

The effect of interference during any particular stage of learning may be small, but subsequent learning compounds the effect. The progressive buildup of interference from previous retrieval leads to a malignant nostalgia resulting in runaway synaptic modification throughout the network.

A Computational Model of the Progression of Alzheimer's Disease

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Computational modeling allows analysis of the role of network dynamics in the initiation and progression of neuropathology in Alzheimer's disease. The model focuses on a final common breakdown in function, termed runaway synaptic modification. This phenomenon could account for evidence that neuropathological markers associated with neuronal death in Alzheimer's disease first appear and attain their highest concentration in subregions of the hippocampal formation, and then successively spread into the temporal lobe cortex and the cortex of the frontal and parietal lobes. The model demonstrates how the spread of neuropathology from the hippocampus into neocortical structures could result from the mechanisms of consolidation.

Initial sensitivity of the hippocampus and entorhinal cortex to the neuropathological process is proposed to result from an imbalance of variables regulating the influence of synaptic transmission on synaptic modification. Memory deficits are described as due to increased interference effects on recent memory

caused by runaway synaptic modification, which ultimately leads to impairments of remote and semantic memory.

In the popular consciousness, Alzheimer's disease is identified as a disorder of memory function. However, theories about the cause of the disorder primarily focus on the molecular components of neuropathological markers found in postmortem studies of the brains of patients with Alzheimer's disease. These markers include amyloid plaques, containing large amounts of β -amyloid protein, and neurofibrillary tangles, containing large amounts of tau protein [1]. Most researchers assume that some malfunction in the production or regulation of these proteins or their precursors causes Alzheimer's disease. However, these theories do not explain why Alzheimer's disease should have as its earliest symptom a disorder of memory function [2], why it affects the structures associated with memory so severely [3,4], or why the neuropathological markers of Alzheimer's disease first appear and attain their highest den-

sity in the hippocampal formation [4,5], a region that is essential for storage of new information in memory [6,7].

Here it will be proposed that the causal process is in fact reversed. The selective cortical neuropathology associated with the progression of Alzheimer's disease may be rooted in the breakdown of the essential mechanisms of memory function. The computational theory presented here accounts for evidence of the progression of Alzheimer's disease—not in terms of molecular biology—but in terms of the processing characteristics of cortical structures and the stability of the learning mechanisms within these structures. This theory was inspired by the phenomenon of runaway synaptic modification, as demonstrated in models of cortical associative memory function [8–10].

Memories are stored in these models by modification of the synaptic connections between neurons, on the basis of the neurons' activity. However, if previously stored memories are retrieved during the storage of new memories, they can interfere with new storage, ultimately leading to exponential growth of a large number of synap-

tic connections between neurons in the network. Runaway synaptic modification of this sort may underlie the neuropathological characteristics of Alzheimer's disease. This theory provides a framework showing why this neuropathology should appear initially in particular cortical regions associated with memory function [3,5], and why it should appear to progress into adjacent regions of the cortex along the observed anatomical connections [3,11]. In addition, the theory suggests that the apparent decrease in levels of the neurotransmitter acetylcholine in the cortex in this disease [12,13] may result from feedback mechanisms placing too great a demand on the regions providing acetylcholine to the cortex.

In terms of specific causative factors, this theory is neutral in many respects. The phenomenon of runaway synaptic modification could be initiated by a variety of changes in the processes of cortical function, due to a genetic predisposition or to environmental influences. The initial appearance of runaway synaptic modification is attributed to an imbalance in cortical function, which could result from insufficient normalization of synaptic strength in each neuron, from lowering of the threshold of synaptic modification, from insufficient feedback inhibition, from an imbalance in the sensitivity of presynaptic and postsynaptic cholinergic receptors, or from direct overload of the information capacity of cortical structures.

In this theory, the progression of Alzheimer's disease depends on the functional interaction of cortical regions, suggesting that the pattern of activity propagated from affected to unaffected regions may be pathological in itself. That is, runaway synaptic modification may cause a breakdown of function in one region, and the patterns of activity elicited may induce runaway synaptic modification in connected regions.

Runaway Synaptic Modification

This theory of Alzheimer's disease focuses on the phenomenon of runaway synaptic modification as the final common pathway by which different etiologic influences can result in Alzheimer's pathology [9]. Runaway synaptic modification can occur in any system in which synapses are modified during transmission of activity across them. Thus, most neural network models of cortical function have the potential to undergo runaway synaptic modification.

Models of cortical associative memory function [14-16] focus on the anatomic evidence for widely distributed excitatory synaptic connections linking neurons within cortical structures, including the neocortex and hippocampus. While these models differ in detail, they all depend for their function on modification of excitatory synaptic connections according to some form of the Hebb rule [17,18]. The basic feature

of the Hebb rule is a change in synaptic strength proportional to presynaptic and postsynaptic activity during learning. Modified excitatory synapses form the basis for recalling associations between different patterns of activity. Figure 1 shows a simple example of this associative memory function.

Neurophysiologic data suggest that Hebbian synaptic modification depends on combining postsynaptic activation of neurons with presynaptic release of neurotransmitter at the synapse being modified [18]. However, if a modifiable synapse can influence postsynaptic activity during learning, strengthening this synapse will increase postsynaptic activity, and thereby increase subsequent strengthening of the synapse. This positive feedback can rapidly lead to exponential growth of undesired synapses in the network—i.e., runaway synaptic modification.

The mechanism for runaway synaptic modification is illustrated in Figure 2. This figure shows that if synaptic transmission at modifiable synapses is allowed during learning, the spread of activity across previously modified connections causes the new synaptic modification to contain elements of proactive interference from previously learned memories [8,9, 19]. Without the proper balance of parameters of cortical function, this interference during learning can have disastrous effects in models of cortical memory function.

