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Distinct Memory Circuits Composing the Hippocampal Region

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ABSTRACT: The very different anatomical designs of the adjacent circuitries of the cortico-hippocampal pathway, along with their somewhat different synaptic plasticity mechanisms, suggest a nearly serial pathway of distinct memory circuits each contributing its own specialized processing operation to overall hippocampal function. Modeling and formal theoretical analysis of the prominent anatomical design features of particular circuits (piriform/entorhinal cortex; hippocampal field CA3; hippocampal field CA1) are found to identify potential emergent function not readily arrived at in the absence of these formal models, and yet which once derived can be seen potentially to confer unique capabilities to an integrated hippocampal mechanism for processing memories during behavior. © **1997 Wiley-Liss, Inc.**

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INTRODUCTION

Although many different mammalian forebrain systems share common properties of circuit design, suggesting shared functions, some brain regions contain circuits possessing very different architectures, suggesting differential contributions that may act in concert to give rise to overall emergent function of the region. The hippocampal region, much studied for its involvement in a variety of memory-related tasks, is notable for its motley composition of distinct, even unusual, network designs (entorhinal cortex → dentate gyrus → field CA3 → field CA1). What are the unique anatomical designs and physiological rules of these individual subcircuits contributing to the functionality of the hippocampal region as a whole?

The hippocampal region (or the somewhat larger surrounding region which might more descriptively be referred to as the cortico-hippocampal pathway) consists of the hippocampus proper (fields CA3 and CA1), an input stage (dentate gyrus), and enclosing cortical tissue (the entorhinal, perirhinal, and parahippocampal cortices). Of these, the cortical areas bear much similarity to each other, though not to the hippocampal fields or to dentate. Dentate consists of unusual primary cells (the granule cells) which divide very late in development, have no basal dendrites, and give rise to the mossy fiber axon tract, with its extremely atypical characteristics. The cells of fields CA3 and CA1 are more typical of the cortical areas: relatively large pyramidal cells with many points of similarity to those of deep layer cells in neocortex. Field CA3's cells are less likely to have a single apical dendrite (and thus are less strictly "pyramidal") than their more classically pyramidal counterparts in CA1. The design of CA3 is perhaps most unusual in the extremely steep local density gradient of its recurrent collateral system: Within a local neighborhood, CA3 cells contact each other very densely, although the overall density of contact among CA3 cells throughout the field is not uncommonly high.

A point of similarity among all these networks is the occurrence of plastic changes to their synaptic connections. Long-term potentiation (LTP) is a term typically reserved to denote forms synaptic plasticity that possess the particular properties characteristic of behavioral long-term memory systems: rapid induction (seconds), very persistent change (at least months), and high capacity (as with behavioral memory). Although every component of the cortico-hippocampal pathway has been shown to exhibit potentiation, evidence for potentiation with the longevity of memory has as yet only been tested in vivo in field CA1 (Staubli and Lynch, 1987), although it might well occur in other regions as well. Interestingly, potentiation in dentate gyrus has been reported to have a decremental nature, returning slowly to baseline over the course of roughly a week (Barnes, 1979; Green et al., 1990). This may be indicative of its involvement in memory operations other than those of permanent memory; e.g., long-lasting memory may have LTP as a substrate, whereas a recent-memory system may be expected to be subserved by a decremental potentiation system (Lynch and Granger, 1992).

Whereas selective lesions and chronic recording studies attempting to distinguish the functional contributions of distinct cortico-hippocampal areas are extremely difficult, nonetheless the quite different biological features of these circuits suggest their differential operation, and bottom-up modeling of their distinguishing biological features may

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therefore provide a useful tool for identification and analysis of their unique roles.

The goal of these modeling efforts has not been to account for all biological phenomena associated with the modeled regions, if indeed this were even possible at this stage. Rather, the intention has been to attempt to elucidate possible computational function from prominent characteristics, especially robust anatomical design characteristics and the known physiology of synaptic long-term potentiation, on the theory that prominent, robust structural and operational features will be indicative of primary function. It is not contemplated that the resulting simplified computational formulations are "the" function of the modeled area—many areas may have multiple functions, or may serve quite different functions under different operating conditions, and in any event it is likely that a great deal of further biological detail would be needed before any sense of finality could be attained. To the extent that further biological detail turns out to be compatible with the simplified modeling results, that is taken as support of the general findings; but to the extent that adding further biological detail weakens the results, it is an indication that the approach may have been incorrect, and that further modeling, incorporating additional detail, must be undertaken.

Simulation and empirical investigation alone may confirm and provide illustrations of hypotheses that were operative during the simulation's design. The further steps of simplification, rendering of the simulations into algorithms, and formal theoretical analysis have added benefits. It enables rigorous characterization of the primary derived features of the mechanisms that are at work in the simulations and permits these mechanisms to be situated in the literature of comparable computational mechanisms. Moreover, these theoretical treatments on occasion uncover more unusual mechanisms embodied in the circuits that were not previously suspected and thus not contained in prior hypotheses.

It is hoped that the resulting assignation of prominent features to potential function may serve to set guideposts aiding ongoing study. These initial modeling results may be worth further investigation especially when they diverge from typical formulations such as "associative memory" or "self-organization." Of course, a finding of an unusual function derived from a brain circuit model does not necessarily indicate that the more standard formulations of that circuit are in error, but it raises the possibility that certain functions were not looked for, and may for that reason have heretofore been missed.

DIFFERENTIAL MODELING OF INDIVIDUAL STRUCTURES

Superficial Piriform/Entorhinal Cortex

Circuit design

The superficial layers (I–III) of piriform and of ento- and perirhinal cortex exhibit many shared properties, including very diffuse (nontopographic) organization, extremely sparse connectivity between inputs and targets, sparse excitatory collateralization within the field (Van Hoesen and Pandya, 1975), a ratio of roughly 100:1 excitatory to inhibitory cells, and inhibitory cells with relatively short, densely arborizing axons thereby forming dense connectivity with neighboring excitatory cells but sparse or no contacts with more distant cells (Kohler et al., 1985; Kohler, 1986).

