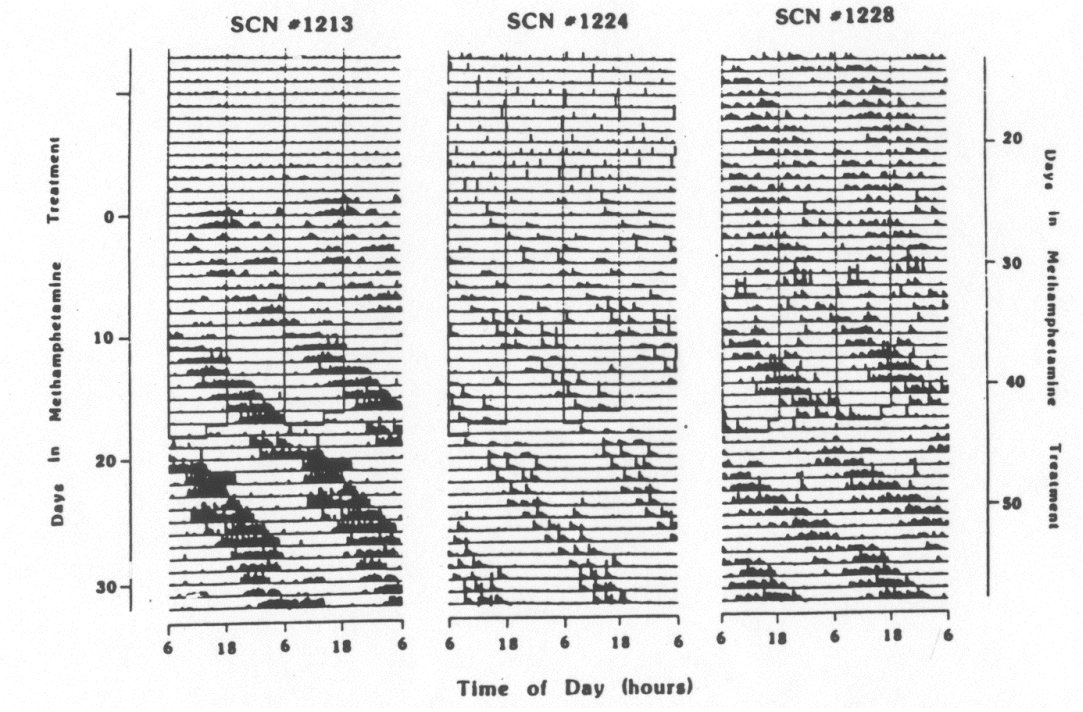
Reading: Chapter 9; parasomnias article on website

Study Questions:

1. Discuss theories of why we sleep. How convincing is the evidence for various theories?

2. How do normal sleep processes go awry to produce parasomnias?

Unexpected result:
Methamphetamine in water of SCN-X rats



Self-test question

What is the period of the circadian rhythm after methamphetamine was given?

A. Less than 24 h

B. 24 h

C. More than 24

D. Impossible to tell from actogram

Self-test question

What can we conclude from the finding that SCN-X rats show circadian activity rhythms if they have methamphetamine in their water?

A. That the SCN is not a clock

B. That there are clocks outside of the SCN

C. That the SCN was not properly lesioned

D. That circadian rhythms are not endogenous

E. Choices A and B

Current Model

SCN sits atop a hierarchy of clocks
Normally coordinates entire system

Additional, weaker clocks throughout brain/body

Normally dampen without SCN

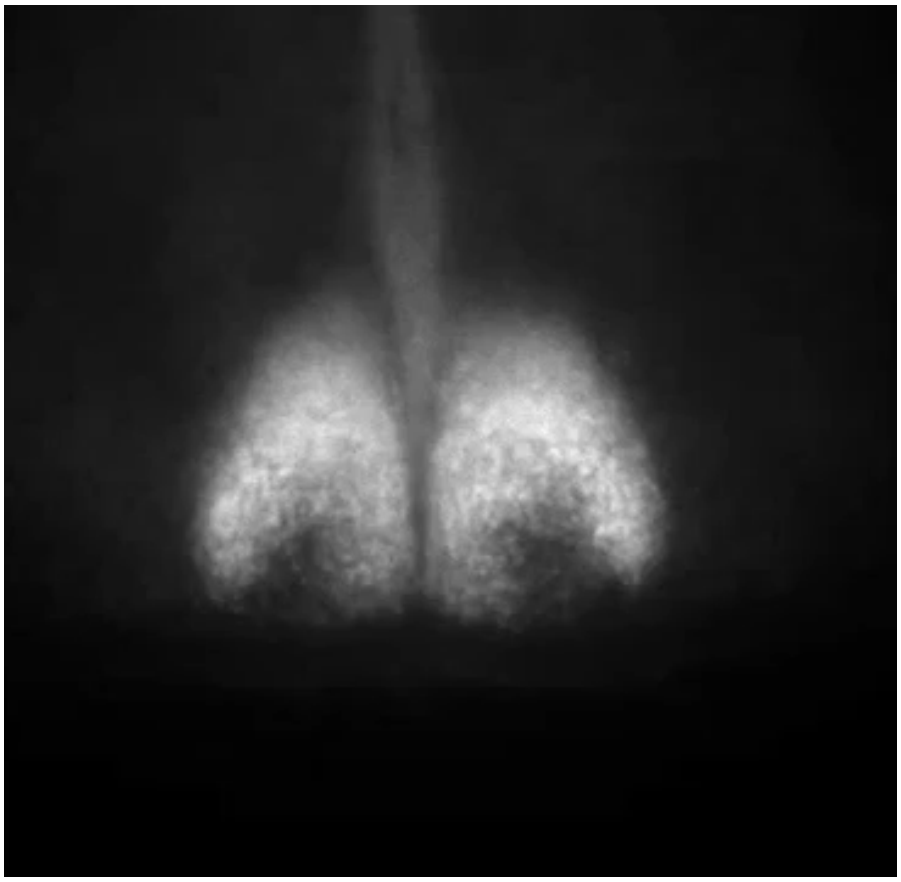
Under permissive conditions, these can be coordinated

Advanced tools make this an incredible model system for understanding how individual neurons work together to control behavior.

~1990 Record from single SCN cells in vitro
grow cells on micro-electrode plate
one cell has a circadian rhythm
different cells have different periods etc

~2005 Switch from electrical recording (a hand or output of the clock) to clock-gene recording (a gear of the clock)

use glow-in-the-dark protein from fireflies
attach to a clock gene



David Welsh

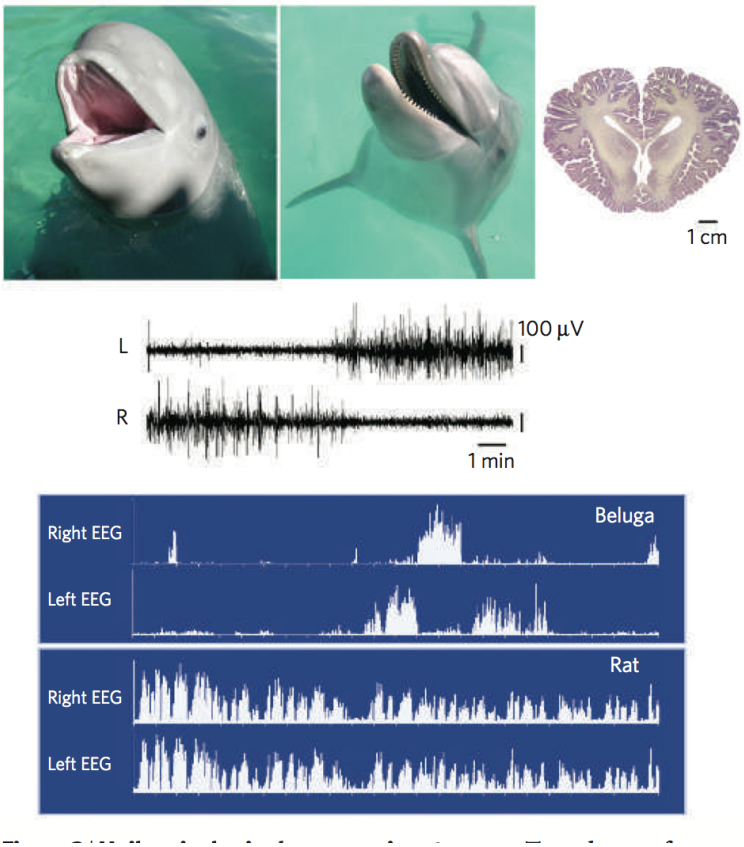
7 days

INSIGHT REVIEW NATURE|Vol 437|27 October 2005|doi:10.1038/nature04285

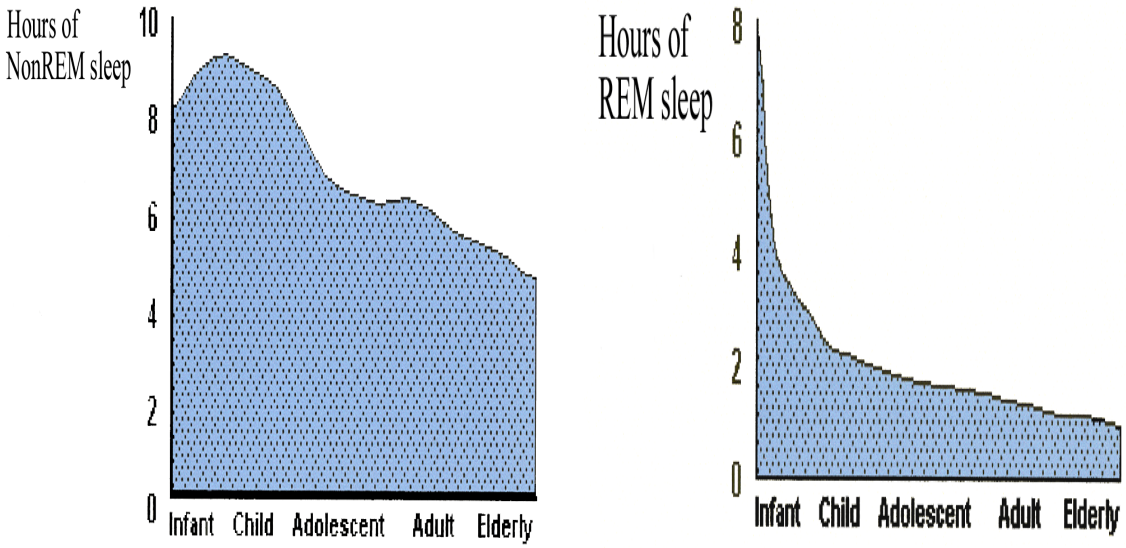
Clues to the functions of mammalian sleep

Jerome M. Siegel[1]

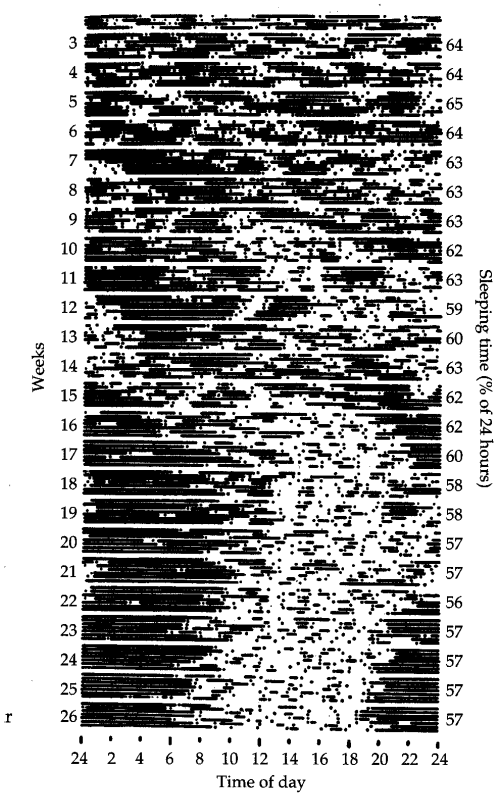
The functions of mammalian sleep remain unclear. Most theories suggest a role for non-rapid eye movement (NREM) sleep in energy conservation and in nervous system recuperation. Theories of REM sleep have suggested a role for this state in periodic brain activation during sleep, in localized recuperative processes and in emotional regulation. Across mammals, the amount and nature of sleep are correlated with age, body size and ecological variables, such as whether the animals live in a terrestrial or an aquatic environment, their diet and the safety of their sleeping site. Sleep may be an efficient time for the completion of a number of functions, but variations in sleep expression indicate that these functions may differ across species.

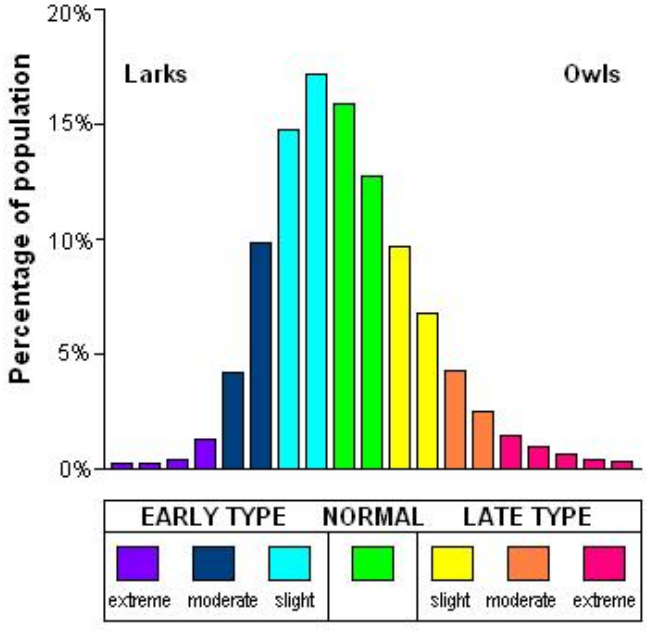


Sleep Across the Ages



Adapted from *Sleep Multimedia*, 1998


Weeks
Sleeping time (% of 24 hours)
3 64
4 64
5 65
6 64
7 63
8 63
9 63
10 62
11 63
12 59
13 60
14 63
15 62
16 62
17 60
18 58
19 58
20 57
21 57
22 56
23 57
24 57
25 57
26 57
24 2 4 6 8 10 12 14 16 18 20 22 24
Time of day


Percentage of population
20%
15%
10%
5%
0%
Larks
Owls
EARLY TYPE
NORMAL
LATE TYPE
extreme
moderate
slight
slight
moderate
extreme

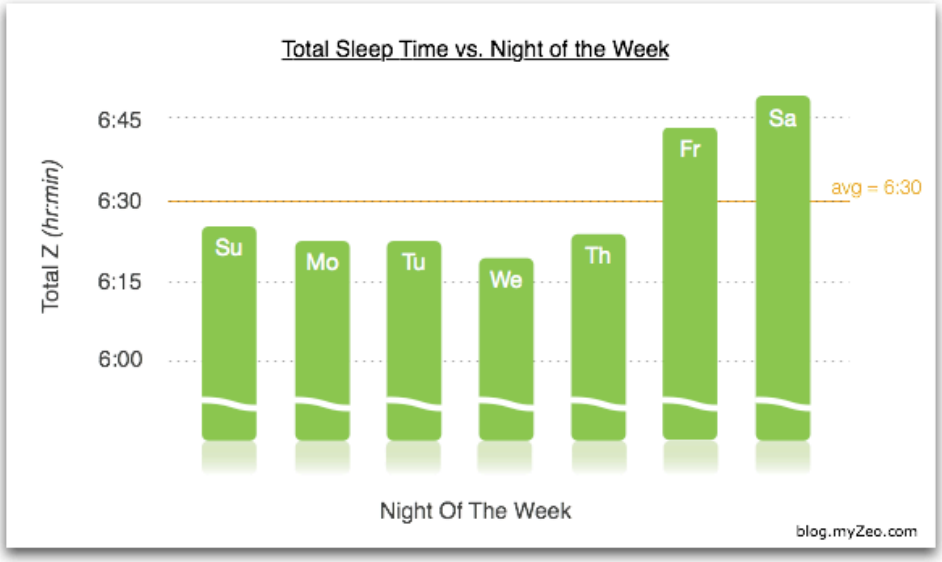
National Health and Nutrition Examination Survey findings

37% of adults report inadequate sleep
29% report severe sleep deprivation

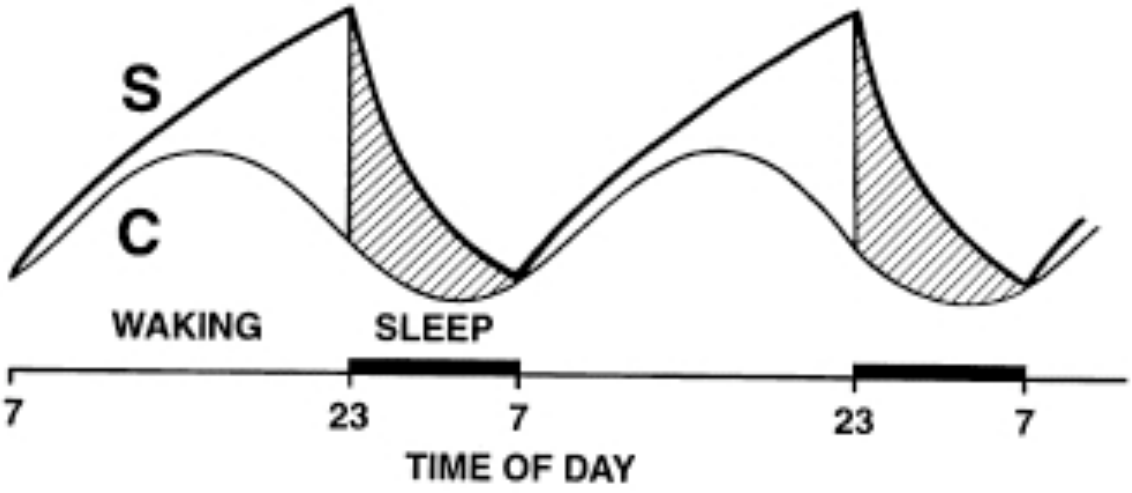
30% of employed adults < 6 h

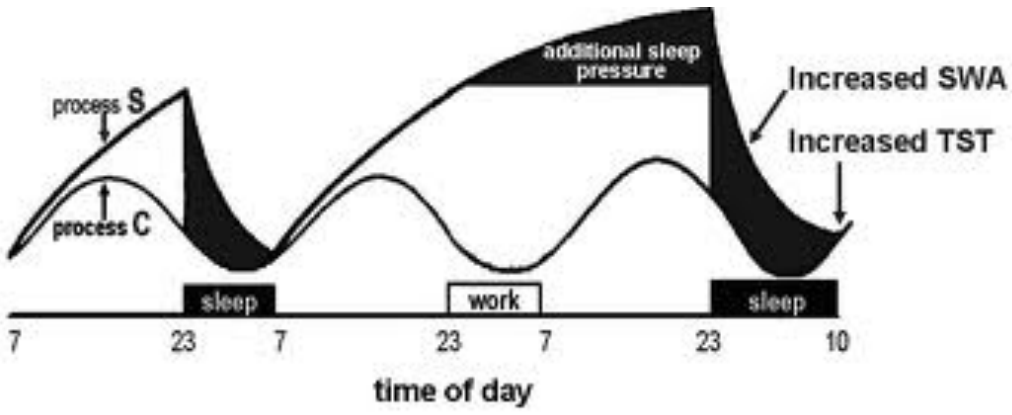
41% of parent with kids under 18 get < 7 h;
8% get less than 6 h

Only 31% of high schoolers get 8 h on school night



Process S – Sleep debt; homeostasis
Process C – Circadian





Rebound after lost sleep

Self-test question

How could one measure the pattern of Process C independent of Process S?

