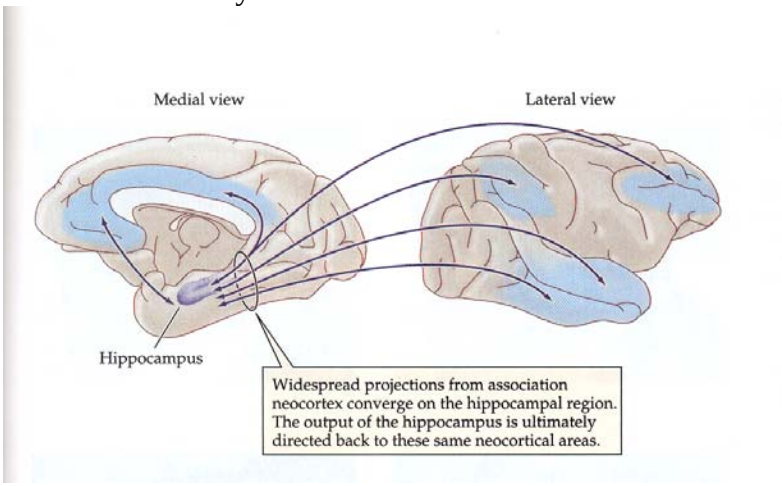
Class Notes Part III – Memory models

Why is there a hippocampus?

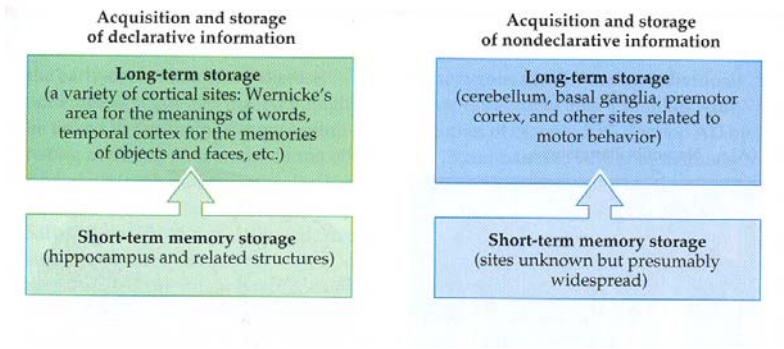
Rolls ET, and Kesner RP. A computational theory of hippocampal function, and empirical tests of the theory. Prog Neurobiol 79: 1-48, 2006 - not mandatory
Alvarez P, and Squire LR. Memory consolidation and the medial temporal lobe: a simple network model. Proc Natl Acad Sci U S A 91: 7041-7045, 1994

The hippocampus

The hippocampus is one of the most widely studied areas in the brain, anatomically as well as functionally.



The hippocampus is a specialized region of the "limbic cortex" located in the temporal lobe. Human patients with extraordinary cases of amnesia have triggered a wealth of research on the role of the hippocampal formation in learning and memory during the last 40 years. The observation of anterograde amnesia (memory for events prior to the injury were intact whereas new declarative memories could not be performed) has triggered a number of theories about the role of the hippocampal formation in declarative memory [aside: amnesia is called retrograde when one cannot remember events that occurred before a brain injury, whereas anterograde amnesia refers to the fact that events that occur after the injury cannot be remembered].
[Aside: terms that have been used to describe two types of memories. The first type, often called procedural, implicit or non-declarative refers to perceptual learning or learning of actions that do not require a memory of these events. For example, amnesic subjects can acquire a nictitating membrane response, but will not remember having undergone the experiment later. The memory of the event itself would be called declarative, explicit or working memory by many researchers.



HM (also known as "H.M." and "Henry M.," born 1926 in Connecticut) is an anonymous memory impaired patient who has been widely studied since the late 1950s and has been very important in the development of theories that explain the link between brain function and memory, and in the development of cognitive neuropsychology, a branch of psychology that studies brain injury to infer normal psychological function. He is still alive today and resides in a care institute located in Hartford, Connecticut, where he remains in ongoing investigation.[1]

HM suffered from intractable epilepsy that has been often—though inconclusively—attributed to a bicycle accident at the age of seven. He suffered from partial seizures for many years, and then several tonic clonic seizures (seizures with a loss of consciousness and convulsions) following his sixteenth birthday. In 1953, HM was referred to William Scoville, a surgeon at Hartford Hospital, for treatment.

Scoville localized HM's epilepsy to his medial temporal lobe (MTLs) and suggested surgical resection of the MTLs as a treatment. On August 25, 1953, Scoville removed parts of HM's medial temporal lobe on both sides of his brain. HM lost approximately two-thirds of his hippocampal formation, parahippocampal gyrus (all his entorhinal cortex was destroyed), and amygdala. We can safely assume his hippocampus is entirely nonfunctional because the remaining 2 cm of hippocampal tissue appears atrophic and because the entire entorhinal (which forms the major sensory input to the hippocampus) was destroyed. Some of his anterolateral temporal cortex was also destroyed.

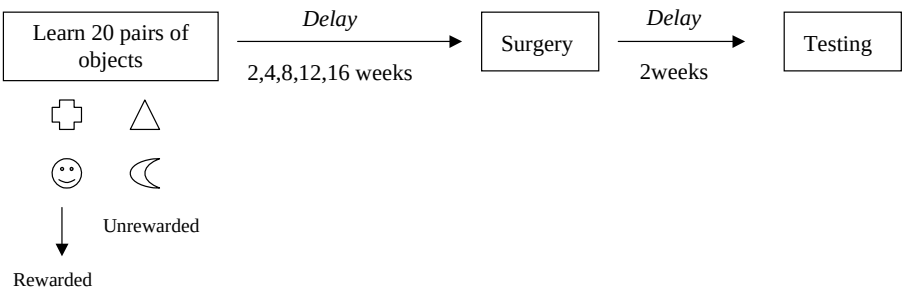
After the surgery he suffered from severe anterograde amnesia: although his short-term memory was intact, he could not commit new events to long-term memory. According to some scientists HM is impaired in his ability to form new semantic knowledge but researchers argue over the extent of this impairment. He also suffered moderate retrograde amnesia, and could not remember most events in the 3-4 day period before surgery, and some events up to 11 years before, meaning that his amnesia was temporally graded. However, his ability to form long-term procedural memories was still intact; thus he could, as an example, learn new motor skills, despite not being able to remember learning them.

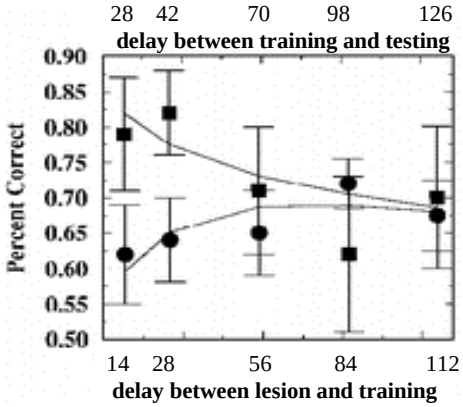
Particularly, the fact that he seems to be able to complete tasks that require recall from short-term memory and procedural memory but not long term episodic memory suggests

that recall from these memory systems may be mediated, at least in part, by different areas of the brain. Similarly, the fact that HM cannot create new long-term memories, but can recall long-term memories that existed well before his surgery suggests that encoding and retrieval of long-term memory information may also be mediated by distinct systems.

Temporal storage of declarative memory events. From HM and other human patients, it became clear that the role of the hippocampus was not only limited to a given form of memory (declarative), but that its role was also temporary. A number of animal studies have replicated this effect by training animals on a given task, then performing a lesions surgery to the hippocampal structures and then testing them at various points in time after the surgery: lesioned animals are impaired when asked to recall events that have been learned shortly before the surgery, but not those that have been trained a longer time before the surgery.
One experiment in particular showed the importance of the hippocampus for the formation of long term memories:
The primate hippocampal formation: evidence for a time-limited role in memory...

Zola-Morgan and Squire 1990: 288-290
Monkeys learned to discriminate 100 pairs of objects beginning 16, 12, 8, 4, and 2 weeks before the hippocampal formation was removed (20 different pairs at each time period). Two weeks after surgery, memory was assessed by presenting each of the 100 object pairs again for a single-choice trial. Normal monkeys exhibited forgetting; that is, they remembered recently learned objects better than objects learned many weeks earlier. Monkeys with hippocampal damage were severely impaired at remembering recently learned objects. In addition, they remembered objects learned long ago as well as normal monkeys did and significantly better than they remembered objects learned recently. These results show that the hippocampal formation is required for memory storage for only a limited period of time after learning. As time passes, its role in memory diminishes, and a more permanent memory gradually develops independently of the hippocampal formation, probably in neocortex.





Controls

Lesions

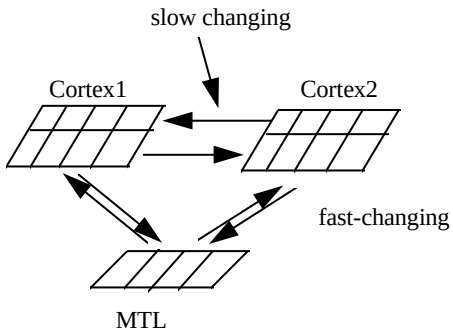
Controls exhibit normal forgetting

Hippocampal lesions impair memory formation only when they occur < 30 days after learning occured

These observations led to a theory for the role of hippocampus in memory consolidation. This theory, proposed by Alvarez and Squire (among others) is based on the following ideas: (1) several areas of neocortex and the medial temporal lobe (MTL) structures participate in the formation, maintenance and recall of long-term declarative memory events; (2) the neocortex communicates with the MTL via reciprocal connections; (3) within the neocortex, memory consolidation consists of gradually binding together the elements that form a given memory; (4) the MTL learns quickly, but has a reduced storage capacity and (5) the neocortex learns more slowly but has a large capacity. Based on these ideas, Alvarez and Squire proposed that consolidation occurs when neural activity in the MTL coactivates several regions of neocortex repeatedly.

Memory consolidation and the medial temporal lobe: a simple network model.
P Alvarez and L R Squire

MTL: Medial temporal lobe, contains hippocampus
Model consists of two "cortical " areas that are reciprocally connected to one MTL area. Each of the cortical are consists of 8 units (neurons), and the MTL are consists of 4 units.



Areas cortex1 and cortex2 represent association cortex. Each unit in a given area is reciprocally connected to each unit in any other are. There are no connections between units of a given area. Connections from and two the MTL are faster changing than connections between the two cortical areas..