These superficial cortical cells contain both AMPA and *N*-methyl-D-aspartate (NMDA) type glutamate receptors apparently colocalized at the synaptic targets of the afferents (Monaghan and Cotman, 1985), and these synapses have been shown to exhibit LTP (Kanter and Haberly, 1990; Jung et al., 1990; de Curtis and Llinas, 1993). LTP increases synaptic efficacy by incremental "steps," up to a fixed "ceiling" at which additional bursts of afferent stimulation cause no further potentiation (Larson and Lynch, 1986). LTP is only induced via unusual stimulation patterns causing significantly more activation of a target cell than normal inputs and raising the target cell to an unusually high voltage (the NMDA-receptor voltage threshold) well above that required for simple spiking. LTP is optimally induced by patterned stimulation consisting of brief (30-ms) high-frequency (100 Hz) bursts of activity repeated at the theta rhythm (approximately 5 Hz) (Larson et al., 1986), which is the naturally occurring pattern of activity throughout the cortico-hippocampal pathway in freely moving, actively learning animals (Macrides, 1975; Macrides et al., 1982; Otto et al., 1991). The resulting plastic change possesses the key properties required of a long-term learning mechanism: rapid induction, long duration, and high capacity.

Modeling results

A model of the olfactory bulb (Anton et al., 1991, 1992, 1993) provides inputs once every simulated 200 ms to a model of the olfactory cortex (Granger et al., 1989; Ambros-Ingerson et al., 1990; Kilborn et al., 1996). The simplified cortical model incorporates the following features of LTP:

- Potentiation requires coactivity of afferent and target.
- Potentiation requires exceeding a threshold above that of the spiking threshold.
- Once consolidated, potentiation is not reversible.
- Potentiation can be elicited by a single induction episode.
- Equally sized increments in efficacy occur in response to each induction episode.
- Increment size can be modulated pharmacologically (endogenously or exogenously).
- After a fixed number of increments, further stimulation elicits no further increase in efficacy.
- This LTP ceiling is also subject to modulation.

It also incorporates the following features of the olfactory system:

- Sparse, nontopographic connectivity of afferents to targets
- Short electrotonic length of excitatory cell dendrites
- 100:1 excitatory-to-inhibitory cells (Coultrip et al., 1992)

- Short inhibitory cell axons with dense local arborization
- Relative synchrony of arrival of inputs at theta rhythm

Simple LTP-based learning of bulb-cortex synapses in the model caused an increase in the similarity of cortical responses to any of a set of similar inputs. The cortical response thereby came to correspond to a family or cluster of inputs: A given cortical response signals membership of the input in a given cluster (e.g., "fruit" odors vs. "meat" odors vs. "floral" odors). This result is a common consequence of correlative learning rules in network models containing lateral inhibitory influences (von der Malsburg, 1973; Grossberg, 1975a; Kohonen, 1984; Rumelhart and Zipser, 1985). Input to a sensory cortical network selectively activates some target cells more than others, on the basis of connectivity of the active inputs with the targets. Afferent stimulation patterns are "similar" to the extent that they share axons, and these, when repetitively activated, can potentiate their target synapses. With repeated training, synapses shared among different inputs become more potentiated than unshared synapses. After training on a number of similar instances, this differential potentiation of shared synapses will cause the target cell that responds to one such instance to respond to others as well, since the contribution from the (familiar) shared, potentiated synapses will outweigh the contribution from the (novel) unshared, weaker synapses. With learning, then, target network responses to similar inputs will tend to become increasingly similar to each other. From the point of view of a given target cell participating in these responses, its receptive field is broadening, since it is responding after potentiation to inputs that it would not have responded to before.

It is worth noting that if these responses are the representations of the inputs passed to other brain regions, the inputs will be treated as though they were more similar than they actually are, an effective learned broadening of the generalization gradient around inputs [reminiscent of the well-known psychological effects of input space distortion (Shepard, 1987) and categorical perception (Smith and Medin, 1981; Harnad, 1987)]. However, the sensory and psychological interpretation of neural responses are remote, and it is unknown how generalization of cell population responses may be related to generalization of the organism's overall behavioral response to a stimulus.

LTP increases synaptic efficacy by incremental "steps," up to a "ceiling" at which additional bursts of afferent stimulation cause no further potentiation. Recent findings have identified endogenous and exogenous agents that modulate these two parameters of LTP (Arai and Lynch, 1992), raising the question of the functional implications associated with the sizes of steps and ceiling. Formal treatment of these parameters of LTP induction have led to the characterization of their effect on the receptive field of the target cells whose synapses become potentiated. A target cell's receptive field, i.e., the set of input patterns to which the cell responds, was found to be broadened with potentiation of the cell's synapses, and broadened more when the LTP step size is smaller, and when the LTP ceiling is higher. The effects of step size and ceiling interact, and their relationship to receptive field breadth was found to be nonlinear (Kilborn et al., 1996).

The above phenomena of clustering and perceptual generalization emerge in the model solely from feedforward connections of the cortical system. Incorporation of the extensive feedback system from cortex back to the olfactory bulb caused iterative sequential responses from the bulb–cortex model, from which more complex structure emerged. In particular, finer-grained subclusters evolved within the initial coarse clusters. After having learned a number of simulated floral odors, the initial sampling of a given odor (e.g., a rose) causes feedforward activation of those cortical cells associated with the floral cluster. Learning in the feedback pathway from these cortical cells back to the bulb inhibitory layer causes that feedback inhibition to be selective to those portions of the bulb response correlated with the cortical "floral" cluster response. Subsequent re-sampling of the odor [at the simulated theta (5 Hz) sampling rhythm] gives rise to an input that arrives against the background of this long-lasting (seconds) feedback inhibition, masking out that portion of the bulb response corresponding to the cluster, and passing only the portion of the response specific to the particular floral odor. The resulting new cortical response therefore corresponds to those components of the odor that differ among different members of the cluster. Subsequent samples yield ever finer-grained subclusters, distinguishing individual odors. Thus, the model generates a multilevel hierarchical memory which is traversed sequentially from general to more specific during recognition (Ambros-Ingerson et al., 1990; Kilborn et al., 1996).

