Theta/Gamma Networks with Slow NMDA Channels Learn Sequences and Encode Episodic Memory: Role of NMDA Channels in Recall

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Abstract

This paper examines the role of slow *N*-methyl-D-aspartate (NMDA) channels (deactivation ~150 msec) in networks that multiplex different memories in different gamma subcycles of a low frequency theta oscillation. The NMDA channels are in the synapses of recurrent collaterals and govern synaptic modification in accord with known physiological properties. Because slow NMDA channels have a time constant that spans several gamma cycles, synaptic connections will form between cells that represent different memories. This enables brain structures that have slow NMDA channels to store heteroassociative sequence information in long-term memory. Recall of this stored sequence information can be initiated by presentation of initial elements of the sequence. The remaining sequence is then recalled at a rate of one memory every gamma cycle. A new role for the NMDA channel suggested by our finding is that recall at gamma frequency works well if slow NMDA channels provide the dominant component of the EPSP at the synapse of recurrent collaterals: The slow onset of these channels and their long duration allows the firing of one memory during one gamma cycle to trigger the next memory during the subsequent gamma cycle. An interesting feature of the readout mechanism is that the activation of a given memory is due to cumulative input from multiple previous memories in the stored sequence, not just the previous one. The network thus stores sequence information in a doubly redundant way: Activation of a memory depends on the strength of synaptic inputs from multiple cells of multiple previous memories. The cumulative property of sequence storage has support from the psychophysical literature. Cumulative learning also provides a solution to the disambiguation problem that occurs when different sequences have a region of overlap. In a final set of simulations, we show how coupling an autoassociative network to a heteroassociative network allows the storage of episodic memories (a unique sequence of briefly occuring known items). The autoassociative network (cortex) captures the sequence in short-term memory and provides the accurate, time-compressed repetition required to drive synaptic modification in the heteroassociative network (hippocampus). This is the first mechanistically detailed model showing how known brain properties, including network oscillations, recurrent collaterals, AMPA channels, NMDA channel subtypes, the ADP, and the AHP can act together to accomplish memory storage and recall.

Introduction

In the previous papers in this series, we examined memory formation governed by fast *N*-methyl-D-aspartate (NMDA) channels. These channels have a deactivation time constant that is about equal to the period of a gamma cycle (12–20 msec). If the cells that fire within a given gamma cycle represent a specific memory, fast NMDA

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channels will form connections between these cells. These connections encode autoassociative long-term memory (LTM) about that item (Jensen et al., this issue). Once formed, this LTM serves to enhance the accuracy with which novel lists of these known items can be kept active in short-term memory (STM) (Jensen and Lisman 1996b, this issue). Such networks would provide accurate repetitive inputs to networks that could encode the sequence into LTM. We show here that networks with slow NMDA channels (Jahr and Stevens 1990; S. Vicini, J.F. Wang, J.S. Poling, and D.R. Grayson, pers. comm.) utilize such inputs to perform heteroassociative sequence learning (Kleinfeld 1986; Sompolinsky and Kanter 1986; Buhmann and Schulten 1987; Manai and Levy 1993). The simulations suggest a biophysically specific and plausible model for how LTM for a novel list of known items (e.g., a phone number) could be learned after a single presentation. A surprising outcome of these simulations is that slow NMDA channels appear well suited to play an important role in the readout of memory sequences at gamma frequency, in addition to their well-known role in the induction of synaptic modification. The reader is referred to the next paper in this series (Jensen and Lisman 1996a, this issue) for the application of these ideas about sequence learning and gamma-frequency readout to data on hippocampal place cells.

Results

The critical argument for the involvement of networks with slow NMDA channels in heteroassociative sequence learning follows from the timing of gamma oscillations and from what is known about NMDA channels and LTP induction. When the presynaptic cell releases the transmitter glutamate, it becomes bound to the NMDA channel within less than a millisecond. Then, with the time constant of activation, the channel makes a transition to a state in which the channel can open, provided postsynaptic depolarization relieves the Mg^{2+} block of the channel. The channel stays in this state until it deactivates, a process governed by the unbinding of glutamate (for review, see Jones and Westbrook 1996). The time constants of deactivation vary among subtypes of the NMDA channel. For the type found in the hippocampus, the time constant is ~150 msec and is therefore the slow type of NMDA channel (Jahr and Stevens 1990; Debanne et al. 1995; S. Vicini, J.F. Wang, J.S. Poling, and D.R. Grayson, pers. comm.). If postsynaptic depolarization occurs before deactivation, Ca^{2+} will enter the dendritic cytoplasm and LTP will be induced (for review, see Bliss and Collingridge 1993). Thus synapses are strengthened even if postsynaptic depolarization occurs with a delay after the presynaptic action potential.

Figure 1 shows what happens when these principles are applied to a network (see Jensen et al., this issue, Fig. 1) in which different memories are stored in different gamma subcycles of a theta oscillation (cells that encode memory 1 fire in subcycle 1; cells that encode memory 2 fire in subcycle 2, etc.) The firing of a representative cell from each group is shown in Figure 1A. The systematic offset in firing time of the different cells corresponds to a period of a gamma cycle. Because the time constant of deactivation of slow NMDA channels is considerably greater than the duration of a gamma cycle, the synapses connecting cell 1 to cell 2 will be strengthened (by Δw_{12}), as shown in Figure 1C.) Importantly, the synapses between