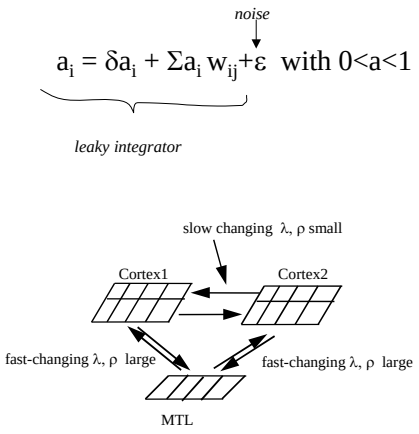
Based on this simple model, the authors propose the following scheme for memory consolidation: (1) events activate neurons in association cortex. If such events occur repeatedly, (2) connections between cortical areas and MTL are rapidly formed that represent these memories. Because the connections between the cortical areas change much slower, in the beginning, memories are stored in the connections between cortex and MTL. During that time, lesioning of the MTL would disrupt those memories. (3) After repetitive learning, the slower changing connections between cortical areas would change, memories can be supported by them and lesioning of the MTL would not disrupt memories.

Neurons: Continuous output leaky integrators

Exercise: Write down the equation that describes a continuous output leaky integrator.

Winner-take-all: Remember, this refers to a network in which only the most strongly activated unit in each layer stays active and all others are silent. Cortex 1 and cortex 2 consist of two layers, MTL of a single layer.

Exercise: Draw a winner-take-all network and describe a neural mechanism that can implement this idea. Write down all equations necessary.



1) Update all a's in Cortex 1 and Cortex 2 at the same time Calculate a's, find most strongly activated unit in each layer and set all others to zero.
2) Then update a's in MTL using previously calculated values from cortex 1&2. Find most strongly activated unit and set all others to zero.
3) Calculate synaptic weight changes using hebbian learning rule.

$$\Delta w_{ij} = \lambda\, a_i\, (a_j - \bar{a}) \quad \text{with } 0<w<1$$

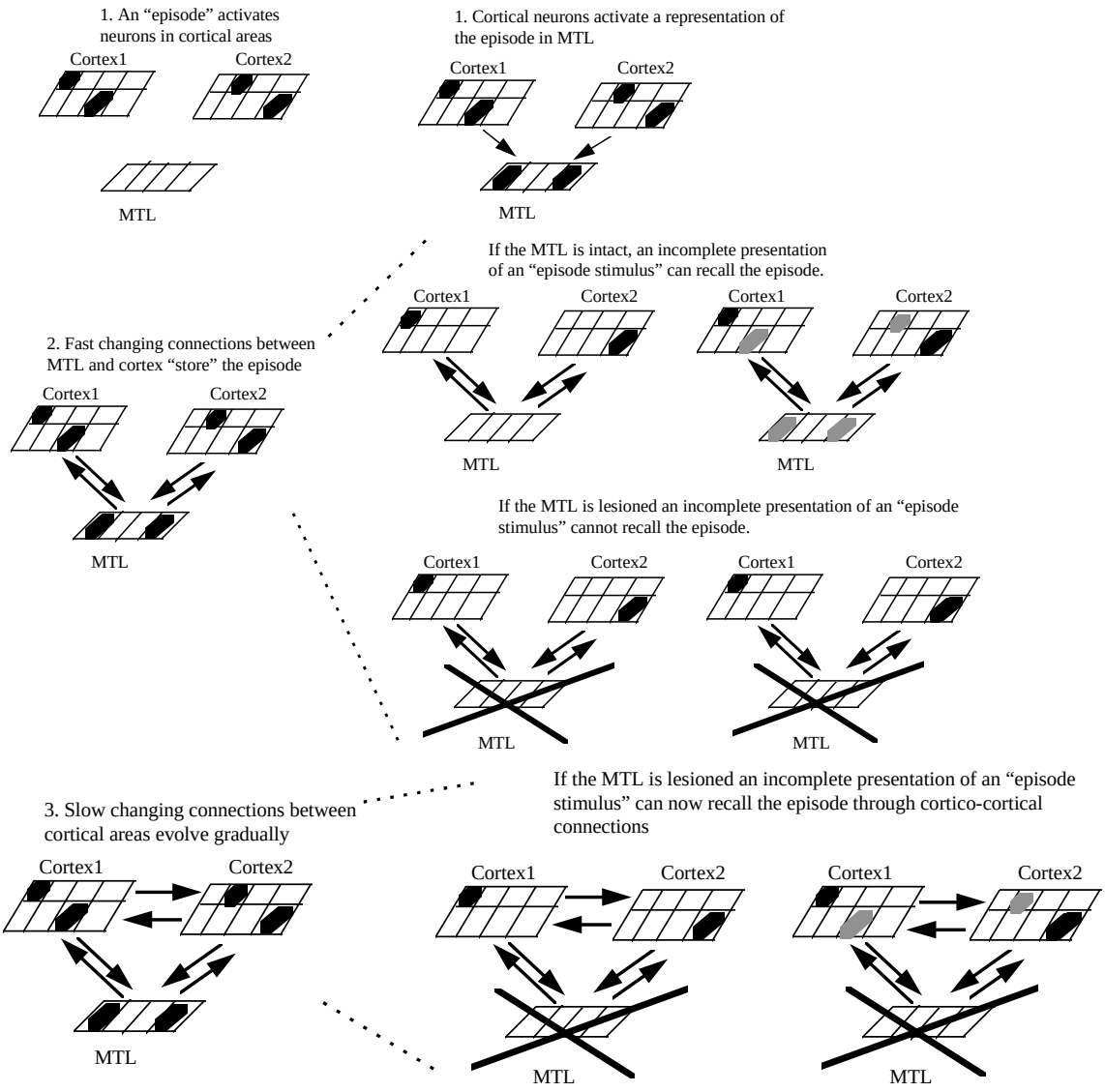
This learning rule produces a positive change if the activity of the presynaptic neuron is larger than the average activity and a negative change if it is smaller.
4) Apply forgetting on the synaptci weight values calculated in 3):

$$\Delta w_{ij} = -\rho\, w_{ij}$$

where the value of ρ defines the speed of forgetting.

Goal: To reconstruct a "stored" or "learned" pattern of input from an incomplete version of that input. Each pattern consisted of two units activated in cortex1 and two units activated in cortex 2.

Exercise: What type of network we talked about in class can do this? What are the equations involved?

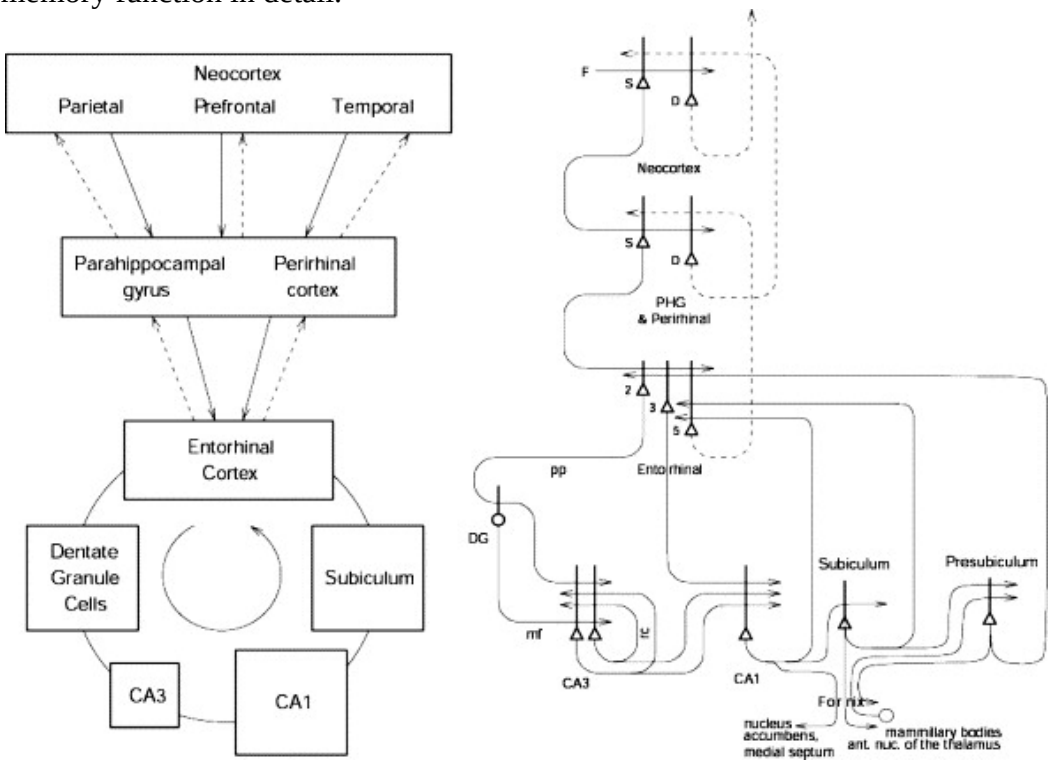


Discussion points: What are the assumptions in this model? How do they correspond to known data? Which choices of parameters are necessary to make this model work? Which are not?

-More details about the hippocampus and how it may be used in memory formation

Hasselmo ME, and Wyble BP. Free recall and recognition in a network model of the hippocampus: simulating effects of scopolamine on human memory function. *Behav Brain Res* 89: 1-34, 1997.

In the last lecture, we contemplated the idea that the hippocampus serves to store memories to keep them fresh while the cortex consolidates those memories that are repeated a lot. The hippocampus and neocortex would thus be complementary memory systems, with the hippocampus being used for rapid, “on the fly”, unstructured storage of information involving activity potentially arriving from many areas of the neocortex; while the neocortex would gradually build and adjust on the basis of much accumulating information the semantic representation. Today, we will discuss ideas about how the hippocampus could be involved in human memory function. First, we'll have a closer look at the hippocampal circuitry and then we'll discuss an existing model of human memory function in detail.

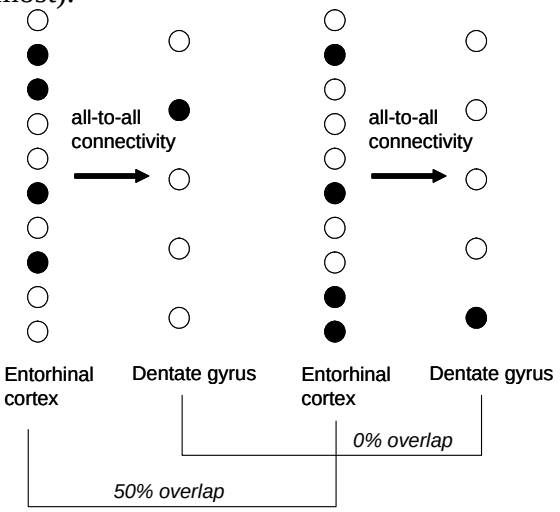


The figure above shows the principal organization of hippocampal interactions with neurocortical structures. Note that most communication uses the entorhinal cortex as a pathway.

The hippocampal circuitry itself encompasses mainly areas CA1, CA3 and dentate gyrus. Each of these is thought to underlie a specific function.

1) The first way is that the perforant path—dentate granule cell system with its Hebb-like modifiability is suggested to act as a competitive learning network to remove redundancy from the inputs producing a more orthogonal, sparse, and categorized set of outputs.