Hippocampal Field CA3

Background

Recording and lesion studies suggest a special role for field CA3 during active interleaving of perceptual and motor behavior, as in exploration of a spatial environment or integration of multiple sensory signals separated by time and space.

One such circumstance is that of delayed match (or non-match) to sample, in which the animal must approach or indicate (or avoid) a previously experienced stimulus. Mumby and others have shown that delayed non-match to sample (DNMS) is strongly and irreversibly impaired by hippocampal damage (Wood et al., 1993). Jarrard (1993) has noted that tasks he describes as "spatial" and "contextual" are more dependent on an intact hippocampus than are other memory tasks, suggesting that the requirement of integrating multiple complex cues over time, as occurs in movement through space, calls on some particular processing capabilities of the hippocampus. It is worth noting that evidence exists suggesting that non-spatial tasks in which information must be held over time are not as dependent on hippocampus as on surrounding cortical regions (Otto and Eichenbaum, 1992a; Jarrard, 1993), although differences among methodologies and lesion sites render direct comparison difficult.

Olton and Rawlins over the years have made a cogent argument for hippocampal involvement in the learning of spatial memory tasks such as the radial arm maze (Olton et al., 1979; Rawlins, 1985). Such tasks have inherently disjoint stimuli; visual spatial information is arrayed such that it cannot all be sensed simultaneously, but must be held in mind and integrated over time. A

large body of lesion work indicates a hippocampal requirement for such tasks (Winson, 1978; Mithcell et al., 1982; Numan, 1991; Olton, 1994). The extrinsic modulation of the hippocampus via the rhythmic theta (5 Hz) input from the medial septum is also required for performance of these memory tasks, and disruption of the hippocampal theta rhythm via drug injections to the medial septum is correlated in a dose-dependent fashion with spatial working memory impairments (Givens and Olton, 1990).

Of special interest is the fact that hippocampal lesions disrupt Pavlovian trace conditioning in which there is a delay of 500 ms or more between the stimuli to be associated (Thompson et al., 1982; Solomon et al., 1986; Olton et al., 1987; Moyer et al., 1990), although conditioning in which there is no delay between stimulus elements, and thus no need to create an internal memory trace bridging the interstimulus gap, remains for the most part unaffected by hippocampal damage.

Hippocampal trace activity can be seen with chronic recordings. Hippocampal units have been shown to exhibit protracted elevated firing rates during the delay between the sampling and matching phases of a spatial delayed match and non-match to sample tasks (Hampson et al., 1993a,b) and during the interstimulus interval in trace conditioning (Solomon et al., 1986) and DNMS (Otto and Eichenbaum, 1992b). This prolonged CA3 response to sensory input is present even outside the context of explicit associative learning paradigms. Responses of CA3 units to even brief sensory events such as tone clicks and light flashes can last for several seconds, gradually returning to baseline levels; in contrast, responses to sensory stimuli of entorhinal neurons, dentate granule cells, and CA1 pyramidal cells return rapidly to background levels of activity upon termination of the stimulus (Vinogradova, 1975; Vinogradova and Brazhnik, 1978; Vinogradova, 1995).

It is worth noting that although lesion data selectively differentiating field CA3 from other regions are, even in principle, extremely difficult to obtain, nonetheless the unique anatomical features of field CA3 serve to effectively distinguish it from its neighbors. Thus, despite the lack of powerful behavioral tools for identifying distinct functional contributions of CA3 versus other regions, the unusual biological characteristics of field CA3 suggest its differential behaviors, and bottom-up modeling of these features may thus provide a useful alternative tool.

Circuit design

CA3 pyramidal cells receive sensory input from two afferent tracts, the perforant path and the mossy fibers, and receive diffuse modulatory input from the septum. As in cortex (and field CA1), the excitatory pyramidal cells in CA3 outnumber inhibitory cells by roughly 100:1 (Misgeld and Frotscher, 1986; Woodson et al., 1989). Inhibitory cells exhibit lower firing thresholds, and a much higher percentage of inhibitory cells than pyramidal cells fire during oscillatory (e.g., theta) activity (Schwartzkroin and Haglund, 1986; Traub and Miles, 1991; Buzsaki et al., 1992). Excitatory cells are extensively interconnected (Swanson et al., 1978) by a system of excitatory axon collaterals. Although estimates of the probability of connections between any two CA3 pyramidal cells throughout the entire field are relatively low (around 5%, roughly as in other fields) (MacVicar and Dudek, 1980; Knowles and Schwartzkroin, 1981; Miles and Wong, 1986; Amaral et al., 1990), local excitatory connectivity among closely neighboring cells may be substantially higher, perhaps more than 30% (Blackstad, 1956; Raisman et al., 1965; Swanson et al., 1978). Moreover, intracellular labeling studies have revealed CA3 pyramidal cell projection zones to be anisotropic: organized into 200- to 800-μm bands (Li et al., 1994) in which innervation is disproportionately more dense. The extensive recurrent axonal projections of CA3 neurons contain spatially restricted areas of high axonal density, reminiscent of the "patches" of the associational collaterals of neocortical neurons and the columns of CA1 axon terminals in the subiculum (Gilbert and Wiesel, 1983, 1989; Kisvarday and Eysel, 1992; Tamamaki and Nojyo, 1990), in which the presynaptic neuron may establish synaptic contacts with most, if not all, neurons (Li et al., 1994; Tamamaki and Nojyo, 1991). Indeed, stimulation elicits local rises in excitation but far less effect at distances greater than 1 mm from the point of stimulation (Traub and Miles, 1991). This concentrated distribution of CA3 recurrent axon collaterals suggests that subpopulations or patches of neurons may share certain firing characteristics and be thought of as functional units.