A. Just calculate which hours people spend most time awake

B. Measure amount of sleep when people are allowed 7 minutes every 20 minutes

C. Sleep deprive people for 3-4 days and measure daily pattern during the make-up sleep

D. All of the above

Sleep. 1989 Feb;12(1):13-21.

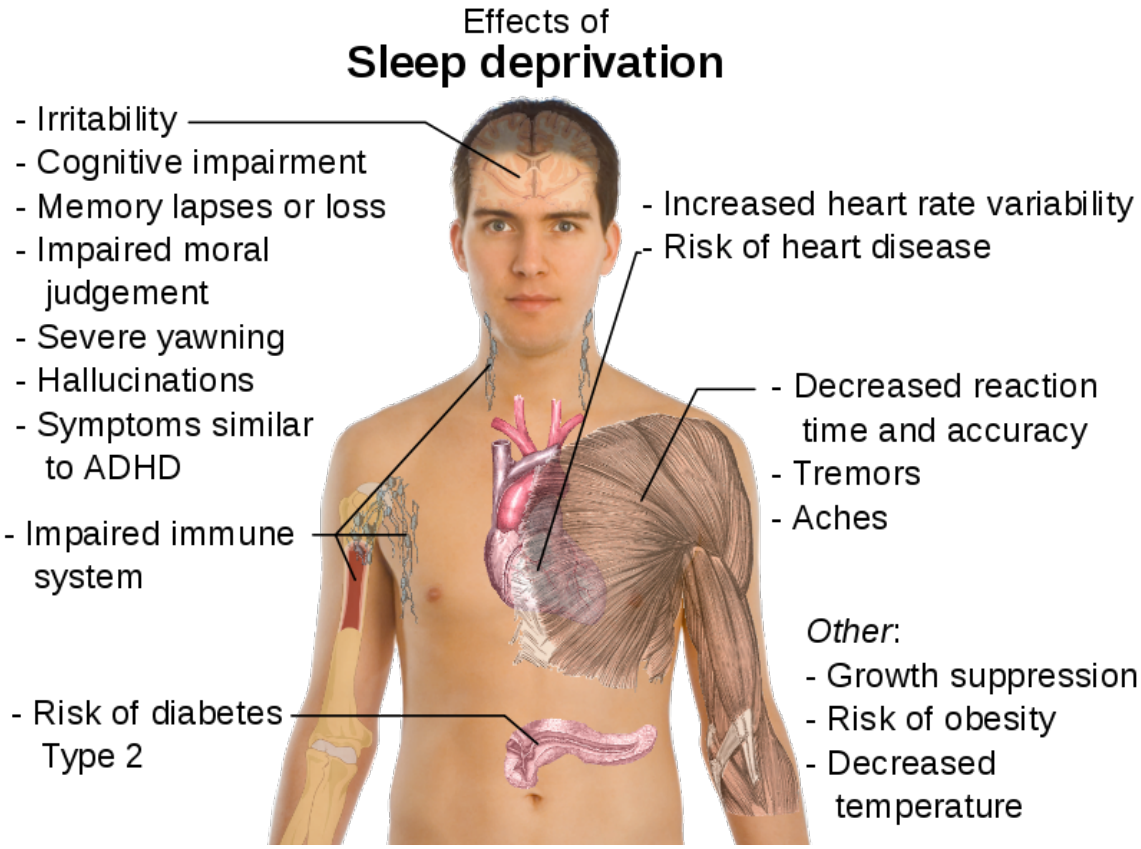
Sleep deprivation in the rat: III. Total sleep deprivation.

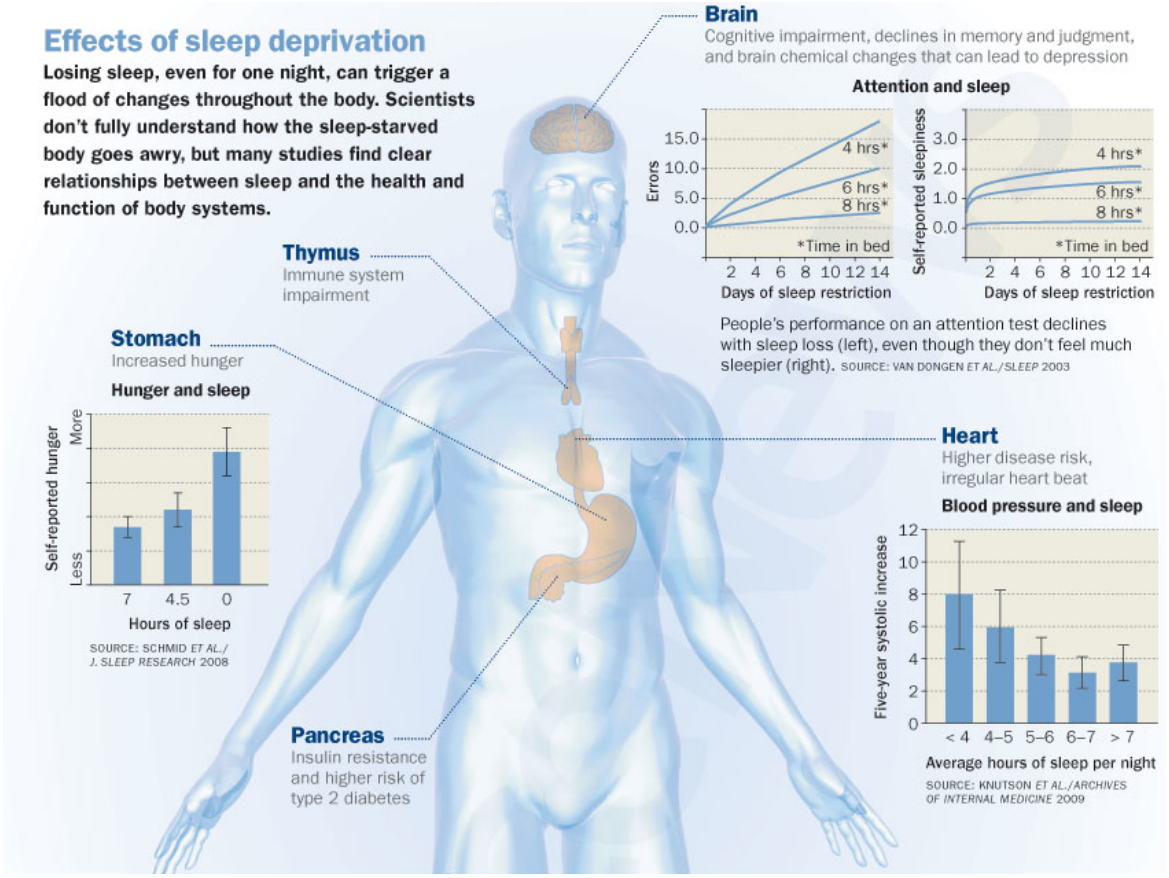
Everson CA, Bergmann BM, Rechtschaffen A.
Department of Psychiatry, University of Chicago, Illinois 60637.

Abstract

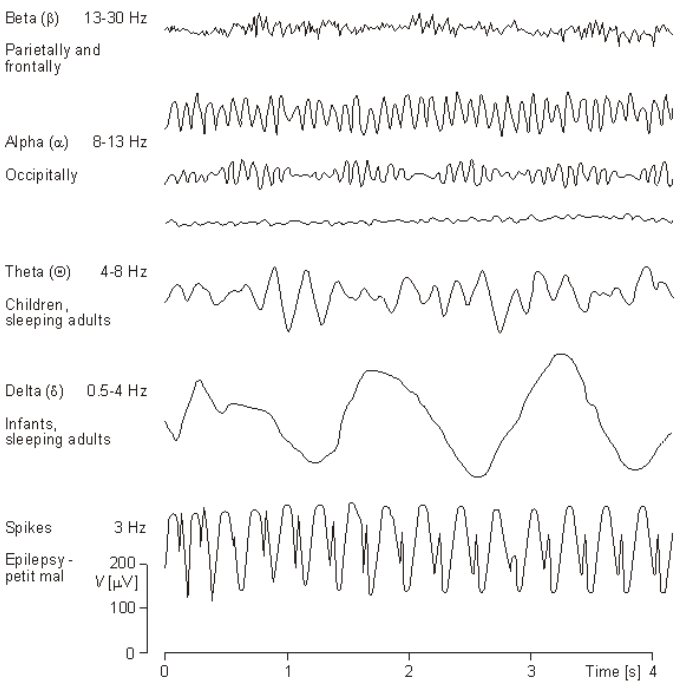
Ten rats were subjected to total sleep deprivation (TSD) by the disk apparatus. All TSD rats died or were sacrificed when death seemed imminent within 11-32 days. No anatomical cause of death was identified. All TSD rats showed a debilitated appearance, lesions on their tails and paws, and weight loss in spite of increased food intake. Their yoked control (TSC) rats remained healthy. Since dehydration was ruled out and several measures indicated accelerated use rather than failure to absorb nutrients, the food-weight changes in TSD rats were attributed to increased energy expenditure (EE). The measurement of EE, based upon caloric value of food, weight, and wastes, indicated that all TSD rats increased EE, with mean levels reaching more than twice baseline values.

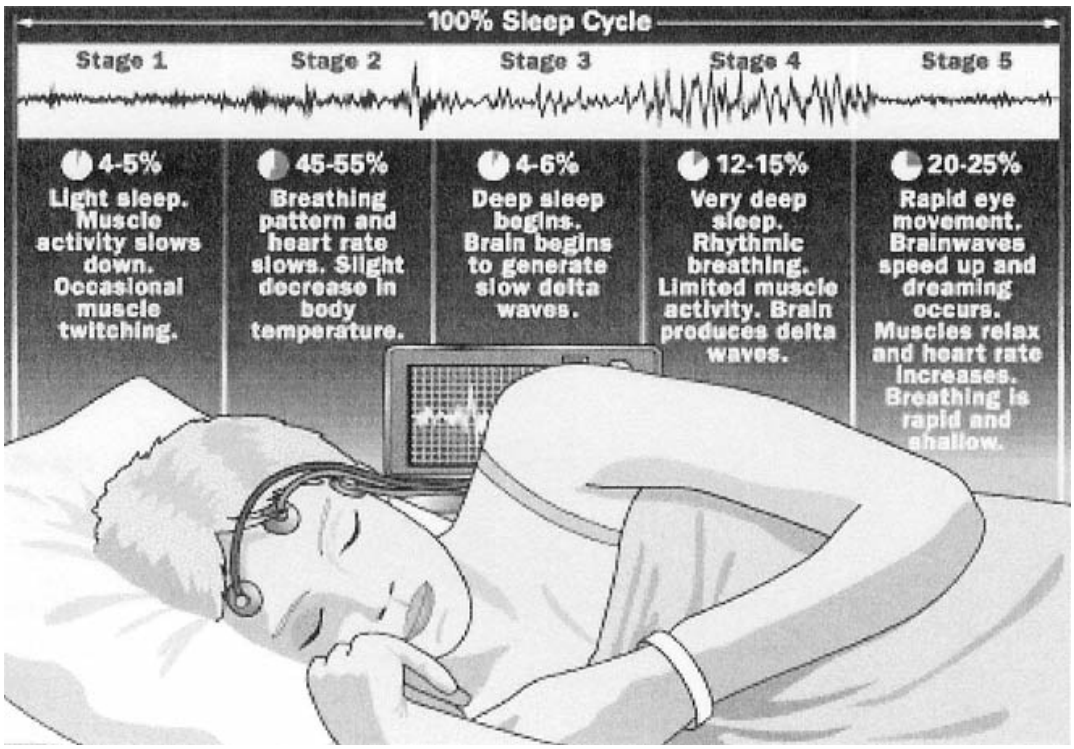
PMID: 2928622 [PubMed - indexed for MEDLINE]




Effects of sleep deprivation
Losing sleep, even for one night, can trigger a flood of changes throughout the body. Scientists don't fully understand how the sleep-starved body goes awry, but many studies find clear relationships between sleep and the health and function of body systems.
Brain
Cognitive impairment, declines in memory and judgment, and brain chemical changes that can lead to depression
Attention and sleep
Errors
15.0
10.0
5.0
0.0
4 hrs*
6 hrs*
8 hrs*
*Time in bed
2 4 6 8 10 12 14
Days of sleep restriction
Self-reported sleepiness
3.0
2.0
1.0
0.0
4 hrs*
6 hrs*
8 hrs*
*Time in bed
2 4 6 8 10 12 14
Days of sleep restriction
People's performance on an attention test declines with sleep loss (left), even though they don't feel much sleepier (right). SOURCE: VAN DONGEN ET AL./SLEEP 2003
Thymus
Immune system impairment
Stomach
Increased hunger
Hunger and sleep
Self-reported hunger
More
Less
7 4.5 0
Hours of sleep
SOURCE: SCHMID ET AL./ J. SLEEP RESEARCH 2008
Heart
Higher disease risk, irregular heart beat
Blood pressure and sleep
Five-year systolic increase
12
10
8
6
4
2
0
< 4 4–5 5–6 6–7 > 7
Average hours of sleep per night
SOURCE: KNUTSON ET AL./ARCHIVES OF INTERNAL MEDICINE 2009
Pancreas
Insulin resistance and higher risk of type 2 diabetes

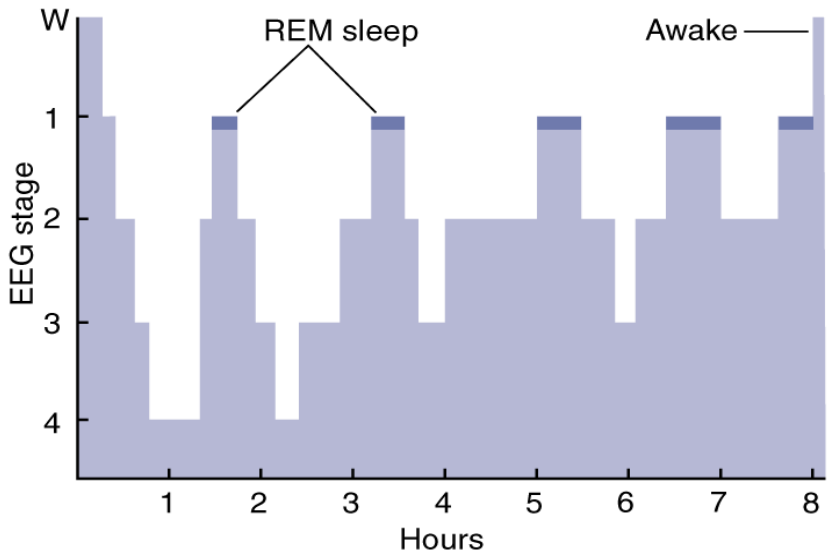
EEG


Beta (β) 13-30 Hz
Parietally and frontally
Alpha (α) 8-13 Hz
Occipitally
Theta (Θ) 4-8 Hz
Children, sleeping adults
Delta (δ) 0.5-4 Hz
Infants, sleeping adults
Spikes 3 Hz
Epilepsy - petit mal
200
V [μV]
100
0
0 1 2 3 Time [s] 4



Cyclical (ultradian) Nature of Sleep

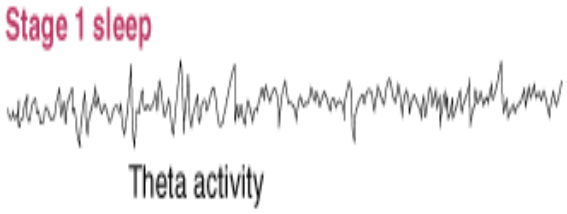
► **Typical Pattern of the Stages of Sleep During a Single Night**

