CN510: Principles and Methods of Cognitive and Neural Modeling

Diffuse-projecting Neurotransmitter Systems Details of Cholinergic System

Lecture 21

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Summary of Psychoactive Drugs

Euphoria usually is a result of stimulation of endorphine or dopamine systems (nicotine, cocaine, amphetamine, etc)

Stimulation of norepinephrine system results in concentration and alertness (NRI, cocaine)

Serotonin system stimulation can lead to hyperactivity (cocaine), but with selective stimulation by amphetamines ADHD can be treated

Norepinephrine and dopamine increase can treat depression

Cholinergic system seems to influence all four above systems as well as memory and concentration (nicotine)

Serotonin system seem to control glutamate release in the cortex (amphetamine, LSD)

Manipulation of glutamate system leads to hallucinations and altered perception (LSD, PCP)

Four Diffuse Projecting Systems

Glutamate system is the information processing system with very specific sources and targets

Endorphine system is an emergency system that is somewhat separate from the rest of the brain activity

That leaves four major systems:

1. Norepinephrine (NE) – Alertness, mobilization of resources
2. Serotonin (5-HT) – Activity levels, maybe depression
3. Dopamine (DA) – Good rewarding feelings
4. Acetylcholine (ACh) – Memory function, muscle relaxation

All these systems act through modulation of activity in the other systems, thus the term neuromodulatory systems

Common Features of Major Systems

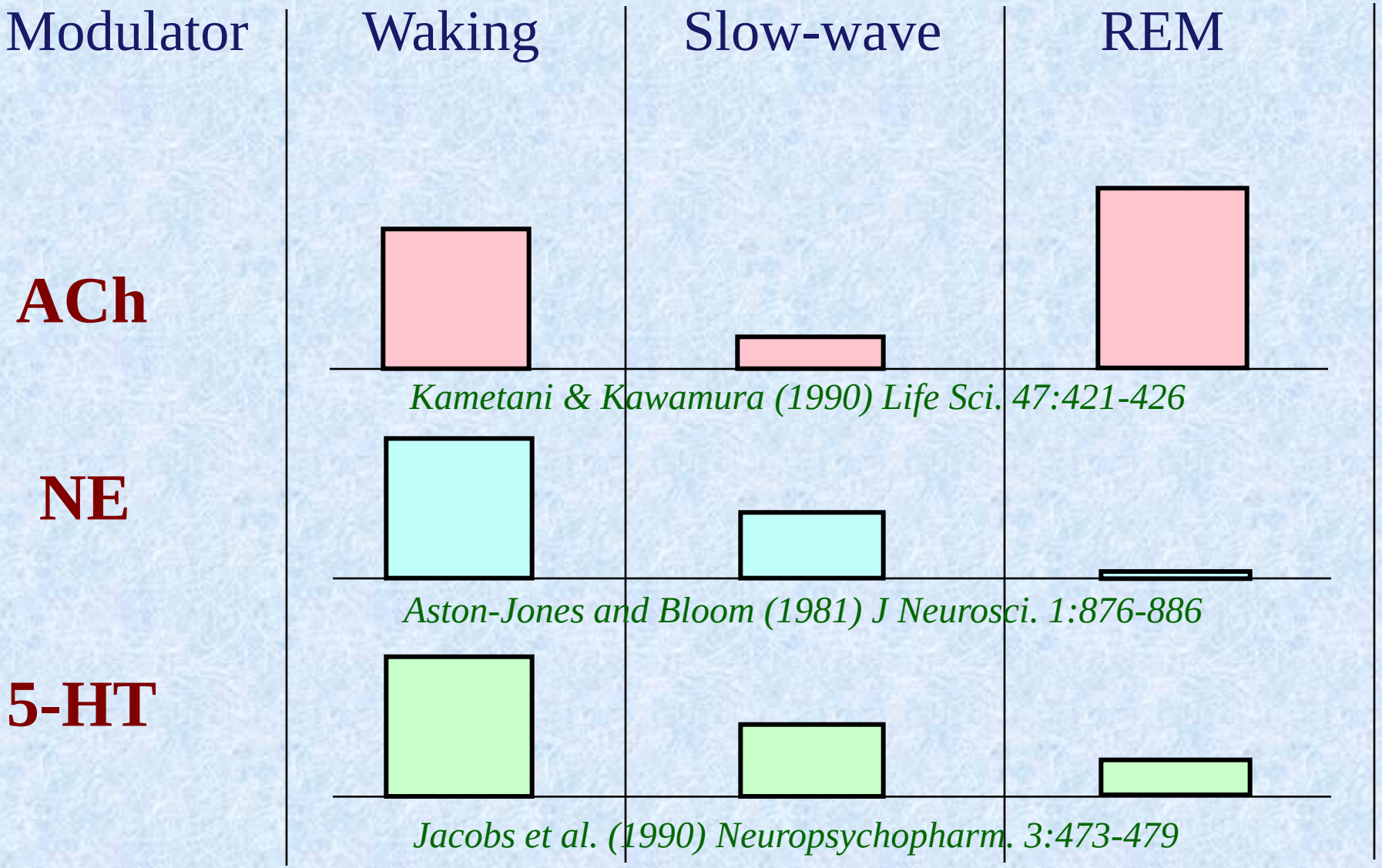
All four major modulatory systems share similarities:

- Source of projections is localized in one or two specific nuclei
- Destinations of projections are widespread and include cortical as well as subcortical areas
- They usually project diffusely into the area, do not target specific neurons, and act through second messenger synapses

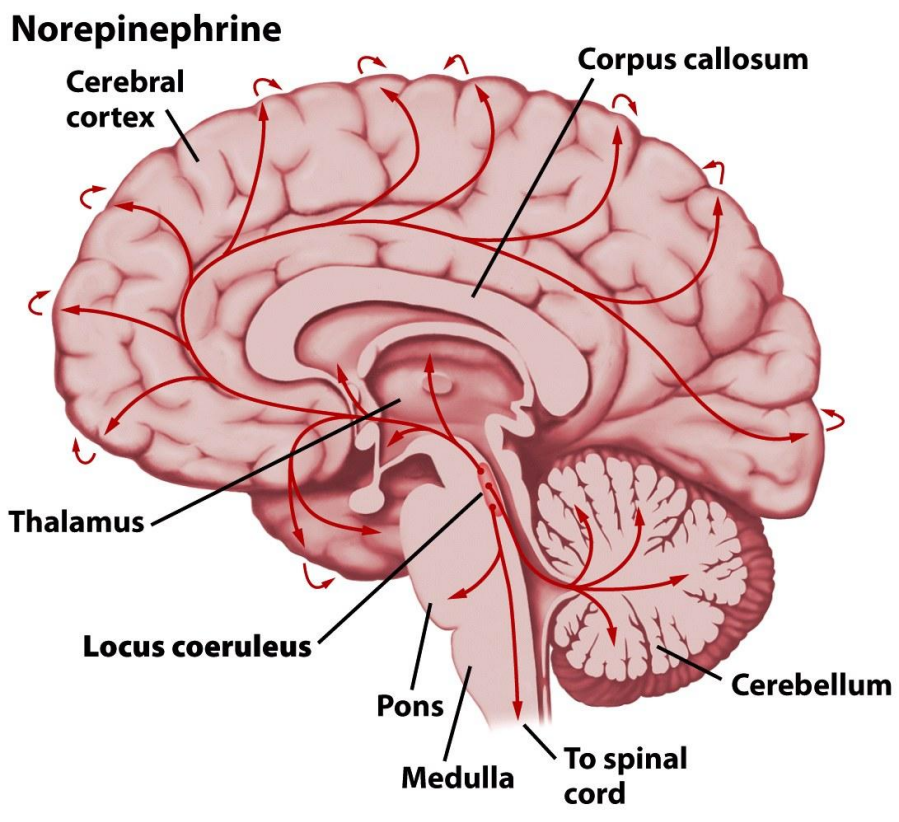
These systems modulate long-term or short-term excitability of large areas of the CNS

Brain area that receives projections from multiple modulatory systems can exhibit different modes of operation for each combination of neuromodulators

Neuromodulatory states



Noradrenergic System (Norepinephrine, NE)



Originates mainly from noradrenergic neurons in the locus coeruleus in the brain stem

Projects to cerebral cortex, thalamus, amygdala, hippocampal formation, cerebellum, midbrain, and spinal cord

Noradrenergic System (Norepinephrine)

The locus coeruleus (LC) contains only about 20,000 – 50,000 neurons in humans

NE system plays a role in response to stressful stimuli, alertness, and concentration

NE release into blood stream increases heart rate, participates in fight-or-flight response, releases glucose from storage, increases blood flow to muscles and brain oxygen supply

Bursts of NE in the cortex coincide with predictive context switches and appearance of salient stimuli

