Learning/Memory CHAPTER 13
Animal Studies

Study Questions

1. What is LTP and what role does it play in learning and memory?

2. From this and the prior lecture, discuss the idea that different brain structures underlie different kinds of memory.

Extra Office Hours: Thursday 10:30 - noon

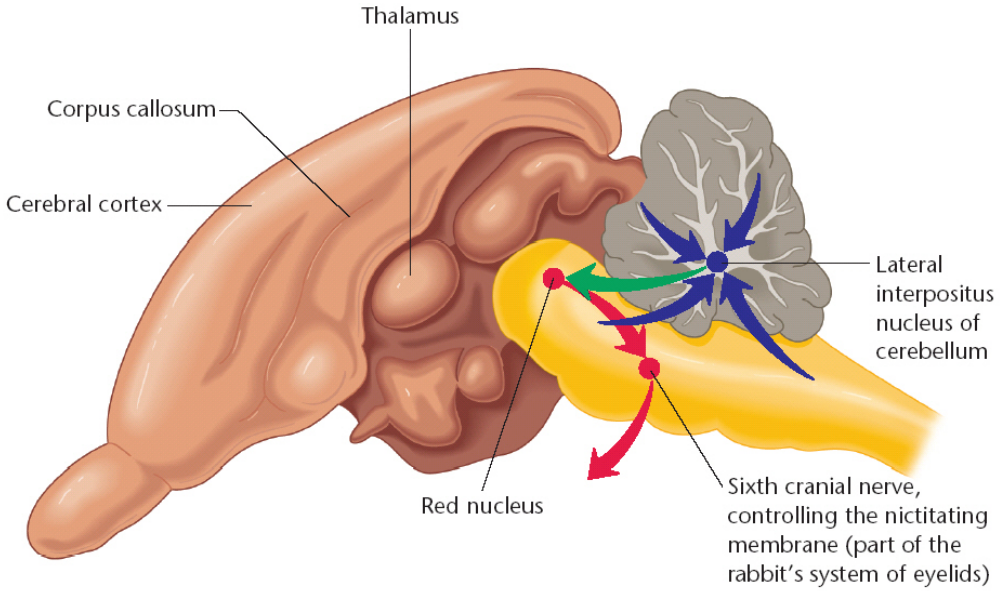
- **Many types of memory**
- **Human memory deficits**
- **Where/how are memories**
  - Encoded
  - Stored
  - Retrieved?

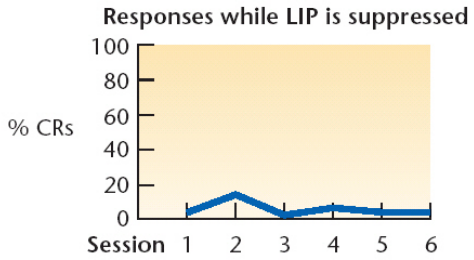
Eye-blink conditioning

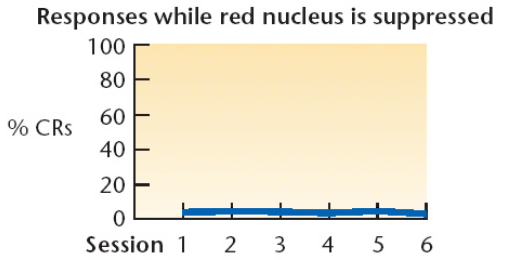
Where is this learning occurring?

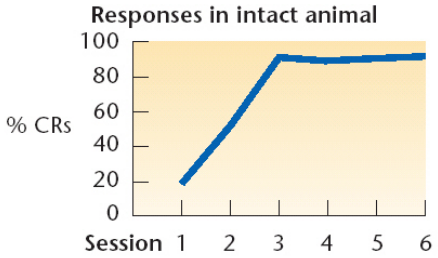
- **Value of simple animal models**

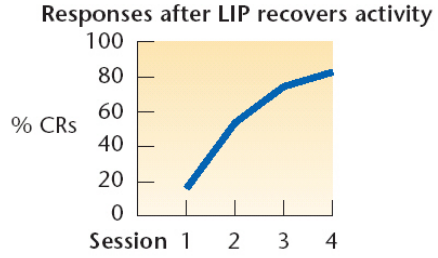
Eyeblink Conditioning

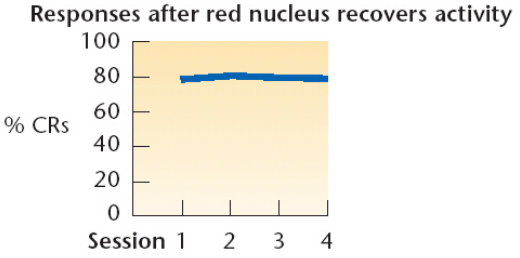




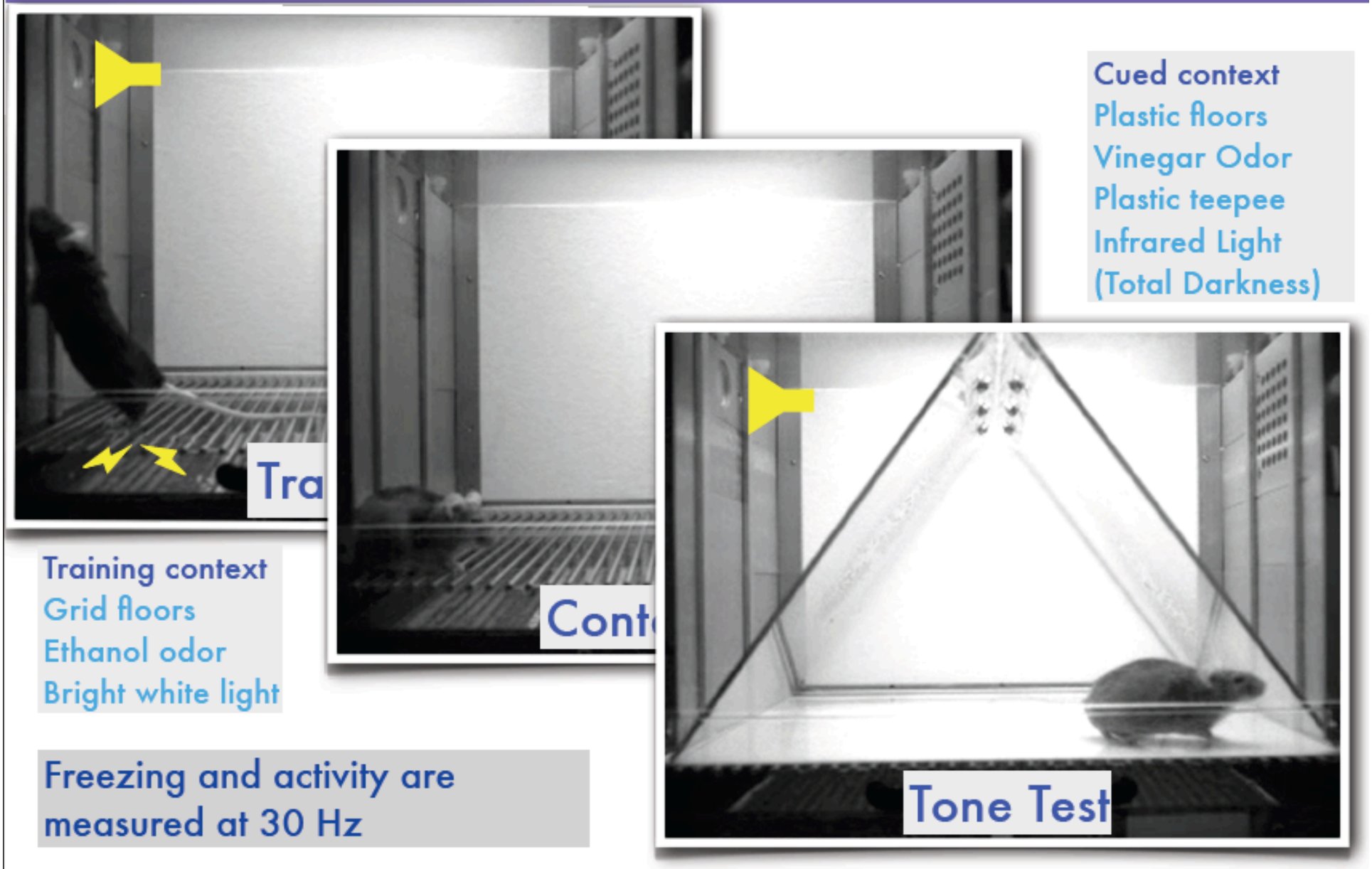








Pavlovian fear conditioning

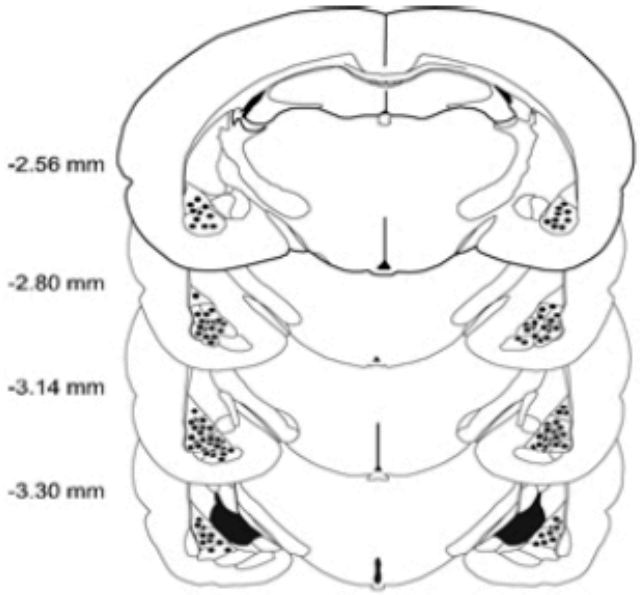


Cued context
Plastic floors
Vinegar Odor
Plastic teepee
Infrared Light
(Total Darkness)

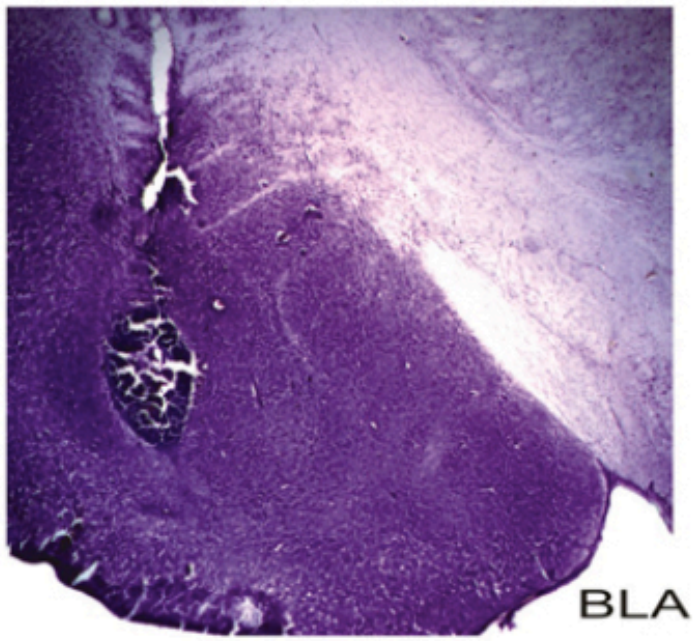
Training context
Grid floors
Ethanol odor
Bright white light

Freezing and activity are measured at 30 Hz

Amygdala Lesion



Basolateral Amygdala (BLA)



Train

Day 1

Lesion

Day 2 or day 60

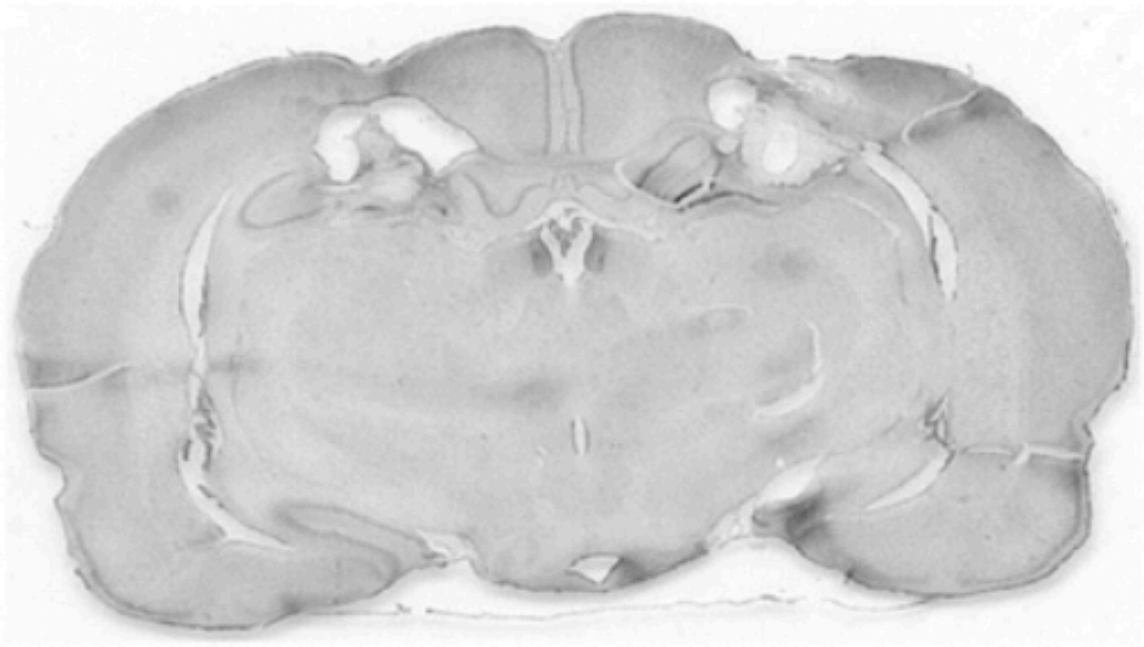
Context Test

Day 70

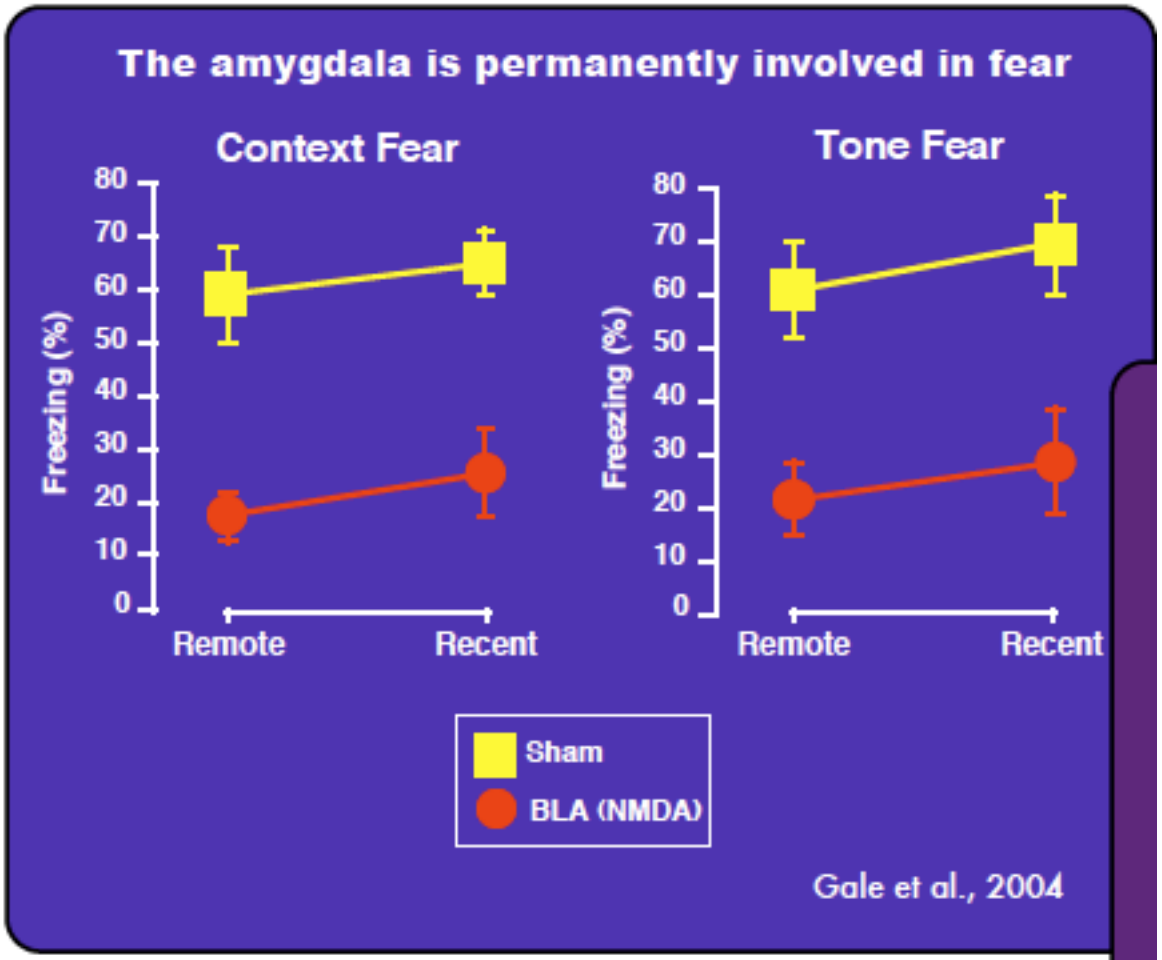
Tone Test

Day 71

Dorsal Hippocampus Lesion



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



High levels of freezing indicate that the animal is fearful – i.e., has a memory of the association with shock

Other controls not shown

Remember for 71 days!

Amygdala lesions reduce learning

Very similar experiment with DH

- **electrolytic lesions of the dorsal hippocampus (DH) produce a severe deficit in contextual fear if made 1 d, but not 28 d, after fear conditioning.**

OLDER MEMORIES SPARED – Like HM???

- **As such, the hippocampus seems to play a time-limited role in the consolidation of contextual fear conditioning.**

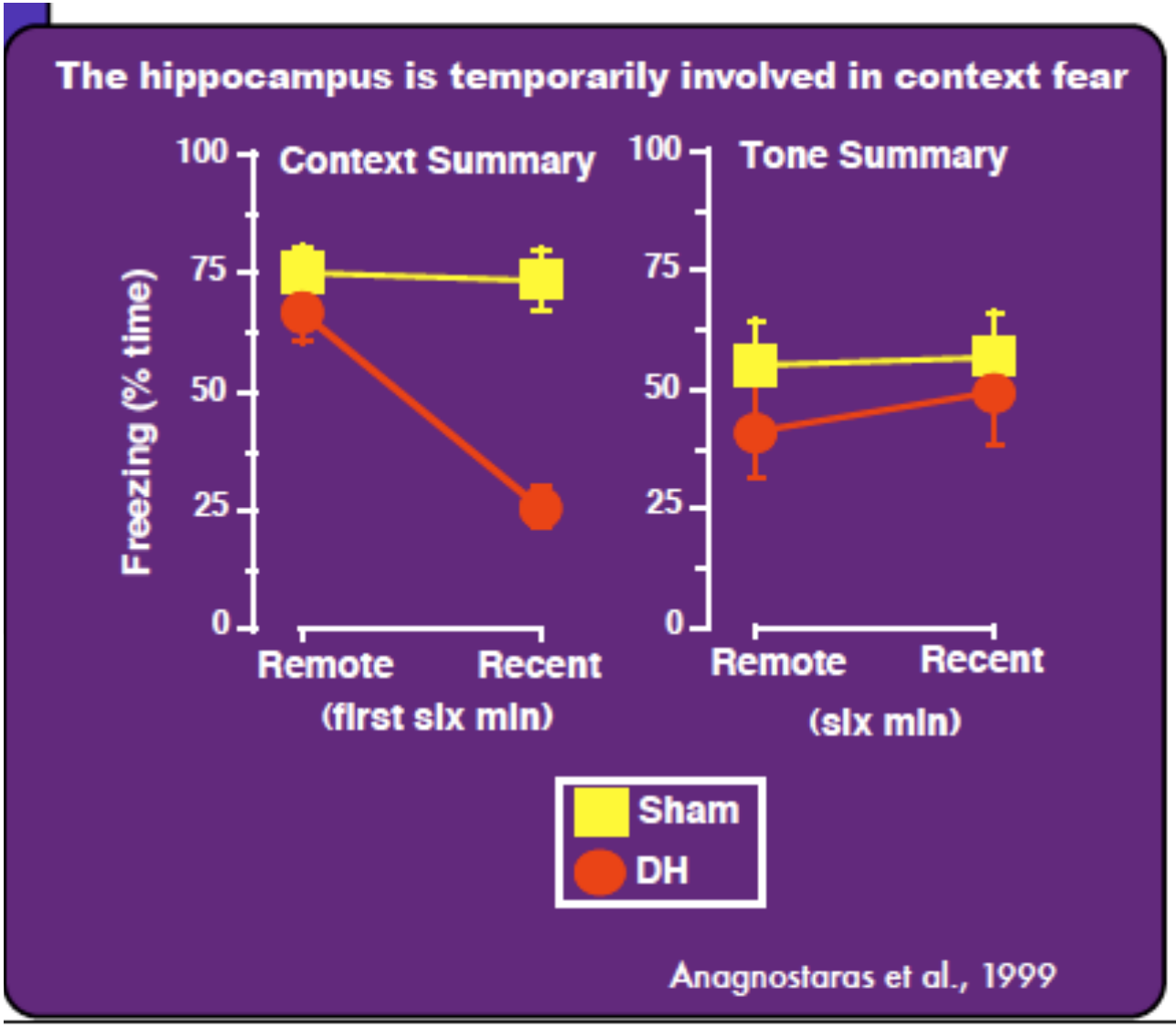
But 2 separate groups of animals

- **retrograde amnesia of rat contextual fear produced by DH lesions in a *within-subjects* design.**

- **(*remote* memory)10 tone-shock pairings in one context**

- **(*recent* memory - 50 d later) 10 tone-shock pairings in a distinct context (with a different tone),**

- **DH or sham lesions 1 d after recent. Relative to controls, DH-lesioned rats exhibited no deficit in remote contextual fear, but recent contextual fear memory was severely impaired. They also did not exhibit deficits in tone freezing. This highly specific deficit in recent contextual memory demonstrated in a within-subjects design favors mnemonic over performance accounts of hippocampal involvement in fear.**



Similar expt with hippocampus

Don't need hippocampus to remember association with tone

Sometimes need hippocampus to remember context

Exp Brain Res (1993) 93:462–470

Experimental
Brain Research

© Springer-Verlag 1993

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

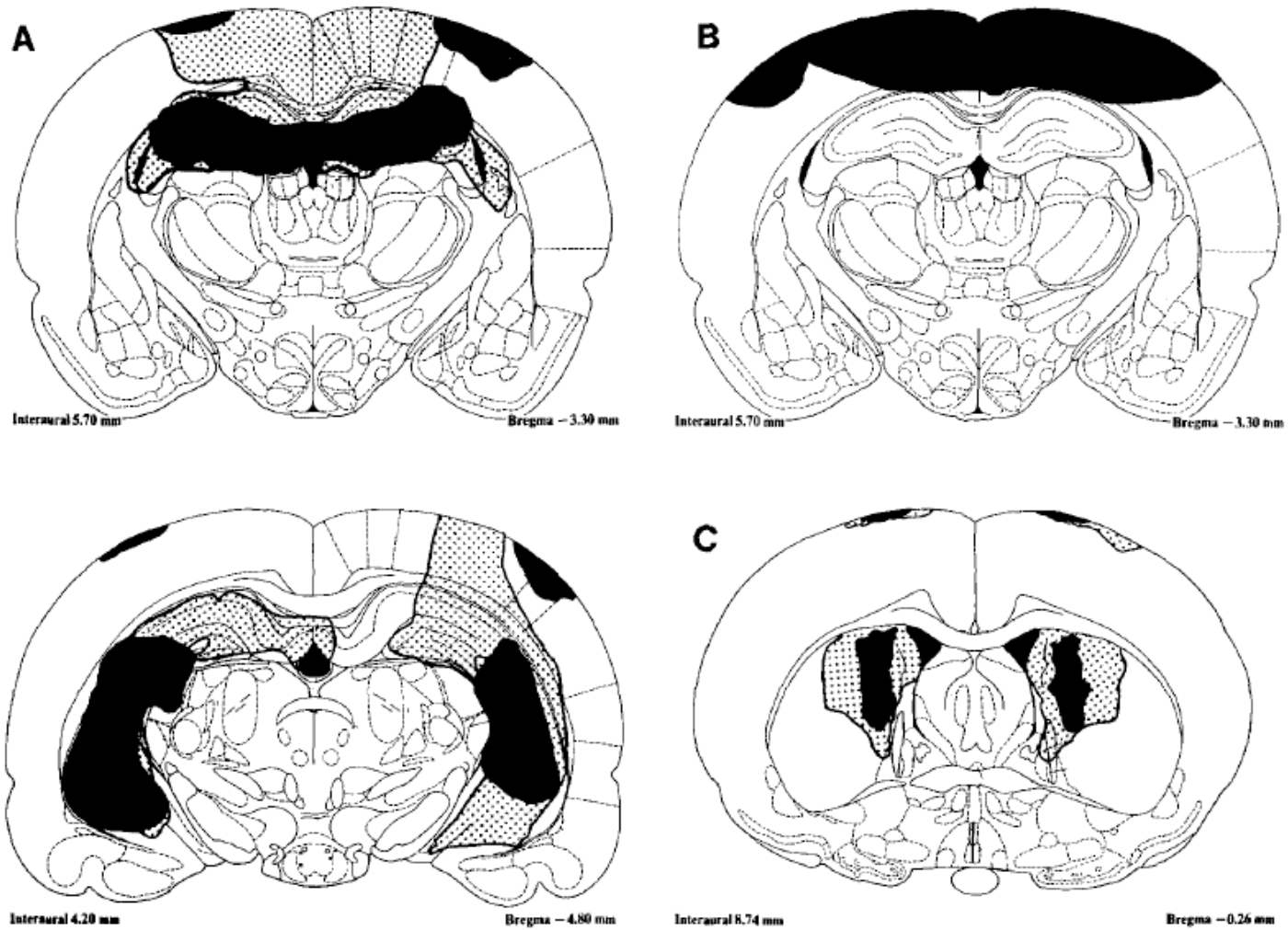
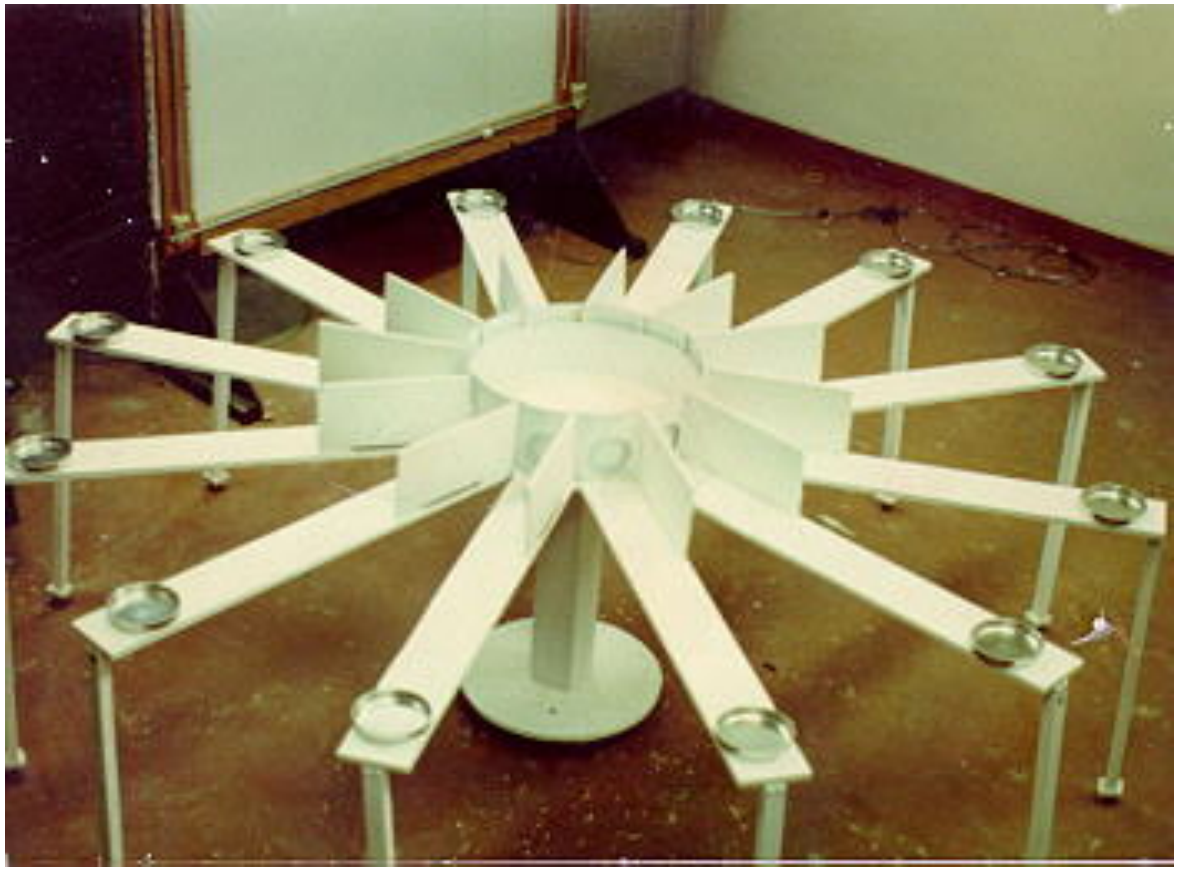


Fig. 2. **A** The smallest (*black*) and largest (*stippled*) dorsal and ventral hippocampal lesion (two sections) **B** A representative cortical control lesion; and **C** the smallest (*black*) and largest (*stippled*) caudate lesion

