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Review article

Free recall and recognition in a network model of the hippocampus: simulating effects of scopolamine on human memory function

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Abstract

Free recall and recognition are simulated in a network model of the hippocampal formation, incorporating simplified simulations of neurons, synaptic connections, and the effects of acetylcholine. Simulations focus on modeling the effects of the acetylcholine receptor blocker scopolamine on human memory. Systemic administration of scopolamine is modeled by blockade of the cellular effects of acetylcholine in the model, resulting in memory impairments replicating data from studies on human subjects. This blockade of cholinergic effects impairs the encoding of new input patterns (as measured by delayed free recall), but does not impair the delayed free recall of input patterns learned before the blockade. The impairment is selective to the free recall but not the recognition of items encoded under the influence of scopolamine. In the model, scopolamine blocks strengthening of recurrent connections in region CA3 to form attractor states for new items (encoding impaired) but allows recurrent excitation to drive the network into previously stored attractor states (retrieval spared). Neuron populations representing items (individual words) have weaker recurrent connections than neuron populations representing experimental context. When scopolamine further weakens the strength of recurrent connections it selectively prevents the subsequent reactivation of item attractor states by context input (impaired free recall) without impairing the subsequent reactivation of context attractor states by item input (spared recognition). This asymmetry in the strength of attractor states also allows simulation of the list-strength effect for free recall but not recognition. Simulation of a paired associate learning paradigm predicts that scopolamine should greatly enhance proactive interference due to retrieval of previously encoded associations during storage of new associations. © 1997 Elsevier Science B.V.

Keywords: Free recall; Recognition; Episodic memory; Acetylcholine; Presynaptic inhibition; Medial septum; Feedback; Attractor dynamics

1. Introduction

Most models of human memory function [1–7] are interpretive—they help us understand behavioral data and guide behavioral experiments, but do not address the biological substrates involved. In contrast, the model presented here is mechanistic—directly addressing the physiological and anatomical substrates of performance in human memory tasks such as free recall and recognition. This model extends previous theories of the function of hippocampal subregions [8–20] in four major ways: (1) by simulating specific human memory tasks, such as free recall and recognition (2) by addressing a current issue in human memory modeling—the list strength effect (3) by explicitly modeling the effect of the cholinergic antagonist scopolamine on human memory function, and (4) by generating an experimentally testable prediction about the effect of scopolamine on paired associate learning.

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1.1. Reasons for modeling the effects of scopolamine

Modeling drug effects on memory function allow us to link effects at a cellular level to effects at a behavioral level. In contrast, models of the effects of lesions are less constrained by physiological and anatomical data. For example, we could model the role of the hippocampus in memory function, and then block the function of the model to simulate the effect of a hippocampal lesion. But a study of this sort could use a network simulation of any kind, since it is only the presence or absence of the network that is being manipulated. In contrast, modeling of drug effects on memory function requires that the selective behavioral effects of drugs be simulated in terms of the selective physiological effects of drugs at a cellular level.

A wide range of data supports some role for acetylcholine in memory function. Since the turn of the century, anaesthesiologists have been aware that administration of the muscarinic antagonist scopolamine (to decrease respiratory tract secretions in preparation for surgery) often strongly impairs memory [21]. Experimental work has demonstrated a striking impairment of the free recall of lists of words learned under the influence of scopolamine [22–28]. For example, subjects were able to recall 45 out of 128 words which they encoded after injections of saline, but only 5 out of 128 words which they encoded after injections of scopolamine [24]. Our model simulates the results of the experiment summarized in Fig. 1. This experiment demonstrated two selective features of the effect of scopolamine on human memory function: (1) scopolamine impairs the delayed free recall of a list of words learned after injection, but does not impair delayed free recall of words learned before the injection of scopolamine, and (2) though scopolamine during encoding impairs subsequent free recall, subsequent recognition of the same words is not significantly impaired.

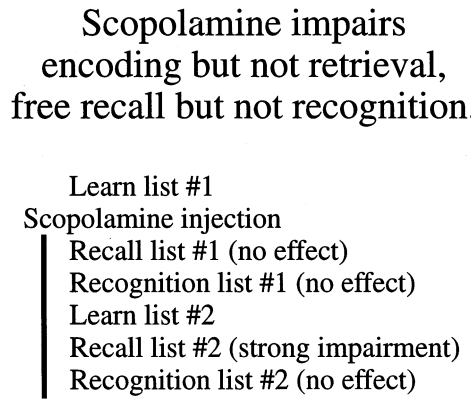

Fig. 1. Design of experiment showing two selective effects of scopolamine. Subjects were trained on a set of eight lists of 16 words each (word set no. 1) before the injection of scopolamine. Half an hour after an injection of scopolamine or saline, the subjects were tested on the delayed free recall and recognition of word set no. 1, and no significant impairment was detected. Subjects were then trained on word set no. 2 and tested on immediate free recall and delayed free recall of these words, and afterward on delayed recognition. Subjects on scopolamine showed strong impairments in the delayed free recall of word set no. 2 compared with controls (subjects injected with saline), but did not show a significant difference in the accuracy of delayed recognition.

The model also generates a prediction about the effects of scopolamine on paired associate learning. Only a few studies have addressed the effects of scopolamine on paired associates. Scopolamine impaired encoding of paired associates in section VI of the Wechsler memory scale [29] encoding of number-color associations [22], and memory for self-generated paired associates [30]. A recent study using very strong pre-existing category associations showed no impairment [31]. Our model generates the prediction that scopolamine should enhance proactive interference between lists of paired associates sharing the same cue word.

1.2. Reasons for modeling the hippocampus

Because the cellular effects of scopolamine cannot be addressed within the framework of current models of human memory function, we have developed a model of hippocampal episodic memory function which can be used to link these effects to specific parameters of cholinergic physiology. Modeling the hippocampus is appropriate because of the neuropsychological data showing that lesions of the hippocampus selectively impair components of memory function which are influenced by scopolamine. Scopolamine strongly impairs delayed free recall, but usually does not affect forward or backward digit span [23,29,32] or the recency component of a serial position curve [22,28]. Similarly, hippocampal lesions impair the delayed free recall of information [33–35], while having little effect on digit span [35], and the recency component of the serial position curve [36]. Both scopolamine and hippocampal lesions appear to spare semantic memory and consolidated episodic memory [37,38].

Some lesion data from non-human primates indicates that the impairments in patients such as HM are partly due to removal of perirhinal cortex and the parahippocampal gyrus [39]. However, severe memory impairments have been demonstrated in patients with damage restricted to subregions of the hippocampus, such as patient RB [38,40]. For example, in tests of the free recall of ten words from the middle of a 15 word list, patient RB only recalls 10% of the words, whereas controls recall about 40% [41]. Similar striking differences between controls and patients with hippocampal lesions appear in tests of the free recall of information from a story—commonly a subtest of the Wechsler Memory Scale [38]. This data supports the specific significance of hippocampal subregions in storage of verbal information.

In addition to drug effects, damage to cholinergic innervation impairs memory function in a range of tasks. In humans, damage to cortical cholinergic innervation caused by anterior communicating artery aneurysms impairs performance in tests of the free recall of lists of words or information from paragraphs [42,43], causes enhanced interference in an A–B, A–C paradigm [44] and also results in considerable confabulation in memory tasks [45]. In non-human primates, lesions of the fornix, which cuts off most of the cholinergic innervation of the hippocampus, have been shown to impair formation of 'snapshot' memories [46].

In addition to the extensive behavioral data suggesting some role for the hippocampus in human memory function, there is a wealth of data on the anatomy and physiology of this structure, and extensive theoretical work on the function of individual subregions. Here we present a simulation of the encoding and retrieval of a set of inputs representing words within a network representing the full hippocampal circuit. We test the sequential encoding of the input patterns, and the delayed free recall and recognition of these patterns.

1.3. Scopolamine blocks specific effects of acetylcholine within the cortex

The combined effects of acetylcholine on cellular physiology may set appropriate dynamics for encoding of new information in cortical structures [47–49]. In the model presented here, the effects of scopolamine on delayed free recall are mediated through blockade of specific cellular effects of acetylcholine. We will discuss the memory impairment with respect to four different physiological effects of the blockade of muscarinic receptors by scopolamine, as summarized in Fig. 2. Most cellular data has been obtained from rat cortex, but data on the response of human cortical neurons to cholinergic modulation indicates an overall consistency with other mammalian species [50].

1.3.1. Scopolamine blocks the selective cholinergic suppression of synaptic transmission

Cholinergic agonists have been shown to strongly suppress excitatory synaptic transmission at specific connections within the hippocampal formation. For example, acetylcholine and cholinergic agonists suppress synaptic potentials elicited in the middle molecular layer of the dentate gyrus [51,52], in stratum radiatum of region CA3 [53,54] and in stratum radiatum of region CA1 [53,55–57]. These effects appear to be selective to specific synapses, since cholinergic agonists have much weaker effects on synaptic transmission in stratum lacunosum/moleculare of CA1 [57] and in the outer molecular layer of the dentate gyrus [52]. Blockade of this selective suppression by scopolamine may enhance proactive interference from previously stored patterns during the learning of new input patterns [47,54,57,58].

Scopolamine blocks effects of acetylcholine in the hippocampus

1. Blocks synaptic suppression	= Stronger feedback (retrieval dominates)
2. Blocks depolarization	= Less depolarization
3. Blocks suppression of adaptation	= Less sustained firing
4. Blocks enhanced modification	= Less synaptic change

Fig. 2. Scopolamine blocks effects of acetylcholine within cortical structures. (1) Acetylcholine decreases the release of the excitatory transmitter glutamate at specific synapses within the cortex [54,57,152]. Scopolamine blocks this suppression of excitatory synaptic transmission, resulting in stronger excitatory feedback. (2) Acetylcholine depolarizes cortical pyramidal cells, bringing them closer to firing threshold [61,62]. Scopolamine blocks this effect, resulting in less depolarization and making neurons less likely to spike. (3) Acetylcholine decreases the adaptation of cortical neurons in response to excitatory input such as current injection, making the neurons spike in a more sustained manner [61,63]. Scopolamine blocks this effect, resulting in less spiking activity. (4) Acetylcholine enhances the rate of synaptic modification in the cortex [65,67]. Scopolamine blocks this effect, resulting in less change in the strength of synapses.

1.3.2. Scopolamine blocks the cholinergic depolarization of hippocampal neurons

Cholinergic agonists have been shown to cause slow depolarizing potentials in cortical neurons in many regions [59–61]. Cholinergic agonists have also been shown to depolarize hippocampal neurons, including both pyramidal cells [62,63] and interneurons [64]. Blockade of this depolarization by scopolamine may prevent the level of excitatory activity necessary for storage of new information, while allowing recall of previously stored information to take place.

1.3.3. Scopolamine blocks the suppression of neuronal adaptation

Cholinergic agonists suppress the adaptation of pyramidal cells in response to excitatory activation in a variety of cortical regions [60,61] including the hippocampus [63]. This suppression of adaptation appears to be due primarily to cholinergic blockade of a calcium-dependent potassium current [63]. Blockade of this suppression of adaptation has the effect of decreasing the spiking response of neurons. This may prevent sustained activity within the hippocampus, thereby preventing the learning of new input patterns.

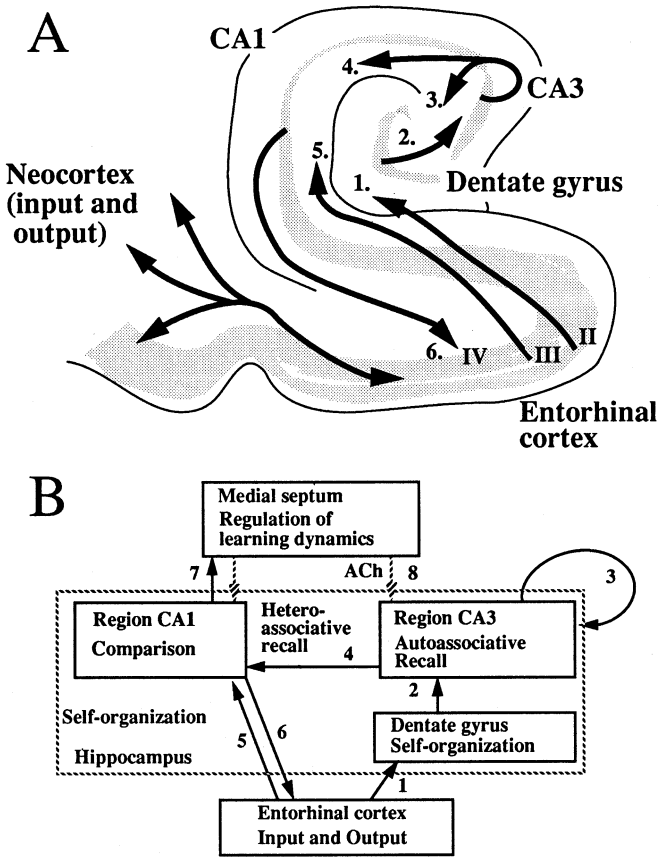

Fig. 3. (A) Anatomical connectivity of the hippocampal formation. Connections between the hippocampus and multimodal association cortices pass through the entorhinal cortex. (1) Fibers of the perforant path connect entorhinal cortex layers II and III with the dentate gyrus. (2) The dentate gyrus projects to region CA3 via the mossy fibers. (3) Longitudinal association fibers connect pyramidal cells within region CA3. (4) The Schaffer collaterals connect region CA3 with region CA1. (5) Perforant path connections also enter region CA1 from the entorhinal cortex. (6) Projections back from region CA1 enter layer IV of the entorhinal cortex either directly, or via the subiculum. Region CA1 can influence activity in the medial septum either directly, or via connections with the lateral septum. The medial septum (and the vertical limb of the diagonal band of Broca) provides cholinergic modulation to all hippocampal subregions. (B) Proposed function of individual anatomical subregions in the model. The entorhinal cortex provides input from neocortical structures and transmits output back to neocortical structures. (1) Perforant path synapses undergo rapid self-organization to form new representations of patterns presented sequentially to the entorhinal cortex. (2) Mossy fibers pass the sparse new representation on to region CA1 for auto-associative storage. (3) Excitatory feedback in CA3 mediates auto-associative storage and recall of these representations. (4) Schaffer collaterals mediate hetero-associative storage and recall of associations between activity in CA3 and the self-organized representations formed by entorhinal input to region CA1. (5) Perforant path inputs to region CA1 undergo self-organization, forming new representations of entorhinal cortex input for comparison with recall from CA3. (6) Feedback from region CA1 stores associations between CA1 activity and entorhinal cortex activity, allowing representations in CA1 to activate the associated activity patterns in entorhinal cortex layer IV. (7) Output from region CA1 regulates cholinergic modulation, allowing a mismatch between recall and input to increase ACh, and a match between recall and input to decrease ACh. (8) Acetylcholine from the medial septum sets appropriate dynamics for learning of new information in the model.

1.3.4. Scopolamine blocks the cholinergic enhancement of synaptic modification

Cholinergic agonists such as carbachol have been shown to enhance long-term potentiation within the dentate gyrus [65], region CA1 [66] and other cortical structures such as the piriform cortex [67], primary visual cortex [68], and somatosensory cortex [69]. Scopolamine may selectively impair learning of new information simply through blockade of this synaptic modification.

The model presented here demonstrates how blockade of the physiological effects of acetylcholine by scopolamine may interfere with encoding of information for delayed recall. Experiments will be proposed which could determine whether the impairment of encoding for delayed free recall is caused by one of the four specific physiological effects described above.

1.4. Focus of the simulation

Given the difficulty of addressing physiological and anatomical data in addition to the behavioral data, we have not immediately addressed the full scope of human memory data. However, we have attempted to address certain sets of data on human memory function in the context of cellular properties of the hippocampus, including the following phenomena:

(1) Effect of scopolamine on encoding, but not retrieval. Blockade of cholinergic effects in the model should impair encoding of new words, but not the retrieval of a list of words learned before blockade of cholinergic effects [24,27].

(2) Effect of scopolamine on free recall, but not recognition. Blockade of cholinergic effects in the model during encoding of a list of words should impair the subsequent free recall of the words, but not the recognition of these words [24,25].

(3) List length effect (LLE). The probability of recall of an individual item should decrease with an increase in the number of items learned [70,71].

(4) List strength effect (LSE). The probability of recall of an individual item should increase with longer or repeated presentation of each individual item [70,71], and the recall of other, non-repeated items from the list should decrease [72].

2. Network model of hippocampal episodic memory

2.1. Summary of hippocampal anatomy

The structure of the model presented here was motivated by experimental data on the anatomy and physiology of the hippocampal formation, and by previous theoretical work on the function of different hippocampal subregions [8–11,13–18,20,53,56,72–74]. Note that

this model contrasts with most previous simulations in that it does not simulate individual effects and ideas in isolation, but combines the functions of different regions into a detailed, self-regulated model including three subregions of the hippocampus along with the adjacent entorhinal cortex. Simulations of the full hippocampal network have been published [75], but those did not address specific human memory tasks such as free recall and recognition, or the effect of drugs on memory function in these tasks. The anatomy of the hippocampal formation and structure of the model are summarized in Fig. 3.