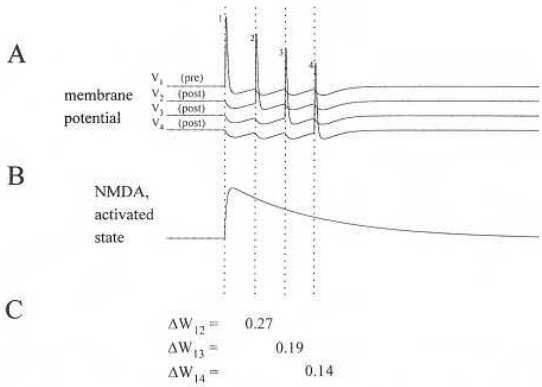

Figure 1: Slow NMDA channels will strengthen connections between memories that fire in different gamma cycles. (*A*) Four cells representing four different memories are shown; each fires in a different gamma subcycle. IPSPs separate each cycle. (*B*) Time course of the active state of NMDA channels on the cells activated by glutamate released from cell 1. During learning the active channels do not open unless the Mg^{2+} block is relieved by a postsynaptic depolarization. (*C*) Cells 2–4 fire in consecutive gamma subcycles as shown in the voltage traces. The change in synaptic strength (Δw_{ij}) at specific synaptic connections between cells *i,j* is shown. The change depends on the magnitude of the NMDA conductances at the time that postsynaptic firing occurs. The larger the number of gamma cycles between the first gamma cycle and post synaptic firing, the smaller the change in synaptic strength.

the cells of memory 1 and memory 3–4 will be strengthened (by Δw_{13}, Δw_{14}), but to a lesser extent because of the gradual deactivation of NMDA channels.

Figure 2A shows how connections became strengthened over time when seven memories were simultaneously firing in the buffer (Fig. 2B). We have used a physiologically plausible learning in which repetition of correlated presynaptic/postsynaptic firing is required to fully modify a synapse. The synaptic weight matrix in Figure 2B shows the strength of the connection (by the size of the square) between a cell i (y-axis) and a target cell j (x-axis) at the end of a 1.6-sec encoding period. It can be seen that the connections are highly asymmetric: A cell encoding a given memory is strongly connected to the cell encoding the next memory, but not to the previous memory. Moreover, it can be seen that the strength of the connections with subsequent memories is graded, falling off as their time separation increases. This may seem obvious to the reader, given the learning rule we have used (Fig. 1), but there is a subtlety worth pointing out. When the seventh memory fires, it will be followed eventually by the firing of the first memory on the next theta cycle. This will lead to strengthening of this connection and violates the rule that cells get connected only to cells that represent subsequent memories. However, the matrix (inset, Fig. 2B) shows that this backward connection is weak compared with the forward connections. This is because of the long delay between the firing of cell 7 and cell 1 resulting from the negative phase of the theta cycle. During this period, NMDA channels deactivate substantially. This is an important point because it illustrates that for asymmetric connections to form, substantial deactivation of NMDA channels must occur within the duration of a theta cycle. The NMDA channels in the hippocampus nicely fulfill this requirement.

The connections that form are appropriate for encoding memory sequences. As can be seen in the matrix (Fig. 2A), the strongest connections are between a cell that encodes a memory and the cell encoding the next memory in the sequence. It would seem likely that this stored information could somehow be used to recall memory sequences. Given the importance of gamma oscillations in brain function and hippocampal function in particular, we wondered whether there was a way in which sequence information might be recalled at a rate of one memory per gamma cycle,

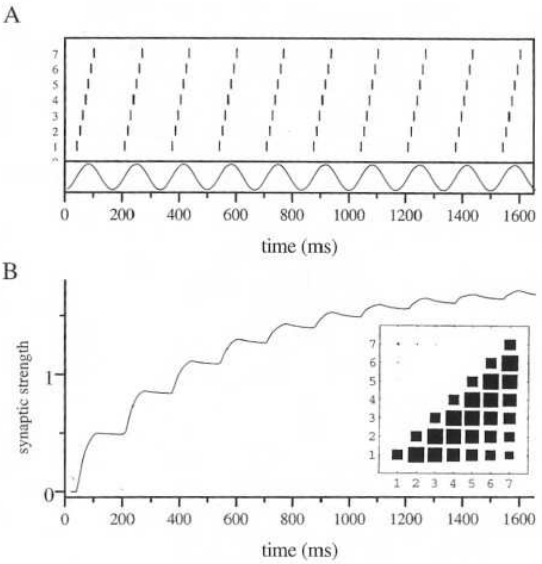

Figure 2: Repeated firing of seven memory patterns leads to incorporation into LTM and the development of a complex, asymmetric synaptic weight matrix. For simplicity each memory is represented by one cell. (*A*) The firing of the seven memories shown in relationship to the ongoing theta oscillation at bottom. (*B*) Repetitive firing causes the sum of all synaptic weights to rise to an asymptote during learning. The asymptote at each synapses is determined by the strength of correlation. Inset shows synaptic weight matrix (strength of cell i, y-axis, synapse onto cell j, x-axis) at the end of a 1.6-sec encoding period. See Methods in Jensen et al. (this issue) for the equations defining the network. We have applied the following parameters: $V_{rest} = -60$ mV, $V_{thres} = -50$ mV, $A_A = -210$ pA, $\tau_A = 70.0$ msec, $A_{GABA} = -150.0$ pA, $\tau_{GABA} = 4.0$ msec, $\tau_{NMDA,r} = 5.0$ msec, $\tau_{NMDA,f} = 50.0$ msec, $\tau_{post} = 2.0$ msec, $\tau_{delay} = 0.5$ msec, $\tau_{npp} = 20.0$ msec, $\tau_{pnp} = 400.0$ msec, $\tau_{pp} = 10.0$ msec, $f_{theta} = 6$ Hz, and $B_{theta} = 150.0$ pA. The synaptic values were initialized to 0. The final synaptic values ranged from 0.06 to 0.48. There are a few but significant differences compared with the two previous papers (Jensen and Lisman 1996b, this issue; Jensen et al., this issue): There is no ADP in the heteroassociative memory network. Slow NMDA channels are the basis for sequence learning and recall. We have applied a long AHP current to prevent a memory from firing multiple times within a theta cycle. LTD occurs mainly when postsynaptic activity is present without presynaptic activity, and to a smaller degree when presynaptic activity is present without postsynaptic activity.

the time-compressed frequency at which it was encoded. Consideration of how this could occur using alpha-amino-3-hydroxy-5-methyl-4-isoxa-

zole proprionic acid (AMPA)-mediated transmission suggested that this is not possible. Consider the following example. If cells encoding memory 2 fire, the synaptic delay of AMPA-mediated transmission is so short (several milliseconds; Miles and Wong 1986; Debanne et al. 1995) that the postsynaptic cells encoding memory 3 will be excited in the *same* gamma cycle. Moreover, by the time the next gamma cycle occurs, the AMPA conductance excited by the firing of memory 2 will have completely decayed due to the fast deactivation of AMPA channels. Why then would memory 3 become active? We conclude that AMPA-mediated transmission is unsuitable for producing memory readout at gamma frequency.