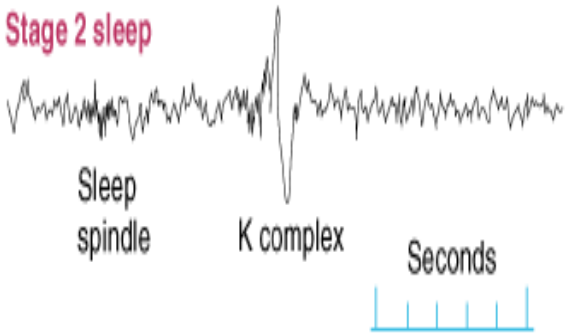


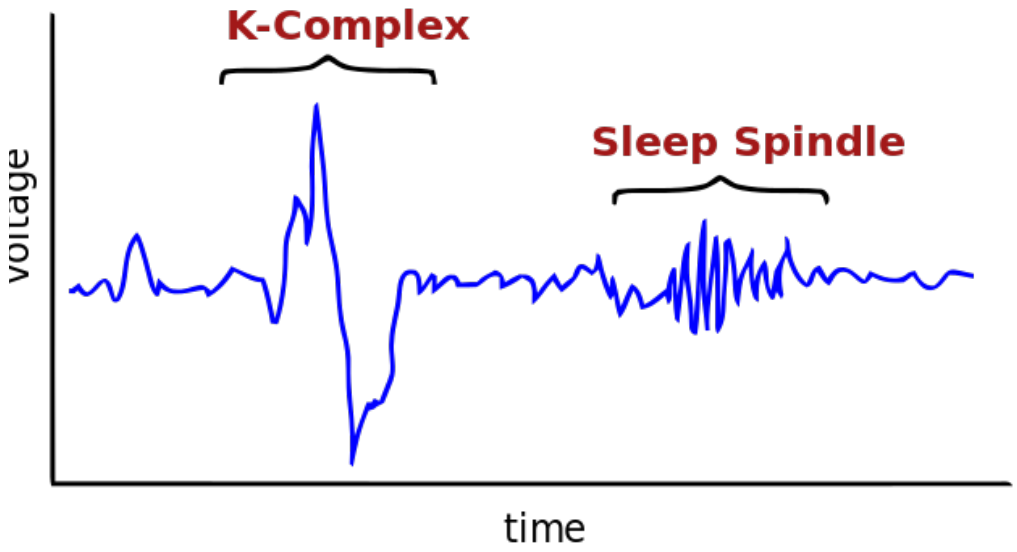
Cortical Activity During Arousal – neurons not synchronized

***Alpha Waves (8-12 Hz)**
relaxed arousal

***Beta Waves (13-30 Hz)**
attentive arousal



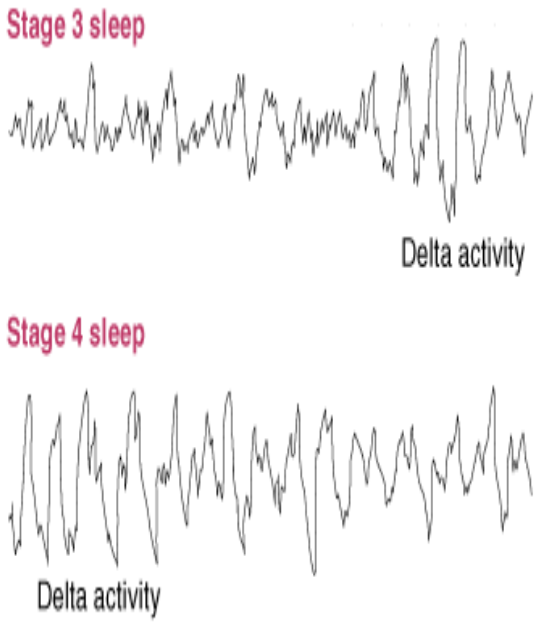


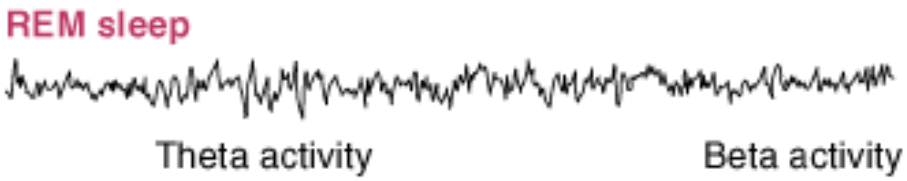


K Complex- transient, high amplitude spike; response to sounds; exact function?

Sleep Spindle (12-14 Hz) transient burst of synchronized potentials; related to IQ, learning?

3-4 are slow-wave sleep (SWS)





Rapid rolling eye movements

Desynchronized EEG (like wakefulness)

Skeletal muscle atonia

Dreaming

Insomnia

Fatal Familial Insomnia

Narcolepsy

Sleep Talking/Walking

Night Terrors

REM Behavioral Disorder

Sleep paralysis

Insomnia

Onset, maintenance, or terminal insomnia

Chronic Insomnia

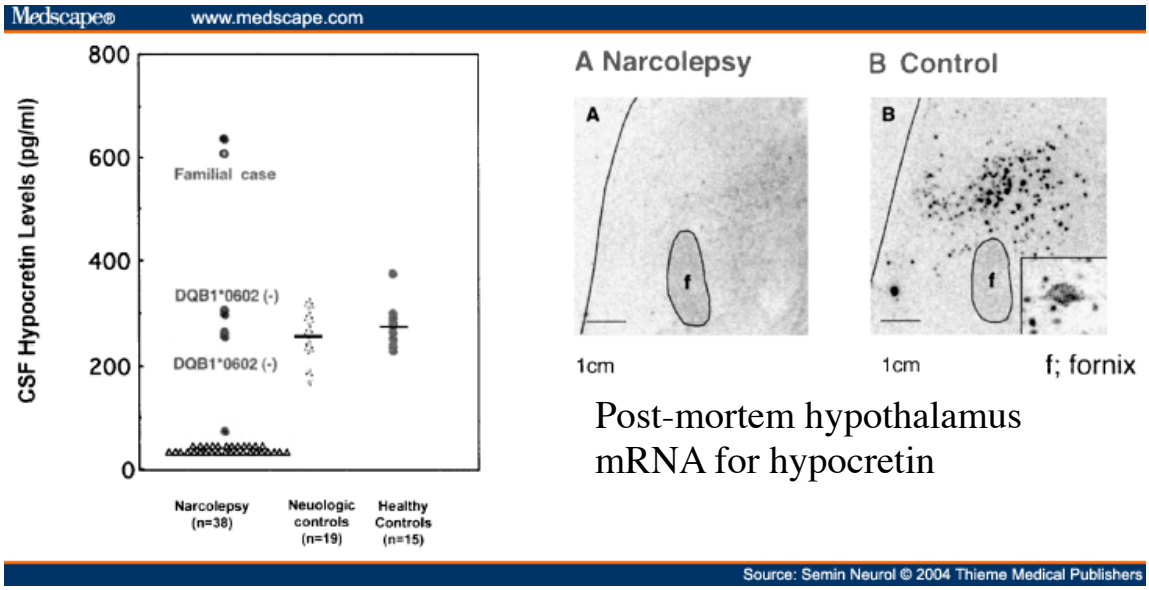
difficulty concentrating
memory problems
auto accidents
inability to enjoy family/social relationships
2 fold greater risk for major depression

Fatal Familial Insomnia

Prion mutation
stop sleeping die within 18 months
insomnia is cause of death????

Narcolepsy

In dogs – mutation of orexin/hypocretin receptor

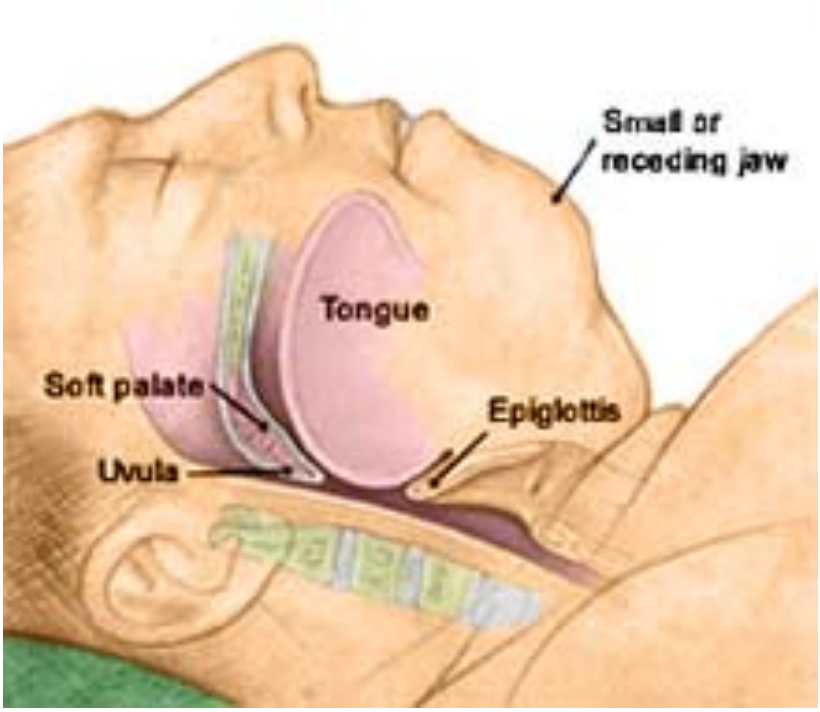


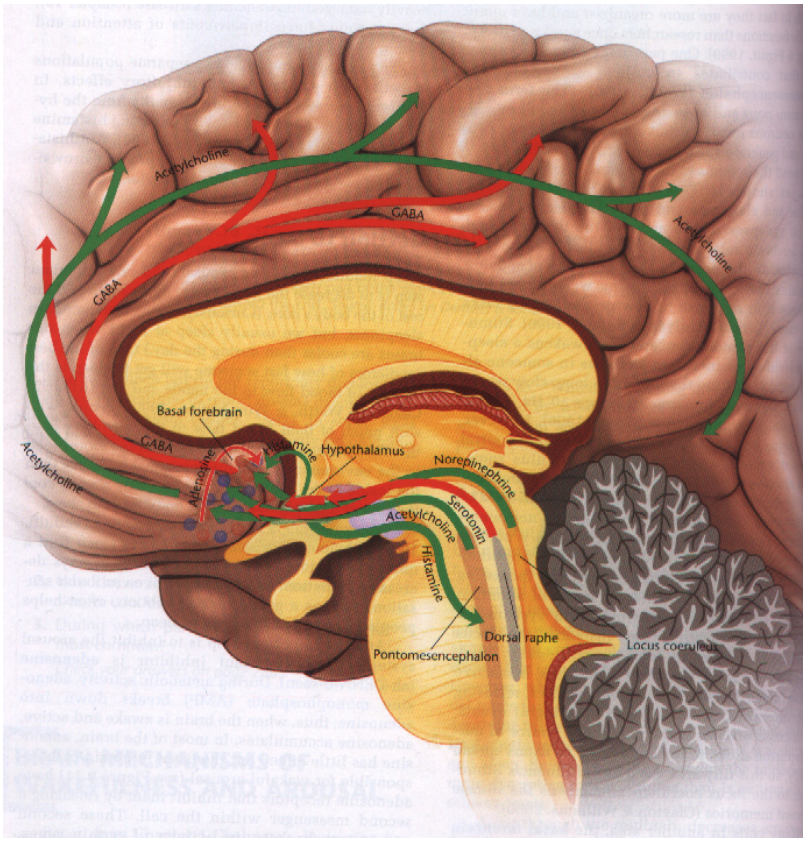
Post-mortem hypothalamus mRNA for hypocretin


Sleepwalking -- running


SHOWN ON
M90
.ORG
Night Terrors

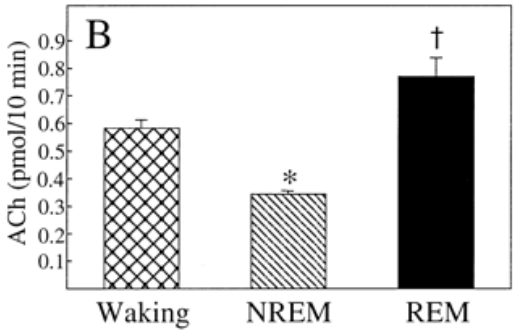
CPAP
continuous positive airway pressure

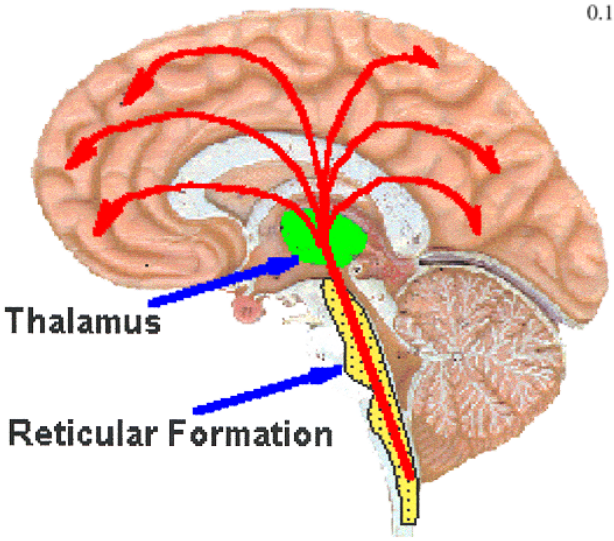




Cortex
Basal Forebrain
Limbic System
Thalamus
Hypothalamus
Hippocampus
Cerebellum
Pons
Medulla

Reticular Formation & ACh
NOTE: high during REM

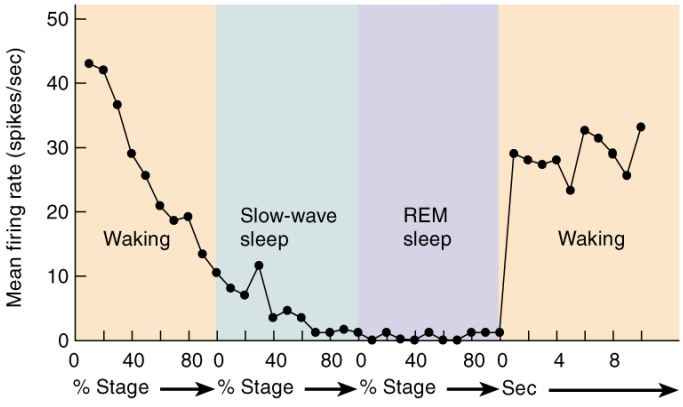




Adapted from *Sleep Multimedia*, 1998

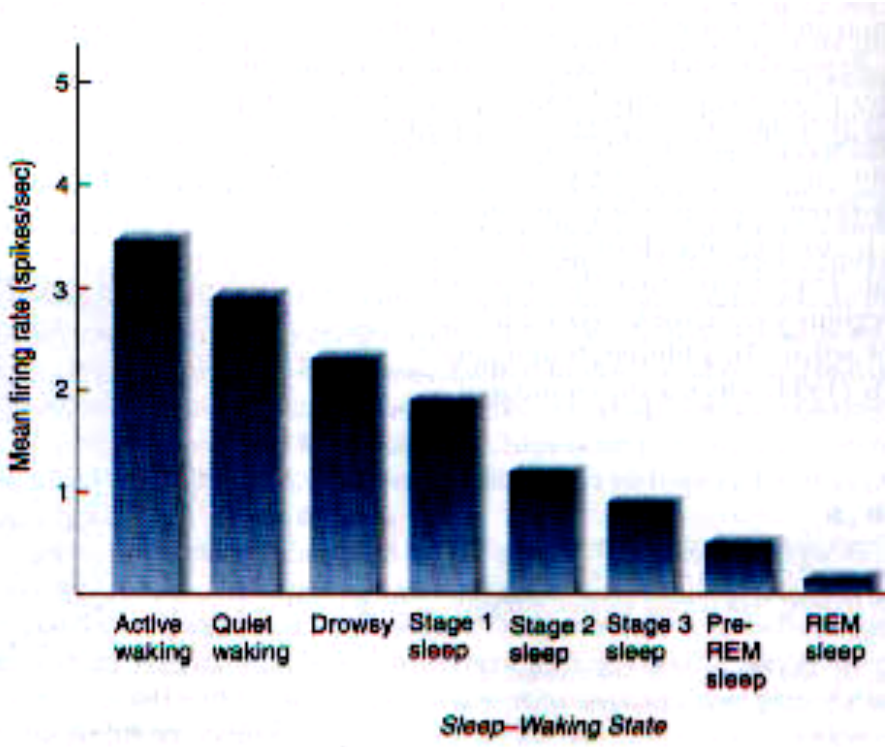
Locus Coeruleus & NE
NOTE: Low in REM

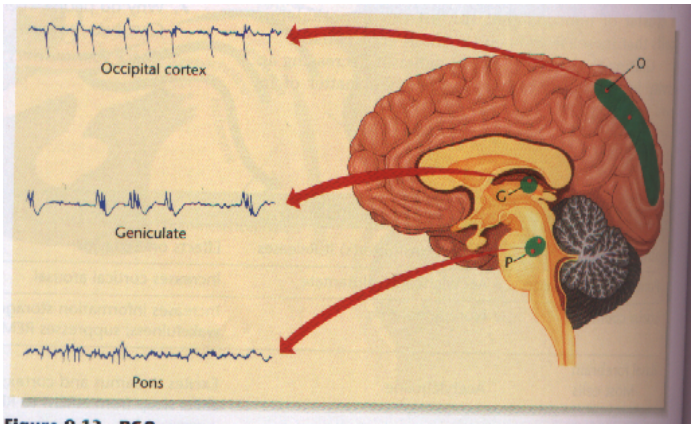
▶ **Activity of Noradrenergic Neurons in the Locus Coeruleus of Freely Moving Cats During Various Stages of Sleep and Waking**



Source: From Aston-Jones, G., and Bloom, F.E. *The Journal of Neuroscience,* 1981, *1,* 876–886. Copyright 1981, The Society for Neuroscience.

Raphe Nuclei & 5-HT
NOTE: Low in REM





REM – deprivation

REM rebound; consequences for learning/memory???
improve mood???

