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Storage, Recall, and Novelty Detection of Sequences by the Hippocampus: Elaborating on the SOCRATIC Model to Account for Normal and Aberrant Effects of Dopamine

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ABSTRACT: In order to understand how the molecular or cellular defects that underlie a disease of the nervous system lead to the observable symptoms, it is necessary to develop a large-scale neural model. Such a model must specify how specific molecular processes contribute to neuronal function, how neurons contribute to network function, and how networks interact to produce behavior. This is a challenging undertaking, but some limited progress has been made in understanding the memory functions of the hippocampus with this degree of detail. There is increasing evidence that the hippocampus has a special role in the learning of sequences and the linkage of specific memories to context. In the first part of this paper, we review a model (the SOCRATIC model) that describes how the dentate and CA3 hippocampal regions could store and recall memory sequences in context. A major line of evidence for sequence recall is the "phase precession" of hippocampal place cells. In the second part of the paper, we review the evidence for theta-gamma phase coding. According to a framework that incorporates this form of coding, the phase precession is interpreted as cued recall of a discrete sequence of items from long-term memory. The third part of the paper deals with the issue of how the hippocampus could learn memory sequences. We show that if multiple items can be active within a theta cycle through the action of a short-term "buffer," NMDA-dependent plasticity can lead to the learning of sequences presented at realistic item separation intervals. The evidence for such a buffer function is reviewed. An important underlying issue is whether the hippocampal circuitry is configured differently for learning and recall. We argue that there are indeed separate states for learning and recall, but that both involve theta oscillations, albeit in possibly different forms. This raises the question of how neuromodulatory input might switch the hippocampus between learning and recall states and more generally how different neuromodulatory inputs reconfigure the hippocampus for different functions. In the fifth part of this paper we review our studies of dopamine and dopamine/NMDA interactions in the control of synaptic function. Our results show that dopamine dramatically reduces the direct cortical input to CA1 (the perforant path input), while having little effect on the input from CA3. In order to interpret the functional consequences of this pathway-specific modulation, it is necessary to understand the function of CA1 and the role of dopaminergic input from the ventral tegmental area (VTA). In the sixth part of this paper we consider several possibilities and address the issue of how dopamine hyperfunction or NMDA hypofunction, abnormalities that may underlie schizophrenia, might lead to the symptoms of the disease. Relevant to this issue is the demonstrated role of the hippocampus in novelty detection, a function that is likely to depend on sequence recall by the hippocampus. Novelty signals are generated when reality does not match the expectations generated by sequence recall. One possible site for computing mismatch is CA1, since it receives predictions from CA3 and sensory "reality" via the perforant path. Our data suggest that disruption of this comparison would be expected under conditions of dopamine hyperfunction or NMDA hypofunction. Also relevant is the fact that the VTA, which fires in response to novelty, may both depend on hippocampal-dependent novelty detection processes and, in turn, affect hippocampal function. Through large-scale modeling that considers both the processes performed by the hippocampus and the neuromodulatory loops in which the hippocampus is embedded, it is becoming possible to generate working hypotheses that relate synaptic function and malfunction to behavior. *Hippocampus 2001;11:551–568.*

KEY WORDS: acetylcholine; associative memory; clozapine; gamma rhythm; heteroassociation; NMDA (N-Methyl-D-aspartate receptors); perforant path; schizophrenia; theta rhythm; ventral tegmental area

INTRODUCTION

Modern neuroscience has made great strides in understanding the cellular and electrical properties of neurons, but our understanding of how brain networks work together to perform function remains rudimentary. The general goals are clear: what is needed is an understanding of the computations being performed by each brain network, the way in which these computations depend on the anatomical, physiological, and molecular properties of the specific cell types, and the way in which different brain networks work together to generate behavior. Theories of this breadth will necessarily be complex and difficult to develop. The pressure to develop them comes from the needs of two related fields. The first is the explosion of work using genetic modification technology. Studies of this kind observe the behavioral modifications resulting from specific molecular changes and need a theory to relate the two. The second is the analysis of brain diseases. Here the hope is that by understanding the linkage between defects in cellular/molecular function and

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behavioral symptoms, it may become possible to devise effective treatments.

In recent years, several theories of hippocampal function of great breadth have been developed (Hasselmo and Schnell, 1994; O'Reilly and McClelland, 1994; Levy, 1996; Rolls, 1996; Tsodyks et al., 1996; Hasselmo and Wyble, 1997). These attempt to specify the types of computations and information storage being performed in each hippocampal subfield, and the relationship of these processes to known network, cellular, and synaptic properties. These models have focused primarily on an agreed-upon function of the hippocampus, the storage and recall of memories. However, there is increasing evidence that the hippocampus is also involved in a second, related function, novelty detection. In this process, expectations based on stored memories are compared to what has actually occurred. For instance, recordings from the hippocampus of the awake rabbit clearly show strong sensory responses to novel stimuli. However, after repeated presentation, memory encoding occurs and the sensory responses become small, a phenomenon referred to as habituation (Vinogradova, 1984). Some of the theories of the hippocampus, including the one we will describe here, suggest how novelty detection might be performed. This consideration of the dual functions of the hippocampus may be important in understanding the role of the hippocampus in schizophrenia, since some of the best-studied deficits in schizophrenics can be related to role of the hippocampus in novelty detection (Schmajuk, this issue).

In this paper we will review and extend a model of hippocampal function developed in our laboratory, which we now term the SOCRATIC model. This model attempts a coherent explanation of all the excitatory synaptic connections in the dentate, CA3, and CA1 regions. Some of the most salient synaptic properties are also taken into consideration. The model relates these synaptic and network properties to experimental observations about place fields, neural coding, network oscillations, and behavioral deficits produced by hippocampal lesions. Despite the complexity of this model, it is nevertheless only a partial model. One area in particular that requires elaboration is the role of the neuromodulatory systems that innervate the hippocampus. Although it is clear that neuromodulatory inputs depend on the behavioral state, it is not yet known how neuromodulators shape hippocampal function. Large theta-frequency oscillations in the field potential occur under some conditions, and our analysis suggests that there may be two theta states, one for learning and one for recall. An important goal is to understand how these states are controlled by neuromodulatory input.

As a step towards understanding neuromodulatory control, we have initiated a study of how dopamine affects the CA1 region of the hippocampus. The initial results, which we review here, show that dopamine can selectively affect one input into CA1 while leaving another nearly unaffected. This effect of dopamine was strongly antagonized by the neuroleptic, clozapine. There is growing evidence that hippocampal malfunction may underlie some of the symptoms of schizophrenia (see other articles in this issue), and the effects of clozapine we observe may be relevant to explaining the success of clozapine in treating this disease. But exactly what does "relevant" mean? To be more specific, one has to have a large-scale theory that assigns an information-processing role to the CA1 region and to its dopaminergic input. In the final part of this paper we discuss the possible role of CA1 in novelty detection, the possible role of normal dopaminergic modulation in this process, and the abnormalities that might arise as a result of the dopaminergic hyperfunction or NMDA hypofunction implicated in schizophrenia.

SUMMARY OF SOCRATIC (SEQUENCES OF CONDENSED REPRESENTATIONS, AUTOCORRECTED, THETA-GAMMA CODED, IN CONTEXT) MODEL FOR RECALL OF EPISODIC MEMORY SEQUENCES

Figure 1 shows the hippocampus and the excitatory connections between principal cells (interneurons are not shown). The inputs to and from the entorhinal cortex are also shown. The diagram has been organized to emphasize the recurrent structure of two of the dentate and CA3 networks. It has long been recognized that the CA3 region is a recurrent network in which massive recurrent collaterals make connections between any given CA3 and a large number of other CA3 cells. It is these recurrent synapses that make CA3 similar to standard neural network models of associative memory, and which have inspired most memory models of the hippocampus. However, the diagram also emphasizes the less well-known fact that the dentate is also a recurrent network, though one more complex than CA3. In the dentate, granule cells make excitatory synapses onto mossy cells, which in turn make excitatory synapses back onto granule cells. These mossy-cell recurrent synapses are numerous, occupying the entire inner third of the molecular layer (Scharfman, 1991; Buckmaster and Schwartzkroin, 1994). The two recurrent networks of the hippocampus are reciprocally connected: the dentate granule cells make large and strong excitatory synapses onto CA3 cells; CA3 cells have collaterals that feedback to the dentate hilar region, where they make excitatory connections onto mossy cells (Scharfman et al., 1990; Hetherington et al., 1994; Jackson and Scharfman, 1996). The model we will now describe assigns a function for these reciprocally connected recurrent networks. We now give this model a name, the SOCRATIC (i.e., Sequences Of Condensed Representations, Autocorrected, Theta-Gamma Coded, In Context) model, which serves as an acronym for remembering the essential features of the model. The appropriateness of the reference to the philosopher will be evident shortly. This model and its experimental support were described in detail elsewhere (Lisman, 1999). Here we review only its general outline and then turn to the question of how it could be extended to account for different functional states under the control of different neuromodulators.