If synaptic transmission during recall was dominated by slow NMDA channels rather than AMPA channels, both of the problems described above would be solved. Specifically, NMDA channels that deactivate slowly also have slow activation kinetics (S. Vicini, pers. comm.) that could provide enough delay so that target neurons would not fire in the same gamma cycle as the neurons that provided the excitatory input. Furthermore, the slow deactivation of these NMDA channels would ensure that excitiation was still present during the subsequent gamma cycles and so could stimulate the firing of appropriate target neurons.

While it is often assumed that the synaptic transmission onto pyramidal cells in CA1 and CA3 is mediated totally by AMPA channels and that NMDA channels are involved solely in the control of learning events, this is not correct: There is a NMDA-mediated component of the postsynaptic response, and this can be enhanced relative to the AMPA component by certain neuromodulators (see Discussion). A further requirement would be that the NMDA-mediated transmission would be unregulated after LTP and there is evidence that this occurs (Muller and Lynch 1988; Bashir et al. 1991; Beretta et al. 1991; Asztely et al. 1992; Xie et al. 1992). Based on this information, we felt that a role of NMDA channels in recall was a reasonable possibility and proceeded to examine whether NMDA-dependent mechanisms would work well for readout of sequence information at gamma frequency.

In setting up these simulations we were faced with the question of what kind of afterpotentials would occur during recall. Many types of neurons have a slow after-hyperpolarization (AHP) that follows action potentials, but during cholinergic or serotonergic neuromodulation, the afterpotential can become depolarizing (Storm 1989; Andrade 1991; Caeser et al. 1993; Libri 1994). In the previous papers in this series (Jensen et al., this issue), we showed that such an after-depolarization (ADP) was crucial in the function of STM and in the production of the repetition of firing required for encoding information into LTM. During recall, however, it seems clear that an AHP is needed (see below), not an ADP, and so we assume that the neuromodulatory conditions during recall are different from those during learning, as others also have assumed (Hasselmo and Bower 1993).

The general operation of the network during recall can be understood as follows: Memory cues corresponding to the initial parts of the sequence are used to probe the network in the first two gamma cycles. The firing of cells that encode these memories (1,2) causes the binding of glutamate to NMDA channels on cells that encode subsequent memories in the sequence. But before these channels become active, feedback inhibition occurs and prevents firing; indeed, it is this inhibition that generates the gamma cycle. As the inhibition wears off, one set of pyramidal cells will have the most NMDA-dependent excitation and will fire in the third gamma cycle. Feedback inhibition will then prevent cells with lesser excitation from firing. The model thus operates as a winner-take-all oscillatory network (Coultrip et al. 1992). At this point two important things happen. First, the cells that fired in the third gamma cycle undergo an AHP, thereby ensuring that they will not fire again until the AHP has worn off (see Fig. 3D). Given the time constant of the medium AHP (Storm 1990), this would not happen until the next theta cycle. Second, the cells that fired in the third gamma cycle release glutamate onto the NMDA channels in their target neurons. When we now come to the fourth gamma cycle, another group of cells will have the most excitation and fire. In this way an entire sequence is readout.

The simulation of recall in a network conforming to these principles is shown in Figure 3. The network previously had learned the sequence 1–7, as in Figure 2. Now in recall mode, the cues (memories 1,2) produce correct recall of the remaining items in the sequence (memories 3–7) at gamma frequency (Fig. 3A).

The graphs of the NMDA current shown in Figure 3B, C show that when firing occurs, it is due to the cumulative buildup of the total cell NMDA current due to input from multiple previous mem-

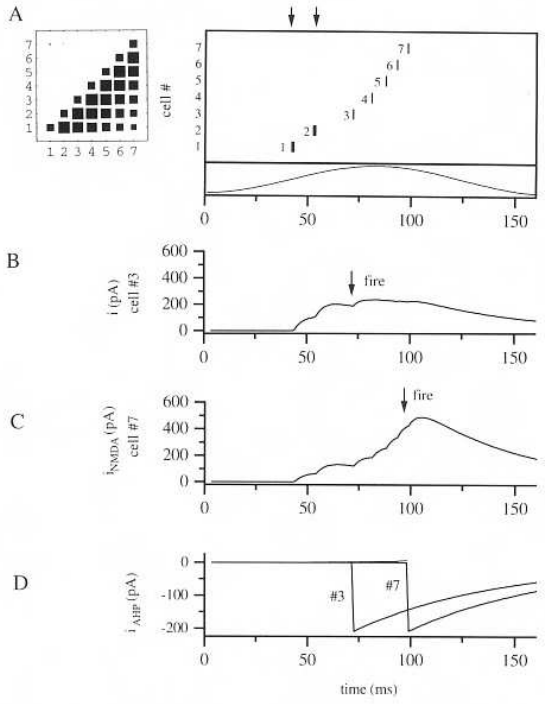

Figure 3: Recall of sequence information through synaptic transmission mediated by the NMDA channel. The network has previously learned the sequence 1–7. (Fig. 2). (*A*) The first two elements of the sequence (1,2) are inserted into the network in the first two gamma cycles as retrieval cues (probe). The network then produces firing of elements 3–7 on subsequent gamma cycles. (*B*) The magnitude of the active state of NMDA conductance in cell 3 rises because of input from memory 1 and 2, leading to firing on the third gamma cycle. (*C*) The active state of the NMDA conductance in cell 7 integrates multiple inputs and leads to firing on the seventh gamma cycle. (*D*) The slow AHP in cell 3 and 7 occurs after the cell spikes, preventing sustained firing. Parameters as in Fig. 2 except for $A_{NMDA} = 325.0$ pA.

ories. Thus although the strongest input comes from the cells that encode the previous memory in the sequence (the $n-1$ memory), inputs from the $n-2$ and $n-3$ memories are also important. This cumulative property seems desirable because it means that the readout of sequence information makes use of all the information stored in the matrix, not just the strongest weights of the $(n-1, n)$ connection.