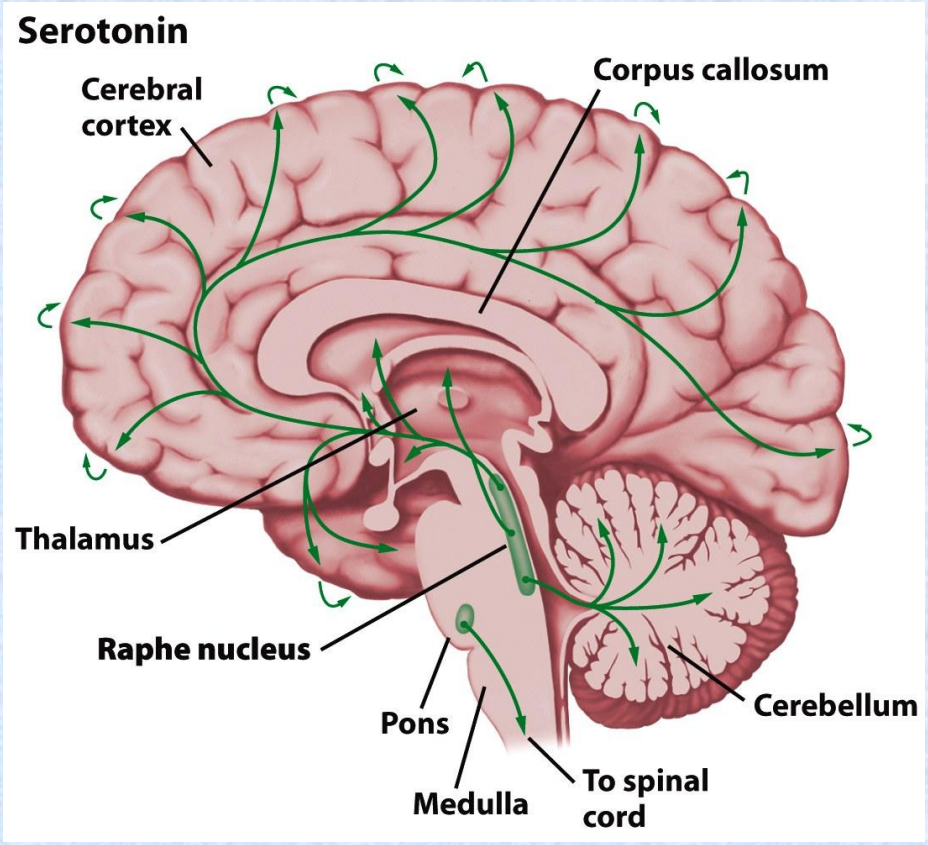
Tonic NE levels correspond to general alertness ranging from drowsiness to alert performance to over-agitation and erratic behavior

Noradrenergic System (Norepinephrine)

Dysfunction of NE system can lead to

- ADHD: selective NE reuptake inhibitors are used to bust alertness and concentration
- Depression: antidepressants are usually affect DA and 5-HT systems in addition to NE, so NE role is unclear
- Schizophrenia: some effects are associated with high NE levels
- Posttraumatic stress disorder: reduced count of right LC neurons, somewhat counterintuitive
- Anxiety, panic attacks: elevated NE levels
- Opioids inhibit LC, withdrawal leads to anxiety due to disinhibition

Serotonergic System (5-HT)



Originate from serotonergic neurons in seven raphe nuclei of the brain stem

Projects to thalamus, cortex, and cerebellum (rostral nuclei) as well as medulla and spinal cord (caudal nuclei)

Serotonergic System

Regulates mood, appetite, and sleep probably through perception of resource availability

The role is hard to analyze due to many receptor types

5-HT_{2C} receptors on DA cells are activated when the food is consumed inhibiting the DA cells and signaling satiation

Expression of these receptors follows daily rhythm peaking in the morning

5-HT_3 receptors induce vomiting as a part of serotonergic reaction on bad quality of food

Social animals compete for food, so serotonin also modulates social status

- Dominant animals have more 5-HT_2 receptors
- Subordinate animals have more 5-HT_1 receptors

Serotonergic System

High activity of 5-HT_{1A} receptors accompanied with low aggression, while blocking 5-HT_{2A} increases the risk of suicide

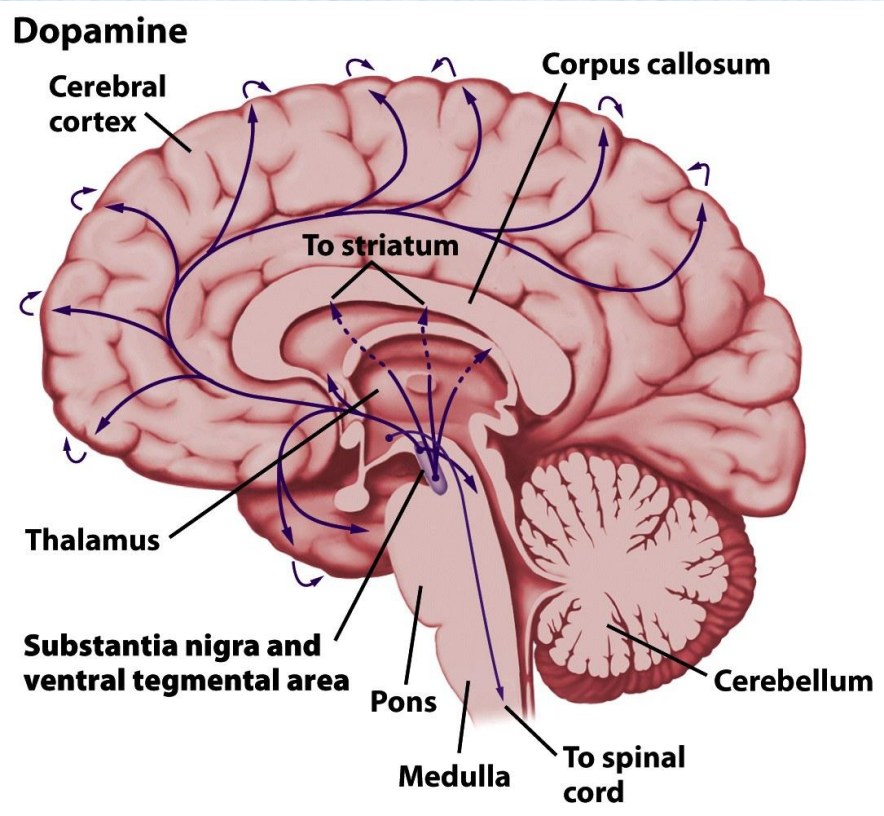
High levels of serotonin are important for mating behavior: if you are starving, you search for food, not for mate

Most of the serotonin is not degraded but taken back into neurons; the distribution of the reuptake plays a role in individual personality differences

Low serotonin levels are implicated in sudden infant death syndrome (SIDS)

While most of the antidepressants are serotonin reuptake inhibitors, some are reuptake enhancers; the selectivity seems to be the key

Dopaminergic System



Originate from dopaminergic cells in the substantia nigra pars compacta (SNc) and ventral tegmental area of the midbrain

Project to striatum (part of basal ganglia), parietal and frontal lobes of cerebral cortex

Dopaminergic System

Major role in reward based learning, any reward alters DA levels

DA reuptake mechanisms are different throughout the brain:

- In basal ganglia it is mediated by DAT
- In PFC there is not much of DAT, and DA is uptaken by NE neurons

That might be the reason for selectivity of amphetamine

Loss of dopamine-containing neurons leads to Parkinson's disease – dramatically slowed movements and tremor by increasing the BG indirect vs direct pathway influence

Low level of DA in prefrontal cortex leads to deficit in attention and problem solving, while high levels are implicated in schizophrenia

Dopaminergic System

DA inhibits prolactin (the hormone that signals sexual satisfaction) and thus creates sexual desire, antipsyhotic drugs that reduce DA lead to loss of libido and disruption of reproductive cycle in both men and women

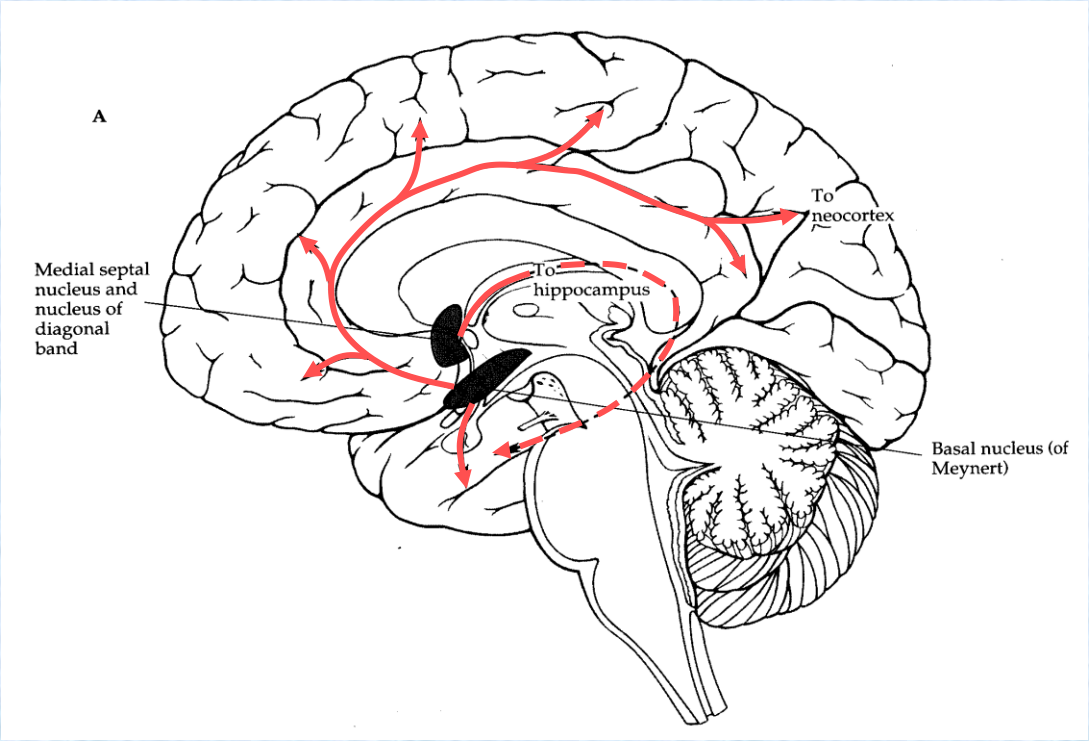
Classical theory of reward associates high levels of DA with unexpected rewards and low levels of DA with lack of expected reward or unexpected punishment