ACh Release by Pons in REM

PGO Waves Pons- Geniculate/Thalamus - Occipital Lobe

All areas important for processing visual info PGO = dreams?
Pons also shuts down spinal cord
Partial lesions of pons lead to movements during REM

Self-test question

The fact that REM-deprivation causes increases in REM sleep in subsequent nights suggests that …

A. REM is the most important sleep stage

B. REM is homeostatically regulated

C. REM is not influenced by circadian rhythms

D. Time in REM is linked to time in NREM

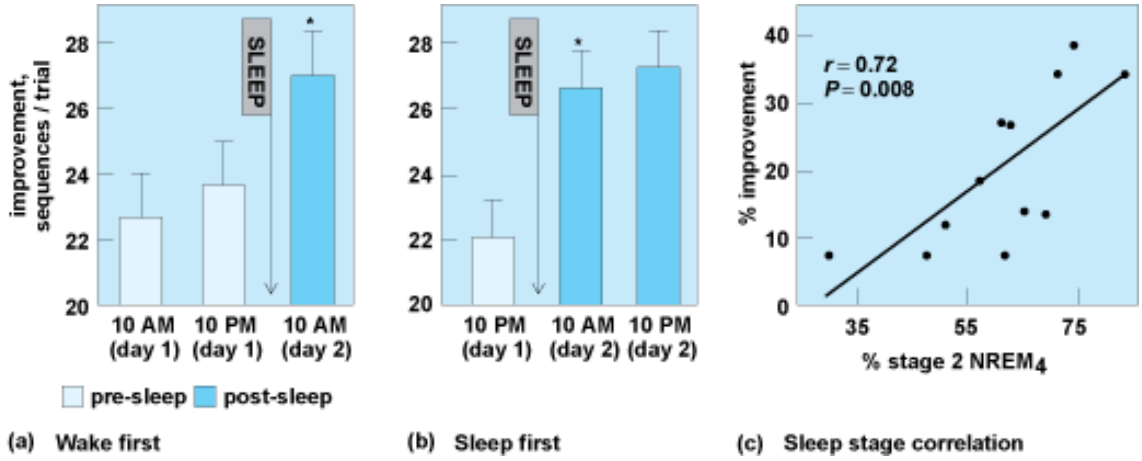
Why sleep?

Physiological restoration

Memory and Learning

Metabolic Processes

Temperature Regulation
ground squirrels de-hibernate to sleep



Weaknesses –
Definitely can learn without sleep
Sleep stages still largely based on correlations

Self-test question

What potential dangers are associated with pulling an all-nighter before a midterm exam?

A. One might oversleep and miss the test

B. One's overall cognitive performance is harmed by sleep deprivation

C. Beneficial effects of sleep on memory are lost

D. Any of the above

Summary:

1. **Sleep is active and structured**

2. **Sleep involves multiple brain systems that can go awry**

3. **Function of one of our most important behaviors remains unknown!**

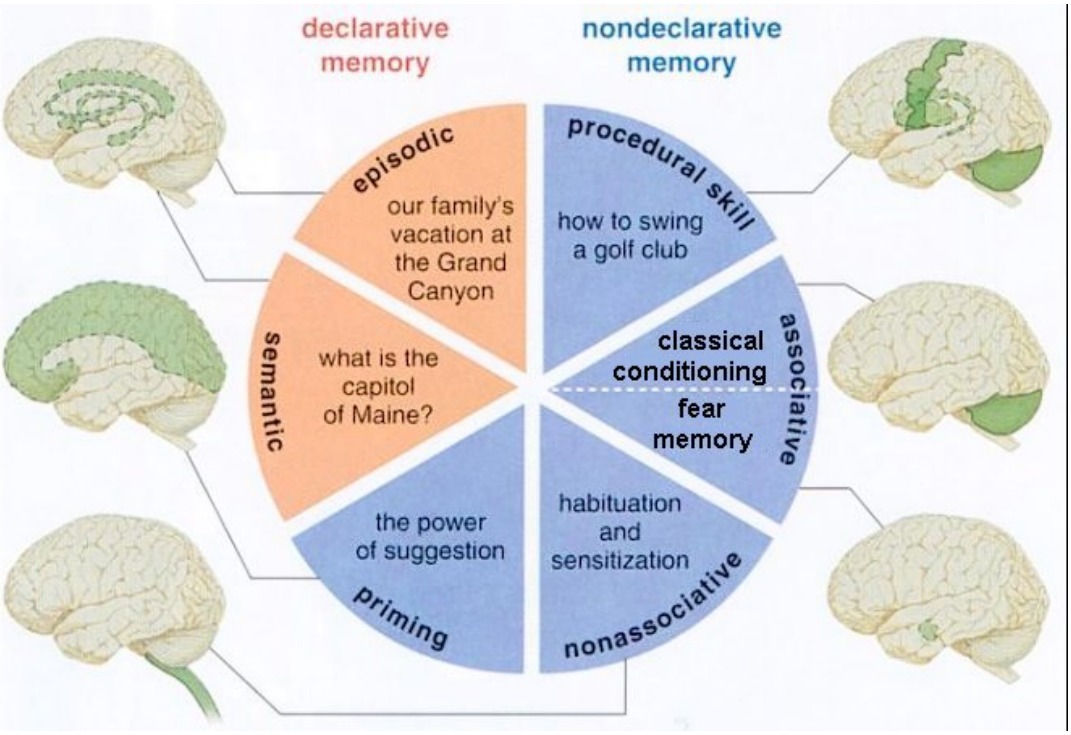
Learning/Memory CHAPTER 13

Study Questions

1. What has been learned about the nature of memory processes through the study of individual human subjects?

- **Definitions**
  Learning -- change in behavior that results from experience
  Memory -- retention of those changes over time separate from development

- **Many kinds of memory**



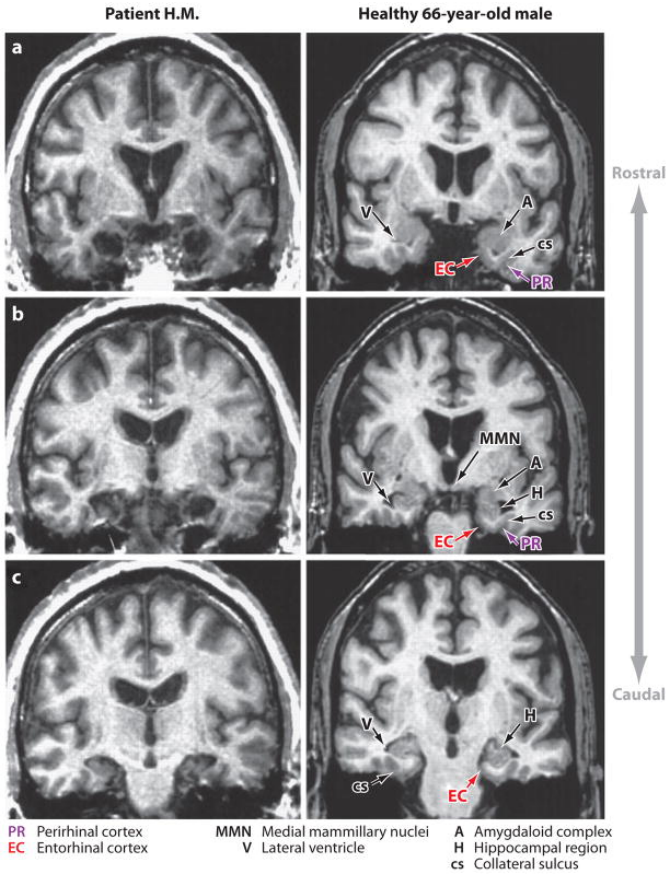
Strategies to understand how memory is represented in the brain?

- Brain-damaged subjects
- Exceptional memory
- Comparative research
- Physiological studies in animals
- In vitro studies of neuron function

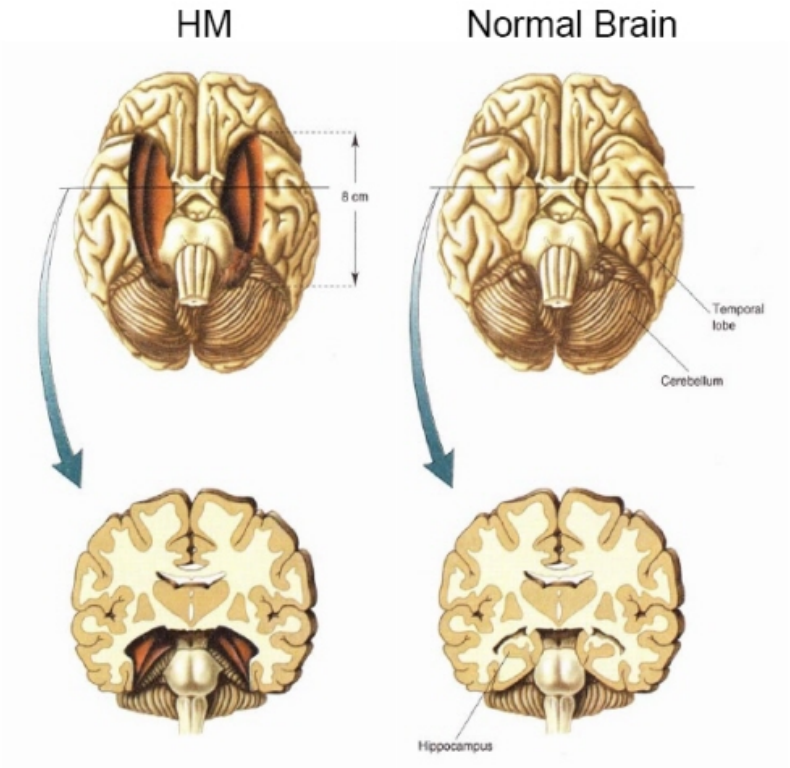
Henry Molaison (H.M.)

Most studied case of human amnesia
Severe seizures at age 16; surgery to remove epileptic focus at age 27 (1953)

Severe memory loss - amnesia



Medial temporal cortex
Amygdaloid complex
Entorhinal cortex
Rostral ½ of hippocampus



Retrograde Amnesia – Loss of memories from the past

Anterograde Amnesia – inability to form new memories

Could HM learn anything?

- **Whole categories of things**
- **Mirror writing task**
- **Demonstrated functional dissociation of different types of human memory**

Self-test question

Patient HM was least impaired with respect to which type of memory?

A. Episodic

B. Declarative

C. Anterograde

D. Procedural

Self-test question

What inference can you draw from the fact that HM's most intact memory was for the distant past?

A. Those memories are stored outside of the medial temporal lobe

B. Early memories are encoded more strongly in the brain

C. The aging brain switches strategies for how it stores memories

D. Earlier memories have less declarative content than later memories

CLIVE WEARING

Jill Price

Neurocase (2006) **12**, 35–49

ISSN: 1355-4795 print
DOI: 10.1080/13554790500473680

Psychology Press
Taylor & Francis Group

A Case of Unusual Autobiographical Remembering

ELIZABETH S. PARKER[1], LARRY CAHILL[2] and JAMES L. McGAUGH[2]

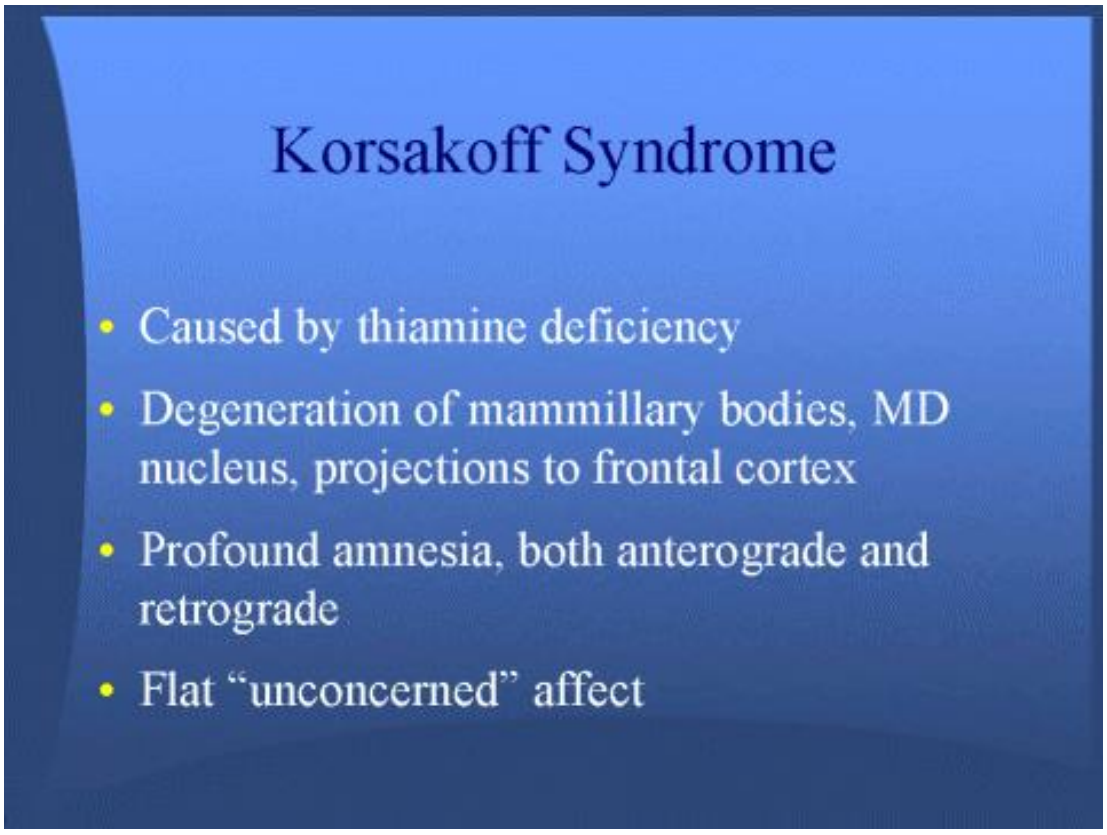
[1]*Department of Neurology, University of California, Los Angeles, Irvine, and Psychiatry & Neurology, University of Southern California, California, USA*
[2]*Center for the Neurobiology of Learning and Memory and Department of Neurobiology and Behavior, University of California, Irvine, California, USA*

This report describes AJ, a woman whose remembering dominates her life. Her memory is "nonstop, uncontrollable, and automatic." AJ spends an excessive amount of time recalling her personal past with considerable accuracy and reliability. If given a date, she can tell you what she was doing and what day of the week it fell on. She differs from other cases of superior memory who use practiced mnemonics to remember vast amounts of personally irrelevant information. We propose the name *hyperthymestic syndrome*, from the Greek word thymesis meaning remembering, and that AJ is the first reported case.

Table 5. AJ's deficits on neuropsychological tests

Deficits: Defined as performance more than 1.5 sd above/below average			
	Raw Score	Z-score	Comment
Executive Function and Reasoning Tests			
Concept Formation and Shifting from WCST			
Perseverative Responses	38	<2.0	impaired
Executive Functions from HCT	78 errors	−2.3	impaired
Analogical Reasoning from WAIS-R	5	−1.67	impaired
Anterior Left Hemisphere Tests			
Motor Speed, Right Dominant Hand	36.5	−1.6	impaired
Dysnomia from Boston Naming	51/60	−2.7	impaired
Organizationally-Demanding Memory Tests			
Recall of Word-List from CVLT		>−2.0	impaired
Recall of Complex Figure, both delays	13/36 & 11.5/36		impaired
Face Memory Test			
Face Recognition, Warrington Test	38/50	−1.6	impaired

There are indications from AJ's neuropsychological test results, as well as her self-reports, that her hyperthymestic syndrome may be related to and possibly caused by poor executive functions in the areas of abstraction, reflection, and inhibition. Her vulnerability to dwelling on her personal past, recalling memories over and over, may reflect a form of dis-inhibition such that she lacks the normal capacity to switch memories off. Her rich storehouse of memories may have developed because of her use of concrete, highly structured encoding and retrieval processes, one of which is the calendar as will be discussed further.



Korsakoff's syndrome – Mammillary bodies
Source: Kopelman et al Alcohol and Alcoholism Jan 2009 pp 1-7

(1) *Anna Thompson:*
Anna Thompson of South Bristol, employed as a cleaner in an office building, reported at the Town Hall police station that she had been held up on the High Street the night before and robbed of 15 pounds. She had four little children, the rent was due, and they had not eaten for two days. The officers, touched by the woman's story, made up a purse for her.

Healthy controls 45 min later

"She worked at the Town Hall."

"A hospital worker (was) stopped by the police."

"She lost her purse. The police thought she was a thief."

"Anna Stevenson aged forty-four."

"Her children were starving. The police made up £50."

"She was attacked on her way home from Bristol. She was very poor and her children were starving."

Korsakoff's

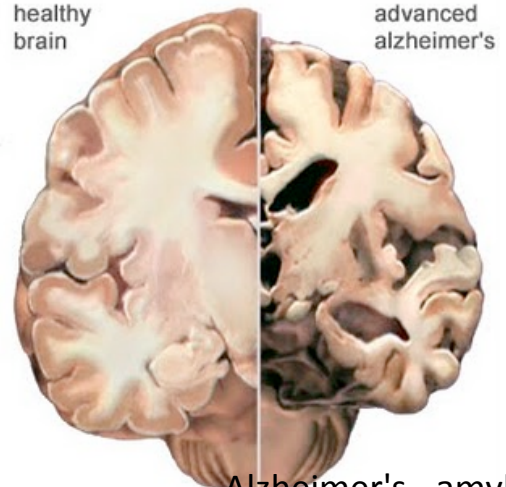
"Mrs Joyce who lived at Brighton and Hove was hanging out her washing." (Added "I'm not very happy about that (though) I think I've got the gist of it.").

"It concerned a man going somewhere and his time of arrival—whether he'd be late or not."