Simultaneous intracellular recordings from pairs of CA3 neurons indicate that the time for conduction of an action potential along the axon collateral, either between pyramidal cell pairs or pyramidal cell–interneuron pairs, is on the order of 1–2 ms (Miles and Wong, 1984, 1986).

Modeling results

The model presented by Wiebe et al. (unpublished observation), incorporates features of CA3 shown in Figure 1. Coupled delayed nonlinear differential equations of the following form were used to describe the dynamics of mean pyramidal cell and interneuron activity in the i^{th} neuron population or "patch" denoted by $\xi_i(t)$ and $\zeta_i(t)$, respectively, in response to afferent sensory information $I_i(t)$.

$$\dot{\xi}_i(t) = -\omega_d \xi_i(t) + h_e(t) * \left(\omega_{ee} \xi_i(t - \tau_d) + \sum_{j=1, j \neq i}^{N} \omega_{EE}^{ij} \xi_j(t - \tau_D) + I_i(t) \right) + \omega_{ei} \xi_i(t) h_i(t) * \zeta_i(t - \tau_d) \quad (1)$$

$$\dot{\zeta}_i(t) = -\omega_d \zeta_i(t) + \omega_{ie} h_e(t) * \xi_i(t - \tau_d) - \zeta_i(t) \theta(t) \quad (2)$$

where

$$h_{e/i}(t) * u(t) = \int_0^t h_{e/i}(\tau) u(t - \tau)\, d\tau \quad (3)$$

These equations incorporate some features used by Grossberg and Schmajuk and colleagues (Grossberg, 1975b; Grossberg and Schmajuk, 1989; Schmajuk and DiCarlo, 1992; Schmajuk and Blair, 1993; Schmajuk et al., 1993), but add a number of features not included in those models: i) recurrent excitation, ii) time delays for local and for long-range axonal transmission, iii)