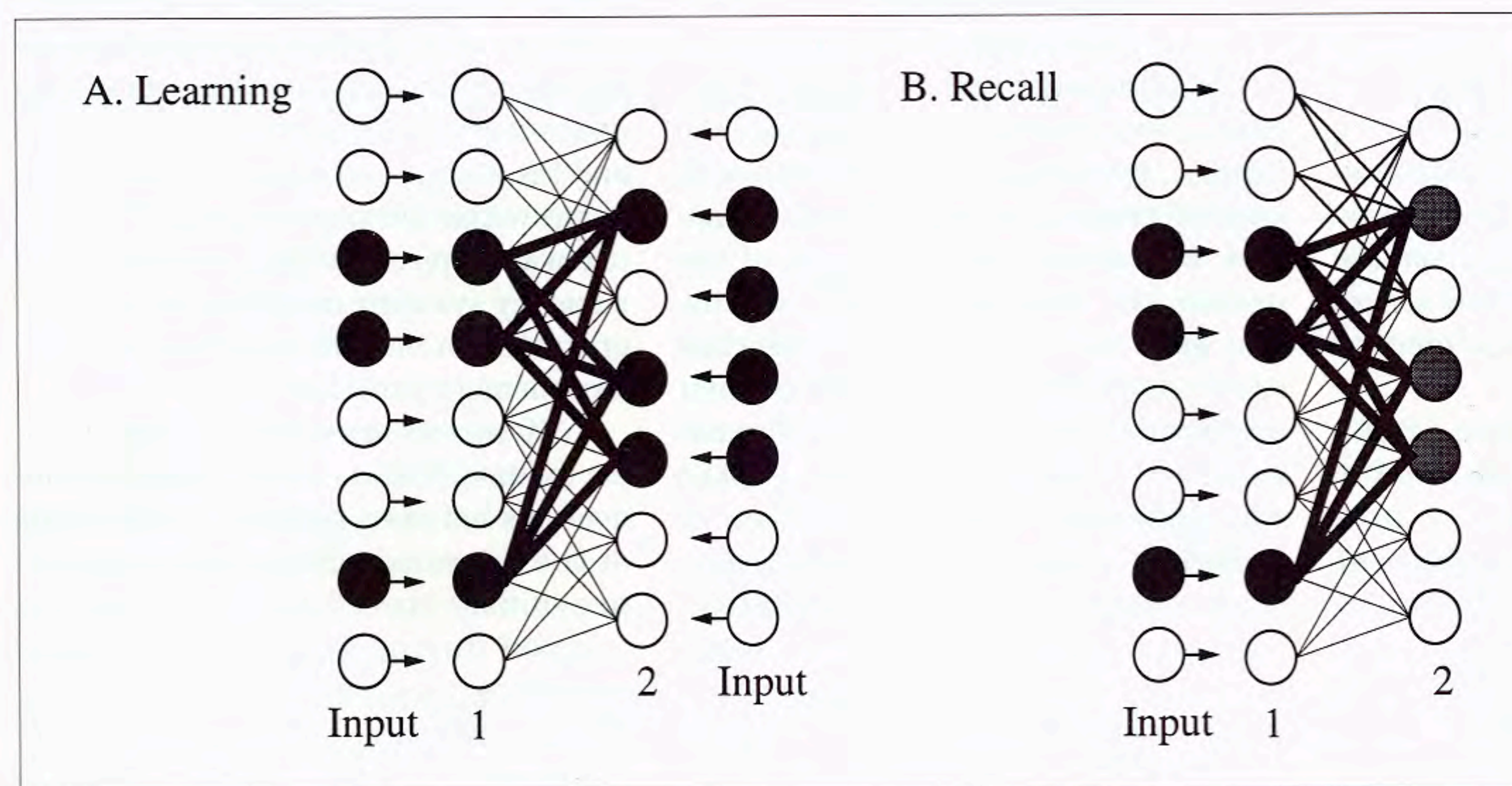


Figure 1. Associative memory function. In learning (Part A) separate input patterns are presented to regions 1 and 2. The synapses between active neurons are strengthened (thick lines) according to a Hebbian learning rule (dependent on presynaptic and postsynaptic activity). In recall (Part B), input is presented to region 1 only. The spread of activity along previously strengthened connections (thick lines) induces activity in region 2 resembling the pattern previously associated with pattern 1.

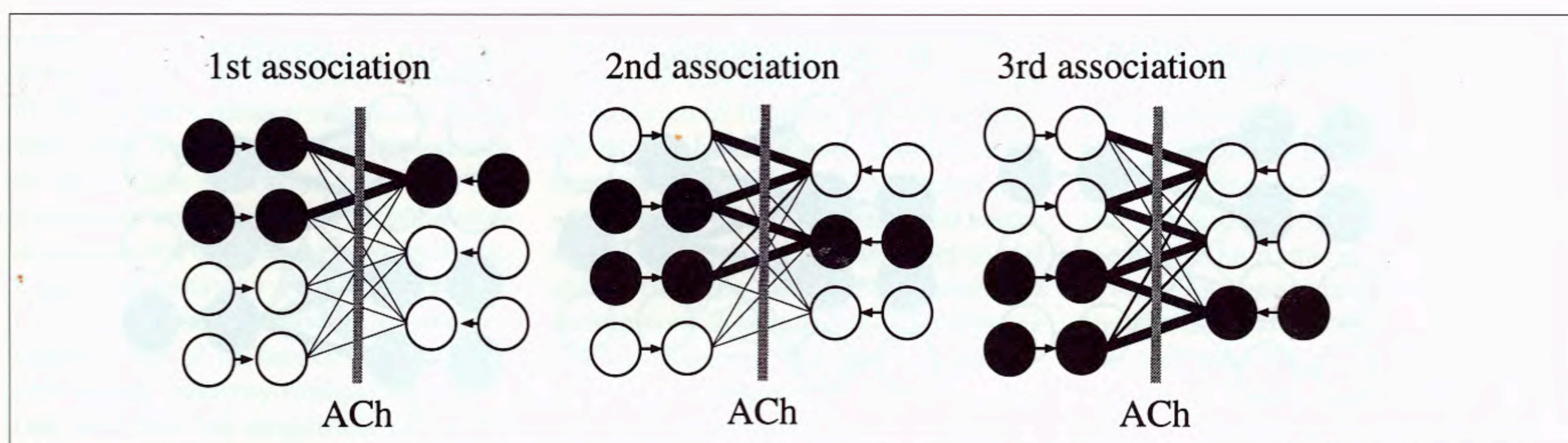


Figure 2. Runaway synaptic modification. As more overlapping memories are stored in the network, greater interference during learning occurs. Learning of the first association shows no interference (Part A). Interference due to recall of the first association during learning of the second (Part B) causes strengthening of one additional undesired connection (dashed line). Recall of the first and second associations during learning of the third (Part C) causes strengthening of two additional undesired connections.