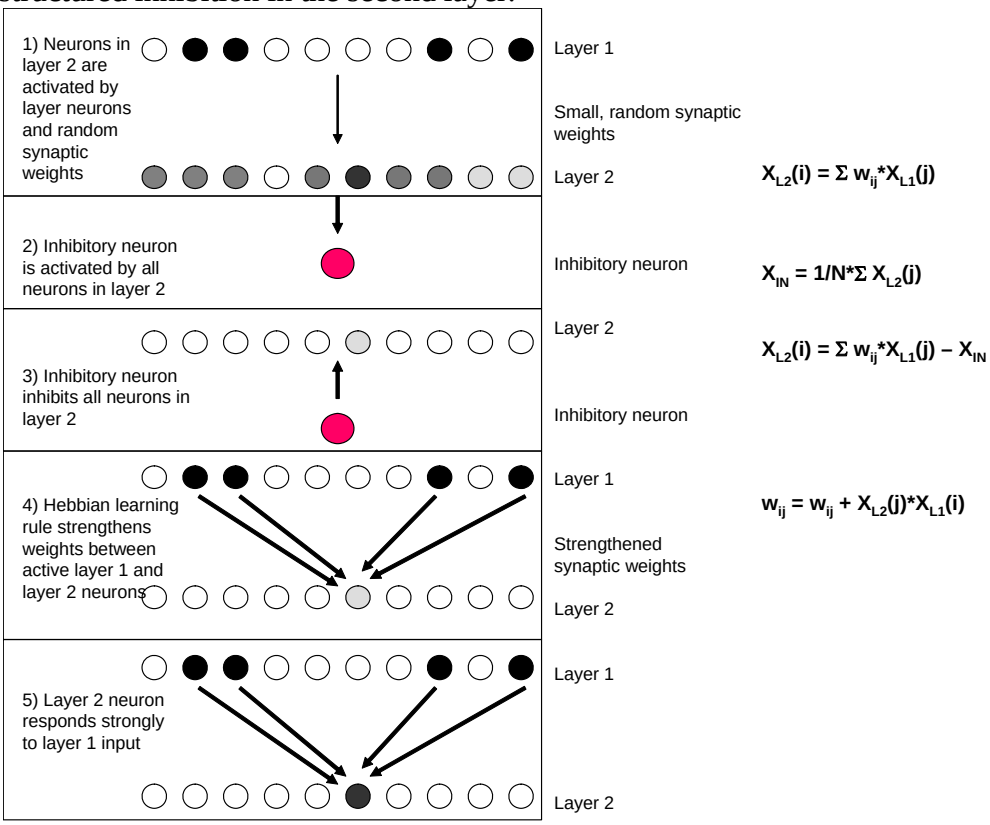
The idea here is that a pattern with many active neurons could be transformed into one with fewer active neurons by a process of self-organization (winner-take-all, winner-take-most).



Sparsening: from a representation in which many neurons represent a particular piece of information to a representation in which very few neurons represent a piece of information.

Orthogonalization: from a representation in which patterns are non-orthogonal (have high overlap) to a representation in which patterns are orthogonal (have little or no overlap).

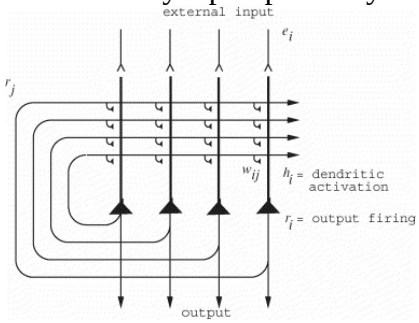
This type of functionality can arise by using a hebbian learning rule in conjunction with structured inhibition in the second layer.



This particular process is termed “self-organization” because the pattern in layer 2 is not imposed by outside input but is driven from Layer 1 activity.

2) There seems to be a general consensus that area CA3 serves as an associative memory device. This idea is mainly based on anatomical evidence showing that pyramidal cells in area CA3 have a dense network of association fibers (pyramidal cells making synapses

onto other pyramidal cells within this area) as well as data showing that these synapses can exhibit synaptic plasticity under the right conditions.



We have extensively discussed the process of auto-associative memory in previous lectures, this concept will not be repeated in detail here.

3) The connections between areas CA3 and CA1 could serve the purpose to compare the pattern processed through the dentate-gyrus CA3 pathway to that imposed onto CA1 directly by the entorhinal cortex. This could happen via a hetero-associative process (association between two imposed patterns), as discussed in detail in previous lectures about linear associators.

Hasselmo and Wyble present a theory for human memory function in the hippocampal network that is similar to other theories that have been proposed (see for example McClelland, Posner, Rolls) and is supported by large scale simulations and a wealth of experimental data. Note that this particular theory does not address the short –term storage function of the hippocampus, nor the spatial coding issues. It does address the theory of list learning in humans and the importance of ACh for this function.

Why model the effects of drugs? A main issue with abstract models of memory is validation. One possible means to validate a model is to manipulate a parameter in the system to be modeled, manipulate the same parameter in the model, and test if both react to this manipulation in the manner. In way, modeling the effect of drugs is a way to validate a model. If the cellular effect of a drug are known, and the behavioral effects are known, then the model should reproduce the behavioral effects when the cellular effects are implemented.

In this paper, the cellular effects of the neuromodulator acetylcholine are added into the model, and the presence of an antagonist, scopolamine, is modeled. Remember, an antagonist is a substance that can bind to a receptor but does not lead to the changes in neural activation that the natural agonist (neuromodulator or neurotransmitter) would produce. Thus, the antagonists occupies the space that the neuromodulator would need to have its effects, and hence blocks its action.

The justification for why a model of episodic memory should be situated in the hippocampus is somewhat less clear, but there is some evidence that the hippocampus is necessary for episodic memory. However, it seems that the principal conclusions from this model are somewhat independent of the brain structure modeled. The main points addressed are these:

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

(2) Effect of scopolamine on free recall, but not recognition. Blockade of cholinergic effects in the model during encoding of a list of words should impair the subsequent free recall of the words, but not the recognition of these words. [Free recall: name the words on the list. Recognition: was this word on the list, yes or no.]

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

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

Neurons were implemented as leaky integrators with continuous output functions (no spikes):

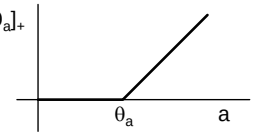
Leaky integrator: $\tau\, da(t)/dt = - a(t) + Input$

$\Delta a = - \eta\, a + Input$

$$\Delta a_i = A_i - \eta\, a_i + (E_{NA} - a_i) \Sigma\, w_{ij} [a_j - \theta_a]_+ (E_{Cl} - a_i) \Sigma\, H_{hl} [h_l - \theta_h]_+ + \mu\, c_i (E_k - a_i)$$

Afferent input — *Decay* — *Excitatory synaptic input* — *Inhibitory synaptic input* — *Calcium dependent K+ current*

$[a_j - \theta_a]_+$: linear threshold function



Patterns to be learned consisted of input line Ai to a given neuron being activated (A_i = 1.0). Synaptic weights between neurons were updated according to a Hebbian learning rule (somewhat more complicated than what we discussed in class):

levels of ACh — *slow, thresholded, average of presynaptic activity*

$$\Delta W_{ij} = \kappa\, (1-\chi_s(1-\psi))\, ([s_i-\theta_w]+\omega_{pre} W_{ij})([s_j-\theta_w]+ - \omega_{post}\, W_{ij})$$

learning rate — *slow, thresholded, average of postsynaptic activity*

θ_w high: learning occurs not easily, low interference with previoulsy stored patterns that may be reatcivated

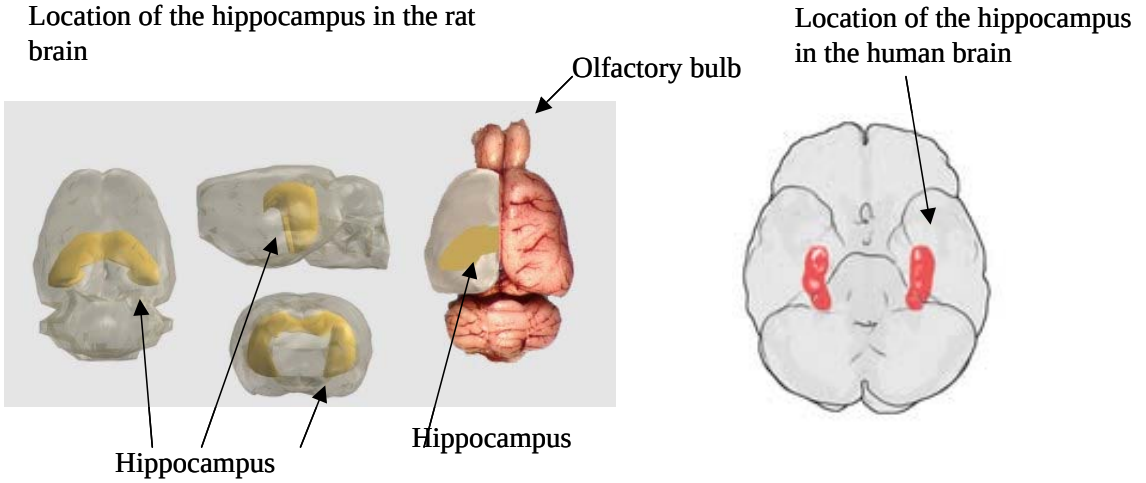
θ_w low: allows self-organization

The above defined learning rule allows, with varying parameters, to implement self-organization, hetero-association and auto-association.
The details of the simulations will be discussed in class.

Working memory

As described previously, ongoing and/or stimulus-evoked oscillations have been recorded in many brain areas over the last 30 and more years. (Stimulus-evoked refers to the fact that often, these oscillations occur in response to a stimulus rather than spontaneously). It is generally thought that these oscillations are due to both intrinsic oscillatory properties of individual neurons and two oscillatory network properties that arise because of extensive feedback interactions between different types of neurons.

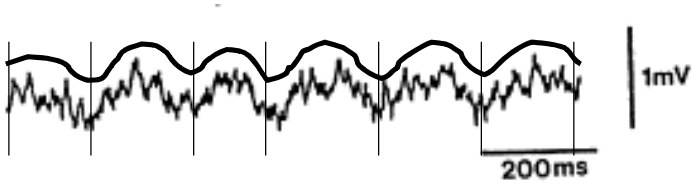
The rat hippocampus is a brain region in which oscillations, their functional role and their modulation by behavior have been extensively studied.



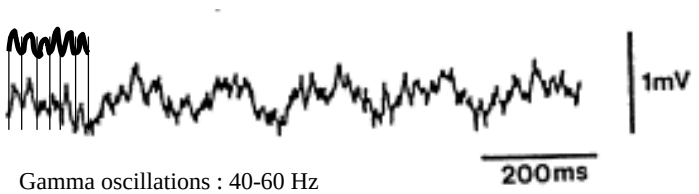
To date, the hippocampus (which is part of the limbic system) is believed to play a role in short-term memory, declarative memory and memory consolidation. In rats, there is also abundant evidence that the hippocampus is involved in spatial orientation and in representing configurations among stimuli.