New research suggests that only ventral SNc and VTA neurons signal expectation of reward, while dorsal SNc neurons signal orienting responses

DA-depleted rats have shown no desire to eat, but enjoyed the food as much as controls when force-fed

DA is also implicated in mild suppression of pain

Cholinergic System



Cholinergic neurons in the basal nucleus of Meynert (also called nucleus basalis) in the basal forebrain project to various sites in the cerebral cortex (both medial and lateral)

Cholinergic neurons in the medial septal nucleus and nucleus of the diagonal band of Broca project to the hippocampus

Cholinergic System

High levels of acetylcholine in the hippocampal system correspond to active exploration, quiet attention, and REM sleep; REM sleep can be induced by ACh agonists

Low levels correspond to non-exploratory behaviors and slow wave sleep

ACh has an important role in the enhancement of sensory perceptions and in sustaining attention

In cortex high ACh leads to inhibition of layer IV neurons and excitation of layer II/III and V neurons: filters out weak thalamic inputs and emphasizes the survivors

In the hippocampus and cortex high ACh emphasizes feedforward projections by suppressing transmission through recurrent projections

Cholinergic System

Effects of ACh metabotropic receptors can depend on the time the receptor is active with transient inhibition and prolonged excitation

Lesions of cholinergic system impair the ability to detect target, but not the ability to reject non-target trials

Reduction of ACh leads to slower plasticity changes, while infusion of it leads to faster plasticity

Reaction time in recognition based tasks is often inversely proportional to ACh levels (smokers beware!); agrees with theory that ACh signals the novelty/uncertainty

Alzheimer's disease, caused by degeneration of cholinergic neurons, results in loss of memories and cognitive function

Other Diffuse Projection Systems

Diffuse-projecting thalamic nuclei –

- The intralaminar and midline thalamic nuclei project diffusely to cortex
- Thought to play a role in arousal and excitability of large regions of cortex
- The thalamic reticular nucleus projects to other parts of thalamus and may regulate arousal there

GABAergic modulatory system does not have localized source, and sometimes can even be indirect (acting through local interneurons but driven from external source)

Other Diffuse Projection Systems

Reticular formation –

- Located in the brain stem
- The reticulospinal tracts help control posture and balance
- Includes cardiovascular control and suppression of pain transmission
- Other reticular formation cells receive inputs from all sensory systems and project to wide areas of the cerebral cortex and thalamus, regulating arousal (i.e., wakefulness and vigilance; ascending arousal system) and attention/habituation

Some Functions of Diffuse-Projecting Systems

In addition to causing increases in overall arousal levels, and determining the sleep state, neuromodulators can change the way certain circuits work

One example is learning/recall switch for ACh

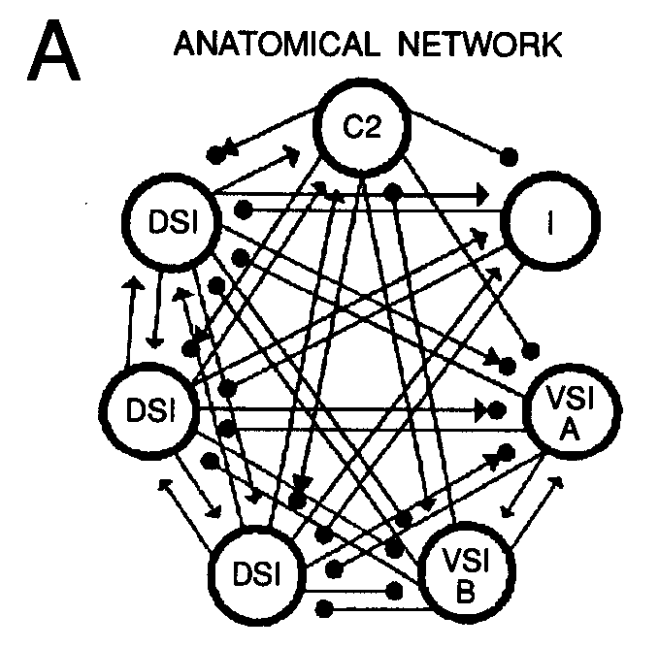
Another example: the presence of a neuromodulator may cause a circuit to act in an oscillatory fashion, while its absence might lead to phasic behavior

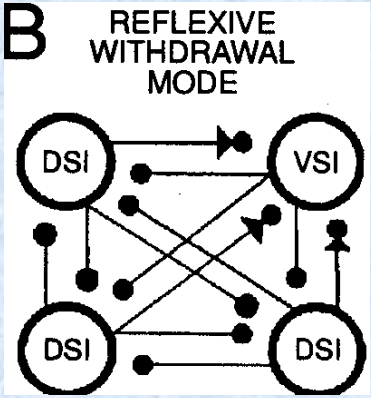
- ACh seems important for theta oscillations, and so is GABA
- A burster neuron in the lobster pyloric network (a stomach-related oscillating system) can only oscillate in the presence of appropriate neuromodulators, and its oscillations are of different amplitudes and frequencies for different neuromodulators

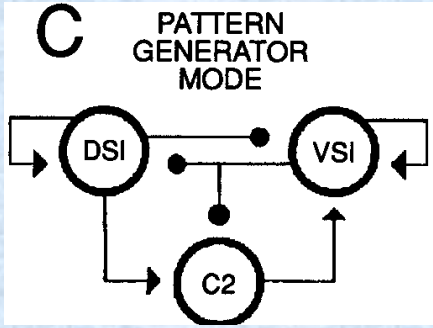
Some Functions of Diffuse-Projecting Systems

Also, *Getting and colleagues* have studied the swimming pattern generator/reflexive withdrawal in the sea slug *Tritonia*

- Activation of the C2 neuron, which projects to all neurons in the circuit, leads to an oscillatory swimming pattern
- Inactivation of the C2 neuron leads to a phasic withdrawal reflex by allowing inhibitory connections to dominate

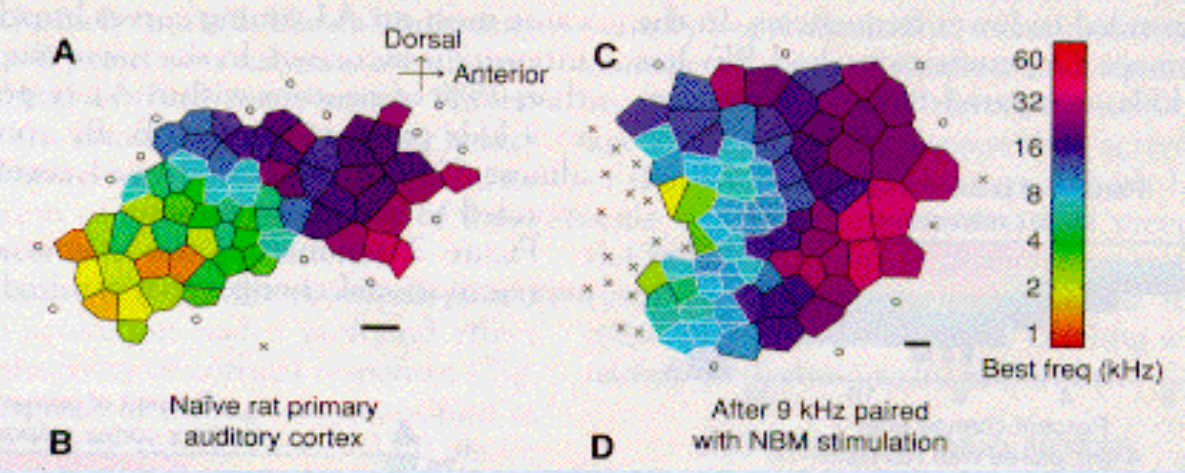






Some Functions of Diffuse-Projecting Systems

Kilgard and Merzenich (1998) showed that pairing a tone of a particular frequency (9 kHz in following plots) with nucleus basalis activation caused an increase in the size of the auditory cortical representation for this tone frequency:



Nucleus basalis is the source of the diffuse-projecting ACh system

It receives inputs from limbic structures and might signal behavioral importance of stimuli