The cumulative basis of sequence readout has a further useful function: It solves the disambiguation problem of sequence learning (Levy et al. 1995). To understand this problem, consider a network that has learned two sequences with a common element (1,3,5,7,6,4,2 and 13,11,9, 7,8,10,12). When the initial part of the first sequence, 1,3,5,7, is recalled, a pairwise recall mechanism would provide no basis for next recalling 6 as opposed to 8. However, if the synaptic buildup in 6 is due to the cumulative input from both 1,3,5, and 7, then the excitation in 6 will be stronger than in 8 and the entire sequence will be correctly recalled. This solution to the disambiguation problem is demonstrated in Figure 4. When the network is probed with memory 1 and 3 (Fig. 4A1), it correctly recalls the full sequence. Figure 4A2 illustrates the cumulative build-up of the NMDA current in cells encoding memory 6. As can be seen, not only the input from memory 7 helps bring memory 6 above threshold, but also the input from memories 1, 3, and 5 (Fig. 4A2). By contrast, cell 8 receives input only from cell 7. Figure 4B shows complementary results when the network is probed with the beginning of the second memory sequence, 13,11.

In the simulations thus far, we have not specified how the repetition required for synaptic encoding occurs. In a previous paper (Jensen et al., this issue) we showed that if an ADP is present in the principle cells of a network, the network can capture multiple memories (items) in real time, segregate their firing into different gamma cycles, and repeat each memory once every theta cycle in a time-compressed form (see right side of Fig. 6A for a nice illustration of what is meant by time compression). We further showed that this repetitive firing could drive the encoding of autoassociative LTM, provided the encoding was governed by fast NMDA channels. Finally, we showed that if memory items already had a representation in LTM (in the recurrent collateral synapses of the network), the STM for a novel sequence of memories could be accurately maintained in the order of presentation (Jensen and Lisman 1996b, this issue). Such a network would provide the ideal input to a network that uses slow NMDA channels to incorporate sequence information into LTM. Such dual networks are shown in Figure 5. Because fast NMDA channels have been found in cortex (S. Vicini, J.F. Wang, J.S. Poling, and D.R. Grayson, pers. comm.) but not hippocampus, we tentatively label the initial autoassociative network "cortex." Because the CA3 hippocampal network has slow NMDA channels and recurrent collaterals, we tentatively label the heteroassociative sequencing network "hippocampus." This is obvi-

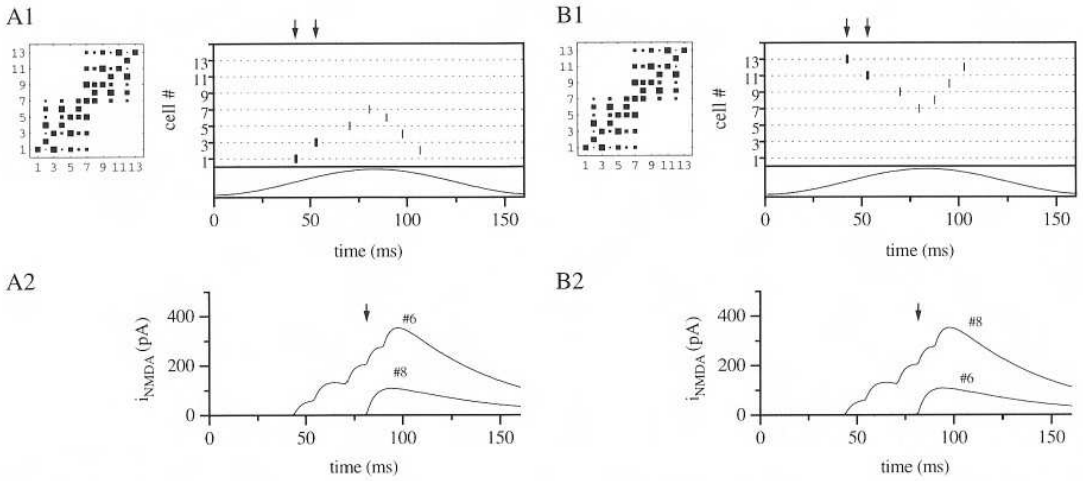

Figure 4: Cumulative recall solves the disambiguation problem of sequence learning. The network previously learned two sequences with one common central element (1,3,5,7,6,4,2 and 13,11,9,7,8,10,12). (*A1*) Network is cued with first two elements (arrows) of the first sequence and produces the subsequent sequence. The inset shows the synaptic weight matrix. (*A2*) Active NMDA channels in cell 8 is much larger than in cell 6. (*B1,2*) Same as in *A* but for the other learned sequence.

ously a highly simplified model and we do not mean to imply that the connections between cortex and CA3 have to be direct.

Figure 6 shows how this dual network performs episodic memory encoding. The episode consists of seven brief events that arrive randomly over many seconds and occur only once. Each of the items, for instance, a digit in a novel phone number, is a known item and therefore has a representation in the LTM of the cortex. The cortex is able to accurately keep the seven memories firing in their correct gamma cycle, with one repetition each theta cycle. Thus as multiple memories are entered into the cortical buffer, they are repeated in a time-compressed form. These repetitive firing patterns are transferred to the hippocampus, where the particular sequence is encoded into LTM. Thus by the end of 10 sec, the sequence, that is, the particular phone number, is stored. This is shown in the connectivity matrix (Figure 6B). By then probing the network with the first two digits from the list, the full sequence is recalled.

