Long-term memory disorders: measurement and modeling
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CHAPTER 10
ACETYLCHOLINE AND THE HIPPOCAMPUS

It has been suggested that hippocampal mode shifting between a storage and a retrieval state might be under the control of acetylcholine levels, as set by an autoregulatory hippocampo-septo-hippocampal loop. The present study investigates how such a mechanism might operate in a large scale connectionist model of this circuitry that takes into account the major hippocampal subdivisions, oscillatory population dynamics known to occur in this region during the performance of memory tasks, and the time scale on which acetylcholine exerts its effects in the hippocampus. The model assumes that hippocampal mode shifting is regulated by a novelty signal generated in the hippocampus. The simulations indicate that this signal originates in the dentate gyrus. When novel patterns are presented to this structure this leads to brief periods of depressed firing in the hippocampal circuitry. During these periods an inhibitory influence of the hippocampus on the septum is lifted, leading to increased firing of cholinergic neurons. The resulting increase in acetylcholine release in the hippocampus causes network dynamics that favor learning over retrieval. Resumption of activity in the hippocampus leads to the reinstatement of inhibition. Despite theta-locked rhythmic firing of acetylcholine neurons in the septum, acetylcholine efficacy in the model fluctuates smoothly on a time scale of seconds. It is, furthermore, shown that the enduring postsynaptic effects of acetylcholine in the hippocampus are compatible with the time scale on which memory processes take place. A number of predictions regarding memory function are derived from the model.

10.1 INTRODUCTION

The hippocampus has been the focus of much research effort over the last decades. It has been implicated in various functions, amongst which are episodic memory (Eichenbaum, Dudchenko, Wood, Shapiro, & Tanila, 1999; Squire, 1992) and novelty detection of the contextual or spatial aspects of an experience (Johnson & Moberg, 1980; Kitchigina, Vankov, Harley, & Sara, 1997; Knight & Nakada, 1998; Lisman & Otmakhova, 2001; Montag-Sallaz et al., 1999; Mumby et al., 2002; Xiang & Brown, 1998; Zhu et al., 1997). From existing studies it is difficult to understand how the above functions are interrelated and whether they are subserved by the same or different processes at the circuit level. Moreover, it is often unclear how different hippocampal subregions contribute to the functions of the hippocampus.
One technique that has been used extensively to study these questions is computational modeling. It has allowed researchers to explore novel views on hippocampal functioning, and to propose roles for different components of the hippocampal system. Computational modeling of memory function has, hereby, uncovered a paradox. The hippocampal circuitry appears to be important for both storage and recall of episodic information (Cabeza & Nyberg, 2000). However, the network requirements for learning and for retrieval are not compatible (Grossberg, 1976, 1987a; Hasselmo et al., 1996; Murre, 1992). Indeed, the strengthened recurrent connections, necessary to achieve pattern completion during retrieval, could erroneously 'complete' new patterns towards similar, already stored ones (Hasselmo & Schnell, 1994; Hasselmo, Schnell, & Barkai, 1995). Moreover, strong synaptic plasticity, needed to accomplish fast episodic learning, could alter representations that ought to remain stable (Grossberg, 1976, 1987a).

As a solution to this dilemma, it has been suggested that there may be two 'modes' of hippocampal functioning. During retrieval, activity should be driven predominantly by modifiable recurrent synapses, while strong input fibers that are relatively less modifiable should determine which nodes become active during learning (Hasselmo et al., 1995). In the case of for example the CA3 region of the hippocampus, this might predict that activity during processing of new information is dominated by inputs from the entorhinal cortex, whereas excitation over recurrent Schaffer collaterals prevails during retrieval. Thus, learning would occur only between neurons that reliably represent the 'on line' sensory input, while, during retrieval, degraded cues entering the system over the perforant path could lead to reinstatement of a stored representation. Clearly, learning and memory require different dynamic behavior of the circuitry and, consequently, a mechanism to set the appropriate dynamic state.

Neuromodulatory substances, in particular acetylcholine (ACh), may be involved in setting the 'mode' of hippocampal functioning (Hasselmo et al., 1996). Indeed, many behavioral experiments suggest that ACh is necessary for episodic learning, while it is unimportant in retrieval (Aigner, Walker, & Mishkin, 1991; Ghoneim & Mewaldt, 1975, 1977; Kopelman, 1986; Mewaldt & Ghoneim, 1979; Orsetti, Casamenti, & Pepeu, 1996; Peterson, 1977; Wishaw, 1989). Moreover, substances that activate muscarinic receptors exert various influences that are compatible with the above hypothesis, amongst others a selective suppression of transmission over excitatory recurrent synapses in CA3 (see later sections of this paper). Finally, a recent study showed that activation of the forebrain cholinergic pathways occurs during the acquisition of a rewarded operant response, while recall of the same behavior was not associated with the same activation of the cholinergic system (Orsetti et al., 1996). This study demonstrates differential hippocampal ACh levels during behavioral learning and retrieval, supporting a role of this transmitter in mode shifting.

It is here proposed that hippocampal levels of ACh, and possibly other neuromodulatory substances, are set in accordance with a novelty signal that is generated in the hippocampus proper. The adaptive value of such a mechanism is that information with high novelty content 'automatically' induces hippocampal dynamics that favor learning of the input. Thus the system preferentially encodes novel stimuli. On the other hand, input that is similar to already stored patterns induces a state that enhances retrieval of related information, so that the animal can generate predictions regarding the situation at hand. During this latter state little learning takes place so that existing patterns are protected from modification.

A hippocampal novelty signal could be relayed to the basal forebrain regions involved in hippocampal ACh secretion by hippocampo-septal fibers running in the fimbria (Alonso
& Kohler, 1982; Tóth & Freund, 1992). In support of this notion, fimbria stimulation (McLennan & Miller, 1974) and hippocampal sharp waves (Dragoi, Carpi, Recce, Csicsvari, & Buzsaki, 1999) were shown to inhibit neuronal activity in the medial septum. In addition, recent microdialysis studies show that during explorations of a new environment ACh levels are increased relative to baseline (Aloisi, Casamenti, Scali, Pepeu, & Carli, 1997; Ceccarelli et al., 1999; Giovannini et al., 2001), while levels decrease during consecutive explorations of the same test environment (Giovannini et al., 2001). This suggests that hippocampal Ach levels are positively correlated to the degree of environmental novelty.

Although the interaction between the hippocampus and ACh-excreting regions has been modeled previously, existing models do not address the time course of ACh modulation in the hippocampus (Hasselmo & Schnell, 1994; Hasselmo et al., 1995; Hasselmo & Wyble, 1997). In these models, hippocampal activity increases with learning of a pattern, and directly suppresses ACh. As a consequence, ACh levels made transitions from high to low on the scale of tens of milliseconds, concomitant with the fast learning dynamics in the modeled regions.

Biological evidence, however, suggests that ACh may exert a more sustained influence on hippocampal activity than these models assume. Both the depolarization of pyramidal cells (Cole & Nicoll, 1984; Hasselmo & Fehlau, 2001; Stewart & Fox, 1989a) and dampening of transmission in Schaffer collaterals (Hasselmo & Fehlau, 2001) may develop slowly, in the course of a few seconds after ACh release, and may then last for ten or more seconds. This has led some authors to conclude that, though ACh may have a role in shifts over longer intervals (for instance between learning and consolidation), its dynamics are too slow to underlie mode-shifting between encoding and retrieval, which is assumed to occur on the time scale of hundreds of milliseconds (Hasselmo & Fehlau, 2001). These authors propose that other substances may set dynamics on a scale fast enough for the system to switch between learning and retrieval mode (Hasselmo et al., 2002; Hasselmo & Fehlau, 2001).

Considering the time scale at which natural learning and retrieval take place, however, the time course of cholinergic modulation is not inappropriate for regulation of mode-shifts. For instance, judging from their exploratory responses, it takes rats many minutes to familiarize themselves with a novel environment, and at least many seconds to a few minutes to explore known objects in locations where they have not previously encountered them (Mumby et al., 2002). Moreover, in free recall experiments with human subjects, learning times of under two seconds per list-item lead to poor long-term performance (Murdock, 1974; Roberts, 1972). This is not a result of failing perceptual processing, as visual scenes can be processed at speeds of up to 8 per second (Potter, 1976).

The present study investigates the notions of novelty detection and dynamic mode shifting under influence of acetylcholine in a large-scale model of the hippocampal formation and basal forebrain, featuring the entorhinal cortex (EC), dentate gyrus (DG), CA3, CA1 and the medial septum. The model incorporates many features of this circuitry, including structural and functional properties of the subregions and connections, feedback and feedforward inhibition, and oscillatory population dynamics in the theta (4-10 Hz) and gamma (20-40 Hz) frequency range (Shimono, Brucher, Granger, Lynch, & Taketani, 2000). In addition, most of the known effects of ACh at the cellular level were modeled.

The biological detail in the model places a high level of constraint on the mechanisms underlying novelty detection and memory function, and allows differential contributions
of various network components to be distinguished. Furthermore, with the introduction of realistic onset and decay time constants for ACh effects, the model is to some extent explicit with regard to the timing of events in the circuitry.