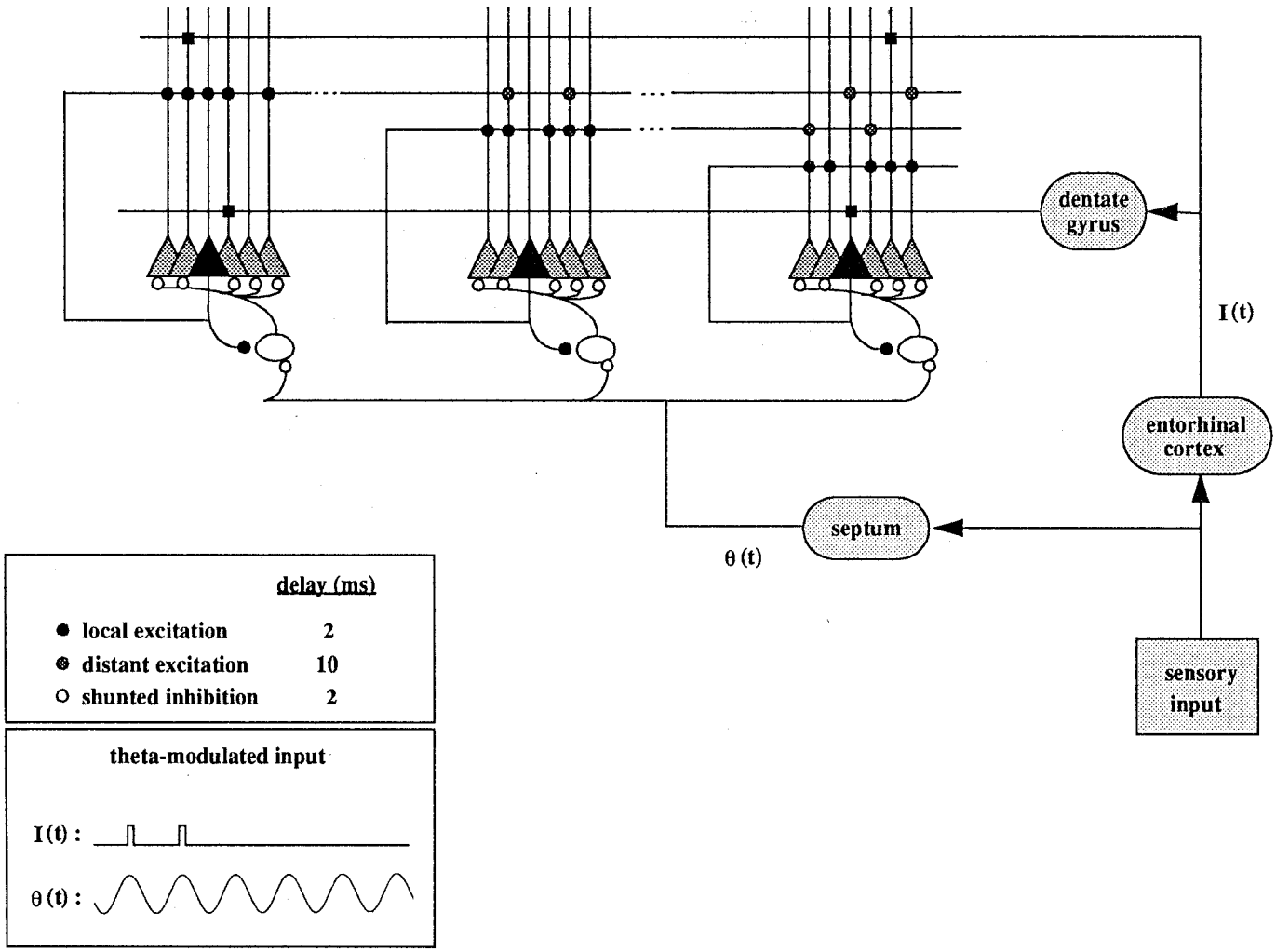

FIGURE 1. Schematic representation of CA3 model. Sensory input to the CA3 field arrives via two afferent streams, the perforant path and the mossy fibers, along with a diffuse ascending modulatory signal from the septum. The cortical signal arrives at the hippocampus phase-locked to the ongoing septal theta oscillations. Cortical input I(t) is modeled as a theta-burst signal arriving over a few periods to two pyramidal cell patches; septal input ~(t) is modeled as periodic GABAergic inhibition of interneurons. All neuronal dynamics are taken as continuous, real-time processes, including the incorporation of time delays for cell–cell interactions. Local, within-patch and distant, interpatch signal transmission delays of $\tau_d = 2$ ms and $\tau_D = 10$ ms are incorporated, respectively. Impulse response functions (kernels) for excitation, $h_e(t) = te^{t/2ms}$, and inhibition, $h_i(t) = te^{t/18ms}$, are modeled after fast glutamatergic current and composite $GABA_A$- and $GABA_B$-mediated current time courses. A random 20% interpatch connectivity is assumed; i.e., Probability $(\omega_{EE}^{ij} \neq 0) = 0.2$ in equation 1. The set of continuous delay ordinary differential equations was integrated using a combined Adams/Gear predictor-corrector method.

differential time courses for excitation and inhibition, and iv) time courses and dynamics of entorhinal and septal inputs (Wiebe et al., 1996).

The resulting dynamical network activity revealed that simulated information-bearing input from the entorhinal cortex over a few consecutive theta cycles is capable of entraining the CA3 model system such that an oscillatory limit cycle is induced which, by synchronizing to the rhythmic disinhibitory septal input, can persist for several seconds beyond termination of the brief (milliseconds) afferent signal. Figure 2 shows a sample pyramidal cell ensemble response to two different input patterns. Only two patches of principal cells receive direct excitatory input, but it can be seen that all patches exhibit sustained theta responses due to the strong recurrent excitation in the network. The magnitude and relative timing of activation in each patch, however, is dependent on the specific spatial configuration of the input signal. Hence, the cross-correlegram of activity of any two patches is significantly different for different input patterns, indicating the specificity of the sustained signal to the particular input. The dynamical activity is sustained and prolonged for many seconds following the brief input due to the interplay of two factors: i) the differential time courses and strengths of recurrent excitation and inhibition, and ii) the rhythmic septal disinhibition (inhibition of interneurons). The persistent traces decay rapidly once the phase locking of the

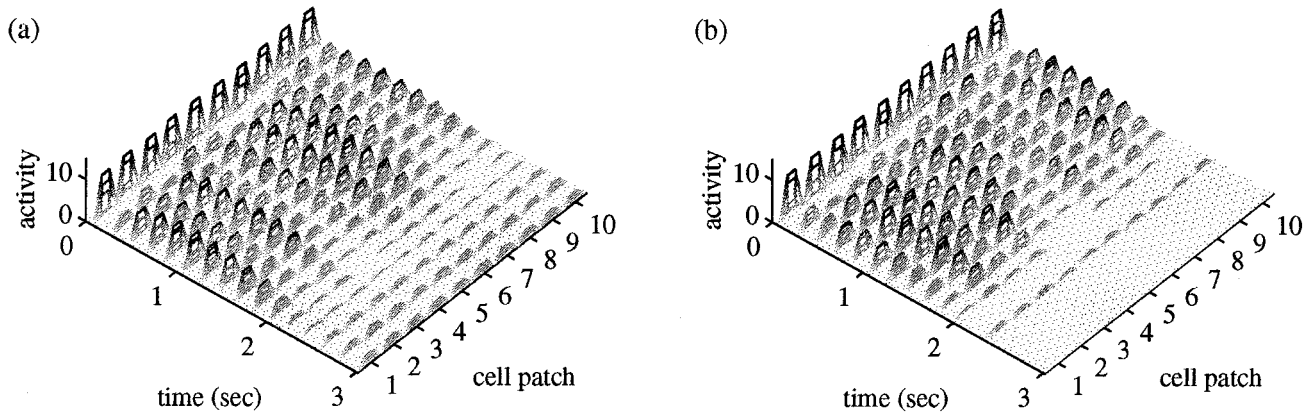

FIGURE 2. Sustained input-specific trace activity supported by rhythmic septal input. Pyramidal cell patch ensemble response to brief entorhinal input over first two theta cycles to patches (a) 4 and 9 and (b) 7 and 8. All patches exhibit sustained theta-burst activity due to the strong recurrent excitation in the network. The relative strength of the burst signal from each patch, however, is dependent on the particular spatial configuration of the input signal. Trace activation persists for a few seconds, as long as the ensemble theta activity remains in phase with the rhythmic septal input. Decoupling of the two processes terminates the reverberatory memory of the cortical signal.

patch activity and the rhythmic disinhibition becomes broken; this decoupling is dependent on a number of factors in the model, including the strength of the original entorhinal input signal and the frequencies and phase relationships of the septal and cortical inputs (Wiebe et al., 1996).

Field CA1

Background

Field CA1, with its large true pyramidal cells and relatively little lateral excitatory collateral connectity, most resembles cortical circuitry. In contrast to the exotic granule cells of dentate gyrus and the dense excitatory collaterals of CA3, field CA1 exhibits what is in many ways a classical telencephalic cell layer and as such has been much studied for its anatomy and physiology. Long-lasting plasticity has been extensively studied in field CA1, and it is in this field that the only extant demonstration of long-lasting (weeks) non-decremental potentiation in vivo has been demonstrated (Staubli and Lynch, 1987). In addition, much study has been given to physiological response properties of field CA1 cells in behaving animals during various learning paradigms, from place cells and direction cells (McNaughton et al., 1983; Breese et al., 1989; Thompson and Best, 1989; Muller and Kubie, 1989) to Ranck's pioneering studies of single-unit responses and their interpretations in terms of expectation (Ranck, 1973).