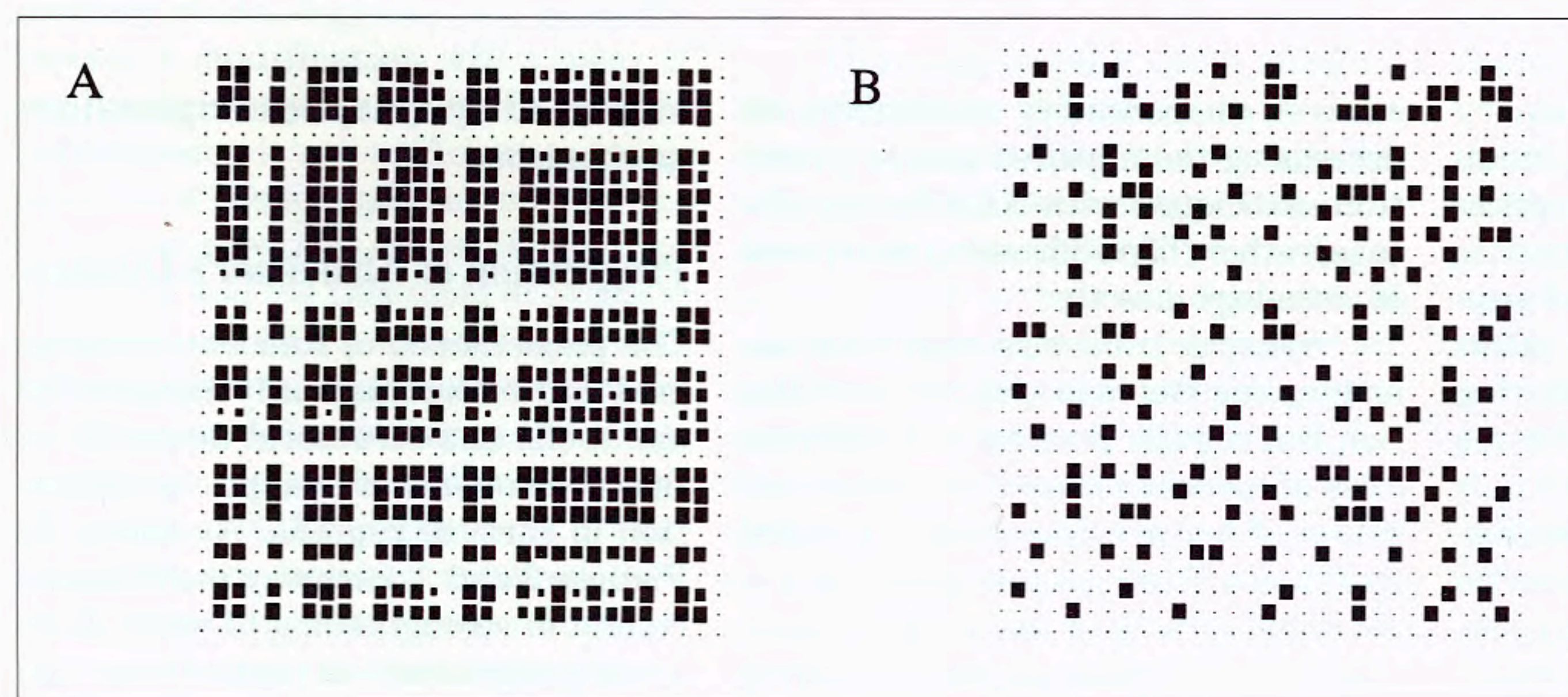


Figure 3. Changes in the matrix of synaptic connectivity in an associative memory model. The size of a black square represents the strength of a synapse after runaway synaptic modification (Part A) and after normal learning (Part B).

Although the effect of interference during any particular stage of learning may be small, this phenomenon can severely affect the function of the network over time, because the effects are compounded by subsequent learning. The progressive buildup of interference from previous retrieval leads to a malignant nostalgia resulting in runaway synaptic modification throughout the network (Fig. 3). In this case, severe proactive and retroactive interference results in a complete breakdown of normal memory function. This runaway interference during learning has been examined in detail with mathematical analysis [9] and computational models [8].

Most models of associative memory ignore the effects of synaptic transmission at modifiable synapses during learning [14,16], allowing synaptic transmission only during recall. In computational models, this suppression of

synaptic transmission at excitatory connections between neurons during learning can prevent runaway synaptic modification [8–10]. Although suppressed synaptic transmission during learning has been used for decades in models of neural networks, a neurophysiologic mechanism for this effect was demonstrated only recently.

Recent studies have shown that acetylcholine can selectively decrease synaptic transmission between neurons in a cortical region, without affecting synaptic transmission elsewhere [19–21]. In addition, acetylcholine can enhance the excitability of cortical neurons to the afferent synaptic input [22]. In computational models of cortical associative memory function, application of this selective suppression of synaptic transmission between neurons in a region during learning prevents interference from previously learned memories

[8–10,20]. While the examples here (Fig. 2 and 3) are simplified, the prevention of runaway synaptic modification has also been explored in detailed biophysical simulations of cortical associative memory function [10]. Prevention of runaway synaptic modification by cholinergic suppression of synaptic transmission is illustrated in Figure 4.

In this new framework for learning, synaptic modification must be maximal during the suppression of synaptic transmission by acetylcholine. But how does this allow activation of the postsynaptic receptors necessary for modification? Activation of postsynaptic mechanisms of synaptic modification is still possible because the suppression of synaptic transmission is not complete. In neurophysiologic experiments, the suppression of synaptic transmission by acetylcholine is usually less than 70% [20].