It is generally agreed that there are different types of memories and that the hippocampus is of special importance in episodic memories. Such memories are generally a series of items or events, i.e., a *sequence* (memory item A was followed by memory item B, etc.). An episodic memory is a sequence of items or events that

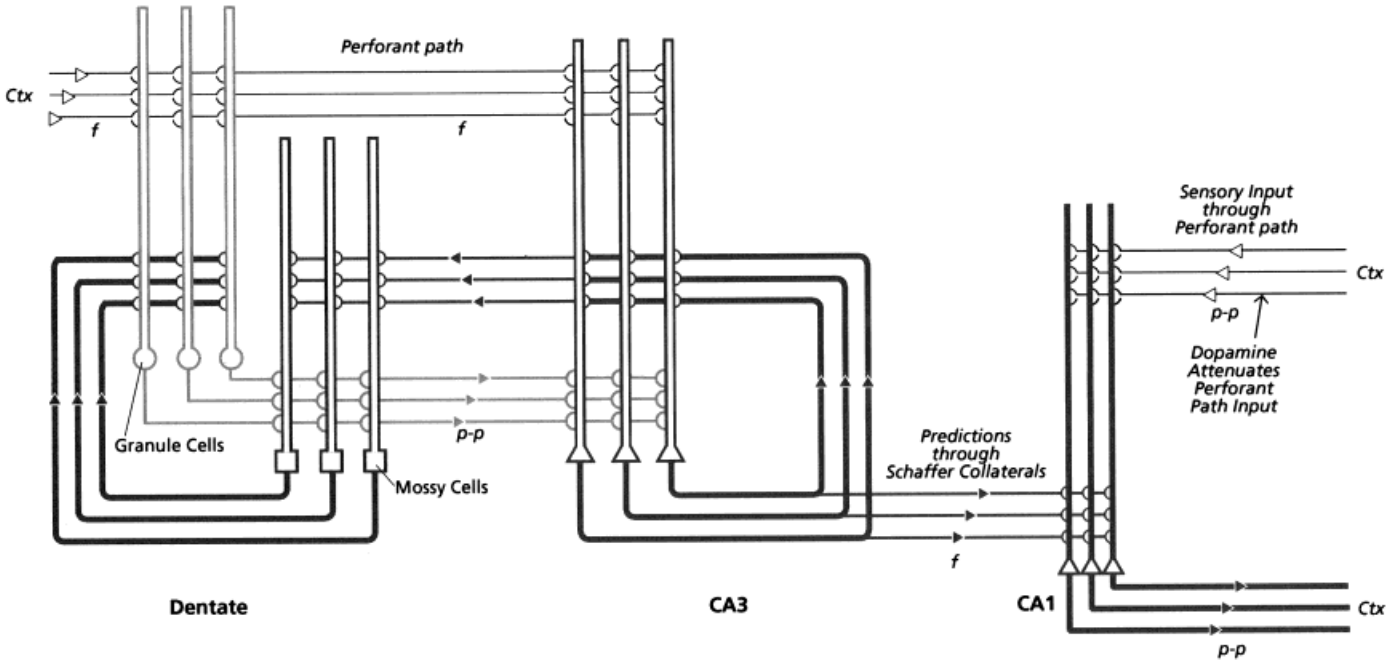


FIGURE 1. Wiring diagram of excitatory pathways of the hippocampal region. The dentate and CA3 are two reciprocally connected recurrent networks. CA1 receives input from CA3 and the entorhinal cortex, and provides an output back to the cortex (for details, see Johnston and Amaral, 1997). Ctx, entorhinal cortex; f, fanning; p-p, point-to-point (see Buzsaki, 1996). For simplicity, pathways are shown connecting to each target cell, but in actuality, only a fraction of these connections occur. The input from Ctx is called the perforant path. The perforant path to the dentate and CA3 comes from layer 2, whereas the input to CA1 comes from layer 3. Minor connections not shown are input onto granule cells from other granule cells (Wolfer and Lipp, 1995) and CA3 cells. Mossy cells also receive excitatory input from the perforant path (Scharfman, 1991). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

occurred in the *context* of a specific time and place. This contextual information must be linked to the items or events, since recall of the events can promote recall of the context and vice versa. The role of sequence storage in hippocampal function is supported by both behavioral lesion data showing specific deficits in behaviors involving memory sequences (Honey et al., 1998) and on physiological data showing replay of temporal sequences (Skaggs et al., 1996; Louie and Wilson, 2001). In addition, as will be discussed later, the phase advance of hippocampal place cells can be interpreted as sequence recall. Other behavioral data (Selden et al., 1991; Nadel and Moscovitch, 1997; Dore et al., 1998; Tulving and Markowitsch, 1998) and physiological recordings (Muller and Kubie, 1987; Thompson and Best, 1989) demonstrate the importance of the hippocampus in forming links between specific memories and the general context in which they occur.

Function of Reciprocally Connected Dentate and CA3 Recurrent Networks: The Importance of Autocorrection in Sequence Recall

The SOCRATIC model postulates that the different fields of the hippocampus have different roles in the sequence storage and recall process. Autoassociative networks have cells that receive different inputs signaling different components of a given memory item, and link these cells together by strengthening their recurrent connections. In contrast to previous models which assumed that the autoassociative memory linkages that contribute to a particular memory (e.g., memory "A") were stored in CA3, we postulate that autoassociative linkages are stored in the dentate recurrent network. This is because there is clear evidence that information from the lateral and medial entorhinal cortex converge onto dentate cells, a convergence suggestive of autoassociative linkage of different components of the same memory. The key capability of an autoassociative network is that it can produce the correct firing of all cells that encode a memory when presented with only a partial or degraded form of that memory. We propose that the CA3 recurrent network has a quite different function. This function is to store "heteroassociations" that links the cells encoding sequential memory items, A-B-C-D, etc.). The key capability of a heteroassociative network is that when presented with a memory cue (e.g., A), the network recalls the subsequent memory items in order (e.g., B-C-D).

A central problem addressed by the SOCRATIC model is how the dentate and CA3 can work together to perform sequence recall without a "concatenation of errors." Such concatenation occurs when only heteroassociative processes are used in recall. Specifically, when cells encoding memory A fire those encoding memory B, there will necessarily be errors such that some cells that are part of B don't fire, whereas others that are not part of B do. The corruption of B is signified as B′. The problem of concatenation is that when B′ is used to excite memory C, the corruptions in B′ lead

to an even more corrupted version of the next memory, C″. How might this core problem of sequence recall be solved?

Abstract theoretical models of sequence recall suggested that accurate sequence recall could be achieved by having autoassociative processes interact with heteroassociative processes (Kleinfeld, 1986; Sompolinsky and Kanter, 1986), and we have adapted this concept to the specific circuitry of the hippocampus. According to the SOCRATIC model, the heteroassociative links in CA3 produce the slightly corrupted memory B′ when presented with the cue A. In the next step, B′ is sent back to the autoassociative dentate network. There, B′ is corrected to its "ideal" form, B (*autocorrection*). This form is sent forward to CA3 to initiate the recall of the next item, C′. The advantage of referring information back to an idealized form was described by Socrates, and hence the model's name. In summary, it is proposed that the reciprocally connected recurrent networks of the dentate and CA3 are specifically configured to learn and recall sequences.

Linkage of Sequences With Context at Perforant Path Inputs to Mossy Cells and CA3

Recordings from rat hippocampal place cells reveal an important role of context (the particular environment). It appears that the firing of place cells is both determined by very specific information (e.g., distance from walls) that makes a cell fire in a particular place, and by more general information about the environment that is independent of the particular rat's position and which is termed "context." Context by itself does not cause cells to fire, but rather enables a place cell to be activated by the specific input about a particular place. In a different environment, a different but partially overlapping set of cells will be potentially active, and these are mapped quite differently onto the environment (Muller and Kubie, 1987; Thompson and Best, 1989). This way of dealing with context makes sense; contextual information (general place and time) may be rich in details, but because the details are relatively constant, encoding this information fully in each successive item in a sequence would produce redundant storage and make undesirable demands on memory utilization. It makes better sense to only encode the novel aspects of each item in a sequence (position for the rat) and to link this in some way to context (properties of the particular environment). This contextual link can be of great aid during retrieval as a way of reducing the set of relevant memories that must be searched.

According to the SOCRATIC model, the selection of potentially active cells in a given context is done by subthreshold input provided by the perforant path inputs to the dentate mossy cells and CA3 cells. Relatively static contextual information may be filtered out by rapidly adapting synapses that provide the input to dentate granule cells. Such synapses act like a "high pass" filter. In contrast, the nearly static contextual information arriving at the perforant path input to CA3 and dentate mossy cells can produce a subthreshold depolarization in a subset of target cells and thereby "enable" them. Thus, for example, in a particular environment, only a subset of CA3 cells will receive the subthreshold enabling signal from a group of entorhinal cells representing the given context. When any of these "enabled" cells receives even a single input from a dentate granule cell (representing a particular place), the large excitatory postsynaptic potential (EPSP) generated by the giant granule cell/CA3 synapses can fire the enabled CA3 cells (but not ones that are not enabled). In this way, a given CA3 cell will fire in a particular place, but only in a particular context. For an alternate view on context representation, see Doboli et al. (2000).

One Function of CA1: Turning the Condensed Hippocampal Representation Back to a Cortical Representation

The model described above suggests how sequences of memories could be stored in context and how they could be accurately recalled by the reciprocal interactions between the dentate and CA3. What then is the function of CA1? One possible function is in the detection of novelty. This function will be discussed later. The second function is to produce a change in representation. This function can be understood in terms the representation used by the dentate and CA3. As mentioned above, cells from the lateral and medial perforant path converge onto dentate granule cells, where the information from these two pathways becomes mixed (condensed), thereby establishing a new form of representation. We argue that this same representation is used in CA3, thus making possible fluent bidirectional exchange of information with the dentate. For the output of CA3 to influence cortical function, it must be turned back into the representation used by the cortex, and this appears to be one function of CA1 (Treves and Rolls, 1992; McClelland and Goddard, 1996).

These ideas about "hippocampal" and "cortical" representations make it possible to account for a property of all the major excitatory connections. This property has to do with whether the pathway is point-to-point or fanning. "Fanning" connections are highly divergent. Thus, for example, fanning connections allow a single granule cell to receive input from many different regions of both the lateral and medial areas of the entorhinal cortex. The resulting mixing of information produces a change in representation. In contrast, CA3 cells receive "point to point" input from the granule cells from only a tiny subregion of the dentate, indicating that these regions use the same representation. By examining the fanning/point-to-point classification for the pathways in Figure 1, it can be seen that the entire set can be understood in terms of the idea that a new hippocampal representation is established by the dentate, used in CA3, and then converted back into cortical representation by CA1.