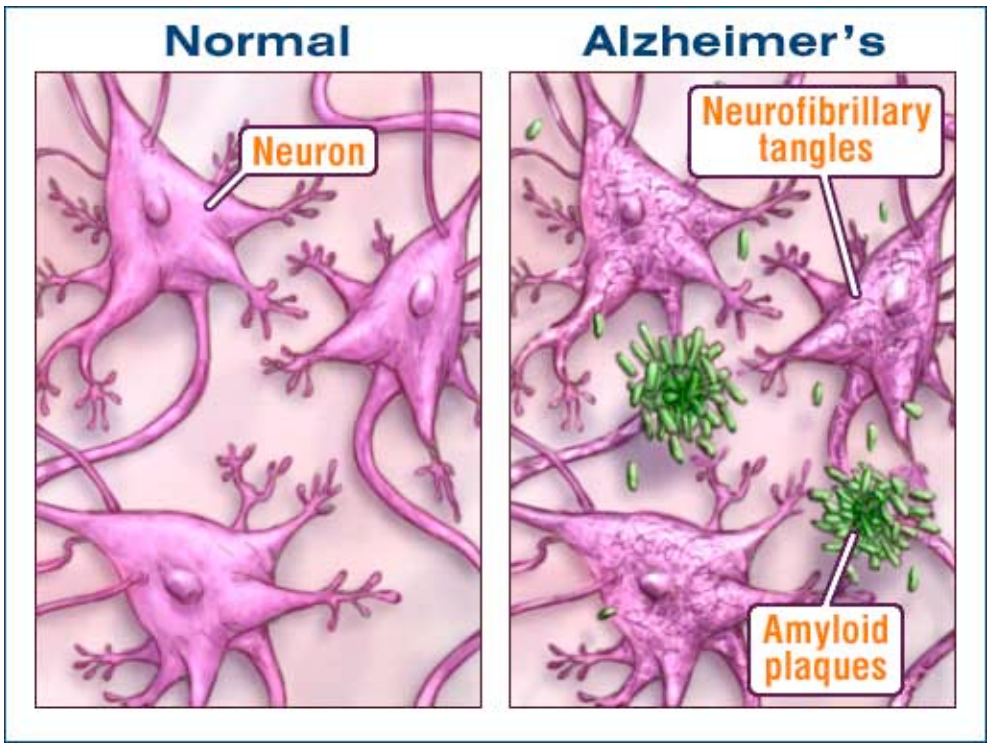
"A man. It was dark at night. They sent someone to catch a robber."

"Jack Brown took his wife down to Brighton."

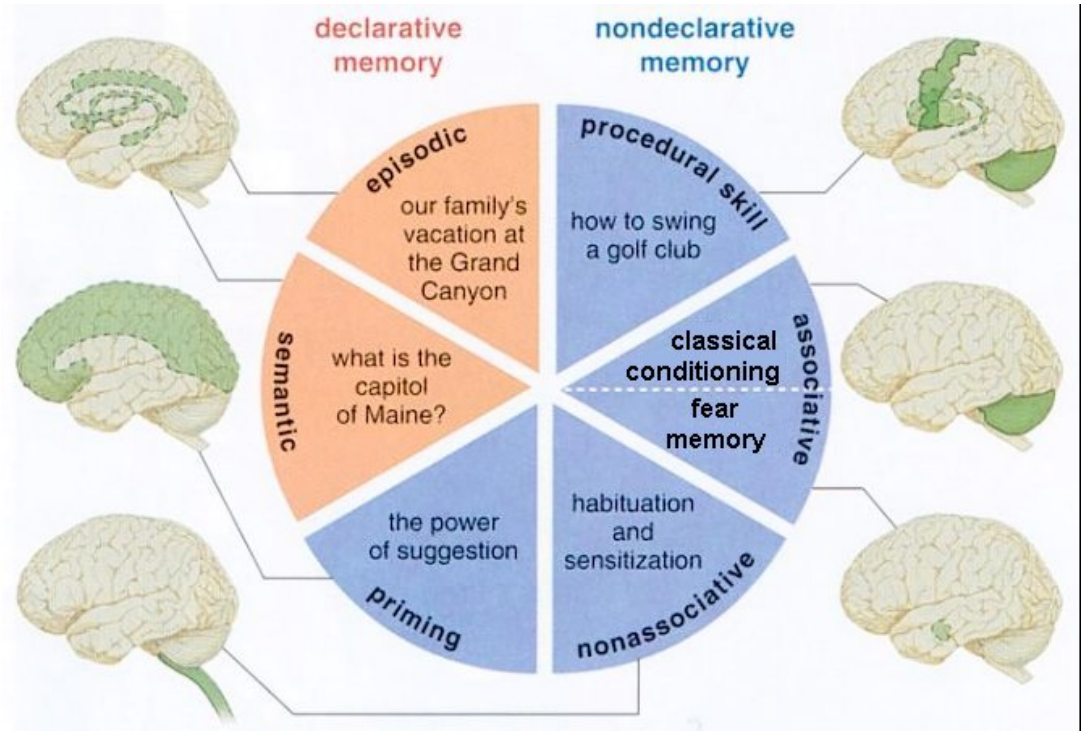
Alzheimer's Disease

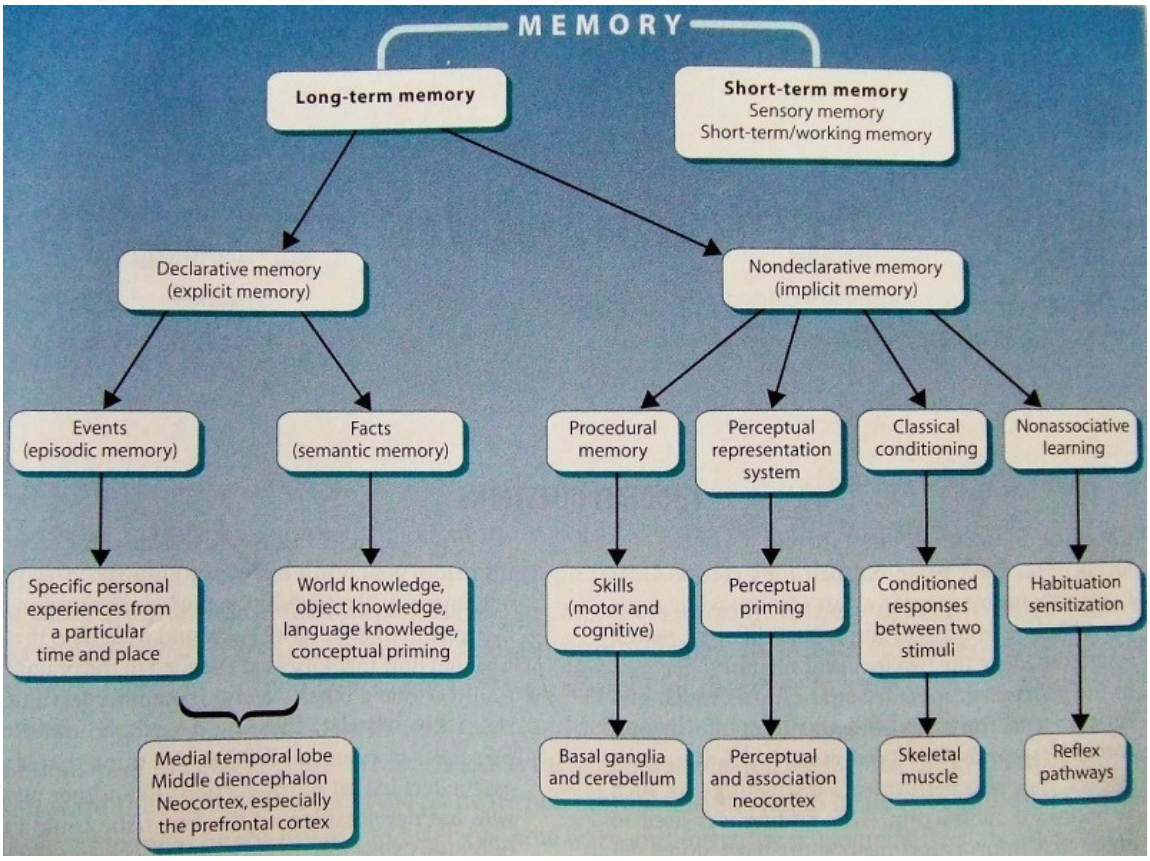


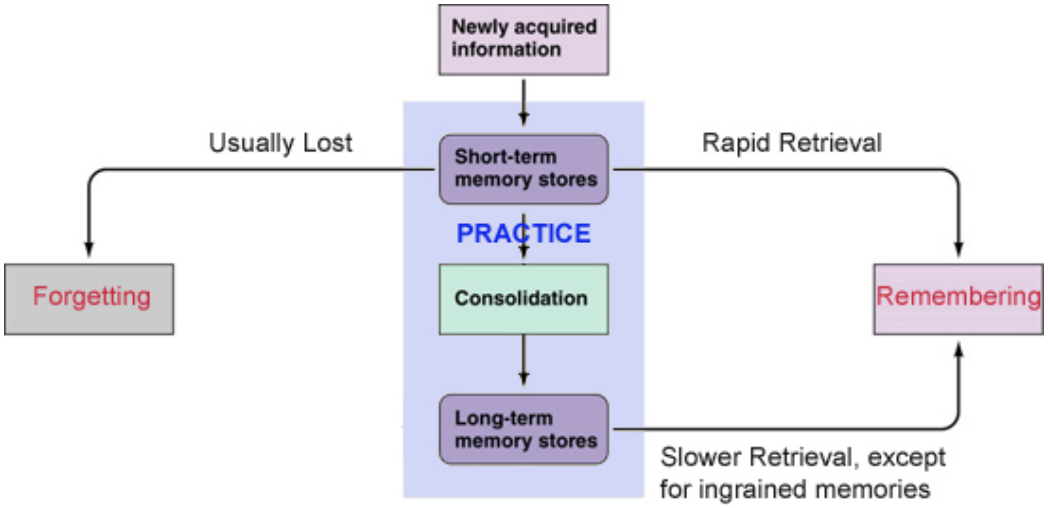
Alzheimer's - amyloid plaques
cortex, hippocampus
basal forebrain = dec in ACh
procedural better than declarative
implicit better than explicit

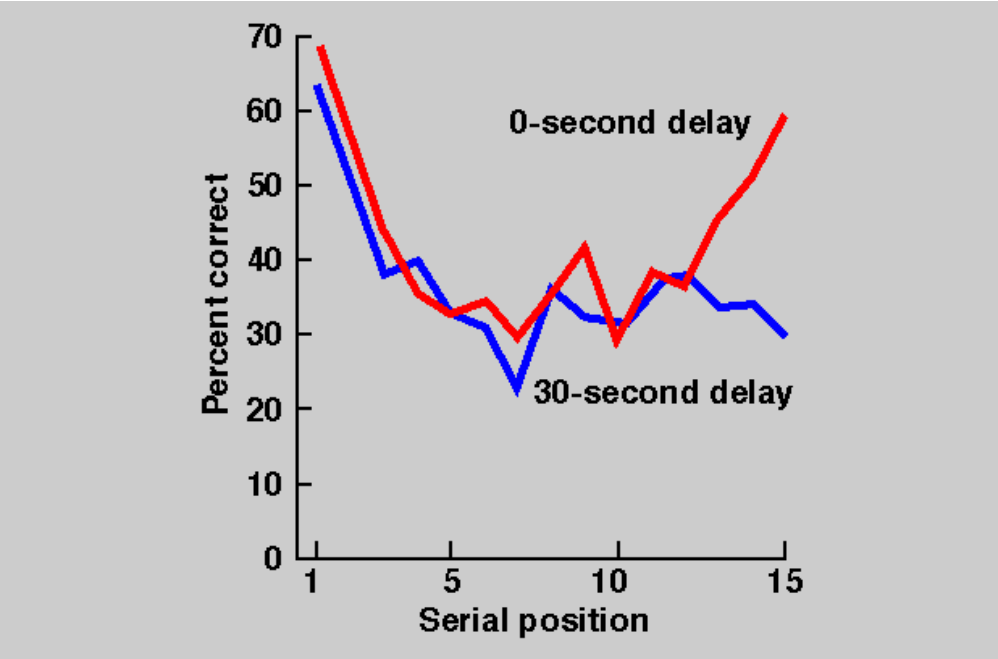


INSULIN TREATMENT
ACh TREATMENTS

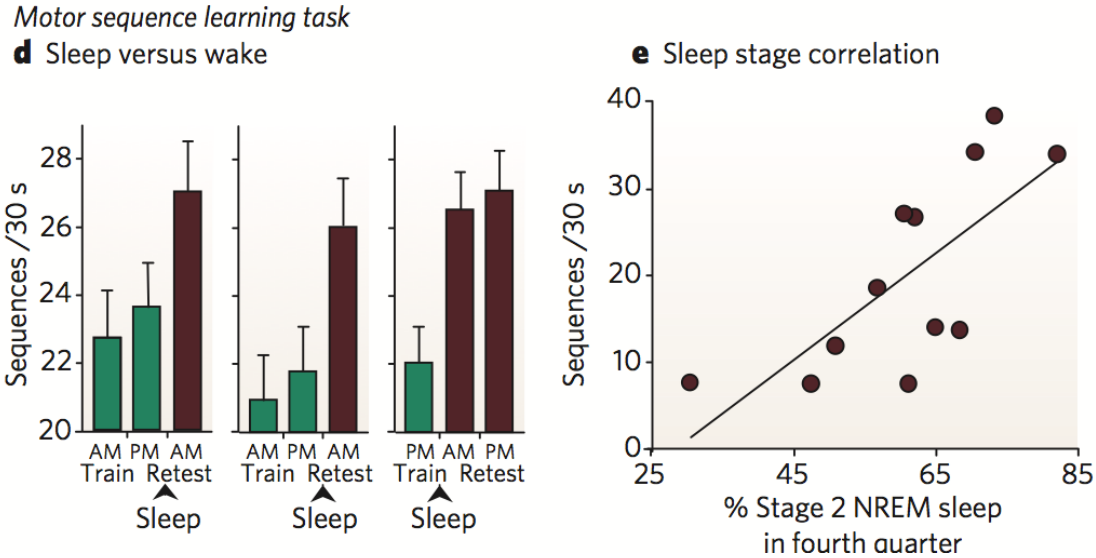



MEMORY
Long-term memory
Short-term memory
Sensory memory
Short-term/working memory
Declarative memory
(explicit memory)
Nondeclarative memory
(implicit memory)
Events
(episodic memory)
Facts
(semantic memory)
Procedural
memory
Perceptual
representation
system
Classical
conditioning
Nonassociative
learning
Specific personal
experiences from
a particular
time and place
World knowledge,
object knowledge,
language knowledge,
conceptual priming
Skills
(motor and
cognitive)
Perceptual
priming
Conditioned
responses
between two
stimuli
Habituation
sensitization
Medial temporal lobe
Middle diencephalon
Neocortex, especially
the prefrontal cortex
Basal ganglia
and cerebellum
Perceptual
and association
neocortex
Skeletal
muscle
Reflex
pathways

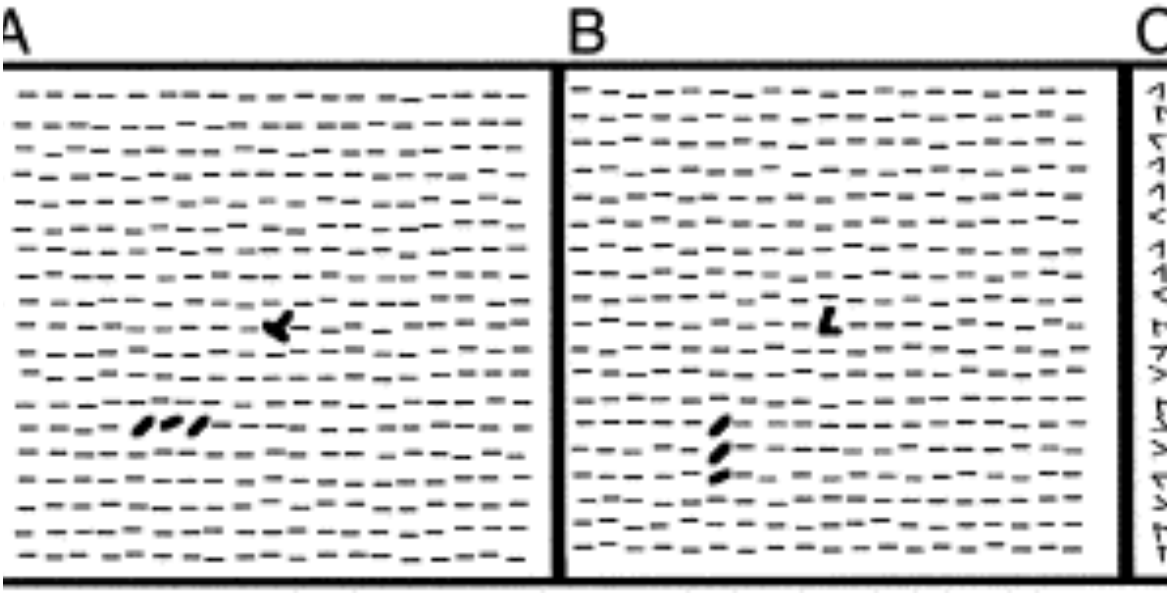

Newly acquired information
Usually Lost
Short-term memory stores
Rapid Retrieval
PRACTICE
Forgetting
Consolidation
Remembering
Long-term memory stores
Slower Retrieval, except for ingrained memories

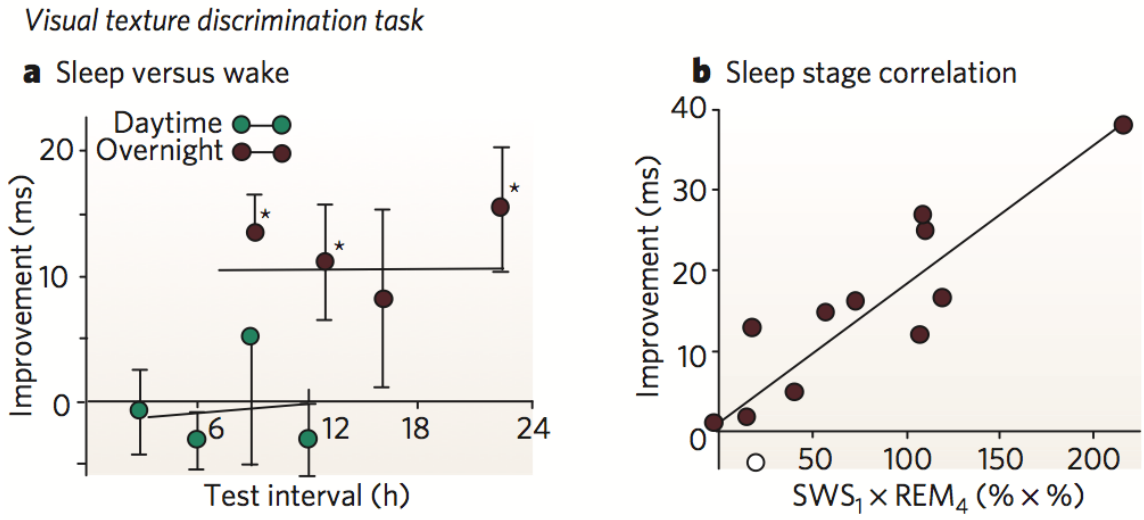


Sleep and Memory Consolidation



Wake first or sleep first





Weaknesses –
Definitely can learn without sleep
Sleep stages still largely based on correlations

Self-test question

What potential dangers are associated with pulling an all-nighter before a midterm exam?