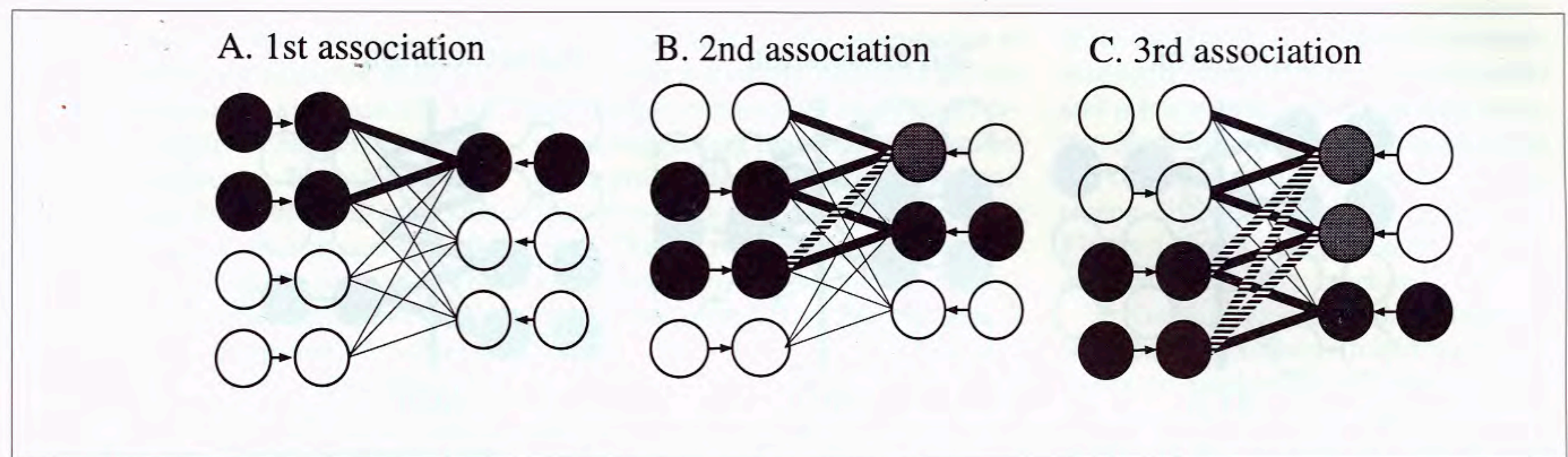


Figure 4. Suppression of synaptic transmission by acetylcholine (ACh) during learning to prevent runaway synaptic modification. The vertical gray line represents diffuse suppression of transmission at modifiable synapses, which keeps the spread of excitation across previously modified synapses from bringing postsynaptic neurons above threshold. This allows Hebbian synaptic modification to occur only between neurons receiving direct external input (only these neurons have sufficient postsynaptic activity). Strengthening of additional undesired connections does not occur (compare with Figure 2).

Analysis of associative memory models incorporating feedback inhibition, a threshold for synaptic modification, and gated decay of synaptic strength shows that this level of suppression is sufficient to prevent interference during learning, while allowing sufficient synaptic transmission for the modification of synapses [9]. In models of cortical associative memory function, interference during learning can be prevented by the proper balance of six cortical properties: presynaptic modulation of synaptic transmission by acetylcholine, regulated decay of synaptic connectivity strength, postsynaptic modulation of cellular excitability by acetylcholine, the level of inhibition in the network, the threshold for synaptic modification, and the nature of the patterns being stored in the network. In addition, acetylcholine has been shown to enhance synaptic modification in cortical structures [10].

Associative memory models with fixed-point attractor dynamics have been used in other modeling studies of Alzheimer's disease [23,24], in which the accuracy of memory recall was analyzed as different numbers of synaptic connections or processing units were deleted from the network. Deletion caused a gradual impairment in memory function that could be offset by postulating various processes for synaptic compensation, in which strengthening of the remaining synapses offset the loss of others. Thus, this research fo-

cuses on compensatory mechanisms for decreasing the impaired memory function associated with Alzheimer's disease, rather than addressing the spread of pathology directly.

Synaptic transmission at synapses undergoing Hebbian synaptic modification is a regular feature of a different class of models, focused on self-organization of feature detectors in cortical structures. These models avoid the exponential growth of the full population of synapses by using techniques such as normalization (in which the sum of strength of individual synapses is constrained to remain constant). However, even slight imbalances in the mechanism of normalization of synaptic strength cause a breakdown of function and runaway synaptic modification in these networks.

Here it is proposed that neuronal degeneration in Alzheimer's disease may result from runaway synaptic modification due to an imbalance of synaptic normalization, which could include flaws in the function of the amyloid precursor protein or the tau protein. The focus of this model differs from that of other models of Alzheimer's disease [23,24], which do not attempt to address the dynamics of spread of cortical neuropathology. These previous models start with the assumption of loss of neurons or synaptic connections in models of cortex, and then analyze how the effects of this loss on memory function may be

influenced by synaptic compensatory mechanisms.

Progression of Alzheimer's Disease

The phenomenon of runaway synaptic modification would greatly increase the metabolic and structural demands on the mechanisms of synaptic modification in cortical regions. As shown in Figures 2 and 3, runaway modification results in strengthening of many additional connections—in proportion to the number of associations stored in the network. Thus, runaway synaptic modification in a network storing 100 different associations would result in modification at a 100-fold greater number of synapses. While cortical structures do not show the complete connectivity used in these models, the axon collaterals of each neuron in a cortical region make from 1000 to 10,000 excitatory synapses on other neurons. An exponential increase in the demands on synaptic modification might explain neuronal degeneration of the sort seen in Alzheimer's disease.

This theory does not stand in opposition to any specific theory of the etiology of the disease, since it suggests that the progression of Alzheimer's disease could start from any of a number of imbalances in cortical function. In fact, this theory could even allow for multiple different initiating factors—including gradual overloading of the capacity of cortical networks.

Onset of Neuropathology

Evidence for specific genetic markers of Alzheimer's disease raises the question: Why does the disease appear late in life? This question might be answered by analysis of how an imbalance of cortical variables can result in the initiation of runaway synaptic modification. This analysis shows the relative importance of different variables in preventing runaway synaptic modification, and how the magnitude of the imbalance relates to the speed of progression of runaway synaptic modification.

As noted above, the imbalance could result from changes in the strength of any of a number of factors. For example, analysis of an associative memory model suggests that runaway synaptic modification will appear if cholinergic suppression of synaptic transmission is not sufficient to bring the level of postsynaptic activity for undesired connections below the level of inhibition and the threshold of synaptic modification [9]. Another important factor in determining whether runaway synaptic modification appears in the network is the normalization of synaptic weights. If the mechanisms of normalization are somehow impaired, then runaway modification can be initiated.