In rodents, it is known to exhibit some of the most robust forms of synchronous rhythmic activity to be observed in the nervous system under certain behavioral states (exploration, sniffing, sleep). Foremost among these synchronous activities are the theta rhythm (4-10 Hz; occurs mainly under active exploration of the environment), the gamma rhythm (40-60Hz) that co-occurs with the theta rhythm and a signal having a frequency around 200 Hz, associated with alert immobility and sleep.

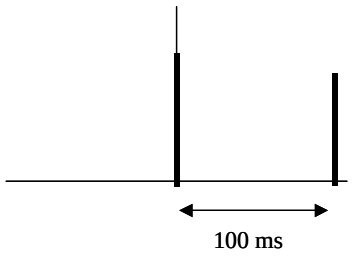
Simultaneous theta and gamma oscillations recoded in the rat hippocampus

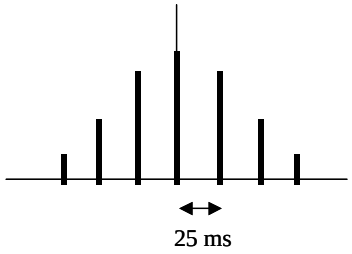


Theta oscillations : 4-10 Hz



Gamma oscillations : 40-60 Hz



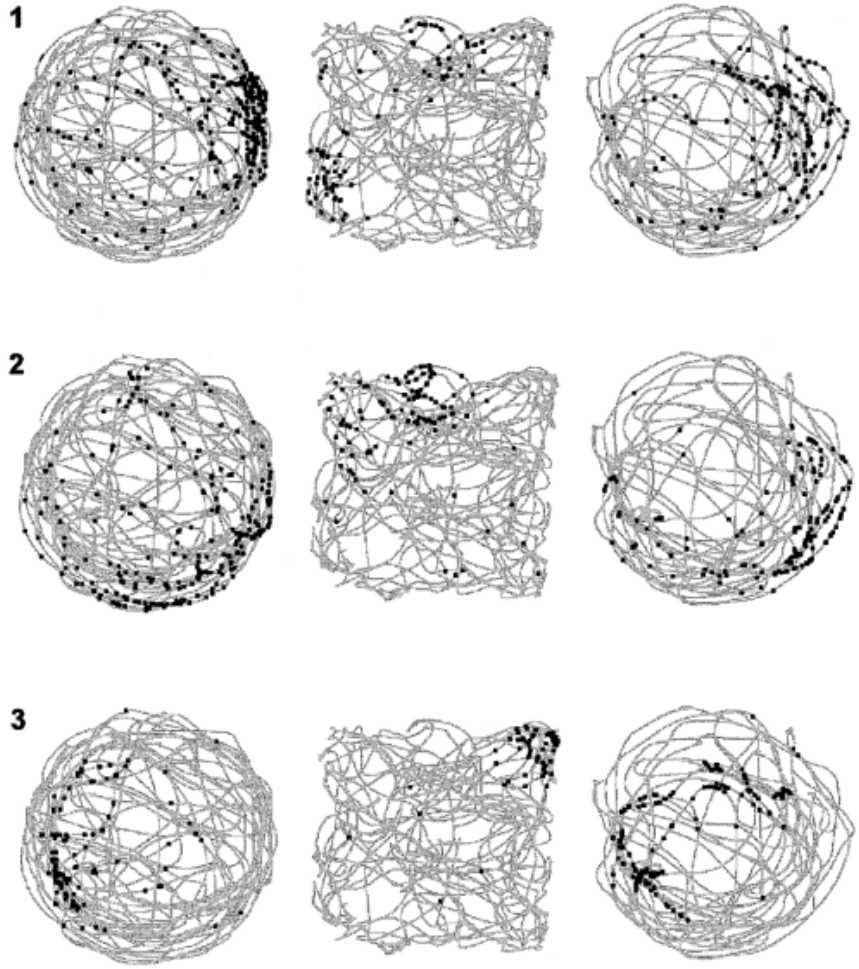


The theta rhythm occurs in non-primate mammals during active exploration and sniffing and is broadly distributed throughout the hippocampus. It can be elicited in the anesthetized animal either by using light urethane anesthetize, or by injecting a cholinergic agonist. It can be elicited in an in vitro brain slice preparation by adding the cholinergic agonist carbachol. In the behaving and anesthetized animal, hippocampal theta is thought to be driven by rhythmically firing GABAergic and cholinergic neurons in the medial septum. But since in a slice preparation, hippocampal pyramidal cells can by rhythmically active in the theta range, it is clear that these oscillations can be generated within the hippocampal network.

Lately it has been shown that the theta rhythm modulates the firing activity of so-called place cells in the hippocampus, this phenomena has been called "phase precession". The observation is that as an animal moves in and out of a particular "place field" (i.e. the location in space for which a given cell fires), the action potentials of that cell change their relative phase with respect to the theta rhythm.

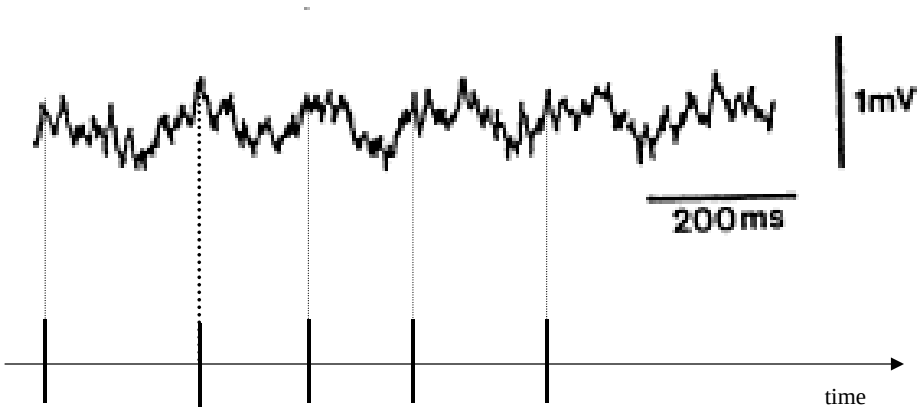
Place fields refer to one of the most intriguing discoveries about the hippocampal formation was that observed by O'Keefe and colleagues in the early 1970's who recorded the activity of individual neurons in the hippocampus as an animal moved around in an environment. They found that some neurons fired at a high rate ONLY when the animal was moving through a particular location in space. Different neurons had different spatial receptive fields. Interestingly, the spatial fields of the neurons would rotate with respect to the absolute orientation when exterior cues were rotated, spatial receptive fields in the

same environment seem to be stable over repetitive placements in the same environment, and a cell can have multiple spatial fields if the rat is moved between environments.



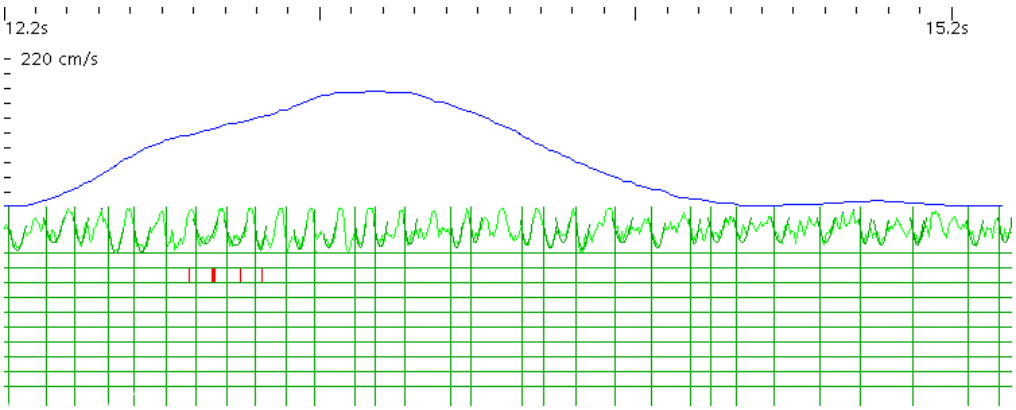
Examples of place fields of hippocampal cells. Rats are made to move around in either either a circular (left and right columns), or square platform. Small food pellets are dropped onto the platform in random locations to animate the animal to move around. The gray lines show the path of the rat during the experiment and the black dots show those locations in the two-dimensional space for which the neuron that is represented here fired at a higher average rate than its spontaneous (rat sits still) rate. After the "place fields" had been recorded on the circular platform, the rat was placed in a square-shaped environment and the same neurons were recorded. One can observe that when the rat had been placed in a different environment, the same cells fired in different locations.

During spatial exploration, the firing of hippocampal cells is modulated by the observed theta rhythm. (Modulation refers to the fact that the firing of action potentials, even though related to the location of the animal, is modulated in time by co-occurring brain rhythms.



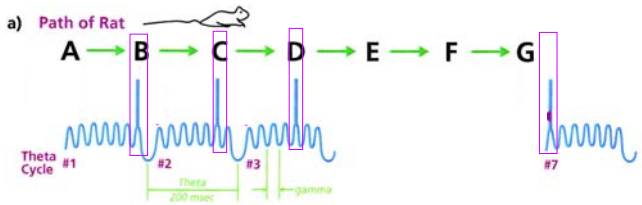
Modulation of firing in the hippocampus by the theta rhythm. The action potentials of individual cells (lower trace) occur preferentially a given phase of the theta oscillation.

Often, the theta rhythm is accompanied by a second rhythmic activity at 40-60 Hz, the gamma oscillation. The firing of individual neurons in the hippocampus is modulated by both the slow activity (theta) and the fast (gamma) activity. Oscillations in this frequency range are also observed in the olfactory system, the visual system and throughout other brain areas in mammals. While their functional role is still open to much speculation, the mechanism through which these oscillations may occur has been extensively studied. Contrary to the hippocampal theta rhythm, which seems to be imposed from the medial septum, the gamma rhythm is thought to be generated locally in the hippocampus. I will lecture in detail about the paper by Traub et al. (1995) which first showed that fast oscillations may be produced by interconnected networks of inhibitory neurons in the hippocampus.

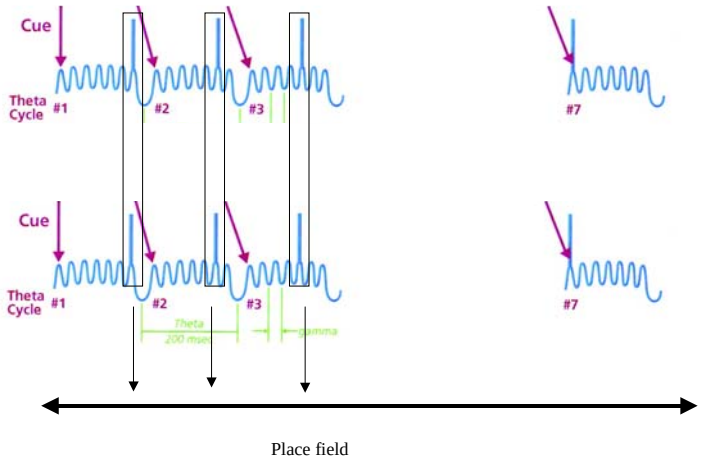


Firing of a hippocampal cell as the rat crosses the cell's place field. The oscillatory trace on the top is the theta rhythm recorded in the hippocampus. The lines below indicate when the cell fired as the rat ran through the place field. The cell fires earlier and earlier with respect to theta as the rat runs through the place field.