A One might oversleep and miss the test

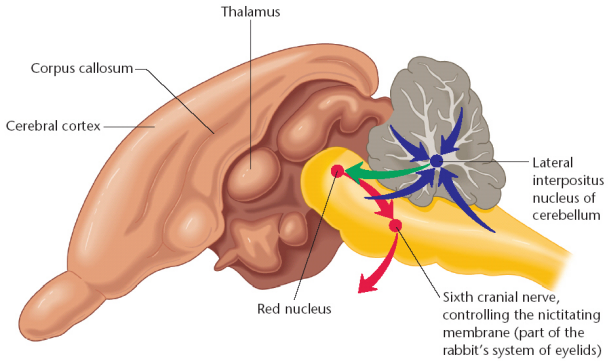
B. One's overall cognitive performance is harmed by sleep deprivation

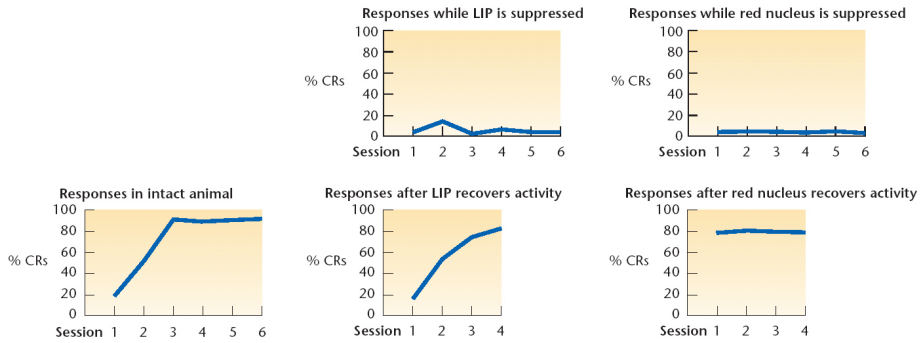
C. Beneficial effects of sleep on memory are lost

D. Any of the above

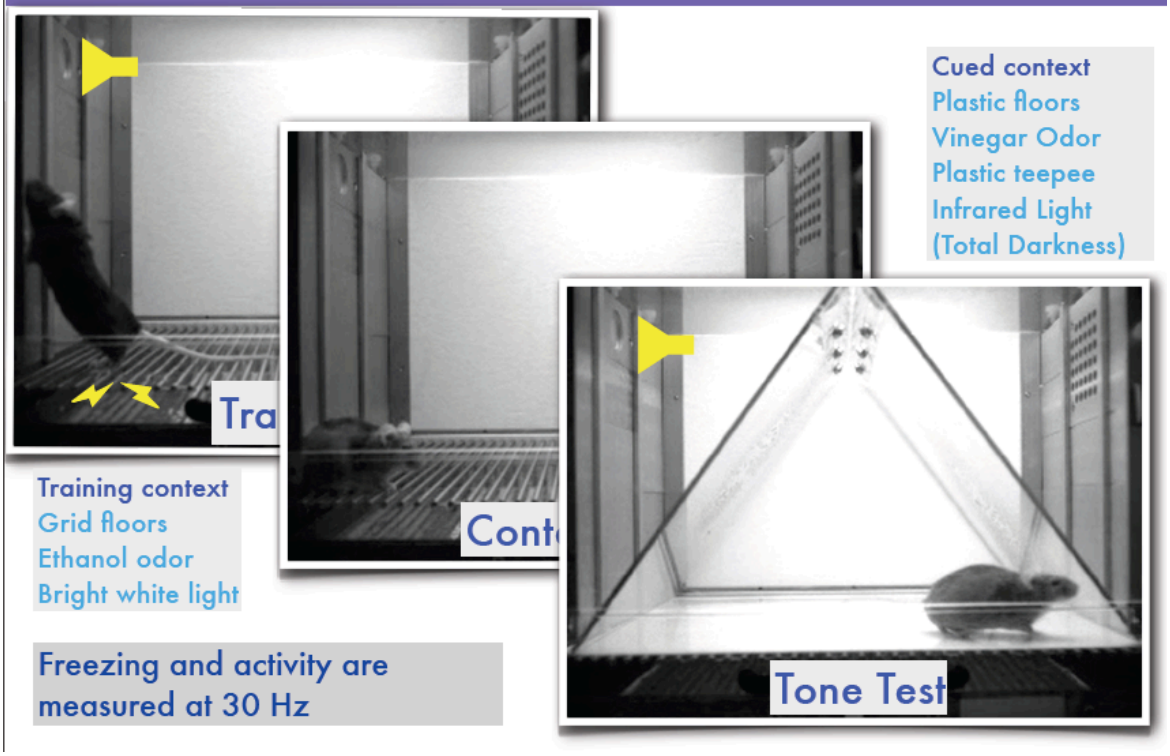
Animal Studies

Eyeblink Conditioning

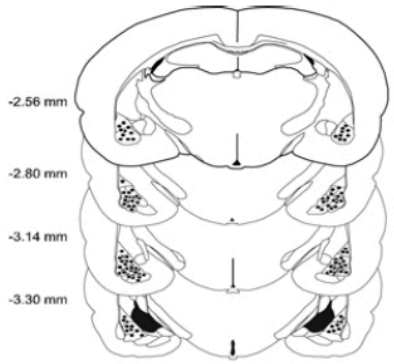




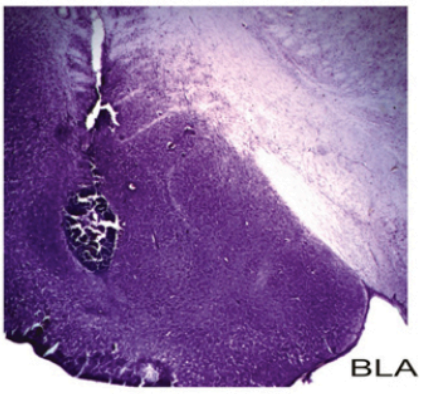
Pavlovian fear conditioning



Amygdala Lesion

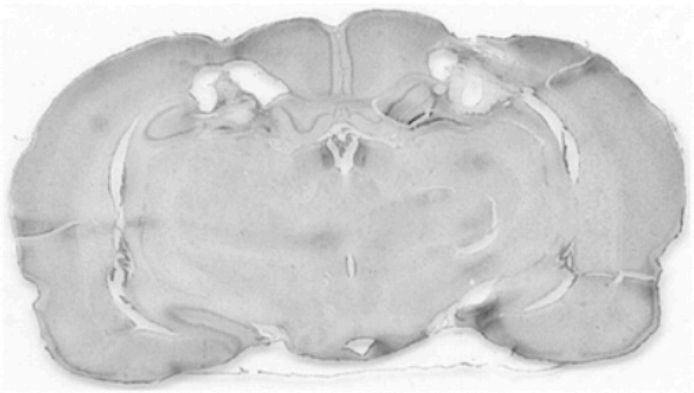


Basolateral Amygdala (BLA)

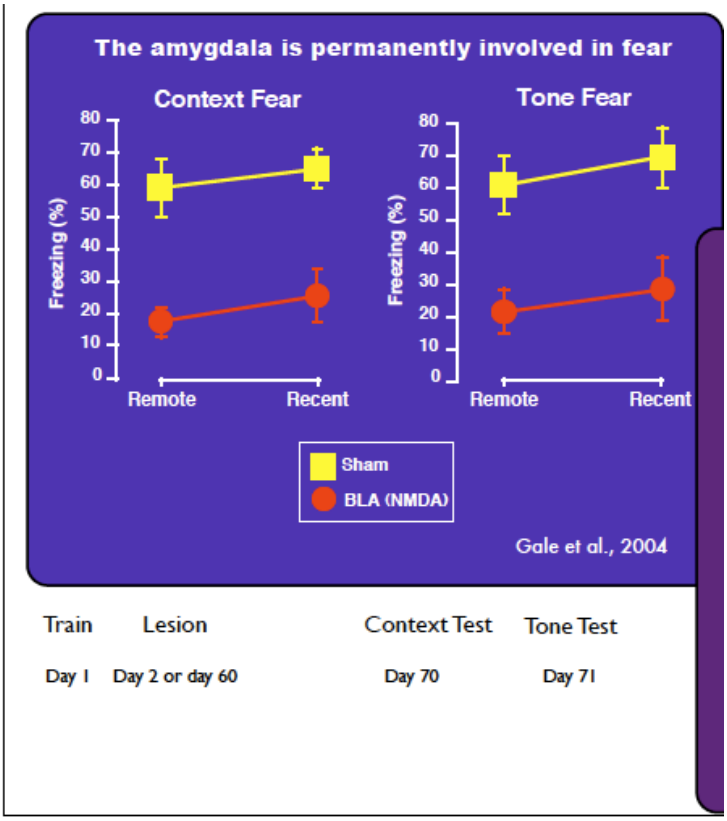


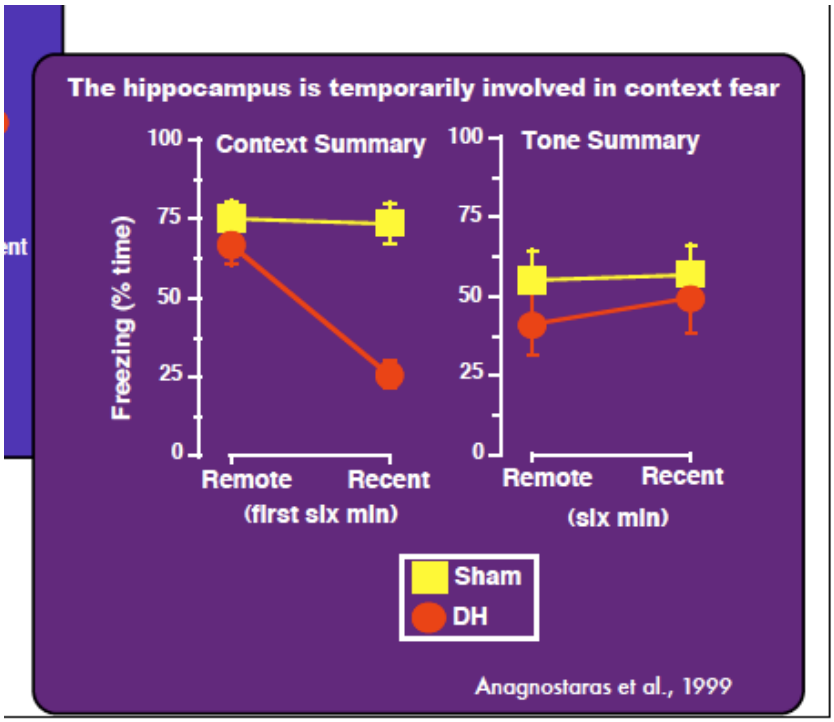
Train	Lesion	Context Test	Tone Test
Day 1	Day 2 or day 60	Day 70	Day 71

Dorsal Hippocampus Lesion



Train	Lesion	Context Test	Tone Test
Day 1	Day 2 or day 60	Day 70	Day 71


The amygdala is permanently involved in fear
Context Fear
Tone Fear
Freezing (%)
80
70
60
50
40
30
20
10
0
Remote
Recent
Sham
BLA (NMDA)
Gale et al., 2004
Train
Lesion
Context Test
Tone Test
Day 1
Day 2 or day 60
Day 70
Day 71


The hippocampus is temporarily involved in context fear
Context Summary
Tone Summary
Freezing (% time)
100
75
50
25
0
Remote
Recent
(first six min)
(six min)
Sham
DH
Anagnostaras et al., 1999

Exp Brain Res (1993) 93:462–470

Experimental
Brain Research

Memory for spatial locations, motor responses, and objects: triple dissociation among the hippocampus, caudate nucleus, and extrastriate visual cortex

Raymond P. Kesner, Bridget L. Bolland, Manoli Dakis

Department of Psychology, University of Utah, Salt Lake City, Utah 84112, USA

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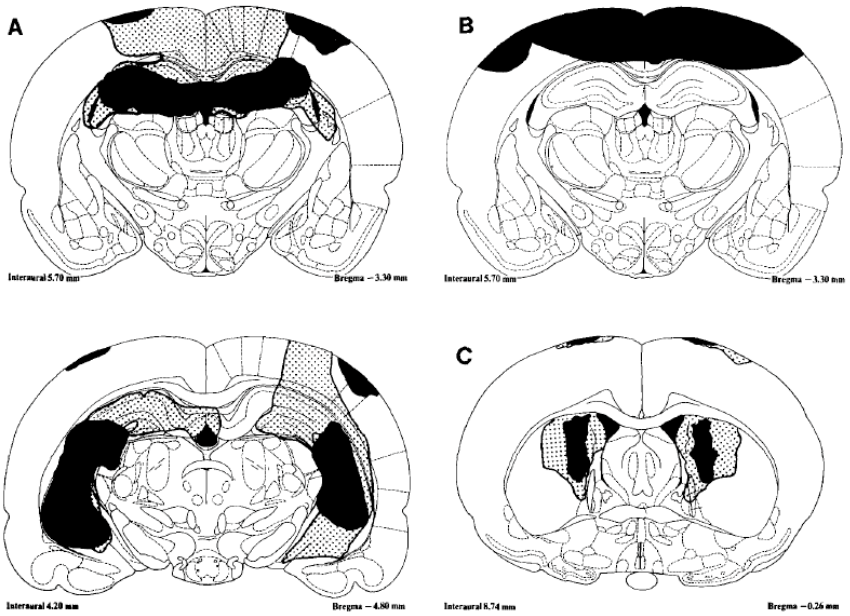
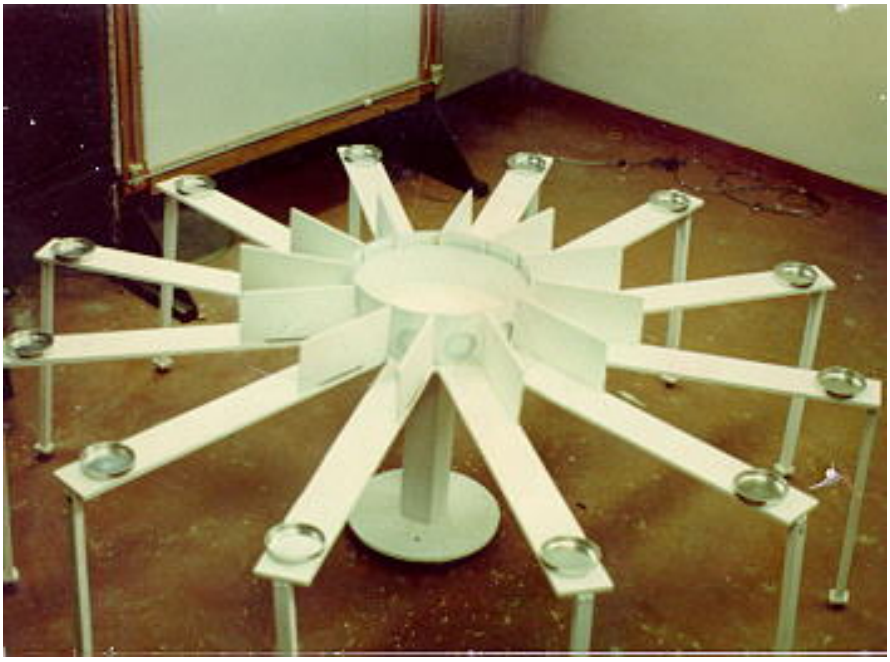


Fig. 2. **A** The smallest (*black*) and largest (*stippled*) dorsal and ventral hippocampal lesion (two sections) **B** A representative cortical control lesion; and **C** the smallest (*black*) and largest (*stippled*) caudate lesion