Discussion

NETWORKS WITH LONG-LIVED NMDA CHANNELS PERFORM HETEROASSOCIATIVE SEQUENCE LEARNING

Our consideration of the role of theta and gamma oscillations leads us to the conclusion that networks with slow NMDA channels, such as the hippocampal CA3 region, serve to link different memories and are thus specialized for learning heteroassociative sequence information. This follows straightforwardly from the assumption that different memories are stored in different gamma cycles and from the fact that slow NMDA channels have a lifetime that spans multiple gamma cycles. Because of the importance of these points, the evidence supporting them will be briefly reviewed.

The strongest evidence that different information is stored in different gamma cycles comes from work on place cells. These cells, which are observed in both CA1 and CA3 regions of the hippocampus, systematically change their phase of firing during theta as they move through their place field (O'Keefe and Recce 1993; Skaggs et al. 1996). Cells with slightly different place fields will thus be firing at different phases of the theta cycle. There is no proof yet that the firing phase of place cells is discretized by gamma cycles, but the fact that pyramidal cells have inhibitory input at gamma frequency (Sik et al. 1995; Whittington et al. 1995) and the observation of synchronous activity in field potentials at gamma frequency (Soltesz and Deschenes 1993; Bragin et al. 1995) provide a strong suggestion that place cell firing occurs in discrete gamma cycles.

The work of Debanne et al. (1995) on CA3 hippocampal synapses demonstrates that the recur-

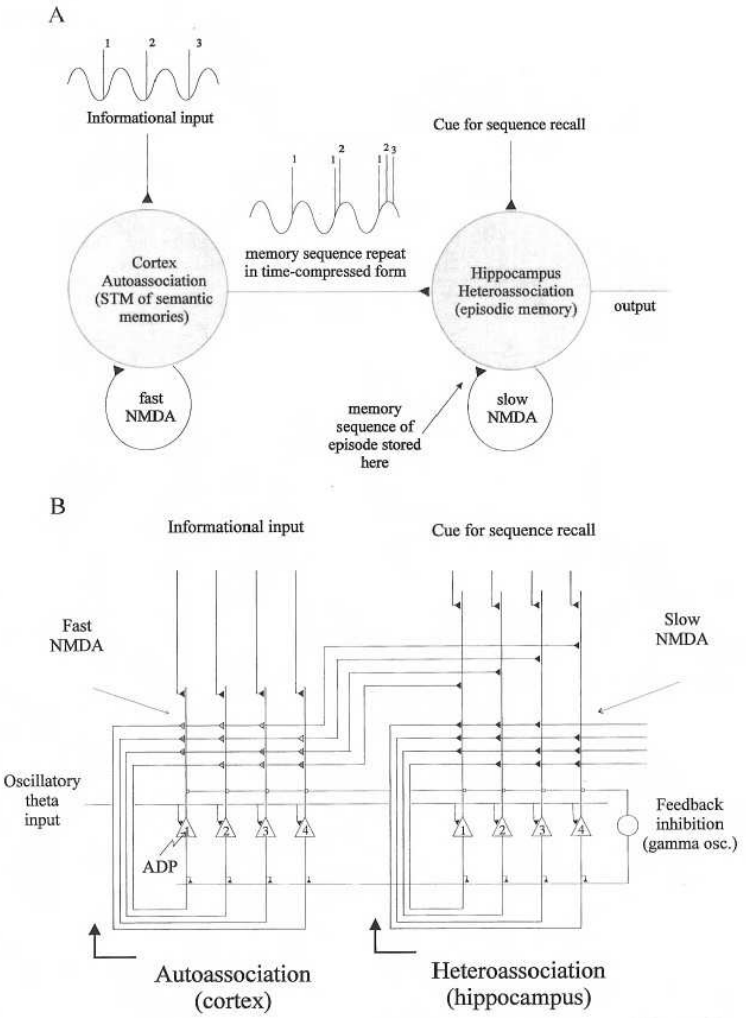

Figure 5A

Figure 5: Dual networks for encoding of episodic sequence information into LTM. (*A*) Black box diagram shows to the *left* the autoassociative network that stores item information using fast NMDA channels. This network can produce accurate STM of novel sequences of known items. The output of this network drives a heteroassociative network that stores the unique sequence of items using slow NMDA channels. In recall mode, a cue to the right network produces the rest of the stored sequence. (*B*) Network model for the two networks shown in *A*. Networks have synchronized gamma due to the common inhibitory interneurons.

rent collaterals have slowly deactivating NMDA channels.

Both in vivo and in vitro work on hippocampal LTP has established that the pre- and postsynaptic requirement for Hebbian plasticity mediated by NMDA channels does not require that the activity on the two sides of the synapse are exactly synchronous. LTP can still occur if postsynaptic depolarization follows presynaptic activity with a delay (Levy and Steward 1983; Gustaffson and Wigström 1986; Kelso and Brown 1986; Gustaffson et al. 1987; Larson and Lynch 1989). All the available data indicates that the duration of this delay is determined by the time constant of the NMDA channel, a time constant that is determined by the duration of glutamate binding (for review, see Jones and Westbrook 1996).