In cortical function, the relative strength of any of these variables could change as a result of toxic factors, or these variables could be improperly balanced because of a genetic predisposition. With low cholinergic suppression, low inhibition, and a low threshold of synaptic modification, runaway synaptic modification will occur after a smaller number of patterns are stored. With strong cholinergic suppression, strong inhibition, and a high threshold of synaptic modification, runaway synaptic modification will take longer to appear, or may be prevented entirely. It is the relative balance of these different variables that determines how well the network resists the initiation of runaway synaptic modification.

The breakdown of function can take one of two forms: the network can start with a given balance of variables, and when the capacity of the network is exceeded, runaway synaptic modification will cause a breakdown of function; or the network can start with a given

balance of variables and undergo a change in this balance that causes the breakdown of function. In either case, the larger the imbalance, the earlier the breakdown appears, and the more rapidly it will progress. A simplified analysis of a linear associative memory model shows that the undesired connections strengthened because of interference during learning will grow exponentially. If suppression by acetylcholine is very low relative to other cortical variables, interference will appear sooner in the network, and spread faster throughout the network. If there is only a slight imbalance, interference will take much longer to appear, and once it appears, it will progress more slowly [9].

This phenomenon could underlie the evidence for differences in the time course of progression of presenile dementia of the Alzheimer type (the term used for patients under 65 years of age) as compared with senile dementia of the Alzheimer type (the term used for patients over 65). Measurements of the anatomical markers of Alzheimer's disease suggest greater severity in presenile dementia than in senile dementia of the Alzheimer type [25]. In addition, some studies suggest a correlation between age and cognitive performance on memory tasks, with younger patients performing worse [26], and clinical evidence suggests that the rate of progression from onset of symptoms to death may be more rapid in presenile dementia [27]. However, other evidence suggests that the progression of neuropsychological deterioration is actually slower in presenile dementia [28].

This model of the initiation of pathology in Alzheimer's disease could also be used to address the epidemiology of this disease. It has been characterized as a disease of old age primarily because its frequency increases rapidly with increasing age. The exponential progression of runaway synaptic modification in these computational models could be used as a model of the epidemiology of Alzheimer's disease. Since the risk factors for onset of runaway synaptic modification include many components of normal cortical function, there may be some probability in all humans that these pathological ef-

fects will be induced. Depending on individual variation in certain variables, the induction will take place at different times, but once initiated, it will progress exponentially. This means that the percentage of cases of senile dementia of the Alzheimer type should increase exponentially with age (although an epidemiologic prediction of this sort must take into account the reduction in the population at each age level). There is certainly a rapid increase in the number of cases of Alzheimer's disease in later life [29], and neuropathological data from normal elderly subjects suggest a rapid increase in the density of tangles with increasing age, even in tissue from subjects without a diagnosis of Alzheimer's disease [3].

A more radical prediction of the model is that runaway synaptic modification will appear more rapidly in proportion to the greater overlap between stored patterns. This suggests that the amount of correlation in the environment could influence the propensity for development of Alzheimer's disease.

Distribution of Neuropathology

If the pathology associated with Alzheimer's disease results from runaway synaptic modification, this suggests that the apparent early and severe involvement of layers II and IV of the lateral entorhinal cortex, region CA1 of the hippocampus, and the adjacent regions of the subiculum [3-5] results from a particular sensitivity of these regions to runaway synaptic modification. It is possible that sensitivity to runaway modification is associated with two features: a strong capacity for Hebbian synaptic modification, and lack of suppression of synaptic transmission by acetylcholine during learning.

Considerable research has focused on how subregions of the hippocampus resemble the structures of associative memory models [30]. As noted above, this region shows robust Hebbian synaptic modification [18] and has been implicated in memory function in extensive research [6]. The greater propensity for synaptic modification could underlie the early sensitivity of the hippocampal formation. The early sensitivity of lateral entorhinal cortex

could be linked to the absence of cholinergic suppression at synapses arising from this region and terminating in the outer molecular layer of the dentate gyrus [31], while the relative sparing of region CA3 could result from the robust cholinergic suppression of synaptic transmission at synapses arising from CA3 pyramidal cells [19,21].

Spread of Degeneration

The pathology of Alzheimer's disease appears to spread from the hippocampus into the neocortex along well-established anatomical connections, the back projections from the subiculum and entorhinal cortex to the association cortex [4,11]. In later stages of the disease, neurofibrillary tangles appear in regions of the temporal, parietal, and frontal neocortex [11]. Neurofibrillary tangles primarily spread into cortical regions, although the plaques associated with terminal degeneration appear in subcortical regions as well [11].

This spread of degeneration is here proposed to result from the spread of runaway synaptic modification between cortical regions. This would occur by the same mechanisms important for transferring information stored in the hippocampus back into the neocortex—the process of consolidation [32]. A network simulation of the hippocampus [33,34] has been used to model the process of consolidation, as shown in Figure 5.

Runaway synaptic modification could spread from the hippocampus back into the neocortical structures by means of the same mechanisms used in consolidation. It has been shown in simulations that if runaway synaptic modification occurs during the initial formation of representations of new memories in the hippocampus, then subsequent retrieval of these representations will result in a spread of runaway synaptic modification. For example, as shown in Figure 6, a decrease in the mechanisms of synaptic decay of the input from entorhinal cortex layer II to dentate gyrus results in the initiation of runaway synaptic modification in this pathway. Even if the properties of other connections have not been altered, the initiation of runaway synaptic modification at these perforant path

synapses results in the spread of runaway synaptic modification into back projections from region CA1 to the neocortex. In simulations with multiple interacting layers, initiation of runaway synaptic modification in one layer results in progressive spread to other layers, even if those layers would not undergo runaway synaptic modification independently.

Modeling suggests that runaway synaptic modification will spread according to functional boundaries. That is, after occurring in neurons encoding a particular category of information, it will influence similar information before influencing unrelated information. This might explain the apparent heterogeneous distribution of tangles in Alzheimer's disease and the apparent specificity for certain modalities in some cases. In particular, the distribution of neurofibrillary tangles may be on the order of the size of cortical columns, with tangles in layers II and III in register with tangles in layers V and VI [11].