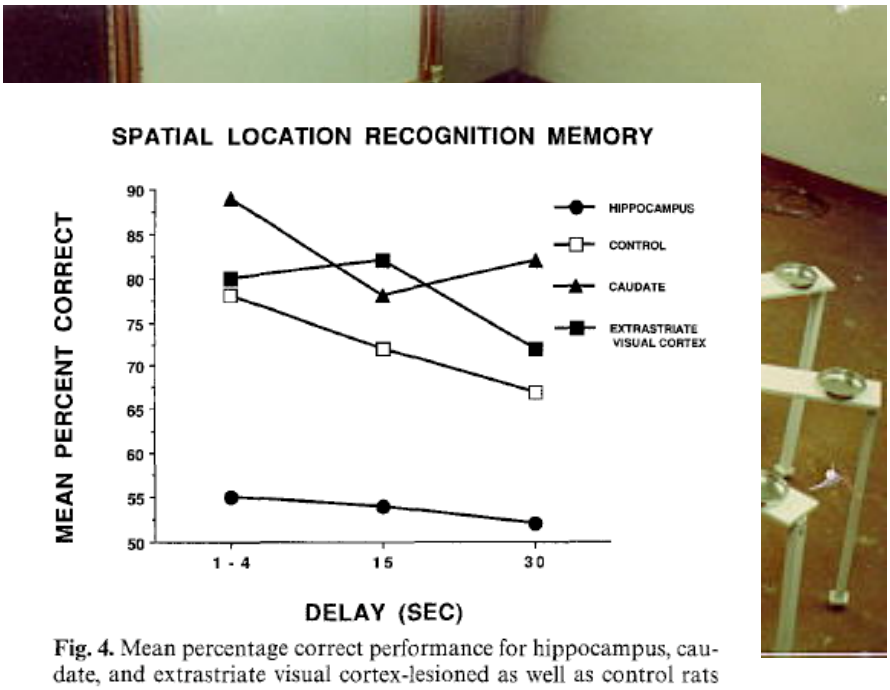
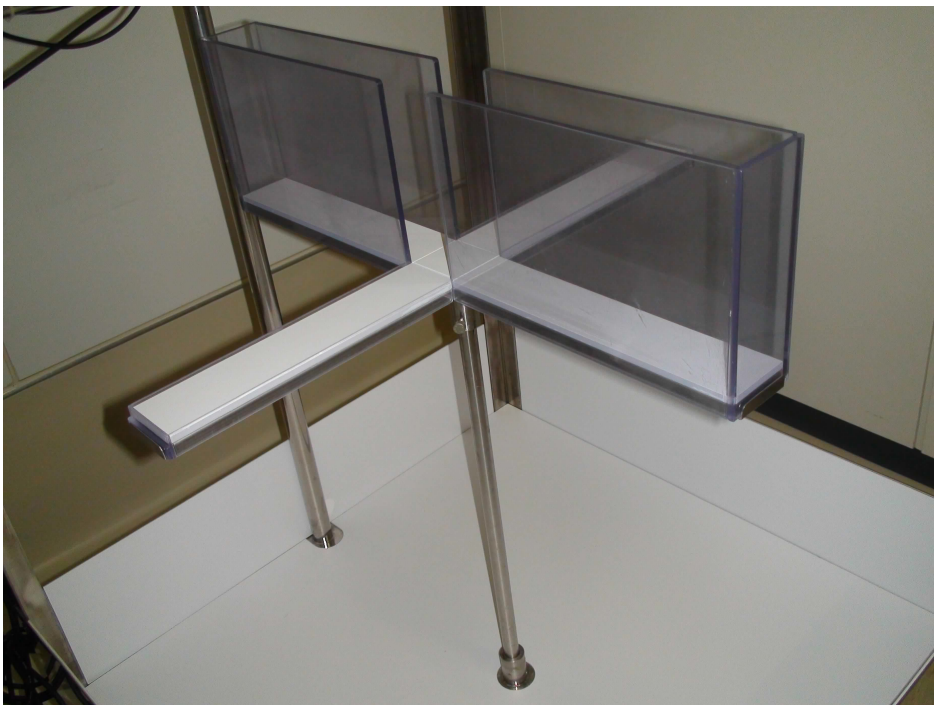


Fig. 4. Mean percentage correct performance for hippocampus, caudate, and extrastriate visual cortex-lesioned as well as control rats as a function of delay for spatial location recognition memory



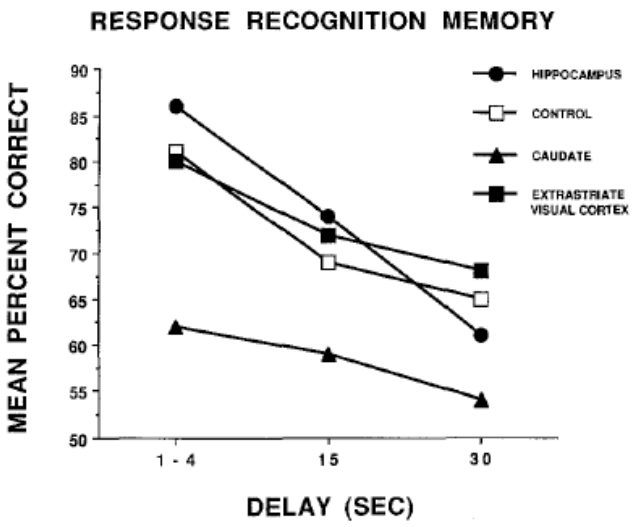
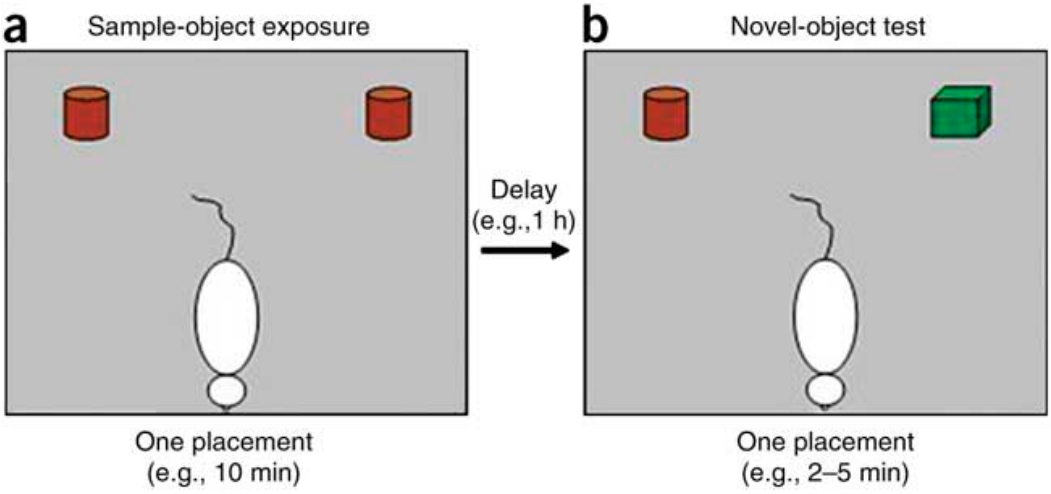


Fig. 5. Mean percentage correct performance for hippocampus, caudate, and extrastriate visual cortex-lesioned as well as control rats as a function of delay for response recognition memory



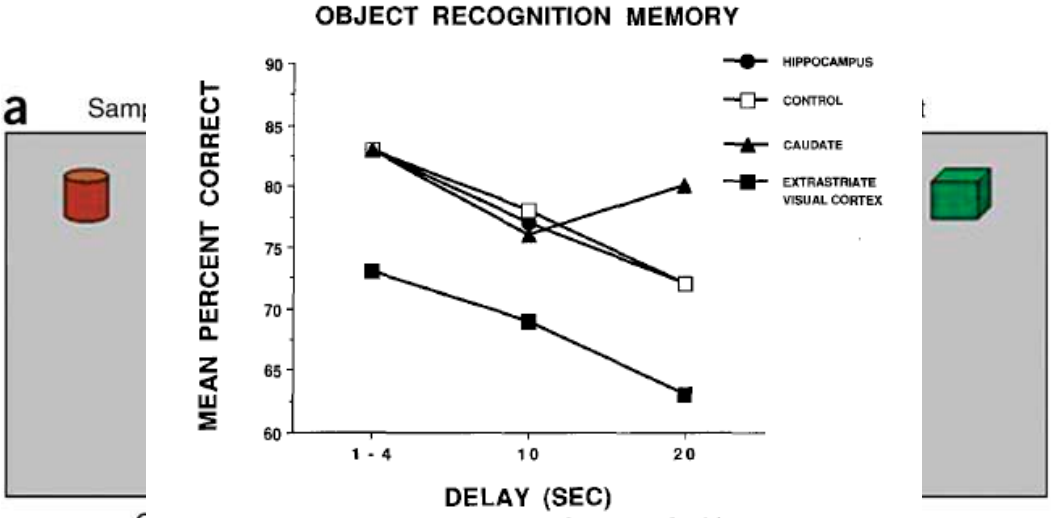
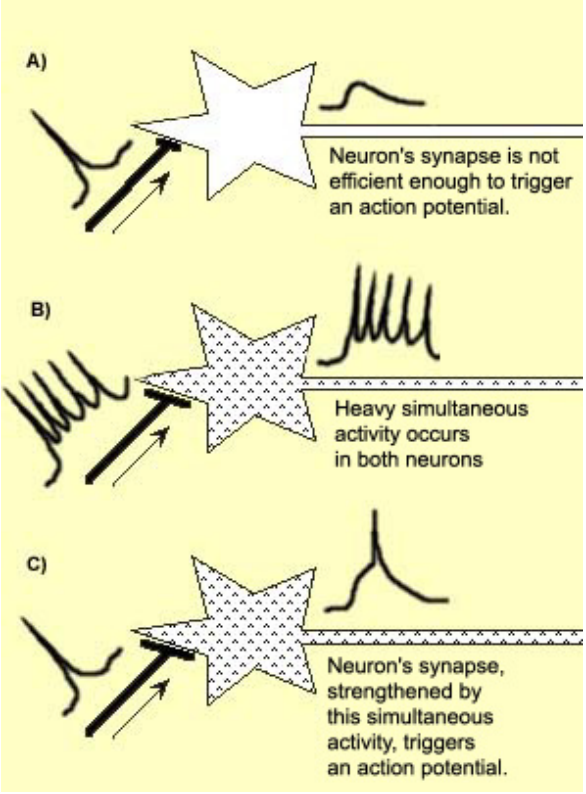
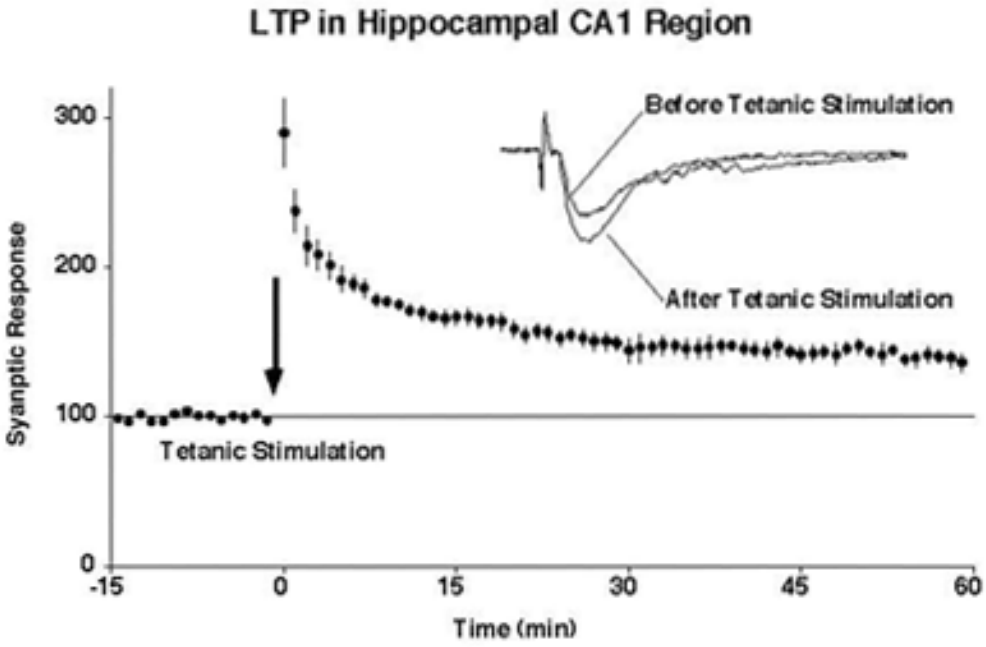


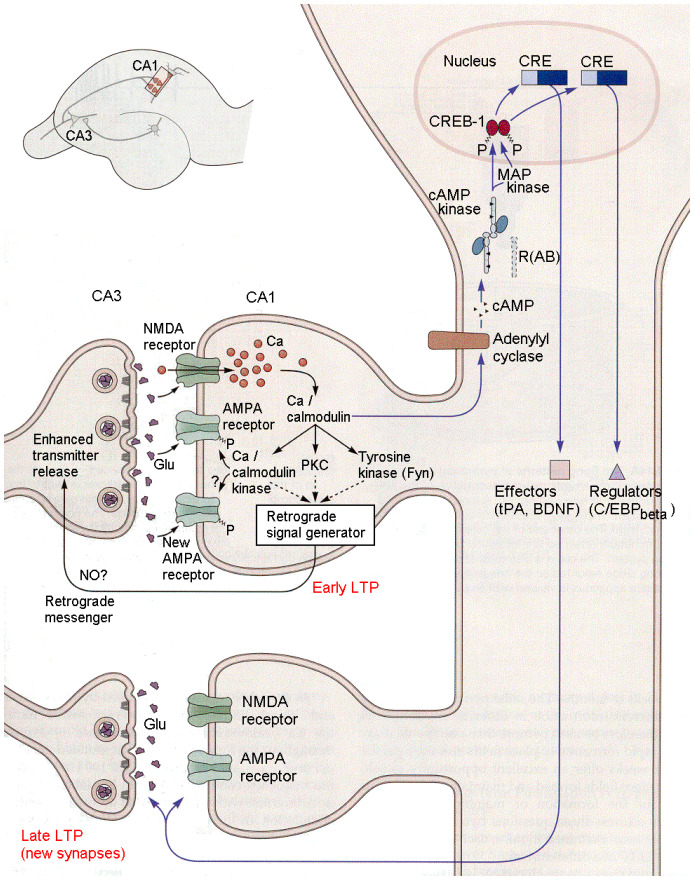
Fig. 6. Mean percentage correct performance for hippocampus, caudate, and extrastriate visual cortex-lesioned as well as control rats as a function of delay for object recognition memory

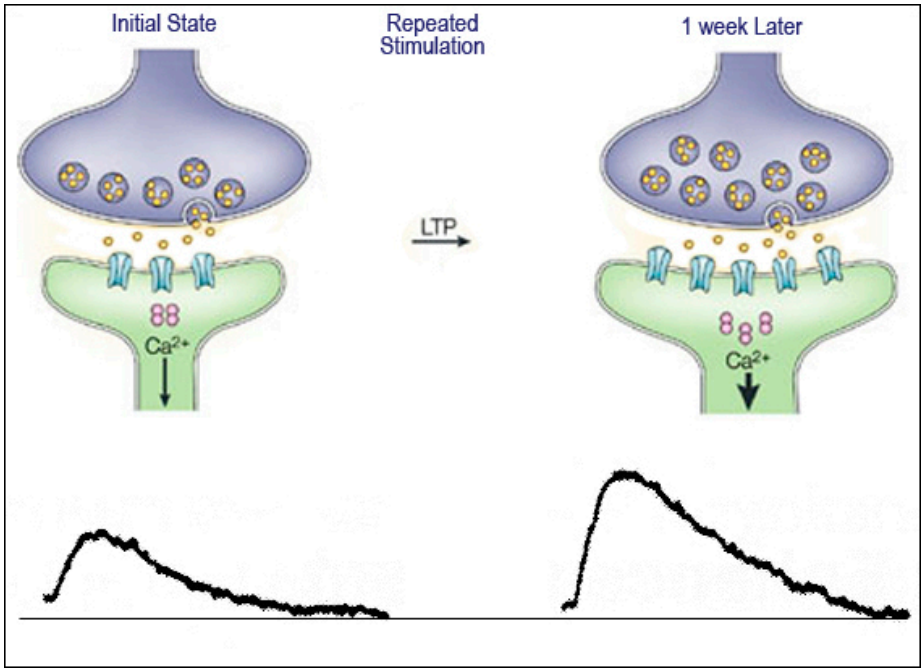
Cellular mechanisms

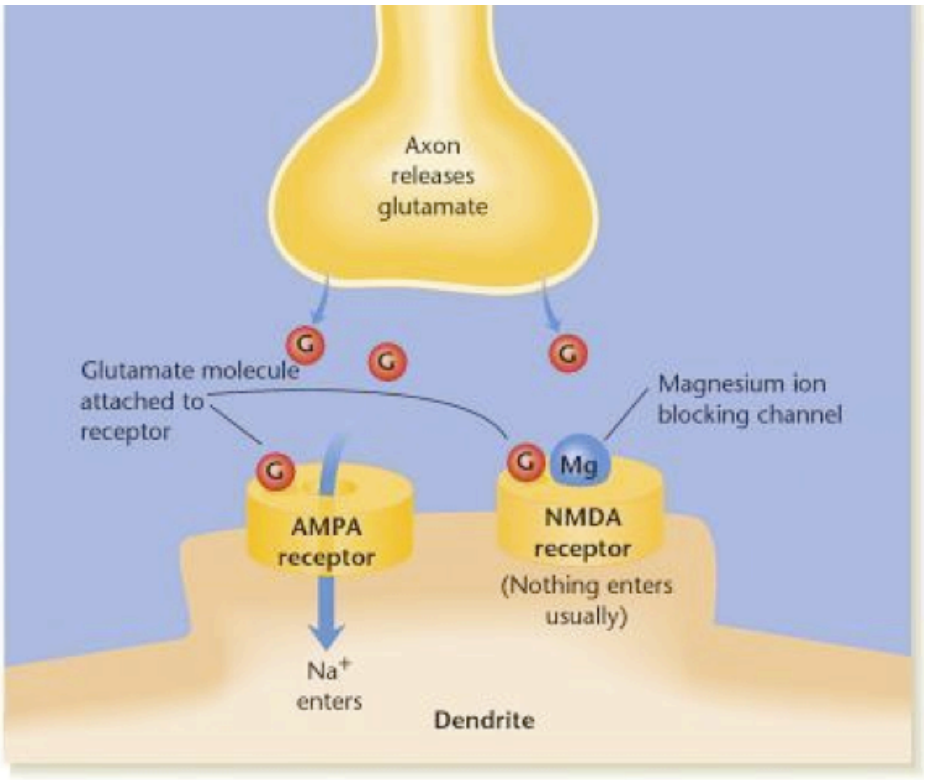
- **Donald Hebb**
- **HEBBIAN SYNAPSE is one that increases effectiveness because of simultaneous activity in presynaptic and postsynaptic neurons**
- **FIRE TOGETHER, WIRE TOGETHER**