The hippocampus extends along the ventromedial border of the temporal lobe, and receives convergent multimodal input from a wide range of neocortical association areas, most of which project to the hippocampus via neurons of the entorhinal cortex. The hippocampus consists of two interdigitated structures: the dentate gyrus (DG) and cornu ammonis (CA)—the model includes regions CA1 and CA3. Researchers often refer to the classical trisynaptic circuitry of the hippocampus, which consists of a feedforward flow of information between the different structures [76]. As shown in the figure, entorhinal cortex layer II projects via the perforant path to the dentate gyrus. The dentate gyrus projects via the mossy fibers to region CA3, region CA3 contains extensive excitatory recurrent collaterals (the longitudinal association fibers) and also projects on to region CA1 via the Schaffer collaterals. Region CA1 projects back directly and via the subiculum to entorhinal cortex layer IV. In addition to the trisynaptic circuit, there are also direct projections from entorhinal cortex layers II and III to regions CA3 and CA1 of the hippocampus.

Different subregions of the model have the following function:

(1) Entorhinal cortex layer II. Input to this region represents activity induced in entorhinal cortex by presentation of specific words in a behavioral experiment and by the shared experimental context.

(2) Dentate gyrus. This structure forms self-organized representations of each input pattern in entorhinal cortex layer II, with less overlap between the stored representations, and passes the representations on to region CA3.

(3) Region CA3. This region encodes and retrieves associations between the shared experimental context and the individual words, providing the driving force for memory function in the model.

(4) Region CA1. This structure compares the direct input from entorhinal cortex layer II with the output of region CA3, regulating levels of acetylcholine on the basis of how well CA3 retrieval matches direct input.

(5) Medial septum. This region sets the level of acetylcholine in all the other regions, influencing synaptic modification, synaptic transmission, depolarization and adaptation.

(6) Entorhinal cortex layer IV. This region stores associations between the full input patterns and the compressed representations from region CA1, allowing full retrieval of patterns.

These functions are described in more detail below.

2.2. Entorhinal cortex layer II: experimental context and word stimuli are represented by sequential input of activity patterns

This model focused on simulating the encoding of word stimuli in a specific experimental context, and the free recall or recognition of these words (items). This allowed simulation of the effects of scopolamine described in previous experimental work [24]. Fig. 4 shows a summary of the representation of experimental context and individual words as binary patterns of activity in entorhinal cortex.

Both experimental context and individual words encoded during the study phase of a memory experiment are represented by highly overlapping binary patterns of neuronal activity, chosen randomly and presented to entorhinal cortex layer II in the model. Different words were represented by different overlapping binary vectors, while all the words in a single list were presented in association with a single pattern of activity representing the experimental context. Each activity pattern was presented to entorhinal cortex layers II and III for 400

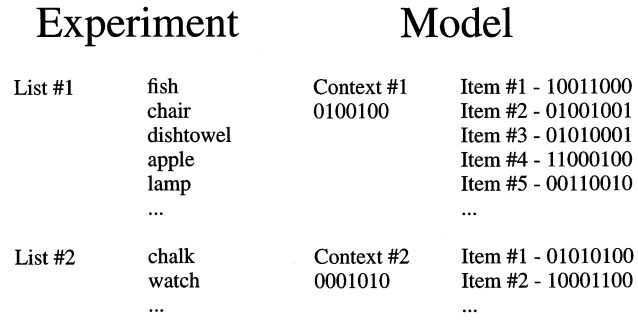

Fig. 4. Relation between experimental stimuli and the input to the simulation. Left: input stimuli in a list learning experiment are illustrated. A specific experimental context consists of features of the testing room, the experimenter and the state of the subject during presentation of each list of words. Each list contains a number of different word stimuli. Right: in the model, experimental stimuli are represented by binary patterns of activity presented to entorhinal cortex layer II. The experimental context is represented by a single randomly chosen binary pattern which does not change during the course of encoding a single list. The individual words are represented by different randomly chosen overlapping input patterns, which are presented sequentially to entorhinal cortex layer II.

time steps. An example of a sequence of such activity patterns is shown on the top of Fig. 10. This input evoked activity in each of the other subregions of the hippocampal formation.

The context vector represents environmental information such as features of the testing room, the presentation medium, and the experimenter as encoded in the form of cortical activity patterns. Presumably such an artificial division of regions into item and context does not exist in the actual hippocampus, but similar dynamics would be obtained as long as item and context information are represented by largely nonoverlapping populations of neurons. This separation of input into item and context resembles the representation of stimuli used in a number of models of free recall [2,77,78]. The variance of context that occurs during exposure to a list is not modeled here as it is in [79], for it is the perseverance of this information that forms the basis of retrieval in this model.

2.3. Context input is provided for free recall, item input is provided for recognition

During retrieval, only partial input was presented to entorhinal cortex layer II. In tests of free recall, subjects are told to recall words from a learned list, with no specific cue for each word. In the model, we simulated this type of retrieval by presenting only the context cue to entorhinal cortex layers II and III. This context cue evoked activity in the dentate gyrus and region CA3 corresponding to context. Within region CA3, this context cue was then able to evoke individual memorized items. Effective recall occurred when the pattern of activity in entorhinal cortex layer IV evoked by the context cue matched one of the item patterns representing a stored word. The free recall of stored items is illustrated in Figs. 8, 10 and 11.

In tests of recognition, subjects are given lists containing words from the learned list as well as distractor words. They are then asked to identify which words had been presented during encoding. In the model, we simulated this type of retrieval by presenting just item patterns to entorhinal cortex layers II and III, some of which had been stored previously, and some of which had not been stored previously. Those items which had been stored previously would evoke the context pattern within region CA3, allowing a 'yes' response. Those items which had not been stored previously would not evoke the context pattern within region CA3, resulting in a 'no' response. The recognition of stored items is illustrated in Figs. 9, 13 and 14.

A recognition process of this sort was first proposed by Hollingworth et al. in 1913 [80,81]. Both he and Norman [82] built from this notion the idea that recognition and recall might be the inverse of one another. This mode of recognition does not yet address the issue of recognition as a function of presentation frequency as do many other models [2,3,7,77]. However, analysis of the temporal delay involved in reactivation of context or items in entorhinal cortex layer IV suggests that it could provide means of simulating effects of cue familiarity on recognition.

2.4. Dentate gyrus: sequential formation of sparse, less overlapping representations

Self-organization of excitatory perforant path connections from entorhinal cortex layer II to the dentate gyrus formed sparse, less overlapping representations of each sequentially presented pattern. The manner in which this occurred involved the initial activation of a subset of dentate gyrus neurons due to the random initial strength of connections from the entorhinal cortex. Neurons which were active then developed stronger connections with active neurons in entorhinal cortex, while connections with other inactive entorhinal cortex neurons became weaker due to synaptic decay regulated by postsynaptic activity. In addition, connections between active entorhinal cortex neurons and inactive dentate gyrus neurons became weaker due to synaptic decay regulated by presynaptic activity. This caused a more selective pattern of connectivity between the active entorhinal cortex neurons and the neurons in the dentate gyrus forming a representation of this pattern. Strengthening of perforant path synapses has been shown to depend upon pre and post-synaptic activity [83,84], and weakening of connections has also been demonstrated [84].

In the model, synapses from the active inhibitory interneuron in the dentate gyrus to the active neurons in the dentate gyrus were also strengthened. This novel mechanism was necessary in order to prevent previously formed representations from dominating learning in response to new representations. This ensured that subsequently it would be more difficult to activate the dentate gyrus units which were members of a particular representation, ensuring that subsequent patterns of activity in entorhinal cortex would evoke different patterns of activity in the dentate gyrus. Without this feature, the network tended to lump all entorhinal cortex patterns into the same representation within the dentate gyrus. Long-term enhancement of inhibitory potentials has been demonstrated after repetitive stimulation in other regions of the hippocampus [85–87].

Previously, the divergent connections from entorhinal cortex to the dentate gyrus have been proposed to distribute activity from overlapping input patterns into sparse nonoverlapping representations [15,17]. These previous theoretical discussions did not focus on modification of synapses of the perforant path. When the dentate gyrus is discussed as a competitive neural network, it is assumed that multiple patterns are repeat-

edly presented during learning [17]. However, this does not effectively account for the apparent role of the hippocampus in episodic memory, where new representations must be formed during a single learning event, without interleaved learning of multiple input patterns. More detailed analysis of the modification of perforant path synapses has been published recently [20], showing that pattern separation can be enhanced via modification, but that study did not explicitly focus on the sequential presentation of different input patterns. For the parameters presented here, it was necessary to utilize the modification of inhibitory connections to allow effective sequential learning of overlapping input [13,14].

2.5. Region CA3: formation of attractors and associations between attractors

The primary locus for memory function within the model was region CA3. This structure mediated the formation of robust episodic representations of items and context, in the form of attractor states set by modification of excitatory recurrent connections. This structure also mediated the formation of associations between item and context information, in the form of weaker associative links between context and item attractors.

Simplified neural network models with excitatory recurrent connections have been used extensively to model memory function [7,54,88–92]. Many of these models have the characteristic of fixed-point attractor dynamics due to their recurrent connections. In these models, stored memories consist of final stable states of activity. Large differences in initial conditions can result in the network settling on different final memory states. However, each final memory state can be reached from a subregion of initial conditions, and small variations of initial conditions within this subregion do not alter the final memory state of the network. This characteristic is appealing as a model of human memory function, since it allows for a final memory state which is robust to variation in the input cues. Attractor dynamics are particularly important for modeling free recall, where the input cues are weak and associations with the experimental context are shared by a number of items in the same list.

Because of the extensive excitatory recurrent connectivity in hippocampal region CA3, this region has been proposed to function as an auto-associative memory [9–12,16,54]. The strong recurrent excitatory connections could mediate auto-associative memory function in CA3 with attractor dynamics. Even if the activity in region CA3 never actually enters a specific fixed point attractor, the dynamics of this region may be dominated by the approach to an attractor—perhaps within a single gamma oscillation, or during complex spike activity [54].

In the continuous firing rate model of the hippocampus presented here, the primary driving force for recall and recognition consists of the attractor dynamics of the simulated region CA3. These attractor dynamics have been analyzed extensively in previous articles [54]. Some previous simulations have addressed this issue, exploring the stability of the CA3 network with different patterns of connectivity [93]. In more abstract models, exponential growth of excitatory activity has been prevented by assuming normalization of total activity [16]. Here feedback inhibition is used to limit network activity [54], allowing fixed point attractor states resulting from feedback excitation and inhibition.

In the model, once an individual dentate gyrus unit became sufficiently active, the activity passed along the identity matrix representing the mossy fibers and activated individual CA3 units. Initially, when cholinergic suppression was present, the pattern of activity was primarily determined by this afferent input, rather than the strong recurrent excitation. This allowed selective strengthening of synapses between the neurons activated by the dentate gyrus. As these synapses became stronger, the activity in region CA3 increased, resulting in greater output to region CA1. As noted below, increased activity in region CA1 caused a decrease in cholinergic modulation throughout the network. This decreased modulation resulted in greater recurrent excitation in region CA3, such that the network entered a stable fixed point attractor pattern representing the stored context or item.

This stable fixed point attractor was the main driving force for recall within the network. For example, when a cue pattern was presented, it would activate individual neurons in the dentate gyrus. If the input was sufficient to activate a subcomponent of the CA3 representation, then the recurrent excitation would greatly strengthen this activity, pushing CA3 activity into the previously stored fixed point attractor state. Even considerably weaker input could elicit the same amount of CA3 output. The emergence of an item or context attractor state in region CA3 could then drive activity into an associated item or context attractor state, as well as driving output activity in region CA1 and entorhinal cortex layer IV. The attractor states in response to each input could be terminated by one of two different techniques. Neuronal adaptation alone was sufficient to discontinue a particular attractor state. However, in these simulations, this was coupled with a rhythmic activation of inhibitory interneurons within the network, as a representation of the theta rhythm described within hippocampal structures [94].

2.5.1. Context–item attractor interaction

During the retrieval component of a free recall simulation, input of the experimental context would evoke the context attractor state in region CA3. This was

more weakly coupled with a number of item attractor states. Initially activity would spread into a number of these attractor states, but as the item attractor states grew in activity, they would inhibit one another, resulting in persistence of only one attractor state (or in some cases no attractor states). This constituted free recall of a single item. Subsequently, cyclic inhibition would terminate this attractor state, allowing the context attractor to evoke a separate item attractor state. During the retrieval component of a recognition simulation, input of the individual learned item pattern in entorhinal cortex layer II would evoke the item attractor state in region CA3. If this was a familiar (previously learned) item, the item attractor would then elicit activity in an associated context attractor. If the item was novel, the item activity in region CA3 would not elicit associated context activity. The attractor states in a linear form of this network have been analyzed previously [54]. Fig. 6 shows a simulation of free recall in a linear form of this model. The larger scale nonlinear simulations shown in Figs. 8 and 9, provide an example of the interaction of multiple attractor states during free recall and recognition.

2.6. Region CA1: comparison of input from CA3 and entorhinal cortex

At the same time as sequential self-organization took place in the dentate gyrus, it also took place in region CA1 of the hippocampus, with modification of excitatory and inhibitory connections similar to that used in the dentate gyrus. Considerable data on long-term changes of inhibitory potentials has been obtained from region CA1 [85]. However, the considerably weaker input from the entorhinal cortex meant that this input alone could not strongly activate region CA1, but required conjoint input from region CA3. During the initial learning of a novel pattern, the random initial connectivity of the Schaffer collaterals caused a distributed pattern of activity in region CA1, which would interact with the perforant path input to form a new self-organized representation. Subsequently, during recall, the perforant path input did initially have a stronger influence on activity in CA1. However, for familiar stimuli, the pattern of activity arriving from region CA3 via the Schaffer collaterals would usually match perforant path input sufficiently to cause reduction of cholinergic modulation, then the cholinergic suppression of synaptic transmission at the Schaffer collaterals was removed. This allowed Schaffer collateral activity to dominate within region CA1, allowing output from region CA3 to drive neurons which had previously been associated with the particular activity pattern in region CA3.

2.7. Medial septum: feedback regulation of cholinergic modulation

The level of output from region CA1 determined the amount of cholinergic modulation arriving from the medial septum. Activity of the medial septum in the model set the level of cholinergic modulation for all subregions of the model, inducing the full range of cellular effects of acetylcholine: (1) selective suppression of synaptic transmission at connections from CA3 to CA3 and CA1, and from CA1 to entorhinal cortex, (2) depolarization of all neurons, (3) suppression of adaptation in excitatory neurons, and (4) enhancement of synaptic modification. The default levels of cholinergic modulation were high. Output from region CA1 activated modeled inhibitory interneurons in the medial septum, which would inhibit the cholinergic input. Thus, when the output from region CA3 to region CA1 matched the perforant path input to region CA1, this match would act to decrease cholinergic modulation from the medial septum, internally switching the network from encoding to retrieval dynamics.

2.8. Entorhinal cortex layer IV: reactivation of neocortical representations via feedback connections

Free recall and recognition of individual stimuli were evaluated on the basis of the output of the network, which consisted of activity patterns in entorhinal cortex layer IV. This portion of the model received direct input from entorhinal cortex layer II via an identity matrix. Thus, the exact patterns of activity in layer II would be transmitted to layer IV as well, providing output patterns with which episodic representations within region CA1 could be associated during encoding (see below). During retrieval, partial input to layer II would leave portions of layer IV inactive or weakly active until activity would spread from region CA1, evoking particular patterns representing item or context information in entorhinal cortex layer IV. The free recall of individual items was evaluated by comparing the output item patterns in layer IV with learned items. Recognition was evaluated by measuring whether entorhinal cortex layer IV exhibited any context pattern output during the presentation of individual familiar and novel item patterns.

Initially, during learning of a new pattern, the feedback from region CA1 would be suppressed by cholinergic modulation, allowing activity in entorhinal cortex layer IV to be dominated by the input coming via the identity matrix from layer II. This allowed storage of associations between the new pattern of activity in region CA1 and the simultaneous pattern of activity in entorhinal cortex. Subsequently, during recall, cholinergic modulation would be reduced (as described in the previous section), thereby removing the suppression of

synaptic transmission at the feedback connections from region CA1. This allowed activity in region CA1 to effectively reactivate the previously associated pattern of activity in entorhinal cortex layer IV.

The Schaffer collaterals have been proposed to undergo either self-organization [17] or hetero-associative memory function [15]. The relative amount of these two functions depends upon how strongly the Schaffer collaterals influence activity in region CA1. If the Schaffer collaterals dominate postsynaptic activity in region CA1 during learning, then they will predominantly undergo self-organization, as proposed earlier. This must be assumed if no mechanism for modulation of synaptic transmission is incorporated in models. However, with the cholinergic suppression of synaptic transmission at the Schaffer collaterals, the perforant path input can more strongly influence CA1 activity during learning, allowing hetero-associative memory function. This is necessary if the function of region CA1 is to provide a comparison between recall activity produced by region CA3 and direct input from entorhinal cortex, as proposed by some researchers [10,11]. In the simulations presented here, a comparison function of this type played an important role in allowing cholinergic modulation to set appropriate dynamics for learning and recall.