The next section presents the model. First, the different modules -corresponding to areas of the hippocampal formation- will be discussed with their incoming and outgoing connections. Then, the implementation of oscillatory population activity and ACh effects will be described. Later sections of the paper present simulations that illustrate how the model learns and retrieves, and how it switches between these functions. Technical details have been relegated to the appendix to this chapter.

10.2 THE MODEL

Modules and connectivity

The hippocampus has been the focus of much theorizing and modeling efforts (Eichenbaum et al., 1999; Hasselmo et al., 1996; Lisman, 1999; McClelland et al., 1995; Meeter et al., 2002; Murre, In press; Nadal et al., 2000; O'Keefe & Nadel, 1978; O'Reilly & McClelland, 1994; Rolls, 1996; Squire & Alvarez, 1995; Suzuki, 2000). Out of this work, a common architecture has emerged, capturing the most prominent features of the hippocampal system. The architecture of the present model incorporates many of these features, while adding new ones.

The model was built with the Walnut/Nutshell software (NeuroMod, 2000), using spiking McGregor model neurons. These integrate-and-fire nodes were abstracted from the Hodgkin-Huxley formalism and incorporate sodium, potassium and chloride currents, implementing excitatory and inhibitory inputs, leak currents and adaptation (MacGregor & Oliver, 1974). Hebbian learning was used, with the addition of negative Hebbian learning modeling LTD. As the unit of time in our model, we chose two milliseconds per time step. Formal descriptions of the model neuron, inhibition and learning are given in the appendix.

The model consists of four layers representing subfields of the hippocampal formation: the entorhinal cortex (EC), the granule layer of the dentate gyrus (DG), CA3 and CA1. The connectivity between the model components (Figure 38) reflects the existing pathways in the hippocampus (for review see (Witter et al., 2000)). Some known connections were not included in the model -notably the ones from CA3 back to the dentate gyrus (Scharfman, 1996). Parameter settings of the model were based on neurobiological data where available. Table 10 lists several layer parameters as well as data for rat hippocampus, from which model parameters were derived. Table 11 shows the parameter values for the connections in the model, including density, organization and relative strength. Justification for these values is given below.

The EC is the main cortical input structure of the hippocampus (Witter et al., 2000). In reality, layers II and III of this structure project to different subdivisions of the hippocampus proper, but as the current model is mostly concerned with intrahippocampal processing, one single EC input layer propagates the same information to dentate gyrus, CA3 and CA1. The deep layers of the EC, which receive hippocampal output, were not implemented.
Figure 38: A drawing of all hippocampal areas and connections in the model. Gray arrows depict connections that are known, but were not modeled. Solid black connections are fanning, while open ones are point-to-point. Connections ending with a circle are strictly inhibitory.

The EC module itself receives a constant input from lower level regions, which, in interaction with both local feedback inhibition and cell adaptation, leads to gamma frequency firing (Dickson, Magistretti, Shalinski, Hammam, & Alonso, 2000; Whittington, Doheny, Traub, LeBeau, & Buhl, 2001). Input to the EC is activated by clamping a single input node connected to a random subset of EC nodes via uniform weights. Thus, the EC nodes belonging to any given pattern receive a constant input of medium strength. In line with previous findings, the EC projections to the DG and CA3 are random (projection field 40%), while the projection to CA1 is topologically organized (point-to-point; Witter et al., 2000).

The next layer in the circuit is the DG. In line with anatomical findings, this module contains a very high number of dentate granule cells that fire infrequently (see Table 10). The resulting sparseness of activation, as well as the fanning input projection from the EC, are considered a prerequisite for orthogonalization. Orthogonalization implies that patterns that are correlated in a given layer generate uncorrelated representations in the projection field. This is often conceptualized to be an important contribution of the DG to hippocampal processing (McNaughton & Morris, 1987; O'Reilly & McClelland, 1994). The DG nodes send powerful point-to-point excitation to the CA3 layer, which is not modulated by Hebbian learning and is accompanied by strong feedforward inhibition (Acsády, Kamondi, Sik, Freund, & Buzsaki, 1998; Henze, Urban, & Barrionuevo, 2000). Dentate gyrus principal cells tend to have relatively extended refractory periods, but they are capable of firing at around gamma frequency, as they do in the model (Henze et al., 2000). Mossy cells, another type of excitatory cell in the dentate, were not implemented in the model.

CA3 receives inputs from the entorhinal cortex and from the dentate gyrus, and sends strong, fanning, projections to CA1 via the Schaffer Collaterals (Witter et al., 2000). In the literature, it is suggested that CA3 may be involved in either autoassociative learning
Table 10: Values for layer parameters. For comparison, published data about similar parameters in the rat are given for the number of neurons and activity in subregions of the hippocampus.

<table>
<thead>
<tr>
<th></th>
<th>EC</th>
<th>DG</th>
<th>CA3</th>
<th>CA1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of neurons</strong></td>
<td>200,000 (A. '90)</td>
<td>1,000,000 (A. '90)</td>
<td>125,000 (A. '90)</td>
<td>316,000 (A. '90)</td>
</tr>
<tr>
<td><strong>model</strong></td>
<td>200,000 (O'R. '94)</td>
<td>850,000 (O'R. '94)</td>
<td>85,000 (O'R. '94)</td>
<td>250,000 (O'R. '94)</td>
</tr>
<tr>
<td><strong>Prop. active neurons</strong></td>
<td>rat 6.25% (O'R. '94)</td>
<td>0.39% (O'R. '94)</td>
<td>2.42% (O'R. '94)</td>
<td></td>
</tr>
<tr>
<td><strong>model</strong></td>
<td>12/80</td>
<td>10/240</td>
<td>10/60</td>
<td>12/80</td>
</tr>
</tbody>
</table>

Proportion of active neurons, maximal activity in each layer; \( \beta \), feedback inhibition parameter (see Equation 11 in appendix to this chapter). References: A.'90=(Amaral et al., 1990) (average of table 1); O'R.'94=O'Reilly and McClelland, 1994.

and pattern completion (Levy et al., 1990; Marr, 1971; McNaughton & Morris, 1987; Treves & Rolls, 1994), or heteroassociative learning and sequence recall (Lisman, 1999; O'Keefe & Recce, 1993; Skaggs, McNaughton, Wilson, & Barnes, 1996). That is, recurrent connections in CA3 lead either to the completion of incomplete patterns, or to the generation of the next member of a sequence. Both of these proposals are motivated by the existence of extensive recurrent connections among CA3 principal cells (Amaral et al., 1990; Li, Somogyi, Ylinen, & Buzsaki, 1994), but differ in the time scale on which

Table 11: Parameter values for the different connections in the network: EC-DG, connection from EC to DG; density, number of postsynaptic nodes (absolute or as percentage from the layer) targeted by any presynaptic node; initial weight strength, weight at the start of simulation; maximum weight, maximum attainable weight of any connection; \( \lambda \), learning rate; dampening by ACh, dampening of transmission under influence of acetylcholine; feedforward inhibition, strength of this form of inhibition (\( \lambda \) in Equation 11 of the appendix to this chapter).

<table>
<thead>
<tr>
<th></th>
<th>EC-DG</th>
<th>EC-CA3</th>
<th>DG-CA3</th>
<th>CA3-CA3</th>
<th>CA3-CA1</th>
<th>EC-CA1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>density</strong></td>
<td>40%</td>
<td>40%</td>
<td>3 from each Dg-node</td>
<td>75%</td>
<td>75%</td>
<td>1 per node</td>
</tr>
<tr>
<td><strong>initial weight strength</strong></td>
<td>0.08</td>
<td>0.06</td>
<td>1</td>
<td>0.06</td>
<td>0.08</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>maximum weight</strong></td>
<td>0.18</td>
<td>0.12</td>
<td>1</td>
<td>0.12</td>
<td>0.2</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>( \mu )</strong></td>
<td>0.05 *?</td>
<td>0.02</td>
<td>0</td>
<td>0.05 *?</td>
<td>0.05 *?</td>
<td>0</td>
</tr>
<tr>
<td><strong>dampening by ACh</strong></td>
<td></td>
<td></td>
<td></td>
<td>1-0.5 *?</td>
<td>1-0.5 *?</td>
<td></td>
</tr>
<tr>
<td><strong>feedforward inhibition</strong></td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.3</td>
<td>0.4</td>
<td></td>
</tr>
</tbody>
</table>
learning is proposed to take place. In the model, CA3 is the only layer to have internal connectivity, with each node being connected to a random 40% of the other nodes. For the sake of simplicity, CA3 collaterals in the present model only have a weak autoassociative role. It is expected, however, that the proposed regulatory mechanism would also function under the constraints posed by heteroassociative memory function (see 'Discussion').