There are approximately 5-7 gamma cycles in one theta cycle; when a rat moves on a linear track, hippocampal pyramidal cells spike on a given gamma cycle depending on the rat's location (phase precession)



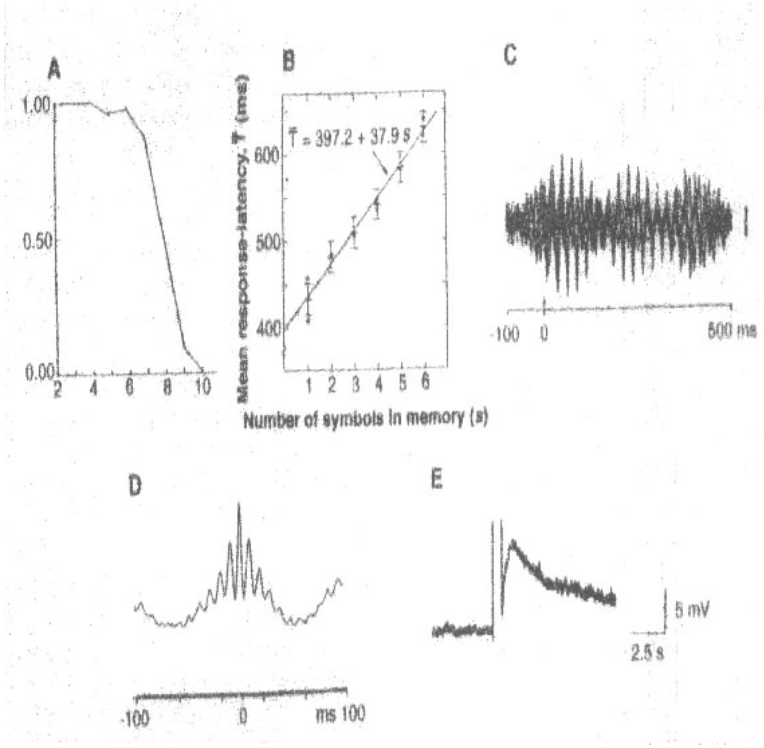
Remember our discussion about neural assemblies: the idea was that separate groups or assemblies of neurons within a larger group that respond to a stimulus fire at the same time. When a rat runs down a track, several neurons fire for each spatial location.



Different “place cells” with the same larger place field fire during the same gamma cycle when the rat is at the specific place within the place field

Lisman JE, and Idiart MA. Storage of 7 +/- 2 short-term memories in oscillatory subcycles. *Science* 267: 1512-1515, 1995
Fransen E. Functional role of entorhinal cortex in working memory processing. *Neural Netw* 18: 1141-1149, 2005

In a model relatively unrelated to experimental knowledge about hippocampal function, John Lisman and Marco Idiart from Brandeis University asked how the fact that neurons in the hippcoampus spike in phase with different gamma-cycles during a given theta cycle could be computationally useful. The suggested that since the hippocampal formation has been related to short term memory, and that since it is known that human subjects can keep up to 7+/- 2 items in their short term memory, and since there are approximately 7 gamma cycle in one theta cycle, maybe a relation could be found between these very different levels of observation.



A. Human short-term memory for lists

B. Serial scanning of the list: response time goes up as numbers of items on the list are increased.

C. Nested oscillations recorded from human EEG

D. Oscillations recorded from rat hippocampus: slow theta waves contain faster (gamma) waves.

E. Afterdepolarization of hippocampal neurons after an action potential.

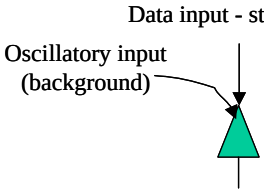
Each neuron in their model receives a subthreshold (meaning the voltage due to this input stays below firing threshold) oscillatory input at 6 Hz as well as a suprathreshold (can frie the neuron) data input (stimulus). The special thing about this neurons is that instead of hyperpolarizing after an action potential, the membrane potential depolarizes after a spike has been fired (afterdepolarization or ADP). Neurons are modeled as leaky integrate and fire neurons similar to those discussed in the lecture:

$$\tau_v \, V(t)/dt = -V(t) + V^{rest} + V^{osc}(t) + V^{ADP}(t) + V^{inh}(t)$$

V is the voltage of the neuron evolving over time, τ_v is the membrane time constant, V^{rest} is the resting membrane potential (-60mV), V^{osc} is the oscillatory subthreshold input (peak 5mV, frequency 6Hz), V^{ADP} is the afterdepolarizing input after an action potential (alpha function with Vmax 10 mV and rise decay time 200 ms) and V^{inh} is an inhibitory input from other neurons in the network. The voltage V is set back to V^{rest} (-60 mV) after it has crossed threshold (-50 mV) and the neuron has fired an action potential.

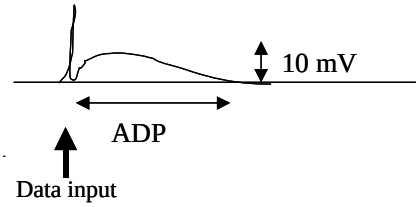
<u>Exercise</u>: What is are the additional parameters in the equations used above and what would their effects be?

1. Each neuron has a subthreshold oscillatory input and a data input.

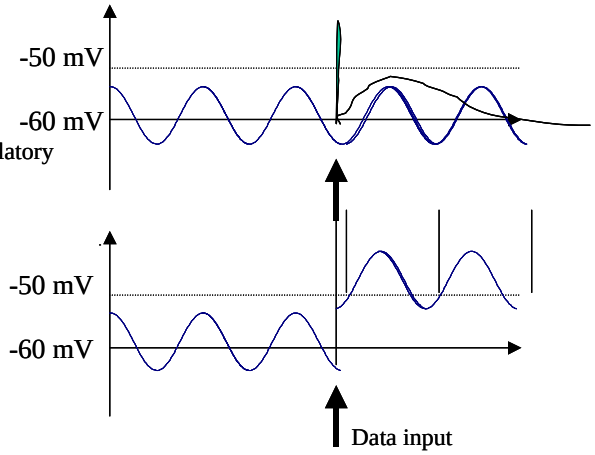


2. The data input alone is strong enough to fire the neuron

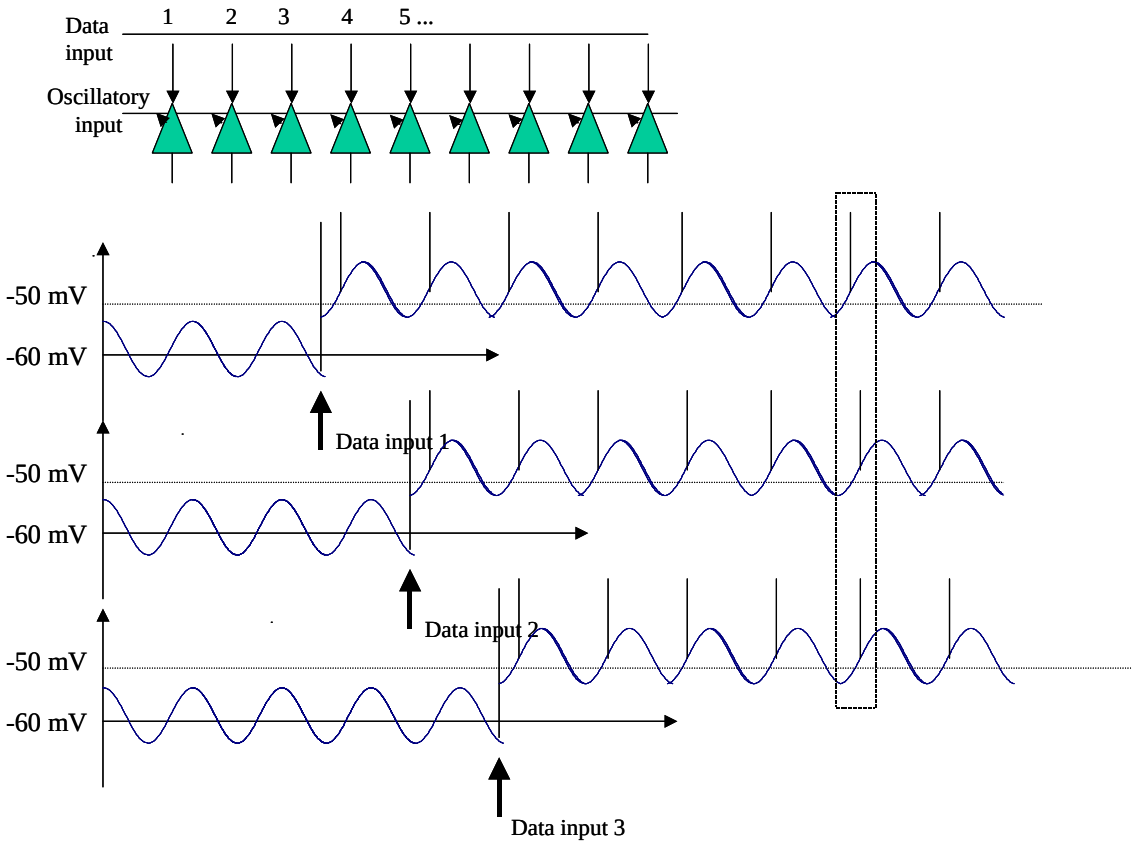
3. After each spike, the neuron is depolarized for ~200 ms because of afterdepolarization (ADP)