3. Details of the computational model

3.1. Each subregion contains interacting populations of excitatory and inhibitory neurons

This network simulation used simplified representations of individual neurons designed to mimic basic properties of excitatory neurons (pyramidal cells and granule cells) and interneurons [13,54,95]. Each unit in the model represented the activity of a population of neurons, with an activation variable a representing the membrane potential. This variable was measured relative to resting potential, taking the value zero at resting potential. As in real neurons, this variable shows passive decay back to resting potential proportional to a constant η. A major simplification concerns the absence of spiking behavior in the model. Thus, the output of a modeled unit consisted of a continuous variable which could be considered as representative of the mean firing rate of a large population of neurons. After the activation variable crossed the firing threshold, the unit output would increase linearly in proportion to the amount by which activation exceeded the threshold.

In contrast to many models of hippocampal and neocortical function [7,19,96–99], this model did not place an artificial constraint on the total output of a neuron, such as that obtained with a sigmoid input-output function or a step function. Intracellular recording from cortical pyramidal cells in brain slice preparations [61] shows that for the range of firing frequencies observed in vivo [100,101] most neurons have a threshold linear input–output function. They never fire at rates close to their maximal possible firing rate. In the model presented here, total network activity was regulated by feedback from inhibitory interneurons, with membrane potential h. A balance of excitatory and inhibitory feedback allowed neurons to enter an attractor state with intermediate levels of activity [54]. The use of separate groups of excitatory and inhibitory neurons also avoids the use of both positive and negative connections between individual neurons, as appears in most connectionist models [19,97–99]. Previous neural network models of human memory have consistently constrained the total output of individual neurons [7,92]. However, some of these models have used only positive connections between units, with global inhibitory effects setting the level of activity [7,18,75].

The basic circuit used to represent the activity in each hippocampal subregion is summarized in Fig. 5A. The local interaction of excitatory and inhibitory neurons within each hippocampal subregion was described by equations for the change in the membrane potential a of each excitatory unit i, the change in intracellular calcium c of each excitatory unit i, and the change in membrane potential h for each inhibitory unit k:

$$\Delta a_i = A_i - \eta a_i + (E_{\mathrm{Na}} - a_i)\sum_j {}_{xy}W_{ij}[a_j - \theta_a]_+ + (E_{\mathrm{Cl}} - a_i)\sum_l {}_{xy}H_{il}[h_l - \theta_h]_+ + \mu c_i(E_{\mathrm{K}} - a_i)$$

$$\Delta c_i = \gamma[a_i - \theta_c]_+ - \Omega c_i$$

$$\Delta h_k = A'_k - \eta' h_k + (E_{\mathrm{Na}} - a_i)\sum_j {}_{xy}W'_{kj}[a_j - \theta_a]_+ + (E_{\mathrm{Cl}} - a_i)\sum_l {}_{xy}H'_{kl}[h_l - \theta_h]_+ \quad (1)$$

In these equations, the external input to unit i is represented by A_i (set to zero in all regions except entorhinal cortex layer II, which received input patterns). The membrane potential shows passive decay toward resting potential proportional to the constant η. The output of the neuron is zero for values below the firing threshold $\theta_a = 8$ and takes the value $a - \theta_a$ when a is larger than threshold (as indicated by $[a - \theta_a]_+$). The excitatory unit i in region x receives input from excitatory unit j in region y with strength ${}_{xy}W_{ij}$. Excitatory unit i in region x receives input from inhibitory unit k in region y with strength ${}_{xy}H_{il}$. The influence of excitatory input is proportional to the distance from the excitatory reversal potential E_{Na}, and the influence of inhibitory input is proportional to the distance from the inhibitory reversal potential E_{Cl}. A calcium-dependent

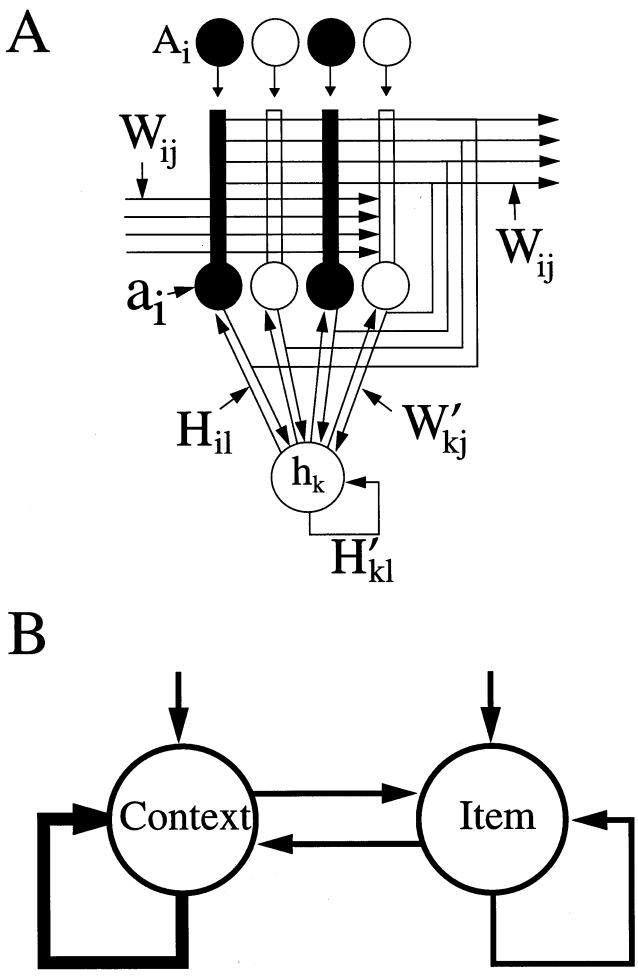

Fig. 5. (A) Connectivity of a local circuit of the hippocampal model. Excitatory neurons with membrane potential a_i receive external input A_i and receive excitatory input from units within the region and in other regions via the connectivity matrix W_{ij}. These units also receive input from inhibitory interneurons via the connectivity matrix H_{il}. Inhibitory interneurons with membrane potential h_k receive input from excitatory neurons via connectivity matrix W'_{kj} and receive input from inhibitory neurons via the connectivity matrix H'_{kl}. Each subregion of the hippocampal model contains all of these connections except the excitatory recurrent connections from other units within the region (which are only incorporated in region CA3 of the model). (B) Schematic representation of interacting attractor states in the model. Stored representations of individual items consist of attractor states within region CA3, formed by strengthening of recurrent connections within the population of neurons representing item. Stored representations of context also consist of attractor states, with stronger recurrent connections due to the more extensive learning of context. The context and item attractors interact via shorter associative connections within region CA3. During learning, both context and item are present. During testing of free recall, only experimental context is present—multiple associated items must be sequentially recalled. During testing of recognition, only individual items are present—recognition is modeled as the generation of activity within a specific context state. The asymmetry of effects on free recall and recognition within this model result from the difference in strength of recurrent connections within these two sub-populations of units.

potassium current drives the membrane potential toward the potassium reversal potential E_K in proportion to the intracellular calcium concentration c and a constant μ which varied among regions between 0.00015 and 0.003. This computational mechanism was the basis for the intrinsic adaptation properties of the cells that is crucial in free recall. This feature is most important within the item region of CA3 where it prevents items from repeatedly being recalled (the constant μ was set at 0.003 in region CA3). Intracellular calcium increases in proportion to the amount by which the membrane potential exceeds a threshold $\theta_c = 8.0$, in proportion to a calcium influx constant $\gamma = 0.0006$. The calcium levels decrease in proportion to calcium concentration and a diffusion constant $\Omega = 0.0001$. The basic components of the network representing each local region are summarized in Fig. 5A.

The membrane potential h of inhibitory unit k also changes in proportion to external input A' and the passive decay constant h. Inhibitory unit k in region x receives input from excitatory unit j in region y with strength ${}_{xy}W'_{kj}$ and receives input from inhibitory unit k in region y with strength ${}_{xy}H'_{kl}$. These inputs are also proportional to the aforementioned reversal potentials.

Reversal potentials for membrane currents were expressed relative to the resting potential. Thus, $E_{Na} = 70$, $E_{Cl} = 0$ and $E_K = -10$. Threshold potentials were equivalent for all neurons: $\theta_a = \theta_h = \theta_c = 8.0$. Afferent input to active neurons in entorhinal cortex layer II was set at $A = 0.35$ and all passive decay parameters η were set to the same value ($\eta = \eta' = \eta_\psi = 0.01$). Synaptic connectivity strengths took the values described in Fig. 7. In all cases, inhibitory connections to inhibitory units were of strength $H' = 0.0055$. Excitatory connections to inhibitory units varied from $W' = 0.0005$–0.013. Inhibitory unit connections on excitatory neurons were between $H = 0.003$ and 0.0053. However, these connections were modifiable in the dentate gyrus and region CA1.

Note that in the simulations described here, when region x is connected to region y, then every neuron in x contacts every neuron in y. Variations in the percentage connectivity of the network does not prevent attractor dynamics until connectivity reaches sufficiently low values (Van Vreeswijk and Hasselmo, unpublished simulations). Thus, the fully connected network here is used as an approximation to a much larger network with smaller percent connectivity. In addition, most simulations used a single feedback neuron to represent the population of neurons mediating feedback inhibition. These physiologically unrealistic features allow the model to function with smaller numbers of neurons.

3.2. Dynamics of free recall in a simple linear model

A simple network with threshold linear neurons was simulated in order to illustrate the essential dynamics of free recall in region CA3 of this model, as shown in

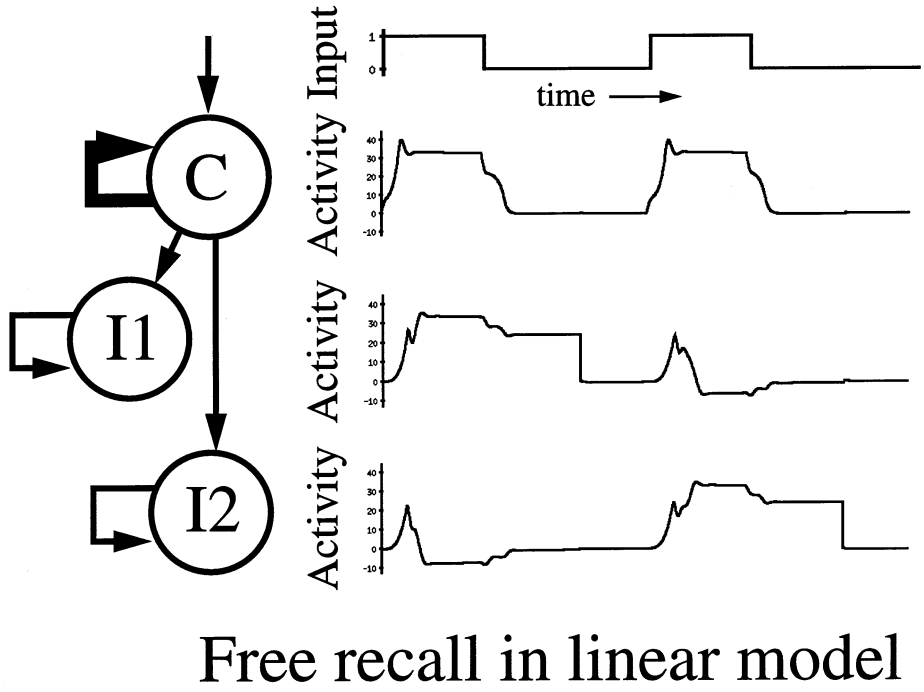

Fig. 6. Example of free recall in a simple threshold linear model of region CA3 [54]. On the left, the connectivity of the interacting attractors within region CA3 is summarized. For this example, one unit represents context and two units represent different items. Strong recurrent connections allow each unit to display self-sustained activity in the absence of feedback inhibition. The context unit has weak associative connections to both item units (a slight difference in associative strength is required for symmetry breaking). The top trace shows the input to the context unit during recall. Activity in the context unit initially spreads to both item units. The difference in associative input to items allows item unit 1 (I1) to enter an attractor state first, preventing unit 2 from being active via feedback inhibition. This attractor state persists until it is terminated by resetting activity levels (termination of attractor states can also be obtained from a buildup of slow inhibition or adaptation). Subsequent presentation of the input to context again evokes activity in both item units. However, unit 1 is now at a disadvantage due to the buildup of intracellular calcium, mediating adaptation. This results in unit 2 (I2) entering an attractor state and inhibiting activity in unit 1. Thus, the network performs sequential recall of multiple items associated with a single context.

Fig. 6. This simple example network consisted of three neurons, one representing context (C) and two representing different items (I1 and I2). In this example network, learning consisted of setting the strength of excitatory connections within the network to weights used in previous simulations [54]. Attractor states were set by making strong recurrent connections from each neuron to itself ($W = 0.16$). This excitatory feedback was balanced by inhibitory interneurons. One interneuron had reciprocal connections with only the two item neurons. The other interneuron had reciprocal connections with only the context neuron. The connections from excitatory neurons to inhibitory neurons all had strength $W' = 0.052$, and from inhibitory neurons to excitatory neurons had strength $H = 0.6$. The interneurons inhibited themselves with strength $H' = 0.08$. These connections allowed each item neuron to enter an attractor state in isolation, but prevented both item neurons from entering an attractor state at the same time. These neurons were threshold linear. Thus, there was no use of reversal potentials for synaptic interactions in this example. All neurons had zero output below activation of 8.0, and then increased linearly in output above this value. Membrane potentials decayed back to zero with rate 0.1. Each neuron had calcium influx of strength $\gamma = 0.001$, calcium diffusion of strength $\Omega = 0.001$ and calcium-dependent potassium current of strength $\mu = 0.01$. These parameters mediated adaptation of the individual neurons.

Retrieval dynamics for free recall could be obtained within the model due to interaction of the context attractor with the item attractors. In order to obtain symmetry breaking, it was necessary to have a slight difference in connectivity from the context neuron to each of the item neurons. Thus, the strength of input from the context neuron to I1 was 0.042 and from context to I2 was 0.04. As shown in the Fig. 6, the context unit received short step functions of input. During the first input, activity spreads from the context neuron into both item neurons, but the slightly greater activation of I1 causes it to win the competition, driving down the activity of I2. I1 maintains its attractor state even after input is terminated. The attractor state is only terminated by inhibitory activation (not shown). Subsequently, the next input to the context neuron evokes activity in both item neurons, but the adaptation which built up in I1 prevents it from dominating again, and I2 wins the competition, driving down the

activity of I1. Thus, the network can sequentially recall different stored items associated with the same context unit. The full network simulation had a considerably greater number of neurons, contained nonlinearities in the form of reversal potentials for different synaptic currents, and had much greater complexity of connectivity. However, the essential function of region CA3 during retrieval resembles that of the example in Fig. 6.

3.3. Modification of synapses

This model focused on the learning and recall of sequentially presented patterns which could be either novel or familiar. Learning of sequential patterns in the model presented here required Hebbian synaptic modification of excitatory connections between excitatory units and modification of connections from inhibitory units to excitatory units. The properties of learning in this model contrasts with the learning characteristics utilized in many previous models. For example, previous models often assume a certain pattern of connectivity and then focus on the dynamics of recall of that information [17,91]. On the other hand, connectionist models utilize repeated presentations of the components of behavioral tasks and guide learning with an explicit computation of error [19,97,99]. The representation here did not externally induce learning and recall stages, and did not utilize an explicit computation of error.

Modifiable synapses all utilized a similar Hebbian learning rule presented below. This same learning rule provided self-organization of perforant path synapses from entorhinal cortex to dentate gyrus and region CA1, and associative memory function at the longitudinal association fibers in region CA3 and the Schaffer collaterals projecting to region CA1. The different functional properties of modification at these two sets of synapses did not arise from difference in the learning rule, but from differences in the amount of cholinergic suppression of synaptic transmission during learning. As described in previous publications [49,102], cholinergic suppression of synaptic transmission during learning resulted in associative memory function, while the absence of suppression during learning allowed self-organization.

Excitatory synapses between excitatory units in the model were modified continuously according to a learning rule dependent upon post-synaptic activity a_i and pre-synaptic activity a_j, in keeping with experimental evidence on the Hebbian nature of long-term potentiation [84,83,103,104]. To reflect the slow development of potentiation, the learning rule depended upon cumulative build-up of pre and post-synaptic variables s_i and s_j which increased with separate dynamics. This could be construed as the build-up of pre and post-synaptic calcium, or activation of pre and post-synaptic second messengers such as protein kinase C. Increase of each variable s was proportional to a constant ϕ and the amount by which unit activity exceeded the output threshold, while decrease in each variable s was proportional to the value of s and a decay constant β. (For all excitatory units, $\phi = 0.015$, $\beta = 0.04$). For modification to occur, the s variables had to exceed pre and post-synaptic modification thresholds θ_w (set between 0.1 and 0.9 for all excitatory units). This threshold had to be tailored to the needs of each region. For instance, the modification thresholds in CA3 were relatively high to prevent interference while those in DG were low to allow rapid self-organization. The rate of synaptic modification was also regulated by an overall modification rate κ which also varied according to the needs of each region. For instance, DG had much more rapid modification than region CA3, which had representations designed to reflect the amount of time a given pattern had been presented to the system. This rate varied between 0.00004 and 0.2. The rate of synaptic modification was also scaled to the level of cholinergic modulation, as suggested by experiments showing cholinergic enhancement of long-term potentiation [65,102].