The CA1 region of the hippocampus receives a direct projection from the entorhinal cortex via the perforant path (Yeckel & Berger, 1990), and an indirect one, via the so-called tri-synaptic loop (the pathway over DG and CA3). Both projections are incorporated in the model. CA1 has been proposed to function as a translator between the code of CA3 and the cortical code (Lisman & Otmakhova, 2001). In the present model, CA1 associates the pattern in CA3 with the pattern in entorhinal cortex. In case of a high ACh level, transmission through the Schaffer collaterals is dampened and activity in CA1 is dominated by the EC. This allows the CA3-CA1 connection to store the association between the EC pattern and the CA3 pattern. With low ACh levels, on the other hand, the influence of Schaffer collateral input in CA1 is relatively larger, and will be the major determinant of which nodes are activated in CA1. The function of CA1 in those instances is that of relaying the reinstated CA3 pattern to the EC and to other output structures. As the reciprocal connections between EC layer III and CA1 are topologically organized, CA1 neurons innervated by particular EC layer III neurons may be able to reactivate these neurons during retrieval. The connections from CA1 to the deep EC layers might also contribute to this 'closing of the loop'. This would complete the transfer of information back to neocortical areas. In the current version of the model, however, output of CA1 to either layer III or the deep EC layers is not implemented.

The above rationale requires that EC inputs determine which nodes fire in CA1 during learning. However, evidence suggests that the EC-CA1 pathway has a large inhibitory component and does not usually trigger CA1 pyramidal neurons by itself (Canning, Wu, Peloquin, Kloosterman, & Leung, 2000; Empson & Heinemann, 1995). Moreover, if CA1 nodes would be made to fire by EC inputs, they would likely fire before CA3 nodes, which might, in view of the temporal asymmetry in real-brain Hebbian learning, lead to LTD instead of LTP in the Schaffer collaterals. A solution is that EC inputs lead to subthreshold depolarization in those CA1 cells targeted by the pattern in EC (Hasselmo & Wyble, 1997). As a new pattern in CA3 will send relatively nonspecific activation to CA1, these depolarized CA1 nodes will have a high likelihood to be brought to fire by Schaffer collateral inputs. While EC thus biases some CA1 nodes to fire, it is CA3 input that triggers them. Indeed, stimulation of CA3 in the rat hippocampus does elicit firing in CA1 (Canning et al., 2000).

Activity in the model was controlled by fast modular inhibition provided by one, fully connected, inhibitory node for each layer (see appendix). Hereby, the plausible assumption was made that all types of inhibition are relatively untargeted within a layer (Acsády et al., 1998; Buhl, Halasy, & Somogyi, 1994; Cobb, Buhl, Halasy, Paulsen, & Somogyi, 1995; Miles, Toth, Gulyas, Hajos, & Freund, 1996). The inhibitory nodes did not have integrate-and-fire dynamics, but instead emitted a continuous output approximating the summed activity of a whole population of interneurons. The magnitude of the inhibitory signal they sent out depended on activity in the layer they were connected to (feedback inhibition), and on activity in modules projecting to this layer (feedforward inhibition). The feedforward inhibition was conveyed via excitation of the inhibitory node of the receiving layer (Wierenga, 2002). Each modeled pathway thus consisted of an excitatory and an inhibitory component, which were balanced in
strength. To further control the network, there was a maximum 'k' to the number of nodes that could fire in a layer at any given moment.

**Oscillatory activity**

An additional input to the inhibitory node varied with the theta rhythm. Oscillatory population dynamics, in the range of 4-12 Hz (theta frequency), occur in the hippocampus, septum and various cortical regions of the brain during alert waking and rapid eye movement sleep (Green & Arduini, 1954; O'Keefe & Nadel, 1978). They have been suggested to set the temporal dynamics needed to organize synaptic plasticity and implement learning at the network level (Hasselmo & Fehlau, 2001; Huerta & Lisman, 1993; Larson & Lynch, 1986).

The medial septum-diagonal band complex is thought to entrain hippocampal cells to this rhythm, through a dual septo-hippocampal pathway. One component of this pathway originates from cholinergic septal cells, and targets both pyramidal and inhibitory cells in the hippocampal formation (Frotscher & Leranth, 1985). Although this projection enhances hippocampal and entorhinal theta (Alonso & Klink, 1997; Shimono et al., 2000; Stewart & Fox, 1990; Tóth, Freund, & Miles, 1997), it is not crucial to its expression (Lee et al., 1999; Stewart & Fox, 1989a, 1989b). The other component emanates from intrinsically rhythmic GABAergic neurons in the MS-DB. It targets a wide variety of non-pyramidal hippocampal neurons (Acsády, Halasy, & Freund, 1993; Freund & Antal, 1988; Gulyás et al., 1991; Gulyás, Görcs, & Freund, 1990) and phasically disinhibits them at theta frequency (Tóth et al., 1997). This results in concerted oscillations of hippocampal inhibitory cells, which induce rhythmic hyperpolarizations in the principal target cells and, in the background of tonic excitation by cholinergic and possibly other excitatory inputs, paces them into theta rhythm (Stewart & Fox, 1990; Ylinen et al., 1995).

Faster oscillations, at 20-100 Hz, are also prominent in the hippocampal formation. In vivo, these so-called gamma rhythms occur during the theta state, superimposed on theta-waves, with interneuron firing entrained to both gamma and theta frequencies (Bragin et al., 1995; Sik, Penttonen, Ylinen, & Buzsáki, 1995; Soltész & Deschenes, 1993; Traub, Spruston, Sótesz, & Konnerth, 1998). The mechanisms generating these gamma oscillations involve networks of mutually inhibitory interneurons, likely basket and axo-axonic cells, that are excited by principal cells and ACh. These cells fire in gamma bursts, concomitant with increased principal cell activity, providing fast feedback inhibition to the perisomatic region of principal cells (Chrobak & Buzsáki, 1998; Shimono et al., 2000; Traub et al., 1998).

In the model, the inhibitory septal oscillator and a cholinergic node were simulated algorithmically (see appendix to this chapter). The septal oscillator phasically inhibits the ACh node and hippocampal inhibitory nodes, at theta frequency. The cholinergic node determines ACh levels in the hippocampal modules, as will be explained in the next section. In accordance with the aforementioned findings, gamma frequency oscillations in the model arise from an interaction of excitatory activity and fast feedback inhibition over the inhibitory nodes. In the simulations, this fast inhibitory feedback provides a powerful mechanism, limiting the recruitment of neurons into cell assemblies coding for system input.
Acetylcholine and learning dynamics

A proportion of hippocampal inhibitory neurons, mostly located in stratum oriens of CA1 and CA3 (Alonso & Kohler, 1982; Tóth & Freund, 1992), projects back to the MS-DB and appears to target GABAergic septal projection neurons and ACh neurons (Tóth, Borhegyi, & Freund, 1993). These hippocampo-septal projection cells receive convergent input from large numbers of hippocampal principal cells (Tóth et al., 1993).

In line with these findings, ACh release in the model is regulated by the summed activity in layers CA3 and CA1. This effect is obtained by subtracting inhibition, caused by activity of the CA1 and CA3 layers in their respective inhibitory nodes, from base-line activation of a septal cholinergic node. As a result the amplitude of the theta band rhythmic activity of the ACh node decreases with increasing activity in CA3 and CA1. The formula governing septal activity contains a moving average implementing hypothesized slow kinetics in the inhibitory inputs from Ammon’s horn to the septum. Rhythmic oscillations in hippocampal inhibition, particularly in the gamma range, are to large extent absorbed by this moving average, resulting in a relatively smooth fluctuation of ACh levels.

The activity of the cholinergic node is assumed to correspond, in linear fashion, with ACh release in the hippocampus. ACh release in turn determined the value of a variable symbolizing ACh efficacy in the hippocampus. This latter variable determined all effects of acetylcholine on several other variables in the model. Septal ACh release influenced ACh efficacy via a dual exponential with onset and decay time constants obtained from Hasselmo and Fehlau (2001). The authors fitted these constants to their data on the time course of ACh modulation of excitatory synaptic potentials in slices of rat hippocampus. These time constants, together with slow kinetics in the inhibition of the septum, result in slowly changing ACh-modulation in the model, in line with various experimental findings (Cole & Nicoll, 1984; Hasselmo & Fehlau, 2001).

The following effects of ACh were implemented as formulas modulating transmission, membrane kinetics and learning in various layers and connections (formulas and parameter settings are given in the appendix to this chapter):

1) Preferential dampening of transmission over CA3 recurrent fibers (Hasselmo et al., 1995) and Schaffer collaterals to CA1 (Hasselmo & Schnell, 1994; Hounsgaard, 1978).


3) Enhancement of LTP at CA3 recurrent collateral synapses, at Schaffer collateral synapses in CA1 (Blitzer, Gil, & Landau, 1990), and at the perforant pathway innervation of the dentate gyrus (Burgard & Sarvey, 1990).


5) ACh suppresses inhibition of dentate granule cells (Bilkey & Goddard, 1985) and also decreases perisomatic inhibition of pyramidal cells, probably by suppressing release from basket cell terminals (Behrends & ten Bruggencate, 1993). Accordingly in the model ACh suppresses inhibition in all model layers.