Bait arm; return to center; win-stay task; repeat over and over



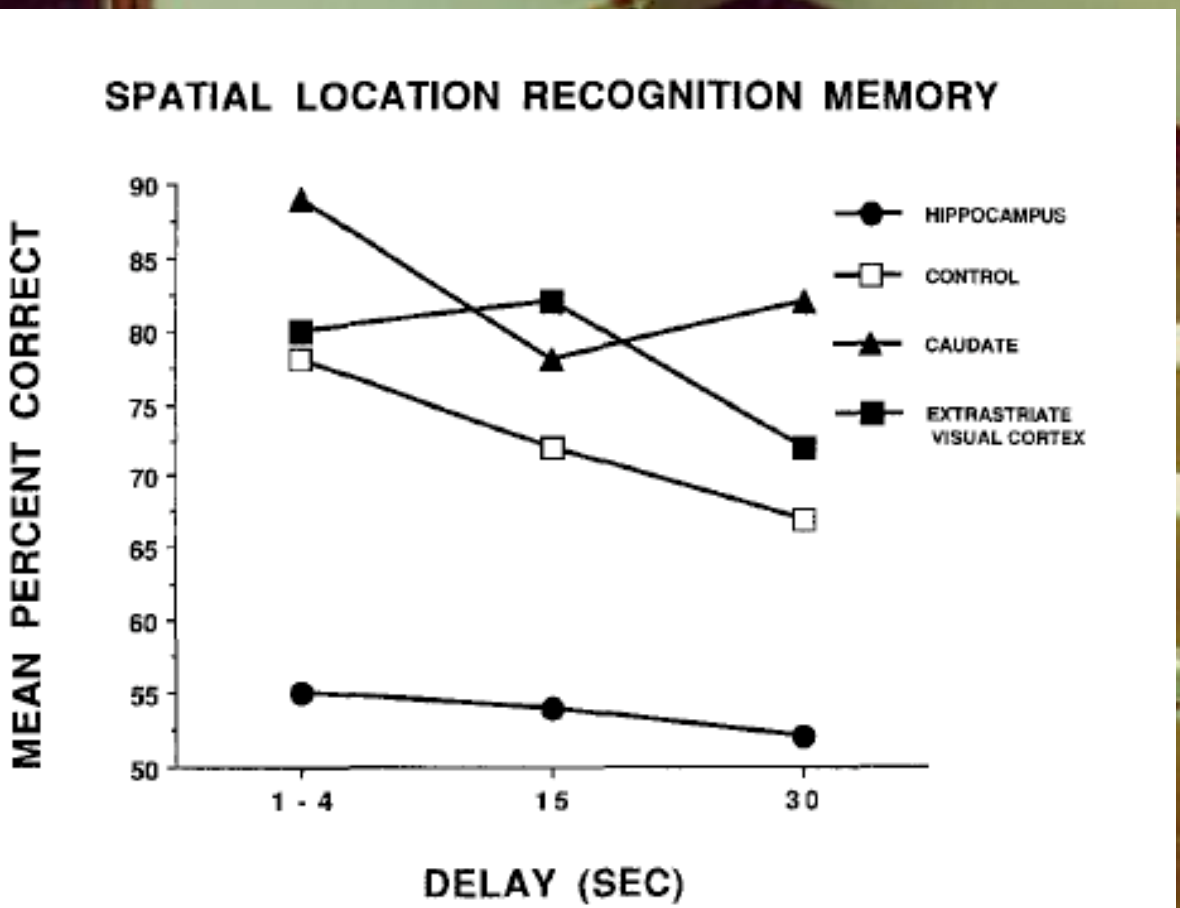
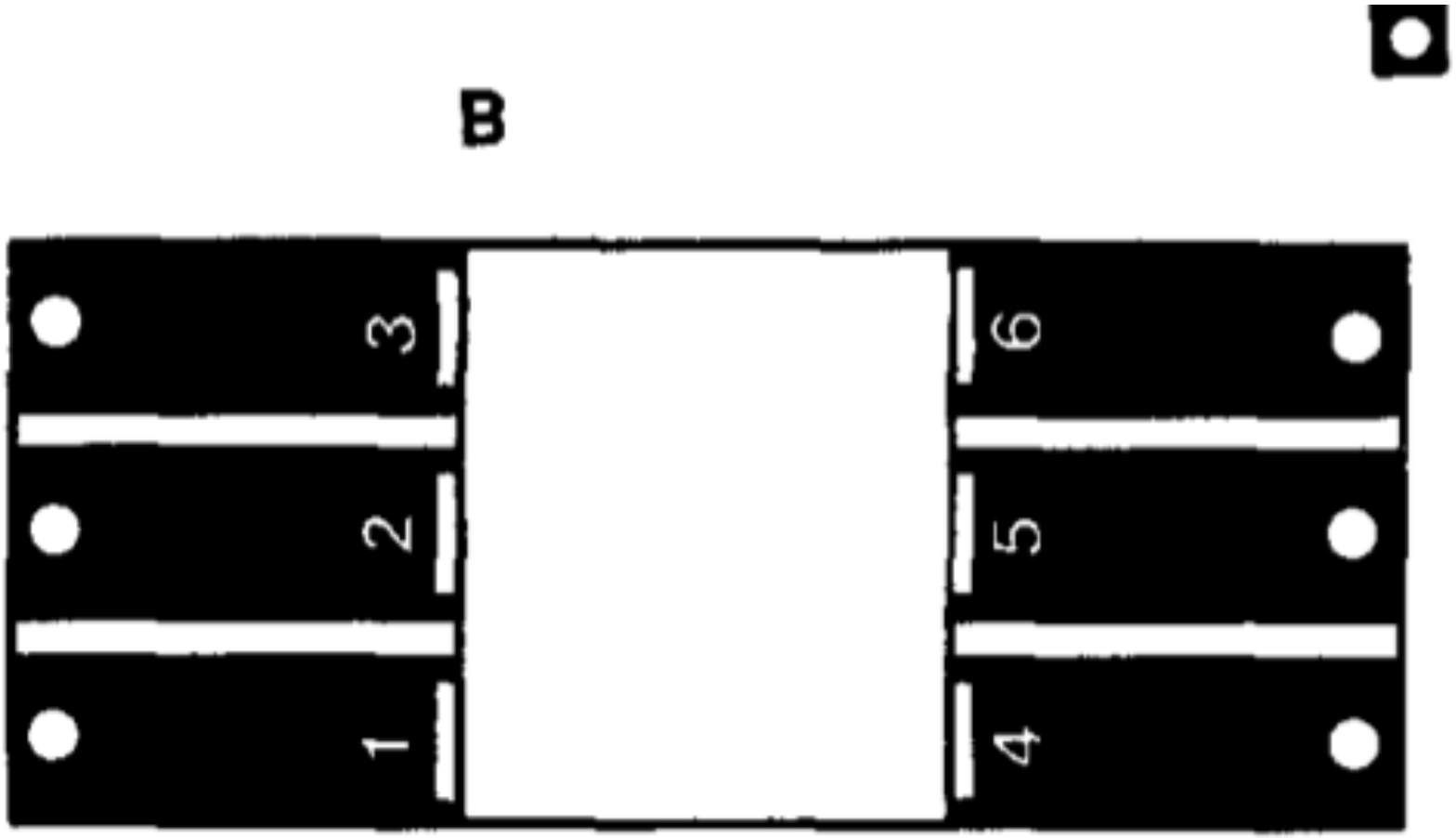
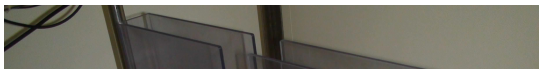


Fig. 4. Mean percentage correct performance for hippocampus, caudate, and extrastriate visual cortex-lesioned as well as control rats as a function of delay for spatial location recognition memory

Rat turns left or right on one side; then must do the same thing on the other side





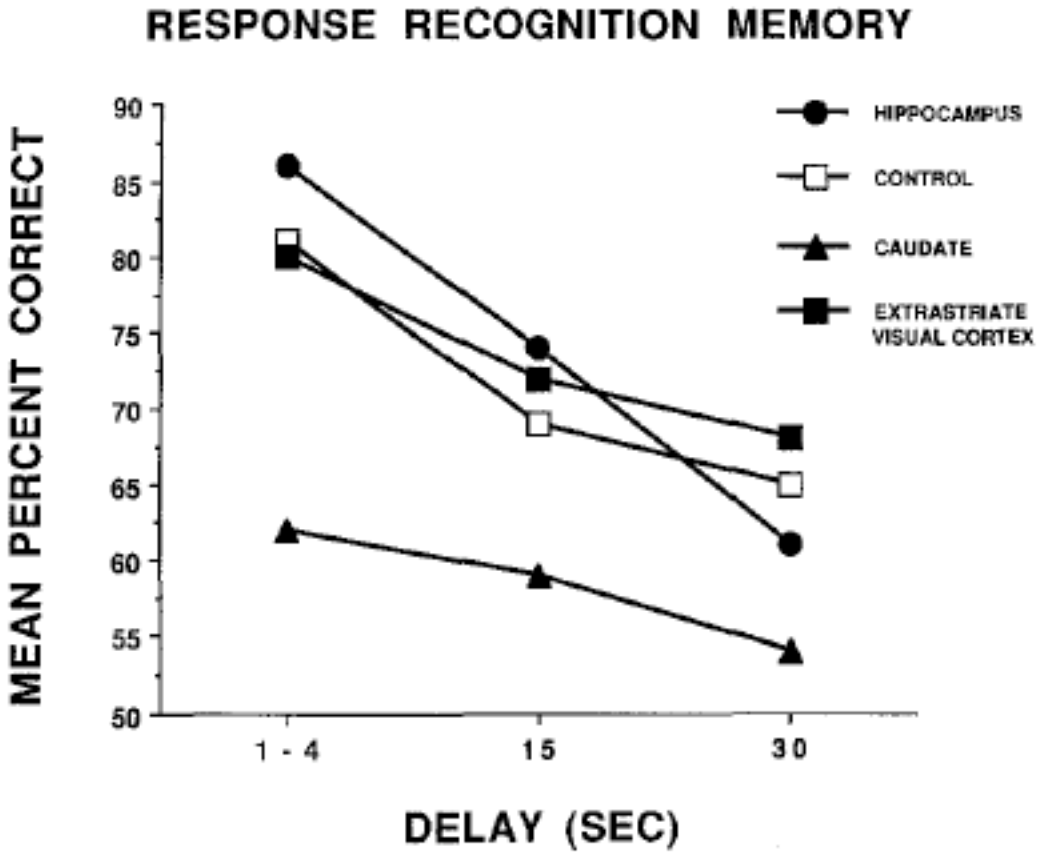


Fig. 5. Mean percentage correct performance for hippocampus, caudate, and extrastriate visual cortex-lesioned as well as control rats as a function of delay for response recognition memory

On left rat gets food under object; then on right must go to the novel object to get food

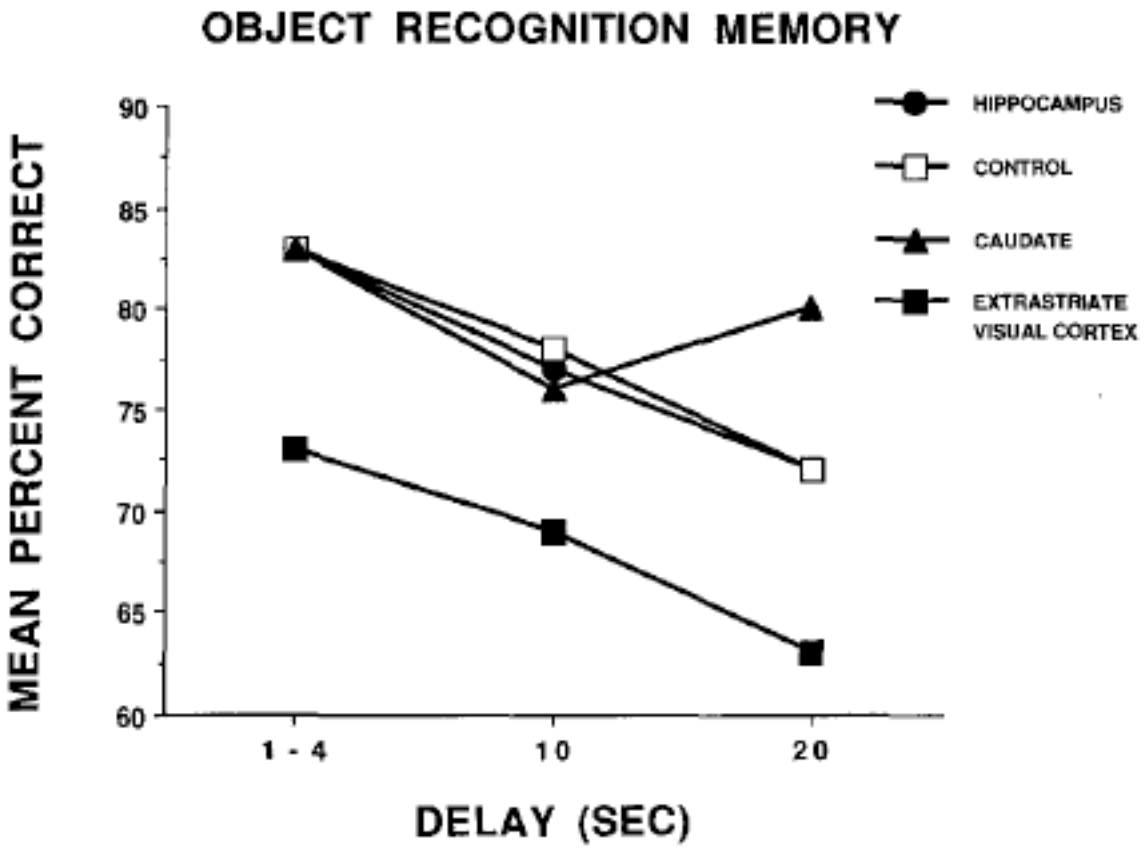
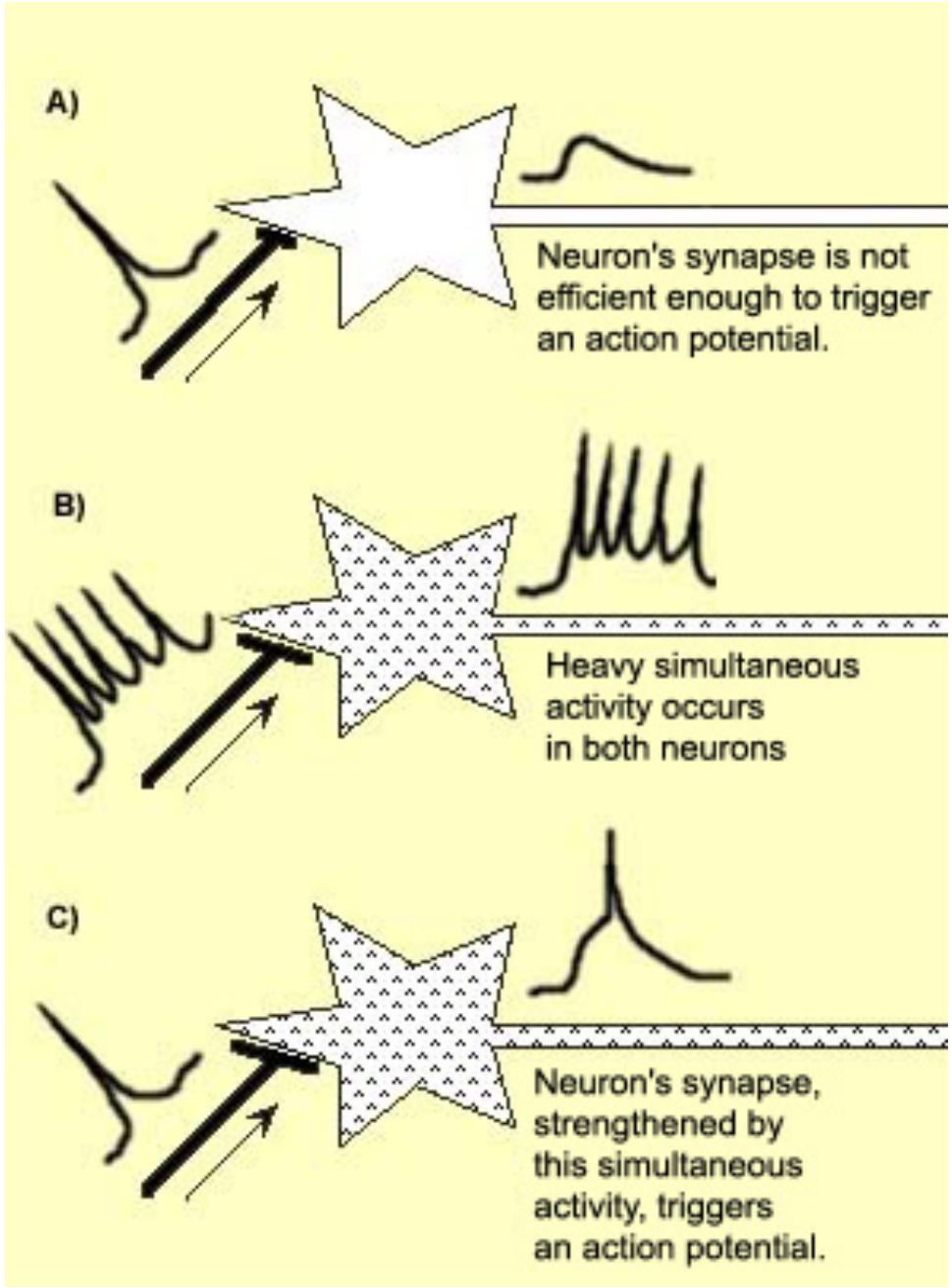


Fig. 6. Mean percentage correct performance for hippocampus, caudate, and extrastriate visual cortex-lesioned as well as control rats as a function of delay for object recognition memory

Cellular mechanisms

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



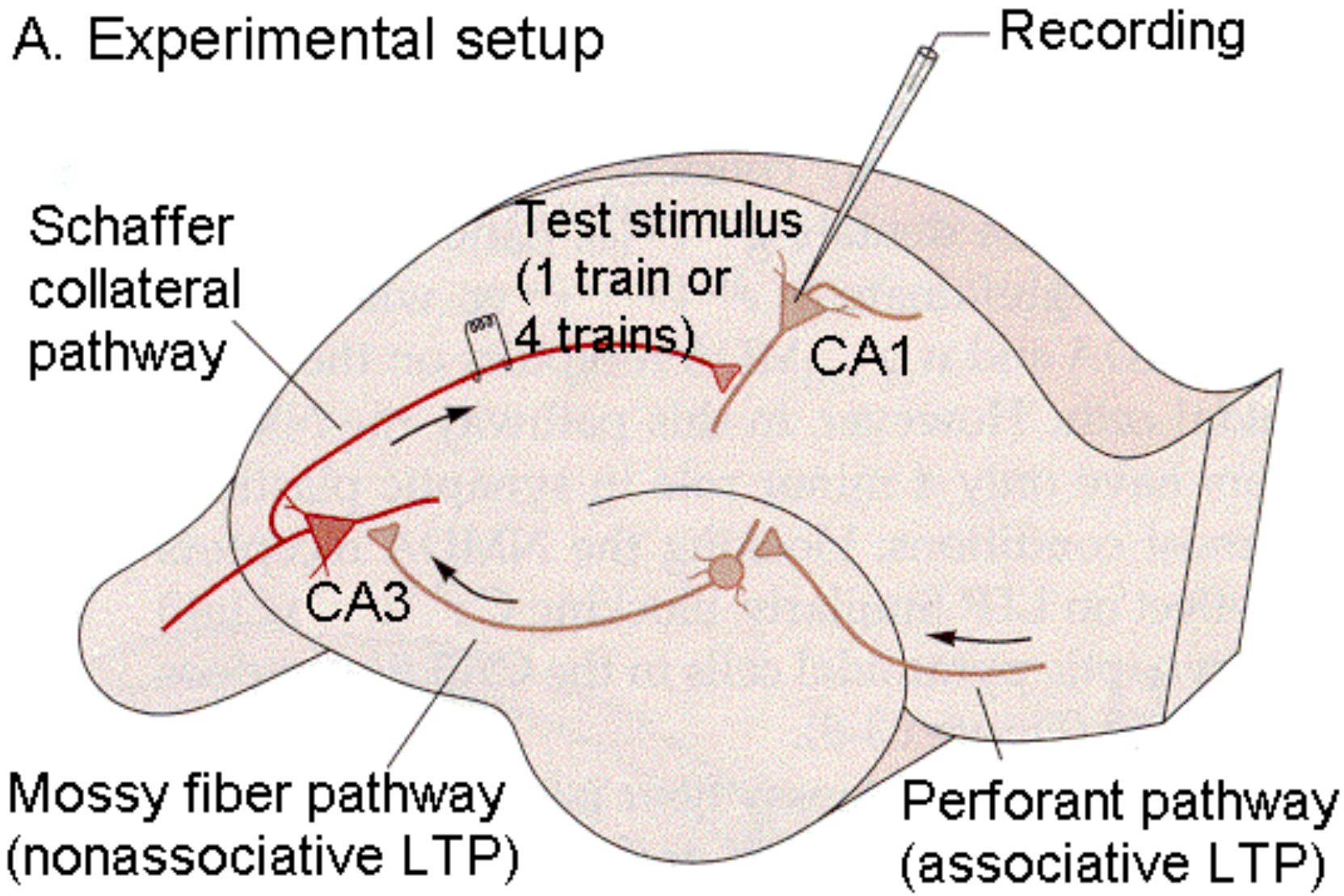
(LTP)
Hippocampus Slices (in vitro)

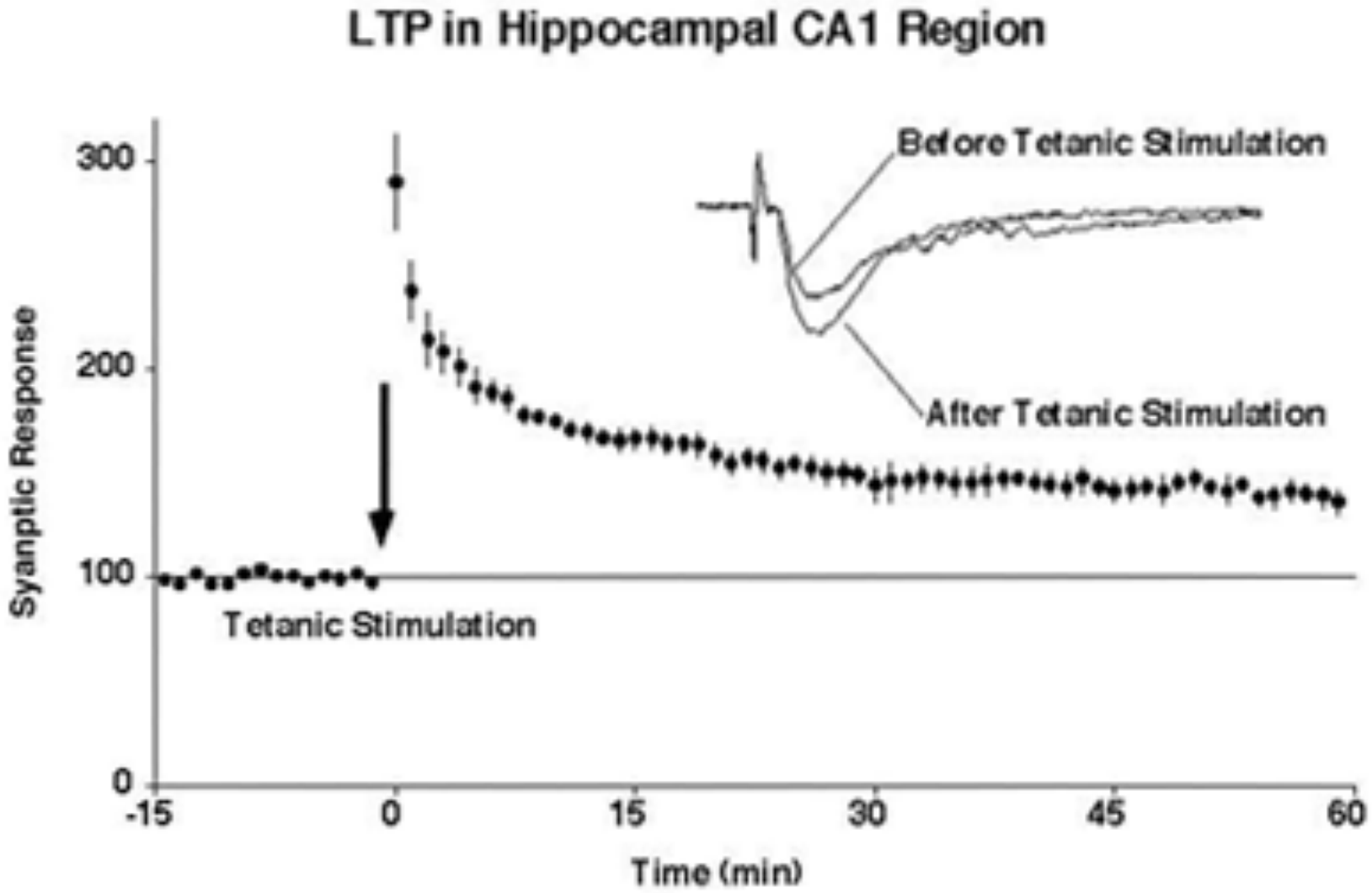
1) Measure "baseline" postsynaptic response to single "pulse" onto afferent (i.e., presynaptic) fibers

2) Tetanus: Administer 10 seconds of intense, high frequency stimulation of presynaptic fibers

3) The response to a single pulse is now much larger than before.

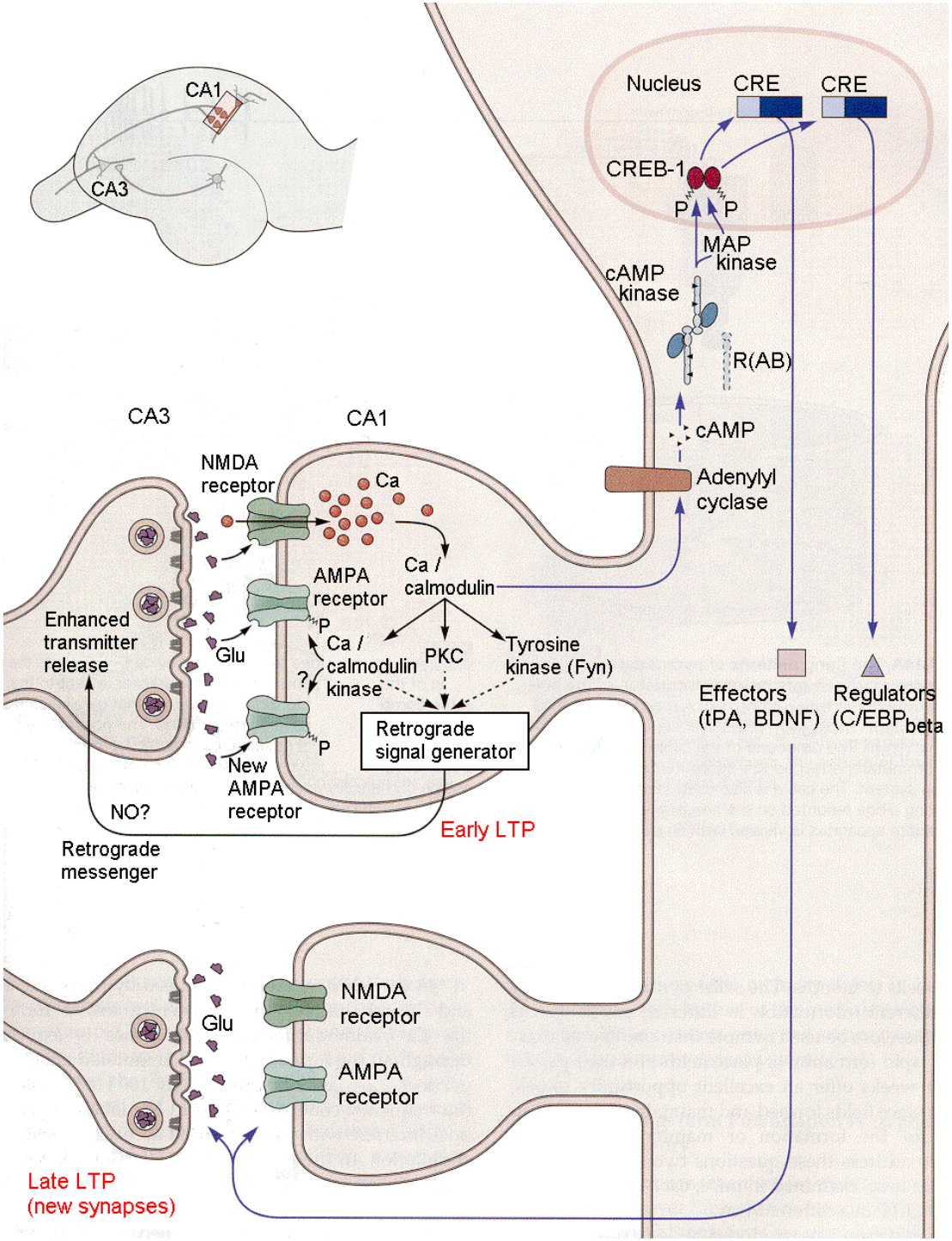
Lasts for 1 hour -> 4 days

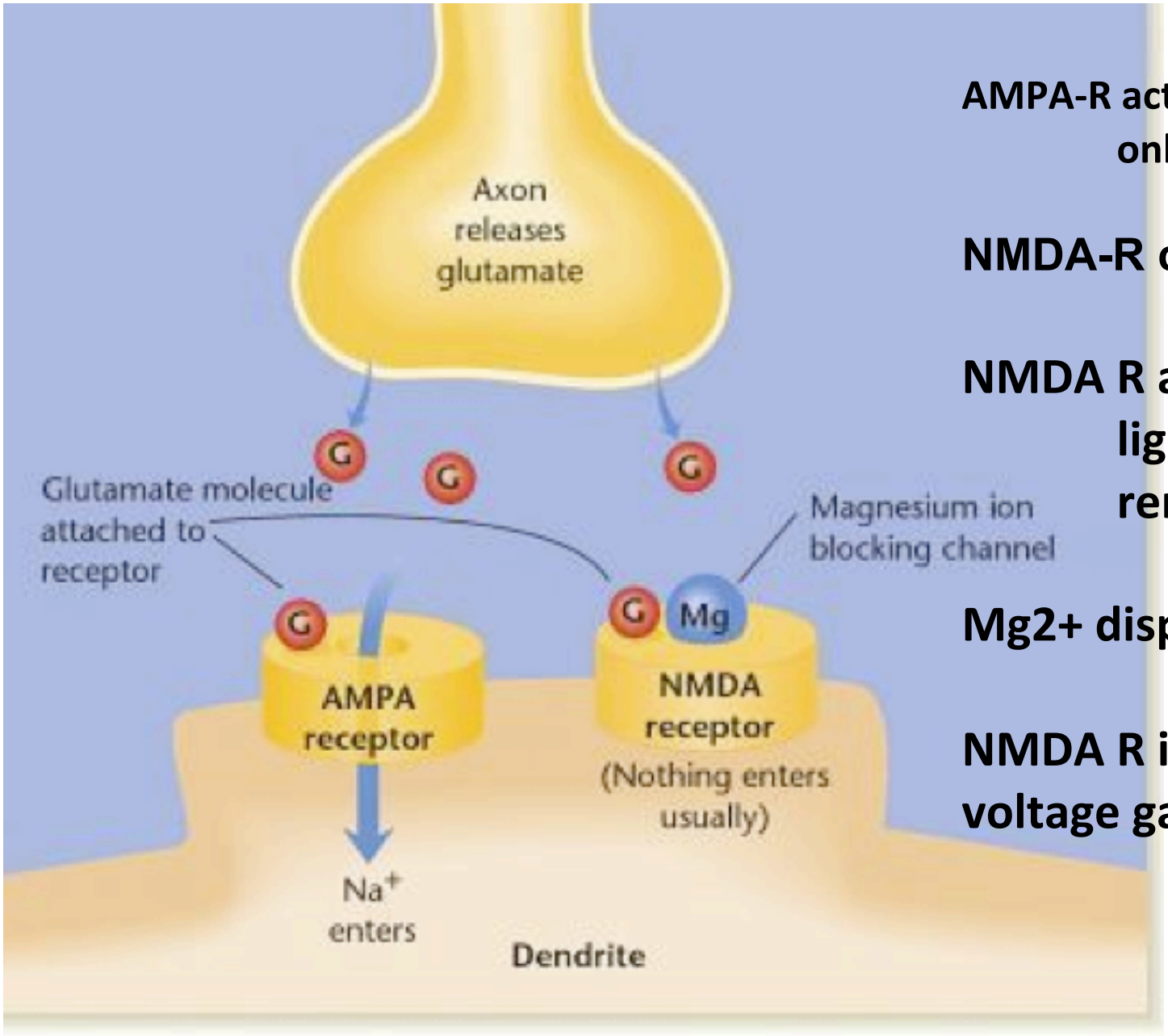

A. Experimental setup
Recording
Schaffer
collateral
pathway
Test stimulus
(1 train or
4 trains)
CA1
CA3
Mossy fiber pathway
(nonassociative LTP)
Perforant pathway
(associative LTP)



Here the synaptic response is measured differently

100 = 100%; measuring EPSP size


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)