OTHER ARGUMENTS FOR A SEQUENCE FUNCTION OF THE HIPPOCAMPUS

The hippocampal CA3 region has long been considered (Marr 1971; McNaughton and Morris 1987; Treves and Rolls 1994; Hasselmo et al. 1995) the archetypical example of an autoassociative network because it has the key features of autoassociative neural network models: Abundant recurrent collaterals (Li et al. 1994) and Hebbian synaptic modification (Bliss and Collingridge

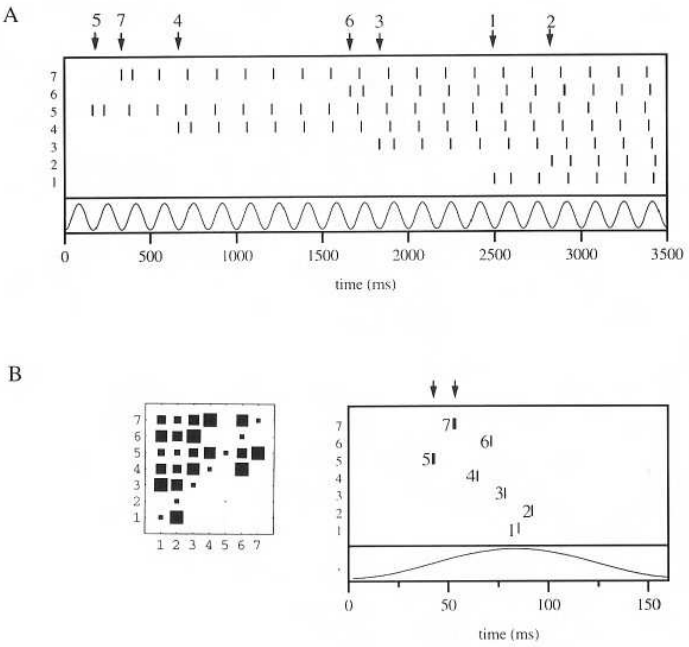

Figure 6: Dual networks store episodic LTM (e.g., of a phone number). (*A*) Seven digits are presented at random intervals in the troughs of the theta oscillations. Firing in seven cells of the hippocampal network is shown. Each memory continues to fire in the correct gamma cycle because of the repetition properties of the STM network (the sequential firing of cells representing each of the seven digits within each theta cycle to the right nicely illustrates the concept of time compression). (*B*) Demonstration of proper encoding after single presentation. Hippocampal network is cued by entry of the first two numbers and produces subsequent numbers in the stored sequence at gamma frequency. The inset shows the synaptic weight matrix.

1993) at the recurrent synapses. Through autoassociative learning, cells that are active at the same time become linked synaptically. The full memory can then be recalled by presenting a partial form.

Our conclusions that CA3 may be specialized for sequence learning follow from consideration of gamma oscillations that have not been considered in previous models. However, related conclusions regarding sequence learning have been reached by other investigators based on the potential of the slow NMDA channels to form links between cells that fire at different times because of changing sensory input. This mechanism has been incorporated into several models (Muller et al. 1991; Manai and Levy 1993; Granger et al. 1994; Blum and Abbott 1996). These ideas have been tied directly to the concept of place cells in the hippocampus and to theories of path navigation. The specific idea that sequence learning occurs in the hippocampus has also been proposed by Prepscius and Levy (1994). More generally, based on a large body of work on the effect of lesions on behavior, it has been concluded that the function of the hippocampus is to link together different memories into different relationships (Eichenbaum and Otto 1992; Squire 1992; McClelland et al. 1995). Our view of the function of the CA3 recurrents would be compatible with this view if the information to be linked has a temporal separation. More generally, our model in no way preludes other kinds of information storage elsewhere in the hippocampus.

Experimental evidence for a role of the hippocampus in the recall of sequence information is provided by an analysis of place cell activity during sleep. Buzsáki (1989) proposed that place fields are reactivated during the sharp waves that occur during slow wave sleep. Experiments show that the temporal order of place cell firing during locomotion actually can be recalled during slow wave sleep (Skaggs and McNaughton 1996). This implies that the rat stores a sequence of its path during exploration; parts of this sequence are recalled during each sharp wave. The dominant frequency of sharp waves is 200 Hz. Although we have not modeled sharp waves, it seems clear that sequence information, once stored, can be read out at different frequencies depending on neuromodulatory changes. Fast AMPA-mediated transmission would seem appropriate for generating recall at 200 Hz rather than the NMDA-mediated transmission that we propose underlies gamma-frequency (40 Hz) readout.

There has been no previous indication that the gamma oscillations observed during the wake state are functionally important in recall, as we have proposed. However, the qualitative success of our model when applied to hippocampal place cell data (see Jensen and Lisman 1996a, this issue)

strongly suggests that there is a recall mode in which memories are recalled at one memory per gamma cycle.

Our work suggests that a different type of process is required for autoassociative memory storage of items and for learning of sequences (episodic memory), and we tentatively view the cortex as the site for item learning and recognition and the hippocampus as the site for item learning and recognition and the hippocampus as the site for sequence learning. The type of specialization is consistent with recent lesion studies in monkeys showing that removal of the hippocampus does not strongly impair item recognition memory (Alvarez et al. 1995).

A MODEL FOR EPISODIC LEARNING

At the pinnacle of human learning is the ability to store LTM after a single presentation. The simulation shown in Figure 6 suggests how such one trial learning could occur in a physiologically realistic way through the interplay of two specialized networks, a cortical network that serves as an STM buffer and a hippocampal network that stores sequence information. In terms of the phone number analogy, the cortical STM buffer captures the items (digits) as they occur in real time and repeats them. Because the digits themselves are not novel items, they have a LTM representation in cortex. Importantly, this representation makes it possible for the STM for all items to be maintained without error (Jensen and Lisman 1996b, this issue). The representation provided by the cortical STM buffer drives synaptic modification in the hippocampal heteroassociative network, thus forming LTM for the novel sequence (e.g., a phone number). Given some poetic license, an episode could be described as a unique sequence of events, each of which alone has some familiarity. Because of the ability of the cortical buffer to capture items that occur seconds apart and repeat them in a time-compressed way, the hippocampus potentially can link memories that occur many seconds apart. The overall episode might thus be quite long in duration.