The physiology of LTP has been particularly well studied in field CA1, and it is worth noting that a range of constraints or "rules" have been identified characterizing the conditions required for the induction and expression of LTP. For instance, the time course and refractory period of GABAergic synapses dictates the optimal input signaling pattern for LTP to be brief high-frequency bursts separated by 200 ms, i.e., "theta-burst" stimulation (Larson et al., 1986; Mott and Lewis, 1991). Moreover, in slice experiments synaptic weights appear to increment at a relatively fixed rate and up to a fixed ceiling before saturating.

The dynamical activity of field CA3, the primary afferent to CA1, suggests that inputs to CA1 may be somewhat asynchronous, as opposed to the typical synchronized bursts given in most slice experiments. Experiments investigating the effects of this asynchrony revealed a temporal dependency of LTP induction in field CA1. When successive afferents arrived within the time period of a single theta wave (i.e., separated by less than ~70 ms), the earlier afferent caused significantly more potentiation than expected, whereas the later one caused significantly less than expected (Larson and Lynch, 1989). This finding, and its implications for processing by CA1 of asynchronous inputs arriving from field CA3, were central to the modeling effort described here.

Circuit design

This region shares with superficial olfactory cortex the anatomical features of sparse, random connectivity between inputs (Shaffer collaterals) and target pyramidal cells, very sparse excitatory collateralization within the field, and excitatory-to-inhibitory cell ratio. However, there are no local densely collateralizing excitatory axons as in field CA3, and nothing resembling the mossy fiber system. Much of the phenomenology of LTP induction and expression has been shown to be similar in CA1 and in superficial olfactory cortex, but two notable points distinguishing these regions exist in the literature:

1. The cholinergic modulation of activity and of potentiation exhibit differences of operation and of laminar specificity across cortex, field CA3, and field CA1; the details of this cholinergic modulation and its computational implications have been extensively investigated and modeled by Hasselmo and colleagues (Hasselmo et al., 1995; Hasselmo and Barkai, 1995; Hasselmo, 1995).

2. The induction of LTP in field CA1 has been found to have temporally specific properties resulting in dependencies on the sequential order of arrival of afferent potentiating stimulation (Larson and Lynch, 1989). Modeling of these temporal dependencies of LTP has been reported by Granger et al. (1994).

In the experiments reported by Larson and Lynch (1989), a rapid staggered sequence of afferent stimulation gave rise to a pattern of potentiation in the target cell synapses that was not predicted by simple associative or Hebbian rules. Of a sequence of three afferent bursts via different electrodes, the first-arriving burst induced larger potentiation than it would have had all three bursts arrived simultaneously, implying a retrograde enhancement of the potentiation via the subsequent arriving stimulation; the second-arriving input induced roughly the same potentiation as it would have had all three arrived simultaneously, implying an anterograde suppression of potentiation by the prior inputs. In sum, the size of the potentiation corresponded to the order in which inputs arrived. A "Hebbian" co-activity rule would predict that as asynchronous afferents arrive, increased depolarization of the target neuron over the staggered arrival times would cause later inputs to be strengthened more than earlier inputs. Although Hebb's (1949) postulate ("... [when cell A] repeatedly or persistently takes part in firing [cell B], ... A's efficiency, as one of the cells firing B, is increased") has been a useful guide to simple correlative synaptic learning rules in the artificial neural network literature, it has been shown to be neither strictly necessary nor sufficient for induction of LTP: The target cell (cell B) need not be fired, only depolarized, for LTP to occur (McNaughton et al., 1978; Kelso et al., 1986) (necessity) and yet even repeated firing will not induce LTP unless the depolarization exceeds the NMDA receptor channel voltage threshold (Collingridge et al., 1983) (sufficiency). These and other discrepancies between the true physiological constraints on LTP versus the Hebb correlation rule might be viewed as simply extraneous biological detail, irrelevant to the computational properties of networks employing an LTP learning rule, or these subtle properties may yield a learning rule that confers novel and useful functional abilities to circuits that use them.

Modeling results

Granger et al. (1994) reported on a simple network model of field CA1 incorporating the temporal induction and expression constraints described in above in which the amount of potentiation depends on the temporal order of arrival of afferent activity to a target, a rule that strictly obeys neither Hebb's postulate nor generalized Hebb-like correlational rules. (It is interesting to note that a correlational or Hebbian rule emerges as the special case occurring only when all afferents arrive simultaneously.)

Perhaps not surprisingly, incorporation of this temporally dependent LTP learning rule into the CA1 model enabled the network to learn to store brief simulated temporal sequences of inputs. Less intuitively, the network did not exhibit the familiar generalization characteristics so typical to neural networks, but rather orthogonalized its learned inputs, increasing slight differences between them, resulting in an "accept/reject" function, i.e., responding selectively to ("accepting") those input sequences on which it had been trained, and rejecting all others (Granger et al., 1994).

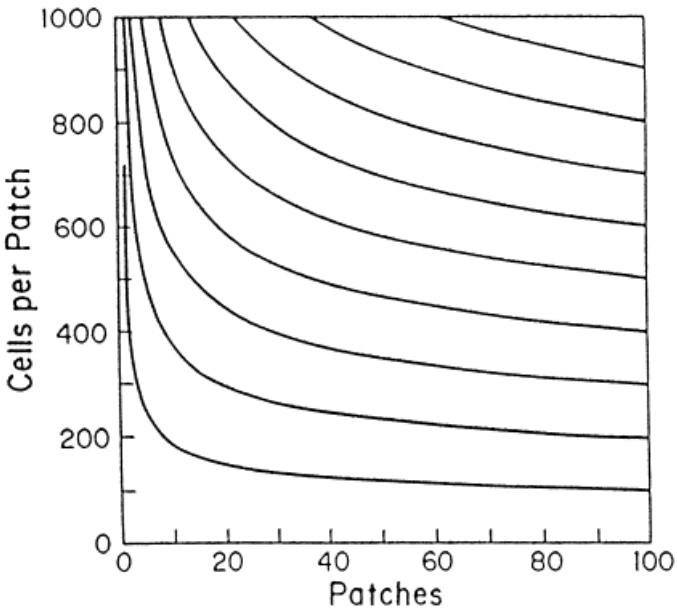

FIGURE 3. Capacity of CA1 model incorporating temporal LTP induction rule. Each contour line denotes an additional 5 million random sequences of length 10, learned in a network composed of a given number of patches each comprising a given number of cells per patch.