The rapid self-organization of perforant path synapses in the dentate gyrus and region CA1 of the model required decay of synaptic strength regulated by the amount of pre and post-synaptic activity. This decay could also enhance the accuracy of auto-associative storage at the synapses of the longitudinal association fibers in region CA3 and hetero-associative storage at the Schaffer collaterals. Decay of synaptic strength can be taken as a representation of the phenomenon of long-term depression, as described in experimental preparations [73]. The learning rule incorporated decay of synaptic strength proportional to the current strength W_{ij} and the amount of pre or postsynaptic activity (scaled to a presynaptic decay constant w_{pre} and a postsynaptic decay constant w_{post}). For all regions except CA3 $w_{\text{pre}} = 2 \times 10^{-5}$ and $w_{\text{post}} = 2 \times 10^{-3}$.

Incorporating these parameters, the cumulative learning rule took the form:

$$\Delta W_{ij} = \kappa(1 - \chi_s(1 - \psi))([s_i - \theta_w] + \omega_{\text{pre}} W_{ij})$$
$$([s_j - \theta_w]_+ - \omega_{\text{post}} W_{ij})$$
$$\Delta s_i = \phi[a_i - \theta_a]_+ - \beta s_i$$
$$\Delta s_j = \phi[a_j - \theta_a]_+ - \beta s_j \quad (2)$$

In most simulations, weights were clipped at specific values to maintain them within the region of stable attractor dynamics. Thus, the strength of modifiable connections did not exceed parameters termed $W_{\max}$, as summarized in Fig. 7.

In addition to the modification of excitatory weights between excitatory units, the connections from inhibitory interneurons in the dentate gyrus and region

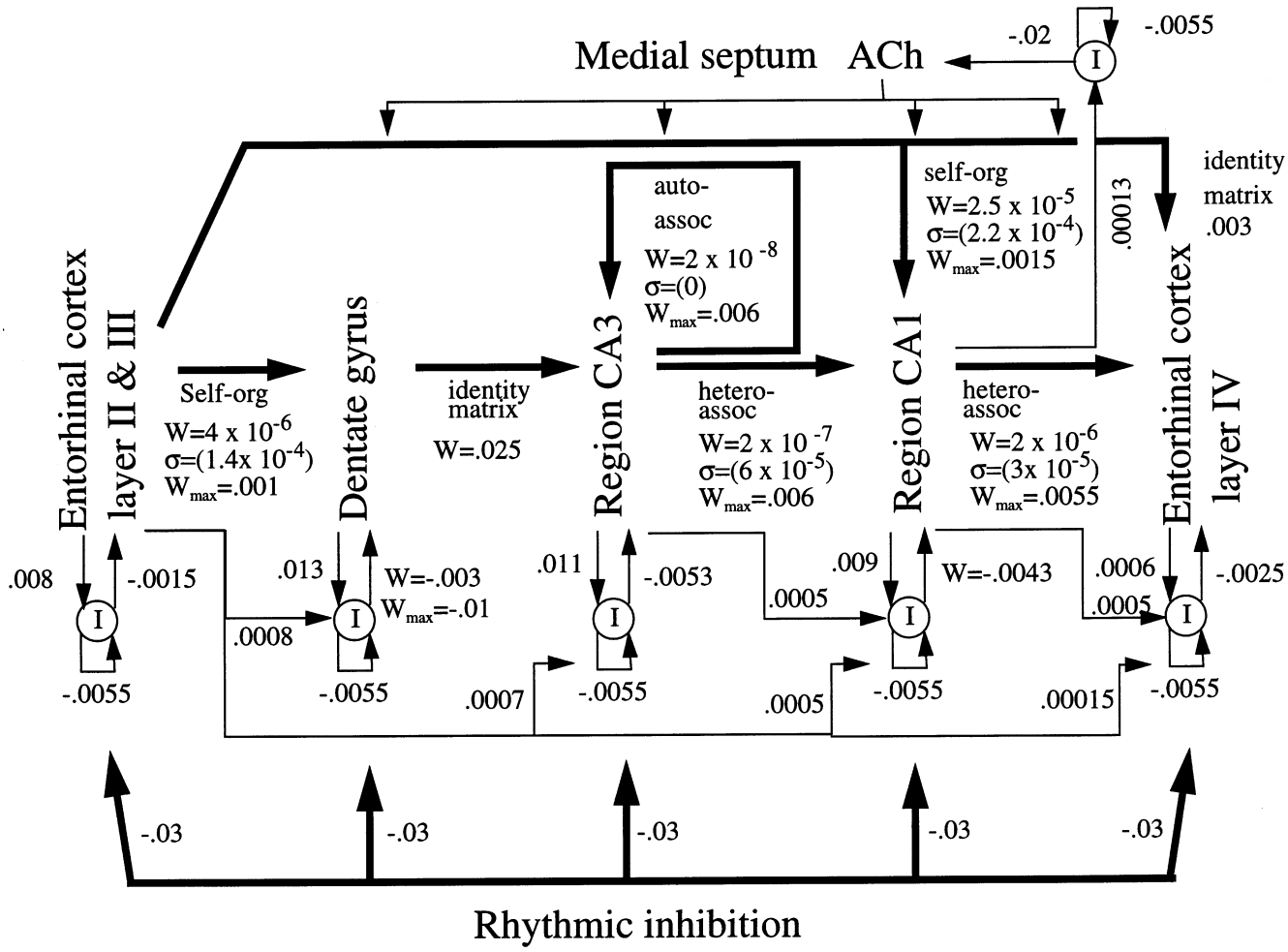

Fig. 7. Strength of individual connections within the network simulation of the hippocampal formation. When a single number appears, this shows the homogeneous strength of a set of nonmodifiable connections. When three numbers appear, these show the mean initial strength, the standard deviation of the initial strength, and the maximum possible strength of a set of modifiable connections. Each entorhinal cortex region contained forty excitatory units, while the other hippocampal regions each contained ten excitatory context units and fifty excitatory item units. Excitatory connections between regions represent the perforant path projecting from entorhinal cortex layer II to dentate gyrus, and entorhinal cortex layer III to region CA1, the mossy fibers from dentate gyrus to CA3, the recurrent longitudinal association fibers in region CA3, the Schaffer collaterals from CA3 to CA1, and projection back from region CA1 to entorhinal cortex layer IV. In each region the pyramidal cells are fully connected with an inhibitory interneuron (marked I) by excitatory connections of the strength shown. The inhibitory interneuron sends back inhibitory connections of the strength shown. In the dentate gyrus and region CA1, these inhibitory connections had random initial strength and were modifiable.

CA1 were also modified. This proved necessary to allow self-organization of input to these regions in response to sequential presentation of different patterns. Modification of inhibitory connections from the interneuron to active excitatory units allowed inhibition to be selectively increased for units which responded strongly to an individual input pattern. This made it more difficult for these same units to be activated by other patterns, thereby ensuring their selectivity primarily for patterns closely matching the pattern to which they first responded. The modification of inhibitory connections followed the same learning rule as described in Eq. (2) with the exception that the presynaptic variable s was replaced by the amount that presynaptic activity directly exceeded the output threshold. These inhibitory connections did not undergo decay, but were limited to maximal strengths as listed in Fig. 7. Connections from excitatory units to inhibitory units and connections between inhibitory units were not modified in these simulations.

3.4. Connectivity between different hippocampal subregions

The network simulation of the hippocampal formation contained five subregions, including entorhinal cortex layers II and III, the dentate gyrus, hippocampal region CA3, region CA1 and entorhinal cortex layer IV. Local circuits representing these subregions were linked together to represent functional interactions

within the hippocampal network. The anatomical structure of the hippocampus is summarized in Fig. 3A [76], with a schematic representation of the function of each set of connections and each hippocampal subregion in Fig. 3B. The connection strengths utilized within this network are summarized in Fig. 7. For each subregion, parameters describe the strength of connections from excitatory units within other regions and within the same region (W), connections from excitatory units to the inhibitory unit (W'), connections from the inhibitory unit to the excitatory units (H) and feedback inhibition on the inhibitory unit (H').

3.4.1. Entorhinal cortex layers II and III to layer IV

Input to the hippocampus from neocortical structures was represented by sequential presentation of input patterns in the local circuits representing layers II and III of entorhinal cortex. Output from the hippocampus to cortical structures resulted in a pattern of activity in the local circuits representing entorhinal cortex layer IV. In addition, activity spread directly from entorhinal cortex layer II to entorhinal cortex layer IV via an identity matrix (maintaining the same pattern of activity, for ease of visualizing the relationship between input and output), with strength $W = 0.003$.

3.4.2. Entorhinal cortex layers II and III to dentate gyrus and CA1

The spread of activity from entorhinal cortex layers II and III to dentate gyrus and region CA1 was via distributed modifiable excitatory connections representing synapses of the perforant path. These connections started out with random initial connectivity, but had a very low threshold of modification (input to dentate gyrus: $W = 4 \times 10^{-6}$, $\sigma = 1.4 \times 10^{-4}$, $W_{max} = 0.001$, $\theta_w = 0.1$; input to CA1: $W = 2.5 \times 10^{-5}$, $\sigma = 2.2 \times 10^{-4}$, $W_{max} = 0.0015$, $\theta_w = 0.4$). These connections were modifiable, allowing rapid self-organization dependent upon the pattern of entorhinal cortex activity. In addition, inhibitory feedback in the dentate gyrus was modifiable ($H = 0.003$, $H_{max} = 0.01$).

3.4.3. Dentate gyrus to CA3

The activity in the dentate gyrus spread to region CA3 via an identity matrix representing the sparse but strong influence of mossy fiber synapses in stratum lucidum of region CA3. These connections were not modifiable in this network model ($W = 0.025$).

3.4.4. Region CA3 longitudinal association fibers

The activity in region CA3 could spread to other neurons in CA3 via broadly distributed excitatory feedback connections representing the longitudinal association fibers synapsing in stratum radiatum of region CA3 ($W = 2 \times 10^{-8}$, $\sigma = 0$, $W_{max} = 0.006$, $\theta_w = 0.9$). Modification according to a Hebbian learning rule provided the basis for auto-associative memory function in this region, as simulated previously [54]. The learning in CA3 was modeled in greater detail than in other parts of the model because the temporal learning dynamics of this region were extremely important. LTP here was limited to prevent rapid learning because activation values rose quickly. The limit mandated that only 0.19% of the W_{max} could be added to a connection during a single time step. This limit was also subject to the suppression of LTP without acetylcholine. There was a delay from the time cholinergic modulation ceased until the suppression of LTP began. In the model, this value was set at 240 time steps. This feature was necessary in that acetylcholine tended to shut off too quickly to allow the presence or absence of scopolamine to have a significant impact on the strength of CA3 traces. The mechanisms of LTP have slower time courses which should be correspondingly slower to respond to changes in external modulation. In addition, in order to obtain symmetry breaking during retrieval, it was necessary for the rate of synaptic modification in region CA3 to vary by 30% for each block of 400 time steps, so that different stored associations would have differential strength.

3.4.5. Schaffer collaterals projecting from region CA3 to region CA1

The activity in region CA3 could also spread to region CA1 via broadly distributed excitatory feedforward connections representing the Schaffer collaterals synapsing in stratum radiatum of region CA1. These connections also started out with random initial connectivity and were also modifiable ($W = 2 \times 10^{-7}$, $\sigma = 6 \times 10^{-5}$, $W_{max} = 0.006$, $\theta_w = 0.4$). This Hebbian synaptic modification provided the basis for hetero-associative memory function by these connections, as simulated previously [57]. Region CA3 also activated inhibitory units in region CA1.

3.4.6. Region CA1 to entorhinal cortex layer IV

The activity in region CA1 could spread back to entorhinal cortex layer IV via broadly distributed excitatory connections, representing connections from CA1 to entorhinal cortex. (Note that with no direct representation of the subiculum, these connections also represent activity spreading via the subiculum). These connections had initial random connectivity and were modifiable ($W = 2 \times 10^{-6}$, $\sigma = 3 \times 10^{-5}$, $W_{max} = 0.0055$, $\theta_w = 0.4$). Hebbian synaptic modification of these connections provided the basis for hetero-associative memory function by these connections, allowing compressed representations formed in region CA1 to recall the full patterns in entorhinal cortex which originally elicited the formation of these compressed representations. Region CA1 also excited inhibitory units in entorhinal cortex layer IV.

3.5. Separation of input patterns into context and item components

Information about context was represented by ten of the neurons in the input layer of the entorhinal cortex. This information was spatially segregated from the item information upon entering the dentate gyrus and followed a parallel pathway through the CA subfields, emerging again in layer IV of the entorhinal cortex. Strength of connections were similar to those in the item pathway.

In the DG, CA1 and CA3, the separation was complete to the extent that each pathway was mediated by an inhibitory interneuron not connected to the other side in any way. Likewise, projections did not cross this pathway boundary, except in region CA3. In the CA3 region, the auto-associative fibers did connect the item and context information. These connections were modifiable but only became 1/40th as strong as those between neurons within the same pathway. Justification for limiting these connections to weaker values stems from findings that connection probability and synaptic strength of excitatory projections from a pyramidal cell decrease with distance. Accordingly, it is assumed that these pathways represent longer hippocampal pathways that are not immediately adjacent as they are in the model.

Bear in mind that this separation may correspond only to general characteristics of cell responsiveness and not to an explicit division of labor between different regions. The small size of our model mandates the distinct and rigid division of item and contextual information. This separation of representations for context and item is not a strict theoretical requirement, as long as the two representations are kept sufficiently distinct so that a single context can be associated with multiple items.

3.6. Feedback regulation of cholinergic modulation

The total output from units in region CA1 determined the level of cholinergic modulation within the hippocampus, with increased region CA1 output causing decreased modulation. This is consistent with experimental evidence suggesting that activity in region CA1 and region CA3 can inhibit activity in the medial septum, and thereby downregulate cholinergic modulation [105]. This allowed the network to respond initially to patterns with dynamics set by strong cholinergic modulation, suppressing the auto-associative and hetero-associative function of excitatory connections. This prevented previously stored representations from interfering with the storage of new associations at excitatory recurrent connections in region CA3, at the Schaffer collaterals connecting region CA3 and region CA1, and at the feedback connections from region CA1 to entorhinal cortex layer IV. When a sufficient level of activity in region CA1 was obtained, the cholinergic modulation would be reduced, allowing strong synaptic transmission to mediate associative recall at synapses in region CA3, region CA1 and entorhinal cortex layer IV. Thus, the feedback regulation of cholinergic modulation sets appropriate dynamics for encoding and retrieval, though the cholinergic modulation goes through the same transition from high to low during presentation of each input pattern. Note that rather than modeling acetylcholine effects at specific synapses, we assume that levels of acetylcholine change on a regional basis, in keeping with the concept of volume transmission [106].

The model contained a variable representing the level of acetylcholine ψ within the entire cortical region, which varied between 0 and 1. This variable was determined by multiplying the output of the cholinergic neuron by 0.2. This insured that a membrane potential of 13.0 in the cholinergic neuron would provide full modulation (the output threshold was set at 8.0). The antagonistic effects of scopolamine were modeled by reducing this gain constant from 0.2 to 0.07, representing a 65% attentuation of the effects of acetylcholine on all parts of the system. In addition, the model incorporated several different effects of cholinergic modulation demonstrated experimentally. This included selective cholinergic suppression of excitatory synaptic transmission $(1-\chi_W\psi)$ at a subset of connections. Suppression was implemented at the longitudinal association fibers (recurrent excitation) in CA3 [54], at the Schaffer collaterals from region CA3 to region CA1 [53,57], and at the projections from region CA1 back to entorhinal cortex. Suppression at these connections used $\chi_W = 0.7$. Simulations also included the suppression of inhibitory synaptic transmission $(1-\chi_H\psi)$ [64] in dentate gyrus, region CA3 and region CA1 (with $\chi'_W = 0.5$ in most regions, 0.3 in CA1), and the suppression of excitatory input to inhibitory interneurons in region CA1 (with $\chi'_W = 0.5$). The cholinergic enhancement of excitatory synaptic modification [65,67,102] was represented at all modifiable connections using the learning rule in Eq. (2) with $\chi_s = 0.75$. Finally, cholinergic modulation caused direct depolarization of inhibitory and excitatory neurons in all regions [62–64], using a depolarizing input χ_d sufficient to bring resting potential to 2.0. With inclusion of cholinergic effects, the activation equations took the following form.

$$\Delta a_i = A_i - \eta a_i + \chi_d\psi + (E_{\mathrm{Na}} - a_i)\sum_j (1-\chi_w\psi) W_{ij}[a_j - \theta_a]_+ - (E_{\mathrm{Cl}} - a_i)\sum_l (1-\chi_H\psi) H_{il}[h_l - \theta_h]_+ \quad (3)$$

$$\Delta h_k = A'_k - \eta' h_k + \chi_d \psi$$
$$+ (E_{\mathrm{Na}} - h_k) \sum_j (1 - \chi_w \psi) W'_{kj} [a_j - \theta_a]_+$$
$$- (E_{\mathrm{Cl}} - h_k) \sum_l (1 - \chi_H \psi) H'_{kj} [h_j - \theta_h]_+$$

Experimental evidence suggests that increased output from the hippocampus reduces activity in the medial septum [105]. Here, the sum of output from region CA1 reduced cholinergic modulation through the use of a feedback circuit in which single units represented the activation dynamics of basal forebrain populations of GABAergic neurons and cholinergic neurons. The GABAergic neurons had the same activation dynamics as the interneurons mediating feedback inhibition in the network, with the same parameters. The following activation dynamics applied for the cholinergic neuron output rate ψ and membrane potential α:

$$\psi = \Psi[\alpha - \theta_\alpha]_+$$
$$\Delta\alpha = A_\psi - \eta\alpha - H_\psi [h - \theta_h]_+ \quad (4)$$

Where θ_a is the output threshold for the cholinergic neuron, A_ψ is tonic input to the cholinergic neuron (set to 0.13 at all times during simulations to ensure continuous output in the absence of inhibition), and H_ψ is the inhibitory synapse from GABAergic neurons (set to -0.02). Simulations used the values: $\theta_\alpha = 8$ and $\theta_h = 8$. The feedback regulation of cholinergic modulation is also summarized in Figs. 3 and 7.