AMPA-R activation
only ligand – glu

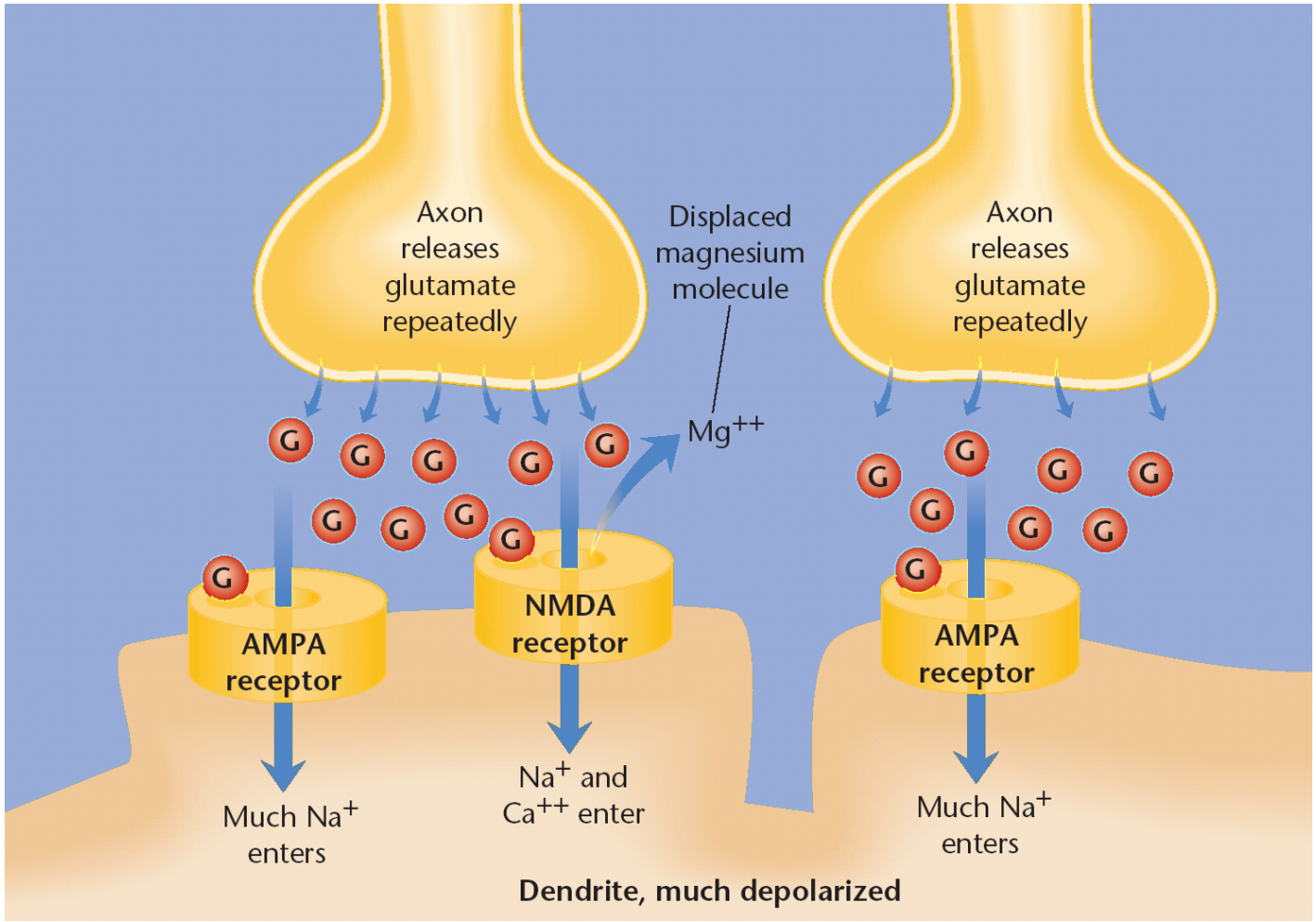
NMDA-R critical for LTP

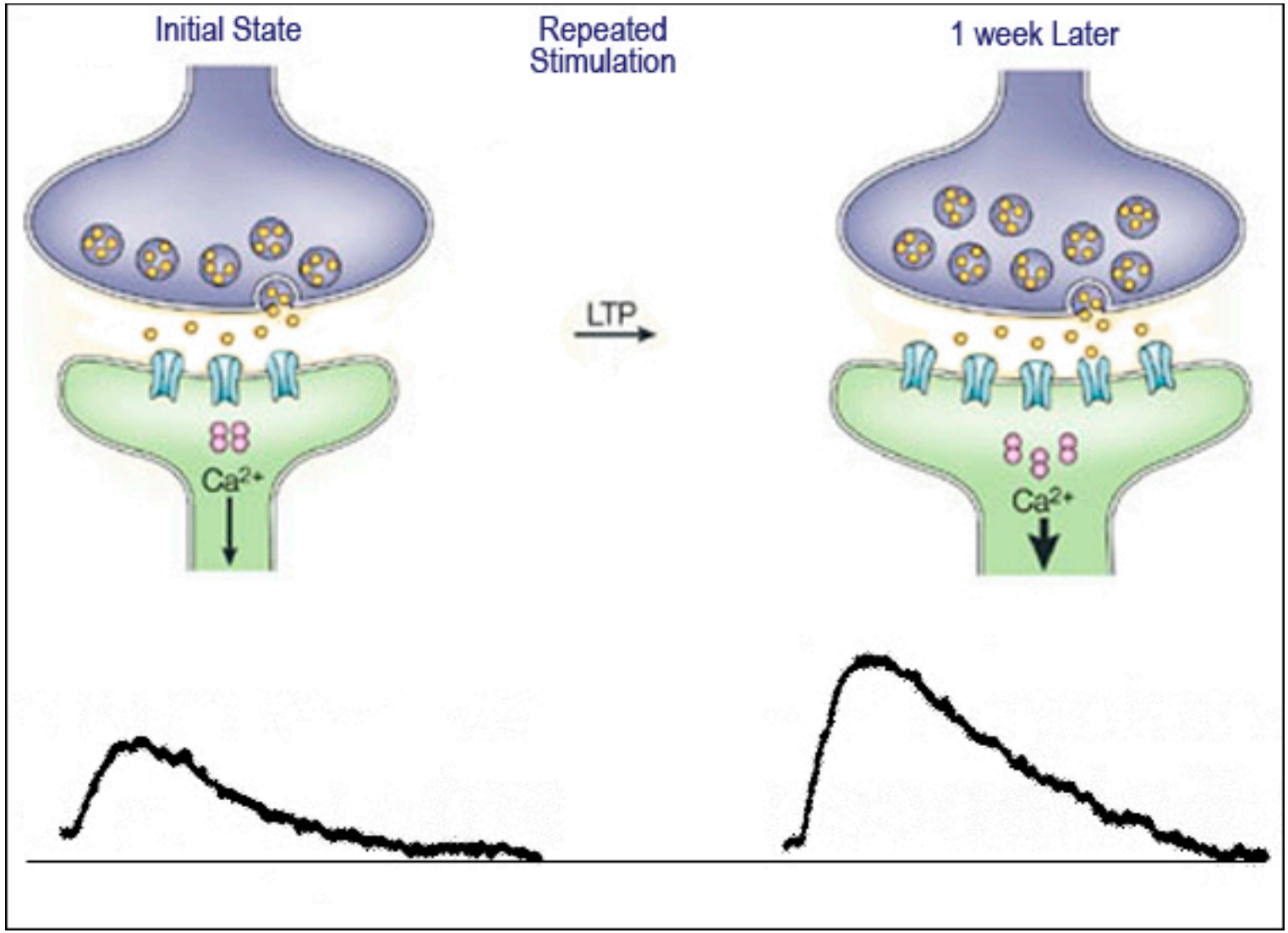
NMDA R activation needs
ligand – glu
removal of Mg2+

Mg2+ displaced by EPSP

NMDA R is ligand AND voltage gated

Synapse that will potentiate




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

LTP

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

  Changes in AMPA receptors

  More NMDA

  More dendrite branching

  Change in AMPA sensitivity

Predictions of LTP and hippocampal learning

Does LTP underlying learning?
Known: NMDA receptors are required for the induction of LTP in vitro
Prediction: Drugs that block NMDA receptors should block learning

Exp: Rats in the "shock" chamber ->

NMDA-blockers OR saline given during "training"

Result: NMDA-blocked rats show STM but not LTM

**Drugs that block NMDA receptors block some, but not all, types of learning.

Predictions of LTP and hippocampal learning

Learning → LTP at hippocampal synapses,
Whitlock study (presented here)

Abolish LTP after learning→ poor performance
Pastalkova et al. in next slide (not covered)

25 AUGUST 2006 VOL 313 **SCIENCE** www.sciencemag.org
Published by AAAS

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? Whitlock et al.

- **Test rats before and after learning something simple**

  Avoid half of a cage where you got shocked once

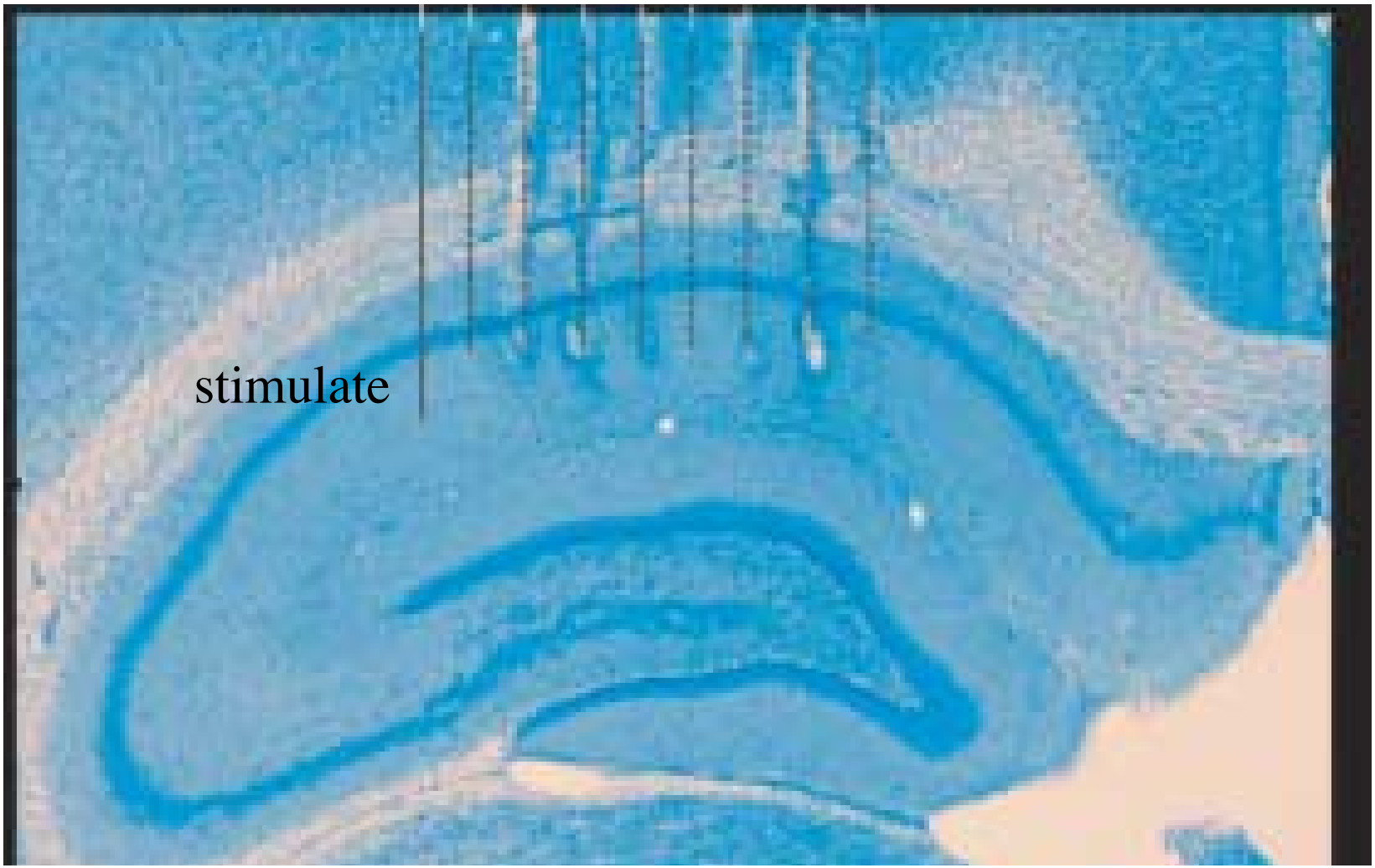
- **Controls**

  No exposure at all

  Walk around the cage

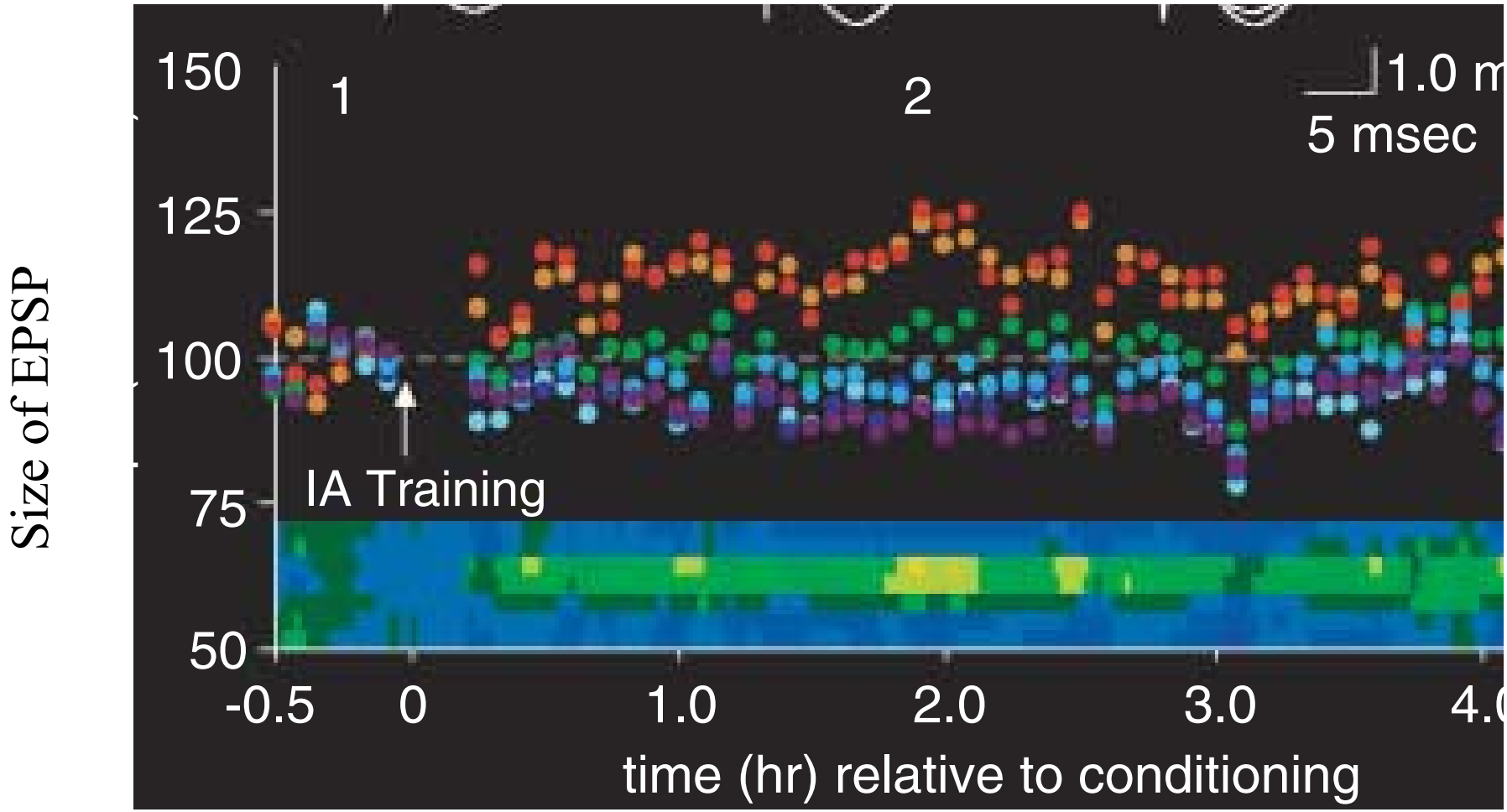
  Shocked once somewhere else

Electrodes to measure activity in hippocampus

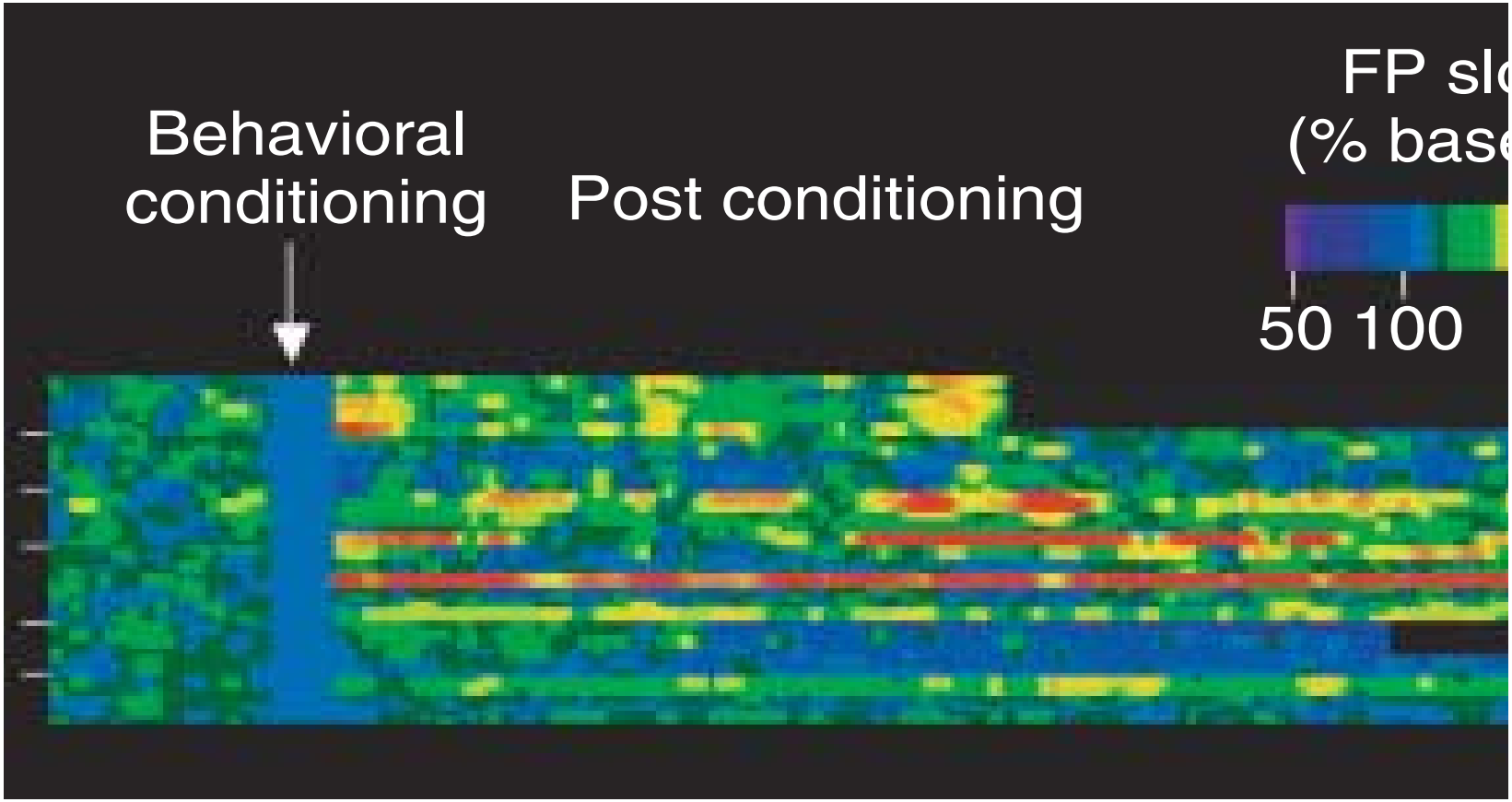


Single animal

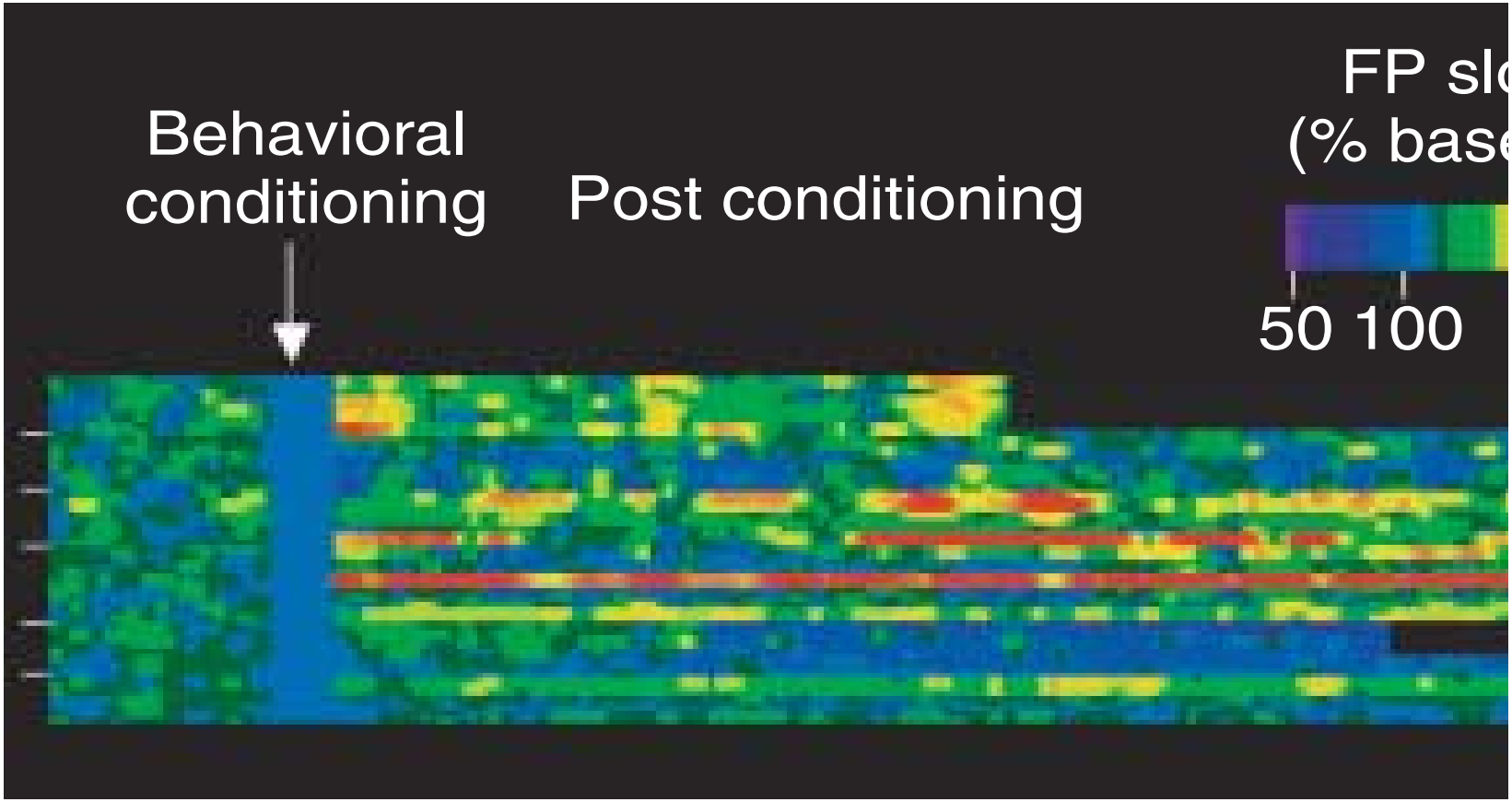
Before learning, 8 electrodes at 100%; few go up after training



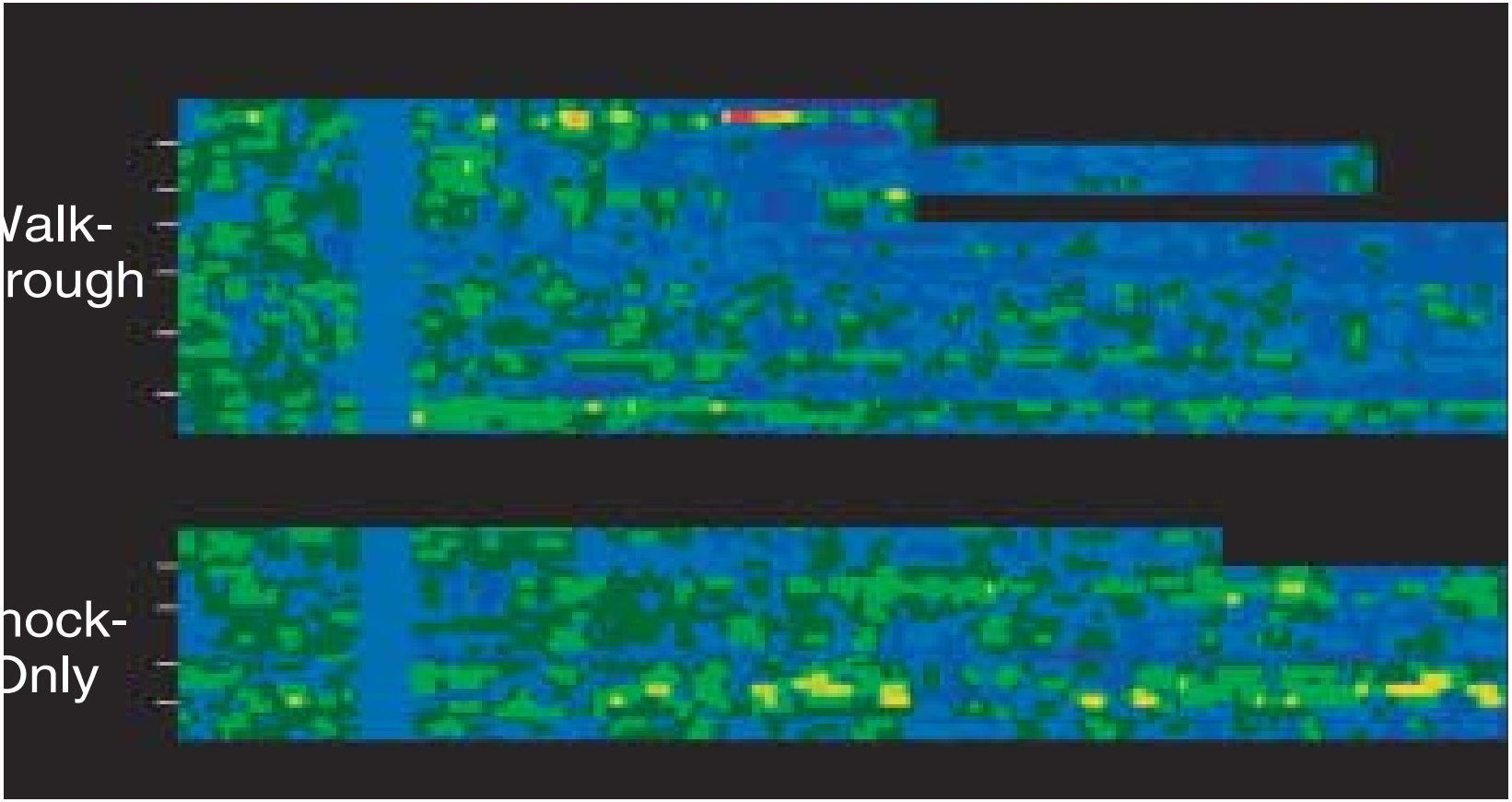
6 trained animals; ~8 electrodes each



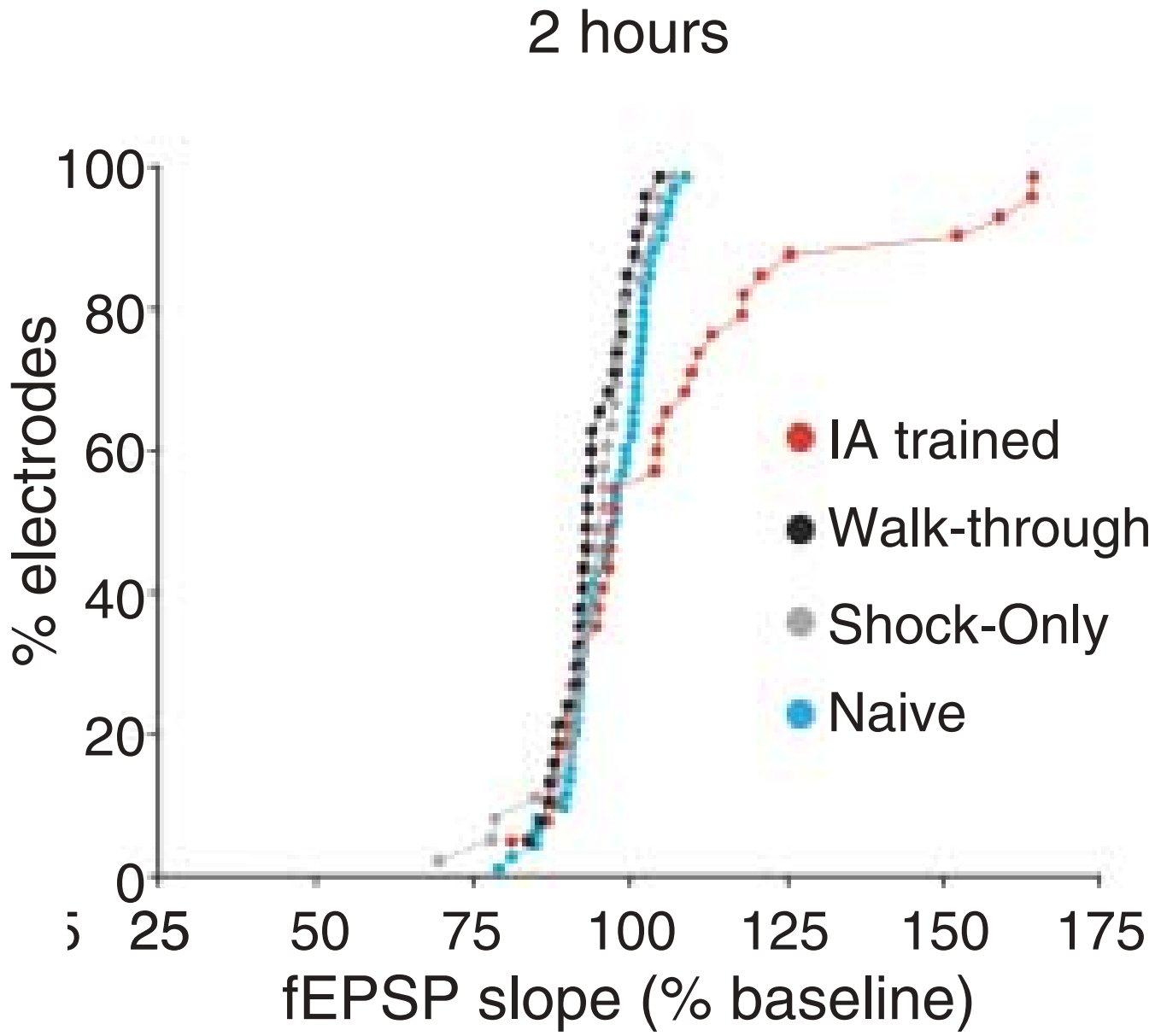
6 trained animals; ~8 electrodes each



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

Only animals to show LTP had the learning experience

Most neurons do not change

One trial learning/association of two stimuli causes a number of synapses to be potentiated for a long time

Suggests parallels/homologies/continuities with synaptic learning seen in very simple invertebrate organisms

Does LTP suggest category of memory drugs???

- **Not globally**
- **Memantine (NMDA-R) is drug for severe Alzheimer's Disease**
  - NMDA R antagonist
  - May prevent excitotoxicity
  - Does retard eye-blink conditioning in humans
- **Other drugs target memory related processes like arousal, sleep etc**

Final exam
Friday 3 – 4:30

Material since last midterm

Martinez article

Today's highlights

Same format as midterms

- **Learning by doing**
- **Scientific literacy**
- **Understanding basis for conclusions**
- **Understanding what ongoing work looks like**

Reading scientific research articles

- Abstract
- Introduction
- Methods
- Results
- Discussion
- References

Abstract

- **Dense outline of entire paper**
- **Read it first AND read it last!**

Final exam paper

OPEN ACCESS Freely available online

PLoS one

Sensorimotor Experience Influences Recovery of Forelimb Abilities but Not Tissue Loss after Focal Cortical Compression in Adult Rats

Marina Martinez, Jean-Michel Brezun, Christian Xerri*

CNRS UMR 6149, Integrative and Adaptive Neurosciences, Pôle 3 C, IFR 131, University of Provence, Marseilles, France

ABSTRACT: Sensorimotor activity has been shown to play a key role in functional outcome after extensive brain damage. This study was aimed at assessing the influence of sensorimotor experience through subject-environment interactions on the time course of both lesion and gliosis volumes as well as on the recovery of forelimb sensorimotor abilities following focal cortical injury. The lesion consisted of a cortical compression targeting the forepaw representational area within the primary somatosensory cortex of adult rats. After the cortical lesion, rats were randomly subjected to various postlesion conditions: unilateral C5–C6 dorsal root transection depriving the contralateral cortex from forepaw somatosensory inputs, standard housing or an enriched environment promoting sensorimotor experience and social interactions. Behavioral tests were used to assess forelimb placement during locomotion, forelimb-use asymmetry, and forepaw tactile sensitivity. For each group, the time course of tissue loss was described and the gliosis volume over the first postoperative month was evaluated using an unbiased stereological method. Consistent with previous studies, recovery of behavioral abilities was found to depend on post-injury experience. Indeed, increased sensorimotor activity initiated early in an enriched environment induced a rapid and more complete behavioral recovery compared with standard housing. In contrast, severe deprivation of peripheral sensory inputs led to a delayed and only partial sensorimotor recovery. The dorsal rhizotomy was found to increase the perilesional gliosis in comparison to standard or enriched environments. These findings provide further evidence that early sensory experience has a beneficial influence on the onset and time course of functional recovery after focal brain injury.

Introduction

- **Background**
- **What is already known? What is the new question to be addressed?**

Methods

- **How was the NEW experiment conducted?**
  - Subjects?
  - Measures?
  - How analyzed?
- **Enough detail for someone else to repeat**

Results

- **What was found in this new experiment?**
  - Averages values
  - Statistical differences

Discussion

- **What do the results mean?**
  - Do they refute/support a hypothesis
  - Do they fit with previous research?
  - Do they raise new questions?
  - Were there problems with the experiment?

A REPORTER AT LARGE

THE POVERTY CLINIC

Can a stressful childhood make you a sick adult?

BY PAUL TOUGH

Nadine Burke at her San Francisco clinic. Photograph by Alessandra Sanguinetti.

Adverse Childhood Experiences (ACE) Study

ACE Home
About ACE
Pyramid
Major Findings
Questionaires
Data and Statistics
Future Directions
Related Links
Publications
Contact Us

The Adverse

Childhood Experiences (ACE) Study is one of the largest investigations ever conducted to assess associations between childhood maltreatment and later-life health and well-being. The study is a collaboration between the Centers for Disease Control and Prevention and Kaiser Permanente's Health Appraisal Clinic in San Diego.

More than 17,000 Health Maintenance Organization (HMO) members undergoing a comprehensive physical examination chose to provide detailed information about their childhood experience of abuse, neglect, and family dysfunction. To date, more than 50 scientific articles have been published and more than100 conference and workshop presentations have been made.

The ACE Study findings suggest that certain experiences are major risk factors for the leading causes of illness and death as well as poor quality of life in the United States. Progress in preventing and recovering from the nation's worst health and social problems is likely to benefit from understanding that many of these problems arise as a consequence of adverse childhood experiences.