Equally surprising was the storage capacity of the network: It was found that the number of sequences that could be stored in a given network was a linear function of the size of the network, unlike many other networks wherein the amount of stored information is typically a fractional exponent (root) of the network size, severely limiting capacity in large networks. Figure 3 illustrates the scaling properties of the network, i.e., how the capacity changes as a function of the size of the network:

$$n = \frac{C \log (1 - E_M^{1/SM})}{\log (1 - (1/A))} \quad (4)$$

The figure is a contour graph of the relationship among the number of patches in the network, the number of cells per each patch, and the number of sequences of a given length that can be stored without exceeding a fixed recognition error arbitrarily set at p(commission) = 0.001. Each contour line denotes 5 million random sequences of length 10. If cells are assumed to receive 10,000 synaptic contacts on their dendrites, then a 100,000 cell network (100 patches of 1,000 cells each) stores approximately 5×10^7 (50 million) random sequences of length 10. It is worth noting that this would correspond to one sequence learned every minute for 100 years with a 0.001 recognition error rate. (Granger et al., 1994). It is worth noting that although these temporal dependencies were identified in field CA1, corresponding tests in other regions have not been performed, and it is not known whether the effect may occur in CA3 or cortex as well as in field CA1.

DISCUSSION

Quantitative Modeling Yields Findings Beyond Qualitative Reasoning

The models of superficial cortex, of field CA3, and of field CA1 have on the one hand confirmed functional traits that were suspected from the anatomical layout of the circuit in question, but on the other hand have also given rise in each case to surprises: properties not previously suspected and not readily deducable (except perhaps in retrospect) in the absence of detailed modeling efforts.

Superficial layers of olfactory and of entorhinal cortex not only perform a form of self-organization, which might be expected, but also have been shown capable of hierarchical organization via iterative activation over cycles of the theta rhythm (Ambros-Ingerson et al., 1990).

Hippocampal field CA3 not only exhibits dynamical activity but also acts to extend very brief afferent activation over seconds of time in an input-specific fashion, thereby providing a potential "bridge" memory between the very different time courses of perceptual and motor behaviors (Wiebe et al., 1996).

The order-specific potentiation identified in hippocampal field CA1 (Larson and Lynch, 1989) gave rise, not surprisingly, to a capability for temporal sequence detection in a simplified model of this LTP learning rule in CA1; however, in addition, formalization and analysis led to the finding that such a sequence memory performed not the usual generalization but rather an accept/reject, or match/mismatch function, and that it had unusually large capacity, due to its parsimonious use of synapses in the network. The resulting network was able to store tens of thousands of brief sequences in a relatively small network, and exhibited linear growth of the capacity with network size, thereby addressing the issue of memory capacity in networks of realistic sizes, and over realistic lifetimes (Granger et al., 1994).

In retrospect, the utility of such devices may be appreciated. The three primary findings reported here,

1. Use of iterative synchronous activity in sensory cortex to elicit different types of information over time, traversing a hierarchy of memory;
2. Dynamical recurrent firing in field CA3 actively sustaining a transient perceptual memory to bridge the gap between brief (tens of milliseconds) neural time and long (seconds) behavioral time;
3. Sequential sensitivity of LTP in field CA1 to enable not a typical generalizing recognition network but rather a relatively non-generalizing "accept-reject" network,

are to varying extents unanticipated by the neurobehavioral literature and yet in concord with that literature in terms of potential explanations of substrate-level mechanisms underlying observed functional characteristics of the different cortico-hippocampal structures. That is, these surprising findings from bottom-up modeling efforts arrive at novel methods that nonetheless can be seen as candidates for subserving the functions of the different brain areas under discussion.

Imagine a rat exploring a complex visual maze environment. From his vantage point, to the northwest there may be a shelf on the wall; to the east there may be a window. Every new view of the shelf is slightly different; a device that groups similar inputs into clusters acts as a form of learned generalization that aids in recognition. Such a device presumably is relatively peripherally sited, taking the noisy inputs from the external environment and passing as output far less noisy cluster names in their stead.

The rat may rear and move his head, an operation requiring perhaps as much as a second, to swing from the view of the shelf to that of the window. Once he moves his eyes away from the shelf, toward the window, the visual image of the shelf is gone, and any neural activity accompanying that visual image presumably ceases within a few tens of milliseconds. By the time the visual image of the window arrives, presumably hundreds of milliseconds have passed. A device that produces a signal specific to one sensory cue, and sustains that signal during behavior, thus allowing it to be combined with a subsequent cue, enables the internal integration of features in a scene that are not colocalized. A device of this kind would ideally be sited so as to receive inputs from multiple sensory modalities, and would be logically subsequent to the clustering operation just described. Such a device embodies an unusual form of memory, with traits distinct from those of more typical memory systems; desired duration of a sensory memory in this system is extremely short—just long enough to bridge the temporal gap between a given input and its successor—as opposed to a system in which memories were permanently stored.

A device holding a sustained image of one cue until another arrives might ideally be followed by a device that permanently stores sequences of signals—the information that cue B follows cue A after behavior X could readily be logged in such a device, which would constitute a repository for "expectations" (and thus, also, a recognizer of surprises). It might be expected that a system so sited would have long-lasting rather than transient memories.

Finally, it can readily be imagined how this more-or-less sequential processing of information (clustering → dynamical bridge memory → match/mismatch) during exploration might be crucial for the establishment of long-term memories; lacking this kind of integrative action during learning, new information might never be successfully acquired, whereas it is possible that already-learned information might give rise to recognition responses even without this processing.