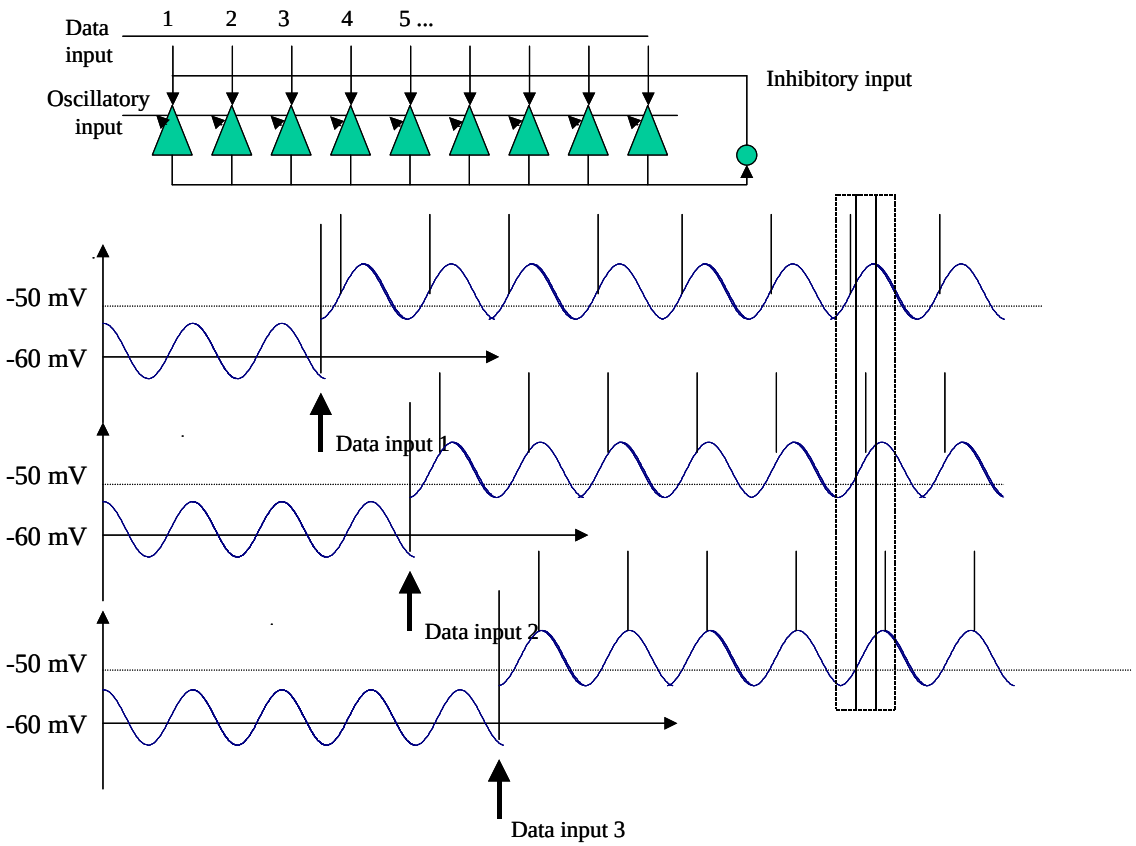
4. After a data input, the ADP and the subthreshold oscillatory input add up in such a manner that the neuron can fire repeatedly at the same phase of the oscillatory input.



Each individual cell of this type is able to fire repeatedly after a single, brief, data input event because of the superposition of the subthreshold oscillatory input and the ADP (afterdepolarization). If a network of such cells is modeled, each of these cells could "store" a given data input because each individual cell is capable of repeatedly firing after a single, brief, data input. If all data inputs occur at the phase of the oscillatory input, then all neurons would fire more or less in synchrony!

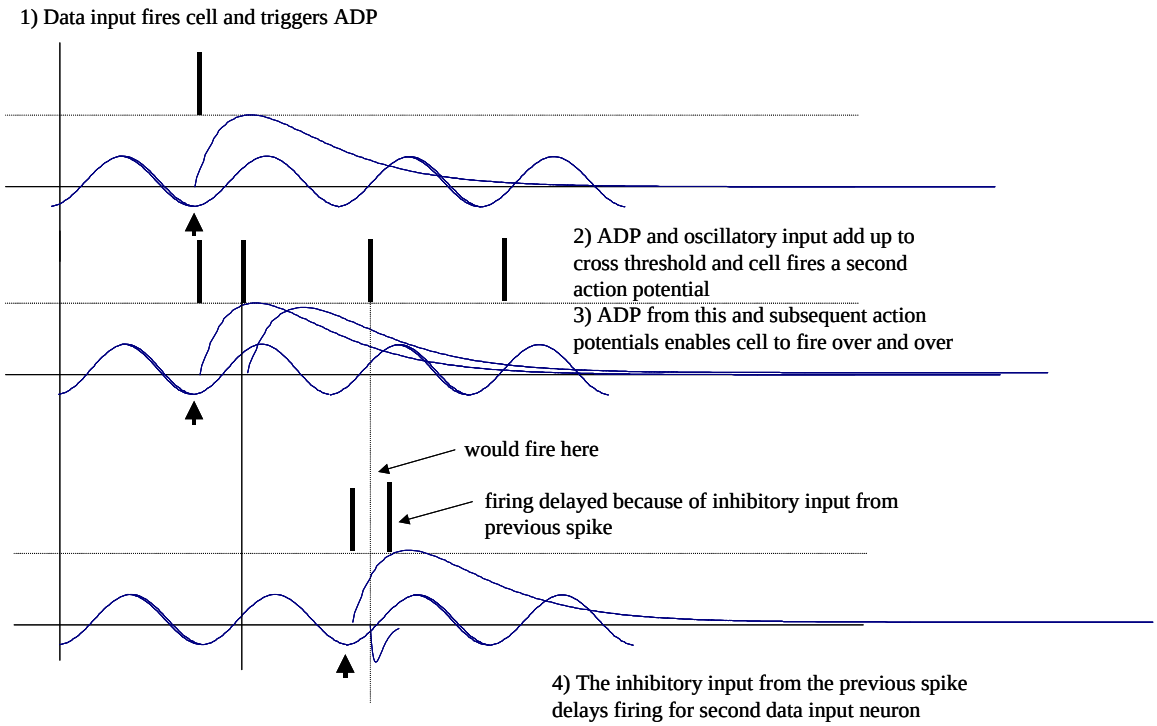


If inhibition is added to the network in such a manner that each pyramidal cell activates a common inhibitory interneuron which feeds back inhibition to all neurons in the network, and if the time constant of this inhibition is exactly right, then the network parameters can be arranged in such a fashion that neurons responding to different data inputs fire at different phases of the theta cycle. This happens because inhibition due to cell1 firing delays the firing of cell2 by a few milliseconds.



<u>Exercise</u>: Why does this work?

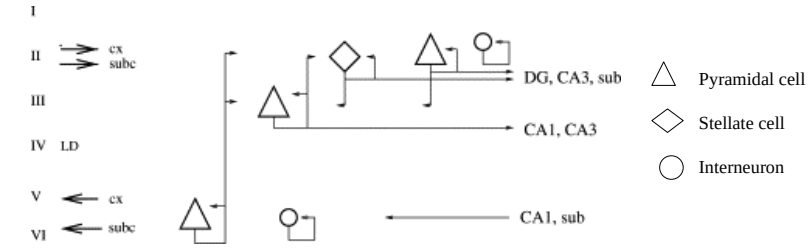
When the action potential occurs due to the data input, the ADP in conjunction with the positive phase of the oscillatory input raise the membrane potential above threshold during a fraction of the period of the oscillatory input. As a consequence, the neuron fires again.
The parameters of this simulation need to be very tightly tuned: oscillation frequency, ADP and inhibitory time constants need to be precisely attuned to each other.

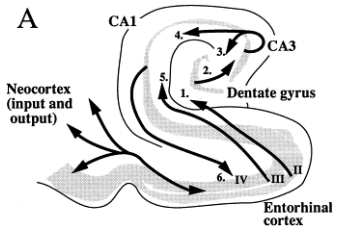


Exercise: Which parameters in this model have to be precisely tuned with respect to each other to make this work?

Entorhinal cortex. A quite different hypothesis for short term (or working memory) has been proposed by others. The next paper discusses working memory function in the entorhinal cortex. Remember from previous lectures that the entorhinal cortex constitutes the major input and output pathway for information to and from the hippocampus. As such, the entorhinal cortex (EC) is very important as it is positioned as a 'gateway' between neocortical association areas and the hippocampal system. It has been suggested to work as a temporal buffer of incoming information for hippocampus .

Anatomically, the superficial layers of EC receives the input from neocortex and provides the main input via the perforant path to the dentate gyrus of the hippocampal formation. The deeper layers receive input mainly back from hippocampus field CA1 and the subiculum and provide the output back to the neocortical areas. The deeper layers also project to the more superficial layers, creating a loop through the entorhinal-hippocampal system. Sensory, motor and associational information is thereby processed in EC and hippocampus before being stored permanently in neocortex.





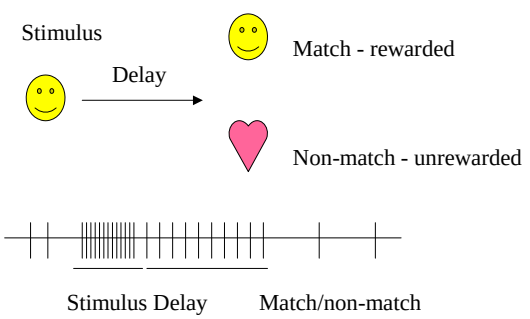
Working memory. Working memory (WM) is a non-permanent memory, sometimes also referred to as short-term memory. Based on findings in psychological memory research, working memory is assumed to depend on continuous activation or neurons even after the trigger stimulus has been turned off.

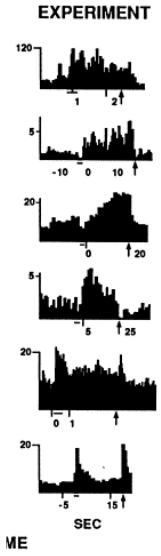
Fuster JM. Cortical dynamics of memory. *Int J Psychophysiol* 35: 155-164, 2000.

Fransen E. Functional role of entorhinal cortex in working memory processing. *Neural Netw* 18: 1141-1149, 2005

In the entorhinal cortex, cells are found which show activity related to the main behavioral components of a working memory task. Furthermore, entorhinal and perirhinal cortex ablations impair performance in delayed match-to-sample tasks.

A delayed match-to-sample task is a task in which an animal is shown a stimulus, and after a delay is given a choice between that stimulus and a novel, unrelated stimulus. To obtain a reward, the animal has to choose the previously shown stimulus. A different version of the task, call delayed non-match-to stimulus task requires the animal to choose the novel stimulus in order to obtain the reward. In many cases, it has been shown that the neural activity triggered by the first stimulus stays high during the delay period.



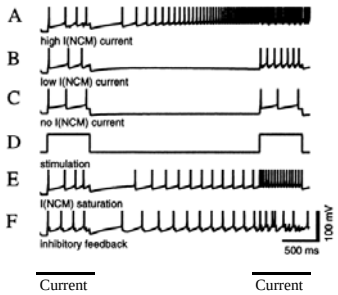


<u>Acetylcholine again!</u>

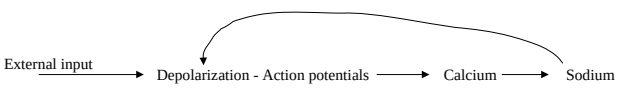
Cholinergic modulation in the entorhinal cortex may be particularly important for performance in delayed match-to-sample tasks. Systemic injections (into the blood stream using a drug that will cross the blood-brain barrier) of muscarinic cholinergic antagonists have been shown to impair performance on recognition memory tasks, while sparing performance at zero second delays.

Persistent activity can be seen in EC pyramidal cells that are isolated from their network, this appears to be an intrinsic property and depends on the presence of a specific type of Na+ channel.