Text size: S M L XL
Email page
Print page
Bookmark and share

Contact Us:

Centers for Disease Control and Prevention
1600 Clifton Rd
Atlanta, GA 30333

800-CDC-INFO
(800-232-4636)
TTY: (888) 232-6348
24 Hours/Every Day

cdcinfo@cdc.gov

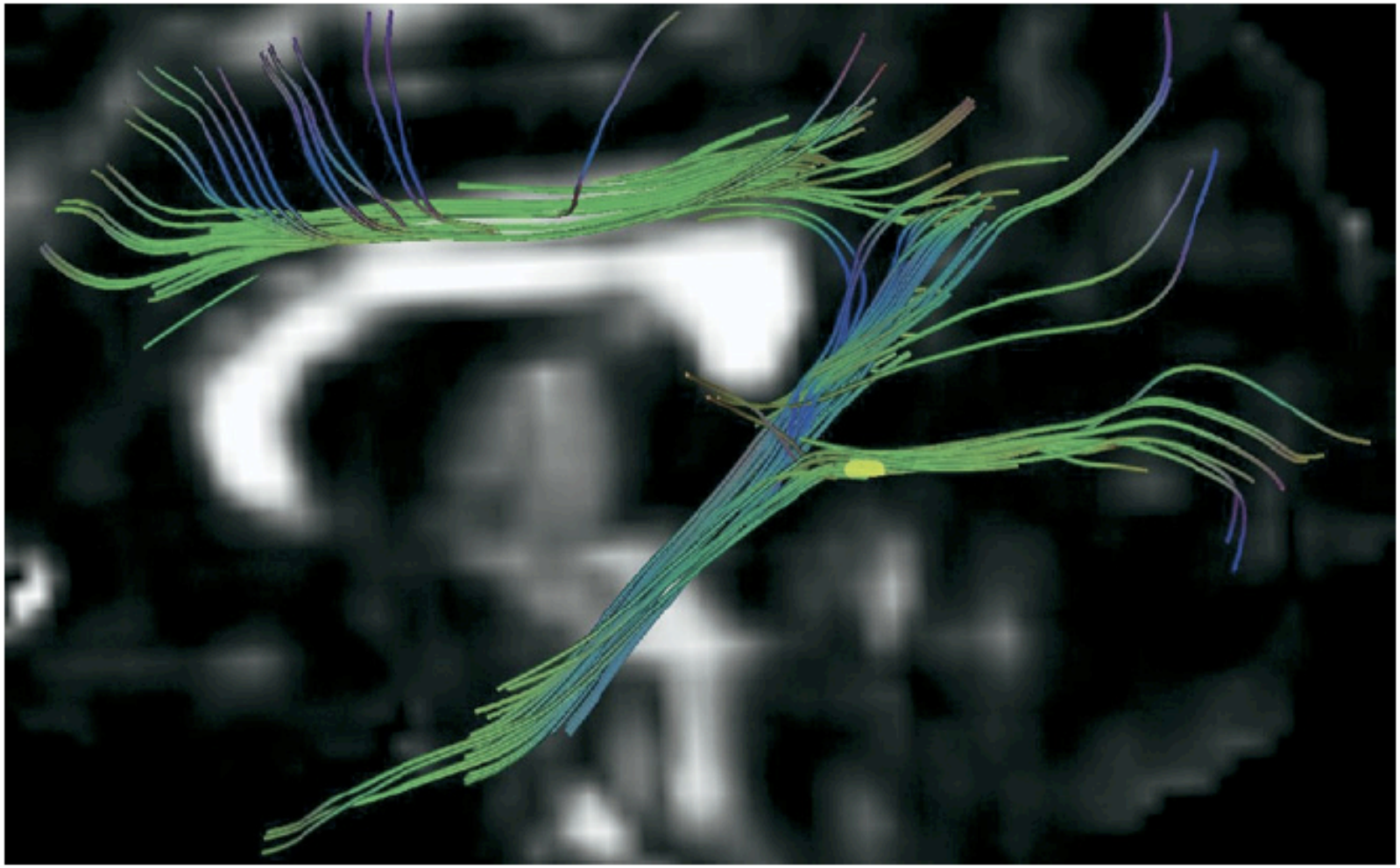
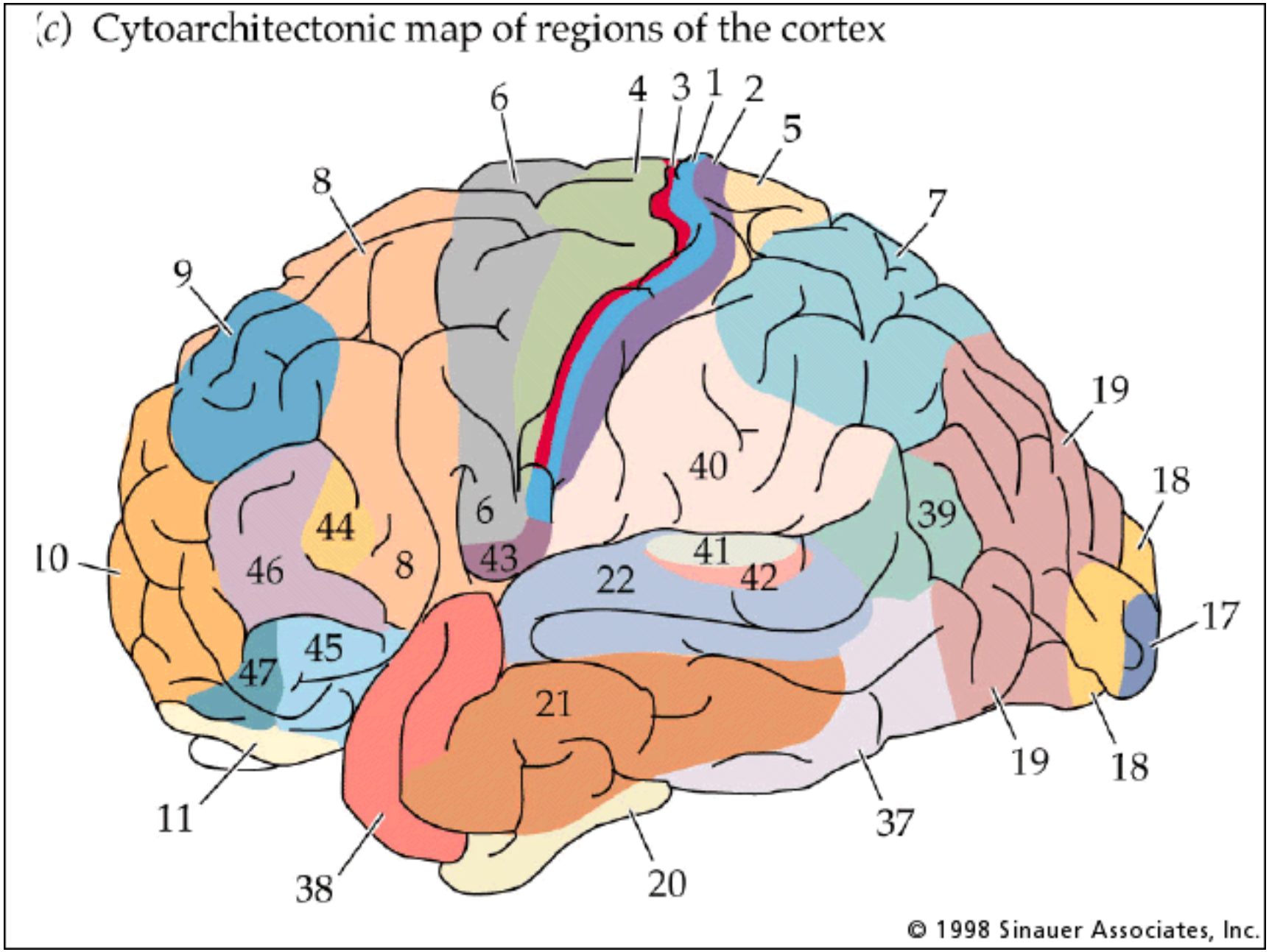
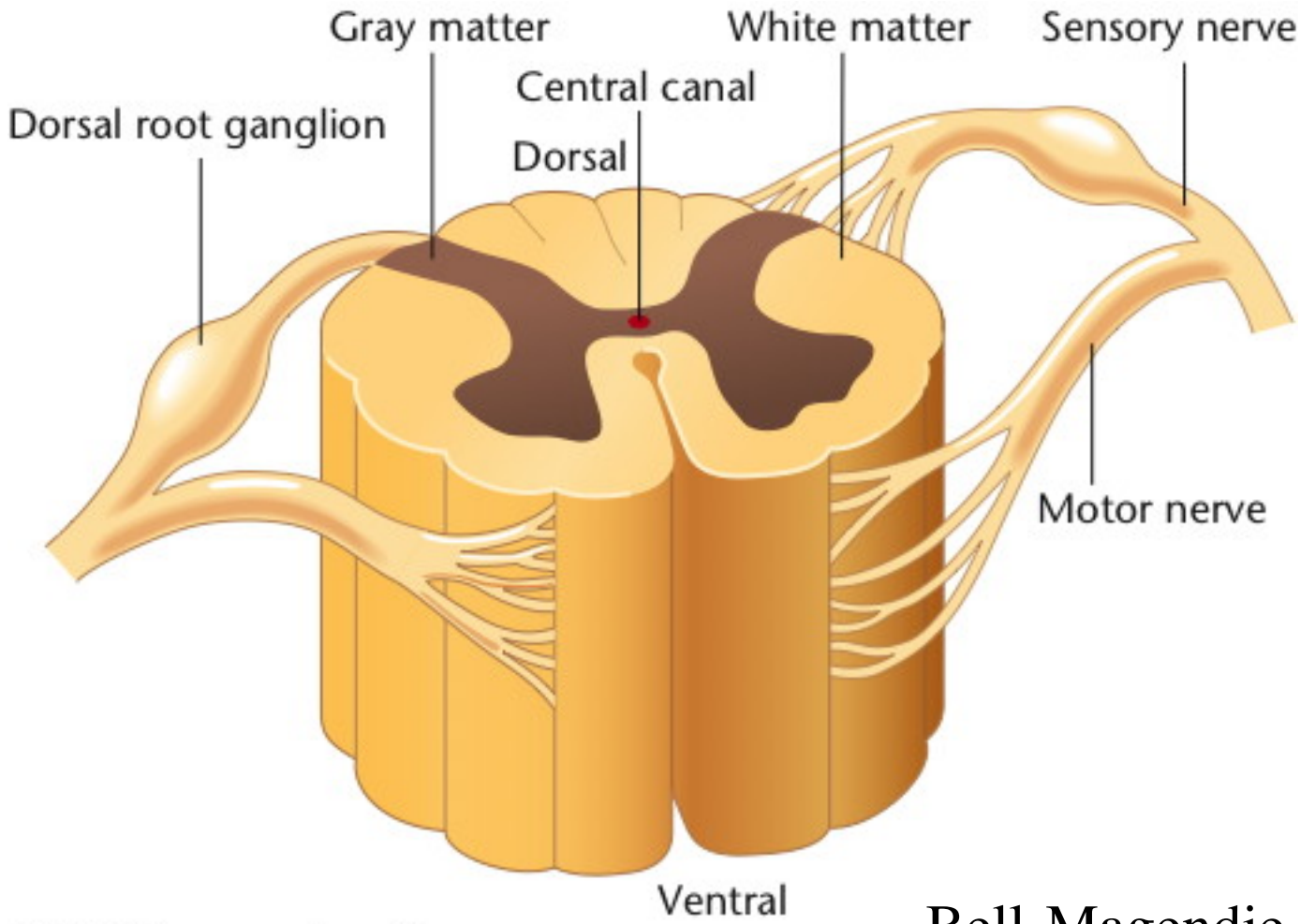


Figure 6. Detailed tractography of left cingulum bundle fibers in a representative subject color coded by fiber direction. Yellow region marks segment of the pathway delineated by TBSS as having significantly lower FA in subjects with PVA versus control subjects. FA, fractional anisotropy; PVA, parental verbal abuse; TBSS, tract-based spatial statistics.

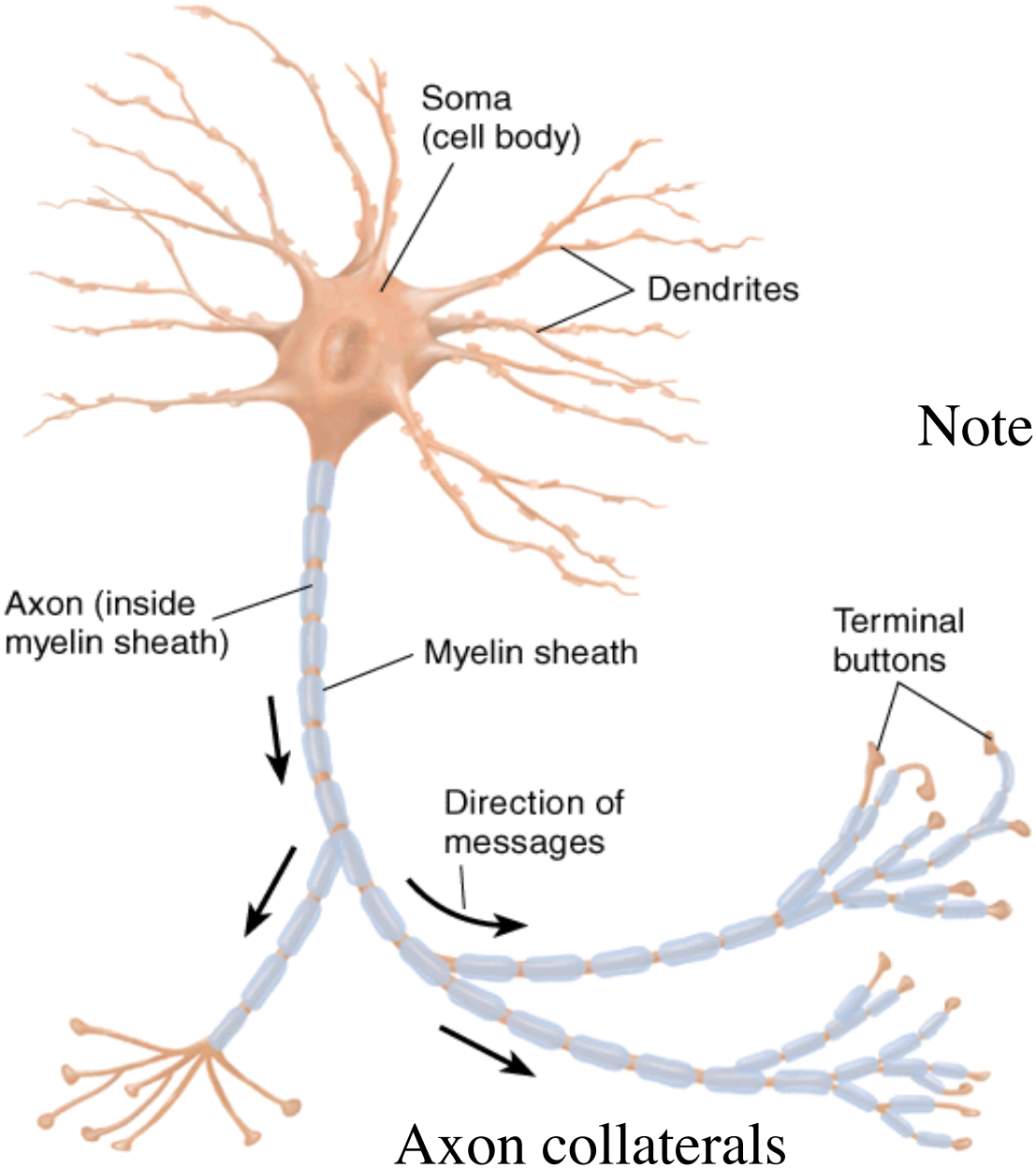
Choi, BIOL PSYCHIATRY 2009;65:227–234


(c) Cytoarchitectonic map of regions of the cortex
6
4
3
1
2
5
8
7
9
19
40
18
6
39
44
41
10
46
8
43
22
42
17
45
47
21
19
18
11
37
38
20
© 1998 Sinauer Associates, Inc.



Bell-Magendie Law

- Multipolar Neuron



Note arrows!

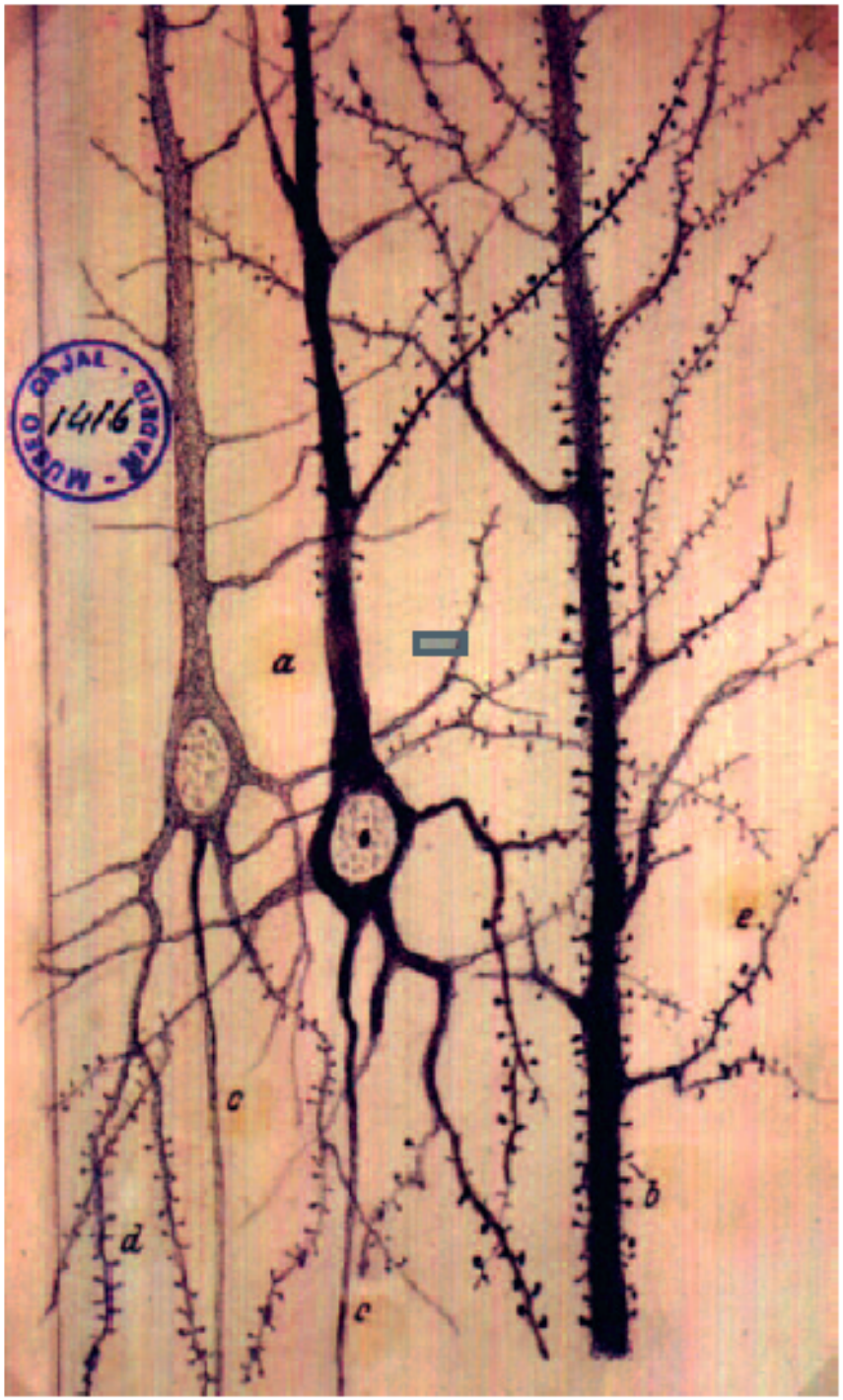
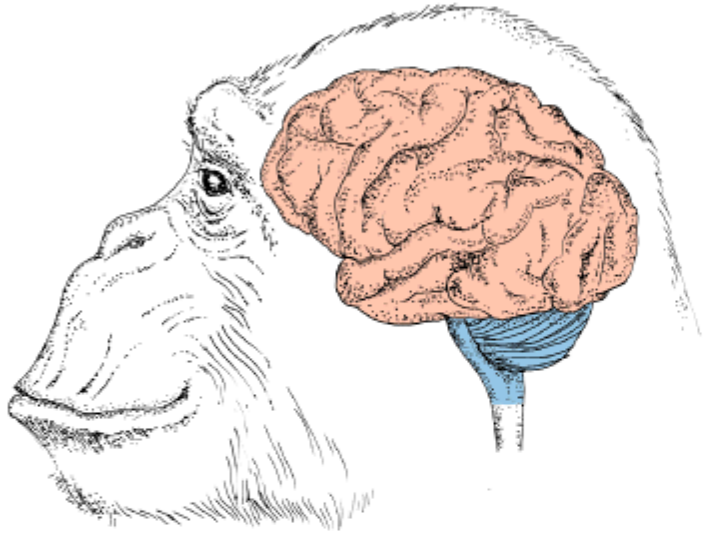


Figure 5. Methylene blue stained pyramidal cortical cells [16]. Cajal's demonstration of the presence of spines on cortical cells stained with an entirely different technique from Golgi's method.

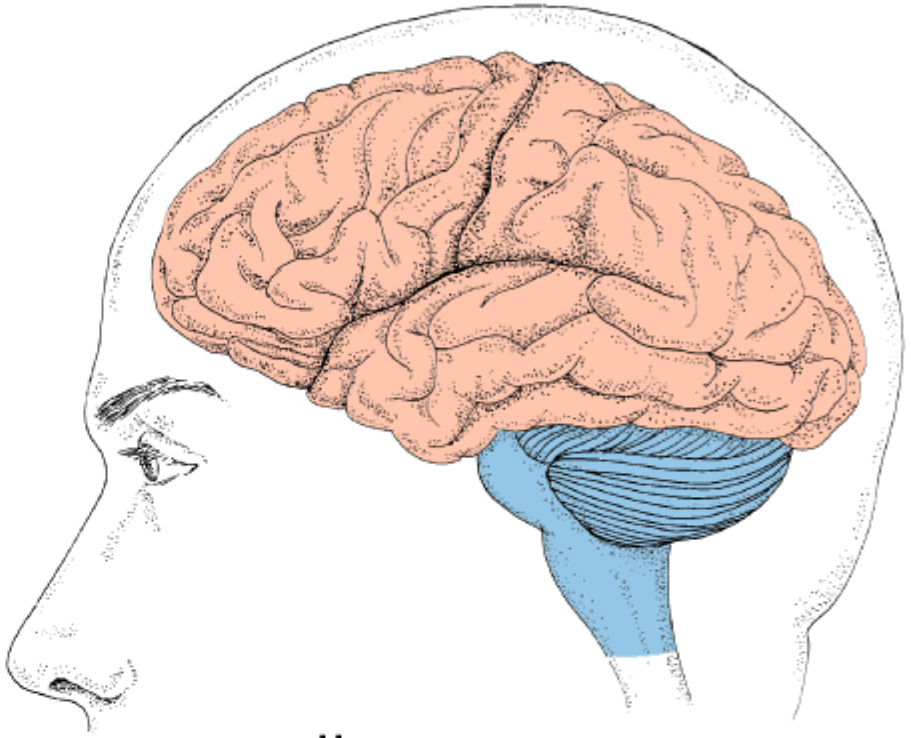
Santiago Ramon y Cajal –
neurons are individual units, not fused together

Glickstein; Current Biology Vol 16 No

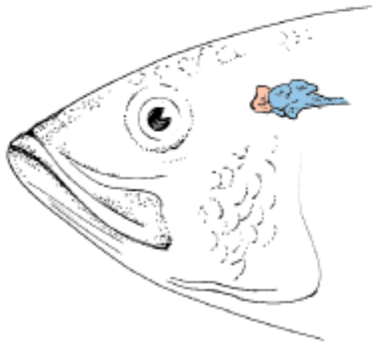
► Animal Brains



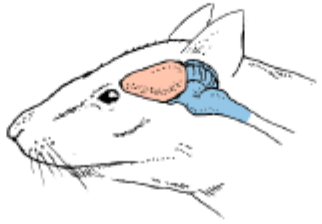
Chimpanzee



Human



Bass



Rat

Cat

Fly, worm, bacterium?

Add positive charge

depolarization

initially get graded potential

then get *action potential*

Action Potential

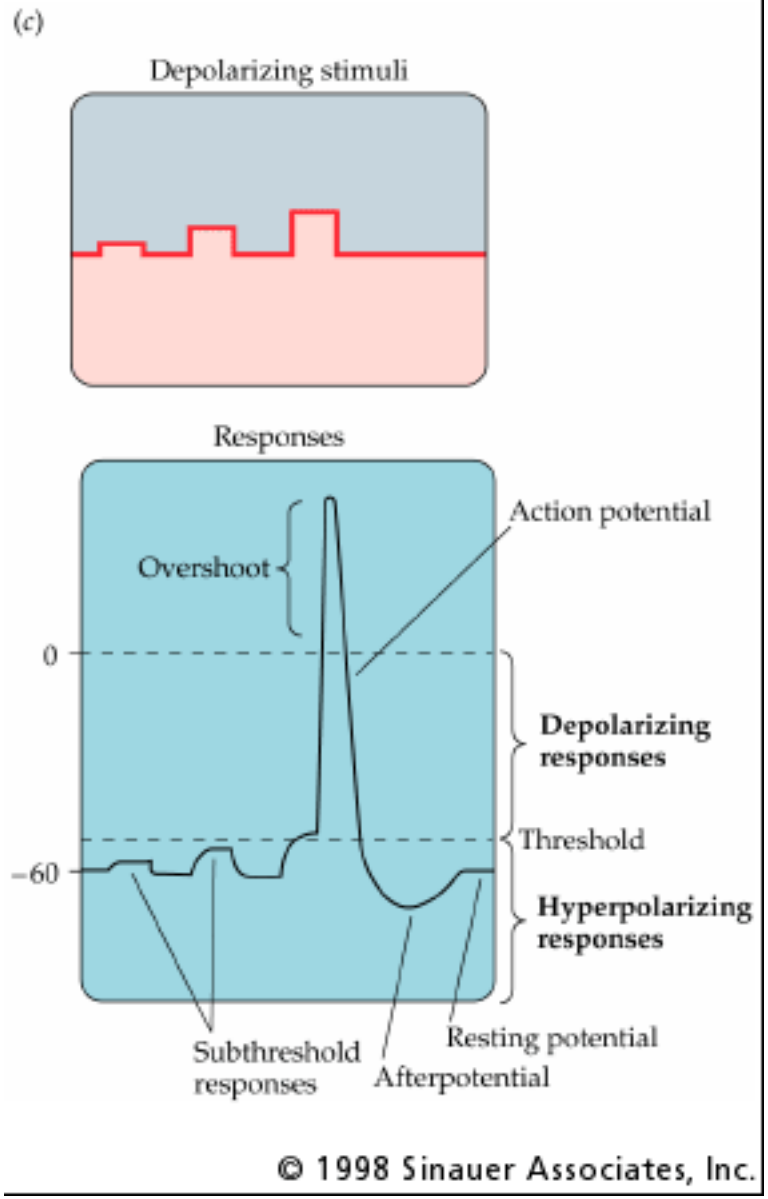
not proportional

always the same size/shape

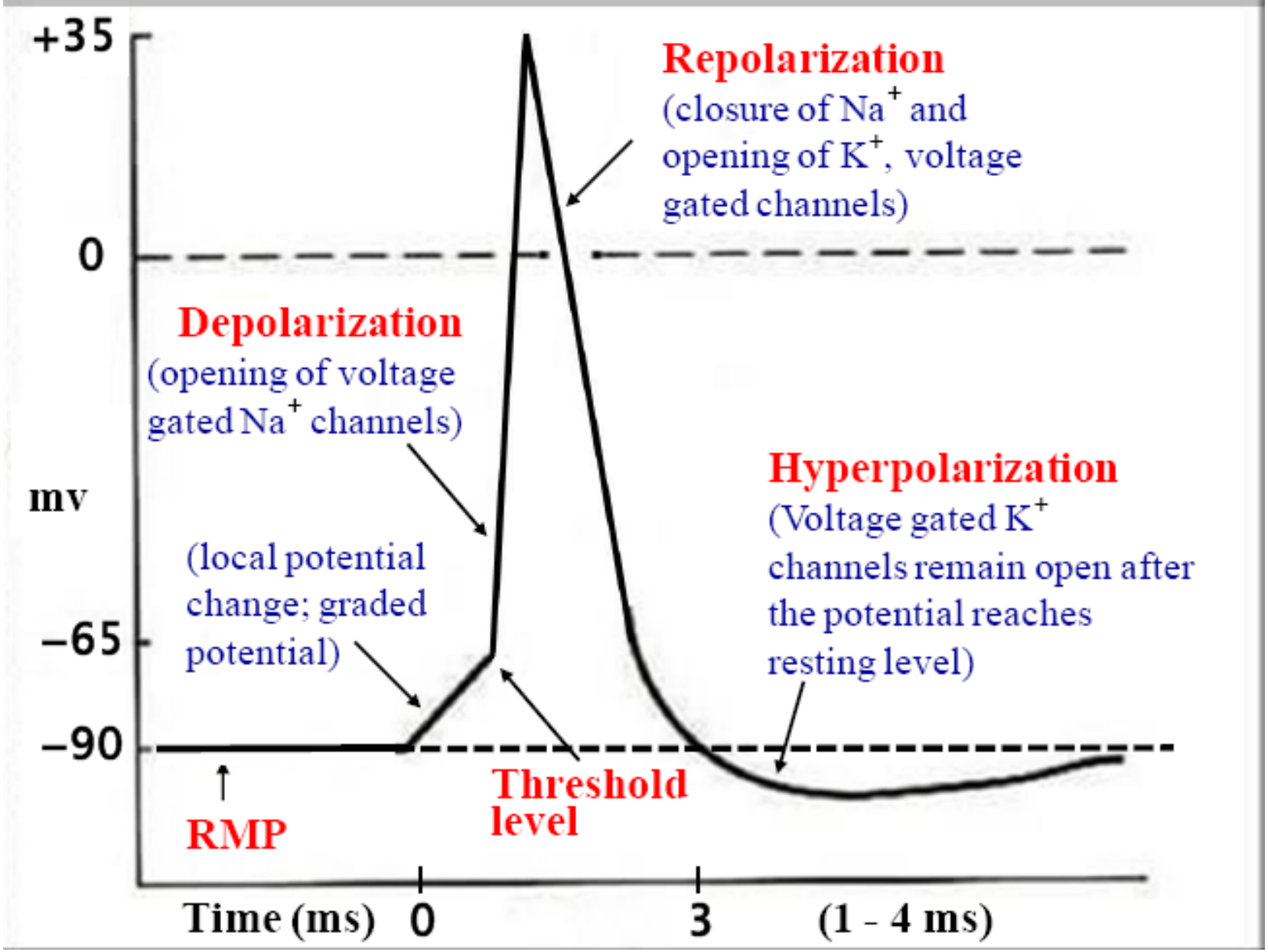
will run down axon

When do you get it:

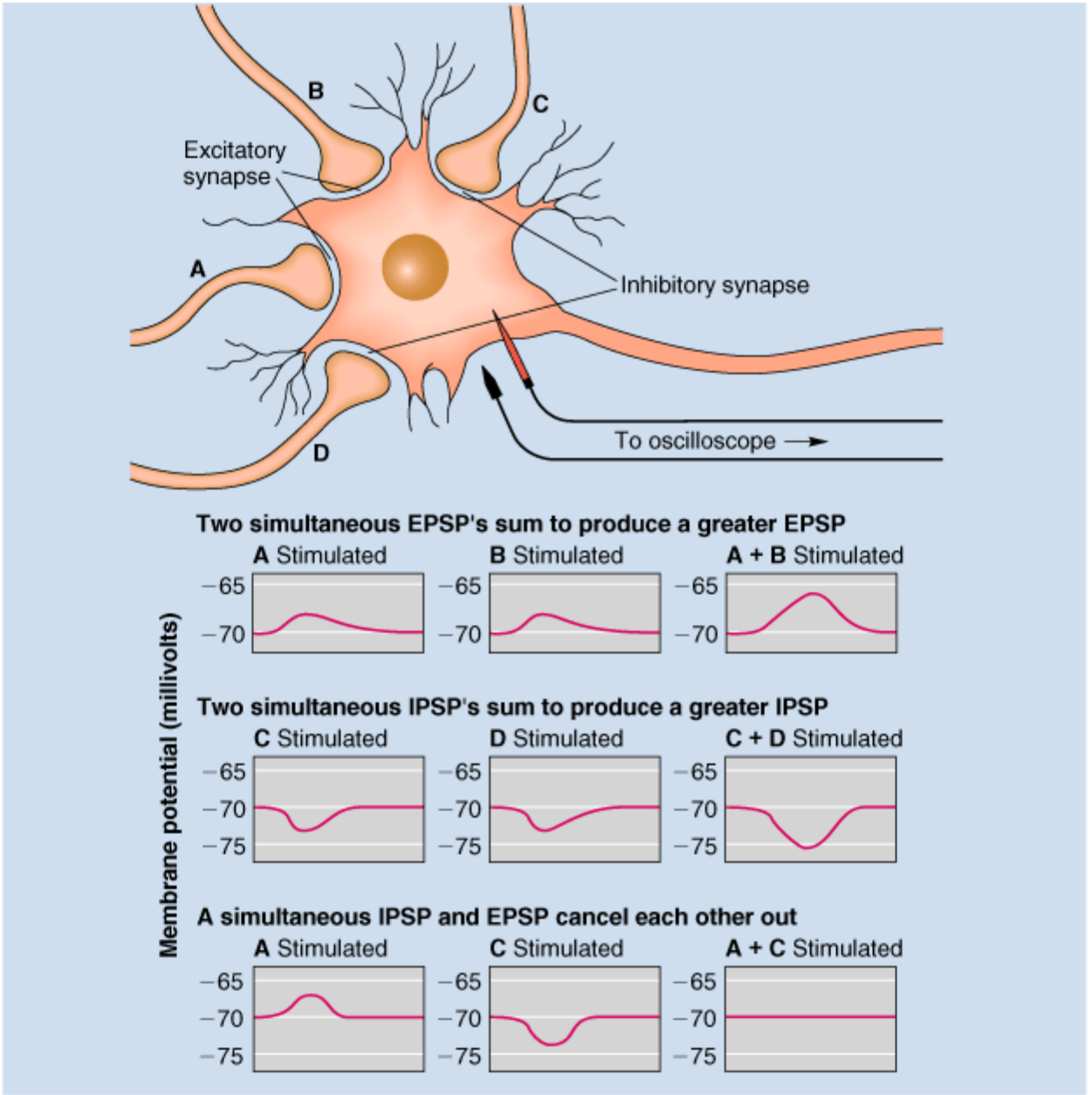
if voltage gets to "threshold"