The combined aforementioned effects may put the network in a state that promotes new learning: the suppression of transmission in intrinsic fibers by ACh would make the hippocampus more 'attentive' to online input, while its effects on LTP enhance learning. Its effects on adaptation and inhibition, and the depolarizing effects enable hippocampal
principal cells to fire at greater frequency at lower input levels. Thus, high ACh may set the hippocampal network to a learning mode (Figure 39a), while low ACh sets the appropriate dynamics for recall (Figure 39b).

**How does the model store and retrieve patterns?**

As mentioned earlier, a primary aim of the model is to explain how correct dynamics for learning are set as a function of novelty detection. A primary assumption herein is that if the organism is in a known environment, and not engaged in a new task, the hippocampus will be in what has been called retrieval mode. In this mode, patterns in EC representing the outer and inner milieu lead to retrieval of similar, stored patterns in the hippocampus, enabling the organism to anticipate unobserved, but known, features of its surroundings. The hippocampal excitatory activity accompanying the reinstatement of stored patterns induces matched activity in the inhibitory nodes. This inhibition not only limits hippocampal activity, but also depresses the septal cholinergic node. In view of maintained low ACh levels, little learning takes place.

If the animal is suddenly faced with an unknown situation, the observation-and-retrieval stream breaks down, because there are no stored patterns in the hippocampus that match the on-line EC pattern. More specifically, there are no strengthened connections from this EC pattern to the DG, so that very few DG nodes will reach firing threshold. The stark decrease in DG firing then leads to decreased firing in CA3 and CA1, both in excitatory and in inhibitory nodes. Due to decreased activity in the latter nodes the septum is disinhibited, resulting in elevated ACh release in the hippocampus, and therewith a shift to learning mode.

**Figure 39:** Functioning of the network in two modes: retrieval mode and learning mode. (a) In retrieval mode, ACh efficacy is relatively low. Thin gray lines indicate sites of ACh action in the system. (b) In learning mode ACh efficacy is relatively high. As a consequence, LTP in several connections is boosted (black arrows), while transmission in some of these is dampened (thick gray block). Several effects of acetylcholine lead to easier and more prolonged firing in pyramidal cells of the hippocampus (thick gray underlining).
In learning mode, the effects of ACh outlined above collectively facilitate storage of the new pattern. The subthreshold depolarization of DG nodes, combined with suppression of feedback inhibition and adaptation, induces some DG nodes to fire in response to the new EC pattern. As the mossy fiber input from DG to CA3 is very strong, DG firing triggers nodes in CA3. Subsequently CA1 nodes, depolarized by ACh and receiving inputs from both EC and CA3, also fire. Through Hebbian learning, enhanced by ACh, connections between the patterns in EC and DG, EC and CA3, CA3 and CA1 are all strengthened, as are the recurrent collaterals within CA3. This leads to storage of a representation of the new pattern in all layers. Restored firing in CA3 and CA1 then starts inhibiting the septum again, leading to a decrease in ACh release and a gradual return to retrieval mode.

An unresolved issue is how long the hippocampus takes to store a pattern. This is not a critical variable in the model, however, as there is a trade-off between time available for storage and the learning rate, another unknown. In the present simulations, the maximal learning rate of the model, i.e. with maximal ACh efficacy, allows storage of an input pattern over a single theta cycle, while with intermediate ACh efficacy various theta cycles are necessary for reliable storage. These settings are loosely based on in vivo LTP induction with stimuli patterned after natural activity (brief burst stimulation on the positive phase of theta). Such stimuli induce LTP within one theta cycle (Huerta & Lisman, 1995), while LTP is saturated after approximately 3 cycles (Holscher, Anwyl, & Rowan, 1997).

10.3 RESULTS

To investigate the model outlined above, several simulations were run. The first two center on behavior of the model in the learning and retrieval modes. Subsequent simulations evaluate the effect of ACh on activity and learning, and the switch from one mode to another. A final simulation shows how the relatively slow mode-shifting dynamics induced by ACh may affect behavior of a simulated rat in a novel environment. For each simulation, results were averaged over at least twelve runs, each with random activation values at onset. All simulations were performed with the same parameter settings.

Storing and retrieving a pattern

In our first simulation, we presented a new pattern for the model to store. The pattern was activated by clamping a single input node, representing neocortical input sources, that was connected to a random subset of EC nodes via uniform weights. The input node was switched on in the down phase of the theta cycle, where it could not lead to immediate firing in EC. In this simulation, the model started out in learning mode, with the ACh efficacy in the hippocampus set to a value of 0.75.

Following learning over one theta cycle, the pattern was presented again in retrieval mode, with the ACh concentration set to 0.1 at the start of the trial. This simulated a later attempt at pattern retrieval and tested whether the pattern had indeed been stored. A second, random, pattern was then presented in retrieval mode (also with ACh at the start of the trial at 0.1), to control for the possibility that unlearned patterns would also be 'recalled', or that a stored pattern would be recalled with a random cue.
Storage. The activity level of the different layers during the learning trial is shown in Figure 40a. At the start of the trial, in the down phase of theta, the various layers are silent. During the rising phase of theta septal inhibition decreases. As can be observed in the figure, the constant input then leads to gamma-range firing bursts in the entorhinal cortex. Dentate gyrus nodes respond to the input from entorhinal cortex with one gamma cycle delay. Within the same gamma cycle, activity of the dentate triggers the formation of firing patterns in CA3 and CA1. Towards the end of the simulation activity in the various layers subsides under the influence of increasing theta inhibition. Figure 40b shows how the various types of inhibition, including theta-, feedback- and feedforward inhibition, shape activity in one layer of the system, CA1.

Figure 40: Storage of a new pattern. (a) Activity in all model layers during the simulated theta cycle. At iteration 0, the pattern is presented. This leads, during the up-phase of the theta cycle, to gamma-frequency firing in EC, followed after one gamma cycle by firing in DG and CA3. Activity of CA1 takes longer to build up. After several gamma frequency activity bursts, the system shuts down due to mounting inhibition, as the down phase of theta sets in. (b) Interplay of summed excitation (black) and inhibition (gray) in CA1. Inhibitory activity (a scalar, see main text) reflects theta modulation, feedforward excitation by layers projecting to CA1, and feedback excitation by CA1 excitatory nodes (arrows point to examples of each). (c) Membrane potential of two CA1 nodes: one receives an EC pattern node innervation (black), one does not (gray). The timing of population bursts in EC and CA3, the respective inputs of the CA1 layer, are depicted as dots in black and gray along the time axis. Only the membrane potential of the innervated node crosses firing threshold (horizontal gray line, with think black lines marking emissions of a spike).
CA1 binds hippocampal patterns to cortical representations. The patterns in DG and in CA3 are formed by self-organization. This means that random weights in the feed-forward connection determine which nodes are part of the pattern, without requiring any outside supervisor. These self-organized patterns need to be associated with the cortical representations that give rise to them, in order to enable pattern completion in the cortex (Meeter et al., 2002). As explained earlier, our model assumes that this occurs through the reciprocal topological connections between CA1 and the entorhinal cortex: firing triggered in CA1 neurons with a connection from EC may lead to pattern completion in the EC through strengthened topological back projections. As output measure we therefore used the number of firing CA1 nodes that receive a one-to-one connection from an entorhinal pattern node. These will be referred to as ‘correct CA1 nodes’, whereas other firing CA1 nodes will be referred to as ‘incorrect CA1 nodes’. Since there are 12 EC nodes per pattern, the number of correct CA1 nodes can vary between 0 and 12.

Figure 41 shows that most nodes firing in CA1 during retrieval indeed receive a connection from the EC. This is not a direct result of triggering by entorhinal input, however. In panel c of Figure 40, the membrane potentials of one CA1 node receiving entorhinal excitatory input and one node without such input are plotted over time. The timing of both EC and CA3 bursts has been marked. While the EC bursts cause subthreshold depolarization in the CA1 node receiving a connection from EC, the node only crosses the firing threshold after receiving additional input from CA3. In the other CA1 node, EC input causes hyperpolarization due to the broad feed-forward inhibition accompanying targeted excitation in perforant path projections.

Notably, not all CA1 nodes receiving excitation from EC become active. This is the result of sampling variance: though most CA1 nodes receive sufficient excitation from CA3 to cross threshold, some are not innervated by a sufficient number of active CA3 nodes. Strengthening the Schaffer collaterals would make the latter nodes reach threshold, but would lead to many nodes not targeted by the EC pattern to fire as well. This mechanism for binding hippocampal patterns to cortical representations thus crucially depends on the balance in strength of the two inputs to CA1.