Exercise. Find three ways to implement persistent firing in a network with leaky integrate and fire neurons. Discuss if these would also work if you use straight integrate and fire neurons.

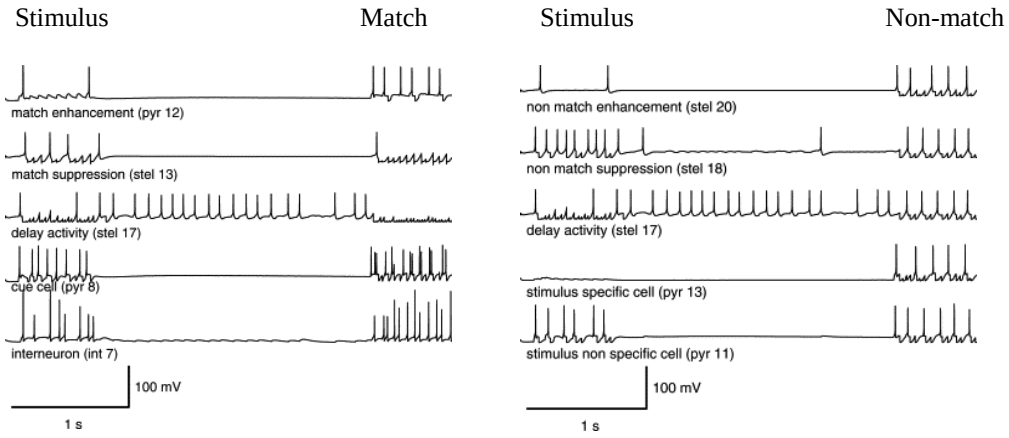


Calcium dependent sodium channel provides excitatory feedback of cell onto itself.
External input is necessary to start the process but not needed to keep it active.



Persistent activity in single cells can be attributed to a specific type of Na+ channel which is calcium dependent and very slow rising. Briefly, the cell is first depolarized and fires action potentials because of some external input (current injection for example). After the stimulus is switched off, a high accumulation of Ca+ opens Na+ channels which lead to further depolarization of the cell and can lead renewed spiking.

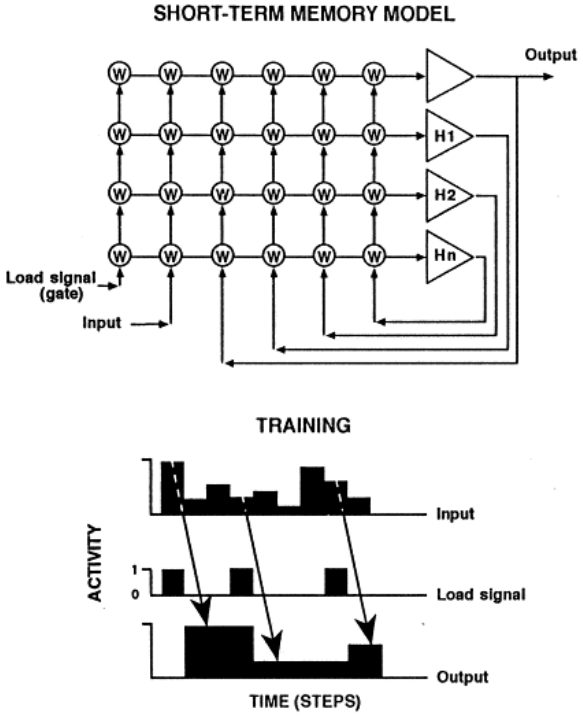
A simulation of a network of these cells interconnected together produces all the different scenarios which have been described when recordings in behaving animals have been made during a delay-to-(non)match task: (1) Match suppression (neurons response is suppressed when second stimulus occurs), which could result from inhibition of neurons by other neurons undergoing match enhancement; (2) Non-match enhancement (neural response occurs only to non-match stimulus), which could result from strong excitatory input from non-selective cells; (3) Non-match suppression, which could result from greater activation of inhibitory interneurons by non-selective cells; (4) An explanation for the role of the non-selective cells. In the non-match simulations, the differential action of the selective and the non-selective cells and their connectivity to interneurons provide a mechanism for causing non-match enhancement and suppression activity. The specific combination of these different types of responses could suffice to encode the match/non match information. What is important here is that the activity in the network in response to the second stimulus is influenced by the response to the first stimulus. It is also important to note that the persistent activity is not a network, but an individual neuron property here.



The third paper, by Fuster, proposes that persistent activity results from the activation of a memory network and is carried by feedback excitatory synapses rather than by intrinsic neuronal properties:

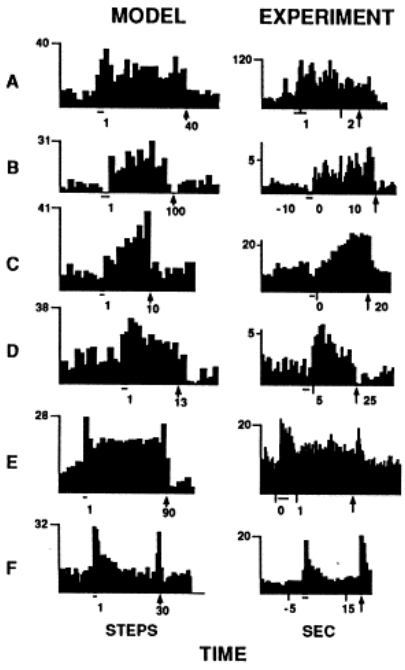
"Working memory essentially consists in the temporary activation of a memory network, as needed for the execution of successive acts in a temporal structure of behavior. That activation of the network is maintained by recurrent excitation through reentrant circuits. The recurrent reentry may occur within local circuits as well as

between separate cortical areas. In either case. recurrence binds together the associated components of the network and thus of the memory it represents. "



The connection weigts are determined using a learning algorithm in such a way that for a given analog input value the network will drive the output to a given analog output value.

Once the connection weights have been determined, one can drive the network with a given input signal and observe the activities of the "hidden" or "internal" neurons.



Comparison of activity of hidden neurons in the model network during the delay period to recordings in monkey prefrontal cortex.

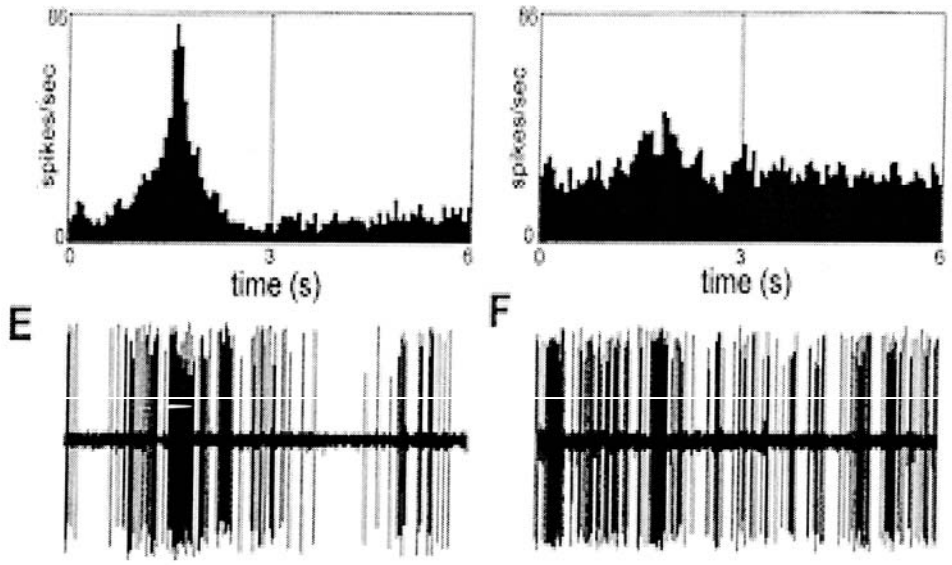
Signal-to-noise ratio

Signal-to-noise ratio is an engineering term for the power ratio between a signal (meaningful information) and the background noise:

$$\mathrm{SNR} = \frac{P_{\mathrm{signal}}}{P_{\mathrm{noise}}} = \left(\frac{A_{\mathrm{signal}}}{A_{\mathrm{noise}}}\right)^2$$

When thinking about neurons, we often define the "signal" as those action potentials elicited by a stimulus of interest, and the "noise" as all other spikes. Since neurons in many areas in the brain have a high background activity, and many stimuli evoke few action potentials, it is often of interest to measure the signal to noise ratio and to aks how it can be improved.

For example, if a neuron in auditory cortex has a high background activity rate (~15 Hz), and changes its activity rate minimally in response to an auditory signal, then we would say that its signal-to-noise ratio is low because it is difficult to determine whether or not the neuron responds to the stimulus of interest. In contrast, if its background rate is low, the same rate in response to a stimulus of interest would be easily detectable.



The signal to noise ratio of neurons could be modulated by a number of factors, including changes in synaptic efficacy, excitability, degree of inhibitory inputs the neuron receives, spike threshold and others. In particular, the neuromodulator noradrenaline has been proposed to modulate signal-to-noise ratio in many brain areas.

Norepinephrine is released when a host of physiological changes activated by a stressful event, unleashed in part by activation of an area of the brain stem called the locus coeruleus. This nucleus is the origin of most norepinephrine pathways in the brain. Neurons that are activated by norepinephrine project bilaterally (send signals to both sides of the brain) from the locus ceruleus along distinct pathways to many locations, including the cerebral cortex, limbic system, and the spinal cord.

Noradrenaline (NA) has a multitude of effects on pyramidal cells in many cortical areas: its has been shown to depolarize neurons by affecting leak currents, to change synaptic efficacy between pairs of neurons, to modulate spike frequency adaptation, to name only a few. In may brain areas, NA is known to inhibit the spontaneous activity of neurons and to enhance their responses to sensory stimuli (render them more sensitive to sensory stimuli). In general, NA is thought to supress noise by increasing inhibition and to render neurons more sensitive to stimuli from sensory inputs by decreasing excitatbility of modulating synaptic efficacy.
A wealth of experiments point to NA as a modulator for learning: blocking NA receptors effects learning in animals and LTP/LTD in brain slice experiments. A mis-regulation of NA is thought to be at the root of disorders like attention deficit disorder, often treated with NA reuptake inhibitors (which increase the amount of available NA in the brain).

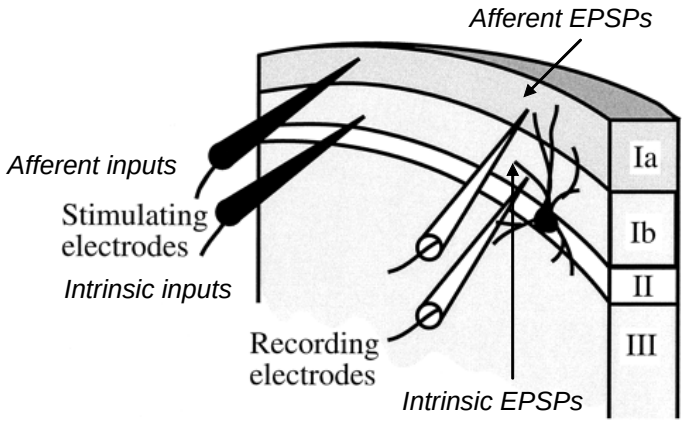
The papers we are reading today focus on the role of noradrenaline in signal-to-noise modulation.