The rate of spread of runaway synaptic modification depends on the ongoing capacity for Hebbian synaptic modification and the amount of excitatory associative connectivity. Primary sensory and motor cortexes have more restricted and specific connectivity of excitatory connections in the region [35, 36], and are further removed from the highly plastic structures of the hippocampal formation. This may explain why the neuropathology in Alzheimer's disease is far less pronounced in the primary sensory cortexes [11,36].

Levels of Acetylcholine

Postmortem studies have shown decreases in cortical levels of various neurochemicals in patients with Alzheimer's disease, with a primary focus on markers for acetylcholine. Concentrations of the enzymes that create and break down acetylcholine (cholineacetyltransferase and acetylcholinesterase) are markedly decreased in the cortex among patients with Alzheimer's disease [12]. In addition, the regions of the basal forebrain that provide the cholinergic innervation of cortical structures show decreased numbers of neurons, suggesting that they undergo

degeneration in Alzheimer's disease [13,37].

Even in young normal subjects, drugs such as scopolamine that block acetylcholine receptors strongly impair memory function [26,38]. This finding led to the suggestion that the memory deficits of Alzheimer's disease are somehow related to the loss of cortical cholinergic innervation. Administration of acetylcholinesterase blockers alleviates the memory impairment associated with Alzheimer's disease. However, other evidence from patients with this disease indicates increased sprouting of the fibers bringing acetylcholine to the dentate gyrus—part of the hippocampal formation [39]—and increases in cholineacetyltransferase staining levels in the dentate gyrus and stratum moleculare of the subiculum [40]. In addition, memory impairment has been correlated with enlargement of basal forebrain neurons in aged non-human primates [37].

The latter effects have been suggested to reflect the reafferentation of hippocampal neurons that have lost their innervation from the entorhinal cortex. However, the effects of acetylcholine on dentate gyrus granule cells are different from the effects of the glutamate released by the terminals of the perforant path. It is unclear why sprouting would occur to replace such innervation. The model presented here provides a different perspective on these data.

As shown above, acetylcholine can help prevent runaway synaptic modification in models of cortical associative memory. Although deficiencies of acetylcholine could underlie the initiation of runaway modification, this could also be due to changes in other variables, without any notable change in the level of acetylcholine. However, it is likely that once runaway synaptic modification begins to appear, the normal feedback mechanisms that regulate the level of acetylcholine are increased as a mechanism for preventing the breakdown of function. The increasing demand for acetylcholine might initially result in a strong enhancement of its levels. This effect could underlie the increased sprouting of axons that brings acetylcholine to the dentate gyrus [39]

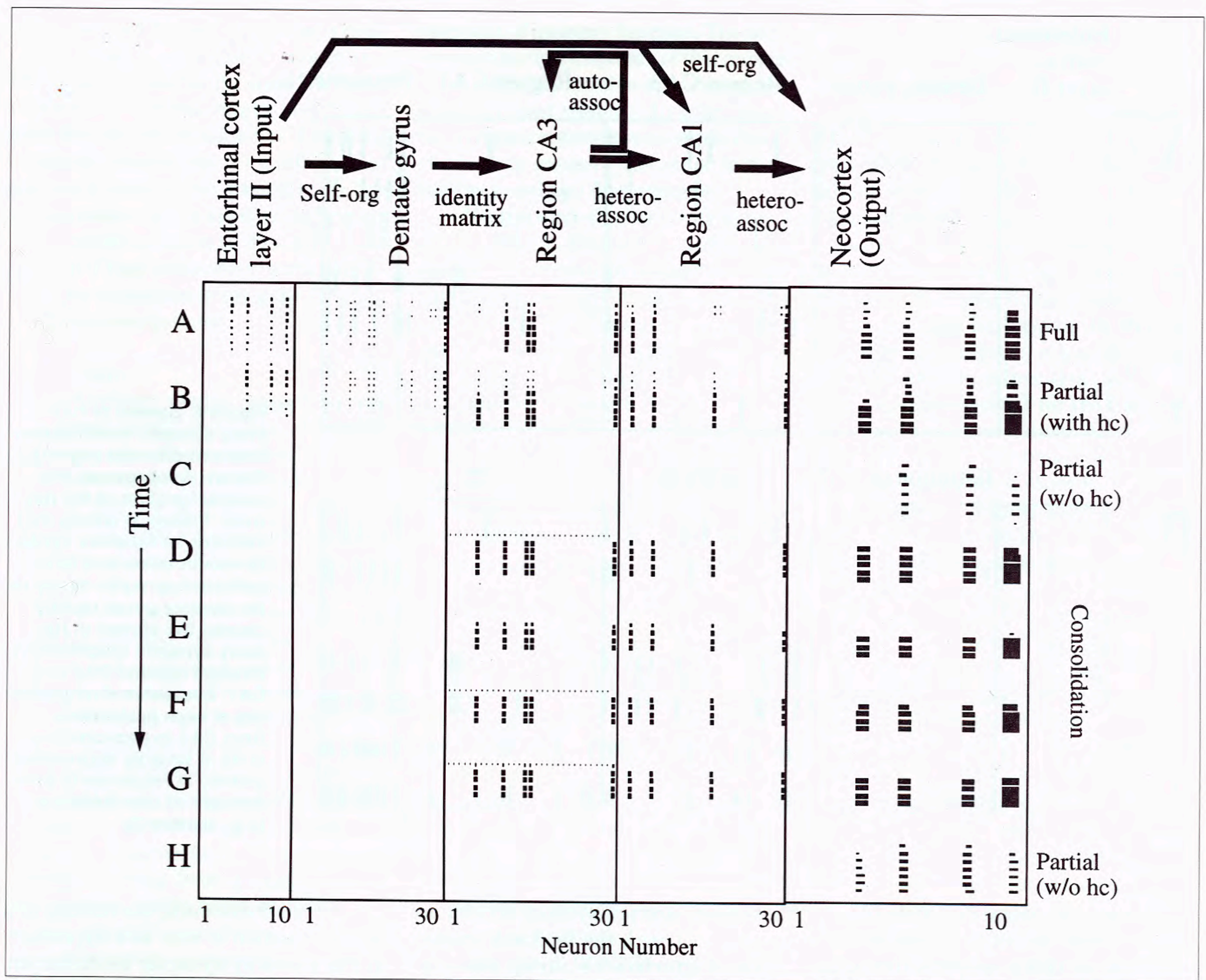


Figure 5. Consolidation of a single pattern in a network model of the hippocampal formation. The size of a black square represents the activity of individual neurons.