PHASE ADVANCE OF HIPPOCAMPAL PLACE CELLS: ITS INTERPRETATION AS CUED SEQUENCE RECALL

If the hippocampus is specifically configured to store and recall sequences, there should be electrophysiologically observable signs of such function. Some evidence for this was alluded to earlier. We now turn to an analysis of the "phase advance" which we believe

provides strong evidence for high-speed sequence recall. An understanding of this phenomenon requires first that we discuss the evidence for a form of neural code termed theta/gamma phase coding.

The Hippocampus Uses Phase-Coded Information Organized by Theta and Gamma Oscillations

The concept of neural coding refers to how spikes are used to encode information. It is commonly thought what is important about the firing of neurons is their average rate (rate coding), which can vary from the spontaneous rate (usually <10 Hz) to several hundred spikes per second. Quantitatively, rate is defined as the total number of spikes that occur in a period (irrespective of their exact pattern) divided by the duration of that period. The hippocampus has provided the clearest example in the brain that the neural code is not a simple rate code, but rather utilizes theta phase coding (Fig. 2A). In this form of coding, information is carried by the phase at which a cell fires with respect to the hippocampal theta rhythm, a rhythm that is synchronous over the entire structure.

The first indication of such coding came from experiments (O'Keefe and Recce, 1993) that monitored the firing of single place cells as a rat crossed the place field of that cell. This crossing takes several seconds, during which there are many successive theta cycles. What was observed is that the cell tends to fire with an earlier and earlier phase on successive theta cycles (Fig. 2B). This phenomenon is termed "phase precession." The importance of phase-coded information was confirmed in a subsequent study that quantitatively reconstructed the animal's position from the firing of an ensemble of 38 simultaneously recorded pyramidal cells (Jensen and Lisman, 2000). By comparing the reconstructed position to the actual position, it was possible to rigorously test whether a phase carries useful information. The results show dramatic improvement in reconstruction accuracy (Fig. 2D) when phase is taken into account. Indeed, using this decoding strategy, it was possible to predict the animal's position to within a few centimeters.

The available evidence suggests that theta phase coding is probably a *discrete* phase code in which firing only occurs in about seven discrete phases during a theta cycle. This evidence comes from intracellular and field recording studies in both anesthetized and awake behaving animals, showing that in addition to theta, there is a simultaneous second oscillation at gamma frequency ($\sim$40 Hz). Recordings show that inhibitory neurons fire at gamma frequency (Fig. 2E), and that pyramidal cells receive this gamma frequency inhibition (Buzsaki, 1997). Spiking occurs out of phase with this inhibition (Bragin et al., 1995), dividing the theta period into discrete phases of firing. For this reason, the coding scheme in the hippocampus is best described as *theta-gamma phase coding*.

The Phase Precession as Sequence Recall Organized by Theta/Gamma Oscillations

We now turn to an explanation of how the phase advance can be understood in terms of sequence recall. This explanation was developed by Tsodyks et al. (1996) and by Jensen and Lisman (1996a), who provided a quantitative explanation of the magnitude of the phase advance. Figure 2C illustrates how the phase advance can be understood quantitatively in terms of cued sequence recall (Jensen and Lisman, 1996a). It is assumed that during encoding, the distance between successively encoded positions is simply the distance the animal travels during a theta cycle when running at average velocity. During recall, the current sensory input provides a recall cue at the beginning of each theta cycle (i.e., in the first gamma cycle) and excites the cells that represent the current position. Because previous learning has led to a strengthening of selective connections to cells representing the next position along this known path, the cued firing of cells corresponding to current position will lead to the firing of cells encoding the next position (in the next gamma cycle). These cells, in turn, will fire cells encoding the next position. In this way, within one theta cycle, one gets the serial readout of the next six expected upcoming positions along the track. The phase precession occurs simply because on each successive theta cycle, the sensory cue moves as a result of the movement the animal made during the previous theta cycle. Figure 2C shows how the theta-gamma model leads to the quantitative prediction that the average magnitude of the phase advance will be one gamma cycle per theta cycle, and that the total number of theta cycles during which a place cell fires will therefore be about seven. Figure 2F shows that this is a reasonable approximation of what happens. It is thus possible to account, at least approximately, for the magnitude of the phase precession in terms of the properties of theta/gamma coding.

The idea that phase precession is cued by sensory input has been directly tested in two ways. If the phase-advance is cued sequence recall, the rate of phase advance should depend on how fast the animal is running though the environment and thus arriving at new cues. Consistent with this, Skaggs et al. (1996) found that the rate of phase advance was directly dependent on the velocity of the rat. Stated differently, the cell stops firing when it reaches the last position within its field, irrespective of velocity; the only thing that velocity controls is how long it will take the rat to reach that position. Recently, Buzsaki's laboratory made a further strong test of the role of spatial cueing. They recorded place-cell activity while the animal was in a running wheel (Hirase et al., 1999). In this situation, running does not lead to any change in spatial cue. Thus if the phase advance depends on progressive cueing, it should not occur in the running wheel, and this is what was found.

HOW CAN THE HIPPOCAMPUS *LEARN* SEQUENCES: THE ROLE OF NMDA-DEPENDENT SYNAPTIC PLASTICITY AND A MULTIITEM BUFFER

It is now well-established that the excitatory synapses in the hippocampus undergo activity-dependent synaptic modification. Plasticity at most synapses depends on processes triggered by activation of the NMDA channel. A key question is whether this form of synaptic modification can be used to explain how the hippocampus learns realistic event sequences. When what is to be learned is continuous information, such as the positions along a path, this

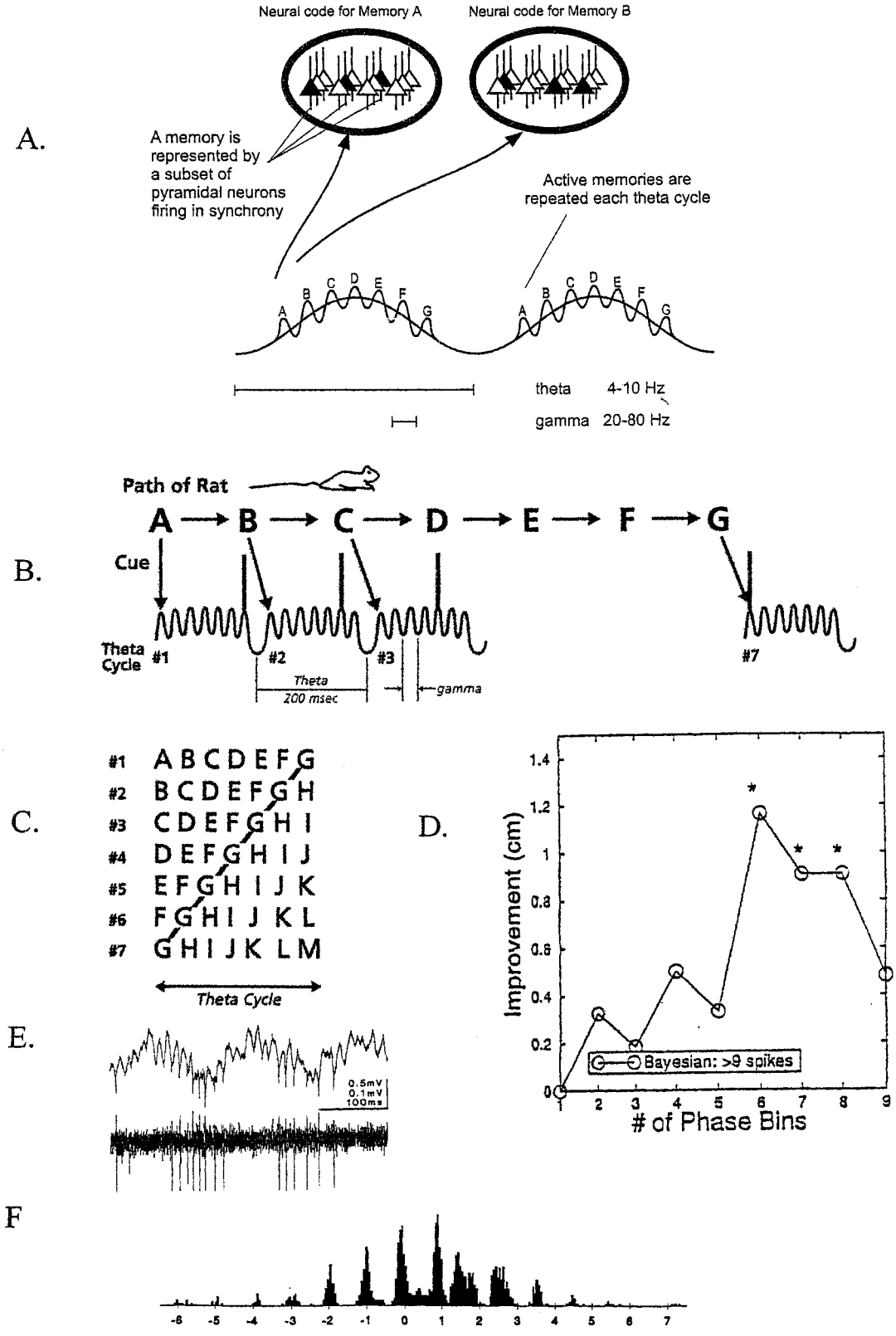

A.
Neural code for Memory A
Neural code for Memory B
A memory is represented by a subset of pyramidal neurons firing in synchrony
Active memories are repeated each theta cycle
A B C D E F G
theta 4-10 Hz
gamma 20-80 Hz
B.
Path of Rat
A → B → C → D → E → F → G
Cue
Theta Cycle #1
#2
#3
#7
Theta 200 msec
gamma
C.
#1 A B C D E F G
#2 B C D E F G H
#3 C D E F G H I
#4 D E F G H I J
#5 E F G H I J K
#6 F G H I J K L
#7 G H I J K L M
Theta Cycle
D.
Improvement (cm)
Bayesian: >9 spikes
# of Phase Bins
E.
0.5mV
0.1mV
100ms
F
-6 -5 -4 -3 -2 -1 0 1 2 3 4 5 6 7

FIGURE 2

mechanism alone may be sufficient to account for sequence learning (Blum and Abbott, 1996). However, for many realistic sequences in which the interval between items is more than a few hundred milliseconds, the intervals are too long to fall into the window of long-term potentiation (LTP; see below). However, if sequential items are simultaneously held active in a multi-item buffer, we will show that NMDA-dependent LTP can lead to successful encoding of sequences. We first review the evidence that the hippocampus does in fact operate as a buffer. Then we describe how such a buffer makes possible the learning of realistic sequences.