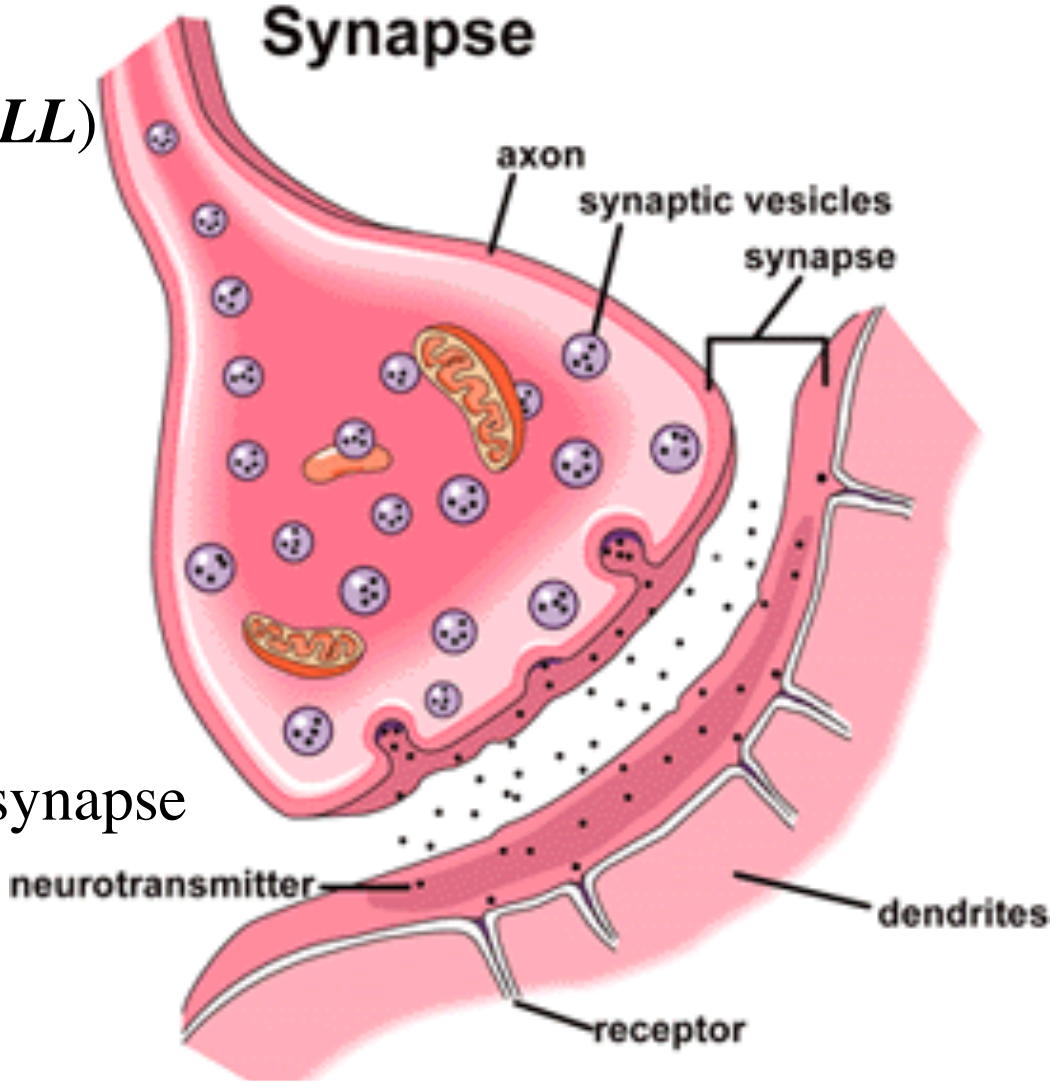
Action potential



► Possible Combinations of Spatial Summation



1. AP reaches terminal (***PRE-SYNAPTIC CELL***)

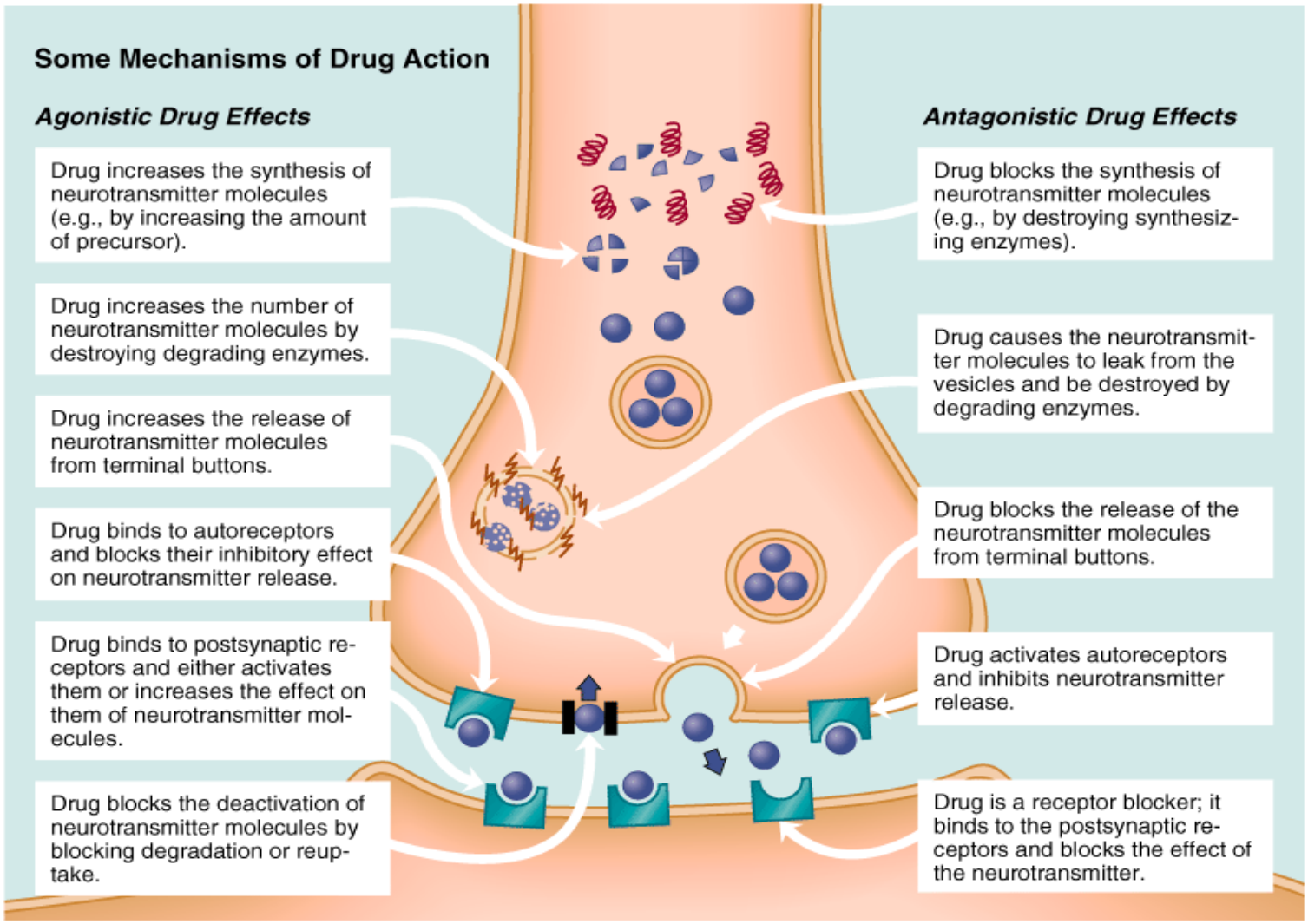


2. Release of NT into synapse

3. Next cell receives NT (***POST-SYNAPTIC CELL***)
4. NT causes electrical change in post-synaptic cell

Each stage of neurotranmission is potentially a site of drug action

► **Mechanisms of Drug Effects**



► Dose-Response Curves for the Analgesic and Depressant Effects of Morphine

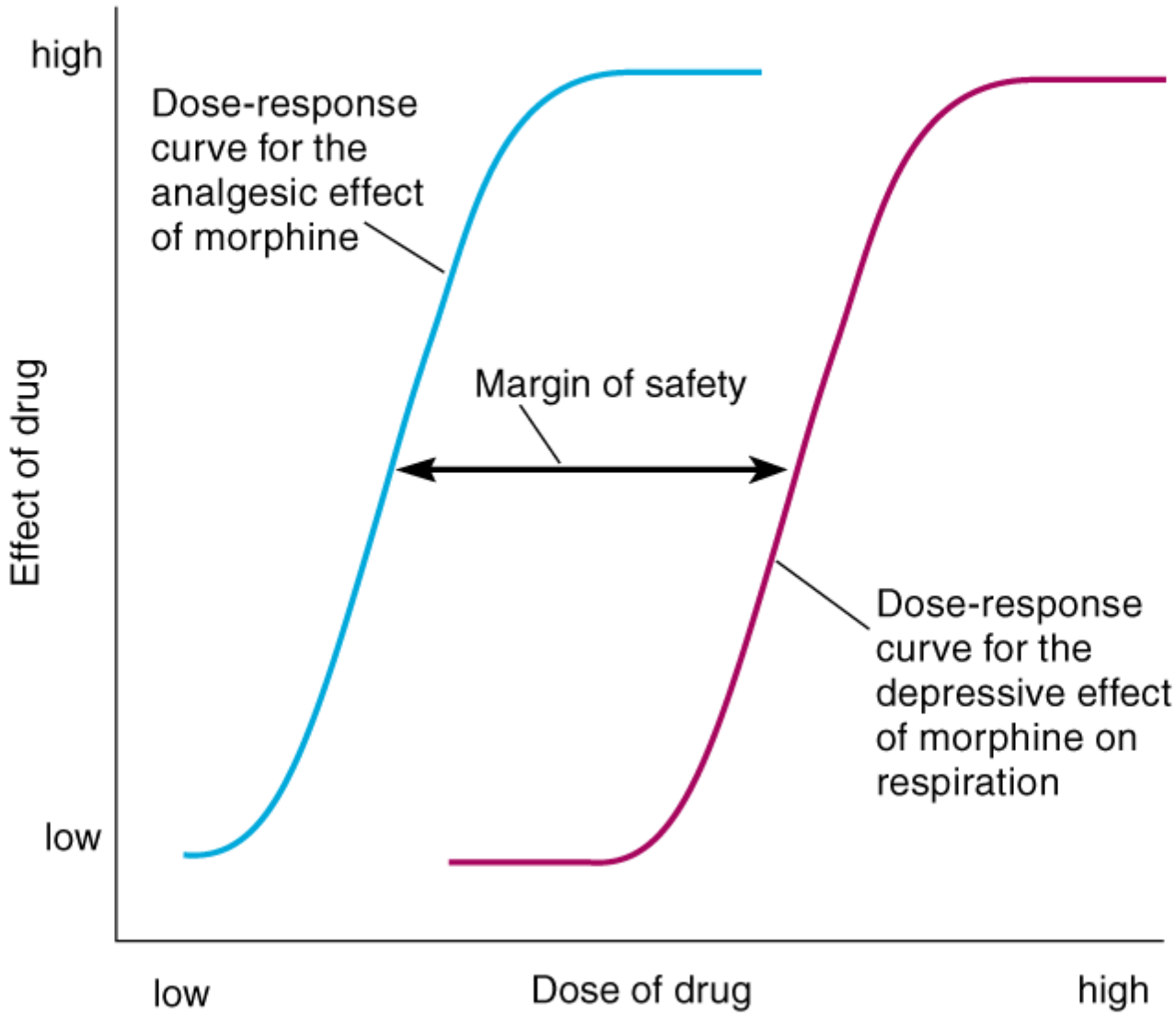
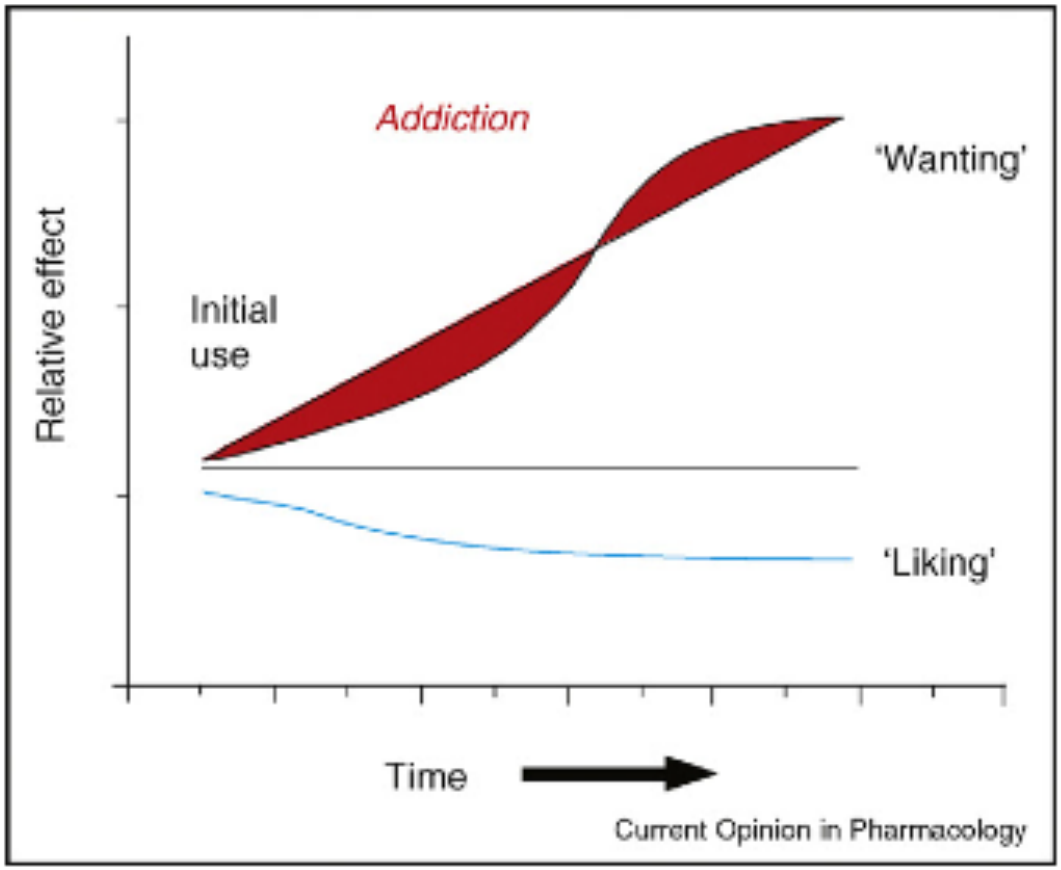


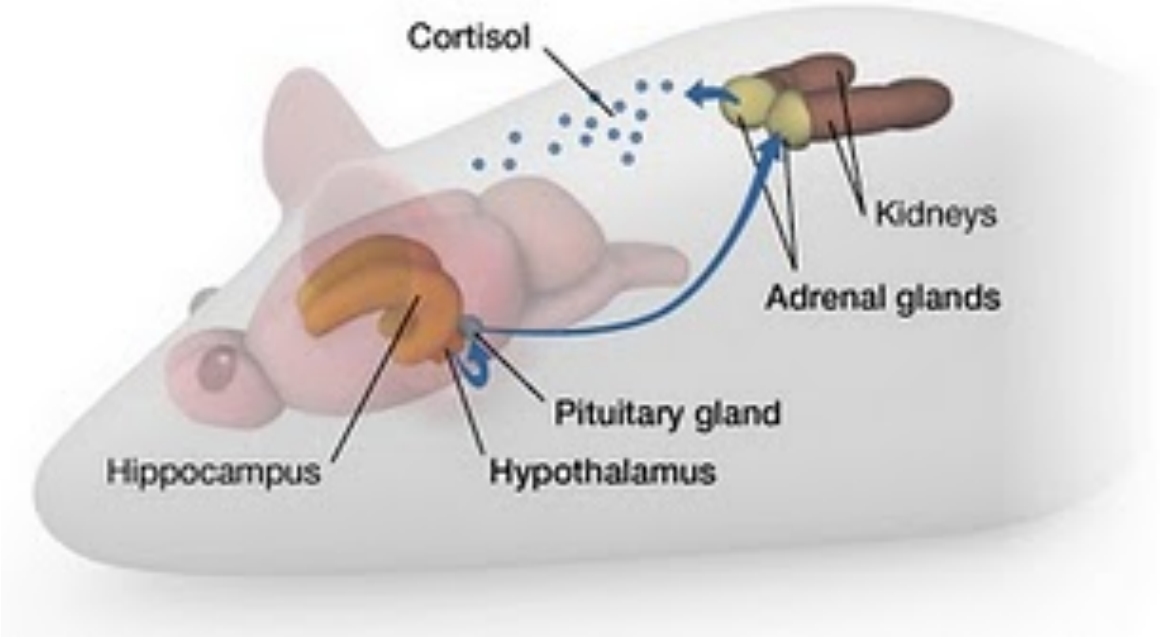
Figure 5



Incentive-sensitization model of addiction. Schematic model of how 'wanting' to take drugs may grow over time independently of 'liking' for drug pleasure as an individual becomes an addict. The transition from casual drug use to compulsive addiction is posited to be owing to drug-induced sensitization of mesocorticolimbic mechanisms of incentive salience. Modified from [42].

Jared Compiano, a normal healthy boy with PKU, poses with his siblings Hannah and Nathan.

Enz deficiency + phenylalanine → retardation
Enz deficiency – phenylalanine → normal
Enz sufficiency ± phenylalanine → normal

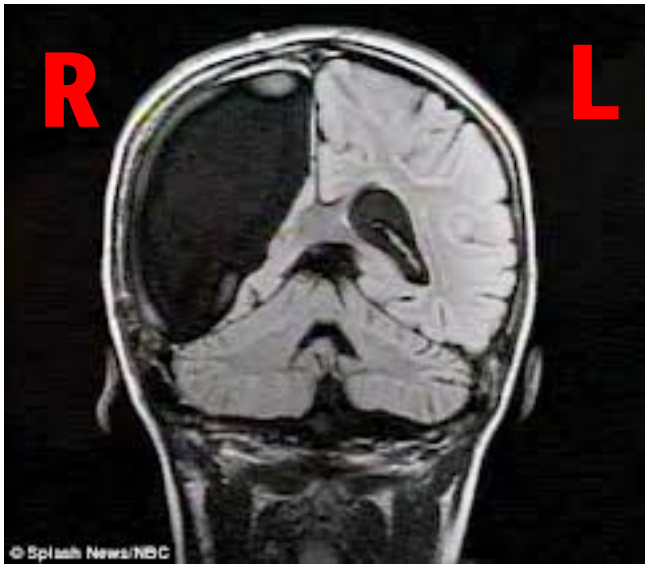


Compare high vs low-licked rats in adulthood
Microarray of gene expression in hippocampus (tests 30,000)

900 genes differed between groups!
Treated adults with drugs that alter epigenetic mechanisms
Reversed some behavior effects and some gene expression

Cameron Mott video

Rasmussen's Syndrome



Mechanisms of recovery

Treatments

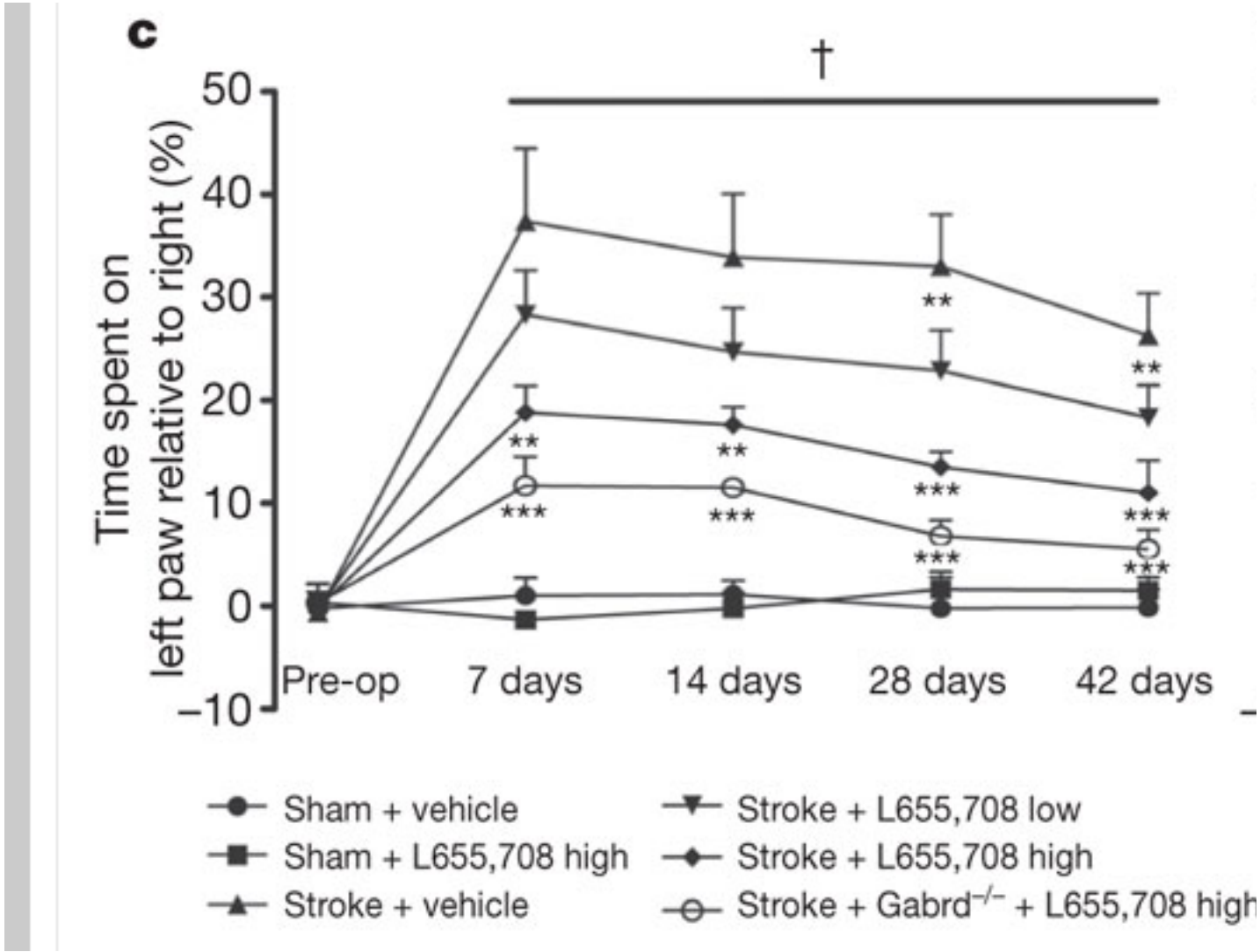
- tPA – tissue plasminogen activator
  - dissolves clots (3 h window only)
- hypothermia – prevents cell death in animals?
- antagonize glutamate – careful!!!!
- occupational therapy

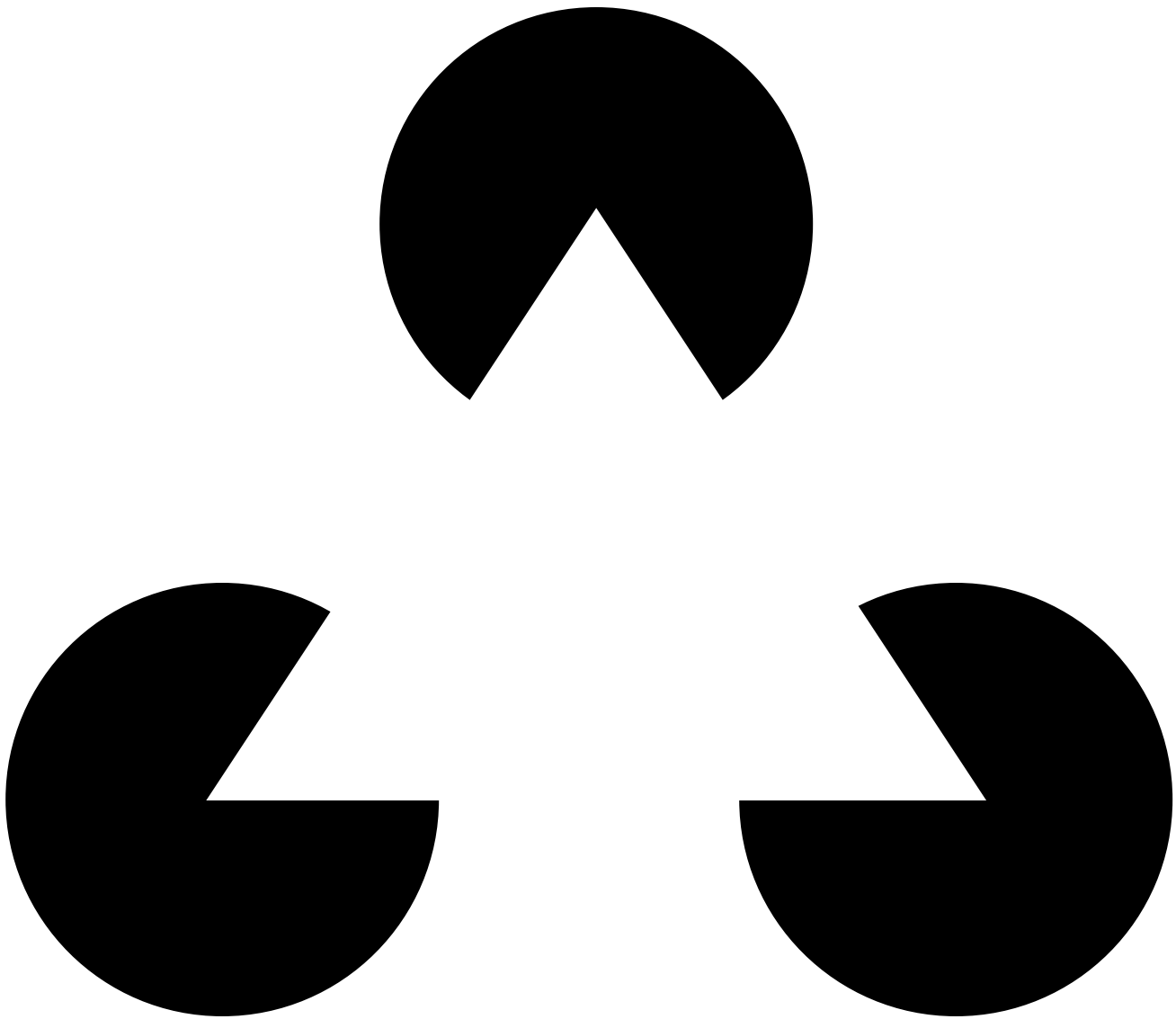
Brain cooling after cardiac arrest

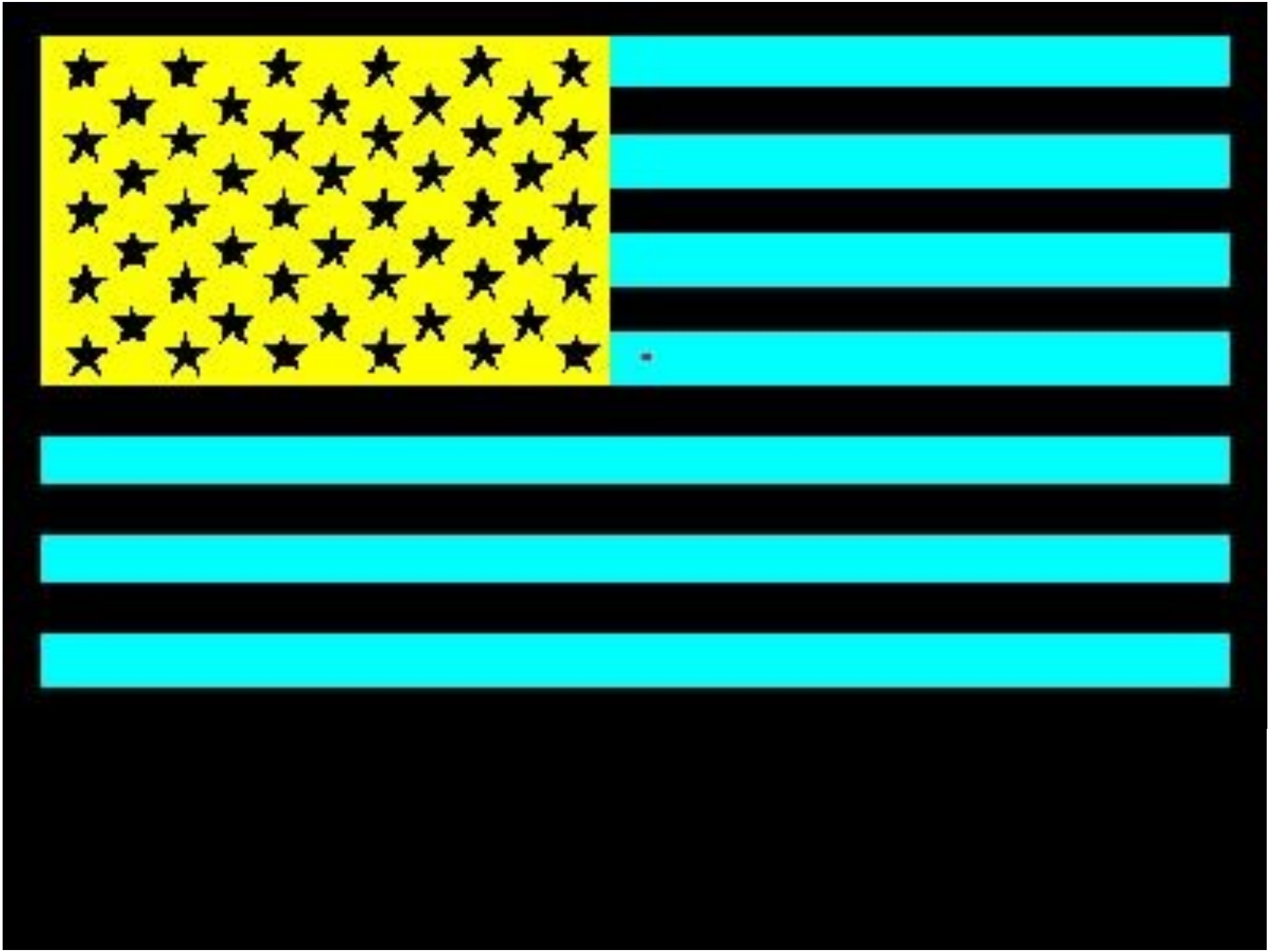
w cooling	35% minimal disability	50% mortality
without cooling	21%	67%