Some Functions of Diffuse-Projecting Systems

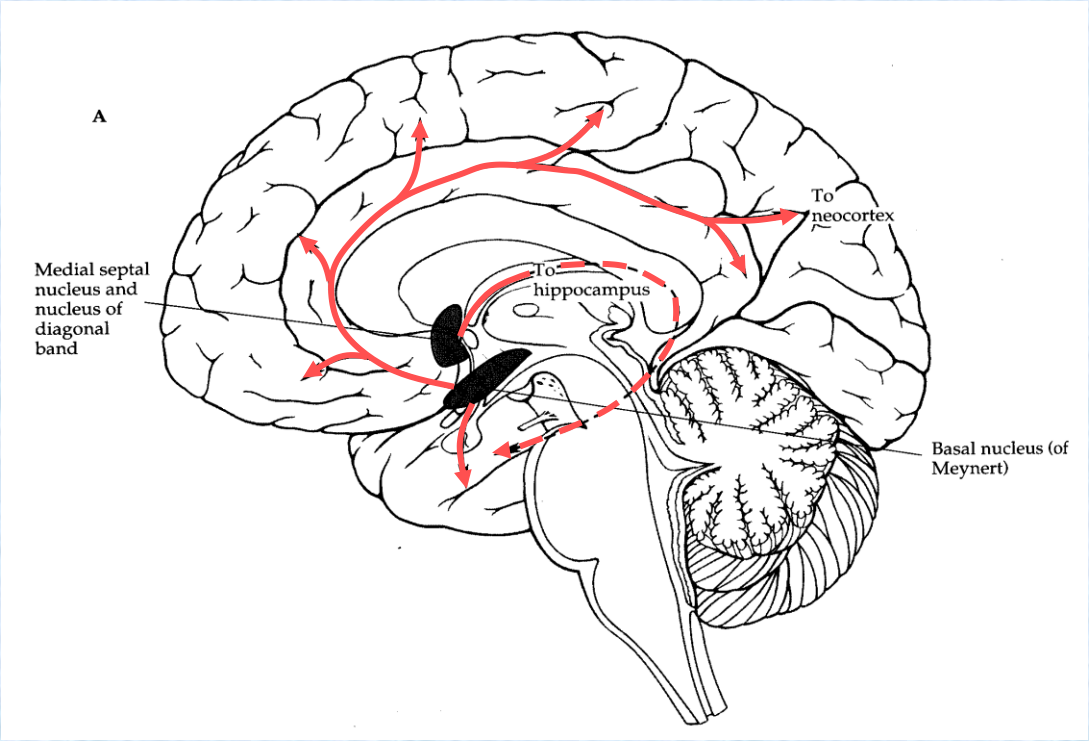
Another role of neuromodulators is to regulate long-term synaptic strength changes

Hasselmo and colleagues showed that ACh and GABA lead to increase in synaptic modifications of recurrent synapses within hippocampus and other areas

Related studies that showed how stimulation at certain frequencies lead to better synaptic modification

For example stimulation at 5Hz leads to long-term potentiation while random stimulation leads to long-term depression

Cholinergic System



Cholinergic neurons in the basal nucleus of Meynert (also called nucleus basalis) in the basal forebrain project to various sites in the cerebral cortex (both medial and lateral)

Cholinergic neurons in the medial septal nucleus and nucleus of the diagonal band of Broca project to the hippocampus

Behavioral Experiments: Cholinergic Effects

ACh (muscarinic) blockade suppresses the learning process but not the recall process *(Ghonheim and Mewaldt, 1975; Peterson, 1977)*

Encode list #1

Scopolamine injection (muscarinic antagonist)

Recall list #1 (no effect)

Encode list #2

Recall list #2 (strong impairment)

Behavioral Experiments: Cholinergic Effects

ACh (muscarinic) blockade impairs learning more when there is an overlap with previous learning *(Atri et al. 2004)*

Learn paired associations A-B

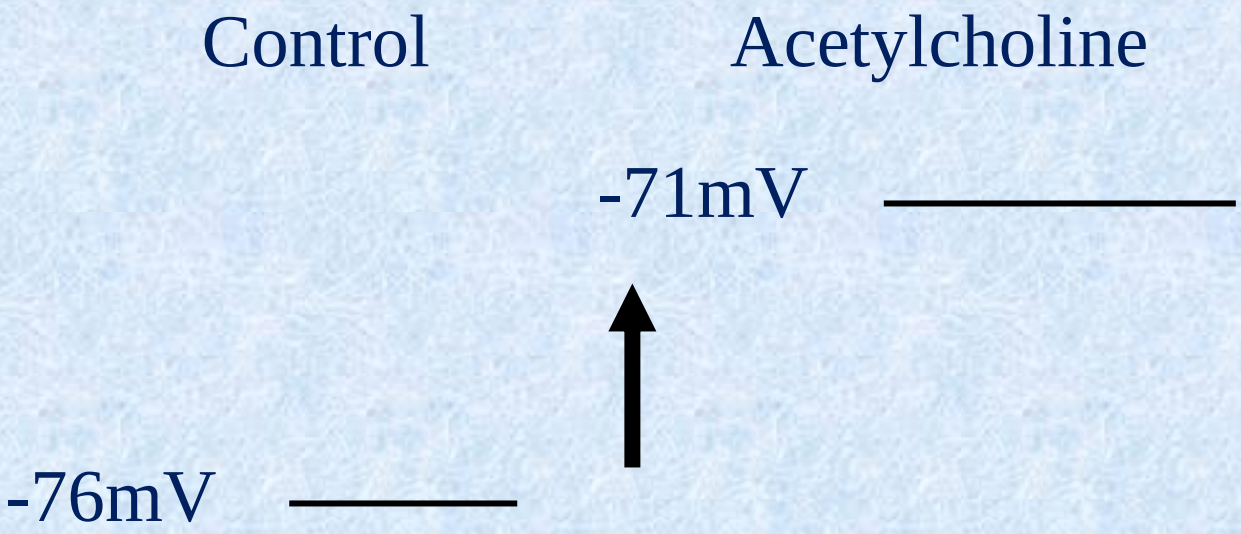
Inject scopolamine

Learn associations A-C and D-E

Result: both learned not as well as A-B, but A-C learned worse than D-E

Slice Experiments: Cholinergic Effects

ACh depolarizes pyramidal cells



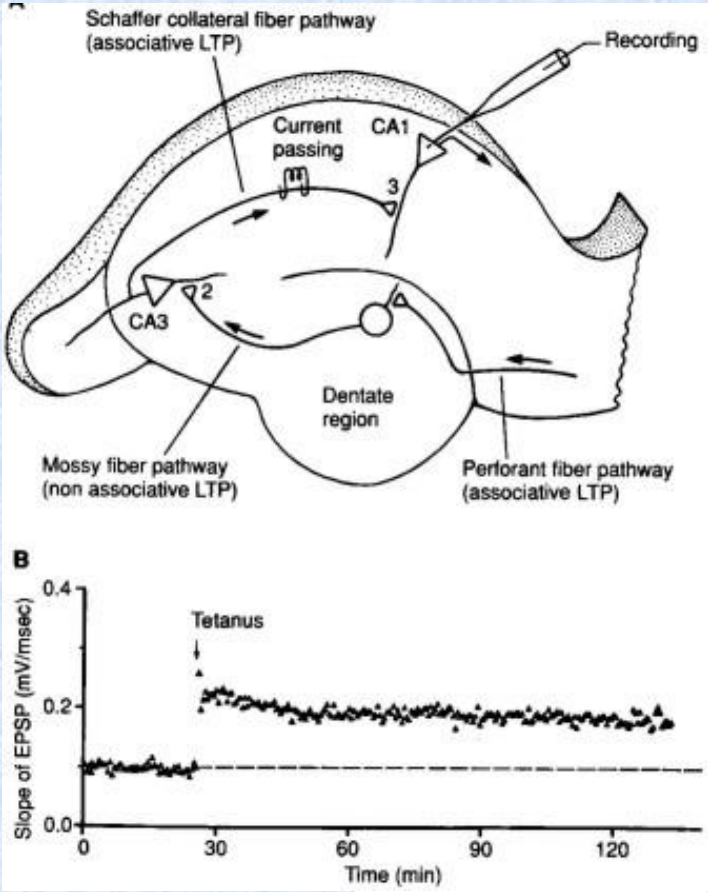
Barkai & Hasselmo (1994) J. Neurophysiol. 72: 644-658.

Krnjevic, Pumain and Renaud (1971); Cole & Nicoll (1984)