Evidence for a Buffer in the Theta-Learning State

The criteria for demonstrating a working memory "buffer" have been established in work on the prefrontal cortex. First, after a brief presentation of a stimulus, the evoked activity will persist for many seconds after the stimulus is removed. Second, the firing of any given neuron depends on which stimulus is presented (Goldman-Rakic, 1995; Constantinidis et al., 2001). We found at least four reports indicating that the first criterion is met in the hippocampus: a novel sensory stimulus evokes neural activity that persists after the stimulus is removed (Fig. 3). Somewhat surprisingly, these reports have come from studies of humans, primates, and rabbits, but not from rats. Whether the second criterion is met is less certain. It has generally been found that only a small fraction of the recorded cells show persistent activity that is sensory-specific. One of the most extensive studies of sensory responses comes from the work on rabbits by Vinogradova (1984). She reports that although sensory-specific responses are common in the entorhinal cortex and present in ~40% of CA1 neurons, they are nearly absent in the dentate gyrus and CA3. Some explanation is required for why sensory-specific responses are so infrequently found in these regions.

One possible explanation of the difficulty in detecting stimulus specificity follows from the idea that the hippocampus may be a multi-item buffer that stores sequences of items, each at a different phase of theta (see below for details). The information encoded during an experimental trial may therefore represent much more than just the stimulus presentation. For instance, before stimulus presentation there may be movements of the experimenter, sound emanating from the equipment, or explicit warning signals. All these form a relevant sequence that the animal no doubt learns and which a buffer dedicated to sequence learning must handle. Because what is being held in the buffer is much more extensive than just the nature of the sensory stimulus, the overall firing, as would be determined by analysis based on rate coding, would not generally detect strongly tuned, stimulus-specific firing. This perspective suggests that stimulus specificity in the dentate gyrus and CA3 circuit might be more readily detected if data analysis was based on phase coding rather than simple rate coding.

To perpetuate firing, special cellular or network processes are required. It is possible that what perpetuates firing (Fig. 3) arises from such processes in the hippocampus itself. Alternatively, persistent activity in the hippocampus may arise from inputs which are themselves buffered. Interestingly, the existence of buffered information is much stronger in the input regions of the hippocampus than in the hippocampus itself. Recordings from rats and monkeys show robust persistent activity throughout the delay period in working memory tasks (Young et al., 1997; Hampson et al., 2000; Suzuki and Eichenbaum, 2000). One interesting possibility is that the activity stored in this multi-item buffer is only *transiently* gated into the hippocampus (for a few seconds). This might be sufficient to allow storage of the buffered sequence information by the LTP process. One advantage of such transient utilization of the learning state of the hippocampus is that it would maximize the availability of the recall state, a state that is desirable to keep on line in order to make predictions based on recently acquired information. If input to the hippocampus is only transiently gated, persistent activity during a working memory task should be seen throughout the trial in the entorhinal cortex (or subiculum), but only for the initial part of the trial in the hippocampus.

Although it is clear that the entorhinal cortex can act as a buffer, there have so far been no specific tests of whether it is a multi-item buffer. However, the available information indicates that all the biophysical mechanisms thought (Lisman and Idiart, 1995) to be required for a multi-item working memory buffer (theta oscillations, gamma oscillations, excitatory recurrent collaterals, and intrinsic conductances that produce activity-dependent positive-going afterpotentials) appear to be present in layer 2 cells of the entorhinal cortex that provide the input to the hippocampus (Dickson et al., 2000; Hasselmo et al., 2000). The hypothesis that the entorhinal cortex is a multi-item buffer is therefore promising and should be pursued further. Taking all this information to-

FIGURE 2. Theory and experiment regarding theta/gamma phase coding in the hippocampus. A: Concept of theta/gamma phase coding. Slower theta cycles are divided into discrete segments by gamma oscillations, as observed in field potentials. A subset of cells fires during the excitable phase of the gamma cycle, and these cells encode a given memory. Different subsets of cells fire in other gamma cycles, leading to encoding of multiple items. All memories repeat on the next theta cycle. B: Phase precession. Locations A–G are all within the place field of a given place cell. As the rat enters the place field, the place cell fires, but at a late phase within the theta cycle. On each successive theta cycle, firing occurs with an earlier phase, until the other end of the place field is reached. C: Model of phase advance, based on rat running at average velocity. The concept is that cue is the current position and that the hippocampus uses stored information about this well-known path to predict the next six positions (B–G) along the path. On the next theta cycle, the spatial cue is now B, so the predicted positions are C–H. It can be seen that such a cueing process leads this cell, which represents position G, to fire with an earlier and earlier phase until firing ceases after seven theta cycles. D: Evidence for phase coding, derived from the use of ensemble data to predict the animal's position. This can be compared to the actual position and the error determined. The graph shows that when analysis is redone, taking increasing number of phase divisions into account, there is improvement in the ability to predict the animal's position, at least up to six phase divisions. Modified from Jensen and Lisman (2000). E: Recording from the hilus of the rat, illustrating theta and gamma in the field potential and the spiking of an interneuron (below) phase locked to gamma. Modified from Bragin et al. (1995). F: The model in C predicts the phase magnitude of the phase advance as one gamma cycle per theta cycle. It follows that the cell should fire on about seven successive theta cycles. The record, which is taken from a place cell in CA1, shows that this is approximately the case. Modified from Skaggs et al. (1996).

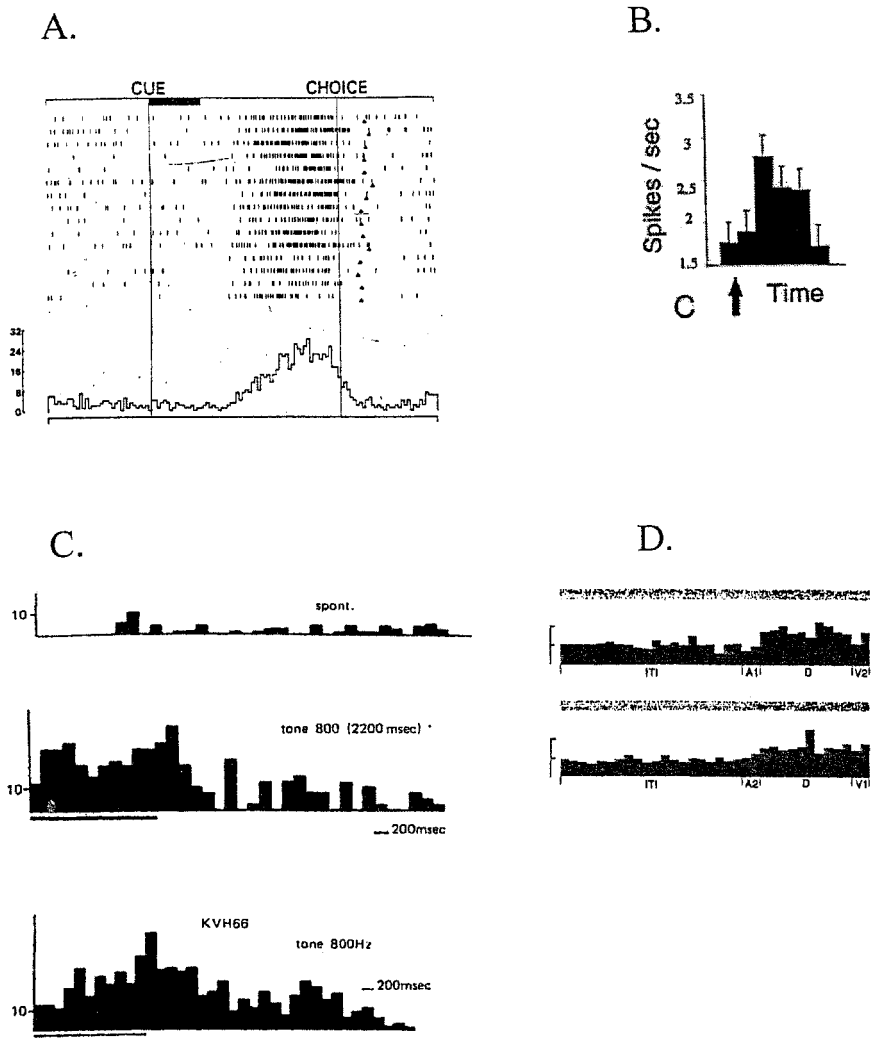


FIGURE 3. Published evidence for hippocampal "buffer" activity. A buffer is defined by persistent firing activated by brief sensory input. A: Single-unit activity in the hippocampus during a delayed response task. Animals were given a 1-s cue and then made a memory-based response several seconds later. Spikes during individual trials are shown; at bottom, average histogram of rate. Adapted from Watanabe and Niki (1985). B: Recording from human hippocampal cell during encoding of faces. Image of face is presented for 1 s at arrow. Adapted from Fried et al. (1997). C: Recording from CA3 cell of a rabbit during and after tone presentation (bar). Adapted from Vinogradova (1984). D: Recording from hippocampal cell during and after presentation of 1-s tones (A1, A2). Rate calibration ticks are 10 and 20 spikes/s. Adapted from Colombo and Gross (1994). spont., spontaneous; ITI, intertrial interval; A, auditory stimulus; V, visual stimulus; D, delay period.

gether, our tentative conclusion is that the hippocampus is likely to receive information from a multi-item buffer, at least for several seconds. We therefore take the next step and analyze how NMDA-dependent plasticity could lead to the storage of realistic sequences organized by a multi-item buffer.