Hasselmo ME, Linster C, Patil M, Ma D, and Cekic M. Noradrenergic suppression of synaptic transmission may influence cortical signal-to-noise ratio. *J Neurophysiol* 77: 3326-3339, 1997
Usher M, Cohen JD, Servan-Schreiber D, Rajkowski J, and Aston-Jones G. The role of locus coeruleus in the regulation of cognitive performance. *Science* 283: 549-554, 1999.

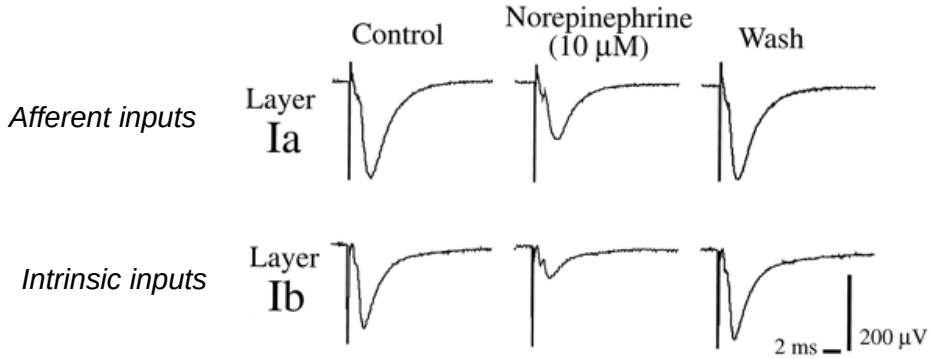
In the Hasselmo et al. paper, the authors show that NA suppresses excitatory synaptic transmission between cortical pyramidal cells and that this can lead to a change in signal-to-noise ratio. The authors propose a novel mechanisms for signal-to-noise ratio modulation not previously proposed by others. As discussed above, signal-to-noise ratio modulation is generally thought to be due to changes in inhibitory and/or neuronal properties.

Its is first shown that NA suppresses intrinsic, but not afferent excitatory synaptic transmission in piriform cortex brain slices. The experimental setup for this experiments is very similar to that previously discussed (lectures on associative memory function and acetylcholine). Briefly, recording electrodes are placed in layers 1a and 1b of piriform cortex to record population EPSPs in response to the stimulation of presynaptic axons. These population EPSPs reflect the average strength of synaptic transmission in response to a presynaptic input. Stimulation electrodes are then placed in layers 1a (to stimulate afferent inputs from the olfactory bulb) or 1b (to stimulate feedback/intrinsic inputs from other pyramidal cells). Under control conditions, the amplitude of EPSPs in response to

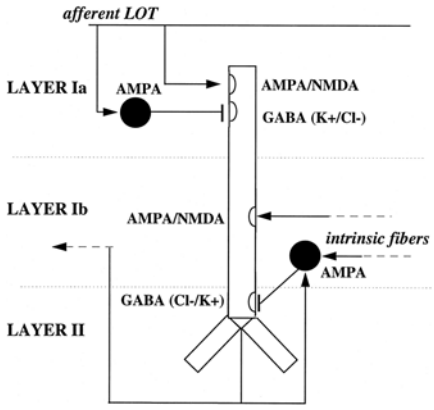
both stimulations are recorded. Noradrenaline is then added to the preparation by adding it to the artificial brain fluid surrounding the cell and the stimulations are repeated to measure the effect of activating noradrenergic receptors on synaptic transmission.



The results from these experiments show a strong suppression of intrinsic, but not afferent, excitatory synaptic transmission in the presence of NA.



A model of piriform cortex is then implemented to test wether the suppression of intrinsic synaptic transmission could contribute to the modulation of signal-to-noise ratio in this brain structure. We have discussed the anatomical organization of the piriform cortex before. Here, probabilistic leaky integrate and fire neurons are modeled.

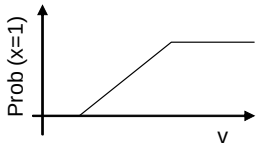


$$V_i(t) = v_j(t_0) g_{syn} \frac{\tau_1 \tau_2}{\tau_1 - \tau_2} [-e^{-(t_0/\tau_1)} - e^{-(t_0/\tau_2)}]$$

A change in v elicited by a change in synaptic fonductance is modeled by a double exponential Function,

$$\tau \frac{dv_j(t)}{dt} + v_j(t) = v_i(t) + I(t)$$

Equation for a leaky integrator. Whether an action potential occurred was decided based on a probability function of the membrane potential:



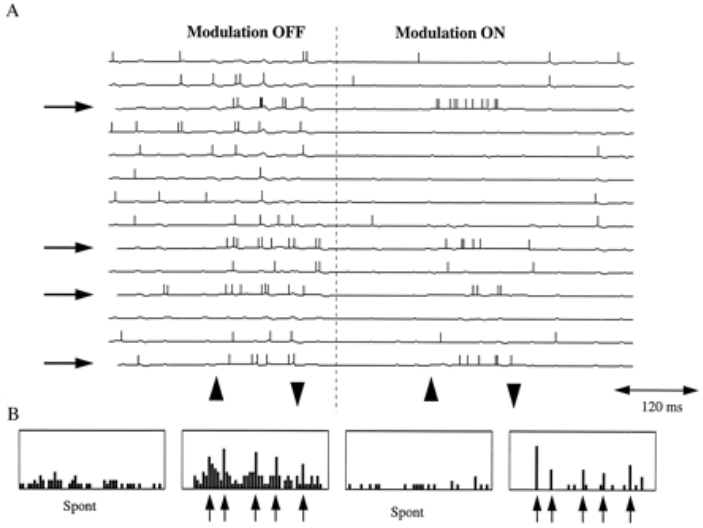
Each neuron has a small probability to fire in the absence of synaptic input (0.0012).

$$I_j(t) = \sum_i w_{ji} [E_{ci} - v_j(t)] V_i(t)$$

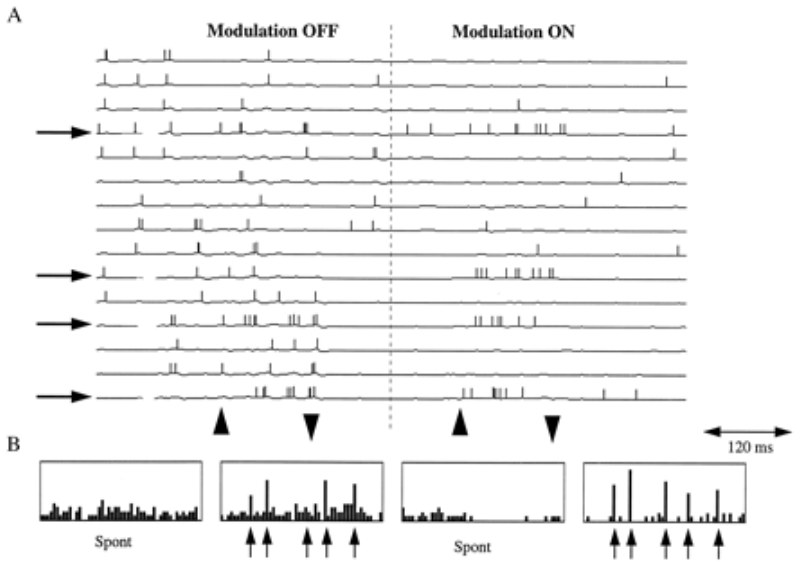
The input of each cell is given by the weighted sum of changes in V elicited by synaptic current from other cells.

Because each neuron has a small probability to emit an action potential in the absence of synaptic input, and because pyramidal cells have excitatory synapses on other pyramidal cells, the low spontaneous activity of individual neurons is multiplied into a relatively high spontaneous activity in the connected network.

In this paper, the signal-to-noise ratio is defined as the ratio of spikes evoked in those neurons receiving afferent input divided by the total number of spikes elicited in the network. The simulations clearly show that suppression of excitatory synaptic transmission in the pyramidal cell network (by lowering w_{ji}) increases the signal-to-noise ratio in the network. A less straightforward result is the fact that suppression of inhibitory synapses, as has been shown experimentally, also helps the increase of signal-to-noise ratio. The authors present a theoretical analysis of this result which will be discussed in detail in class.



Suppression of feedback excitation only.



Suppression of feedback excitation and inhibition.

The paper by Usher et al. focuses on the role if noradrenergic neuron activity in performance on a task. To measure such a role, the authors record the firing of noradrenergic neurons in monkeys while there are performing a task and correlate neuronal activity with task performance. They noted some relationship between noradrenergic cell firing and taslk performance and propose a model of this relationship.

The LC network is a population of 250 spiking neurons, each of which is a leaky integrate-and-fire cell that exhibits temporal dynamics similar to those in compartmental models. In the model, LC cells interact with each other in two ways. First, lateral inhibition simulates the effect of local NE release. Second, a voltage-dependent interaction among LC units simulates the effects of hypothesized electrotonic coupling among LC neurons. In addition, each LC cell receives input from the behavioral network (see below), as well as noise that is responsible for a spontaneous firing rate of about 1 spike/s [as observed in vivo.

Each LC cell integrates its input current and fires when its voltage at time t, $V(t)$, reaches threshold (V_{th}), after which it is artificially reset to rest ($V = 0$) and remains refractory until its voltage begins to rise again. Refractory refers to the fact that neurons cannot fire immedialty after having fired an action potential, independently of their inputs.

$V_i(t + 1) = \lambda V_i(t) + I_i$, where λ is related to the membrane integration constant and I_i is an input current. This is an iterative version of a leaky integrator equation in which the voltage at time t+1 depends on the voltage at the previous time step as well as on the neuronal input. The parameter λ determines the degree to which the voltage depends on the previous voltage (similarly to the membrane time constant τ).

The gap-junction current $I_i^g \propto \sum_j (V_j - V_i)$ on each LC unit is proportional to the sum of the ohmic currents contributed by the other LC units (which depend on the differences in voltage); for spiking neurons, V_j is taken as $V_{spike} = 5V_{th}$.A gap junction is an electrical (instead of chemical) coupling between two neurons. It is usually represented as a resistance through which current flows. Any voltage change in one of the two coupled neurons will result in a current flow through this resistance and change the voltage in the second cell proportionally.

The behavioral network is a “connectionist” network consisting of two input, two decision and one response unit. In this context, this refers to the idea that this network is not modeled to represent a realistic neural network in a brain area, but used to produce the right response to the right input. Networks of this kind can be “trained” to learn a certain input-response relationship and sometimes their parameters can be compared to physiological parameters. In the case represented here, the network has been hardwired to produce the desired responses and the gain, or activation function, of the decisions units is supposed to be modulated by NA.