Blockade of learning but not recall could be obtained by simply turning LTP and synaptic transmission off and on in the model. However, this is not consistent with experimental evidence, which demonstrates that acetylcholine causes a quantitative change in the magnitude of LTP and causes only a partial suppression of excitatory synaptic transmission. In addition, scopolamine does not completely block the effects of acetylcholine. Finally, complete blockade of learning would prevent the sparing of recognition. Thus, we cannot model cholinergic effects in a simple on-off manner. Therefore, our simulations address whether a system with these physiologically realistic partial effects can predict the scopolamine effects in behavioral experiments.

4. Simulation results

4.1. Free recall and recognition of sequentially presented episodic memories

The network model of the hippocampus was used to simulate the encoding, free recall and recognition of lists of word, with the same parameters used to simulate the full range of behavioral tasks. Simulation of the effects of scopolamine within the model influenced memory function in a manner consistent with previous experiments in human subjects [24,25,27].

In these simulations, the network sequentially encoded overlapping input patterns representing lists of words and experimental context. This encoding consisted of forming sparse representations of each word (item) and of the experimental context, and forming associative links between the context representation and the representation for each word (item) on the list. As shown in Figs. 6, 8, 10, 11, 13 and 14 free recall could be simulated in the network by presenting context only as an input cue and obtaining output containing the individual stored item patterns. As shown in Figs. 9, 13 and 14, recognition could be simulated in the network by presenting individual stored items and other non-stored (novel) items and observing which items resulted in output containing the stored context pattern.

As described above, region CA3 of the model was the primary locus for storage of associations between context and item. Therefore, we will initially present figures illustrating the dynamics of free recall and recognition within region CA3 during the function of the full network.

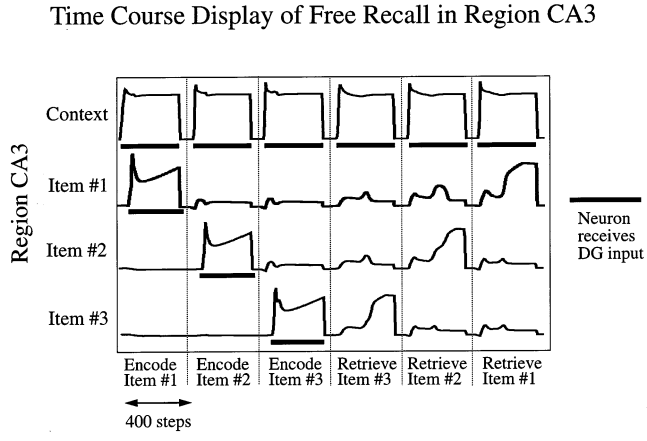

Fig. 8. Activity within region CA3 of the full network model of hippocampus during encoding and free recall of three different items. Encoding: during each 400 step interval from 0–1200, different patterns of activity were presented to entorhinal cortex layer II representing different individual items with the same context pattern. This evoked a new representation in the dentate gyrus which was passed along to region CA3. In region CA3, separate attractor states were formed for both item and context information, with weaker connections between context and item. Here, the formation of three different attractor states is shown in the order 1, 2, 3. Retrieval: during free recall, the context portion of the input pattern was presented repeatedly to entorhinal cortex layer II. This input evoked context activity in the dentate gyrus, which then elicited an active attractor state for context in region CA3. The CA3 context attractor state initially evoked activity in all the item attractors, but differences in associative strength and prior adaptation caused one attractor to dominate each time. Once an individual item attractor state was activated, the build-up of intracellular calcium prevented this same state from being activated again, resulting in a different attractor state being evoked during each cycle. Here the items were recalled in order 3, 2, 1.

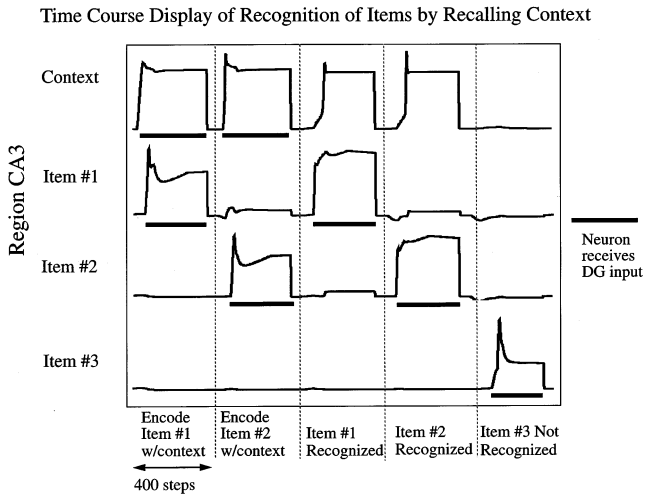

Fig. 9. Encoding and recognition of two stimuli, and failure to recognize a third (novel) stimulus within the full hippocampus model. Encoding: two different patterns of activity were presented to entorhinal cortex layer II, representing both item and context information. This evoked new representations in the dentate gyrus which were passed along to region CA3. In region CA3, separate attractor states were formed for both item and context information, with weaker connections between context and item. Recognition: During recognition, only the item portions of each input pattern were presented sequentially to entorhinal cortex layer II. This evoked partial activity in the dentate gyrus, which then activated the item portion of region CA3. Even without entering the item attractor state, this CA3 activity induced activity sufficient to activate the context attractor. Once the context attractor state was activated, this evoked patterns of activity in region CA1 and entorhinal cortex layer IV corresponding to the previously learned context, allowing a 'yes' response for recognition. For an item which had not been presented previously, the network did not evoke the context attractor state, allowing a 'no' response for recognition.

Activity in region CA3 during the encoding and free recall of three different items is illustrated in Fig. 8. Individual traces show the change in activation of four neurons which were recruited in the self-organized representations of the experimental context and of three stored items. The activity of individual neurons was determined by the self-organization of representations in the dentate gyrus, which then sent activity via the mossy fibers into region CA3.

Encoding occurs during the initial 1200 time steps of this fig. Three different items are presented to entorhinal cortex layers II and III for 400 time steps each. Each of these three items is presented in conjunction with the same experimental context (top trace) in entorhinal cortex layers II and III. Each item evokes activity in a different region CA3 unit. The initial peak in the activation response is due to the build-up of feedback excitation due to recurrent synapses. The subsequent trough is due to activation of feedback inhibition and the loss of depolarization due to feedback regulation of cholinergic modulation. The ensuing slow growth in activation is due to the gradual enhancement of synaptic strength in the recurrent connections. Each activation is terminated by a wave of inhibition applied to the full hippocampal model, based on evidence for cyclical waves of inhibition underlying gamma and theta oscillations.

Retrieval takes place during the subsequent 1200 time steps of this fig.. During retrieval, only the pattern representing experimental context is presented to entorhinal cortex. This activity spreads through the dentate gyrus to activate the context unit in region CA3. In each retrieval cycle, activity in the context region of CA3 spreads via excitatory collaterals to the item region of CA3. Here, all items originally associated with this set of context cues is excited. As a result of winner take all dynamics, mediated by lateral inhibition, one of the patterns becomes dominant. The winner's activity, mediated by attractor dynamics, increases until it completely suppresses the other. After sufficient activation has built up, the corresponding representation in CA1 is activated via the Shaffer collaterals and then translated into the appropriate entorhinal cortex representation (not shown).

Recall of items, punctuated by the aforementioned inhibitory pulses, continues in this manner as long as a context cue is provided. Intrinsic calcium-dependent adaptation currents within each neuron weaken the CA3 representations temporarily, preventing them from being recalled again for a period. In this manner, additional items are able to reach attractor states during the competitive dynamics.

Note that the order of retrieval does not depend upon the order of learning but on the random variation in strength of associative connections between context and item. Thus, in the example of Fig. 8, item no. 3 is retrieved first because it happened to receive the strongest encoding. On the next cycle of activity, activation of the context neuron again spreads activity into all three item neurons just as before, except that item no. 3 has been weakened by adaptation, and no. 2 is able to emerge. As can be seen in later Fig. 8, retrieval follows variable order for different sets of patterns. Activity in region CA3 during an encoding and recognition test is illustrated in Fig. 9. Encoding dynamics are similar to those of Fig. 8.

Recognition is then tested during the subsequent 1200 time steps of this figure. This time, the patterns representing individual items are presented to entorhinal cortex. This activity spreads through the dentate gyrus to activate the individual item units in region CA3 which then spread through the excitatory collaterals to the context region. If the item actually had been previously stored in association with the context, this spread of activity pushes the appropriate context unit into an attractor state, which then activates CA1 and entorhinal representations as above. When the context activity is evoked in entorhinal cortex layer IV, the item

is considered to be recognized (positively response). Inhibition terminates the CA3 attractors as before, and recognition occurs whenever an item is presented.

In this example, the item no. 3 pattern was not associated with context during encoding, therefore presentation of this item alone evokes a high initial level of activity, but does not enter a previously stored attractor state in the item region and does not activate a context representation. Thus, no activity spreads on to region CA1 and entorhinal cortex layer IV. Based on this lack of recalled context activity, a negative response is scored. (The new items can be presented with a different testing context. This does not interfere with the distinction between positive and negative responses based on retrieval of the previously stored experimental context).

4.2. Scopolamine impairs the encoding but not retrieval of words in a free recall experiment

In the network model of hippocampal function, partial blockade of cholinergic effects—as a model of the effect of scopolamine—results in a pattern of impairment corresponding to the results of the experiment by Ghoneim and Mewaldt [24]. In the simulation, retrieval of items learned before the onset of scopolamine is not impaired by scopolamine, whereas encoding of new items is strongly impaired by scopolamine. These results are presented in Figs. 10–12.

Fig. 10 shows how scopolamine affects the output of the network in a simplified simulation of the Ghoneim and Mewaldt experiment (Fig. 1). This figure shows input to the network in entorhinal cortex layer II and output from the network in entorhinal cortex layer IV. We have used a smaller list size in this example so that the individual activity patterns are clearer. The actual simulation of the experiment for Fig. 12 used 16 items in each list. On the left, activity is shown during the learning of four different item patterns (words) associated with the first context pattern before the onset of scopolamine effects. Similar patterns of activity appear in the input and output layers. Scopolamine effects are then initiated within the model. Subsequent to the onset of scopolamine effects, presentation of the first context pattern only in layer II can still effectively retrieve individual stored words from the network. Note that these individual patterns do not come up in the same order as the originally learned list of item patterns, but all patterns exhibit robust free recall in entorhinal cortex layer IV. Thus, the scopolamine effects do not block retrieval.

In contrast, simulation of scopolamine effects in the model strongly impairs the encoding of a second list of item patterns. Subsequent to the effective recall of the first set of items, the network is presented with a second list of item patterns (words) associated with a second context pattern. Note that during learning, activity appears in both input and output layers. However, retrieval of this second list is strongly impaired. When the second context alone is presented to layer II, no free recall of individual items appears in entorhinal cortex layer IV. The activity in the full network model of hippocampus is illustrated in Fig. 11. The input and output to the network in this figure is the same as in Fig. 10, but the activity is also illustrated in the dentate gyrus, region CA3 and region CA1.

Fig. 11 illustrates the sequential self-organization of different representations within the dentate gyrus. As

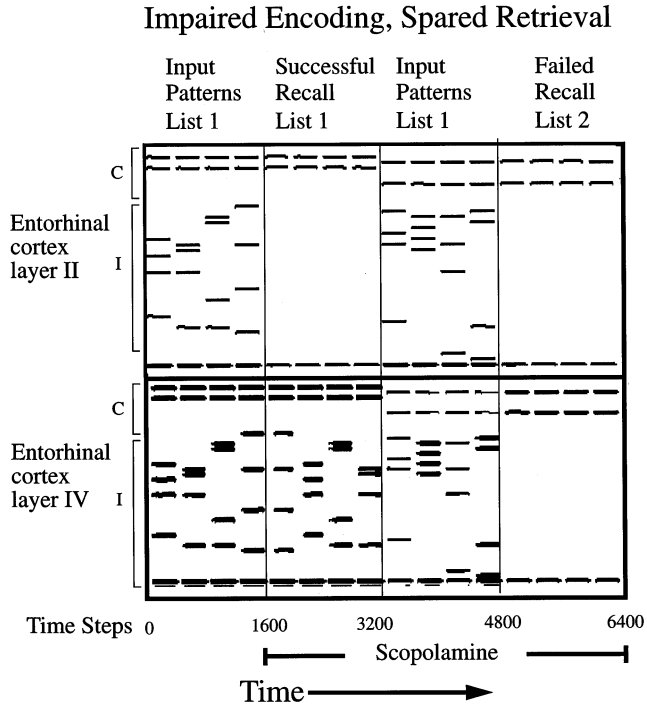

Fig. 10. Impaired encoding but not retrieval in the presence of scopolamine. Simulated input to and output from the hippocampal network model during encoding and free recall of word stimuli in the scopolamine study. The horizontal width of black lines represent the activation level of each individual unit at each time step of the simulation (time is plotted horizontally). Top. Word list no. 1 consists of four highly overlapping input patterns presented sequentially during steps 1–1600 to the local circuits representing entorhinal cortex layers II and III, each with the same context no. 1 (denoted with a C). Free recall is tested by presenting only the context for each of these items during steps 1600–3200. Word list no. 2 consists of another set of four highly overlapping input patterns presented with a shared context no. 2. Free recall is tested by presenting only the context for each of these items (context no. 2). Bottom. Output of the network. Example of the final pattern of activity in the local circuits representing entorhinal cortex layer IV. In response to context no. 1 during recall, the network responds with free recall of each of the different items from word set no. 1, indicating no impairment of the retrieval of words learned before the injection of scopolamine. In response to context no. 2 during recall, the network responds with no free recall of the different items from word set no. 2, indicating impairment of the retrieval of words learned after the injection of scopolamine.

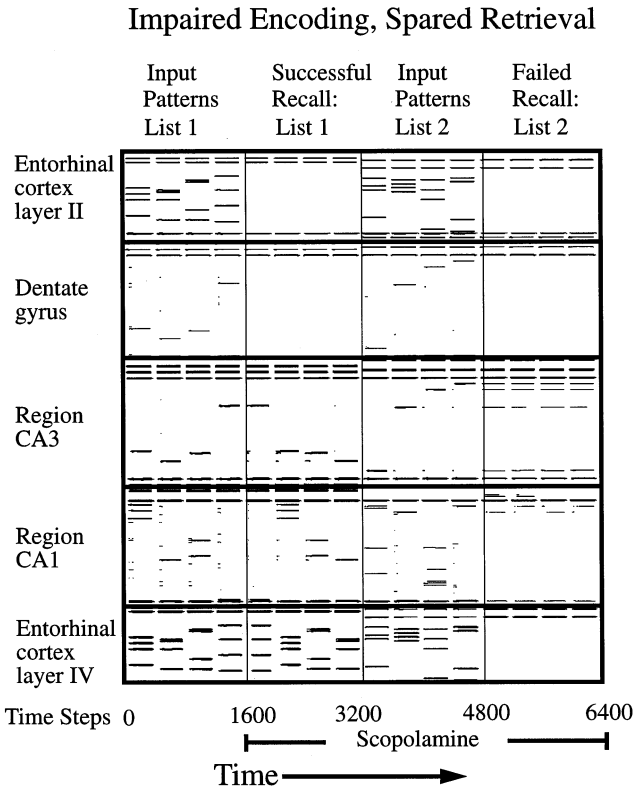

Fig. 11. Full hippocampal activity during impaired encoding but not retrieval in the presence of scopolamine. This includes the entorhinal cortex activity shown in Fig. 8. Vertical width of black lines represents the output value of each neuron in the network during the full time period of the simulation. This includes 40 excitatory and one inhibitory neuron in EC II, 60 excitatory and one inhibitory neuron in the dentate gyrus, region CA3 and region CA1, 40 excitatory and one inhibitory neuron in EC IV. In addition, activity is shown for one inhibitory and one cholinergic basal forebrain neuron regulating cholinergic modulation. During the initial 1600 time steps, four different patterns of activity are induced in entorhinal cortex layers II and III for 400 steps each. In response to each pattern, the network rapidly forms a self-organized representation of the pattern in the dentate gyrus and region CA1. The dentate gyrus pattern is auto-associated in region CA3, and associations are stored between the activity in CA3 and CA1 and between CA1 and entorhinal cortex layer IV. After the first list is encoded, scopolamine is introduced and context cues are given to the system initiate free recall of that list during steps 1600–3200. After the first list has been successfully recalled, another bout of learning ensues during steps 3200–4800 with a different context. This second list is encoded under the influence of scopolamine. During steps 4800–6400, the simulation attempts and fails to recall the second list.

can be seen during learning of the first four item patterns (steps 0–1600), the dentate gyrus responds to each of the input item patterns with initially, broadly distributed activity which then converges to a single active unit. This representation is then passed directly to region CA3, where the individual representations are stored as attractor states due to strengthening of recurrent connections. Associations are also formed between the individual item attractor states and the context attractor. Meanwhile, the direct entorhinal cortex input to region CA1 contributes to the formation of self-organized representations in that region. The Schaffer collaterals projecting from region CA3 to region CA1 associate the CA3 attractor states with region CA1 activity, and connections from CA1 to entorhinal cortex layer IV associate the CA1 representations with output corresponding to the individual item patterns.