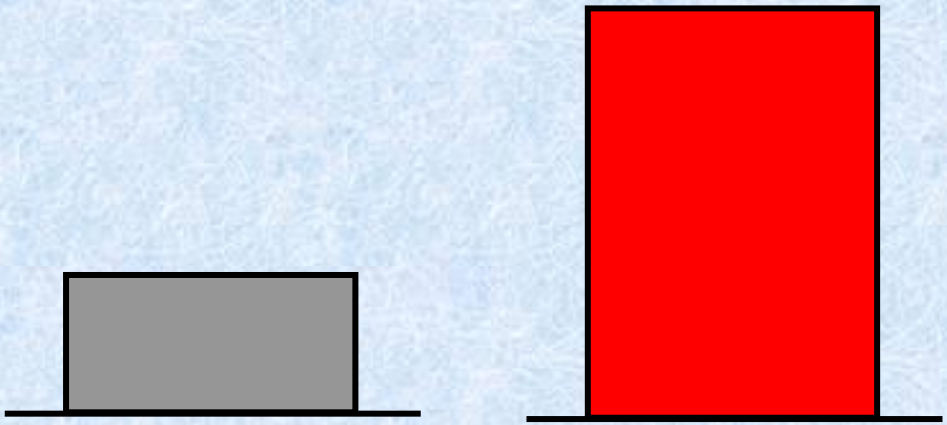
Slice Experiments: Cholinergic Effects

ACh enhances long-term potentiation

Hasselmo & Barkai (1995) J. Neurosci. 15(10): 6592-6604

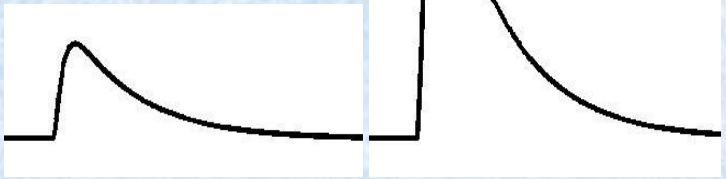


Control 20mM carbachol



13.7% 41.5%

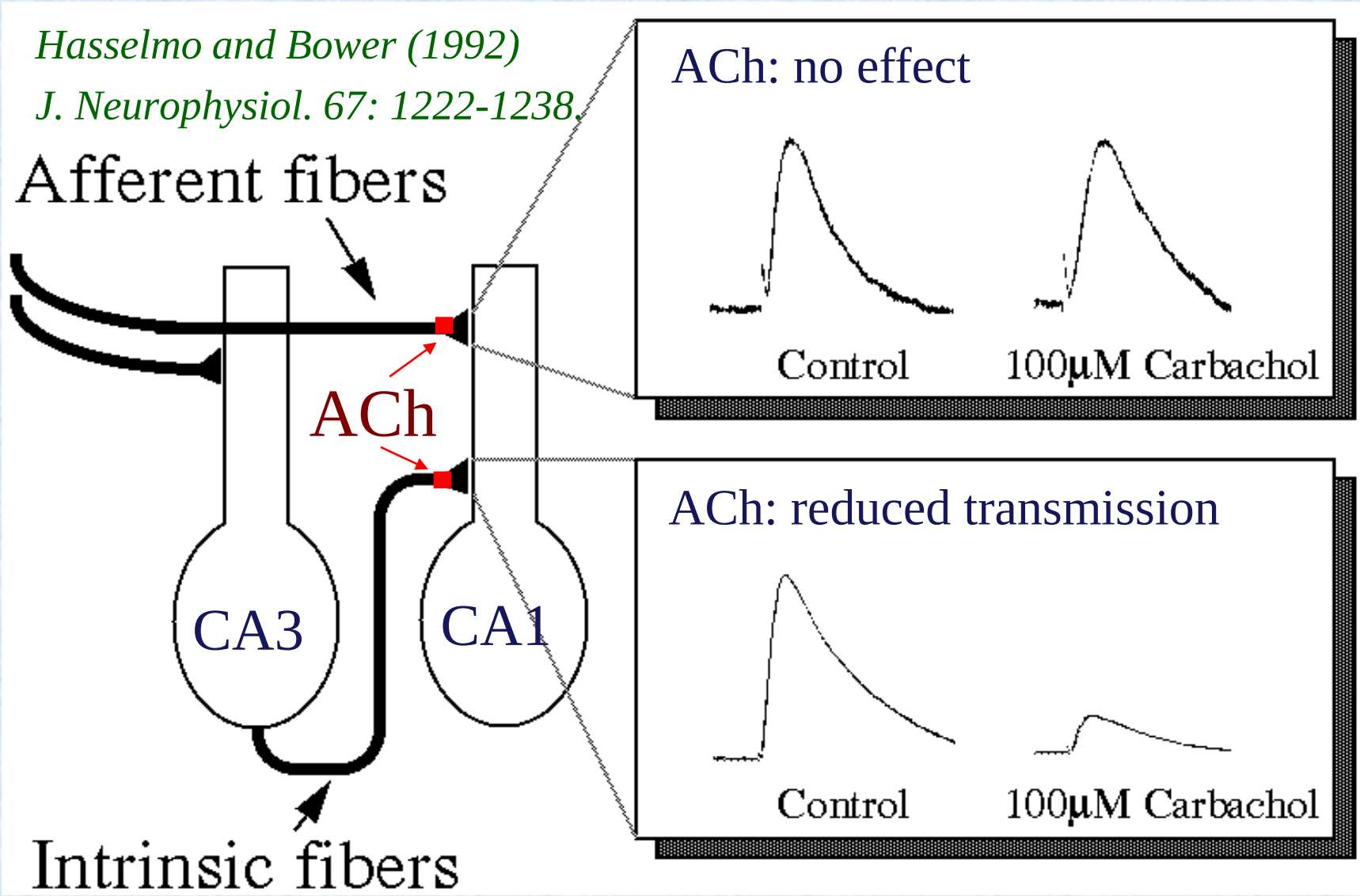
Increase in EPSP height



Slice Experiments: Cholinergic Effects

Hasselmo and Bower (1992)

J. Neurophysiol. 67: 1222-1238.

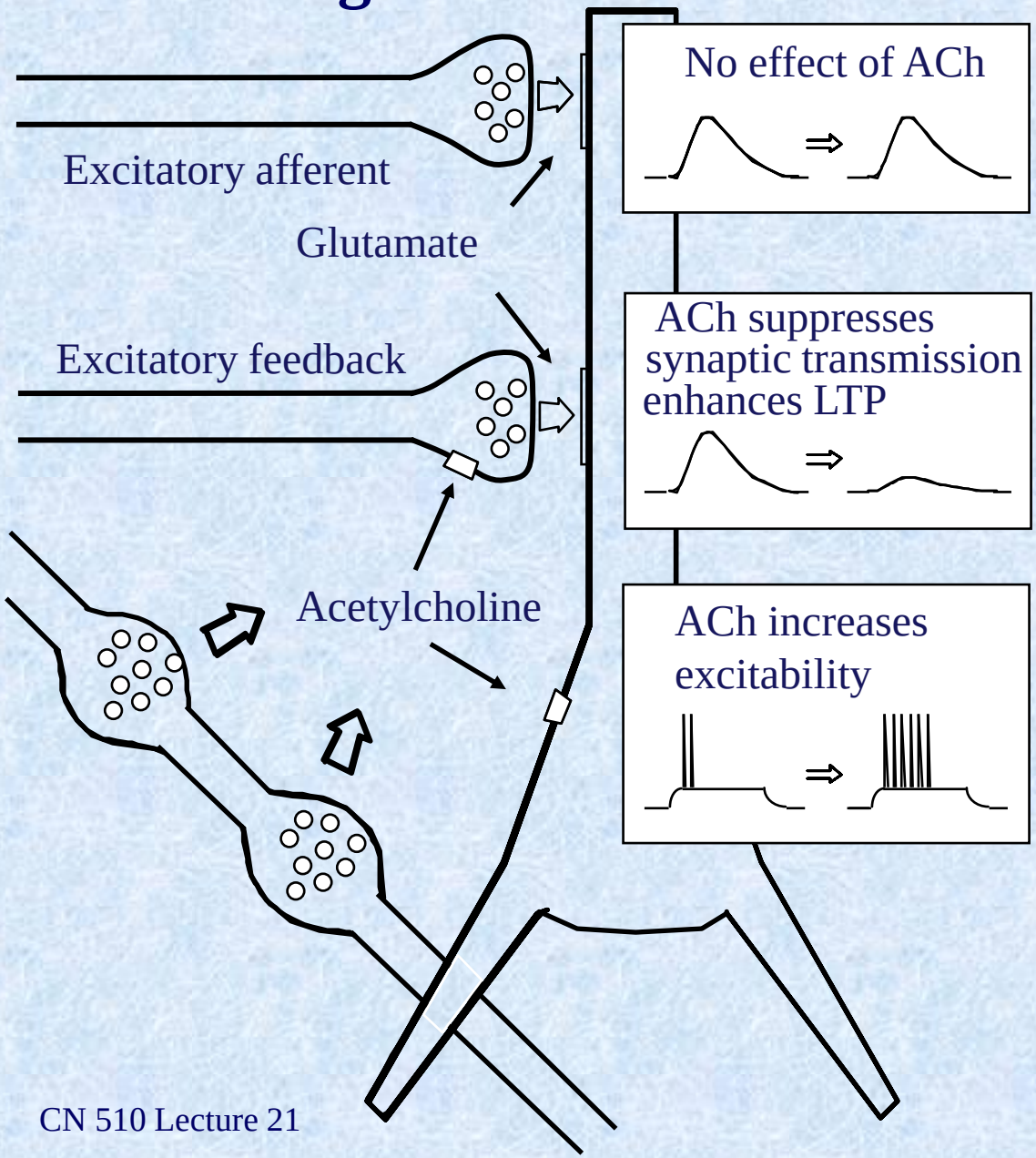


Summary of Cholinergic Effects

- Selective decrease of EPSPs
- Enhancement of LTP
- Depolarization or increase of excitability

Functionally:

- Helps to learn overlapping patterns



Summary of Cholinergic Effects

Slice preparations showed:

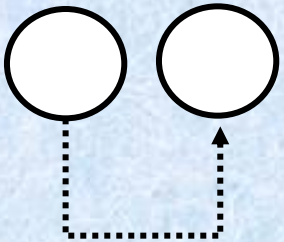
- High ACh partially suppresses recurrent projections in the hippocampus, piriform cortex, and other cortices
- High ACh enhances learning in these projections
- High ACh enhances excitability of the cells

Thus by changing the level of ACh one can switch the network from a state that is dominated by feedforward projections with excitable and fast learning cells to a state dominated by recurrent projections with little learning and more conservative activity