Row A shows the presentation of input to the entorhinal cortex layer II. Synaptic modification in dentate gyrus forms a sparse self-organized representation, and modification in region CA3 forms an attractor state. Row B shows testing recall with degraded (partial) input with the hippocampus (with hc) present. Representations are activated in the dentate gyrus and region CA3. Attractor dynamics in region CA3 govern recall activity in CA1 and neocortex. Row C shows that with a simulated hippocampal lesion (w/o hc), no recall can occur. Input to neocortex alone does not result in recall before consolidation. This corresponds to temporally limited retrograde amnesia.

Rows D to G show consolidation. Homogeneous depolarization of region CA3 results in activation of the previously stored attractor state. This activates the full pattern in neocortex, allowing gradual strengthening of synapses in neocortex. In row H the preceding period of consolidation allows neocortex to respond to the partial input cue with the full learned pattern. Thus, after consolidation, memory recall is not impaired by lesions of the hippocampus.

and the increase in acetylcholinesterase staining in the dentate gyrus and subiculum [40]. This enhanced staining appears in exactly those regions where insufficient acetylcholine during learning may underlie the initiation of runaway synaptic modification.

Whereas a large increase in acetylcholine might slow the progression of

runaway synaptic modification, once the breakdown has been initiated it is difficult to forestall. Even at very high concentrations of acetylcholine some synaptic transmission remains [20], allowing continued runaway synaptic modification. The continually increasing demands that would result could lead to initial hypertrophy and eventual degeneration of

cells of the basal forebrain nuclei from which this innervation arises [13]. Thus, the model suggests two phases: an initial increase of innervation and subsequent degeneration.

Molecular Components

The phenomenon of runaway synaptic modification in models suggests how

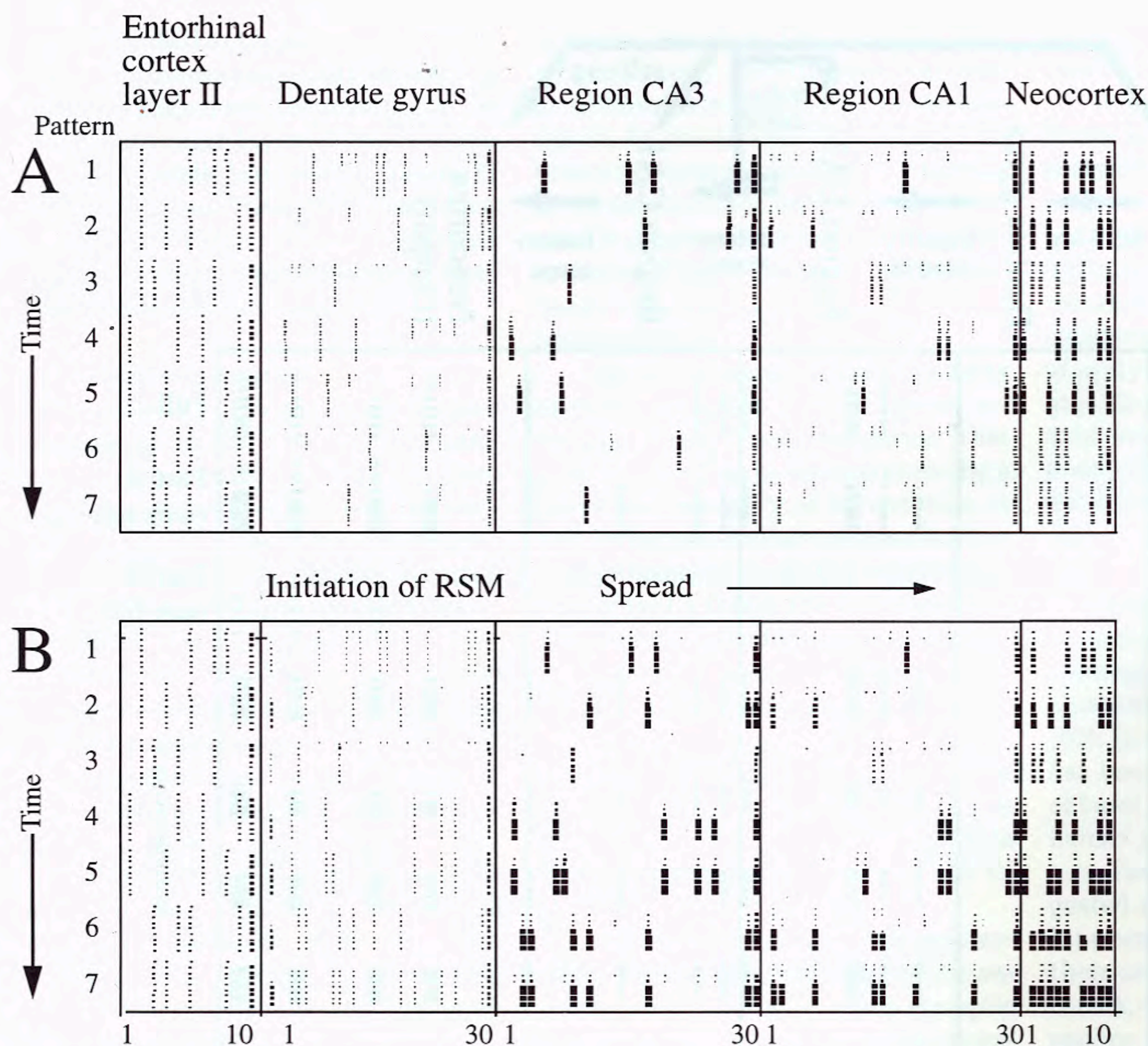


Figure 6. Spread of runaway synaptic modification between different regions. Pattern A represents the normal function of the network. Pattern B shows that initiation of runaway synaptic modification due to insufficient synaptic decay in the dentate gyrus rapidly causes the spread of runaway synaptic modification through regions CA3 and CA1. Excessive strengthening of back projections from CA1 to neocortex results in broadly distributed activity in response to presentation of later patterns (e.g., pattern 7).

molecular components of Alzheimer's disease might underlie the initiation of runaway synaptic modification, and how runaway synaptic modification could result in large-scale deposits of these substances.