During the effective retrieval of these representations, it can be seen that only the context portion of layer II and dentate gyrus are activated. However, within region CA3, the activation of context slowly activates each of the stored attractor states. (Note that before each attractor state starts to dominate, there is a period of time during which activity appears in many of the individual units associated with that context.) Once an attractor state is reached, it activates the associated representation in region CA1 and the appropriate output pattern in entorhinal cortex layer IV. (The patterns come up in a different order).

The effects of scopolamine on encoding in the network are subtle. This is because for effective recognition function, attractors need to be stored in the network. Thus, even during learning in the presence of scopolamine, activity is visible in region CA3. However, the activity proceeding on to region CA1 is considerably weaker, due to the decreased depolarization and lower rate of synaptic modification throughout the hippocampus. The presence of scopolamine during encoding has a strong effect on retrieval of the second list. As can be seen, the context activity arriving via the dentate gyrus activates the context attractors in region CA3, and the activity spreads into all of the units previously associated with that context. However, recurrent excitation is not sufficient for any individual unit to dominate. Thus, the network shows distributed weak activity without converging to an individual at-

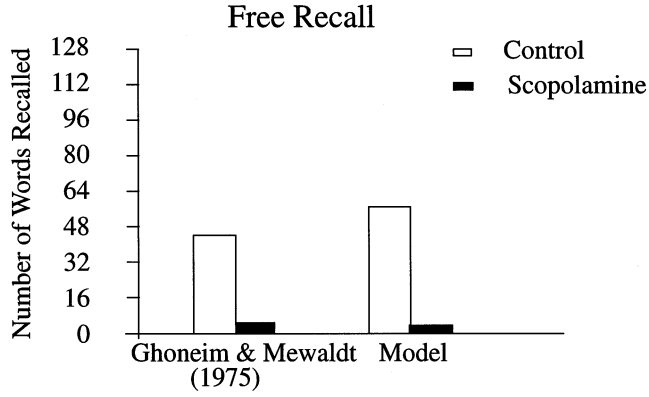

Fig. 12. Left: Bars show the percentage of words retrieved during free recall in the experiment by Ghoneim and Mewaldt by subjects who received injections of scopolamine (filled bar) or saline (open bar). Right: bars show the percentage of words recalled in the network simulation of the hippocampus during dynamics representing injections of scopolamine (filled bar) or saline (open bar).

tractor. Activity does not spread on into region CA1, and no item patterns appear as output in entorhinal cortex layer IV.

To quantitatively simulate the Ghoneim and Mewaldt experiment, the network was trained on eight lists of 16 words each in conditions with scopolamine and without scopolamine (corresponding to the scopolamine condition and the saline controls in the experiment). Fig. 12 shows the number of item patterns recalled by the network after learning with and without scopolamine, and compares these numbers with the number of words recalled by the human subjects when encoding took place after injections of scopolamine or after injections of saline (control). Parameters of the model were found which could effectively match the quantity of words retrieved in the two different conditions of this free recall task. Note that in certain regions of parameter space, the model performed much better than the human subjects. It was necessary to choose parameters such that the model would match the low retrieval rates observed in the control subjects.

4.3. Scopolamine during encoding impairs free recall but not recognition of words during retrieval

Implementing the effects of scopolamine within the network simulation of the hippocampus selectively impaired the free recall but not the recognition of lists of words. These results are presented in Figs. 13–15. Note that these effects were obtained with the same structure and parameter values presented for the simulations described in the previous section. Spared recognition put considerable additional constraints on the function of the model, requiring that there still be some learning within the network. In the example shown in Figs. 13 and 14, the network was presented with a single list of three item patterns and an associated experimental context in the presence of scopolamine. Again, we used a reduced list of patterns so that the individual patterns would be clearer in the figure. Subsequently, the network was tested on the free recall and recognition of this single list of words.

During the encoding period (first 1200 time steps) the activity in entorhinal cortex layer IV closely resembles the activity in entorhinal cortex layer II. Subsequently (steps 1200–2400), the network was presented with only the context input in layer II. As in the figures discussed above, the network does not perform effective free recall. The output item patterns do not appear in entorhinal cortex layer IV. In contrast, recognition is successful during the final steps of this example (steps 2400–3600). During this period, only the input item patterns are presented to layer II. In response to each item pattern in layer II the network retrieves the context pattern in layer IV. This satisfies the criterion for a 'yes' response for recognition.

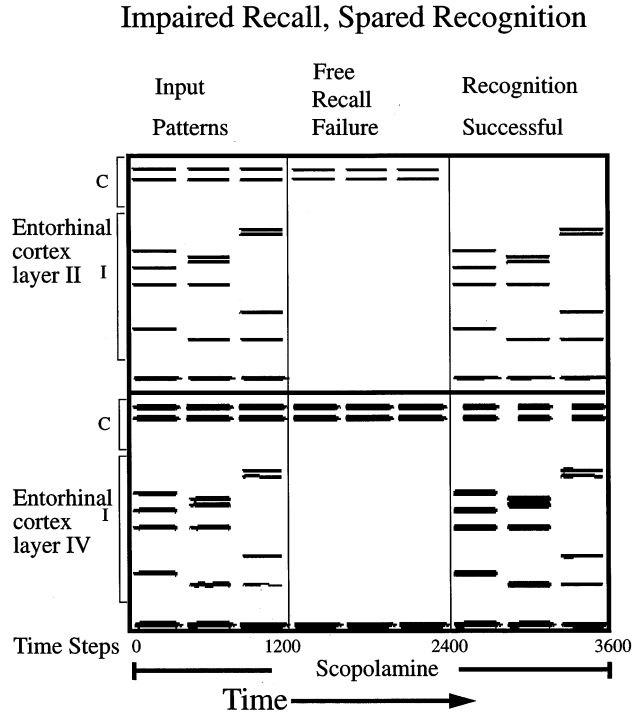

Fig. 13. Simulation of how scopolamine present during encoding impairs the free recall but not the recognition of individual patterns. Input to and output from the hippocampal network model is shown during testing of recognition. The horizontal width of black lines represent the activation level of each individual unit at each time step of the simulation (time is plotted horizontally). Top. Example of three highly overlapping input patterns presented sequentially to the local circuits representing entorhinal cortex layers II and III. The complete version of each of three patterns was presented during encoding in the presence of scopolamine during steps 0–1200, coupled with a context cue. Free recall was tested by presenting only the context cue during steps 1200–2400. Recognition was tested by sequential presentation of old or new item cues without context during steps 2400–3600. Bottom. Output of the network. Example of the final pattern of activity in the local circuits representing entorhinal cortex layer IV. Note that in response to the context cue alone, the network only responds with one or two of the item patterns. However, when old item patterns are presented, the network consistently responds with the previously associated context, whereas new item patterns do not evoke the previously associated context. Thus, recognition shows little effect of scopolamine, whereas free recall is strongly impaired.

Fig. 14 shows the activity of the full network during learning and recognition of the individual patterns. The patterns of activity within the network are similar to those discussed previously for the encoding and failed free recall. During testing of free recall, context evokes activity in the dentate gyrus and region CA3 corresponding to context, but as in Fig. 11 above, this context activity evokes distributed activity among the item representations in region CA3, without inducing the approach to a single attractor state. Little activity spreads on to region CA1, and no item patterns appear in entorhinal cortex layer IV. Thus, the free recall within the network was strongly impaired. During test-

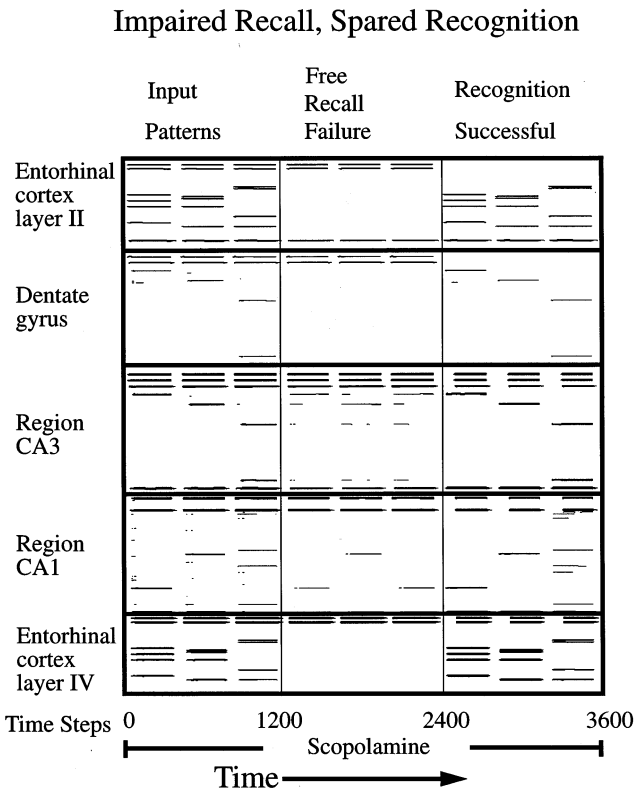

Fig. 14. Activity in the full hippocampal network during impaired free recall and spared recognition. The size of the different subregions is the same as in Fig. 11, and the input and output are the same as in Fig. 13.

ing of recognition, the network was presented with the individually stored items. These items evoke the previously formed item representations in dentate gyrus and region CA3. In many cases, this activity was not strong enough to elicit the item attractor state. However, even when the item attractor state was not activated, the network was often capable of evoking the context attractor state. This context attractor state then activated region CA1 and resulted in reconstruction of the output context pattern in entorhinal cortex layer IV. In this case, the network provides experimental context for familiar words, allowing a 'yes' response on the recognition test.

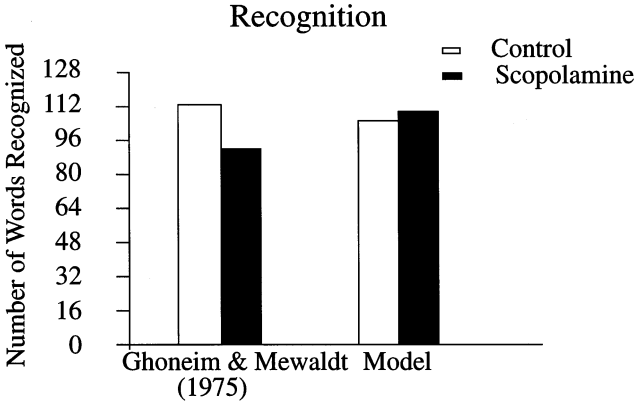

Fig. 15. Left: Bars show the percentage of words recognized in the experiment by Ghoneim and Mewaldt by subjects who received injections of scopolamine (filled bar) or saline (open bar). Right: Bars show the percentage of words recognized in the network simulation of the hippocampus during dynamics representing injections of scopolamine (filled bar) or saline (open bar).

In the example shown above, no unfamiliar words were presented. However, in the larger scale simulation of the Ghoneim and Mewaldt data, the familiar item patterns were intermixed with unfamiliar item patterns to replicate the paradigm used to test human subjects. In this case, unfamiliar words evoke a different context or no context at all—allowing a 'no' response on recognition.

The same network model used to replicate the impairment of free recall shown in Fig. 12 was used to replicate the sparing of recognition in the Ghoneim and Mewaldt experiment. For this simulation, separate networks were again trained on each of eight lists of 16 words each. Recognition was then tested by presenting each network with a list of 32 input item patterns, of which 16 had been encoded. The recognition capability of the network was evaluated on the basis of whether or not context activity was evoked in entorhinal cortex layer IV. If context activity was evoked for a previously learned pattern, the recognition was scored as correct. If no context activity was evoked for a previously learned pattern, or if context activity was evoked for an unfamiliar item pattern, then this was scored as an error. The performance of the simulation is shown in Fig. 15, with comparison to the performance of the human subjects in the Ghoneim and Mewaldt experiment after injection with scopolamine or injection with saline (control). Thus, the different properties of context and item attractor states allows differential sensitivity of free recall and recognition (and may be related to the differential list-strength effects in free recall and recognition discussed below).

Scopolamine has been shown to impair recognition in more difficult tasks, including a task requiring discrimination between a target list and a distractor list [107] and a task in which macaque monkeys were trained on object recognition [108,109]. The model could simulate this data by assuming weaker context representations due to the use of competing lists in the Richardson task. The Aigner data could be due to the difficulty of the task for monkeys (controls perform at less than 80%), or to the use of higher doses of scopolamine in that study (10 and 17.8 μg/kg in contrast to 8 μg/kg in the human studies). Impaired recognition is quite easy to obtain within the model—it is much more difficult to simulate the sparing of recognition during the impairment of free recall. With weaker representations of context, scopolamine has an effect on context similar to the effect on item, and recognition shows an

impairment more closely resembling the impairment of free recall.

4.4. Summary of scopolamine effect on memory

Fig. 16 summarizes how scopolamine selectively impairs memory function in the model, focusing on the interaction of neuronal populations representing context and item within region CA3 of the simulation. In control conditions, the enhancement of synaptic modification and depolarization by acetylcholine is important for strengthening recurrent connections within the context population and the item population. Because context is presented repeatedly, the recurrent connections are stronger for context than for individual items. In scopolamine conditions, the effects of acetylcholine are partially blocked, resulting in less strengthening of excitatory recurrent connections. Though both sets of connections are weaker, the context connections are still stronger than the item connections. These effects of scopolamine do not impair retrieval of previously stored memories. After learning in control conditions, free recall can be induced by input to the context population. This population enters an attractor state and spreads activity to the item population, which goes into an attractor state resulting in successful free recall.

For items learned under the influence of scopolamine, weaker recurrent connections result in a failure of free recall. The context population can still enter an attractor state, but the spread of activity to the item population is not sufficient to evoke an attractor state. Scopolamine results in less strengthening of context connections as well, but not sufficiently to impair recognition. Input to the item units may not evoke an attractor state, but when activity spreads to the context population, recurrent excitation is still sufficient to mediate recognition. Thus, the asymmetry in the strength of recurrent connections for context and item result in the selective impairment of free recall but not recognition. This same asymmetry results in the presence of a list strength effect for free recall but not for recognition.

The example illustrated in the figure focuses on effects of decreased synaptic modification within region CA3 of the simulation. In some cases, other factors contributed to the memory effects. Decreased depolarization of neurons sometimes resulted in a failure of entorhinal cortex input to induce sufficient activity in the dentate gyrus or region CA1 to form self-organized representations. If this occurs in dentate gyrus, no item representation is passed on to region CA3, and the context may evoke an old memory which interferes with the new memory. If a new representation is not formed in region CA1, the new attractor formed in region CA3 cannot be linked to the pattern of activity in entorhinal cortex layer IV. Failure to form CA1

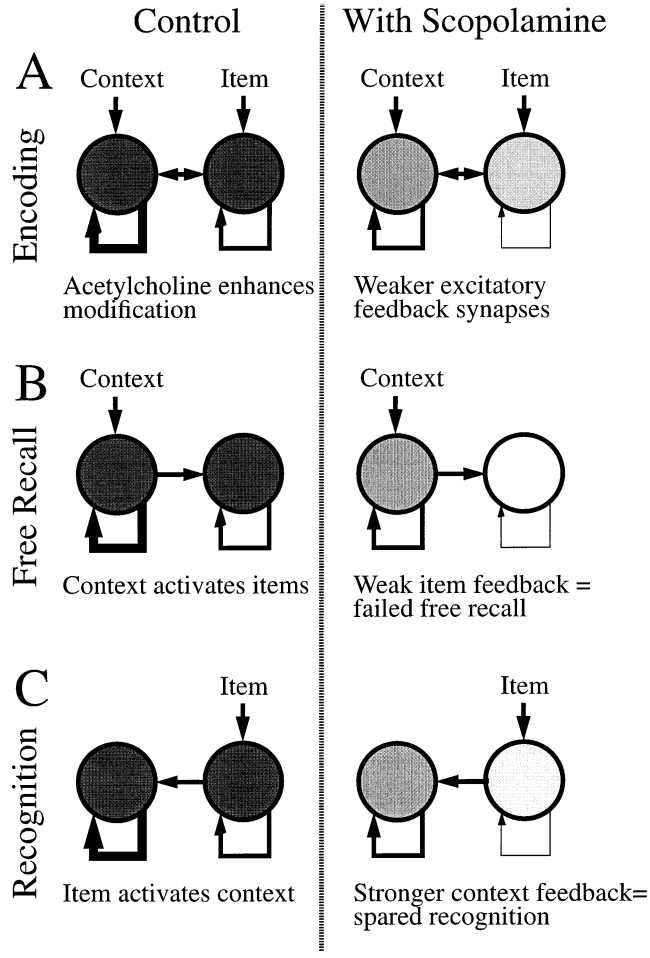

Fig. 16. Summary of the effect of scopolamine. Circles represent populations of CA3 pyramidal cells encoding context and item. Width of lines represent strength of recurrent excitatory connections within each population, and strength of connections between the context and item populations. (A) Encoding. Control: context is present continuously, whereas individual items are present only briefly. This results in an asymmetry of representation, with stronger recurrent connections in the context population than in the item populations. Scopolamine: decreases in depolarization and synaptic modification result in weaker recurrent connections for both populations, but the asymmetry of strength still persists. (B) Free recall impaired. Control: input is presented to the context population, which enters its attractor state. Activity then spreads to the different item populations, which sequentially enter attractor states. After scopolamine: Weaker recurrent connections result in a failure of free recall. Input to context neurons cause them to enter an attractor state, but when activity spreads to the item populations, they do not have sufficient recurrent excitation to enter an attractor state. (C) Recognition spared. Control: input is presented to an individual item population which enters an attractor state. Activity then spreads to the context population and evokes the context attractor state, resulting in recognition. After scopolamine: Input is presented to an individual item population. Due to weaker recurrent connections it may not enter an attractor state, but the activity nonetheless spreads to the context population. The recurrent connections in the context population are stronger than for the item population, so this population can enter an attractor state and mediate spared recognition. The same asymmetry that results in sparing of recognition after scopolamine results in a decrease in list strength effect for recognition.

representations blocks free recall, but does not block recognition, since region CA3 can still evoke the context attractor which is strongly linked with entorhinal cortex.