In Mike Hasselmo's terminology this is a switch between encoding and retrieval

High ACh

Input

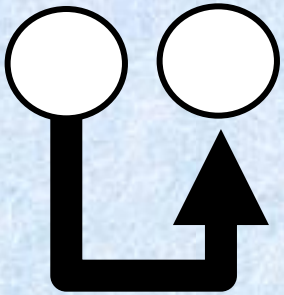


Feedback

Encoding/
Attention

Low ACh

Input

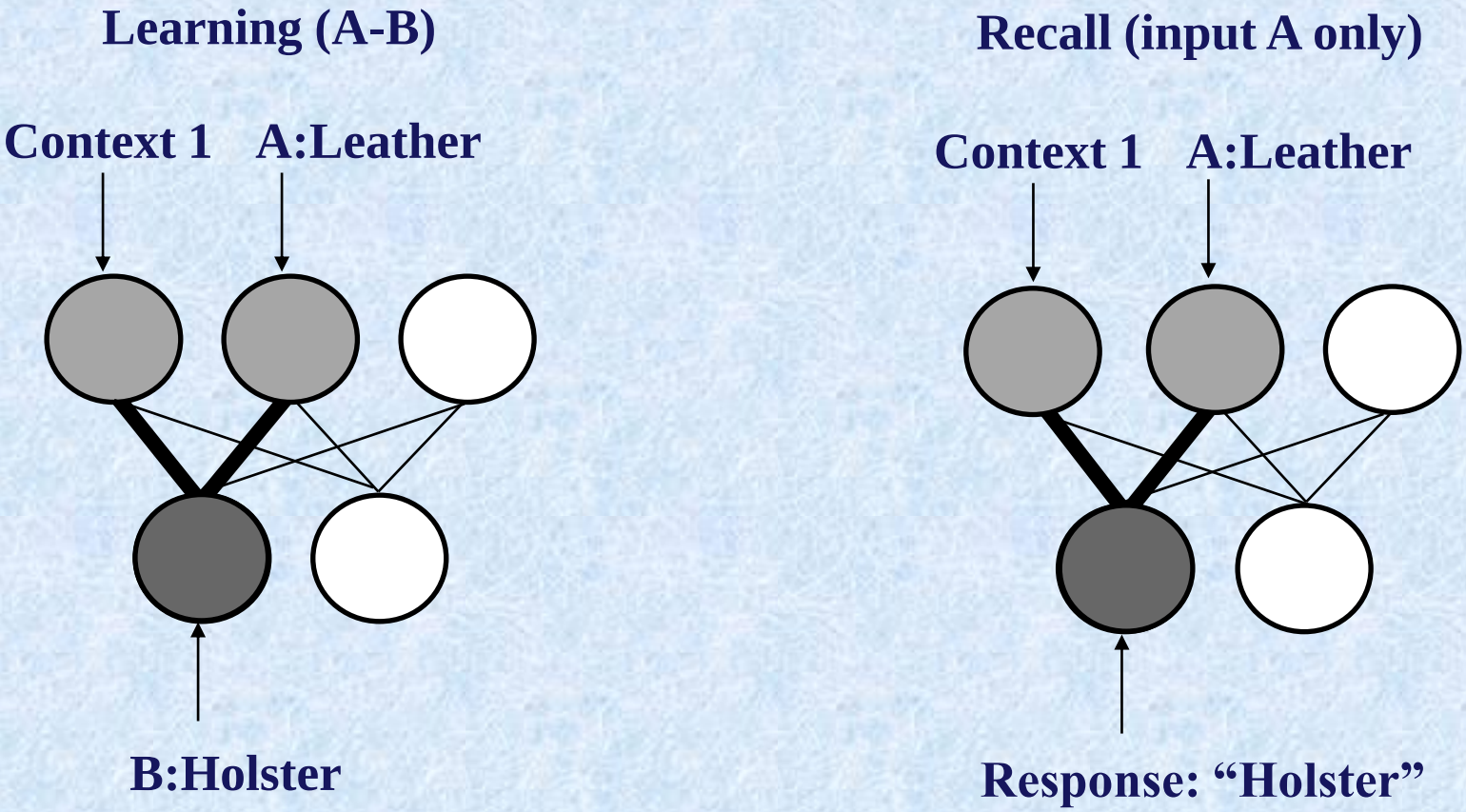


Feedback

Retrieval/
Consolidation

Example: Learning Word Pairs

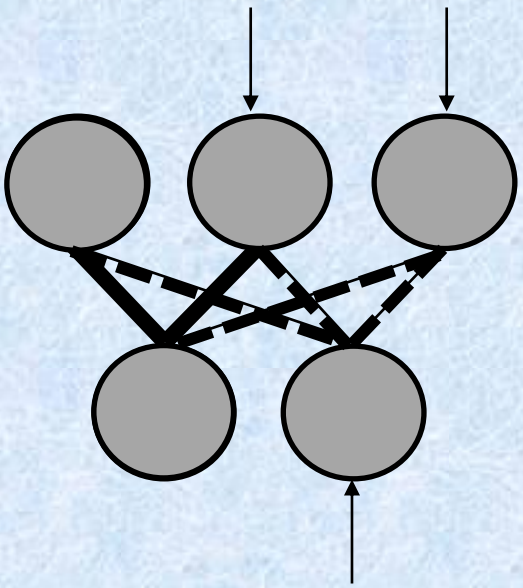
Learning first word pair:



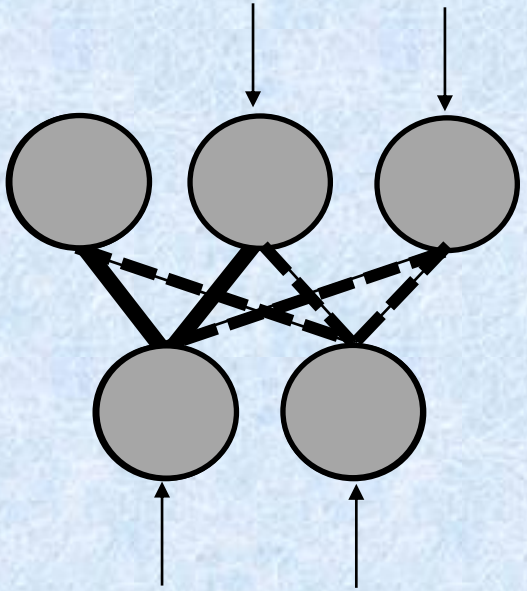
Example: Learning Word Pairs

Learning second word pair:

Learning (A-C)

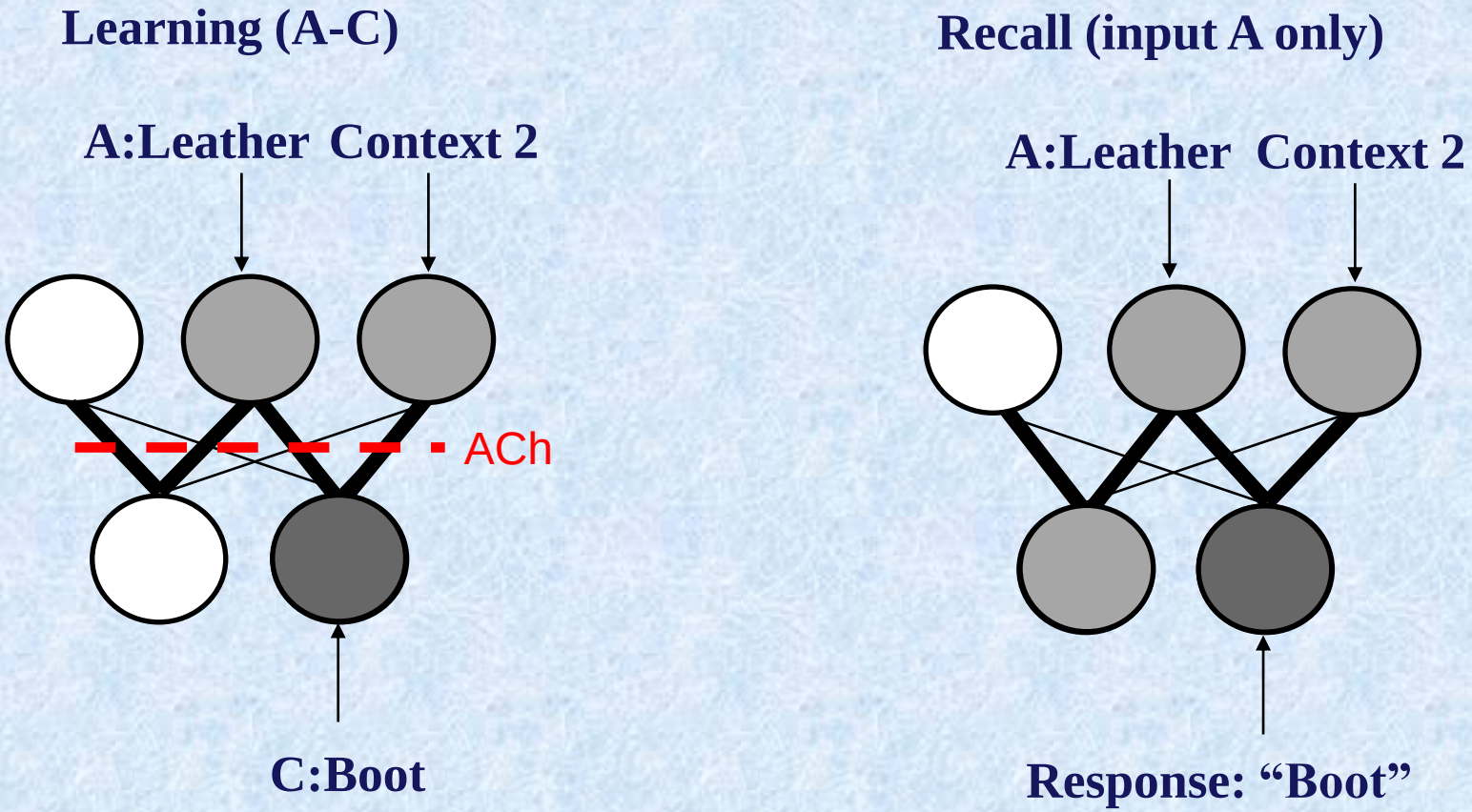


Recall (input A only)