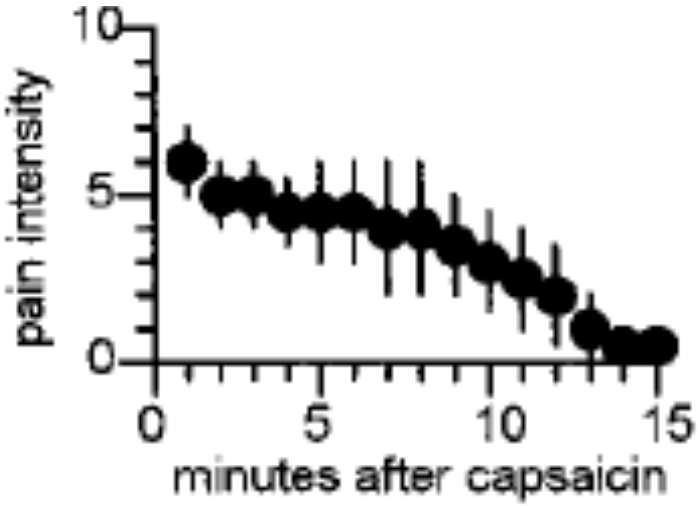
Doesn't work in conscious patients

Glutamate antagonist after induced stroke in animal model

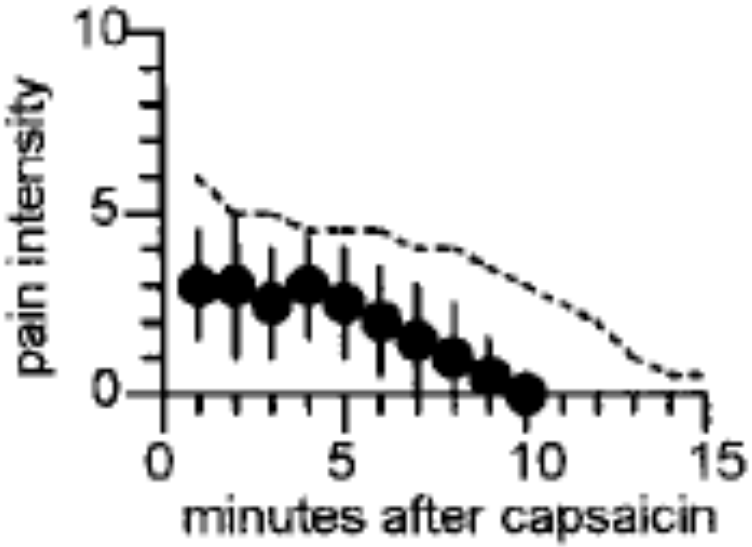






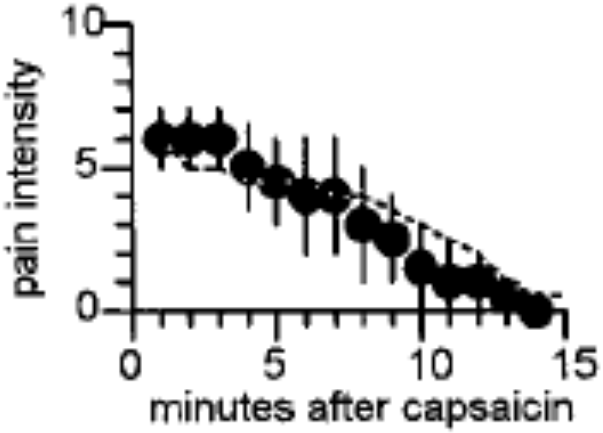


left hand



PLACEBO **left hand**

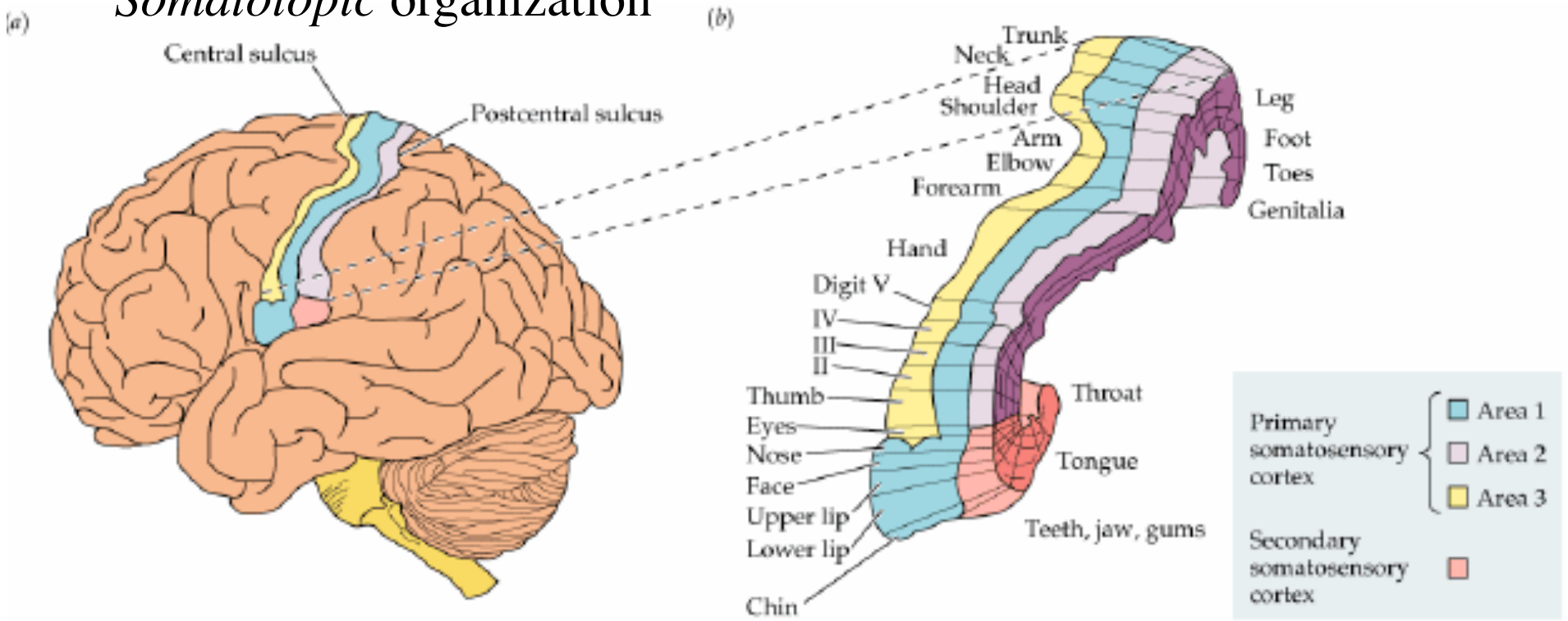
+ NALOXONE



PLACEBO **left hand**

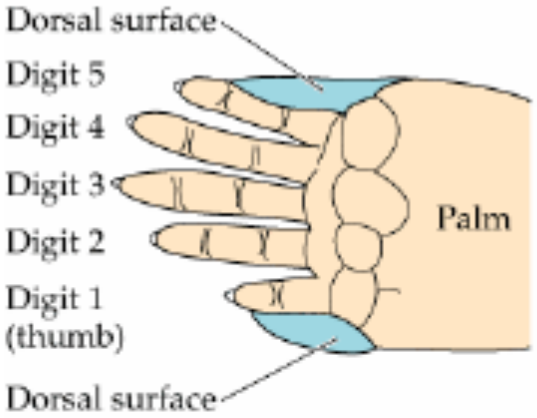
Primary Somatosensory Cortex = S1
Brodmann Areas 3b, 1,2, 3a

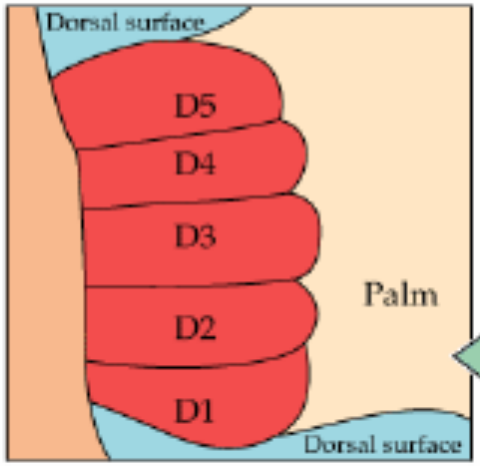
Somatotopic organization

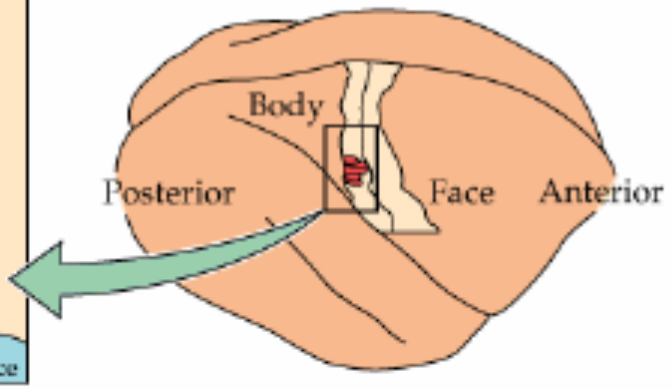


© 1998 Sinauer Associates, Inc

(*a*) Representation of the left hand in primary somatosensory cortex in right hemisphere of monkey brain



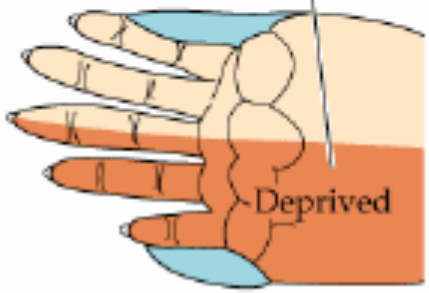




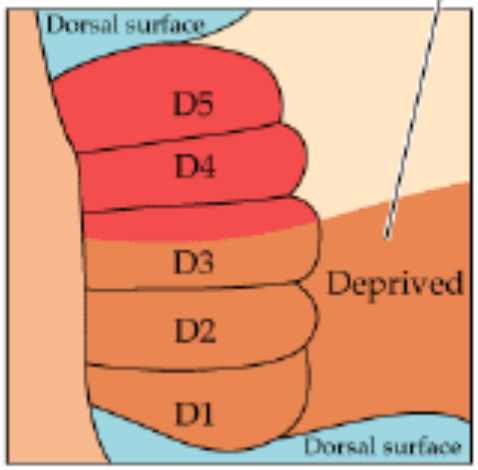
Details of cortical map
(D5 = Digit 5, etc.)

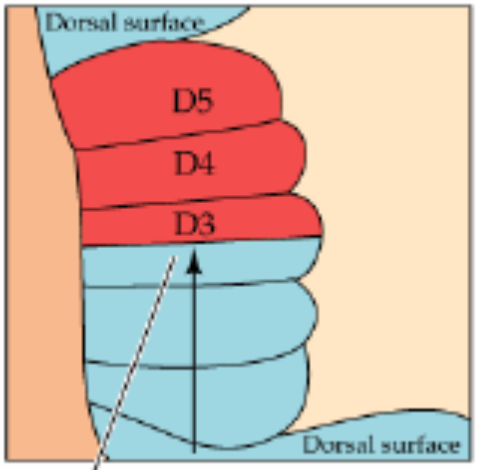
(*b*) Experiment 1

Nerve from thumb (D1) and index finger (D2) severed.



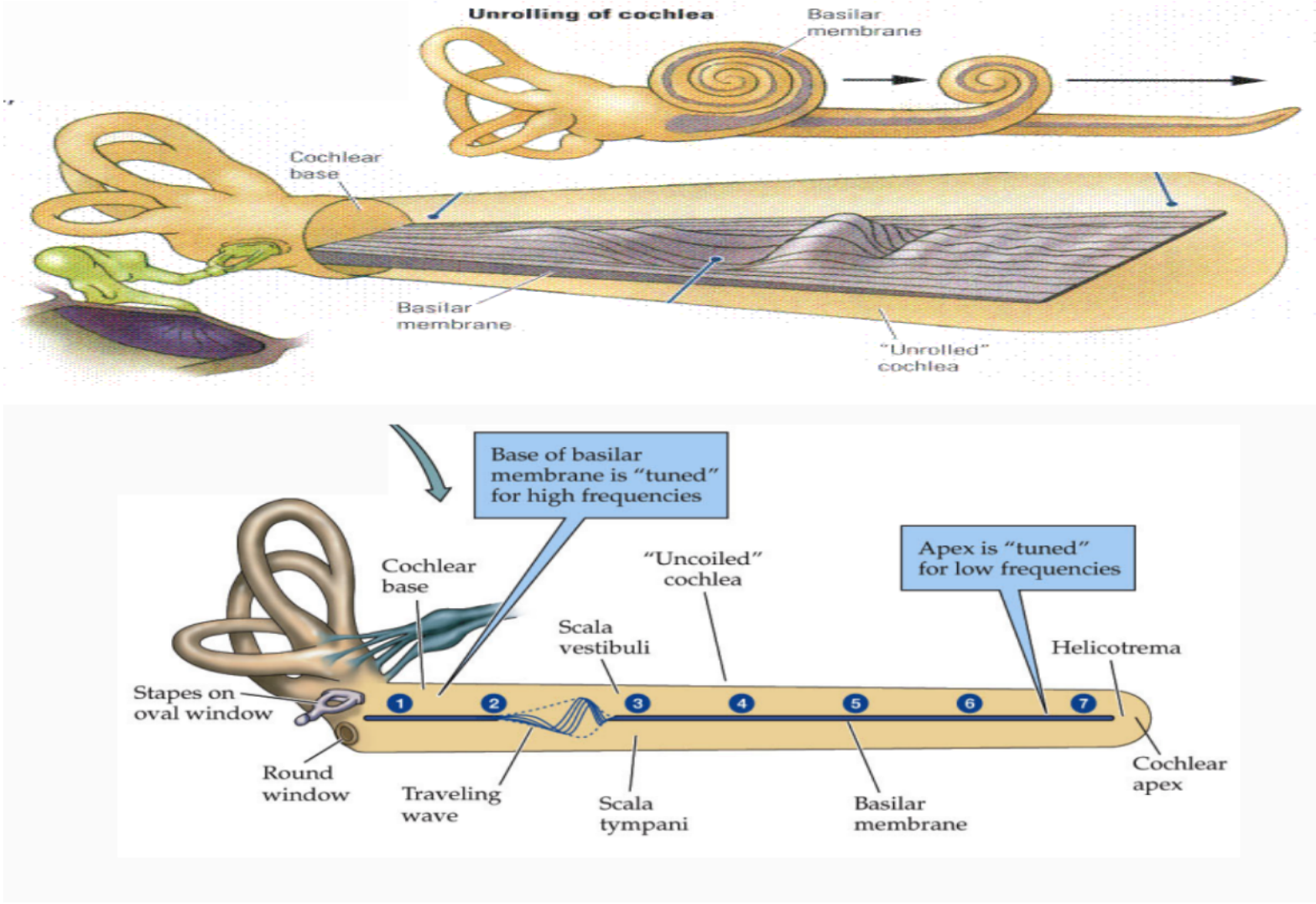
Immediately after severing the nerve, the areas representing D1 and D2 are unresponsive to stimuli.





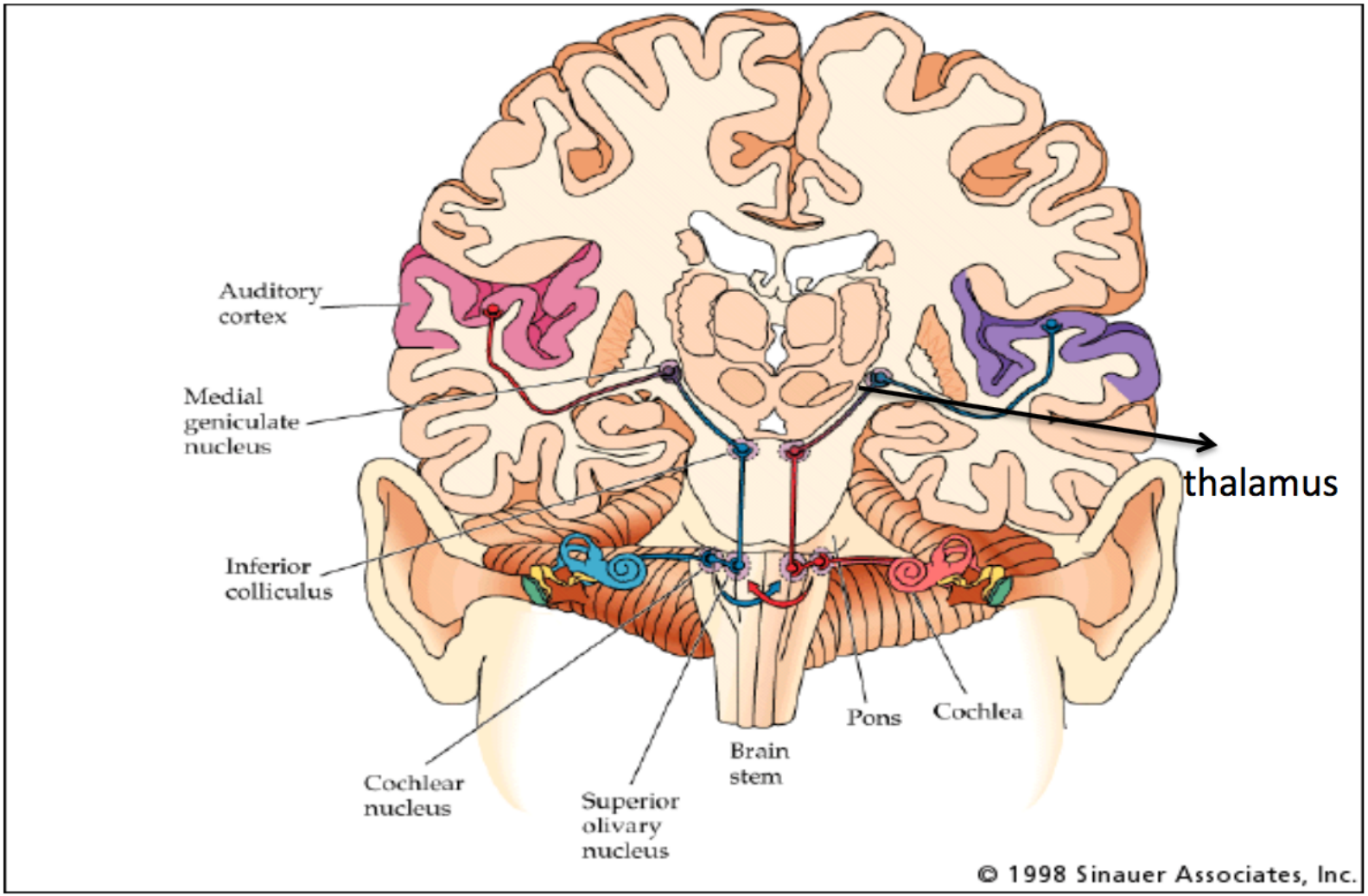
Five months later, the representation of the dorsal surface has expanded into the region that formerly represented D1 and D2.

© 1998 Sinauer Associates, Inc.



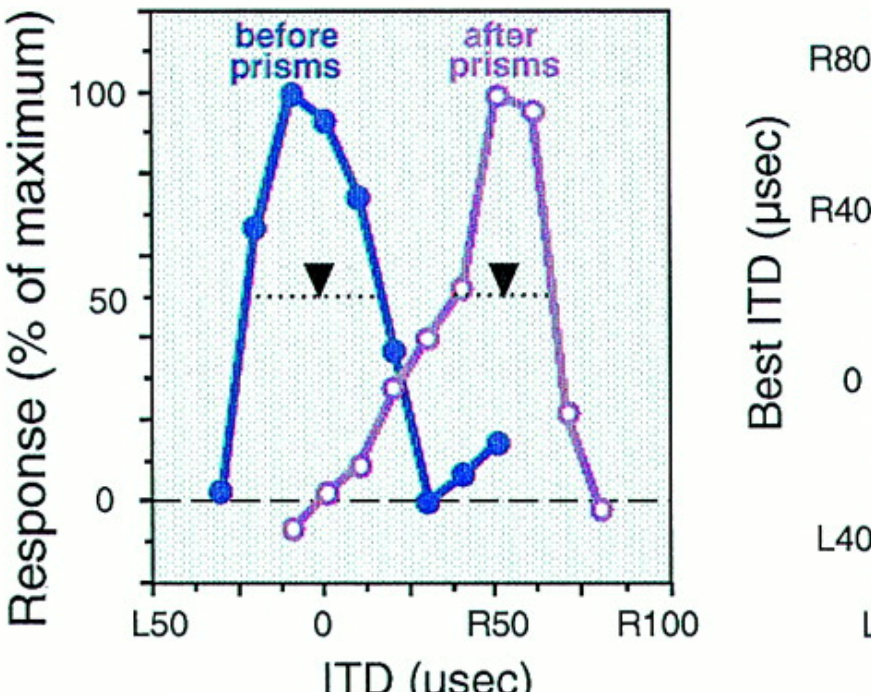
Wave travels through fluid of the scala vestibula, scala media

Ascending auditory pathway

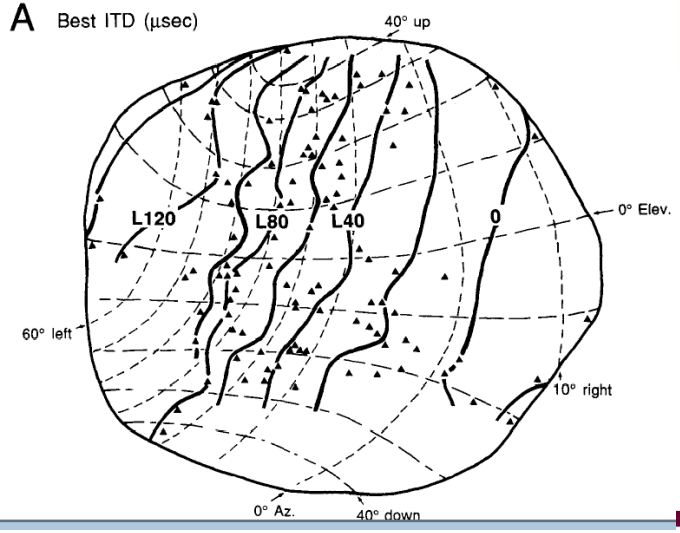


B

Shift of Auditory Tuning After 8 Weeks of Experience

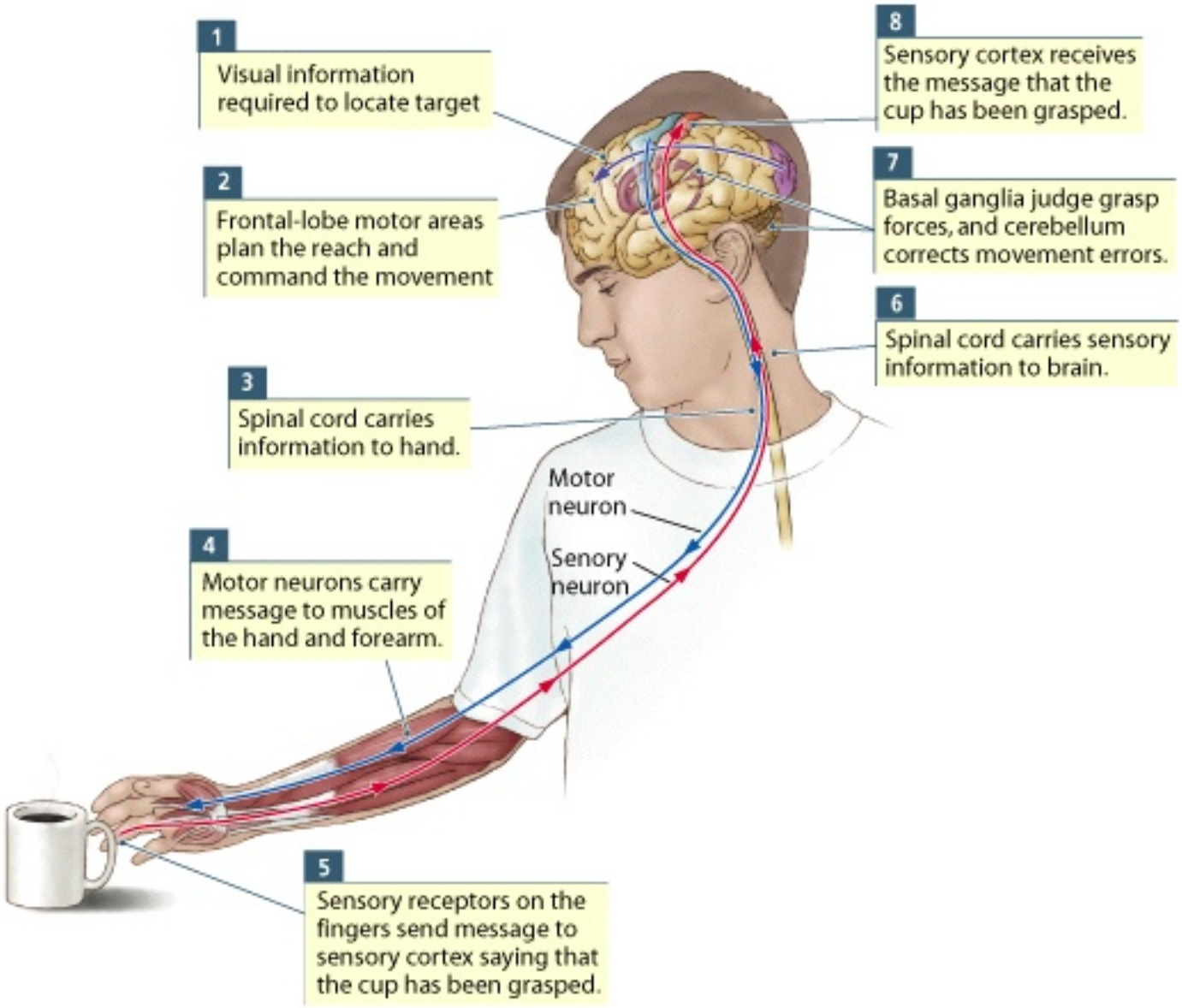


- Tuning curves
- Receptive fields
- What does cell respond best to?

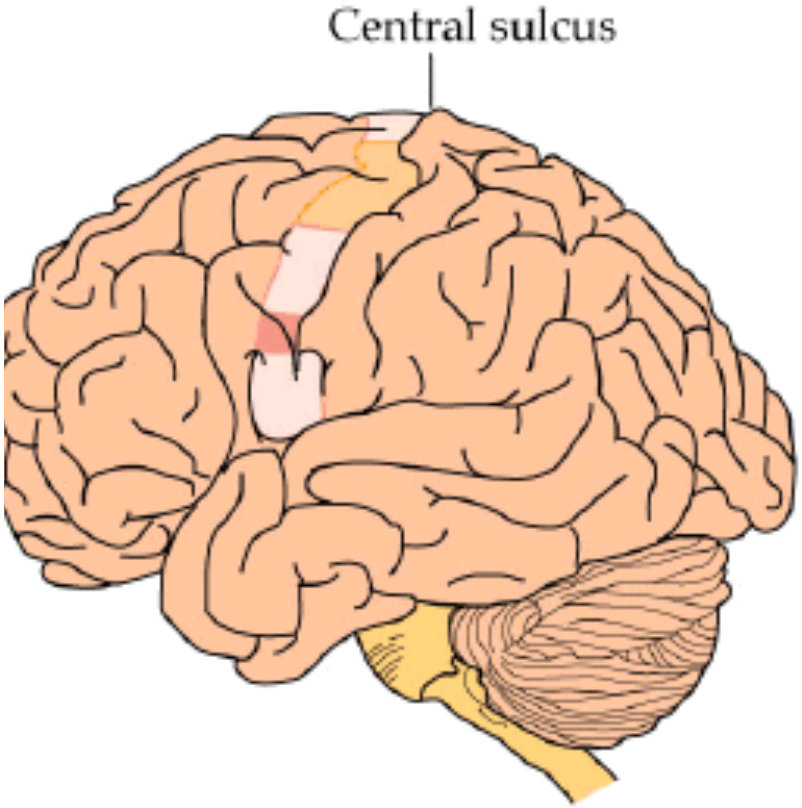


Knudsen

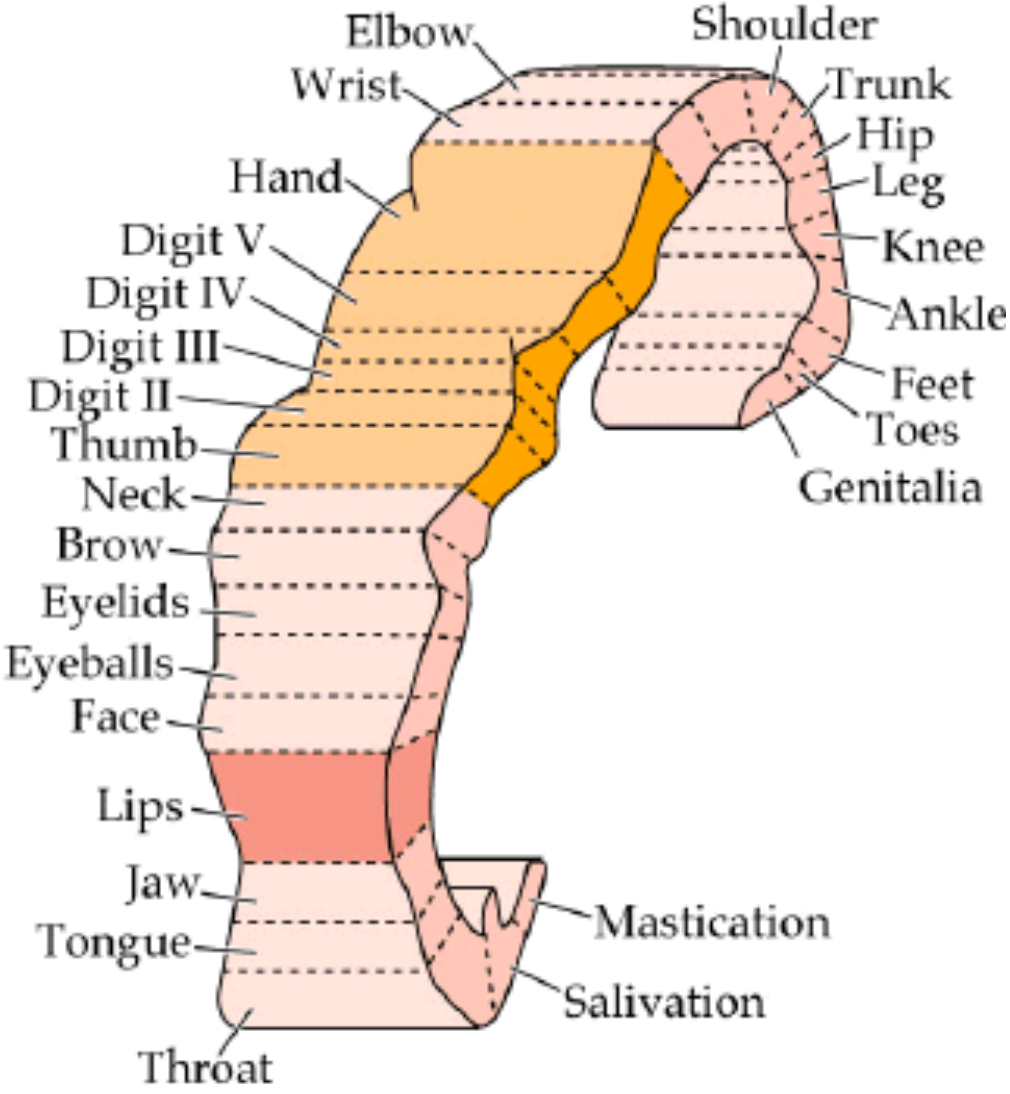
©2000 by The Nationa


1
Visual information required to locate target
2
Frontal-lobe motor areas plan the reach and command the movement
3
Spinal cord carries information to hand.
4
Motor neurons carry message to muscles of the hand and forearm.
5
Sensory receptors on the fingers send message to sensory cortex saying that the cup has been grasped.
6
Spinal cord carries sensory information to brain.
7
Basal ganglia judge grasp forces, and cerebellum corrects movement errors.
8
Sensory cortex receives the message that the cup has been grasped.
Motor neuron
Senory neuron

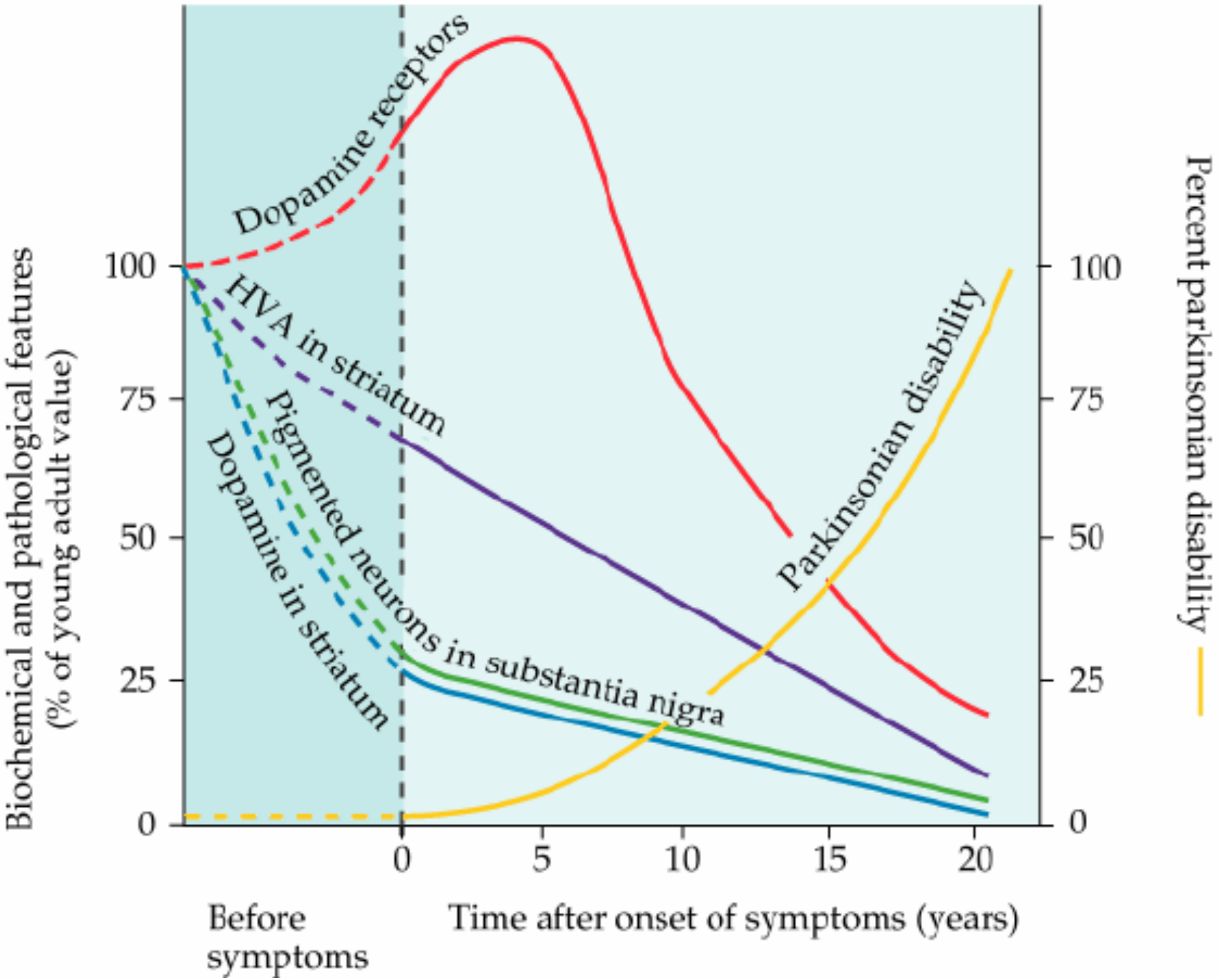
) Lateral view of brain showing location of primary motor cortex