THE IMPORTANCE OF A STM BUFFER FOR SEQUENCE LEARNING

Previous models (Manai and Levy 1993; Granger et al. 1994; Blum and Abbott 1996) show how sensory information that arrives at different times as the animal moves through its environment could be linked by NMDA channel dependent learning. The maximum time over which linkage could occur is for events separated by the lifetime of the NMDA channel, for example, 150 msec. Our model produces linkage over a much longer time scale because information is first stored in a STM buffer. Information that arrives many seconds apart will be stored in adjacent gamma cycles in a time-compressed way (Fig. 6). Because of this time compression, memories of events that occur seconds apart can be linked into a memory sequence by NMDA channels with a time constant of 150 msec.

There has been a debate in the psychophysical community about whether STM really represents a mechanistically different form of memory than LTM (Greene 1986). While early work demonstrating the limited memory capacity of STM suggested the presence of a mechanistically specialized STM buffer, subsequent theorizing suggested that STM might simply represent a fast synaptic modification associating STM items with context and therefore is mechanistically similar to LTM. We would argue that a STM buffer in which information is stored by persistent activity is required. It is precisely because different memories that occurred seconds apart are active in the STM buffer in a time-compressed way that they can become linked by known NMDA-dependent processes that operate over a much shorter time scale.

ROLE OF NMDA CHANNELS IN GAMMA FREQUENCY READOUT

The most novel possibility to emerge from our analysis is a role for NMDA channels in the recall of sequence information. This role is in addition to the generally accepted role of this channel in learning (LTP induction) and is specifically limited to the readout of sequence information. NMDA channels (slow or fast) do not seem well suited for recall of autoassociative item information, whereas AMPA channels are (Jensen et al., this issue).

The kinetics of slow NMDA channels appear well suited for sequence readout in networks governed by theta/gamma oscillations. First, the slow NMDA channels open slowly (~18 msec) (S. Vicini, pers. comm.) and thereby provide the delay that ensures that the next memory in the sequence does not fire in the same gamma cycle as the pre-

vious memory in the sequence. It should be emphasized that the required delay does not need to be a whole gamma cycle; all that is required is that the delay is long enough to ensure that the excitation develops after the onset of the feedback inhibition (it is this inhibition that forms the negative phase of each gamma cycle). The second important feature of slow NMDA channels is that their excitatory influence persists for one or more gamma cycles. S. Vicini, J.F. Wang, J.S. Poling, and D.R. Grayson (pers. comm.) find the deactivation constant $\tau \sim 300$ msec at room temperature. However, a $Q_{10} = 3$ (Hestrin et al. 1990; Feldmeyer et al. 1993) brings the τ down to ~100 msec at body temperature. This persistence ensures that when the inhibition that separates gamma cycles has decayed, the cells that received excitatory input on the previous gamma cycles still have functional excitation. It is this excitation that triggers the next memory in the sequence. If the time constant of the NMDA channel was much greater than the period of a theta cycle, strong symmetric synaptic connections would form from the last elements in the buffer to the first. This would be undesirable because order information would be lost. Thus the fact that the time constant of slow NMDA channels does not exceed a theta cycle can be seen as functionally appropriate.

If NMDA channels function in recall of memory sequences, the NMDA component of the EPSP must be enhanced during Hebbian plasticity, and this appears to be the case (Muller and Lynch 1988; Bashir et al. 1991; Beretta et al. 1991; Asztely et al. 1992; Xie et al. 1992). A second requirement is that the charge carried by NMDA channels has to be greater than that carried by AMPA channels. Although it is generally thought that NMDA channels are not functional near resting potential in hippocampal neurons, this is not strictly correct. The Mg^{2+} block of NMDA channels at resting potential is not complete and both current carried by NMDA channels and the Ca^{2+} entry through these channels can be measured near resting potential (Y. Kovalchuk, J. Eilers, J. Lisman, and A. Konnerth, pers. comm.). Two factors might further enhance the NMDA conductance relative to the AMPA conductance. First, the general level of depolarization of neurons may increase through the action of neuromodulators and this would secondarily increase the NMDA component. For instance, acetylcholine is known to depolarize hippocampal pyramidal cells (Dodd et al. 1981; Madison et al. 1987). Second, direct evidence shows that neuromodulators can directly modulate NMDA channels and increase their relative contribution to synaptic transmission (Markram and Segal 1990; Bekkers 1993).

There is some direct evidence that the role of NMDA channels is not limited solely to learning, but also plays a role in the expression of synaptic function in the hippocampus (Hablitz and Langmoen 1986; Bekkers 1993; Mody and Heinemann 1987). Most directly, the amplitude of the theta oscillation induced by carbachol in hippocampal slices is reduced by the NMDA channel blocker aminophosphonovaleric acid (APV) (Huerta and Lisman 1995). The amplitude of the oscillation, as recorded in field potentials, reflects the number and strength of cell firing, and indicates that some of the synaptic excitation known to drive the oscillation is a result of the NMDA channel. Similar effects of NMDA blockers have been observed in vivo, but the possibility that the drug is acting on the septal structures that drive the hippocampal oscillation cannot be excluded (Buzsáki et al. 1983).

DO NMDA BLOCKERS AFFECT MEMORY RECALL?

If NMDA channels are involved in the readout of memory, recall should be blocked by inhibiting NMDA channels after learning. This is clearly not the case for recall of fear conditioning (Miserendino et al. 1990) or position learning (Morris et al. 1990). These tasks, however, depend on recognition memory rather than sequence memory, and we would not expect recall to involve NMDA channels in these cases. Learning a path would be an excellent example of sequence learning, but effects of NMDA blockers have not been tested on the recall of path information. There are some indications of an effect of NMDA channel blockers on recall in task learning in the water maze (Bannerman et al. 1995; see effect of blocking NMDA channels in their Fig. 3B) and on learned responses in the owl colliculus (Feldman et al. 1996). The strongest indication of the involvement NMDA channels in sequence recall comes from studies of bird song. A brief report describes the inhibition of song production by NMDA channel blockers. This could not be attributed to paralysis of motor systems, because the bird could still make individual notes (A. Lombardino and F. Nottebohm, pers. comm.). If these data are confirmed, it would provide strong evidence for a role of NMDA channels in recall of stored sequences.