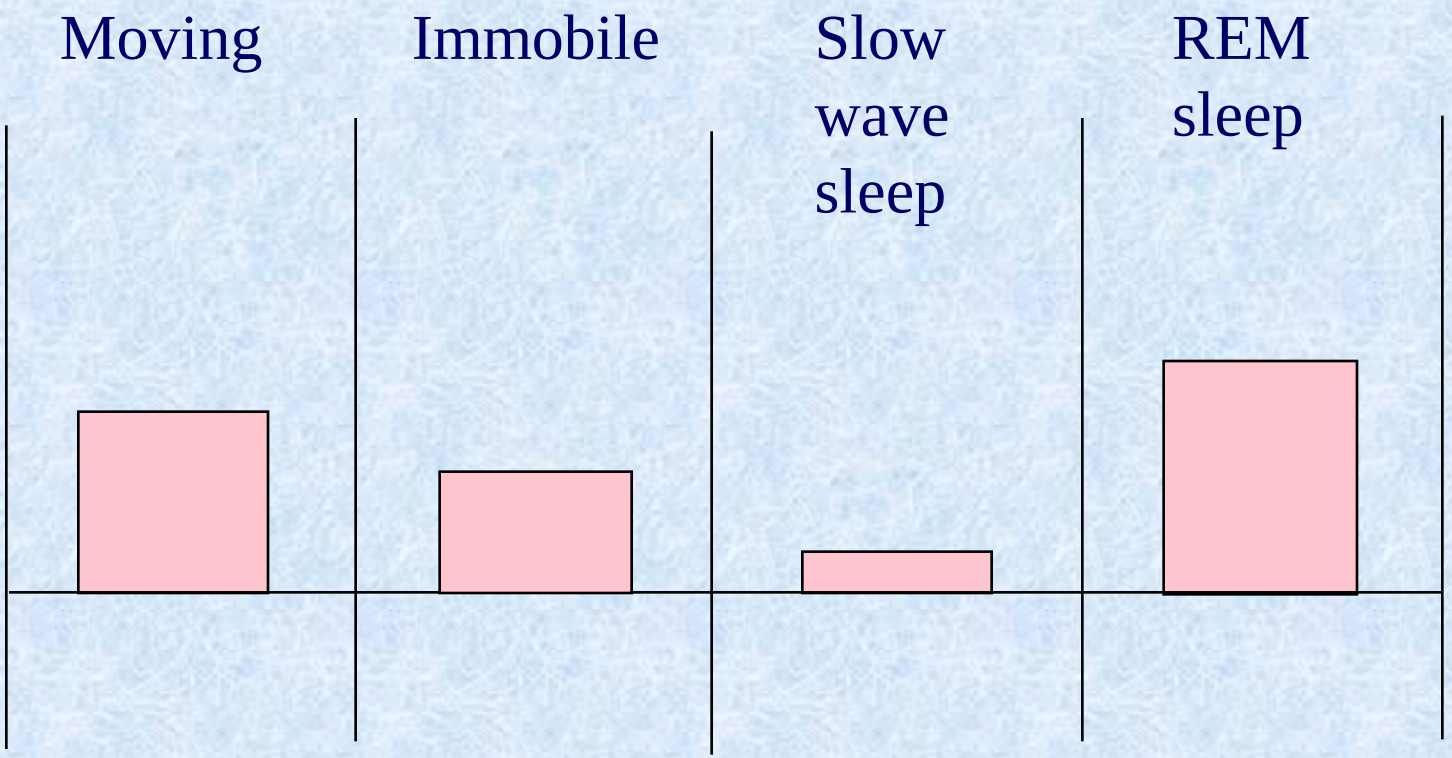


Example: Learning Word Pairs

Learning second word pair with acetylcholine:



Acetylcholine Microdialysis



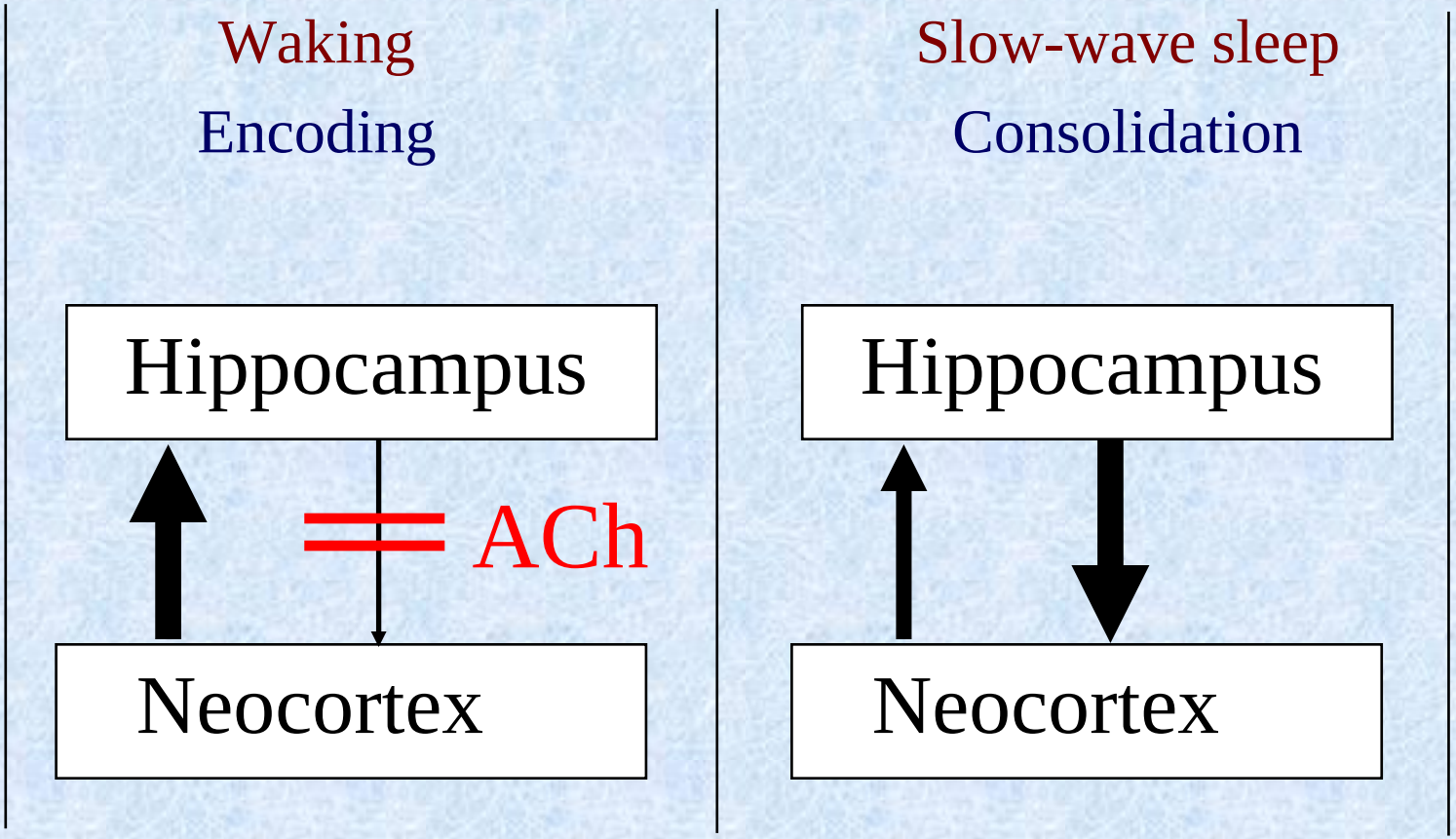
Marrosu et al. (1995) Brain Res. 671: 329-332

Stages of Memory Formation

Waking	Slow-wave sleep
Encoding in hippocampus (intermediate-term episodic memory)	Consolidation from hippocampus to neocortex (semantic and long-term episodic)