4.4.1. List-length effect

Standard memory experiments demonstrate a decrease in the rate of retrieval and accuracy in recall and recognition as list length increases [110–112] Excluding the effects of recency, primacy and other variables, an element of a 10 word list heard at a rate of 2 s per word has a 45% chance of being recalled. For 15, 20, and 30 word lists these percentages drop to approximately 40, 30 and 20% respectively [111]. Note that these data are taken from an immediate recall serial position graph. This drop-off effect has been named the List-length effect (LLE) and is reliably present across recognition [110,112], cued recall, and free recall experiments [111,70].

The presence of the LLE in this model is a result of the dynamics of the free recall process. A given set of context cues excite multiple associated items until one item attractor dominates and suppresses the others. The greater the number of items associated with the same context pattern, the larger the threshold for activation of one item. This increase in recall threshold decreases the percentage of items recalled even if the mean value of item strength remains constant across list lengths. Our model exhibits the qualitative features of the list-length effect found in humans, achieving levels of 67, 42, 15 and 9% for 10, 16, 20 and 30 word lists as shown in Fig. 17.

The LLE is also found in recognition paradigms [110,112]. In contrast to free recall in our model, a recognition LLE does not result from competition between individual items. The potential of an item, once activated, to recall the context is not affected by the number of items in a list. However, as the number of items in the list increases, the chance that a novel item presented during a recognition test is similar enough to a list item to evoke a positive response increases as well. So for a given pair of items, it becomes increasingly likely that the recognition process will recognize both, thus lowering the total score. These intrusions were due to activation of the wrong representation in the dentate gyrus. Note that the curves for the recall and recognition LLEs in Fig. 17 have different shapes, a result of the different processes at work in each case.

4.4.2. List-strength effect

Words shown repeatedly or for longer durations in a list are recalled more readily than words presented less frequently in the same list. However, if all of the items in a list are presented at the same increased level, recall performance on that list will be comparable to that on a list of weaker items. This is the list-strength effect (LSE) and has been demonstrated by several researchers [70–72,113]. It has been found reliably in free recall only, with slight effects present in cued recall and no reliable effects in recognition. As shown in Fig. 18, the model presented here reliably produces the LSE for free recall but not for recognition in accord with the data.

The mechanism behind the LSE in our model during recall is similar to that proposed to explain the human experimental data [72]. During the winner-take-all competition between items in a list with both strong and weak items, the threshold for recall of an item is increased above that of a pure weak list by the strong items. Consequently, weak items are recalled even less frequently than on a pure weak list. Simultaneously, the presence of the weak items on this same list reduces the threshold relative to that of a pure strong list, hence the strong items in the mixed list are more easily recalled. However, in lists composed of only strong or weak

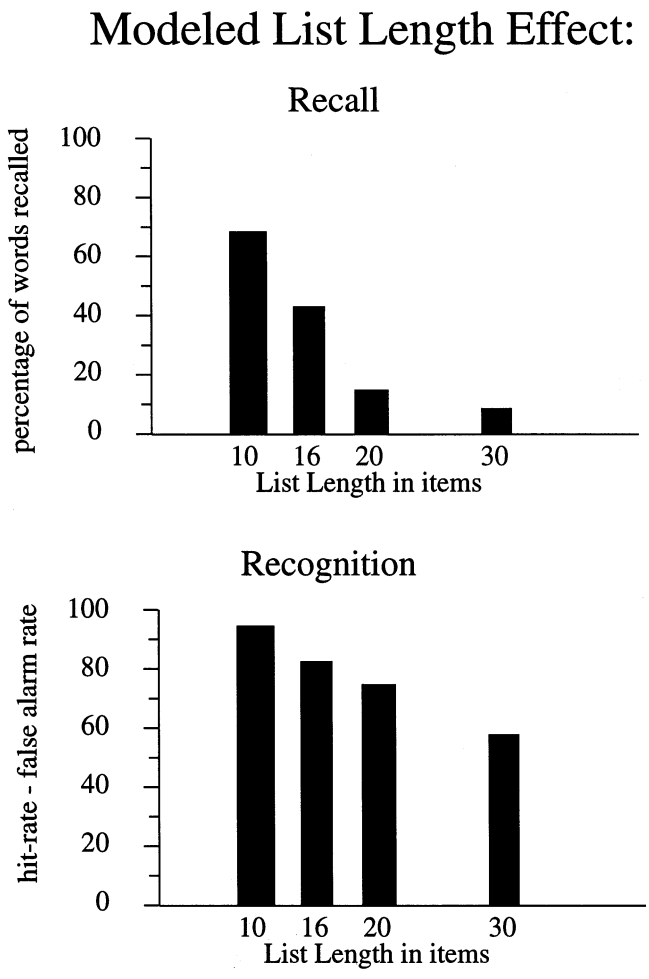

Fig. 17. Simulation of list-length effect for recall (top) and recognition (bottom). Percent recall rates are given for list lengths of 10, 16, 20 and 30. For recognition, the vertical axis represents the difference between hits and false alarm rates. Note the difference in the shapes of the two curves, a result of different causes of the effect in each paradigm.

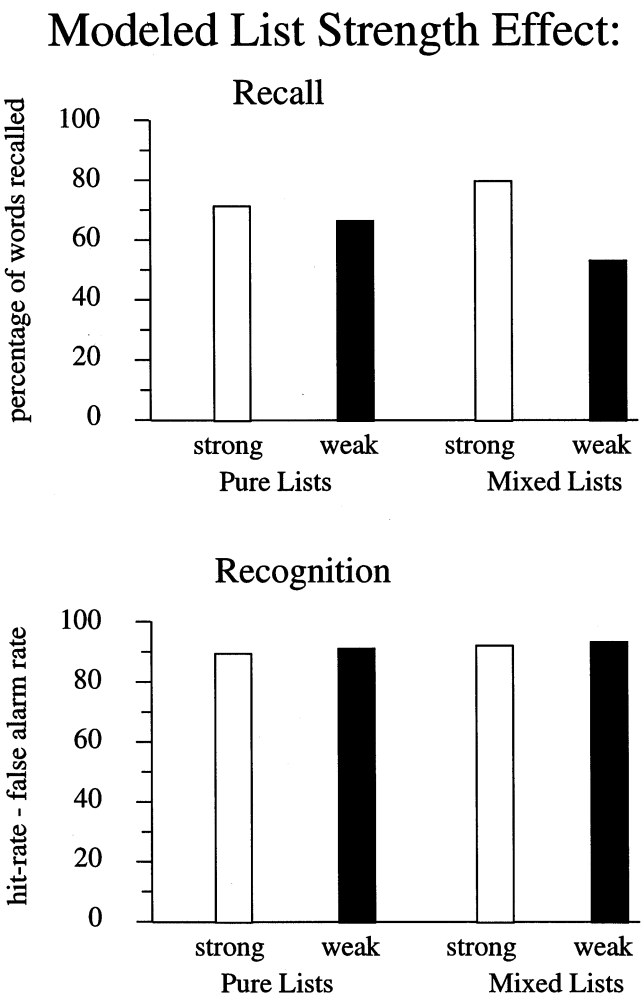

Fig. 18. Simulation of list-strength effect for recall (top) and recognition (bottom). Percent recall rates are given for pure strong, pure weak, mixed strong and mixed weak items. Note that in the mixed condition, strong items are stronger than pure strong items and weak items are weaker than pure weak items. This is the essence of the LSE. For recognition, correct recognition scores (hits—false alarms) are similar across list strength variations.

items, competition occurs only between strong or weak items and therefore the differences in recall rates between these two conditions are less pronounced and usually absent in free recall. In recognition, there is no direct competition between items because they are activated externally. Additionally, each list, and therefore each item in each list, is associated with only a single set of contextual cues. The associations between the items and context are independent of one another, so when one item has been activated, its excitatory effect on the appropriate context is completely uncorrelated with the number of items on the list or their relative strengths.

The use of separate attractor states for item and context allows the correct patterns of LSE and LLE to be addressed. In particular, the context attractor state tends to reach a saturated level which cannot be further enhanced by additional learning, preventing list-strength effects in recognition. In contrast, the item attractor states can be greatly enhanced by additional learning, allowing a strong list-strength effect to appear in free recall.

4.5. Role of individual effects of scopolamine

There are multiple effects of cholinergic modulation within the hippocampus and in the simulation presented here. These multiple effects probably co-exist to counterbalance each other. For example, the increased excitability caused by depolarization and the suppression of adaptation is offset by the decreased spread of excitatory activity due to suppression of excitatory synaptic transmission. Thus, the combined effects of cholinergic modulation could put cortical networks into a different dynamical state without dramatically changing activity levels or inducing instability.

In the simulation, partial blockade of all cholinergic effects resulted in the selective effects of scopolamine described in the previous sections. Since scopolamine influences all of these individual effects of acetylcholine, it is probable that experimental work will demonstrate that a combination of these factors results in the full pattern of encoding impairment. However, it is of interest to understand how much the blockade of individual cholinergic effects contributes to the total effect of cholinergic blockade.

4.5.1. Scopolamine blocks the cholinergic enhancement of synaptic modification

In a network with a low baseline level of synaptic modification, the cholinergic enhancement of synaptic modification becomes essential to the formation of new attractor states, but not to the maintenance of previously formed attractor states. This allows scopolamine to selectively impair encoding but not retrieval. Obtaining selective impairment of free recall but not recognition is difficult to obtain with this parameter alone, but with proper parameter values, the context attractor can be strengthened sufficiently relative to item attractors that recognition can remain unimpaired while free recall is impaired. If the effect of scopolamine on synaptic modification is the primary effect of scopolamine, the deficit should be offset by longer presentation times, or repeated presentation. This could be tested by systematically varying the presentation time or number of presentations of individual words in an experiment. In fact, if the differences between recognition and free recall do result from differences in strength of modified recurrent connections, then repeated presentation of individual items in the same context should enhance the level of free recall relative to the level of recognition. In previous work, repeated presentation of words has been shown to gradually enhance encoding of words under

scopolamine [27], but the increase reaches an asymptote well below control conditions, suggesting other effects of scopolamine are important as well.

4.5.2. Scopolamine blocks cholinergic depolarization of neurons

In simulations, this effect alone can cause a partial impairment of the storage of new patterns, but allows previously stored memories to be recalled. Blockade of cholinergic depolarization impedes new patterns in entorhinal cortex from evoking activity in the dentate gyrus unless the perforant path connections have been previously modified. This also prevents CA3 neurons from becoming sufficiently depolarized to enter an attractor state. However, if the blockade of depolarization is accompanied by a blockade of the suppression of synaptic transmission, the enhanced synaptic transmission allows retrieval of previously stored patterns to overcome the absence of depolarization.

The effect of blocked depolarization could be distinguished from the effect of blockade of other cholinergic effects by attempting to compensate for the size of representations. In contrast to the effect of decreased synaptic modification, decreased depolarization should result in formation of smaller representations, regardless of the amount of time spent learning each word. This effect could be offset by presentation of multiple cues for each word during study, as in a previous study of cued recall which showed that scopolamine did not impair learning of associations with multiple self-generated recall cues [31]. Thus, improved encoding via repeated presentation would support a decrease in synaptic modification, whereas improved encoding via multiple cues would support a decrease in cellular depolarization. Different effects of scopolamine might also show different dose effects. For instance, the loss of LTP facilitation decreases performance in a graduated way as cholinergic effects are attenuated, whereas depolarization and loss of excitatory transmission may exhibit a threshold effect, below which their removal has no effect on performance. As the concentration of scopolamine increases and passes this threshold, the deficits associated with these cholinergic effects might begin to appear.

4.5.3. Scopolamine blocks the cholinergic suppression of excitatory synaptic transmission

This effect of scopolamine applied alone has been shown to impair the encoding of new information in many models [47,48,57,58,114]. In that previous work, removal of the suppression of excitatory synaptic transmission allowed retrieval dynamics to dominate, such that previously stored memories would interfere with the storage of new memories. The shared context used in the simulations presented here could mediate interference effects in the model. However, because scopolamine only reduced the effects of acetylcholine by 65% in this model, enough suppression of excitation remained to prevent interference from occurring in most cases. In simulations during which the suppression of excitation was removed completely, context would cause massive proactive interference in region CA1 and sometimes in region CA3 during list presentation. When the strength of the dentate gyrus input to region CA3 was decreased relative to the excitatory feedback in region CA3, this interference was even more prominent. Note that when scopolamine prevents the suppression of excitatory feedback in region CA3, this stronger feedback drives the network more rapidly into previously stored representations, enhancing the retrieval of items encoded before the administration of scopolamine. Thus, the model suggests enhancement of retrieval by scopolamine. This enhancement of retrieval does not appear in the first Ghoneim and Mewaldt article (1975), but does appear in two other articles [25,27].

Blockade of suppression should become especially apparent for a paradigm testing effects of proactive interference, such as the A–B, A–C list learning paradigm. In the full model, simulation of scopolamine injection after learning of A–B lists results in greater retrieval of A–B during encoding of A–C. This causes representations in region CA1 to combine the representations of B and C pairs, preventing effective retrieval of the A–C pairs. In addition to this direct linking of associations, encoding could suffer due to competition between the B and C attractor states. As shown in Fig. 19, we explored this effect in a simulation of region CA3 alone. In that simulation, retrieval of A–B attractor states during learning of A–C paired associates causes decreased learning of the A–C associates (beyond the direct weakening of A–C associations due to weaker LTP). Subsequently, during retrieval there was a decrease in the number of C words produced, and a striking increase in the number of intrusions from the B list. Across ten simulations with different initial conditions and 10 paired associates in each list, the average number of C words recalled was 6.3 in control conditions and 1.4 after simulated scopolamine injections, whereas the number of B intrusions was 3.3 in control conditions, and 8.1 after simulated scopolamine injections. Increased proactive interference in an A–B, A–C task has been shown with chronic damage to hippocampal cholinergic innervation due to aneurysm of the anterior communicating artery [44], and has also been noted in patients with Korsakoff's amnesia [115].

5. Discussion

Blockade of cholinergic effects within the network simulation of the hippocampus effectively simulates the

effects of scopolamine on human memory function, showing selectivity corresponding to that demonstrated in psychopharmacological experiments [24–27], as shown in Figs. 10–15. In particular, implementation of the effects of scopolamine in the model impairs the encoding but not the retrieval of words in a test of free recall. In addition, simulation of scopolamine impairs free recall without significantly impairing recognition of words.

These impairments in memory function are caused by blockade of cholinergic effects which have been demonstrated in neurophysiological studies of the hippocampus [49]. Thus, the model allows effects of drug administration in a human experiment to be linked directly to data on physiological effects at the cellular level. Bridging this gap between behavior and cellular physiology will allow data from neurophysiology and molecular biology to constrain models of human memory function. We feel work of this sort is an essential step in the progression of cognitive neuroscience—models of cognitive phenomena will only converge on a successful account of both normal function and pathology when these models directly incorporate available neuroscience data at the cellular level. Cognitive neuroscience requires the techniques of computational neuroscience.