It is worth noting that the mapping between the operations performed by a single network, and the overt behavior of a larger circuit or system (or whole organism) within which that network is embedded, may be obscure. As an instance, it should be clear that the lack of generalization performed by the model of field CA1 presented above does not imply that generalization is not performed by organisms, or by different brain networks. Rather, it raises the question of functional interpretation of single modular components (e.g., CA1) embedded in much larger systems (e.g., the corticohippocampal pathway). The primary inputs to field CA1 come from field CA3, and only indirectly from sensory fields (via entorhinal cortex), and the primary outputs from CA1 project

to subiculum and parahippocampal (entorhinal) cortex, and only indirectly to motor fields. The relationship of CA1's function to the overall organism's function is thus far from straightforward. We have hypothesized that a high-capacity, sequence-dependent, non-generalizing "accept-reject" or "match-mismatch" function such as that achieved by the CA1 model may, in combination with the functions of the other constituent circuits of the corticohippocampal pathway, be of considerable utility in internal memory functions such as recognition of recency, expectation, and changing views with movement during exploration (Lynch and Granger, 1992).

Experimental Predictions and Related Work

A wealth of potential experimental predictions emerge from the model results presented here. The cortical model, after learning a set of sufficiently similar stimuli (odors), generates temporally spaced responses corresponding to categorical or cluster responses, followed by sub-cluster, sub-sub-cluster, etc. The network acquires these memory structures with relatively little training, and may be expected to enable animals to learn generalizations whereby similar, albeit recognizably distinguishable, odors, would be treated by an animal as members of a category.

Although results exist in recognition of categories in animals (Stone, 1971; Ehret, 1988; Kuhl, 1988), there have been few studies of acquisition of categories, apart from the work of Herrnstein and his colleagues (Herrnstein, 1979; Cerella, 1979) on pigeons. In learned generalization of the type performed by the computer simulations reported on here, animals would respond similarly to members of an input category only after a number of similar cues are learned; this behavior is distinguishable from stimulus generalization, which would predict that choice behavior should, without learning, arise from physical similarity of stimuli alone, rather than from the existence of a sufficient number of similar stimuli. Initial experiments testing this distinction gave positive results, providing the first evidence that rats may build unsupervised similarity-based perceptual categories, and can do so with widely spaced learning sessions (Granger et al., 1991).

Surprisingly few experimental studies have focused on the responses of single primary sensory cortical units during acquisition of novel olfactory stimuli in behaving, freely moving animals. Some studies addressed physiological predictions from computational models, particularly testing whether cell spiking responses to odors would be sparse, as predicted from the computational models (Ambros-Ingerson et al., 1990; Kilborn et al., 1996), or whether extensive excitatory activity would be encountered, as in alternative hypotheses (see, e.g., Freeman, 1991, for a review). Behavioral studies have shown that mammals in olfactory learning tasks are capable of very rapid locomotor responses (within .5 s) to olfactory cues even though typical odor delivery systems take up to 100 ms from odor onset to time of reception at the epithelium (Eichenbaum et al., 1987; Staubli et al., 1987). Thus, experiments were performed to study processing occurring within this relatively narrow time window during which odors are detected, recognized, and appropriate responses organized. The results indicated that most cells in piriform cortex do not respond to most odors; i.e., coding is extremely sparse. Moreover, a small number of cells do exhibit odor specificity of response (McCollum et al., 1991). A further prediction from computational modeling is that different cortical cells should discharge over successive sampling cycles with progressively more selective tuning; further experiments will be required to test this specific prediction, although it is clear from the sparseness of cortical coding that a large amount of sampling will be required to identify such successive odor-specific responses.

At a behavioral level, extensive predictions of differential lesions of hippocampus proper versus its surrounding cortical regions have been generated by Gluck and Myers (1993), and the capability of this relatively top-down hippocampal-region model to be integrated with a bottom-up cortical model was explored by Myers et al. (1995), identifying a range of predictions consistent with operation of the models and known differential lesions.

As modeling progresses into regions more remote from the sensory periphery, predictions remain amenable to testing via chronic recording, but less by behavioral response. A number of models make predictions about performance, such as Levy and colleagues' proposals that field CA3 produces sequential behavior (see Minai and Levy, 1993; and this volume), and Hasselmo et al.'s (1995, and this volume) proposal that CA3 gives rise to autoassociation. Hasselmo's model of field CA3 bears resemblance to Hopfield-like models, in which all neurons are completely (100%) or nearly completely connected to all others, and, as expected of a Hopfield-like model, their CA3 network thus performs autoassociation, in contrast to the CA3 model presented here.

A great deal of relatively complex behavior emerges from Levy's model (this volume) of field CA3, also in contrast to the simpler emergent dynamical behavior of the model presented here. A number of researchers have proposed that field CA3 serves to store associations among different components of a dentate input (Marr, 1971; McNaughton and Morris, 1987; Levy et al., 1989; Treves and Rolls, 1994), again in contrast to our proposed model. Possibly these discrepancies can be investigated by physiological means, to the extent that each model makes predictions about in vivo unit responses.

A prediction from the CA3 model summarized here and described in more detail by Wiebe et al. (1996) is that specific units should repetitively fire, in phase with the modulating theta rhythm, selectively during gaps between sensory cues and movement; some data of this kind exist, although evidence for cell firing that is specific to a given input is still largely lacking.

Hasselmo et al.'s model of field CA1 is based on a proposal that learning in CA1 acts to compare output of CA3 and afferent input from entorhinal cortex, an idea often proposed in the literature (Levy, 1989; Eichenbaum and Buckingham, 1990; Lynch and Granger, 1991). The model of field CA1 presented here is compatible with this idea, and focuses on the specifics of temporally dependent LTP induction and its effect on learning of the dynamical patterns that might be expected to be received by CA1 from CA3. The CA1 model predicts that units will respond differentially to sequences with expected (familiar) outcomes than to those with unexpected outcomes; Ranck (1973) has reported such "match/mismatch" behavior, but as in field CA3, follow-on studies pertaining to the specificity of unit responses to particular sequences would be of significant interest.

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