Figure 41: Number of active nodes in CA1 during learning, split out in the 12 CA1 nodes that are innervated by one of the 12 EC pattern nodes (‘correct’), and those that are not (‘incorrect’). ‘Missing’ refers to those CA1 nodes that did not fire during learning, even though they are innervated by one of the 12 EC pattern nodes.
Retrieval. To investigate whether the presented pattern had been stored, we sequentially presented the model with two patterns in retrieval mode ($ACh=0.1$): the pattern already presented in learning mode, and a new one. As in the learning mode, the patterns were presented by sending a constant input to a set of entorhinal nodes. Figure 42 shows the activation in the network after presentation of the old and the new pattern. As may be expected, the old pattern elicits activity in DG, CA3 and CA1 (Figure 42a), and does so a little earlier in the theta cycle than during storage (Figure 40b). This occurs because previous strengthening of connections leads to a faster activation of hippocampal neurons recruited during learning. The new pattern, on the other hand, elicits little to no activity (Figure 42b). This causes a steep rise in septal activity and a concomitant rise in hippocampal ACh: the system is shifting to learning mode. Activity levels in the hippocampus and septum thus distinguish between old and novel input patterns.

Pattern completion
To test whether our model would exhibit pattern completion, we investigated the extent to which partial cues in EC would elicit recall of the entire pattern in the hippocampus. After acquisition of a pattern, as in the previous simulation, we deactivated a variable proportion of the EC nodes associated with the pattern and tested retrieval for each level of degradation. In this way, the hippocampal modules were presented with a partial entorhinal pattern without changing other parameters in the system. Retrieval was tested over one theta cycle, with the ACh level set to either 0.1 (retrieval mode) or 0.75 (learning mode). Pattern completion was measured as the maximum proportion of correct CA1 nodes (receiving an input from the complete EC pattern) that were simultaneously active during the theta cycle.

Figure 43a depicts pattern completion in retrieval mode as a function of cue-size (i.e. the number of EC pattern nodes that were allowed to become active). As can be observed, there is a non-linear relation between cue size and pattern completion: near full pattern completion is achieved with cue sizes between 50-100%; there is a steep decline of function with cue sizes around 50%, while with still smaller cues pattern completion is almost zero. A similar non-linear relation between cue size and pattern completion was shown to result from the interaction of orthogonalization in DG with the workings of LTP and LTD (O'Reilly & McClelland, 1994), which are both implemented in the current model.

Figure 43b shows what happens to pattern completion when the model is in learning mode. The high ACh efficacy enhances activity levels in the model so that partial pattern completion tends to occur with relatively smaller cue size than in retrieval mode. In essence, dampening of transmission by ACh, which makes activation of pattern nodes harder, is trumped by the depolarizing effects of ACh, which makes such activation easier. However, firing is also made easier for nodes outside of the already stored patterns. Consequently, retrieval becomes less accurate, as reflected in a considerable increase of incorrect nodes being activated during pattern completion (Figure 43b). Thus, with small cue-sizes more of the pattern is completed in learning mode than in retrieval mode, but this comes at the price of a compromised integrity of retrieval.

At first blush, it may seem surprising that retrieval is not only possible in learning mode, but even enhanced (though less reliable). However, learning and retrieval are in a sense less antithetical as they seem. For example, explanations of the list strength effect have
Figure 42: Activity in retrieval mode in all model layers during two simulated theta cycles. (a) In the first theta cycle a stored pattern is presented, which induces notable activity in all model layers. (b) In the second a new pattern is presented. Now EC activity triggers little or no activity in the other modules.

up to now assumed that when items are repeated, information is stored during the second occurrence in the memory trace of the first occurrence of the item (Shiffrin & Steyvers, 1997). This means that during learning there is retrieval of older memory traces.

Moreover, it may be hypothesized that during effortful retrieval, input cues do not immediately lead to instantiation of a stored pattern, leading to a shift of the system to learning mode, with higher ACh. This would be consistent with the ‘retrieval practice effect’ known in the human memory literature, which implies that effortful and successful retrieval constitutes a powerful learning method (Benjamin, Bjork, & Schwartz, 1998; Gardiner, Craik, & Bleasdale, 1973). It also could be part of the explanation for the success of some memory implantation techniques. In experiments based on these techniques, participants are told to try very hard to remember an event that in fact did not occur. Typically, after several days a percentage of subjects reports that they, indeed, remember the event (Loftus & Pickrell, 1995).

The effect of ACh on activity and learning

To assess the effect of ACh on storage of patterns in the model circuitry, a random pattern was presented during one theta cycle (the acquisition theta cycle). The simulation was repeated several times, with ACh efficacy set at different levels at the onset of simulation (little change to efficacy occurred over one theta cycle). For each level of ACh efficacy, acquisition was evaluated by presenting the same pattern, again during one theta cycle (the retrieval theta cycle), with ACh efficacy set at 0.1. Two measures were extracted from the simulation data: (1) the total number of active nodes in CA1 summated over the duration of the acquisition theta cycle; (2) the maximum number of correct CA1 nodes simultaneously active during the retrieval phase. The two measures assessed ACh effects on activity and on learning performance, respectively.
Figure 43: Activity elicited in CA1 by a partial cue in EC, activated during retrieval mode (a), or learning mode (b). The x-axis marks the number of EC nodes in the stored pattern that were activated as cue the y-axis marks the maximal number of simultaneously active CA1 nodes during the simulated theta cycle. "Correct" refers to those nodes innervated by an EC pattern node (independent of whether this node was cued or not), while "incorrect" refers to other CA1 nodes. The gray line is the identity function, reflecting perfect correspondence between the number of activated correct CA1 nodes and the number of activated EC nodes.

Higher ACh efficacy resulted in higher amounts of activity in CA1 during learning (Figure 44), through the combined effects of increased depolarization, decreased adaptation of excitatory nodes and decreased inhibition. These higher activity levels, combined with the higher learning rate at high ACh efficacy levels, led to larger representations being formed and to enhanced retrieval performance.

As can be seen on the right hand side of the figures, the highest ACh levels tested resulted in suboptimal retrieval performance. This occurs because, under these conditions, CA1 nodes are depolarized by ACh to the extent that they can be triggered by EC input alone. As some CA1 nodes thus fire before the arrival of input from the CA3 layer, Hebbian learning in the Schaffer collateral s connecting to these nodes cannot occur. By the time CA3 activation does arrive, the CA1 nodes that fired ‘prematurely’ are less likely to fire because of adaptation (which eventually sets in, despite the dampening influence of ACh). Neurons that only get input from CA3 are now relatively more likely to fire and to form strengthened connections with CA3. These neurons do not represent the EC input, however, leading to diminished retrieval performance. ACh levels higher than 0.95 do not ‘naturally’ occur in the model and, so, neither does the described ‘pathological’ network behavior.

**Interaction between ACh and activity: old and new patterns**

To systematically investigate the interaction between ACh and activity in the model, we stored one pattern, as was done in the first simulation, and then presented either this ‘old’ pattern, or a randomly selected new pattern, while varying the ACh efficacy at simulation onset (range between 0 and 1.0). Each pattern was activated at the trough of theta. During the theta cycle that followed, ACh was allowed to fluctuate freely under...
the influence of model dynamics, while activity in the various hippocampal modules and ACh release were monitored.

*Figure 45a* shows activity levels in the hippocampal modules during presentation of either the new or the stored patterns, plotted against initial ACh efficacy. Activity levels were summed over the duration of the test (one theta cycle). Activity was also summed over layers CA3 and CA1, as activity in the two layers is closely correlated (CA3 firing usually causes firing in CA1 as well). For the stored pattern, ACh efficacy does not play a very important role: it elicits activity in the network both in learning mode (high ACh) and in retrieval mode (low ACh). This was different for the new pattern, which triggered firing in DG, CA3 and CA1 only in learning mode. The difference in activity elicited by old and new patterns is already apparent in the dentate gyrus. Indeed, it is activity in this module that differentiates between old and new patterns in the present set-up. If activity in the dentate gyrus is clamped to a high level during presentation of a new pattern, activity in the CA3 and CA1 layers are as with presentation of an old pattern (simulation not shown).

ACh release from the septum during the theta cycle mirrors the activity elicited in the hippocampus by the input patterns (*Figure 45b*): it is low when there is activity in CA3 and CA1 (due to the inhibition of septal activity by these layers), but it is high when there is no activity in CA3 and CA1 (i.e., when a new pattern is presented in retrieval mode). This last situation is when a mode shift is necessary, and the release of ACh will cause just that.

**From retrieval to storage to retrieval**

From the previous simulation, the principle underlying mode switching becomes clear. If in retrieval mode no activity is elicited in Ammon’s horn, inhibition of the septum is released, ACh is released, and the network will shift to learning mode. Conversely, the shift from learning mode to retrieval mode occurs when activity in the hippocampus increases, for instance due to build up of a representation of novel input. The increasing

*Figure 44*: Effect of ACh efficacy on learning. A new pattern was presented during one theta cycle, at various levels of ACh efficacy. Activity in CA1 summed over the theta cycle, and the number of activated correct CA1 nodes during a subsequent retrieval theta cycle (with ACh efficacy set to 0.1) are plotted against ACh efficacy.
Figure 45: Effect of different levels of ACh efficacy on model behavior; (a) activity elicited in DG and in the combined CA layers, following presentation of either an old (black lines) or a new (gray lines) pattern at varying initial ACh levels. Activity in DG and in the combined CA1-CA3 layers (referred to as CA) was summated over one theta cycle following pattern presentation. (b) ACh release in the hippocampus during the same theta cycle for the old (black line) and the new patterns (gray line). Variables were normalized dividing them by their maximum value in all simulations.