Table 1: *Physiological mechanisms incorporated into the model and their function*

1. Conductances in pyramidal cells
   - AMPA conductance. In recurrents they perform autoassociative pattern completion in cortex within a gamma cycle. Fast kinetics is crucial for pattern completion since excitation must occur *before* feedback inhibition. In heteroassociative networks, such as the hippocampal CA3 network, they may govern readout of sequences during a 200-Hz sharp-wave.
   - fast NMDA ($\tau < 30$ msec). In recurrents they govern synaptic modifications for autoassociative memory in cortex. Fast enough to govern plasticity *within* a gamma cycle.
   - slow NMDA ($\tau = 150$ msec). Participates in learning and recall in heteroassociative networks. Governs heteroassociative synaptic plasticity linking items over multiple gamma cycles. Note that much longer tau would not work. Mediates synaptic transmission during memory readout in CA3. The slow rise time ($\approx$10 msec) provides vital delay that ensures only one memory per gamma cycle during recall.
   - GABA-mediated IPSPs. Responsible for generating gamma oscillations and memory segmentation through feedback inhibition. The delay in disynaptic inhibitory feedback needs to be long enough to allow pattern completion by monosynaptic AMPA-mediated synaptic transmission.
   - ADP (afterdepolarization). Functions in autoassociative network in cortex during learning mode. Perpetuates firing after brief excitatory synaptic input and thereby maintains short-term memory (sample and hold function). Slow rising edge of ADP provides timing ramp for segmenting different memories into different gamma cycles. Slow rise of ADP may actually be due to medium AHP.
   - slow AHP (afterhyperpolarization). In recall mode it makes sure that a memory that fires is not available to fire again in the same theta cycle.
2. Oscillations
   - Theta oscillation (5-10Hz). Groups 7 memories and controls repeat time for each memory. New information is entered into network once every theta cycle.
   - Gamma (20–60Hz). Defines synchronization: Cells that fire within the same gamma cycle are recognized as part of *same* memory by downstream neurons. Learning and some forms of recall occur at one memory per gamma cycles.
3. Neuromodulators
   - Control functional state: sleep (slow-wave and REM); wake (learning and recall modes). Cholinergic modulation is important in some forms of theta and activates the ADP. Serotonin can also activate ADP.

A final point about a possible role of the NMDA channel during recall is that it would explain why recall so strongly stengthens memory (Slamecka and Graf 1978). There has been little basis for explaining why this should occur. Under standard conditions low-frequency subthreshold or superthreshold synaptic transmission has no effect on the strength of synapses. In our model of recall, NMDA channels usage is specifically enhanced during recall.

NMDA CHANNELS MEDIATE A CUMULATIVE FORM OF LEARNING AND RECALL

An elegant aspect of NMDA channel function in learning and recall is the way the channels provide cumulative recall. The word cumulative here refers to the fact that when a memory is recalled, it is because of the cumulative influence of multiple previous memories. Specifically, the process is not pairwise (memory 1 stimulates memory 2, which stimulates memory 3, etc.). In cumulative recall, the firing of memory 3 is because the cells representing these memories receive excitatory input from cells that represented memory 1 and memory 2. The reason that connections form between cells representing memories 1 and 3 follows directly from the fact that the time constant of slow NMDA channels is longer than the duration of two gamma cycles (Fig. 1). Information about sequences is stored in a doubly redundant way: A memory is excited by multiple cells from multiple previous memories. NMDA channel mediated recall provides a way of using this redun-

dant information and the system thereby gains robustness. Thus if a noise fluctuation prevented the nth memory in a sequence from firing, the $n+1$ memory could still fire as a result of input from the $n-1$ and $n-2$ memory. Psychophysical studies provide evidence that learning of sequences is indeed cumulative and not pairwise (Posnansky 1972; M.J. Kahana, pers. comm.). This can be easily demonstrated by asking someone to give the next letter in the alphabet after one letter of a multiletter cue.

DISAMBIGUATION IN PATH LEARNING

The ability of networks with slow NMDA channels to learn sequence information and use it in a cumulative way (Fig. 4) has important implications for the problem of disambiguation, a classic problem in sequence learning. This problem can best be posed in the context of path learning. Suppose two well-known paths cross at point X. The disambiguation problems deals with the fact that if the only stored information is pairwise, the animial would not know which path to go down upon reaching X. If, however, multiple previous locations also influence the next step in the sequence, the choice that completes the initial path is clear. Levy et al. (1995) have solved the problem of disambiguation somewhat differently by using contextual information to distinguish between two possible pathways.

POSSIBLE RELEVANCE TO SCHIZOPHRENIA

There has been a great deal of interest in the role of NMDA channels in schizophrenia ever since the discovery that NMDA channel blockers, such as phencyclidine, produce behavioral changes that resemble schizophrenia (Moghaddam 1994). Because the abnormalities produced by NMDA channel blockers have nothing to do with learning, they point to a role for NMDA channels in normal synaptic transmission. One possibility that has recently been suggested is that NMDA channels are important in the excitation of hippocampal interneurons (Grunze et al. 1996). The block of interneuron activity could lead to improper segmentation of thoughts. Our results point to another possible site of action, the NMDA channels on the recurrent collateral synapses between CA3 cells. According to our model, blocking the NMDA channels at these synapses would interfere with the recall of sequence information. To the extent that AMPA channels became the dominant source of excitiation at these synapses, the crucial delay between memories would be lost, leading to improper segmentation.

THE ROLE OF CELLULAR AND MOLECULAR PROCESSES IN MEMORY FORMATION

This series of papers is the first to attempt to model memory encoding and recall by taking into account the kinetics of membrane conductances and the oscillatory properties of networks. Particular roles are assigned to different types of glutamate channels, voltage-dependent conductances, and network oscillations. These assignments are summarized in Table 1, and should form the basis for testing the role of these components in memory function.

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