A Model for the Learning of Sequences Based on NMDA-Dependent Synaptic Plasticity and a Theta/Gamma Buffer

Figure 4 shows how information is incorporated into a multi-item buffer as a sequence of items is presented over the course of several seconds. After each item is presented, groups of cells encoding that item fire at a particular phase of theta. Successive items fire at a different phase. The firing of all items held in the buffer repeats each theta cycle. The biophysical principles that could underlie such a buffer were previously described (Lisman and Idiart, 1995; Jensen et al., 1996; Jensen and Lisman, 1996b, 1998). We can now consider what would happen in the recurrent synapses of this network if the synapses used standard NMDA-dependent LTP as the basis for synaptic modification (Jensen and Lisman, 1996c). Three properties of NMDA-dependent LTP are relevant. First, LTP is Hebbian in the sense that a synapse will be strengthened only if there is both presynaptic firing and substantial postsynaptic depolarization sufficient to open the NMDA channel. Second, the pre- and postsynaptic activity need not be exactly coincident; postsynaptic activity can occur with a delay, the duration of which is the time-constant of decay of the NMDA conductance (100–200

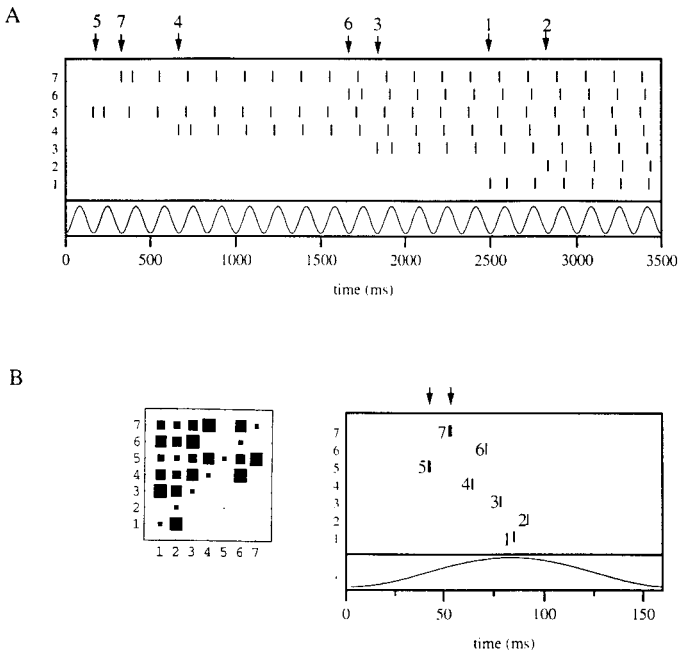


FIGURE 4. Learning of sequences by a buffer that uses NMDA-dependent plasticity. A: Encoding of sequence during presentation of letters at realistic interitem spacing (seconds). Note that after each item is presented, cells that encode it fire at a given phase on each successive theta cycle. Cells encoding different items will fire with a temporal separation of one or several gamma cycles, a time that is within the window of NMDA-dependent LTP. Thus synaptic modification will occur at recurrent synapses that connect cells that encode different memory items. B: Recall by network. Right: After presentation of initial two items of the sequence as a cue at the beginning of the theta cycle, the network successfully recalls the subsequent items in order. Each item is active in a different gamma cycle. Left: Synaptic weight matrix. The y-axis shows the strength of the connection to cells labeled on the x-axis.

ms) (Gustafsson et al., 1987). This is called the window of LTP. Third, repetitive firing is usually required for LTP induction.

If items occur seconds apart and cause firing of cells at this temporal separation, LTP-dependent linkage between these cells could not occur because the firing is outside the window of LTP. However, in a theta/gamma buffer, such linkage can occur. This is because cells representing different items fire one or more gamma cycles apart, an interval (multiples of 25 ms) that is within the LTP window. Furthermore, the firing patterns in the buffer repeat every theta cycle, and this repetition promotes LTP. As a result, there will be strengthening of synapses between cells encoding sequential items in the sequence. However, the window of LTP is not symmetrical; thus, item A will be connected to B much more than the reverse. Furthermore, the connections will not simply be just to the next item in the sequence. As shown in the weight matrix in Figure 4B, although A connects most strongly to B, it also connects to C and D, albeit more weakly. This means that during recall, the stimulus for firing the n-th memory will not just be the n-1 memory, but also n-2 and n-3. This property is useful for the separation of two or more sequences with common element. Such a common element (let's say B) might belong to the sequence $A_1 \rightarrow B \rightarrow C_1 \rightarrow D_1$ but also to another sequence ($A_2 \rightarrow B \rightarrow C_2 \rightarrow D_2$). If the only links were between neighboring items, there would be no way to determine whether C_1 or C_2 should fire. However, if the sequence initiates with A_1, its input to C_1 but not C_2 could keep the sequence along the correct path. We will return to this issue when we consider the consequences of NMDA hypofunction implicated in schizophrenia.

To test this form of sequence encoding, the simulated network was tested for its ability to recall a learned sequence. Figure 4 shows the successful recall of the entire sequence after probing the network with the first two items. When these simulations were performed (Jensen and Lisman, 1996a), we did not yet realize the advantages of performing recall through the reciprocal interactions of the dentate and CA3, as described earlier in this paper. These simulations were done on a single network that was not subject to a concatenation of errors, because the noise was made sufficiently low to avoid them. Efforts to simulate a full model of recall using dual networks are currently underway. The major conclusion we derive from our investigations is that simple properties of NMDA-mediated synaptic plasticity, when combined with the idea of a multi-item theta/gamma buffer, can produce the encoding of realistic memory sequences.

THE ARGUMENT FOR TWO THETA STATES: ONE FOR LEARNING AND ONE FOR RECALL

Above, we argued that phase advance is a reflection of a cued sequence recall, a process organized by theta/gamma oscillations. Then we argued that realistic sequences could be learned by NMDA-mediated synaptic plasticity, provided the information was held in a multi-item theta/gamma buffer. Implicit in this formulation is the idea that theta oscillations occur during both learning and recall. Here we consider more generally whether the idea of two forms of theta, specialized for learning and recall, respectively, is a sound one.

Because a salient stimulus that captures an animal's attention can cause a transition from a nontheta state to a theta state, it has generally been thought that theta occurs during periods when novel stimuli appear and must be learned. Therefore the existence of theta during learning (Theta-L) is not controversial. But does theta also occur during recall? The answer appears to be yes, if one accepts the interpretation of phase advance as cued recall. It is important to consider the conditions under which the phase advance is observed. These are conditions when the animal is running along a well-known track. These are times when nothing new and unexpected is happening. If something unexpected were to happen, the rat would stop moving. The situation is even clearer when the animal is in a running wheel. Surely this is not a case where the animal is learning. It would thus appear that theta can occur under conditions when the animal has no need to learn and when, as judged by the phase precession, it is doing recall (see above). Such continuous recall makes sense: the rat is constantly predicting the near future, i.e., the upcoming position based on its knowledge of

the spatial sequence. Such predictions are of value, since if sensory reality does not meet learned expectations, something must be novel. Such novelty is important to detect, because an unpredictable environment requires both greater caution and a reconfiguration of the hippocampus in a way that is suited to learning. These experimental and theoretical considerations argue that there is indeed a theta state that does not involve learning, but does involve recall. We call this the Theta-R state.

Some previous pharmacological work suggested that there might be two forms of theta. Because of the large cholinergic projection to the hippocampus from the medial septal nucleus, it was suspected that theta generation in the hippocampus depends critically on cholinergic input. However, cholinergic (muscarinic) antagonists do not block the theta activity that occurs during running (Lawson and Bland, 1993). In contrast, the theta that occurs during alert immobility, a condition where the animal may be responding to novel stimuli, is blocked by cholinergic antagonists. This leads to the proposal that Theta-L requires cholinergic modulation, whereas Theta-R does not.

The idea that the Theta-L state depends on cholinergic modulation fits with a great deal of evidence on the role of cholinergic modulation in learning. First, behavioral pharmacology shows that learning, but not recall, can be blocked by muscarinic antagonists (Ghoneim and Mewaldt, 1975; Anagnostaras et al., 1999). Second, activity-dependent stimulus remapping in the brain depends on muscarinic cholinergic modulation (Kilgard and Merzenich, 1998). Third, the network, cellular, and synaptic changes expected to occur during learning are all enhanced by cholinergic modulation. Specifically, as argued above, the learning state requires the following: A) Theta rhythm. B) The biophysical mechanisms needed to produce buffering are enabled. C) LTP occurs, presumably in its most enhanced form. D) Learning networks are configured appropriately for learning. Consistent with these predictions, it has been found that: A) Theta during nonmovement depends on cholinergic modulation (see above). B) The membrane conductance that we believe perpetuates firing in the buffer, the depolarizing afterpotential (Lisman and Idiart, 1995), is turned on by cholinergic modulation (Haj-Dahmane and Andrade, 1998, 1999). C) A greatly sensitized form of LTP is enabled by cholinergic modulation during theta (Huerta and Lisman, 1995, 1996). D) Network connectivity that makes it possible to encode new information without interference from old information is promoted by cholinergic modulation (Hasselmo and Wyble, 1997). Thus, based on all this information, it seems reasonable to suspect that the special properties of the Theta-L state depend, at least in part, on cholinergic modulation.

ROLE OF DOPAMINE AND DOPAMINE/NMDA INTERACTIONS IN SYNAPTIC FUNCTION

In order to develop a framework for understanding the different states of the hippocampus, it is necessary to understand the role of other neuromodulators. Because relatively little was known about the role of dopamine in the hippocampus, it was of interest to explore its effects. This undertaking was of added importance because of the emerging evidence that the hippocampus is a locus of abnormality in schizophrenia (Bilder et al., 1995; Deicken et al., 1995; Schroder et al., 1995; Turetsky et al., 1995; Heckers et al., 1998) and the evidence that hyperfunction of the dopaminergic system (Joyce, 1993) and hypofunction of NMDA receptors (Olney et al., 1999; Tamminga, 1999) have a role in schizophrenia.