Hippocampal activity progressively inhibits ACh release, in time bringing the system back to retrieval mode.

Here, we simulated this process explicitly. At the onset of the simulation, one pattern was stored, as in the first simulation. ACh efficacy was then set to a low value (0.1) to simulate retrieval mode. Subsequently, either the old pattern (control condition) or a new pattern (mode switch condition) was presented to the model at the trough of theta and kept active during 20 consecutive theta cycles (4 seconds). This procedure provides an opportunity to evaluate the temporal characteristics of mode shifting.

In the control condition, in which an old pattern was presented, septal cholinergic activity remained subdued throughout the whole simulation (gray line in Figure 46a) and hippocampal ACh efficacy remained low (gray line in Figure 46b). Results are different in the mode switching condition, in which a new pattern was presented. Figure 46c presents activity in the model layers during the course of simulation. Activity in CA3 and CA1 are taken together for reasons explained previously. As shown also in the first simulation, the new pattern does not initially elicit activity in DG and Ammon’s Horn. The initial lack of activity in Ammon’s horn leads to a drop in inhibition of the septum, which in turn leads to a spike in activity of the septal cholinergic node (Figure 46a). The increase in septal activity results in a gradual rise of ACh efficacy in the hippocampal layers (Figure 46b). As was detailed in the first simulation, rising ACh efficacy enables the formation of a new pattern in the hippocampal layers, leading to a rise in their activity at around 800 ms. The return of activity in the layers of Ammon’s horn leads to renewed inhibition of the septum and a drop in septal activity and ACh release. ACh efficacy remains elevated for a few seconds more, due to its slow synaptic and postsynaptic dynamics. Eventually, it starts to drop under the influence of continued inhibition of the septum by the hippocampal layers (maximum efficacy was reached at 3960 ms). Assuming negligible ACh release to continue after the modeled episode, ACh efficacy returns to a value of 0.2 at 20 seconds after simulation onset, hereby resetting the model to retrieval dynamics.
Figure 46: Example of a shift from retrieval mode to learning mode. At time=0 either a new or an old pattern is presented to the model. Data are averaged over 20 ms intervals. (a) Activity of the septal node in response to either an old (gray) or a new pattern (black). (b) ACh efficacy in the hippocampus during presentation of an old (gray) or new (black) pattern. (c) Normalized activity in EC, DG and the two CA layers (summation of CA3 and CA1) during presentation of a new pattern. (d) Maximum number of active correct CA1 nodes at each subsequent theta cycle (100 iterations within one theta cycle), during the course of simulations (20 theta cycles).

Although activity in the hippocampal layers continues to rise over the entire modeled interval of 4 seconds, the time required to store a representation of the new pattern is much briefer than this. Figure 46d shows how many ‘correct’ CA1 nodes were recruited
at each theta cycle. The largest increase takes place from 1000 to 1600 ms, when most of the representation is formed. When we set the model to retrieval mode after 1800 ms and test for retrieval of the pattern, the number of correctly activated CA1 nodes has already reached 84% of its maximal value.

The simulation demonstrates how a change from retrieval to learning mode occurs within 2 to 4 seconds, while it takes relatively more time to return from learning to retrieval mode.

**Rat in a track simulation**

In the model, it takes a few seconds for a new hippocampal representation to be formed. Whether this is realistic may partly be evaluated by the consequences for behavior. Here some of these consequences are explored through simulation.

Novelty detection may not only be important in setting the dynamics of the memory system; it may also have a function in, for example, exploratory behavior. Rats may use some novelty measure, computed from memory, to decide whether to stop for orientation, or to proceed for exploration of further locations. We investigated this notion by simulating how a rat might move through an L-formed maze at its first encounter with it. The simulated maze consisted of a start box from which the rat entered a leg of 90 cm in length. A shorter leg, 60 cm in length, was placed perpendicularly at the end of the first. The rat was assumed to move at a speed of 0.3 m/s during exploration. The following additional assumptions were made:

- ambulation occurs as a function of novelty: the rat moves if it is to some extent familiar with its environment, stops when it feels the surroundings are novel;
- features in the environment change at irregular intervals;
- when a rat rounds a corner in the maze, many features change at once.

We set the proportion of changing features at corners at 50%, while continuous change was modeled as a Poisson process in which there is a constant likelihood, per unit of distance, that a change occurs (Mensink & Raaijmakers, 1988). Specifically, at every 0.6 mm along the length of the track there was a likelihood of 1/4000 that either 1, 2 or 3 features changed (this is equivalent to an average 50% feature change for every 60 cm the rat moves along the length of the maze).

The hypothesis explored was that ACh efficacy is related or correlated to the perception that a situation is novel. A criterion based on the ACh efficacy was thus used to decide, on each time step, whether our simulated rat in the maze would move, or whether it would stop and form a new representation of the current environment. The criterion used in the model consisted in a simple rule: when ACh efficacy rose, the rat stopped or would remain in the same location; when ACh efficacy dropped or remained constant the rat would set off or continue moving towards subsequent locations.

Figure 47a shows the simulated exploratory behavior of our model rat in the maze. From time 0, when the lid of the home cage is lifted and the rat is presented with the new maze, it takes only a few milliseconds before the level of ACh efficacy starts rising (Figure 47b) and the rat halts its movement. The rat stays put for the next four seconds. Figure 47c shows how during that time regular theta activity builds up in the hippocampus, as a representation is formed of the first part of the maze. When after four seconds ACh efficacy starts to drop, the rat sets off exploring. The new representation is continuously retrieved while the rat is moving. In this simulation the rat keeps walking...
until it gets to the corner (in longer stretches of straight track ACh will sometimes start to rise, as the irregular random changes accumulate and make retrieval of the representation impossible). At the corner (gray dotted stripe in Figure 47), many features change at once and retrieval of the stored pattern breaks down, causing a sudden drop in activity (Figure 47c). Consequently, ACh efficacy starts to rise and the rat stops again. As ACh efficacy is now higher than at the outset of the simulation, a shorter time is needed for a new pattern to form under influence of ACh. ACh efficacy thus tops faster and, after only 2.5 seconds, the rat starts moving again, until it reaches the end of the second leg after 12 seconds in the maze.

Notwithstanding the simplistic implementation, the above simulation illustrates how the slow temporal characteristics of ACh dynamics in the model are consistent with the approximate time course of natural behavior in a learning situation.

**Figure 47:** Results from the track simulation, with data averaged over bins of 50 ms. The gray dotted line signals that the rat has turned the corner, while at 11.7 seconds the rat has reached the end of the track. (a) Speed at which the rat moves through the maze, in cm per second (maximum set at 30 cm/s). (b) ACh efficacy in the hippocampus. (c) Average activity in CA3 and CA1 during the run.
Novelty detection and mode shifting were studied in a large-scale connectionist model of the hippocampal formation. The results show how old and novel patterns may be distinguished based on differential activity levels in the system, and how this differential signal may be used to regulate levels of a neuromodulator, which, in turn, acts to alter system dynamics of the hippocampal-entorhinal circuitry.

According to the present model, input patterns that have been previously learned induce higher levels of activity than novel ones in the first few theta cycles after presentation. The reason is that, only for old patterns, strengthened connections exist from the participating EC neurons to particular DG granule cells. The EC input to CA3 is less important in this respect, because the CA3 nodes are dependent on input from the DG to reach firing threshold. This implicates that the ‘novel versus old’ decision depends crucially on the dentate and on rules governing EC to DG synaptic plasticity. In line with this notion, a number of experimental studies suggest that dentate granule cells may, indeed, play a significant role in novelty detection (Johnson & Moberg, 1980; Lemaire, Aurousseau, Le Moal, & Abrous, 1999). Notably, the orthogonalization between EC and dentate tends to drive the overlap between dentate representations to all or nothing. Hence, the novelty detection procedure tends to produce a binary ‘old-versus-novel’ decision, rather than a graded one.

Not the dentate, but the CA3 and CA1 regions appear to be the largest sources of hippocampal feedback to the medial septal nucleus (Alonso & Kohler, 1982; Tóth et al., 1993; Tóth & Freund, 1992). These subfields may contribute to novelty detection, in vivo, by increasing the amplitude of the novelty signal. Both the denser activity with respect to the dentate, and the propensity of pyramidal cells to fire in bursts may contribute to this amplification. ACh notably affects signal amplitude, through its novelty related modulation of hippocampal dynamics. In particular, the actions of ACh on the hippocampal circuitry preferentially increase activity following presentation of new patterns. Therefore, the differential activity between old and new patterns is most pronounced at low ACh efficacy levels, when the model is in retrieval mode (Figure 8).