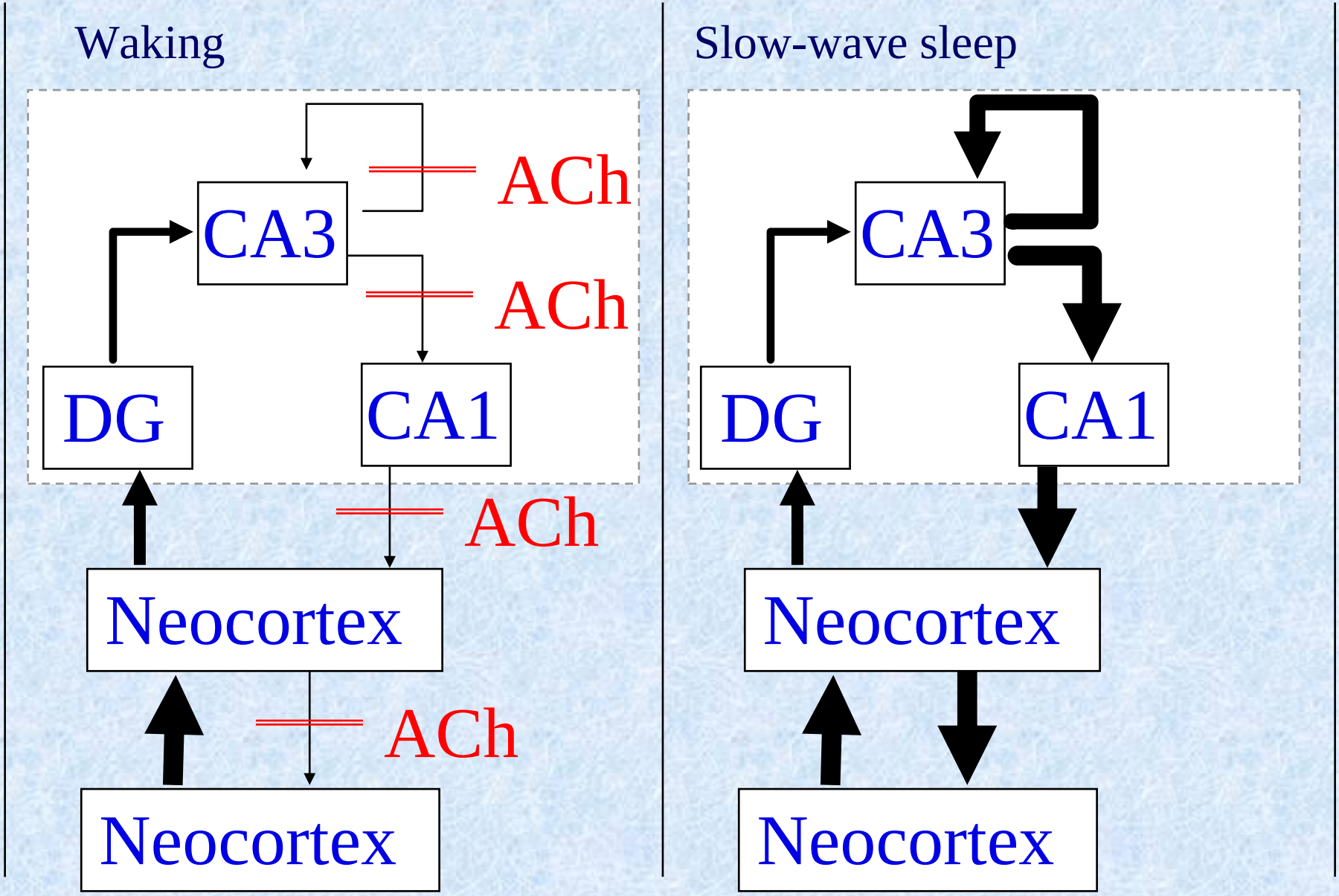
Buzsaki (1989) Neuroscience 31:551-570
Chrobak & Buzsaki (1994) J. Neurosci. 14: 6160-6170
Wilson & McNaughton (1994) Science 265: 676-679
Qin et al. (1997) Phil. Trans. R. Soc. 352 1525-1533

Acetylcholine Regulates Feedback



Hasselmo & Schnell (1994) J. Neurosci. 14: 3898-3914
Hasselmo & Cekic (1996) Behav. Brain Res. 79: 153-161

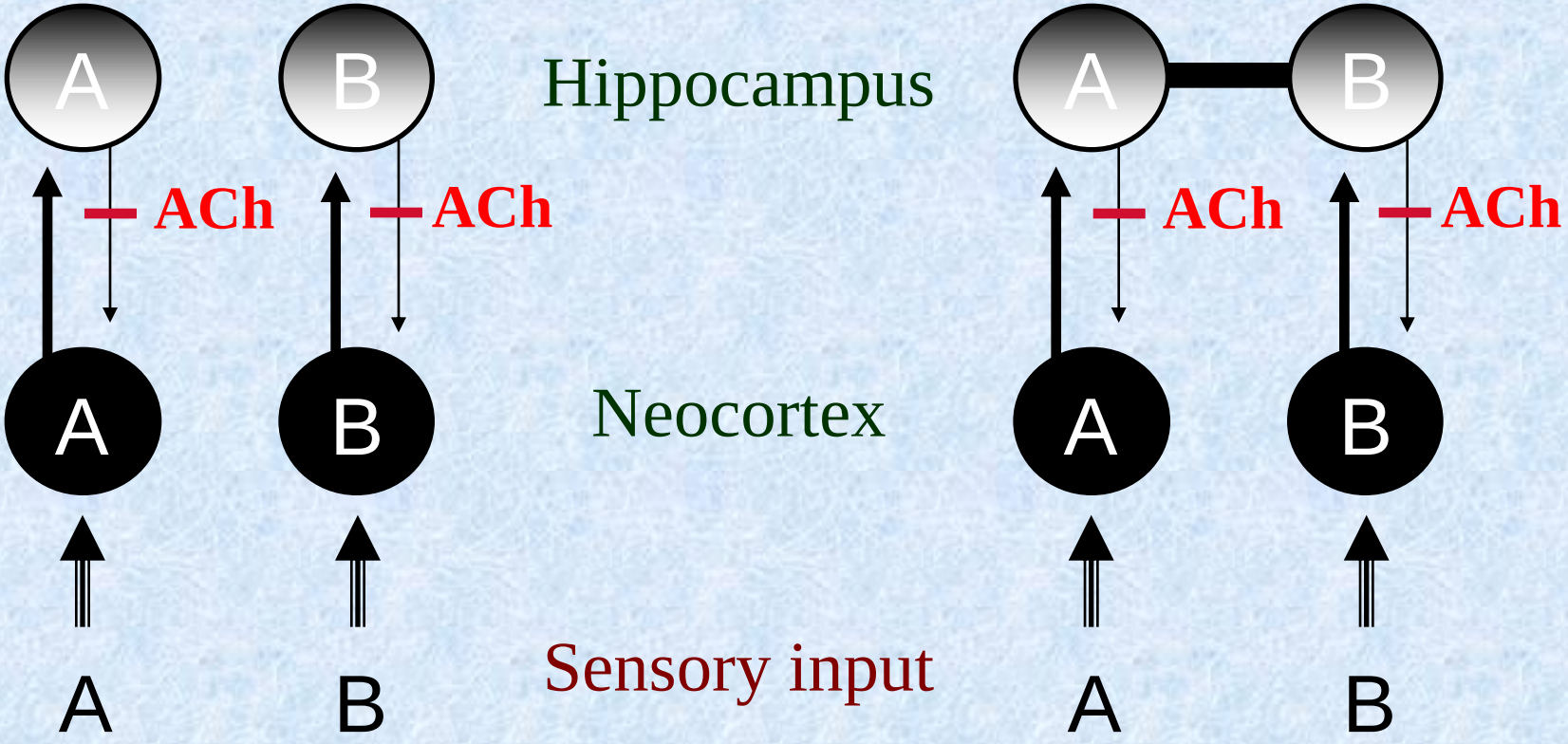
Acetylcholine Regulates Feedback



Waking (high ACh)

Before encoding

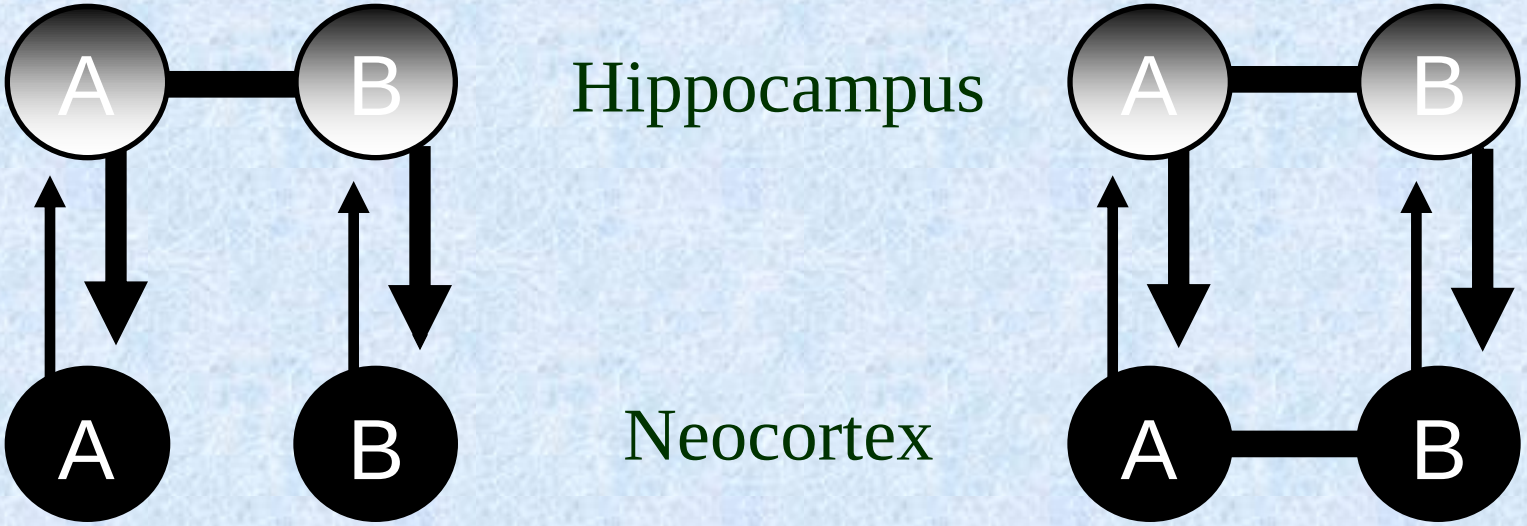
After encoding



Slow Wave Sleep (low ACh)

Sharp wave feedback

Neocortical consolidation



Sensory input (none)

Next Time

Dopaminergic system, predictive reward, reinforcement learning, temporal difference (TD) learning rule

Readings

- D&A Chapter 9 (sections 1-2).