Dopamine Increases NMDA-Dependent LTP and Inhibits Depotentiation

NMDA-dependent hippocampal synaptic plasticity is thought to underlie the mechanisms of memory. To be relevant to the particular task learned, this plastic changes must be activity-dependent and synapse-specific. Previous work implicated dopamine in the late phase of LTP (Frey et al., 1993) and in synapse-nonspecific processes (Huang and Kandel, 1995). We were interested in determining whether the early and synapse-specific forms of plasticity were affected. We found that at the Schaffer collateral (sc) inputs to CA1, activation of D1 dopamine receptors facilitated the induction of early LTP (Otmakhova and Lisman, 1996) and inhibited depotentiation of recently potentiated synapses (Otmakhova and Lisman, 1998). Other researchers confirmed these findings (Swanson-Park et al., 1999). Moreover, the CA1 region is not the only site of this action of dopamine. D1 dopamine receptors facilitate LTP and inhibit depotentiation in the dentate gyrus (Kusuki et al., 1997; Kulla and Manahan-Vaughan, 2000). These data argue that dopaminergic innervation promotes the encoding of information into hippocampal synapses and prevents the erasure of recently acquired information.

Dopamine in the Hippocampus and Learning

When dopaminergic agonists are applied *during training* they improve hippocampal-dependent memory. Spatial memory in a water-maze in aged memory-impaired rats was improved by pretrial systemic injections of the D1 agonist and impaired by injections of antagonists (Hersi et al., 1995). Similarly, D1 agonist improved spatial but not cued learning in a circular maze (Bach et al., 1999). Since dopaminergic drugs were applied systemically, these experiments do not bear on the site of action. However, work with more selective depletion of dopamine *in the hippocampus* (Gasbarri et al., 1996a,1996b) showed impairment of spatial memory in rats, confirming the importance of the intrahippocampal dopaminergic system.

In other studies, dopaminergic agonists and antagonists were injected into the hippocampus after the negative reinforcement avoidance training session (Grecksch and Matthies, 1982; Bernabeu et al., 1997). Although there are some contradictory aspects of these reports, their common finding was that dopamine agonists improve the retention of memory, while antagonists have the opposite effect. A more hippocampal-dependent task that requires spatial memory (win-shift strategy in a radial maze) was improved by post-training intrahippocampal injections of amphetamine, while a cued "win-stay" strategy was not affected by such injections

(Packard and White, 1991). Since dopaminergic drugs were injected into the hippocampus *after the training*, they could not affect the synaptic process occurring during learning. One possibility is that the drugs' action occurred during a "replay" of information needed to transfer information from one network to another (Buzsaki, 1989). The incorporation of information into the second network might involve LTP-like processes and be enhanced by the activation of dopamine receptors. Regardless of specific mechanisms, the current pharamcological data support the importance of *intrahippocampal* dopamine in memory encoding.

The Perforant Path Input to CA1: Inhibition of Synaptic Transmission by NMDA Antagonists and Dopamine

Searching for possible sites of dopamine action, we noticed that D1 and D2 dopamine receptors are enriched in the stratum lacunosum-moleculare of CA1 region (Swanson et al., 1987), the site of the direct perforant path (pp) input from the entorhinal cortex. This suggested the possibility that dopamine might selectively affect pp input in some way. To explore this possibility, the effects of dopamine on sc and pp inputs were examined under the same conditions. The field EPSP (fEPSP) of the two pathways was studied by local stimulating and recording from electrodes placed in each layer (Fig. 5A).

It was previously established that the pp input, like the sc, is glutamatergic and has both NMDA and AMPA components (Colbert and Levy, 1992), a finding we confirmed. Our first unexpected finding was that pp and sc inputs differ in the NMDA/AMPA ratio (Fig. 5). Under conditions that largely removed the Mg^{2+} block of the NMDA channels (0.1 mM Mg^{2+} and 50 μM picrotoxin in artificial cerebro-spinal fluid (ACSF), Fig. 5E,F) application of the NMDA antagonist, APV, decreased the pp fEPSP amplitude by ~40%, while reducing the sc response by only ~20%. Moreover, under control conditions (standard Mg^{2+}/Ca^{2+} ratio), APV did not affect the sc fEPSP amplitude, but reduced the pp fEPSP by ~20% (Fig. 5B–D). This indicates that in normal transmission, NMDA channels have a greater role in the pp than in the sc (Otmakhova and Lisman, 1999).

We next explored the effects of dopamine on the two pathways. We found that in control ACSF, application of dopamine strongly inhibited the response to pp stimulation, but not the response to sc stimulation. Dopamine reduced both the NMDA (by ~65%) and AMPA (~35%) components of transmission at the pp. Importantly, paired-pulse facilitation was increased, suggesting a presynaptic locus of dopamine action. However, NMDA transmission was suppressed significantly more strongly than AMPA transmission, suggesting that there might also be a postsynaptic site of action. These results indicate that the pp input to CA1 is the site of convergence of NMDA involvement in transmission and dopamine modulation. Both the NMDA hypofunction and dopamine hyperfunction implicated in schizophrenia would inhibit this pathway.

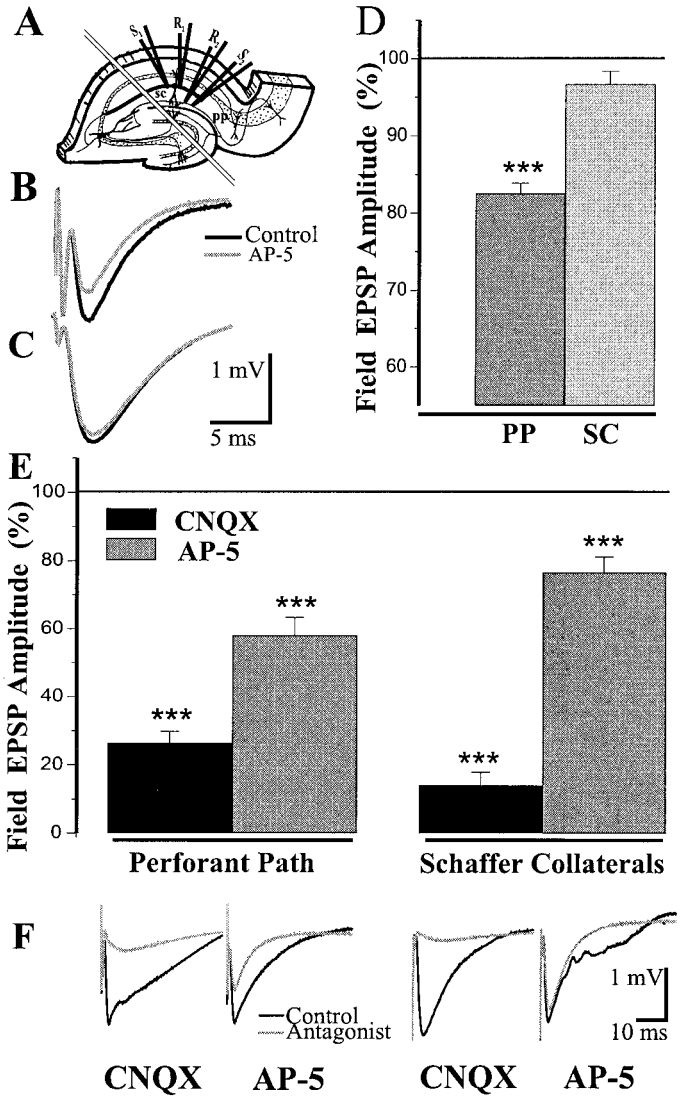
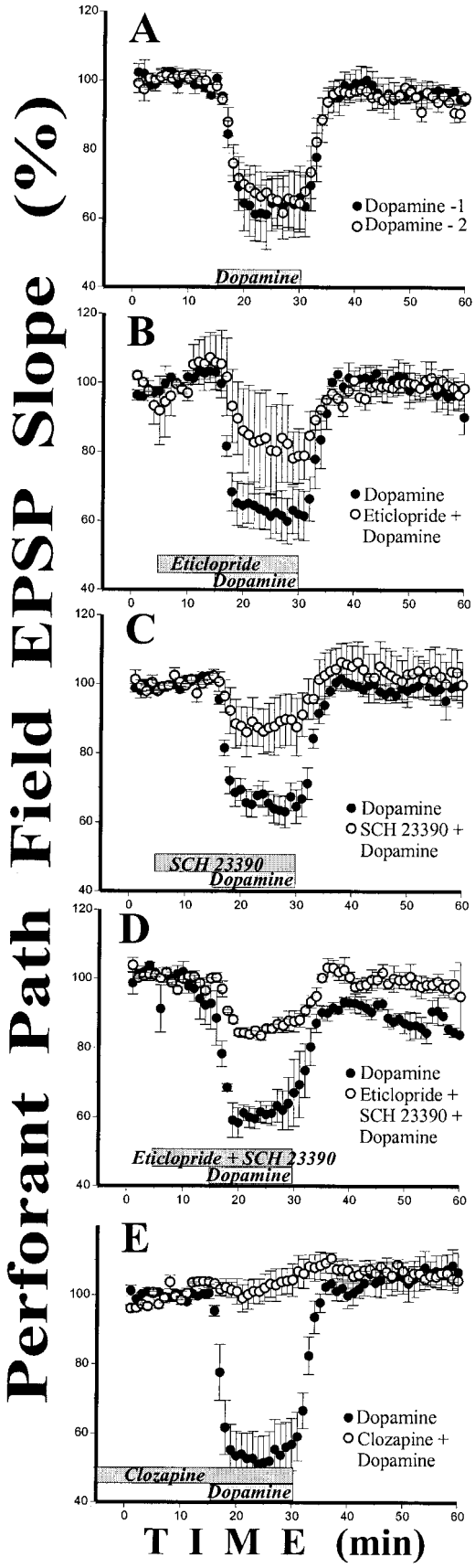


FIGURE 5. Differences in NMDA function in pp and sc inputs. A: Electrode positions for simultaneous pp and sc fEPSP recording. Parallel lines signify cut made to isolate inputs. R, recording electrode; S, stimulating electrode. B: Example of pp fEPSP in regular ACSF, and effect of NMDA-receptors blockade. C: sc fEPSP in regular ACSF shows no substantial effect of NMDA antagonist. D: Averaged data on effect of NMDA antagonist ± APV (100 μM) on pp and sc fEPSP amplitude in regular ACSF. E: Averaged data on effect of NMDA and AMPA antagonists on pp and sc fEPSP amplitude in low Mg^{2+}, picrotoxin, and tetrodotoxin containing ACSF. Horizontal lines (100%) represent fEPSP amplitude before drug application. Data in columns were taken at 10 min after start of application. Significance (in D and E) in paired *t*-test: no asterisk, $P < 0.1$; $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$. F: Field EPSP traces from individual experiments with NMDA and AMPA antagonist applications in low Mg^{2+}, picrotoxin, and tetrodotoxin containing ACSF. Pathway labels below E also refer to F.