The prominent role of dentate gyrus in novelty detection in the current model is one distinction with previous models regarding hippocampal mode-shifting (Hasselmo & Schnell, 1994; Hasselmo et al., 1995). The present work also provides a new reasoning for the existence of separate learning and retrieval modes. While in other work attention has been focused on the detrimental effect of retrieval during learning (e.g., Hasselmo, 1994) and on unwanted changes in existing representations (e.g., Grossberg, 1976), the current work shows how retrieval in learning mode may be unreliable through the activation of features that were not part of the original memory. The separation of learning and retrieval modes, thus, also enhances accurate retrieval.

Other novel insights follow from the incorporation of oscillatory population dynamics in the present model. In particular, to ensure that ACh efficacy fluctuates in relation to novelty, but not with faster theta or gamma rhythms, the hippocampo-septo-hippocampal loop needs to incorporate a low band filter. In the model this is implemented in the form of a moving averaging procedure in the pathway controlling release, and slow time constants governing ACh effects. In the biological circuitry, the first procedure may, for instance, consist in a long integration period for inhibitory hippocampal input to ACh cells, while the slow effects of ACh were shown by Hasselmo and Fehlau (2001) to result, at least in part, from slowly recovering intracellular processes, activated by ACh in the postsynaptic cell. Phase shifts in the theta oscillation
between different hippocampal regions might also contribute to smoothly fluctuating ACh levels by 'widening' the phase of theta during which the septal cells receive inhibition from the hippocampus.

The temporally specific features in the model have implications for the time-course of memory processes. These implications were evaluated using a simulation of a rat moving through a novel environment. Upon first evaluation, the slow temporal dynamics of the system appear to concord with the approximate time-course of natural behavior in a learning context. The results of this simulation should be interpreted cautiously, as the relation between episodic learning and exploratory behavior may depend on factors that were not implemented in the model.

The possible effects of heteroassociative learning on mode-shifting dynamics can also be envisaged. Although the activational difference signal in the present set up is sufficient to drive mode shifting, it is expected that sequence learning in the hippocampus will enhance mode-shifting performance. In a heteroassociative CA3, old patterns would tend to evoke sequences of stored events, while new patterns would not evoke sequences, as no sequence following the new pattern could previously have been stored. Thus, sequence learning dynamics might amplify the differential system activity following old and novel input.

As explained previously, the novelty signal in this model consists in a decreased firing rate in the hippocampus. This contrasts with results showing increased firing for novel images in parts of the parahippocampal region (Xiang & Brown, 1998). Such increases were observed following presentation of simple visual stimuli and were not found in the hippocampus proper (Wan, Aggleton, & Brown, 1999). Although it is not clear what these results imply for our model, it is possible that suppressed transmission of familiar items in lower level regions enhances the efficiency of configurational novelty detection in the hippocampus proper. This notion may be tested in subsequent versions of the model, which will incorporate more detailed in- and output structures.

The present model generates a number of predictions:

* For one, hippocampal novelty detection should concur with a temporary drop of hippocampal activity. It has, indeed, been shown that when an animal is introduced to a new environment or is presented with an unfamiliar object, this leads to a period of depressed firing in the dentate and Ammon's horn, which is followed by synchronous theta modulation. In line with our findings, this so-called 'inhibitory reset' habituates with repeated presentations of the stimulus (Vinogradova, Kitchigina, & Zenchenko, 1998).

* Novel configurations should lead to increased activation of cholinergic cells in the medial septum, and to a surge in hippocampal ACh release. This prediction is to some extent validated in a recent experiment showing that, during exploration of a new environment, hippocampal ACh levels were increased relative to baseline, while levels decreased during repeated exploration of the same environment (Giovannini et al., 2001).

* Novel configurations should produce enhanced synaptic plasticity in the hippocampus proper, via effects on ACh. The first part of this prediction is supported by a c-fos study, in which rats were shown novel configurations to one eye and old ones to the other. The hippocampus contralateral to the eye viewing novel configurations expressed higher levels of c-fos than the ipsilateral hippocampus (Wan et al., 1999).
According to our results, old input patterns are able to recruit hippocampal activity earlier in the theta cycle than novel patterns, irrespective of the level of ACh. This occurs because the fast build-up of excitation over strengthened connections, allows overcoming of theta inhibition earlier in the cycle than when a new pattern is presented. Thus, during a hippocampus-dependent learning paradigm, firing of individually recorded hippocampal neurons should show some theta phase precession associated with task acquisition.

Learning of a new stimulus should occur quicker when the animal is in learning mode than when it is in retrieval mode (in our simulations, this speed difference is 200 versus 1800 ms). The same applies with regard to experimentally induced states of high versus low ACh.

As a consequence, the speed of acquisition depends on the degree of novelty of system input during the ten or twenty seconds preceding stimulus presentation. This could be tested in an experiment of continuous recognition, with configurations as stimuli and short presentation times (in such experiments old and new stimuli are presented in a continuous stream; the subject has to judge which stimuli are new and which ones already appeared in the stream). A new stimulus following twenty seconds of viewing old configurations should be stored less well than a stimulus appearing after one or more new stimuli.

Our simulations suggest that the balance of strength between the direct perforant path and the trisynaptic input to CA1 is essential to pattern encoding. Interference with this balance, for instance through unphysiologically high levels of ACh (see Figure 44), will lead to suboptimal memory performance.

Finally, new patterns should elicit little activity in the hippocampus in absence of ACh. The latter prediction could be tested by subjecting rats to a novel environment following total blockade or depletion of hippocampal ACh, and measuring field potential in any or all fields of the hippocampal formation.

The model is falsified if stimulation of CA3 and CA1 does not inhibit cholinergic cells in the septum, does not influence the release of ACh in the hippocampus, or if any of the above predictions turn out to be untrue. In this respect it is noteworthy that the few studies addressing the function of the hippocampo-medioseptal pathway were performed in anaesthetized rats, and did not characterize the neurons responding to hippocampal input (Dragoi et al., 1999; McLennan & Miller, 1974). Moreover, the clearest effects of hippocampal influence on septal activity were observed during hippocampal sharp waves, rather than REM-associated theta (Dragoi et al., 1999). Therefore, there is at present no direct evidence for a hippocampal influence on acetylcholine release during behavioral learning.

Another consideration regards the following: the GABAergic hippocampo-medioseptal projection appears, from anatomical studies, to terminate preferentially onto GABAergic projection neurons of the septal diagonal band complex. If this pathway were to convey the main hippocampal regulatory influence on ACh cells, the effect might be opposite to the one proposed by models thus far. That is, the GABAergic cells would disinhibit ACh cells in response to hippocampo-septal stimulation. Thus, ACh would rise following presentation of old patterns. We, therefore, suggest that the inhibitory hippocampo-medioseptal projection directly onto ACh neurons, albeit sparse, may nevertheless be sufficient to regulate activity of ACh neurons during ‘mode-shifting’ (Dragoi et al., 1999). The combined effect of the dual hippocampo-septal pathway may be to reduce...
system activity and to dampen the strength of theta modulation accordingly. Alternatively, other pathways may convey the ACh regulation according to novelty.

The present model incorporates various realistic features that are not directly related to novelty detection and mode shifting, but that enhance network performance. One of these, fast feedforward inhibition, is not commonly applied in connectionist models. Being proportional to feedforward excitation, feedforward inhibition assures that recruitment of nodes in the target layer functions with similar selectivity over a large range of input strengths (Wierenga, 2002). The proposed function is clearly distinct from that of fast feedback inhibition, which mostly works to limit the number of recruited nodes and, therewith, the size of memory representations. In our hands this dual control of activity proved to considerably enhance stability of a network, particularly in networks with recurrence amongst layers and varying pattern size. It may, in this context, be noted that the size of representations in the currently modeled system, to some extent, varies depending on the modulation of system dynamics by ACh (see simulations 3 and 4).

Another feature implemented in the model is the way representations are formed in CA1. Through subthreshold inputs via the perforant path, neurons that receive a connection from active EC nodes are ‘predisposed’ to become part of the representation. These nodes are, however, triggered by CA3 inputs, allowing the CA1 representation to be linked to the representation in CA3 through Hebbian learning. In this way, the representation formed through self-organization in DG and CA3 can be associated to the cortical representation relayed to EC. A similar mechanism was adopted in a model by Hasselmo and Wyble (1997), though the timing of the two inputs to CA1 did not play a role in that model.

While hippocampal feedback to the medial septum and diagonal band may set ACh levels, a novelty signal may also be conveyed over other efferents of the hippocampus. A novelty signal over CA3 could, through the intermediaries of lateral septum, raphe nuclei and reticular formation, influence levels of arousal (Vinogradova 2001). In addition, a hippocampal novelty signal via the EC to the ventral striatum could influence the chain of events that leads to destabilization of thalamo-cortical representations involving the prefrontal cortex, facilitating a change of behavioral strategy. Regulation of these circuits in relation to novelty may thus instate beneficial conditions for processing and encoding of novel information.

