased cholinergic innervation of the molecular layer of the dentate gyrus in some cases of Alzheimer's disease (Geddes et al., 1985; Hyman et al., 1986). As runaway synaptic modification progresses, it may place increasing demands on the cholinergic innervation, ultimately resulting in a neuronal degeneration of the feedback pathway. This provides a possible explanation for the degeneration of the basal forebrain (Whitehouse et al., 1982) and the decrease in cortical cholinergic innervation found in Alzheimer's disease (Davies & Maloney, 1976; Perry et al., 1977; Coyle et al., 1983).

Once interference during learning appears in one set of connections, it will increase the amount of overlap in the postsynaptic activity within this region. If this postsynaptic activity provides the presynaptic activity for another set of connections with associative memory function, then the interference during learning can spread between regions (as outlined in Section 13). This characteristic of the spread of interference during learning between regions could provide an explanation for the progression of neuronal degeneration from those regions initially affected into adjacent regions of association cortex. This spread of interference appears to occur along established anatomical connections (Pearson et al., 1985; Arnold et al., 1991). As discussed in Section 14, the progression of runaway synaptic modification from the hippocampus to neocortical structures could explain the characteristic behavioral features of senile dementia of the Alzheimer type.

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APPENDIX: MODEL OF CORTICAL ASSOCIATIVE MEMORY FUNCTION

The role of different cortical parameters in associative memory function has been investigated in a non-linear model of cortical associative memory function Previously this model was based on piriform cortex anatomy, and had an autoassociative structure with either one-step synchronous dynamics (Hasselmo et al , 1992), or longer-term asynchronous settling dynamics (Hasselmo et al., 1991) However, the model has been modified to have a heteroassociative structure that would provide a notion of the functional characteristics of associational connections between different cortical regions. The output of these simulations are illustrated in Figures 2, 3, 6, 9, and 10 The simulations were based on application of one step of the activation rule

$$ {}_2\boldsymbol{a}(t+1) = {}_2\boldsymbol{a}^{(p)} + (1 - c_{sup})\boldsymbol{W}g[{}_1\boldsymbol{a}(t)] - \boldsymbol{H}g[{}_2\boldsymbol{a}(t)] \quad (28) $$

where $g[a_j(t)] = 0$ for $a_j(t) < \mu$ (the presynaptic firing threshold) For $a_j(t) > \mu$, the activity was determined by

$$ g[a_j(t)] = \tanh[a_j(t) - \mu] \quad (29) $$

In this model, learning was applied after a single step of the activation rule (that is, after synaptic transmission at the synapse being modified) The weights between units were limited to an asymptotic value, by first computing a learning rule for the matrix M, and then transforming the result into the weight matrix W

$$ \Delta \boldsymbol{M}(t+1) = \eta[{}_2\boldsymbol{a}(t+1) - \Omega]g({}_1\boldsymbol{a}(t) - \mu)^T $$

$$ W_{ij} = \Psi(1 - e^{-M_{ij}}) \quad (30) $$

where Ω = the postsynaptic threshold of synaptic modification, and Ψ = the gain of the input-output function The recall of this network at many stages of learning is illustrated in Figures 2, 6, 9, and 10. In addition, Figures 2, 6, and 9 illustrate a performance measure based on normalized dot products, in which a measure of similarity to the desired pattern was computed, and a measure of similarity to other patterns stored within the network was subtracted from the measure, as follows

$$ P = \frac{\sum_{p=1}^{m}\left[D(\boldsymbol{a}^{(p)}, \boldsymbol{a}^{R(p)}) - \frac{\sum_{q \neq p} D(\mathbf{a}^{(q)}, \boldsymbol{a}^{R(p)})}{m-1}\right]}{m} \quad (31) $$

where m = the number of associations stored in the network, $\boldsymbol{a}^{(p)}$ represents the full input to all regions of the network for the desired association, $\boldsymbol{a}^{(q)}$ represents the full input for other associations stored in the network, and $\boldsymbol{a}^{R(p)}$ represents the incomplete version of the association presented during testing of recall The function D provides a measure of the change in angle between two vectors It consists of normalized dot products comparing activity after one step of the activation rule, with $g[\boldsymbol{a}(t+1)^{(p)}]$ representing the response to the full input association and $g[\boldsymbol{a}(t+1)^{R(p)}]$ representing the response to the incomplete version of the association D takes the form

$$ D(\boldsymbol{a}^{(p)}, \boldsymbol{a}^{R(p)}) = \frac{\frac{g[\boldsymbol{a}(t+1)^{(p)}]^T \; g[\boldsymbol{a}(t+1)^{R(p)}]}{\|g[\boldsymbol{a}(t+1)^{(p)}]\|\|g[\boldsymbol{a}(t+1)^{R(p)}]\|} - \frac{\boldsymbol{a}(t)^{(p)T} \; \boldsymbol{a}(t)^{R(p)}}{\|\boldsymbol{a}(t)^{(p)}\|\|\boldsymbol{a}(t)^{R(p)}\|}}{1 - \frac{\boldsymbol{a}(t)^{(p)T} \; \boldsymbol{a}(t)^{R(p)}}{\|\boldsymbol{a}(t)^{(p)}\|\|\boldsymbol{a}(t)^{R(p)}\|}} \quad (32) $$

This performance measure is sensitive to the relative rate of growth of desired and undesired connections, increasing as desired connections are strengthened, but decreasing as undesired connections are strengthened. The changes in P after different periods of learning are shown in Figures 3 and 6, showing that in both cases P increases as desired connections are strengthened, but as interference during learning causes poorer recall of the association in Figure 3, the performance measure decreases back below zero Thus, the performance measure shows that increases in the cholinergic suppression of synaptic transmission during learning (c_{sup}) greatly enhance the stability of learning. The performance measure has been computed at different stages of learning for a full range of values of cholinergic suppression, as shown in Figure 9 This shows that with greater values of cholinergic suppression, the decay in performance slows and eventually stops, allowing the network to maintain a high level of recall