The Unique Efficacy of the Atypical Antipsychotic, Clozapine

Analysis of the receptor mechanisms of dopamine action led us to results that may be relevant to the therapeutic potency of the atypical neuroleptic, clozapine. We tried to block dopamine-in-



duced suppression of the pp fEPSP with D1 and D2 receptors' antagonists (Fig. 6). The antagonists of D2 receptors, including the traditional neuroleptic, haloperidol, reduced dopamine-induced suppression of the pp by 30–35% (Fig. 6B). The D1 receptor antagonist SCH 23390 had a stronger effect, inhibiting ~60% of dopamine action (Fig. 6C). However, even the combination of D1 and D2 antagonists did not completely block the dopamine effect (Fig. 6D). This suggests that in the pp area, a small part of dopamine action may be mediated by nondopamine receptors, and there are precedents of such cross-action (Malenka and Nicoll, 1986; Aguayo and Grossie, 1994). Histological data show that the stratum lacunosum-moleculare also contains adrenergic and serotonergic receptors (Swanson et al., 1987) that might be activated by dopamine. Therefore, a less selective antagonist with much broader actions might be more effective at opposing dopamine action in the pp. We decided to try the atypical neuroleptic clozapine, which is known to bind D1 and D2 dopamine, 5-HT_{2B}, 5-HT_6, and 5-HT_7 serotonin, α-adrenergic, muscarinic, and NMDA receptors (Baldessarini et al., 1992; Meltzer, 1995; Arvanov et al., 1997; Thomas et al., 1998; Duncan et al., 1999; Frederick and Meador-Woodruff, 1999; Richelson and Souder, 2000). Remarkably, clozapine completely blocked the DA-induced suppression of the pp fEPSP (Fig. 6E). We later found that noradrenaline and serotonin also suppressed the pp fEPSP, and clozapine partially inhibits serotonin (~20–25%) and noradrenaline (30–35%) action (Otmakhova and Lisman, 2000). This broad range of receptor action might explain the effectiveness of clozapine in treatment of schizophrenia.

UNDERSTANDING THE FUNCTIONAL ROLE OF DOPAMINE IS NECESSARY TO UNDERSTANDING HOW DOPAMINERGIC HYPOFUNCTION IN THE HIPPOCAMPUS COULD LEAD TO SYMPTOMS OF SCHIZOPHRENIA

Here we report on our attempts to understand the functional role of the dopaminergic input to CA1. To accomplish this, one needs a large-scale model of how relevant networks are interacting. The problem can be broken down into several specific questions,

FIGURE 6. Only clozapine completely blocks dopamine-induced suppression of pp fEPSP. A: Repetitive dopamine applications have similar effect on pp fEPSP slope ($F = 0.36$, $P > 0.5$). B: D2 antagonist (−) eticlopride (5 μM) inhibits dopamine effect on pp fEPSP slope by ~35% ($F = 5.87$, $P < 0.03$). Haloperidol and D4 antagonist U-101958 had the same effect ($F = 7.8$, $P < 0.01$, and $F = 5.02$, $P < 0.04$, respectively; not shown). C: D1 antagonist (+) SCH 23390 (5 μM) inhibits dopamine-induced suppression of pp fEPSP by ~60% ($F = 29.8$, $P < 0.001$). D: There is no full inhibition of dopamine effect on pp, even by a mixture of D1 and D2 antagonists (5 μM of each). E: Clozapine (20 μM) completely blocks dopamine-induced suppression of fEPSP slope in the pp. Time of drug applications is marked by shaded rectangles with name of drug.

which we analyze below: Under what conditions does dopamine release occur? How would this release affect the functions of CA1? Is it possible that dopaminergic cells both influence the hippocampus and themselves are influenced by hippocampal-dependent processes? What effects might the tonic release of dopamine thought to occur in schizophrenia have on this circuitry?

Properties of VTA Cells That Supply Dopaminergic Input to the Hippocampus and Other Structures

Dopamine is supplied to the hippocampus by all midbrain dopaminergic nuclei (Gasbarri et al., 1994a,1994b, 1996, 1997), but for simplicity this review will deal only with the ventral tegmental area (VTA), which was designated the A10 cell group. The VTA has long been thought to be involved with positive reinforcement on the basis of self-stimulation, reward, and drug addiction studies (Cooper, 1991; Shankaranarayana Rao et al., 1998). The laboratory of Schultz recorded from VTA dopaminergic neurons in behaving animals. These cells have a tonic activity, but can respond with short-latency (50–110 ms), short-duration (~200 ms) bursts to several types of stimuli. These include unpredictable (unconditioned) positive rewards, novel or salient stimuli, and conditioned stimuli that reliably predict positive rewards (Mirenowicz and Schultz, 1994, 1996; Schultz and Dickinson, 2000).

Other targets of the VTA are affected by dopamine release, and studies of these targets have given some insight into the role of dopamine. For instance, in the medial prefrontal cortex, a structure important for attention, dopamine can inhibit the entry of information, including entry from the hippocampus (Jay et al., 1995; Thierry et al., 2000). Dopamine also inhibits the inputs to the nucleus accumbens, including those from the prefrontal cortex (Carr et al., 1999) and the hippocampus (DeFrance et al., 1985). A short dopamine pulse from the VTA therefore would cause a decrease of excitatory drive of accumbal inhibitory neurons. Since accumbal cells are mostly inhibitory, accumbal targets would be disinhibited. It is thought that as a result, locomotor mechanisms normally inhibited by the nucleus accumbens become activated (Mogenson and Yang, 1991), possibly allowing the animal to approach (or consume, or investigate) or run away from the stimulus source.

Although the dopamine system has been most strongly implicated in reward behavior, there is ongoing debate about whether the term "reward" is the best description of the function of this neuromodulatory system. It was argued recently that the conditions that cause dopamine neurons to burst could be better described as indicating that the sensory input is sufficiently novel or important to warrant a *change* in the animal's behavior, e.g., locomotion or shifting of attention (Redgrave et al., 1999; Spanagel and Weiss, 1999; Schultz and Dickinson, 2000). Schulz et al. (1993a) stated, "None of the dopamine neurons showed sustained activity in the delay between the instruction and trigger stimuli that would resemble the activity of neurons in dopamine terminal areas, such as the striatum and frontal cortex. Thus, dopamine neurons respond phasically to alerting external stimuli with behavioral significance whose detection is crucial for learning and performing delayed response tasks. The lack of sustained activity suggests that dopamine neurons do not encode representational processes, such as working memory, expectation of external stimuli or reward, or preparation of movement. Rather, dopamine neurons are involved with transient changes of impulse activity in basic attentional and motivational processes underlying learning and cognitive behavior." These are precisely the conditions under which new learning would be expected, so sending the dopaminergic signal to the hippocampus to promote learning makes sense from this perspective.

Other Possible Functions of CA1: Switching an Input Source

We turn now to further considerations regarding the function of CA1. This will serve as a basis for interpreting the functional role of the dopamine effects that we have observed. Recordings from CA1 in awake rabbits demonstrated specific sensory responses in this area. Importantly, these appear to have the pp as their source rather than CA3 (Vinogradova, 1984; McNaughton et al., 1989). This conclusion is based on studies showing that cells in the entorhinal cortex (the source of the direct CA1 inputs) generate responses specific to particular stimuli and modalities (Vinogradova, 1984). It could be that these sensory responses are conducted to CA1 through the dentate and CA3, but this does not appear likely, since sensory specificity is rarely observed in CA3 and the dentate gyrus. This points to the importance of the pp input as a continuous source of sensory-specific input to CA1. Consistent with this, it was recently shown, using 2-deoxyglucose methods, that the direct pp input to the CA1 region is the only hippocampal input persistently active (has a very high level of glucose utilization) during working memory and other learned behavioral tasks in monkeys (Sybirska et al., 2000).

Based on our results (Fig. 6), a short pulse of dopamine would temporarily inhibit the pp input, removing CA1 from its most direct source of sensory information and switching its attention to CA3. At the same time, D1 dopamine receptors might facilitate LTP and inhibit depotentiation in the sc input to CA1 (Frey et al., 1993; Huang and Kandel, 1995; Otmakhova and Lisman, 1996, 1998; Swanson-Park et al., 1999). This pattern would make sense from the following perspective: dopamine is released after novel, salient, or reinforcement-relevant stimuli (see above). These are the conditions under which new learning should occur. As we argued before, during learning, the dentate and CA3 may act as a buffer capable of keeping briefly presented information in an active form, as required for LTP induction. This maintained activity may be passed on to CA1, where it should also cause synaptic modification. From this perspective, dopaminergic reduction of the pp input to CA1 may *protect the buffered information from disruption by continuing sensory inputs*. At the same time, working through D1 receptors, dopamine could enhance plasticity at the CA3 inputs to CA1. Thus, a reasonable working hypothesis would be that the brief burst of VTA firing that occurs when novel information arrives promotes the learning of this information by enhancing hippocampal plasticity and by providing protection of this buffered information from disruption by subsequent sensory inputs.