The network presented here constitutes one of the few ‘full blown’ models of the hippocampo-septal formation. Here, it was used to investigate how ACh may effectuate novelty related modulation of hippocampal dynamics. However, the model may also serve as basis to explore other hypotheses concerning this brain system. Our prospective studies will, for instance, focus on the differential characteristics of hippocampal input from EC layers II and III, and on their significance with respect to episodic memory function. By implementing these and other ideas in the model, consequences of assumptions about a given subdivision of the hippocampal system for other components can be traced, leading to testable predictions. In this way, computational modeling of the hippocampus can help the confrontation of theory with data, and ultimately lead to a better understanding of the structure and its functions.
APPENDIX TO CHAPTER 10.

Model neuron
Integrate-and-fire MacGregor model neurons were used for the model. MacGregor and Oliver derived this model neuron from the Hodgkin-Huxley formulas (Hodgkin & Huxley, 1952). The model accounts for firing characteristics in single neurons, while being computationally inexpensive enough for use in large-scale networks. These model neurons show spiking, adaptation, and threshold accommodation (accommodation was not implemented in the present simulations). They are updated in discrete time steps, which in our simulations lasted 2 ms.

The model neuron emits a spike every time the membrane potential $E$ crosses the threshold $\theta$:

Equation 4: \[ E \geq \theta \Rightarrow S = 1 \]

In this equation $S$ is a dichotomous variable that is equal to 1 if the node emits a spike, and equals 0 otherwise. The membrane potential $E$ is dependent on the sodium, potassium and chloride currents over the membrane, as described in the following differential equation:

Equation 5: \[ \frac{dE}{dt} = -\delta E - g_k(E - E_k) - g_{\alpha}(E - E_{\alpha}) - g_i(E - E_i) - SE \]

Here, $-\delta E$ is the leak current, $g_k$ the excitatory conductance, $E_k$ the sodium reversal potential, $g_\alpha$ the inhibitory conductance and $E_\alpha$ the chloride reversal potential. For computational purposes, both the membrane potential and the reversal potentials were mapped onto the interval $[-1, 7]$ via a simple linear transformation (MacGregor & Oliver, 1974). Resting potential was equated to 0 (−75 mV), the firing threshold $\theta$ to 1 (−60 mV), the natrium reversal potential to 7 (+30 mV), and both the potassium and chloride reversal potentials to −1 (−90 mV). The parameter governing the leak current, $\delta$, was set to 1/7. When the node emits a spike, membrane potential is reset to resting level (via the term $SE$).

The potassium conductance $g_\alpha$ models adaptation, and is determined by

Equation 6: \[ \frac{dg_\alpha}{dt} = \frac{-g_\alpha}{T} + bS \]

where $S$ is the dichotomous spiking variable. The time constant $T$ was set to 13, while the gain parameter $b$ was set to 0.35.

Excitatory input to the $i$'th node is a simple linear summation of weighted inputs to that node

Equation 7: \[ g_\alpha = \sum_j w_{ij} S_j \]

whereby $w_{ij}$ is the weight from node $j$ to node $i$, and $S$ is the dichotomous spiking variable of node $j$.

In running the simulations, the discrete-time approximation formulas given by (MacGregor & Oliver, 1974) were used. The model was constructed using the Nutshell
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simulator, developed in our group. This simulator can be downloaded without cost at www.neuromod.org/nutshell.

Simple Hebbian learning was used, modeling LTP, with the additions of negative Hebbian learning, modeling LTD, and a bound on connection weights. Weights are changed according to

\[ \Delta w_{ij} = \mu^+ S_i S_j - \mu^- S_i (1 - S_j) \]

Here, \( w_{ij} \) is the weight from node \( j \) to node \( i \), while \( S_i \) and \( S_j \) are the activation of the receiving, and of the sending node, respectively. This is subject to the constraints that the weight cannot be lower than 0 or exceed a maximum \( W \). The positive learning rate, \( \mu^+ \), as well as the maximum value a weight can attain, \( W \), are set separately for every connection (see Table 11). The negative learning rate \( \mu^- \) was set to 50% of the positive learning rate in all connections.

**Inhibition**

The inhibitory conductance, \( g_i \), in a given layer \( l \) is described by the following equation:

\[ g_{il} = 1 + i^l_t - s_t \]

where \( s_t \) is the activity of the septal interneuron:

\[ s_t = 0.5 - 0.5 \sin(t/f) \]

This is a simple sinusoid between 0 and 1 with a frequency of \( f \) (set to 50, equivalent to a 200 ms theta-band oscillation). The other component of Equation 9, \( i^l_t \), models the activity of intrinsic interneurons:

\[ i^l_t = \alpha_i i_{l-1}^t + \beta_i (A_{l-1}^i) + \sum_p \lambda_{lp} A_{p-1}^l \]

Thus, inhibition in layer \( l \) on time step \( t \) is a function of the feed-forward and feedback activation of inhibitory cells by the pyramidal cells, and of inhibition on time step \( t-1 \) (a proportion \( \alpha_i \), set to 0.5, of the inhibition is retained in the next time step). Feed-forward and feedback inhibition are linear functions of the excitatory activation in the layers connecting to layer \( l \) (feed-forward), and of excitatory activation in layer \( l \) itself (feedback). The activation of each layer (\( A_i \)) is calculated by summing the number of firing nodes, and dividing it by the maximum number of firing nodes \( k \) (see Table 10). The \( \beta_i \) parameters (strength of feedback inhibition to layer \( l \)) in all layers are given in Table 10, and the \( \lambda_{lp} \) parameters (strength of feedforward inhibition from layer \( p \) to layer \( l \)) associated with each connection are listed in Table 10.

In large networks, the inhibition described above will be enough to constrain activity. In networks of the size used here, however, random fluctuations may produce large swings in activity that can be kept in check with a fast cut-off mechanism. This mechanism allows only a maximum number of nodes, \( k \), to fire in a layer \( l \) at any given time step (see Table 10). If more than \( k \) nodes cross the firing threshold \( ? \), only the \( k \) nodes with the highest membrane potential are allowed to fire. This models the characteristic of inhibition to set a bound on the activity of pyramidal cells.
Acetylcholine

ACh levels in the model are regulated by inhibitory activity in layers CA3 and CA1, as discussed in the main text. A moving average of inhibition in the two layers determines the inhibition on septal ACh neurons:

\[
i'_i = \alpha' i'_{i-1} + \beta' (i_{iCA3} + i_{iCA1})
\]

Hereby, the parameter \(a'\) is set to 0.85, and \(b'\) is set to 0.45. In a biological hippocampo-septal network, a slow membrane integration constant of ACh cells could perform a similar procedure on the hippocampal input.

As shown in equation 10, activity of the septal cholinergic neurons, \(A'_i\), was set to \(F - \text{inhibition}\). Here, \(F\) represents excitation of the septum by sources outside of the model, such as the reticular formation (\(F\) was set to 1 in all simulations). The inhibition could come either from the septal oscillator interneurons, \(s_i\) (whose output is the theta-frequency sinusoid given by Equation 10), or from the hippocampal afferents, \(i'_i\) (given by Equation 12).

\[
A'_i = F - s_i - i'_i \quad \text{if} \quad F - s_i - i'_i \geq 0 \quad \text{else} \quad A'_i = 0
\]

Release of acetylcholine (\(\Phi_i\)) was set equal to the activity of the septal cholinergic node. This release in turn fed into ACh efficacy in the hippocampus, for which we use the symbol \(\Psi\), following Hasselmo and colleagues (e.g., Hasselmo & Schnell, 1994). At each time step, the amount of ACh released was fed into a dual exponential:

\[
\Psi_t = \sum \Phi_s (e^{-\tau_1(t-s)} - e^{-\tau_2(t-s)})
\]

The time constants (\(\tau_1, \tau_2\)) of the dual exponential were rescaled from those found by Hasselmo and Fehlau (2001), who fitted a dual exponential to experimental data on the time course of ACh modulation data (\(\tau_1 = 0.001258, \tau_2 = 0.00015\)). These values correspond to a slow rise with a maximum at around 3.5 seconds, and a decrease back to 0 in 10 to 20 seconds.

As the effects of acetylcholine have been discussed in the main text, only their implementation will be listed here.

1) For preferential dampening of transmission over Schaffer collaterals to CA3 and CA1, transmission in these two tracts (\(g_{e}^*\) in Equation 7) is multiplied by a factor 1-0.6 * \(\Psi\).

2) For enhancement of LTP at CA3 recurrent collateral synapses and at CA1 Schaffer collateral synapses, the learning rate (\(\mu^*\) in Equation 3) is multiplied by \(\Psi\) in these connections.

3) Reduction of firing adaptation of DG, CA3 and CA1 excitatory cells is effectuated by multiplication of the adaptation constant (\(b\) in Equation 6) with a factor 1 - \(\Psi\).

4) Suppression of inhibition in all model layers is achieved multiplying the feedback inhibition constant (\(\Psi^*\) in Equation 11) by a factor 1-0.5 * \(\Psi\).

5) A mild depolarization of DG, CA3 and CA1 principle cells is implemented adding a constant factor, 0.12 * \(\Psi\), to the input of cells in these layers (\(g_{e}^*\) in Equation 7).