(*b*) Representation of the body in primary motor cortex



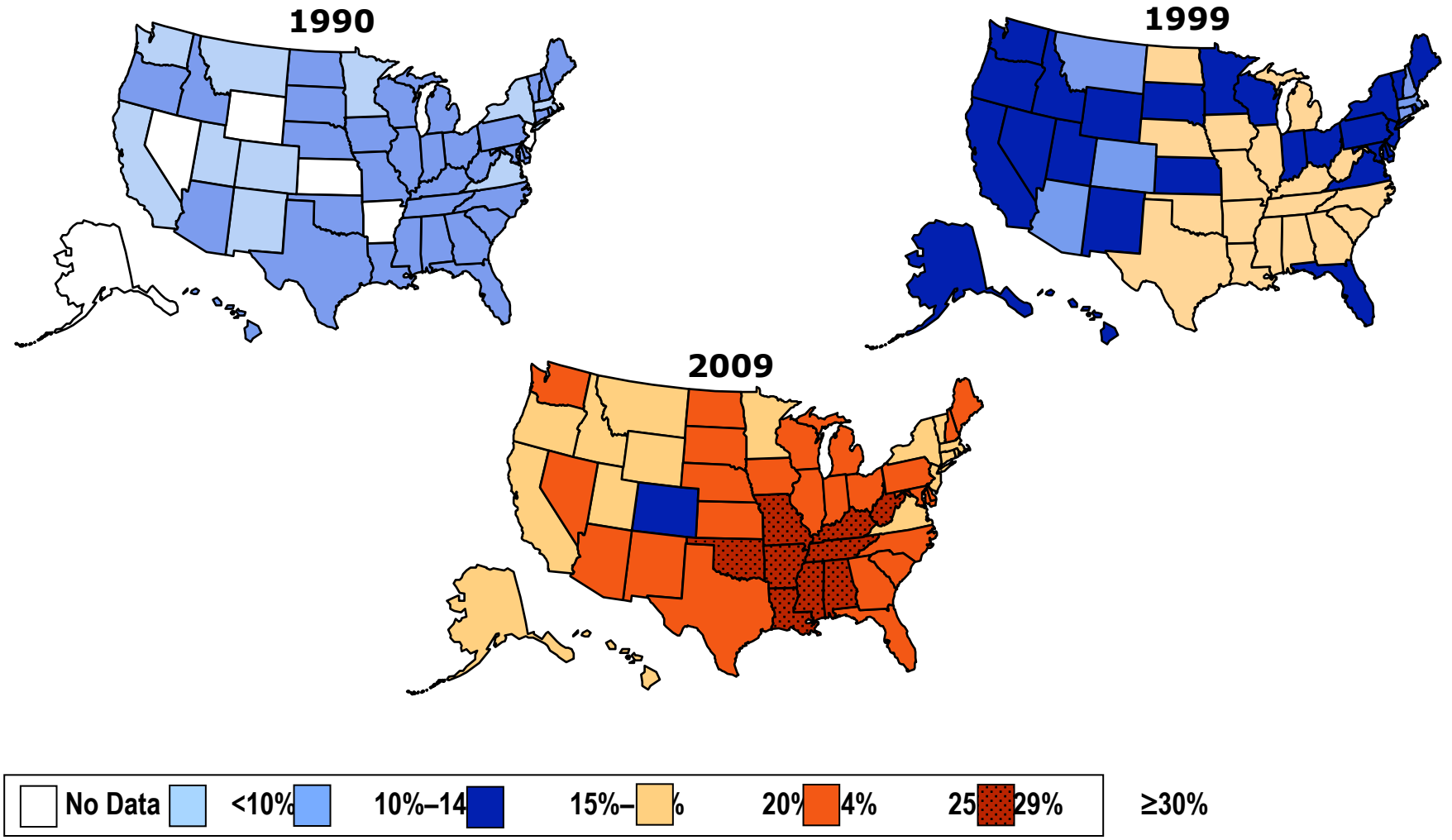

sky NEWS

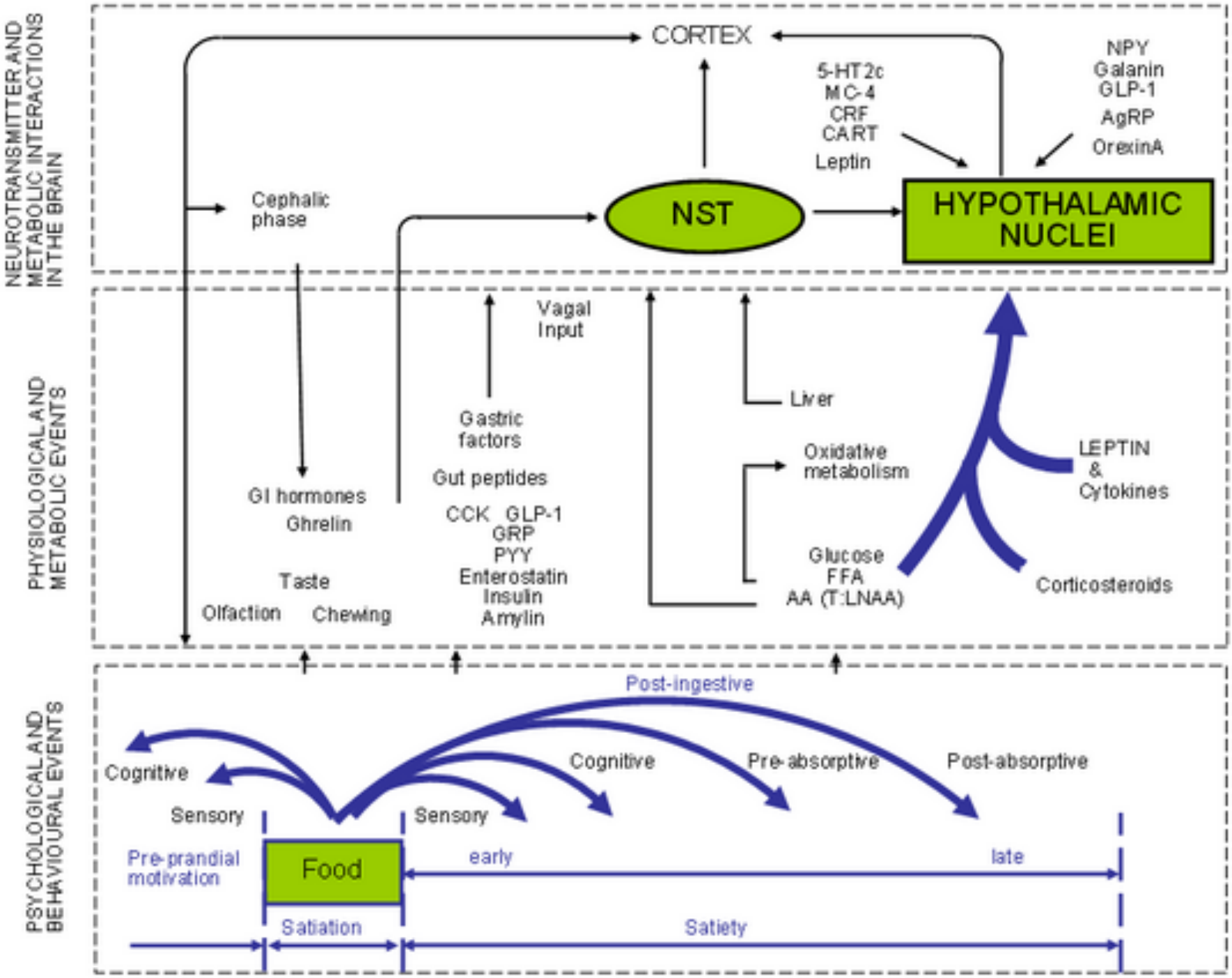

Biochemical and pathological features
(% of young adult value)
Percent parkinsonian disability
Dopamine receptors
HVA in striatum
Pigmented neurons in substantia nigra
Dopamine in striatum
Parkinsonian disability
100
75
50
25
0
0
5
10
15
20
Before symptoms
Time after onset of symptoms (years)

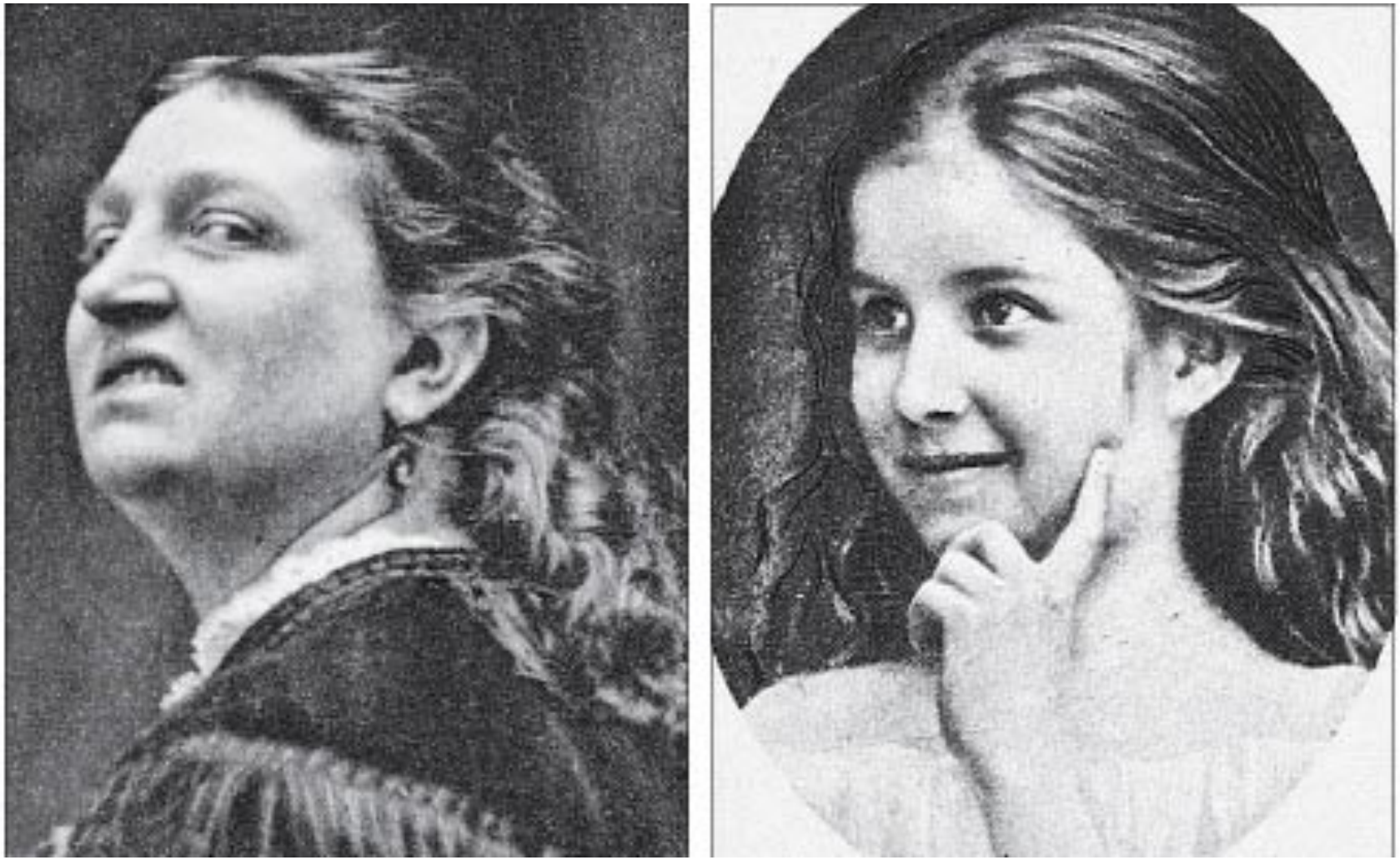
Obesity Trends* Among U.S. Adults

BRFSS, 1990, 1999, 2009

(*BMI ≥30, or about 30 lbs. overweight for 5' 4" person)



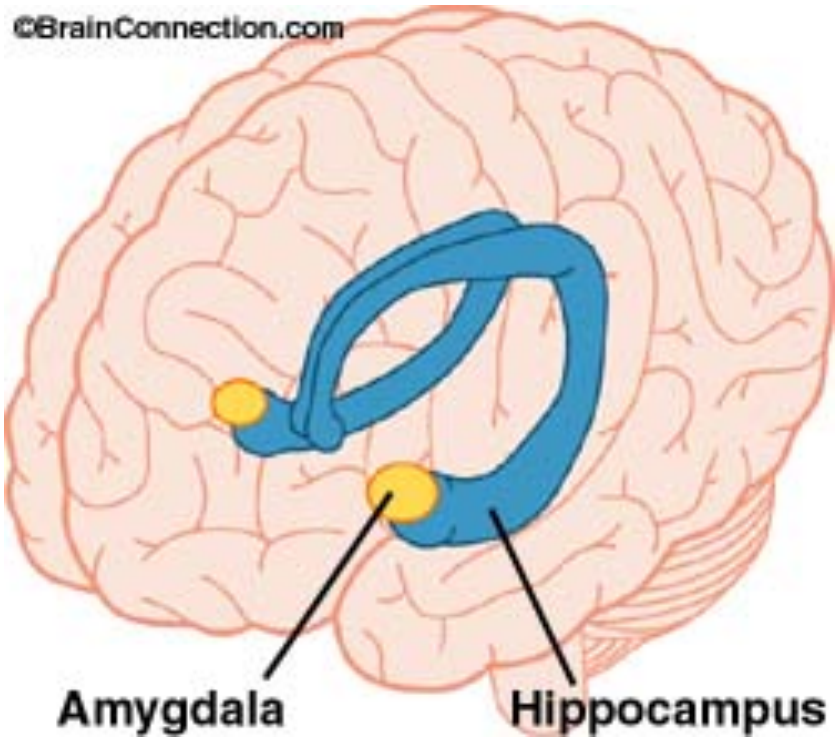

NEUROTRANSMITTER AND METABOLIC INTERACTIONS IN THE BRAIN
CORTEX
5-HT2c
MC-4
CRF
CART
Leptin
NPY
Galanin
GLP-1
AgRP
OrexinA
Cephalic phase
NST
HYPOTHALAMIC NUCLEI
PHYSIOLOGICAL AND METABOLIC EVENTS
Vagal Input
Liver
Gastric factors
Oxidative metabolism
LEPTIN & Cytokines
GI hormones
Ghrelin
Gut peptides
CCK GLP-1
GRP
PYY
Enterostatin
Insulin
Amylin
Glucose
FFA
AA (T:LNAA)
Corticosteroids
Taste
Olfaction
Chewing
PSYCHOLOGICAL AND BEHAVIOURAL EVENTS
Post-ingestive
Cognitive
Cognitive
Pre-absorptive
Post-absorptive
Sensory
Sensory
Pre-prandial motivation
Food
early
late
Satiation
Satiety

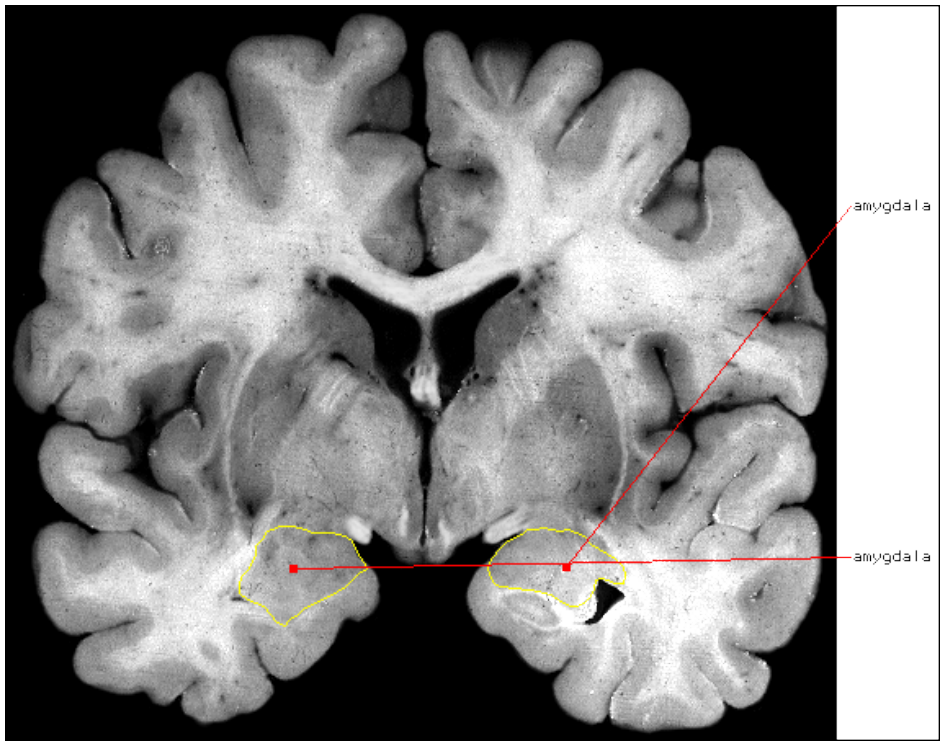


Hatred and love from Darwin's book The Expression of the Emotions in Man and Animals. The images form part of Mark Haddon's piece 24 Emotions. Photograph: Natural History Museum

Rivière. "Dog approaching another dog with hostile intentions" In: ***The expression of the emotions in man and animals London: John Murray, 1872***

mygdala and fear





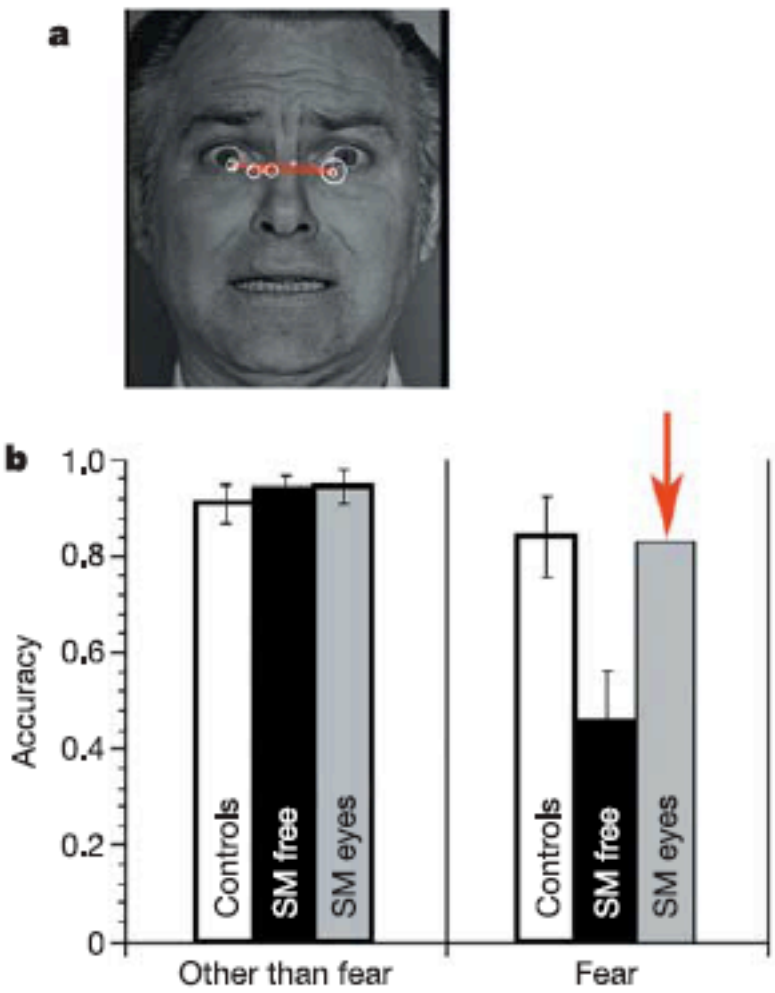
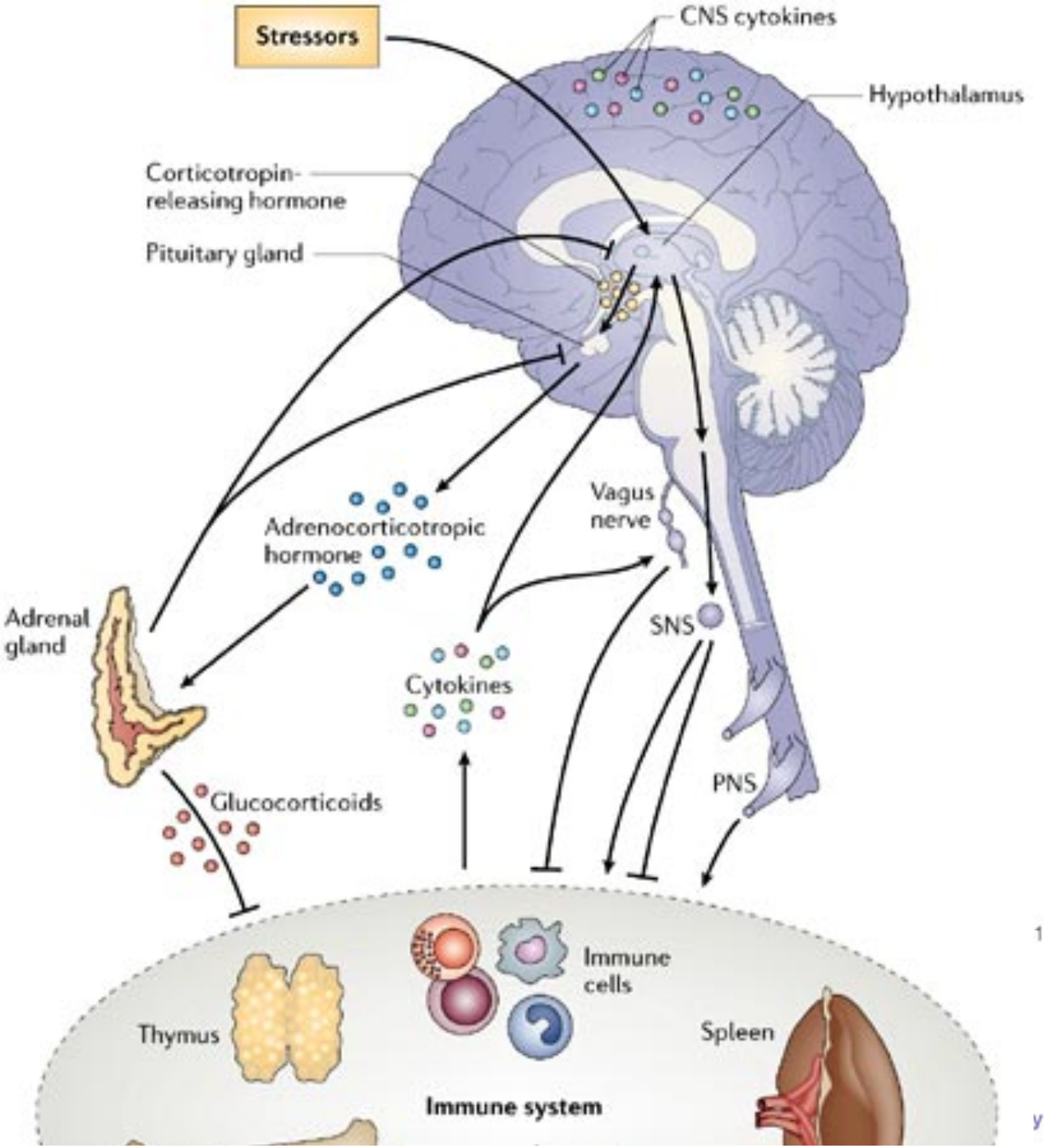
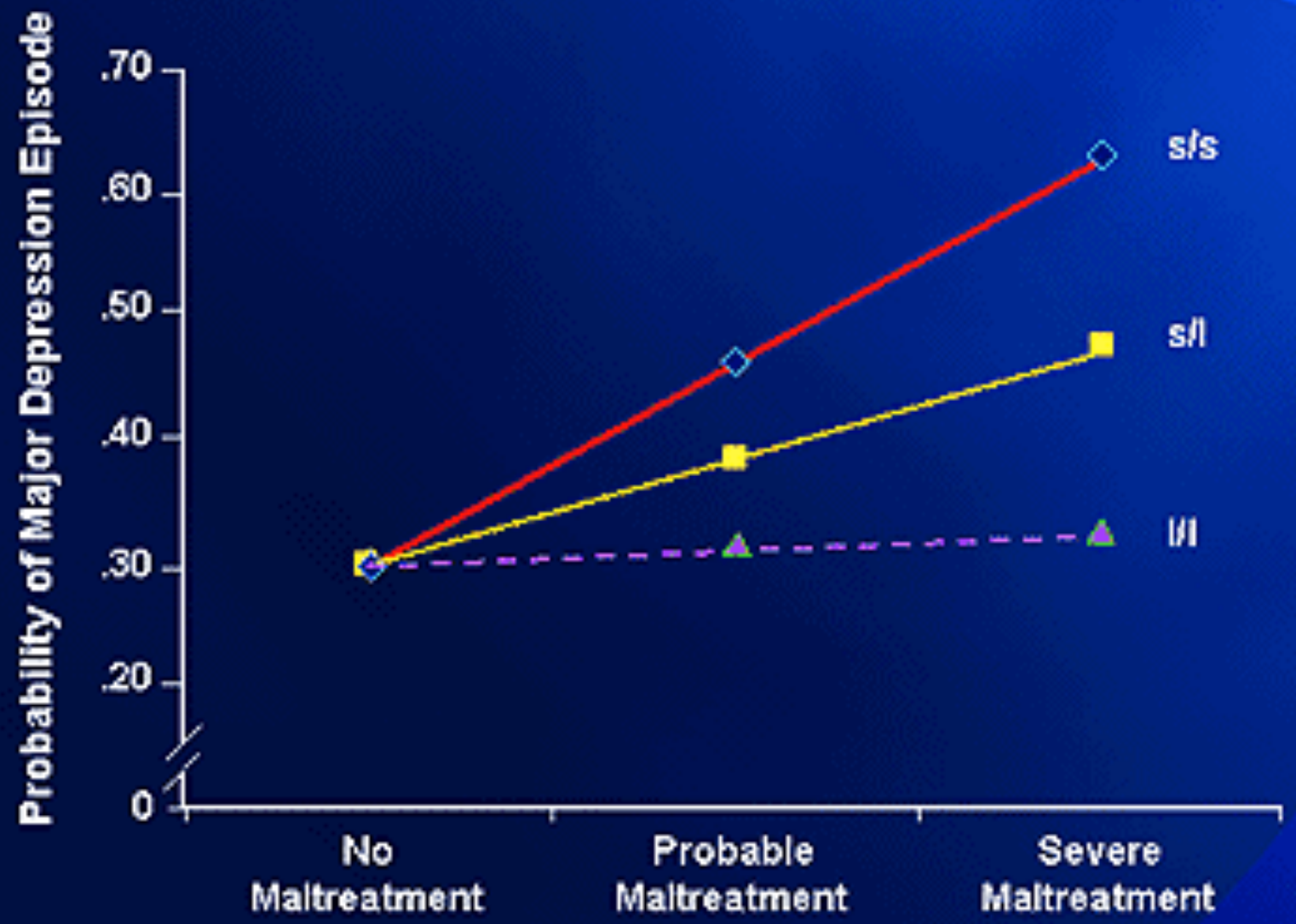


Figure 3 Instructed viewing of the eyes improves impaired fear recognition in SM. **a**, When instructed to fixate on the eyes in facial expressions of fear, SM is able to do so. **b**, Accuracy of emotion recognition (±s.e.m.) for ten control subjects (white) and SM. Whereas SM's recognition of fear is impaired when allowed to look at the stimuli freely (SM free, black bars), her performance becomes normal relative to control subjects when instructed to fixate on the eyes (SM eyes, grey bar, red arrow). The impairment is specific to fear recognition (left panel shows mean recognition accuracy for all emotions other than fear).

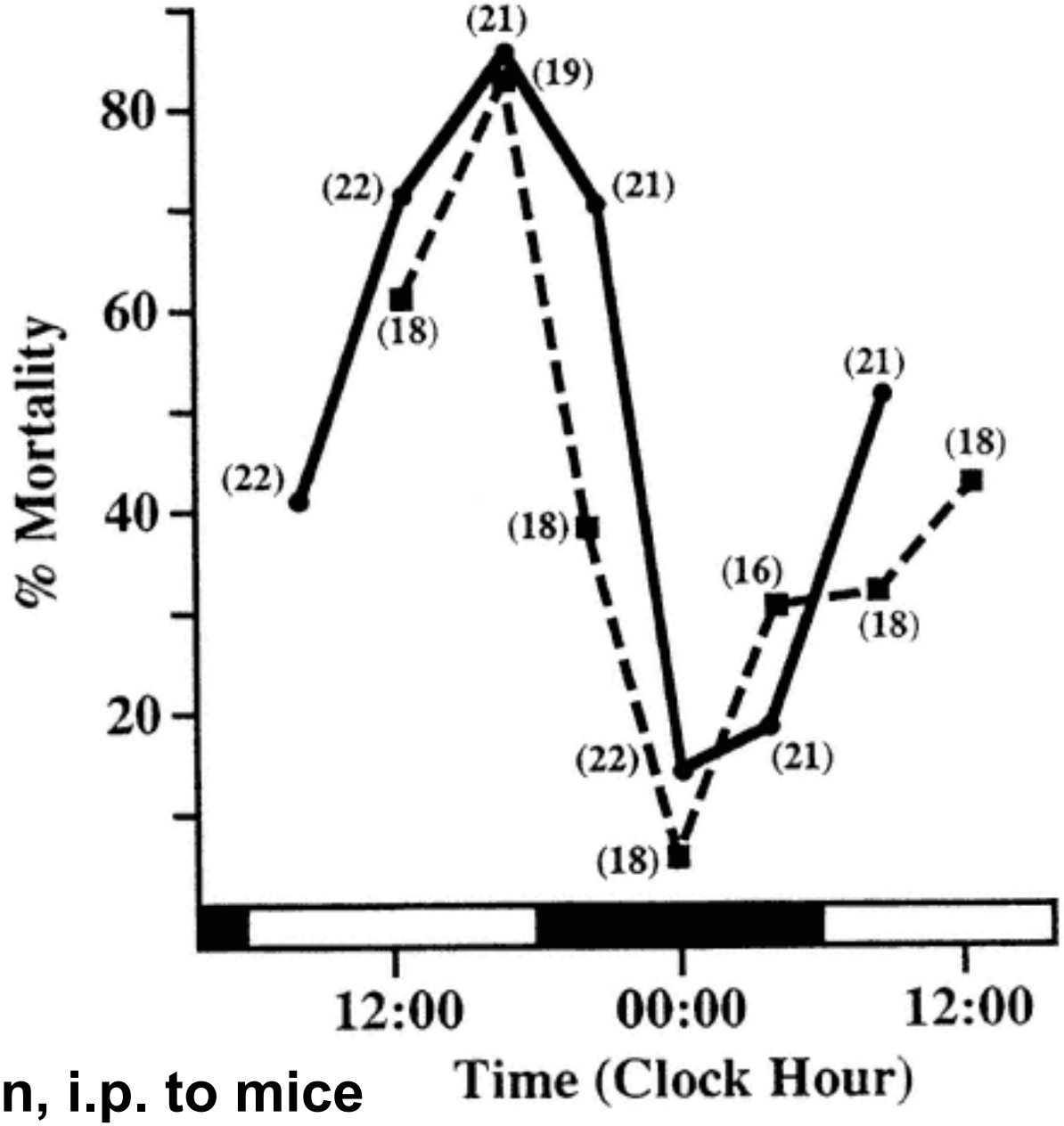
Stress


Stressors
CNS cytokines
Hypothalamus
Corticotropin-releasing hormone
Pituitary gland
Adrenocorticotropic hormone
Vagus nerve
Adrenal gland
SNS
Cytokines
Glucocorticoids
PNS
Immune cells
Thymus
Spleen
Immune system

5HTT Polymorphism and MDD

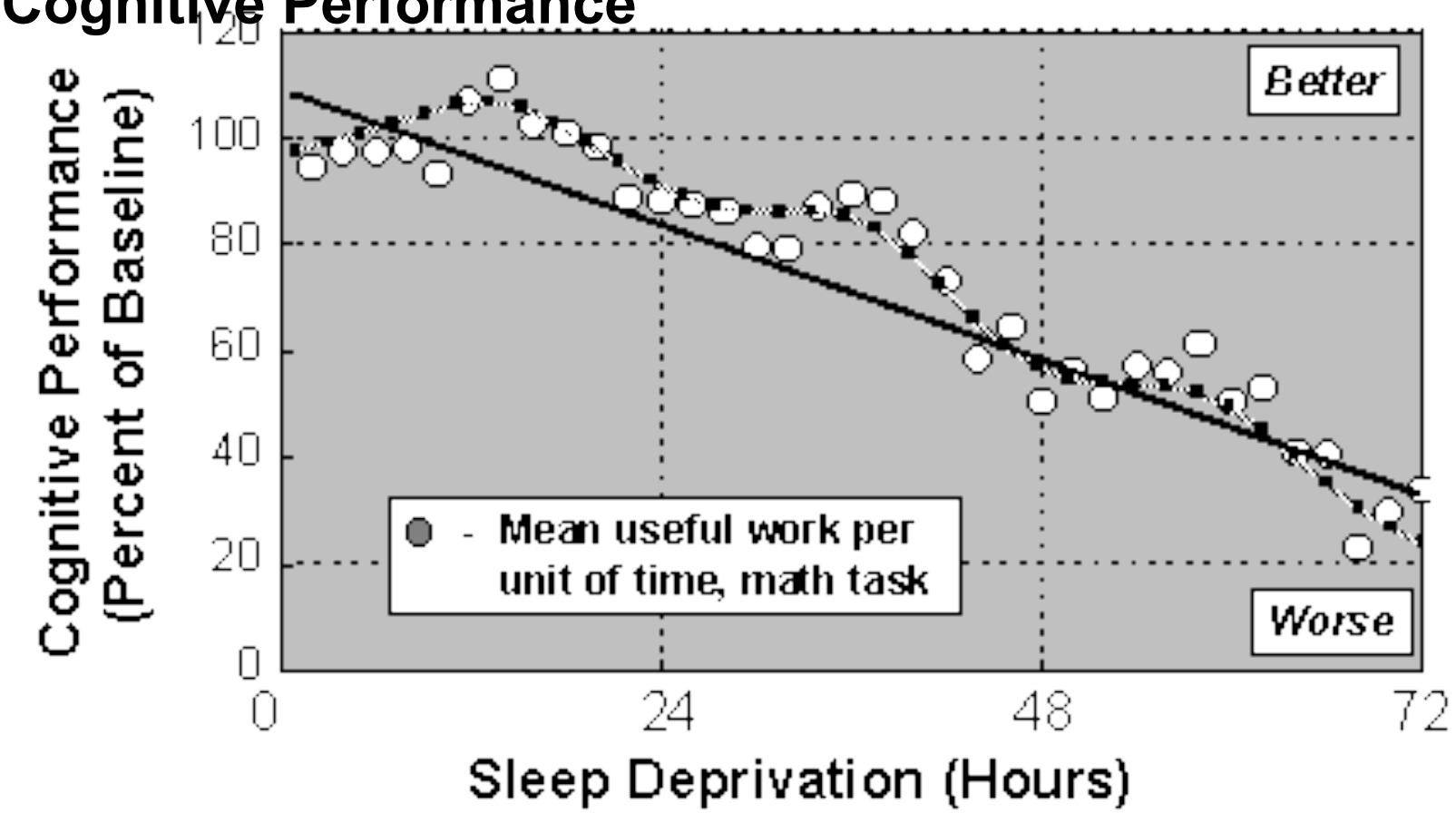


Reprinted with permission from Caspi A, Sugden K, Moffitt TE, et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science*. 2003;301:386-389. © 2003 AAAS.