This learning state would be quite transient, since the effect of the dopamine pulse would be expected to disappear rapidly. One or two seconds would probably be sufficient to ensure synaptic encoding. As we argued before, this transient state would also involve activation of Theta-L, probably as a result of input from the septal cholinergic neurons. The astute reader will notice that we are suggesting a role for both acetylcholine and dopamine in learning, but there may be interesting differences. One possibility is that acetylcholine has a required role in the operation of the buffer in the entorhinal cortex, and that acetylcholine action is sustained as long as information is held in working memory. In contrast, dopamine's action would be to transiently gate the flow of this information into the hippocampus. In this case, both neuromodulators would promote learning, but in different ways.

If there is a transient learning state triggered by the arrival of novel information, one has to ask the further question of how novelty is detected. Novelty signals occur in the VTA, but how does the VTA get the information required to determine that an input is novel? This requires access to memory and brings us back to considering the hippocampus as a storage site for memory that may therefore be involved in the detection of novelty. We explore this idea below.

Another Possible Function of CA1: Novelty Detection

The idea of novelty detection relates to the long-standing proposal that the brain forms a model of the world based on past events (Sokolov, 1963). Novelty detection necessarily involves reference to a memory source, and it is thus logical to consider the memories stored in the hippocampus as such a source. If the activity of downstream regions depends on some kind of novelty detection signal from the hippocampus, then the effect of removing the hippocampus as a source of this signal can be studied. In principle, the comparator could put out a signal meaning match, mismatch, or both. If the signal generated by the hippocampus were a "match" signal, removal of the hippocampus would lead the downstream structures to consider all incoming signals as new (mismatched). Some evidence for this in animal experiments is cited by Vinogradova (this issue). In human studies, however, hippocampal damage appears to reduce electrophysiological measures of novelty (Halgren et al., 1980; Knight, 1996). Knight (1996) recorded the P300 from the cortical surface. This potential, which occurs with a 300-ms delay after an auditory stimulus, is much larger when the stimulus is novel than if it is common. In patients with lesions in either the right or left hippocampus, the P300 evoked by a novel stimulus is greatly reduced. Similarly, in normal controls there is a large galvanic skin response to novel signals that habituates in about 20 trials. This galvanic skin response is greatly reduced in patients with hippocampal damage. Taken together, these results suggest that the hippocampus produces a novelty (mismatch) signal that can then habituate, and that in the absence of the hippocampus, the novelty signal is absent (Mathalon et al., 2000).

Novelty detection requires a comparator that checks whether sensory "reality" is compatible with expectations based on memory. Although there is evidence for novelty detection in the hippocampus, there is not yet any clear experiment showing where exactly the critical computation occurs. Various regions have been proposed, including CA3 (Vinogradova, 1984), CA1 (Lynch and Granger, 1992; Hasselmo and Schnell, 1994; Blum and Abbott, 1996; Levy, 1996; Lisman, 1999), the subiculum (Naber et al., 2000), and the entorhinal cortex (Lorincz and Buzsaki, 2000). We believe that CA1 is in a good position to compare sensory information arriving directly from the entorhinal cortex to predictions of reality made by the dentate/CA3, and so might act as a comparator.

VTA-Hippocampal Loop for Detection of Novelty and the Incorporation of Novel Information

Since VTA cells respond to novelty, one must consider the possibility that the VTA novelty responses are themselves dependent on hippocampal processing. The latencies of the response to a novel stimulus in the VTA and hippocampus are comparable (50–200-ms range) (Vinogradova, 1984; Schultz et al., 1993). Though there is no direct connection from the hippocampus to the VTA, most hippocampal targets send efferents to the VTA. For instance, the medial prefrontal cortex sends excitatory stimuli to the VTA (Phillipson, 1979; Murase et al., 1993; Carr and Sesack, 2000; Chiba et al., 2001). Other possible routes would be through the nucleus accumbens (Packard and White, 1991; Berendse et al., 1992; Kalivas et al., 1993), lateral septal nucleus (Staiger and Nurnberger, 1991), and amygdala (Phillipson, 1979; Price and Amaral, 1981; Kelley et al., 1982). This gives a wealth of possibilities of hippocampal control over VTA cells. One specific path is suggested by Schmajuk (this issue).

Taking all this information into consideration, we suggest the following model. As the animal is acting in a known environment, it is generating Theta-R and using stored sequences in the denate/CA3 system to make predictions. The CA1 region is receiving these predictions through the sc and comparing them to the actual sensory data arriving from the pp. This state continues until there is a mismatch, indicating the arrival of unexpected information. The occurrence of this mismatch is signaled (through intermediaries) to the VTA. The firing of the VTA then signals novelty, and inputs the hippocampus into the Theta-L state. We still have a very limited view of dopaminergic effects in the hippocampus, but the two effects we know about make sense in this context: plasticity in CA1 is enhanced, as one would expect in a learning state, and the pp input is cut off to ensure that the process of incorporation of sensory information in synaptic modifications is not disrupted by subsequent sensory inputs. The briefness of normal release of dopamine should be emphasized here again: shortly after the burst of dopaminergic cells, the hippocampus can return to the recall state.

A Large-Scale Model That Makes It Possible to Understand How NMDA Hypofunction or Dopamine Hyperfunction in Schizophrenia Might Produce Some Symptoms of the Disease

The model we have developed above is clearly speculative, but does provide a reasonable interpretation of the known dopaminer-

gic effects in the hippocampus, and is consistent with the general functions of the hippocampus, as outlined in the SOCRATIC model. With this as a framework, we can try to address how hippocampal synaptic malfunction in schizophrenia might lead to some of the observed symptoms of the disease. We assume as a starting point that in the disease state, tonic dopamine levels are increased and/or that NMDA channels are somehow attenuated, as postulated in two of the leading hypotheses of schizophrenia (Joyce, 1993; Olney et al., 1999; Tamminga, 1999).

Both NMDA hypofunction and dopamine hyperfunction would produce selective inhibition of the specific sensory input via the pp to CA1. This would inhibit novelty detection processes and push the system towards the normally transient state appropriate for learning. Synaptic plasticity would be enhanced. The tonic inhibition of sensory input to CA1 would focus this region towards the dentate/CA3, where old memory states irrelevant to current sensory status are represented. Inability to check internal predictions against sensory reality might allow for the buildup of false ideas. This would be exacerbated by the persistence of the learning state. The resulting strengthening of aberrant, internally focused memories might contribute to the dissociation of mental processes from changing social context and lead to delusions and hallucinations. Hallucinations are observed with sensory and social deprivation, even in healthy individuals (Hayashi et al., 1992; Teunisse et al., 1996), and strongly increase with seclusion in schizophrenic patients (Kennedy et al., 1994).

It is also noteworthy that our network modeling of sequence recall provides some rather specific ideas about why NMDA hypofunction could lead to "loose associations," a prominent symptom of the disease. The problem of loose associations becomes acute when two memories have a common element and when this causes an inappropriate jump from one memory to the other. As we discussed earlier, the correct recall of memories with a common element requires excitatory input from memory n-2 to memory n. In our modeling work, we found that a long-lasting conductance was required during recall to make it possible for the firing of the n-2 memory to influence the firing of the n memory, 50 ms (two gamma cycles) away. Our simulations showed that the NMDA conductance, which is sufficiently long-lasting, can provide a solution to this problem. If the NMDA conductance were inhibited during recall, memories with overlapping elements could not be dealt with correctly, and the result would appear as a "loose association."

These considerations suggest why dopaminergic antagonists are effective against psychotic relapse in schizophrenia. By dampening the dopamine effect, they enhance the specific sensory input and protect the NMDA channels against dopamine-induced suppression. Atypical neuroleptics, like clozapine, could be especially effective chronically, because besides blocking dopamine-induced suppression of the pp, they might provide some protection against serotonin and noradrenaline systems' dysfunctions, also suspected in schizophrenia (Elkashef et al., 1995; Meltzer, 1995). As mentioned above, clozapine partially inhibited the suppression of the pp by serotonin and noradrenaline (Otmakhova and Lisman, 2000). Moreover, clozapine might give the additional benefit of directly enhancing the NMDA receptor function (Arvanov et al., 1997), which is important for synaptic transmission in the pp.

Although the effects we observe for clozapine are immediate, many of the therapeutic effects develop slowly. The ideas we have developed above give some insight into why this might be the case. Dopamine hyperfunction pushes the system towards a learning state and produces "loose associations" without the benefit of mismatch corrections. This leads to the buildup of aberrant memories. These memories will not suddenly disappear after clozapine restores proper pp function. Rather, though proper function it becomes possible to build up the memories that accurately relate to external states, and it may be this slow buildup that restores normalcy to the patient.

CONCLUSIONS

The task set by modern neuroscience is an astoundingly difficult one. The mechanisms by which cells use molecules to perform neuronal function are perhaps fairly well-understood, but the operation of networks and the interplay of networks that produce behavior are hardly understood at all. Some of the most fundamental questions one could ask at the systems level have not been answered. For instance, it remains uncertain whether there are separate learning and recall states of the hippocampus, though we believe the evidence is suggestive of separate states. Similarly, it is not yet possible to assign a precise role for each neuromodulatory input to the hippocampus and explain the way each reconfigures the system for different functions. But one must have optimism that these problems are answerable and that the general approach being developed will succeed. Constraints are being provided by all areas of basic neuroscience and by the study of pathological states. Competing theories need to be generated that account for these findings and experiments designed to distinguish among theories. It is in this spirit that we have put forth our ideas about normal and aberrant hippocampal function, and have attempted to bridge the gap from molecules to behavior.

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