Neuritic plaques have as their main component an accumulation of β -amyloid protein. This protein apparently arises from a normal component protein of the brain referred to as amyloid precursor protein, whose properties are compatible with some role in the growth and maintenance of synaptic connections [41]. For example, amyloid precursor protein may prevent the breakdown of existing or newly strengthened synapses. In this framework, if postsynaptic activity is not correlated with the activity of the presynaptic terminal, the breakdown of amyloid precursor protein will allow extracellular processes to break down the components of the synaptic contact. However, if all synaptic connections show evidence of increased correlation of

presynaptic and postsynaptic activity, as would occur with the feedback mechanisms of interference during learning, then amyloid precursor protein will not be removed, but will continue to accumulate on the presynaptic terminals. This will allow runaway growth of the synaptic connection, and could ultimately lead to high concentrations of the protein throughout cortical regions with excessive synaptic modification. The pathways concerned with the breakdown of precursor protein would come under increasing demands, possibly leading to a buildup of β -amyloid protein in the region of the synapse.

Alternatively, the cell giving rise to the synapse might be unable to cope with the excessive metabolic demands of thousands of growing synapses. Its death would lead to the degeneration of a synaptic terminal with high concentrations of amyloid precursor protein, which might be broken down into β -amyloid protein.

In this framework, the buildup of β -amyloid protein is seen as a byproduct of the runaway synaptic modification due to interference during learning, but this framework could also account for a causal role in Alzheimer's disease—not of β -amyloid protein—but of overproduction of its precursor, amyloid precursor protein. Overproduction due to genetic mutations or the additional copy of chromosome 21 associated with Down syndrome would lead to excessive precursor protein on the presynaptic terminal. This would slow the normal breakdown or weakening of synaptic connections not associated with correlation of presynaptic and postsynaptic activity, and could ultimately trigger the initiation of runaway synaptic modification. This would account for the apparent link of some forms of familial Alzheimer's disease with genetic defects in amyloid precursor protein or in other portions of chromosome 21 as well as the apparent de-

velopment of Alzheimer's-type symptoms in people with Down syndrome. Perhaps the mental retardation found in Down syndrome might also result from insufficient breakdown of existing synaptic connections. Any influence of amyloid precursor protein on the mechanisms of synaptic modification could result in runaway synaptic modification if that influence is somehow altered by mutations in the gene for amyloid precursor protein.

Tau Protein

Neurofibrillary tangles appear to contain considerable levels of paired helical filaments, of which a primary component is an abnormally phosphorylated form of the tau protein [42]. The tau protein may play a role in the assembly of microtubules. Blockade of the expression of tau protein impairs the development of axons in culture [43], suggesting possible involvement in the growth and remodeling of axonal connectivity, or in axonal transport mechanisms. Thus, the tau protein may be involved in the formation and regulation of synaptic connections. A breakdown in normal functioning of the tau protein might lead to slowing of the mechanisms for normalization of synaptic strength arising from a single neuron. A slowdown in this redistribution of synaptic strength could allow the initiation of runaway synaptic modification in a self-organizing network.

Once runaway synaptic modification begins, it may place increasing demands on this aspect of cellular function, since it requires increased transport of substances produced in the cell body to the thousands of growing synapses. Ultimately, this could overload the capacity of the axonal transport system, leading to excessive production of structural elements of cellular transport and, ultimately, increased accumulation of the byproducts of this system, the paired helical filaments. The increased demands on each individual neuron might eventually cause a complete breakdown of function, with the death of neurons, leaving neurofibrillary tangles.

Neuropsychology

In its initial stages, a major characteristic of Alzheimer's disease is the im-

pairment of memory function. The most common early symptoms of this impairment primarily involve episodic or declarative recent memory. In later stages, the symptoms progress to impairments of semantic memory and other factors, such as emotional disturbances.

Neuropsychological tests show a clear deficit in memory in Alzheimer's disease [2]. Impairments appear to be particularly severe on memory for recent events. The computational modeling presented here suggests that runaway synaptic modification could cause increased interference between stored representations, producing impairments in short-term memory tasks requiring free recall [2] and increasing the number of intrusions reported in other tasks [44-48]. Continued interference effects during learning could lead to the spread of runaway synaptic modification into the neocortex by means of the mechanisms of consolidation. This would lead to impairments of remote memory [49] and semantic memory [50].

It is important to discriminate the neuropsychological effects at different stages of Alzheimer's disease. In the early stages, the interference effects predicted by the model should be evident. In later stages, degeneration of cortical structures could affect memory in ways less directly related to interference during learning.

The model predicts that interference between stored memories impairs memory function in early stages of the syndrome. Thus, storage and retrieval of information will still be possible, but encoding of information will be impaired, particularly for overlapping memories. Interference may not only result in erroneous answers due to intrusions from previously learned information, but also, in some situations, it may lead to activation of many conflicting associations, so that the subject is unable to recall any particular association. In any case, this model predicts that in the early stages of Alzheimer's disease, interference effects should become more severe.

The concept of interference between memories is compatible with the presenting characteristics of Alzheimer's disease. The most common complaints refer to loss of memory for the

location of simple household objects, loss of topographical memory, loss of orientation in time, and loss of recognition memory for acquaintances. All these forms of memory require accurate recall of complex associations with a high degree of similarity. Development of higher-order spurious associations between these items would severely interfere with day-to-day memory. A similar effect might underlie associations for days of the week or the various streets in a neighborhood. As summarized in previous work [9], the model can account for the following neuropsychological data on Alzheimer's disease: increased intrusion errors, interference effects in short-term retention, sparing of implicit memory, homogeneous impairment of remote memory, and impairments of semantic memory.

However, this theory is far from complete. The predictions of the model must be tested in experiments using techniques ranging from brain slice physiology to behavioral memory tasks. In addition, more detailed biophysical simulations of the cortical structures affected by the disorder must be analyzed. However, computational modeling of the breakdown of function in cortical structures provides a unique way of linking evidence on this disorder obtained with different experimental techniques. Computational modeling techniques will be vital to bringing together the disparate disciplines of neuroscientific research in the understanding of Alzheimer's disease.

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