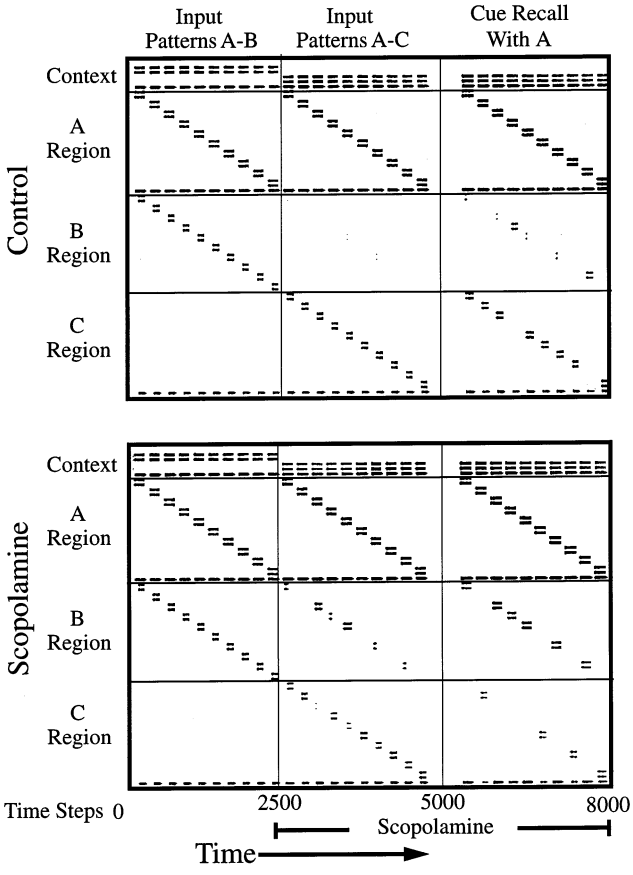

Fig. 19. Simulation of region CA3 activity in an AB–AC cued recall paradigm. Time and neurons are as described in other Figs. In each portion, the top region shows context for the A–B and A–C lists. The middle regions contain the A, B and C items respectively. Proceeding from left to right, the model learns input patterns A-B, input patterns A–C and then is tested for recall of A–C (Cue recall with A). Recall is tested by presenting both the context for the A–C list and the individual A items. Top: simulation of control conditions. C items are recalled with little interference from B items. Bottom: Simulation of the injection of scopolamine after learning of A–B items, before learning of A–C. On the right, recall of C items is strongly impaired and number of B item intrusions is much higher. A–B retrieval during learning causes interference which decreases the learning of A–C associations. This interference should cause poorer learning of A–C items than of a separate set of non-overlapping associations (D–E).

Further experimental work could explore which effects of scopolamine are particularly important for the impairment of memory function. A number of experiments have been proposed here. These include testing the prediction that injections of scopolamine after learning of a list of A–B paired associates should enhance proactive interference effects during learning of a subsequent A–C list of paired associates. If scopolamine enhances proactive interference, this suggests that the blockade of cholinergic suppression of synaptic transmission is an important effect of scopolamine. Enhancement of proactive interference could also be tested in a modified version of the Brown-Peterson task [116]. In addition, if longer presentation times overcome the free recall impairment, this suggests that blockade of synaptic enhancement by scopolamine is an important effect. The model predicts that repeated presentation of individual words should offset the asymmetry of item and context representations, making the difference between free recall and recognition less salient. The model also predicts that scopolamine should enhance the list strength effect by making the repeated (strong) words in a mixed list of strong and weak words proportionately more easy to recall. If additional cues overcome the recall impairment, this suggests that the blockade of cholinergic depolarization by scopolamine is an important effect.

The model specifically focuses on the effect of scopolamine on delayed recall of word lists. Thus, it effectively replicates the primary impairment described in a wide range of experiments on human subjects [22–28]. We have not attempted to simulate the lack of effect of scopolamine on recency [22,28] or digit span [29,23,32] because these tasks do not appear to depend upon an intact hippocampal formation [36]. Development of a model which could demonstrate the sparing of recency and digit span will require addition of a more elaborate neocortical representation which would mediate these phenomena. For a similar reason, we have not yet attempted to replicate the apparent sparing of implicit memory in the presence of scopolamine [117]. Despite this absence of an effect on recency and digit span, scopolamine has been shown to clearly impair recall

performance on the Brown–Peterson task, which tests the free recall of a consonant trigram after performance of a distractor task for short periods [30,118]. This suggests a difference in mechanism for the short-term memory of a Brown–Peterson task versus the short-term memory involved in recency. (In particular, the Brown–Peterson task may involve a short-term synaptic modification within the hippocampus, whereas recency may involve sustained neuronal activity in the neocortex.)

Future modifications of the model will add on neocortical networks, as well as increasing the biophysical detail of the simulation. Addition of neocortical networks will allow the model to address many of the effects of scopolamine which have been described as 'attentional' [21], based on data from continuous performance type tasks. For example, scopolamine impairs the ability to detect small changes in the intensity of a light [119], to detect changes in the movement of a clock hand [120] or to detect specific sequences of digits [152]. We feel these effects can be accounted for on the basis of the same set cellular effects of scopolamine within neocortical structures. For example, detection of a specific stimulus requires a strong influence of afferent input to the cortex, but the decreased depolarization and stronger intrinsic excitation present with scopolamine would decrease the afferent drive relative to intrinsic activity—thereby impairing the influence of external stimuli on cortical activity [49,121,122]. In the extreme case, this could result in a total dominance of recurrent excitation and top-down influences within the network—possibly resulting in the visual hallucinations reported after administration of high doses of muscarinic cholinergic antagonists [119,123].

5.1. Relation to other models of the hippocampus

As noted above, many of the functional properties of individual subregions of this model were based on previous theories of hippocampal function [8–11,15,17,20,54,57,73]. However, these previous theories usually focus on individual subregions in isolation from other subregions, without considering the function of the entire network in a specific behavioral task. For example, the Schaffer collaterals have been proposed to mediate hetero-associative memory function [15,124], allowing predictions of CA1 activity based on CA3 activity [10]. This hetero-associative function has been tested in a model of the Schaffer collaterals incorporating self-regulation of learning and recall [57], but has only been tested in full network simulations recently [12–14]. Longitudinal association fibers in region CA3 have been proposed to mediate auto-associative memory function [8,9,11,16] or storage of temporal sequences of patterns [10,74,93]. This auto-associative function has been analyzed in models of modifiable recurrent excitation in region CA3 [54,74], but has not been combined with the function of other subregions until recently [12,14]. Finally, synapses of the perforant path fibers projecting from the entorhinal cortex to the dentate gyrus have been proposed to form sparse, distributed representations of afferent input to the hippocampus [8,9,11,17], but simulations have not addressed the problem of when these representations should remain stable, and when they should be altered. Reviews have summarized hypotheses about the separate function of a variety of hippocampal subregions [10,11,17,20], but these regions do not process information in isolation and then pass information on to the next region–they interact continuously as a dynamical system. Understanding the interactions within such a distributed network requires explicit simulation of the full network. When full network simulations have been developed, they tend to focus on one level–thus, effective models of behavioral phenomena have not directly modeled physiological structures [19,97], whereas network models of hippocampal physiology have not addressed specific behavioral data [12,18].

In contrast to previous biological models, our model of hippocampal function explicitly simulates specific human memory tasks, such as free recall and recognition, and specific behavioral phenomena, such as the list strength effect and the free recall impairment induced by scopolamine. Some of the effects described here could appear in a simulation of region CA3 alone, but such a simulation would provide only a very abstract perspective on function, leaving many questions open about the mechanisms of human episodic memory function. Simulation of the full hippocampal network provides a more direct bridge to the behavioral data, and required inclusion of additional regions. Specifically, formation of non-overlapping representations required inclusion of the dentate gyrus. The low modification thresholds of the synapses within the dentate gyrus could not be implemented in region CA3 without causing massive interference. In addition, the self-regulation of modulatory state required the comparison function in region CA1 and an explicit representation of the medial septum. Functionally, it is difficult to use CA3 for this comparison function. In particular, there must be some delay between the formation of an attractor and the decrease in cholinergic modulation—this allows the synapses contributing to the attractor state to be strengthened for a period of time, and it allows this attractor to more effectively suppress other attractor activity, preventing interference. Performance of the comparison in a region distinct from the formation of attractors provides this delay in regulation of cholinergic modulation, and allows use of a cleaner recall representation for performing the comparison. Finally, understanding the interaction with neocortical regions required the en-

torhinal regions mediating input and output from the model. These regions have quite simple function in the model, but they provide a stable interface between neocortex and hippocampus—allowing neocortex to decode the episodic representations formed randomly in the hippocampus.

5.2. Relation to other models of human memory function.

The effect of scopolamine on human memory function has never previously been modeled, but the structure of our model can be compared to certain aspects of other human memory models.

5.2.1. Representation of memories

The representation of input patterns in the entorhinal cortex resembles composite trace models in which individual items are represented as a set of individual features [1,77]. However, once sparse representations are formed in the dentate gyrus, the representation resembles those of separate trace models such as MINERVA2 [3] and SAM [2], with no overlap between item traces. However, in a much larger network simulation, the representations in region CA3 could involve multiple overlapping units without interfering with the necessary attractor dynamics.

5.2.2. Context as a cue

The storage of associations in region CA3 of this model reresembles the procedure used in SAM [2] which associations between different stored items and context take values between 0 and 1 in a matrix. However, they simulated retrieval by computing the probality of recall, whereas we use explicit attractor dynamics. This method for storage of associations differs quite radically from convolution-correlation, but our method of using context as a cue resembles that used in convolution-correlation models [77].

5.2.3. Recall

Most human memory models perform recall as an algorithm akin to a flowchart. At the other extreme is our model, motivated by the spread of neural activity within cortical structures. In our model, behavior is controlled by the continuous dynamic processes that govern the activation of multiple units. The only external controls are the presentation of stimuli themselves, which are equivalent to the stimuli present in experimental conditions. The ability of the model to internally regulate its state of encoding or retrieval is a benefit of the use of internal regulation of cholinergic modulation. This is closer to the model of Chappell and Humphreys, which uses units whose activity is controlled by intrinsic dynamics. However, that model uses external modulation to attenuate global inhibition during study and to deactivate learning during recall.

5.2.4. Choice of output

The models of Chappell and Humphreys, MINERVA 2, and our own are similar in this production of output. All three contain some sort of cleanup mechanism that recreates exactly the output. In our model, the act of passing output from CA3 to entorhinal cortex greatly reduces noise. Only a fully active pattern on CA3 can activate a representation in region CA1 and then in entorhinal cortex layer IV. This ensures that in the initial stages of recall, when many different CA3 patterns are competing, none are capable of activating an output pattern. The model of Chappell and Humphreys uses an auto-associator to converge on the pattern closest to the one produced by the intersecting pattern-associators. MINERVA 2 cyclically reapplies its output to itself, resulting in convergence on the closest pattern to the one originally produced by its own recall process.

5.2.5. Preventing reactivation

Other models of free recall [2,77] prevent reactivation of previous responses through a sort of repetitive cued recall, in which previously recalled items provide cues which move recall more efficiently from item to item. In contrast, the cues presented for free recall in our model stay absolutely constant during recall. Instead, adaptation based on previous activation effectively removes a pattern, once activated, from the pool of possible responses. In separate research, we have used the adaptation properties of this model to simulate fMRI data showing a decrease in hippocampal activation during viewing of a single repeated stimulus versus different novel stimuli [125,126].

5.2.6. List length and list strength effect

This model successfully replicates the list-strength effect (LSE) for free recall but not recognition. When some items on a list are presented several times (strong items), while others are only presented once (weak), our simulation shows a ratio of performance on strong items to weak items which is greater than that same ratio when the strong and weak items are on separate lists. Most models achieve the LSE for recall but also exhibit it for recognition, in contrast to human data. The primary reason for this error in composite models is that each item contributes to the variance of the entire system and variance, in turn, is detrimental to recognition accuracy. Therefore, enhancing one item in any way deteriorates all of the rest [72]. In our model, items only interfere when they are concurrently being activated by a common input, as is the case during recall. During recognition, only one item is active at a time, so the others cannot affect its performance, regardless of strength. Recall, however, does force direct competition between items, which allows the differences between strong and weak items to manifest in a mixed

list, correctly producing the LSE phenomenon. Chappell and Humphreys [7] obtained this effect in a similar manner. The list-strength phenomenon might be enhanced after injections of scopolamine because the weakened attractors will benefit more from the extra strength given to strong items.

The manner in which our model produces the list-length effect differs from other models. As the patterns are encoded into CA3, the recall process becomes more and more difficult. Input from context activates many more item neurons in the case of a longer list, so the requisite strength of those items must be higher to win the competition and reach an attractor state. In recognition, a completely different phenomenon is at work. As the dentate gyrus learns more and more patterns, the chance increases that a distractor item presented for recognition matches one of the list items enough to cause a false alarm. Hence, the list-length effect for recognition is almost entirely due to increasing intrusions. In composite models, the list length effects in recall and recognition both obtain from the increase in variance associated with longer lists. This contrasts with our model which exhibits increasing thresholds for recall as list length increases.

5.3. Relation to data on the effect of hippocampal lesions

The network simulation presented in this paper provides a detailed description of how the hippocampal formation could mediate the formation of episodic memories. The loss of a structure which rapidly forms sparse relational representations could result in the profound anterograde and partial retrograde amnesia observed in subjects such as patient HM [33]. The temporally graded retrograde amnesia observed with hippocampal lesions [98] has been simulated in a modified version of this model, in which stored hippocampal representations gradually cause formation of discrete neocortical representations via feedback connections [13]. This demonstrates the consolidation of information proposed in a number of previous articles [17,98,127]. In fact, cortical dynamics in the absence of cholinergic modulation are particularly well-suited to this process of consolidation, which resembles retrieval in that it involves transferring information back from hippocampus to neocortex. Physiological data has already been obtained to support the strong influence of feedback connections from the hippocampus to deep entorhinal cortex during periods when cholinergic modulation is decreased [128].

In the framework presented here, the mechanisms for episodic memory function are identical to those necessary for performance based on configural [129] or relational [130–133] aspects of stimuli used in behavioral tasks with rats. For example, rats may use episodic memory for specific trials in responding to new probe combinations which differ from previous combinations used in an odor association task [130,131]. However, addressing the difference between configural and relational representations will require further development of models which can store sequences of activity [134,135]. The simulation presented here does not address the conditioning data simulated by previous connectionist models [19,97] However, the formation of new representations of input patterns in this model can be considered analogous to the function of the hidden layer in the Gluck and Myers model [97,99]. Models focused on the role of place cell responses in spatial navigation [96,136] have utilized simplified interactions between units with pre-existing responsiveness to specific environmental features. These models have proven effective for simulating behavioral data and generating new experimental predictions, but it is not clear how their components map to the anatomical and physiological features of the hippocampus. Use of a biologically detailed simulation of the hippocampal formation will allow the theoretical work on these models to be interpreted in the context of anatomical and physiological details [134].

5.4. Relation to neurobiological data

The model presented here is strongly motivated by neurobiological data on a cellular and synaptic level. Thus, we have incorporated representations of experimentally demonstrated cellular phenomena such as suppression of adaptation and depolarization [61,63] and the modulation of neurotransmitter release [53–55,57] which are commonly neglected in most cortical models. However, the effort to address neurobiological data has only just begun.

Extensive data on the hippocampus has been obtained using single-unit and multiple unit extracellular recording techniques [101,137,138]. This technique allows observation of the timing of action potentials in a single neuron or over 100 simultaneously recorded neurons. The model presented here can easily address data on place cell responses, in which single neurons respond selectively when a rat is in a particular spatial location [138,139]. These place cell responses consist of highly selective responses to particular configurations of input stimuli. This is exactly the nature of the representations being formed in the model by the self-organization of input to the dentate gyrus and region CA1. Place cells are not explicitly considered episodic representations—but these responses form within a period of minutes [138], and can then be reactivated with partial cues. The representations in this model have a similar capacity for rapid formation and completion of degraded cues. Of course, during verbal learning, the nature of the cues are quite different, but analogous responses might be

detectable in humans if they were required to repeatedly recite passages of text—resulting in repeated activation of the initial verbal episodic representations (litany cells). The model presented here already demonstrates the ability to form much sparser representations of environmental cues in region CA3 compared to entorhinal cortex. This is in keeping with the much smaller place fields and sparser activity found in region CA3 versus entorhinal cortex in rats exploring an eight-arm radial maze [140].

The single neuron activities in this model are meant to correspond to neuronal activity in a population of neurons in a larger scale network. This model addresses some aspects of the complex temporal features of single unit recording. In particular, inhibitory interneurons appear to fire regularly on each theta cycle, whereas excitatory units show much sparser and more intermittent activity. This is consistent with the representation in the model which requires feedback inhibition during all patterns, with different subsets of excitatory neurons being activated. The termination of each attractor state is a general representation of some cyclical function, but the model does not directly address the time course of gamma and theta oscillations observed with field potential recording in the hippocampus [141–143], or the effect of cholinergic modulation on oscillatory dynamics [144]. Nor does it address the consistent phase relationships of neuron firing with theta rhythms [145]. Analysis of these properties requires models with detailed spiking dynamics, such as compartmental biophysical simulations [67,146]. We have developed a more detailed biophysical simulation of the hippocampus to address these temporal dynamics [134,135].

Attractor dynamics require some repetitive activity within short time periods to function, which may be difficult to obtain given the low baseline firing rate of neurons. However, neurons do show short periods of high frequency activity around 30–40 Hz [101,137], and the tendency of excitatory neurons to fire tight clusters of 3–4 action potentials ('complex spikes') could form the basis for a rapid approach to an attractor state within one gamma oscillation, partly driven by the intrinsic properties of neurons which induce bursting behavior [147]. Integrate and fire models demonstrate fixed-point attractor dynamics analogous to the attractor dynamics of the model presented here [148,149], and approach these attractors in a rapid manner [149], suggesting that the results presented here should apply to spiking models as well. Models with spiking dynamics are more versatile for the storage of temporal sequences of patterns [10,12,135,150,151]. Use of these types of models will allow the flexibility necessary for simulating the storage of inter-item associations and performance of relational tasks [131,133]. Further development of detailed compartmental biophysical simulations of cortical networks [67,135] will allow us to more effectively link behavioral data on memory function to neurophysiological data at a cellular and circuit level.

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