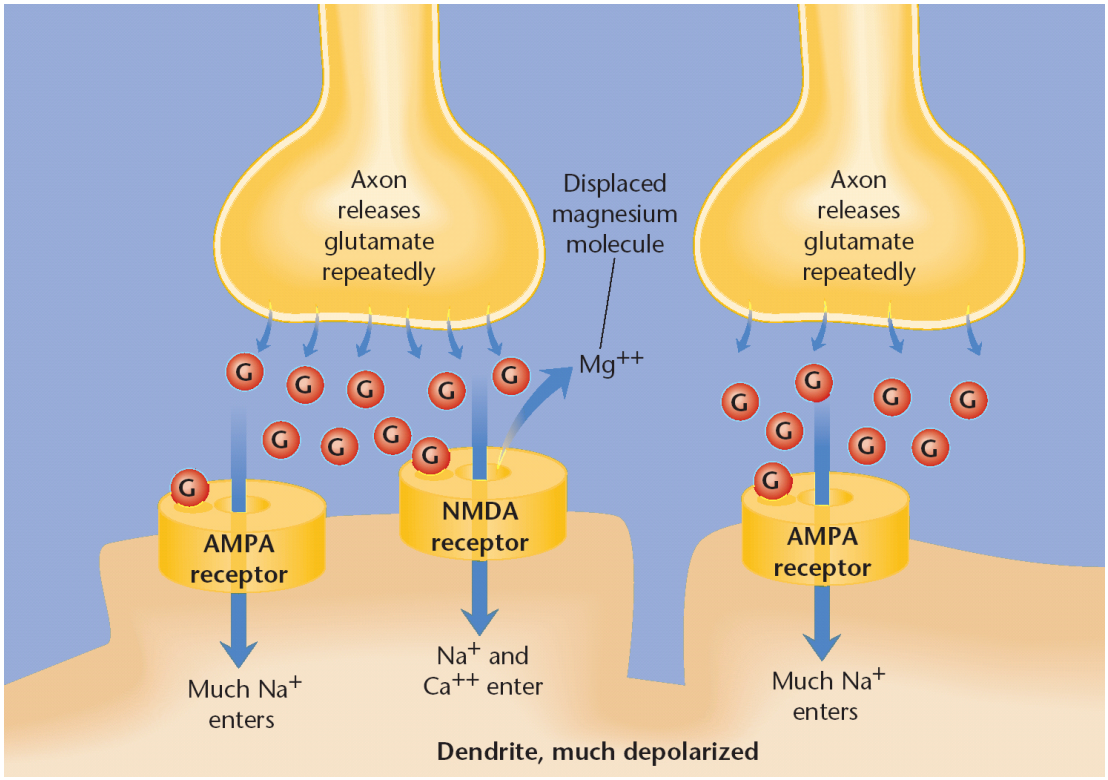



LTP in Hippocampal CA1 Region
Before Tetanic Stimulation
After Tetanic Stimulation
Tetanic Stimulation
Synaptic Response
300
200
100
0
-15
0
15
30
45
60
Time (min)


CA1
CA3
Nucleus
CRE
CRE
CREB-1
P
P
MAP kinase
cAMP kinase
R(AB)
cAMP
Adenylyl cyclase
CA3
CA1
NMDA receptor
Ca
Ca / calmodulin
AMPA receptor
P
Enhanced transmitter release
Glu
Ca / calmodulin kinase
?
PKC
Tyrosine kinase (Fyn)
Retrograde signal generator
P
New AMPA receptor
NO?
Retrograde messenger
Early LTP
Effectors (tPA, BDNF)
Regulators (C/EBP beta)
Glu
NMDA receptor
AMPA receptor
Late LTP (new synapses)


Initial State
Repeated Stimulation
1 week Later
LTP
Ca2+
Ca2+


Axon releases glutamate
Glutamate molecule attached to receptor
Magnesium ion blocking channel
Mg
AMPA receptor
NMDA receptor
(Nothing enters usually)
Na+ enters
Dendrite



LTP

- **NMDA ligand and voltage gated**
- **Ca++ enters**
- **CaMKII**

  Changes in AMPA receptors

  More NMDA

  More dendrite branching

  Change in AMPA sensitivity

3 predictions of LTP and hippocampal learning

Suppress LTP → poor spatial learning
NMDA blockers impair long-term learning

Learning → LTP at hippocampal synapses,
?

Abolish LTP after learning→ poor performance
?

25 AUGUST 2006 VOL 313 **SCIENCE** www.sciencemag.org
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This Week in *Science*

Linking LTP with Learning and Memory

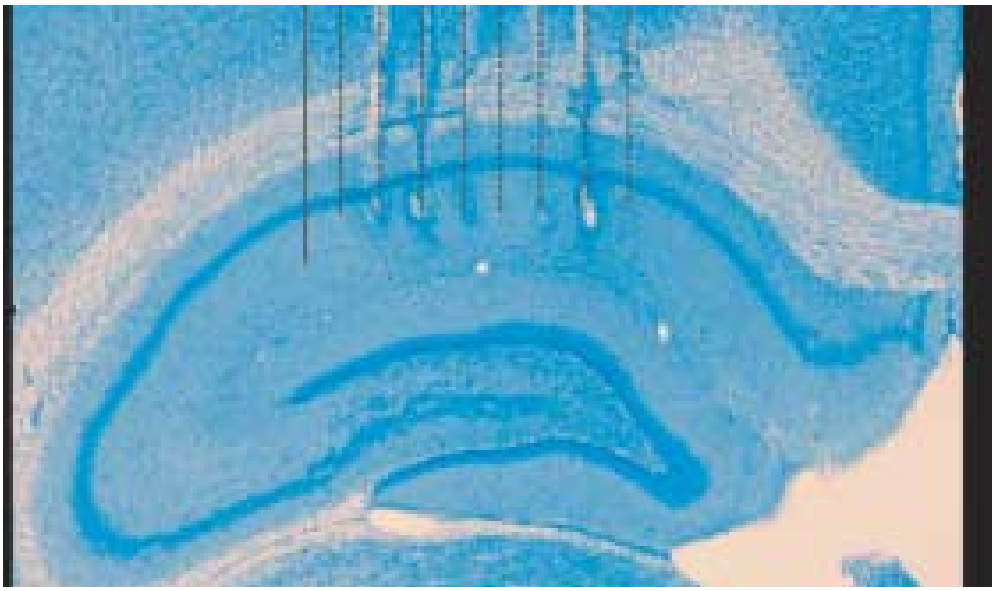
The phenomenon of synaptic long-term potentiation (LTP) was discovered more than 30 years ago in the hippocampus. Although it is commonly thought that hippocampal LTP is induced by learning, there has not been a direct demonstration (see the Perspective by **Bliss *et al.***). **Whitlock *et al.*** (p. 1093) recorded field potentials from multiple sites in hippocampal area CA1 before and after single-trial inhibitory avoidance learning. Field potentials increased on a subset of the electrodes, and these could be specifically related to the learning event. **Pastalkova *et al.*** (p. 1141) reversed hippocampal LTP in freely moving animals using a cell-permeable inhibitor of a protein kinase. Reversal was accompanied by a complete disruption of previously acquired long-term memory in a place avoidance task, even when the kinase inhibitor was infused only during the consolidation interval. This result suggests that LTP was necessary for storing spatial information.

Does learning lead to measureable LTP?

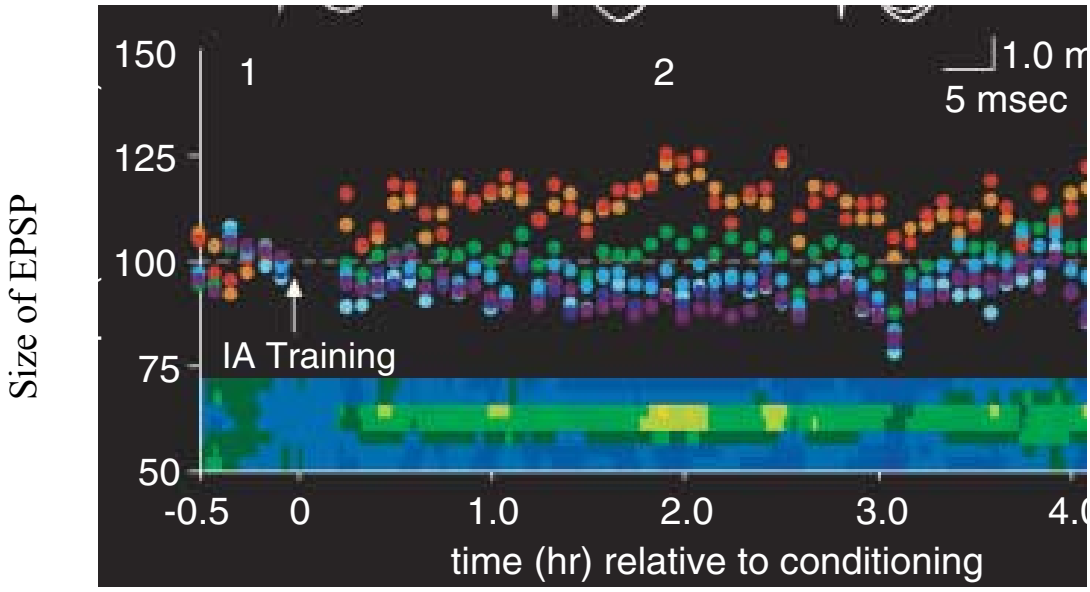
- **Test rats before and after learning something simple**
  Avoid half of a cage where you got shocked once

- **Controls**
  No exposure at all
  Walk around the cage
  Shocked once somewhere else

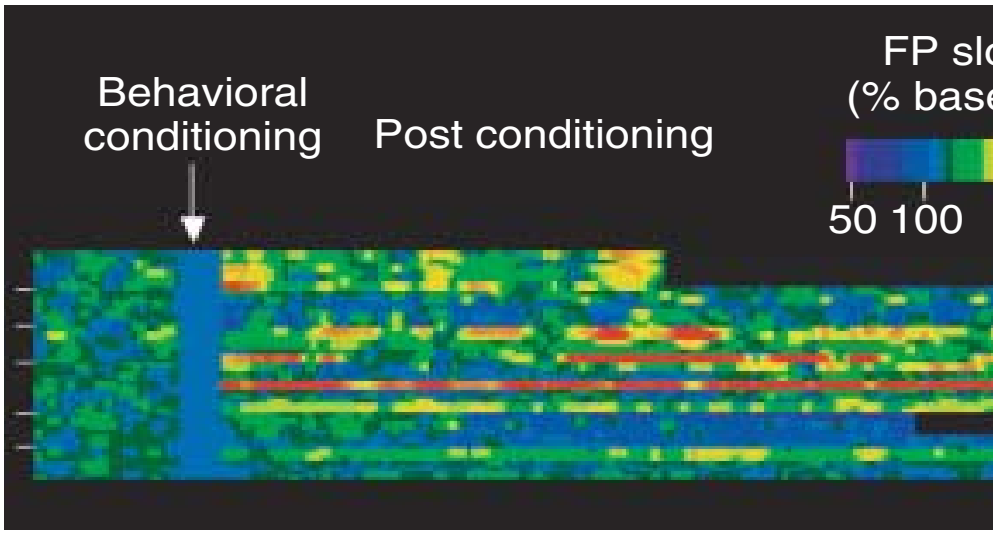
Electrodes to measure activity in hippocampus



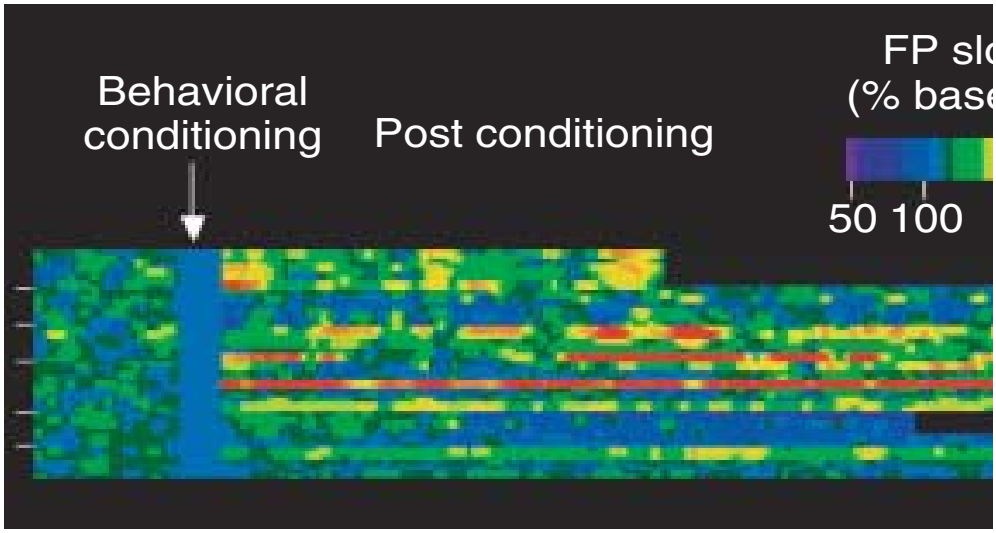
Before learning, 8 electrodes at 100%; few go up after training



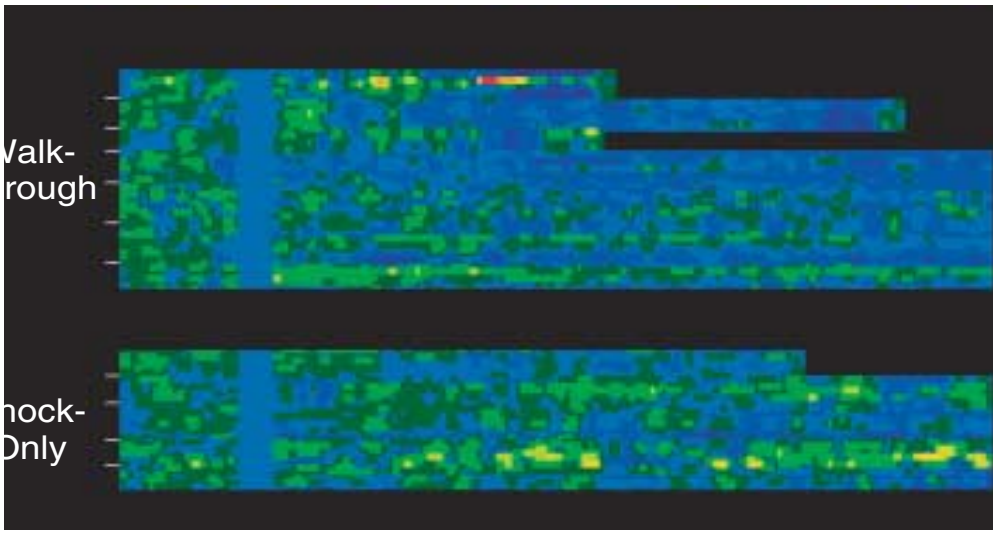
6 trained animals; ~8 electrodes each



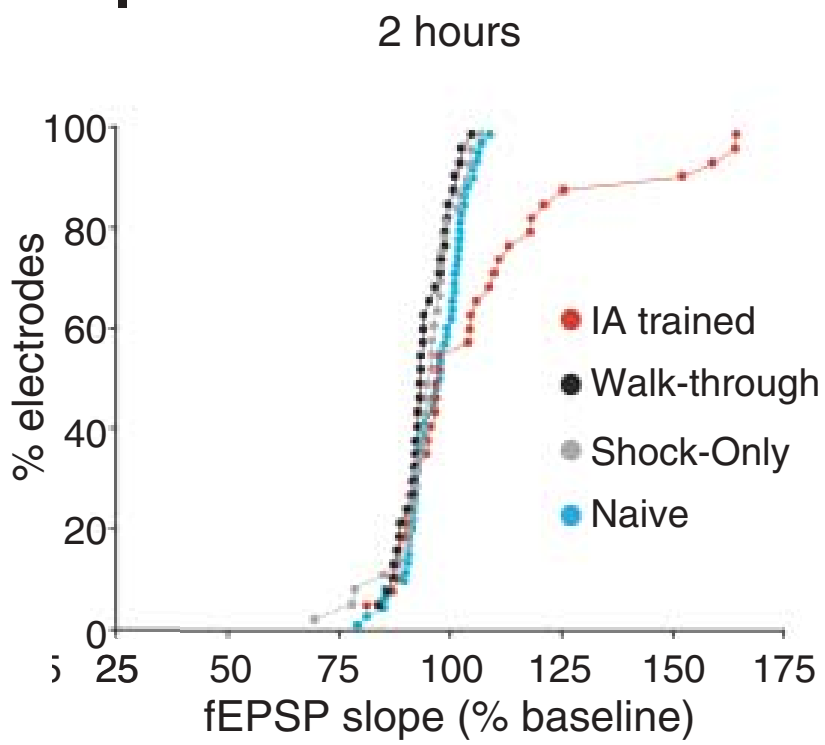
6 trained animals; ~8 electrodes each



No changes in controls



I


2 hours
100
80
60
40
20
0
% electrodes
25
50
75
100
125
150
175
fEPSP slope (% baseline)
IA trained
Walk-through
Shock-Only
Naive