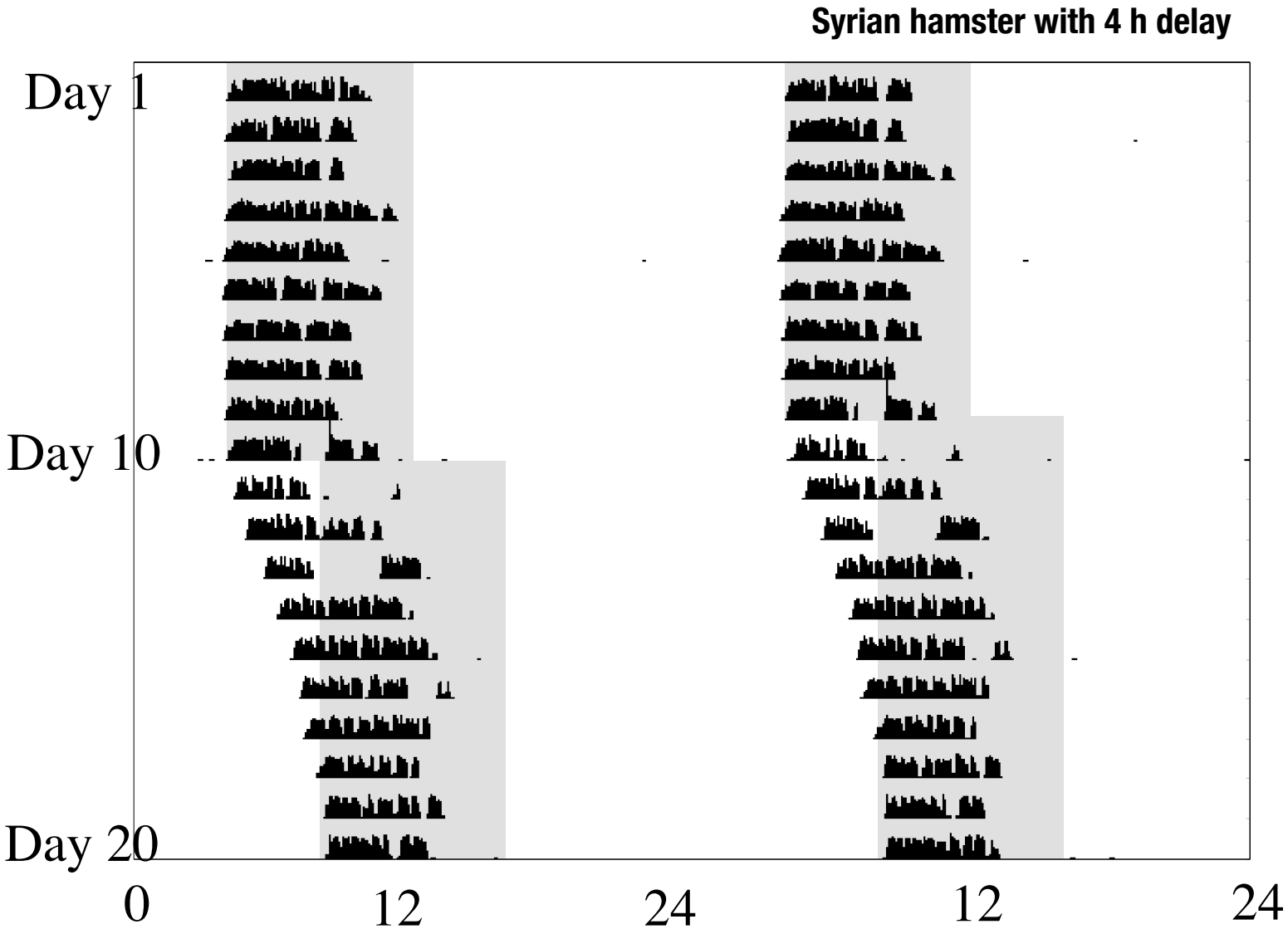
E. Coli endotoxin, i.p. to mice

Figure 2. Effect of 72 Hours of Total Sleep Deprivation on Cognitive Performance



NOTE: General trend for performance over time is downward (solid line), but in an undulating pattern that continues to reflect the daily performance rhythm (small squares).

Phase-shifting is slow business



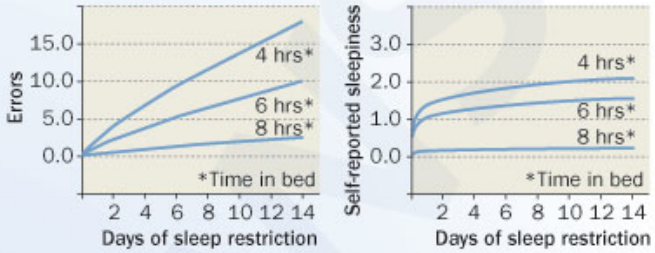
Effects of sleep deprivation

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



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

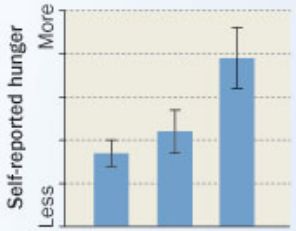
Thymus

Immune system impairment

Stomach

Increased hunger

Hunger and sleep

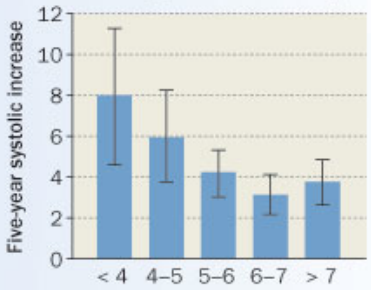


SOURCE: SCHMID *ET AL./ J. SLEEP RESEARCH* 2008

Heart

Higher disease risk, irregular heart beat

Blood pressure and sleep



SOURCE: KNUTSON *ET AL./ARCHIVES OF INTERNAL MEDICINE* 2009

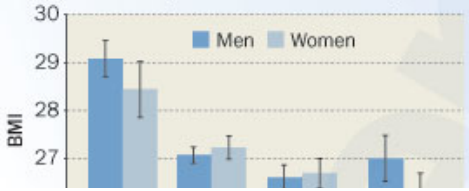
Pancreas

Insulin resistance and higher risk of type 2 diabetes

Fat layer

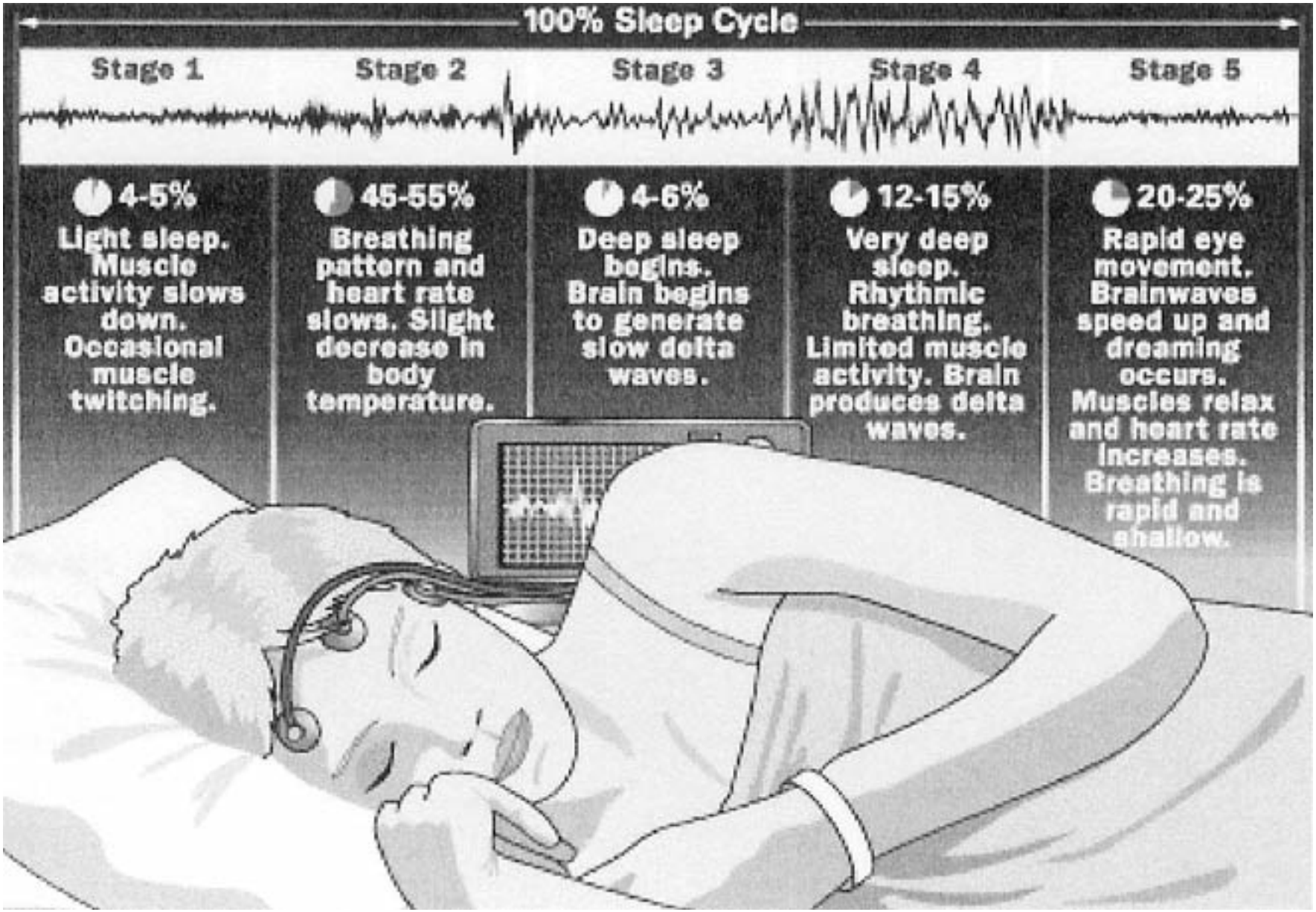
Increased risk of obesity

Body mass index and sleep



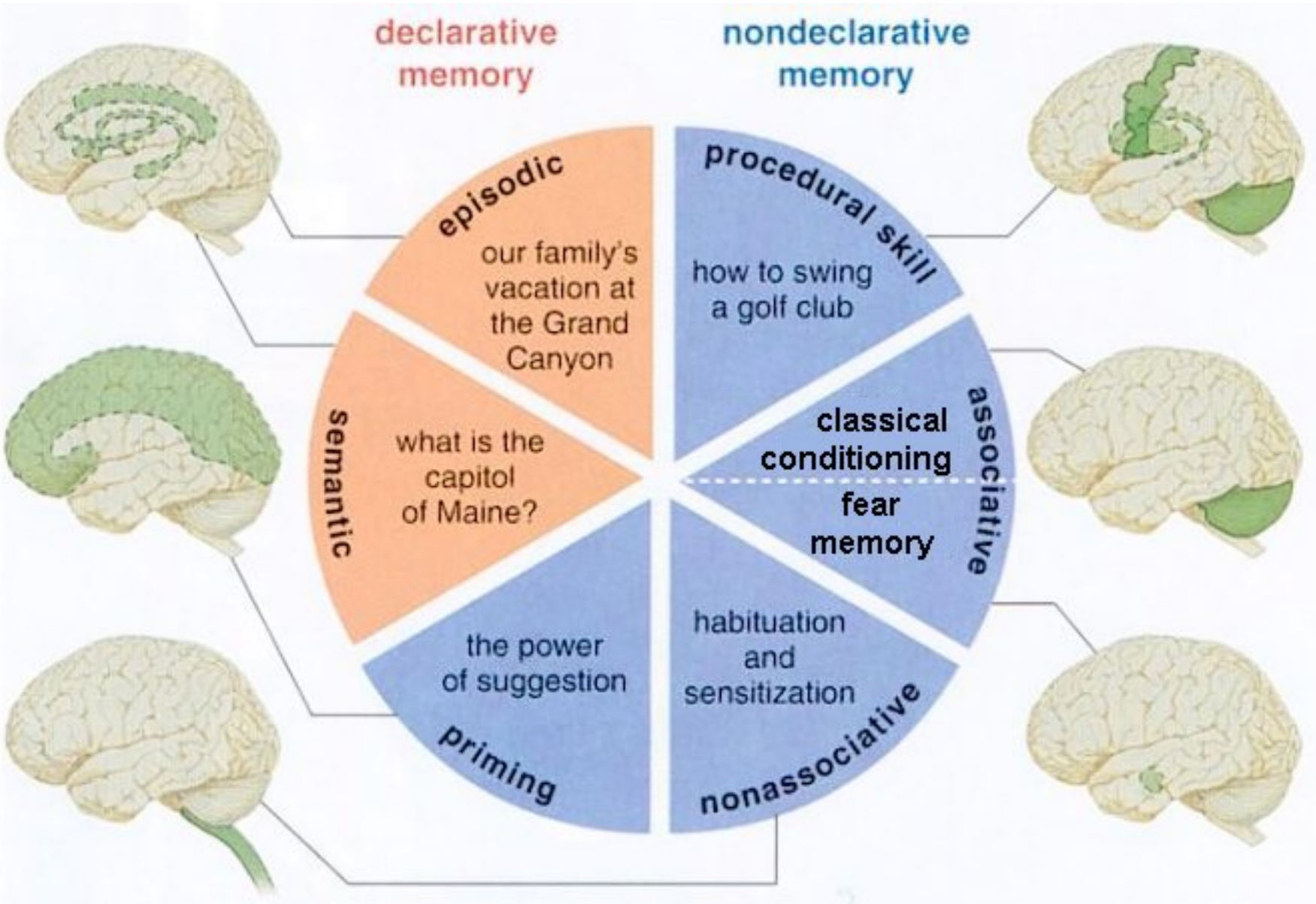
Joints

Increased inflammation, which can lead to atherosclerosis (artery hardening) and rheumatoid arthritis


100% Sleep Cycle
Stage 1
Stage 2
Stage 3
Stage 4
Stage 5
4-5%
Light sleep. Muscle activity slows down. Occasional muscle twitching.
45-55%
Breathing pattern and heart rate slows. Slight decrease in body temperature.
4-6%
Deep sleep begins. Brain begins to generate slow delta waves.
12-15%
Very deep sleep. Rhythmic breathing. Limited muscle activity. Brain produces delta waves.
20-25%
Rapid eye movement. Brainwaves speed up and dreaming occurs. Muscles relax and heart rate increases. Breathing is rapid and shallow.

CPAP

continuous positive airway pressure

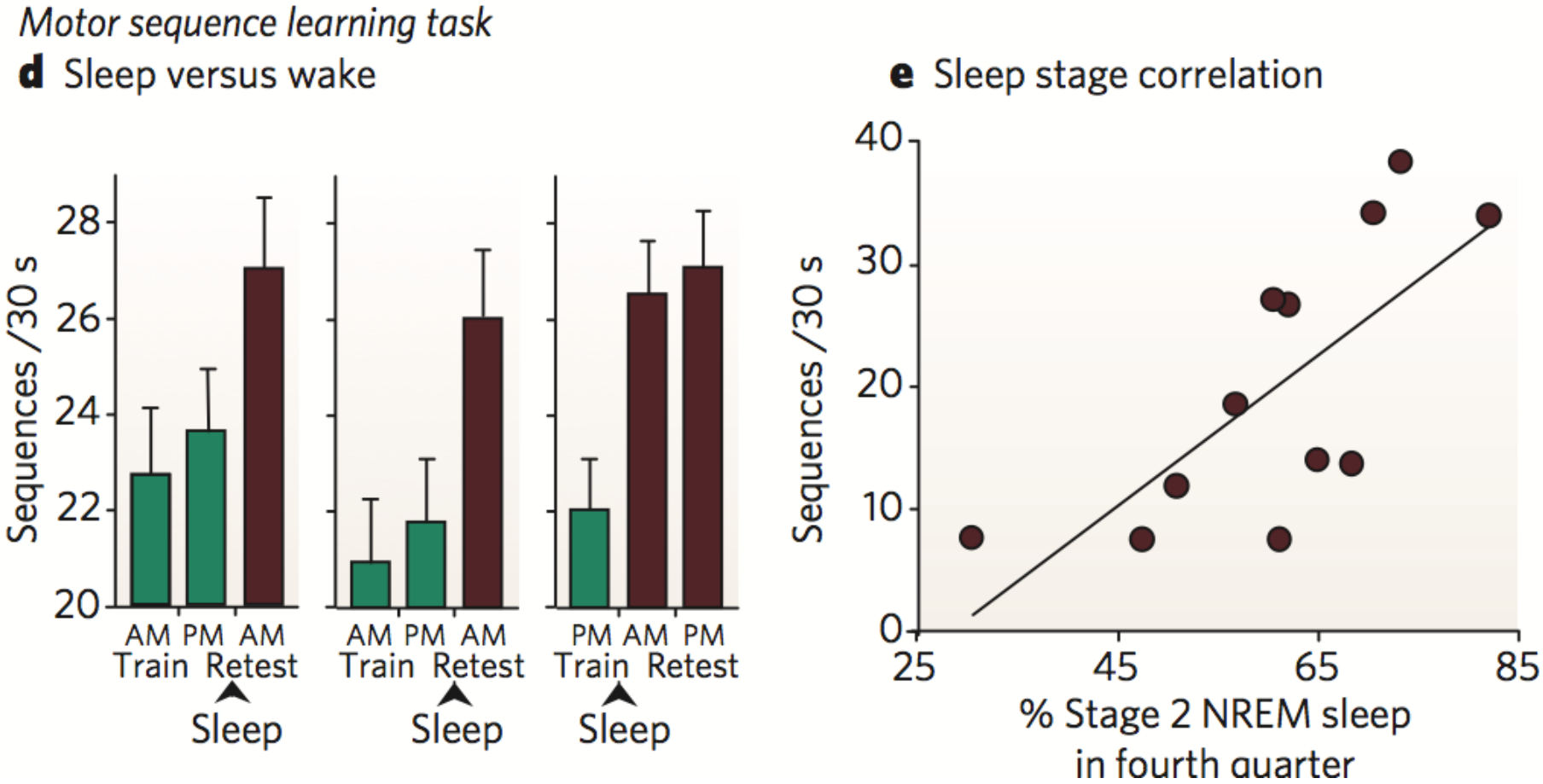

declarative memory
nondeclarative memory
episodic
our family's vacation at the Grand Canyon
semantic
what is the capitol of Maine?
priming
the power of suggestion
procedural skill
how to swing a golf club
associative
classical conditioning
fear memory
nonassociative
habituation and sensitization

Henry Molaison (H.M.)

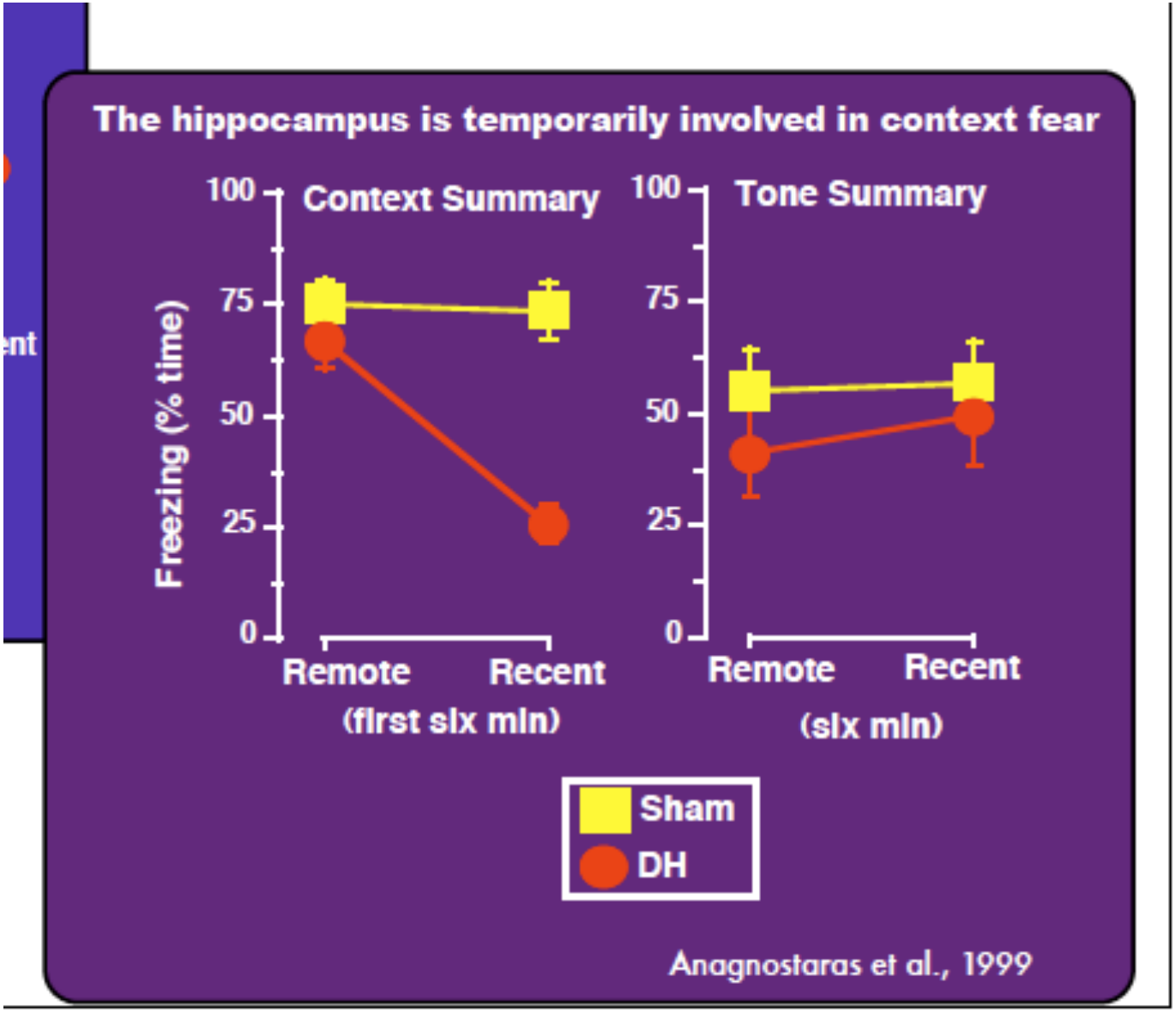
Most studied case of human amnesia
Severe seizures at age 16; surgery to remove epileptic focus at age 27 (1953)

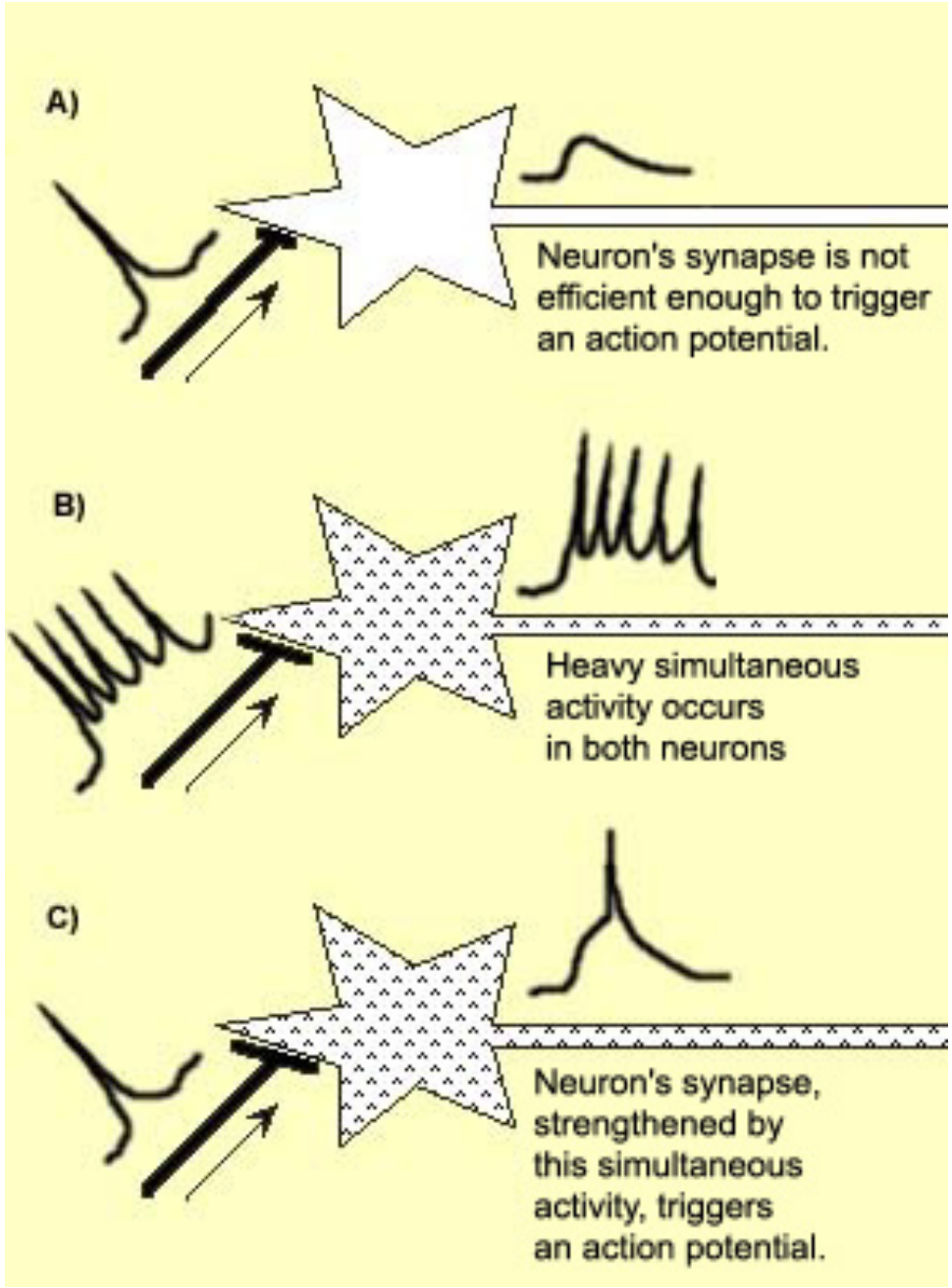
Severe memory loss - amnesia

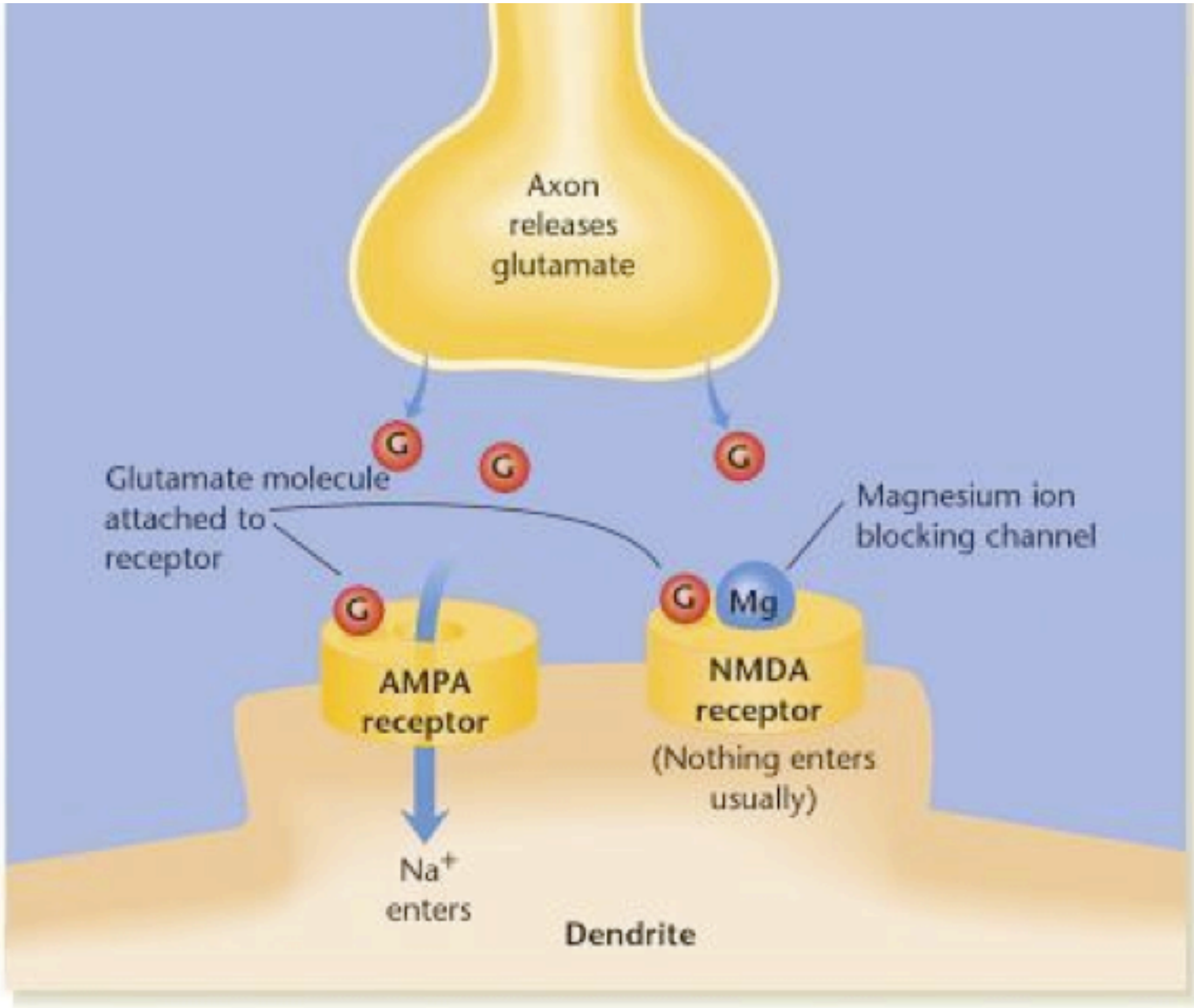
Sleep and Memory Consolidation

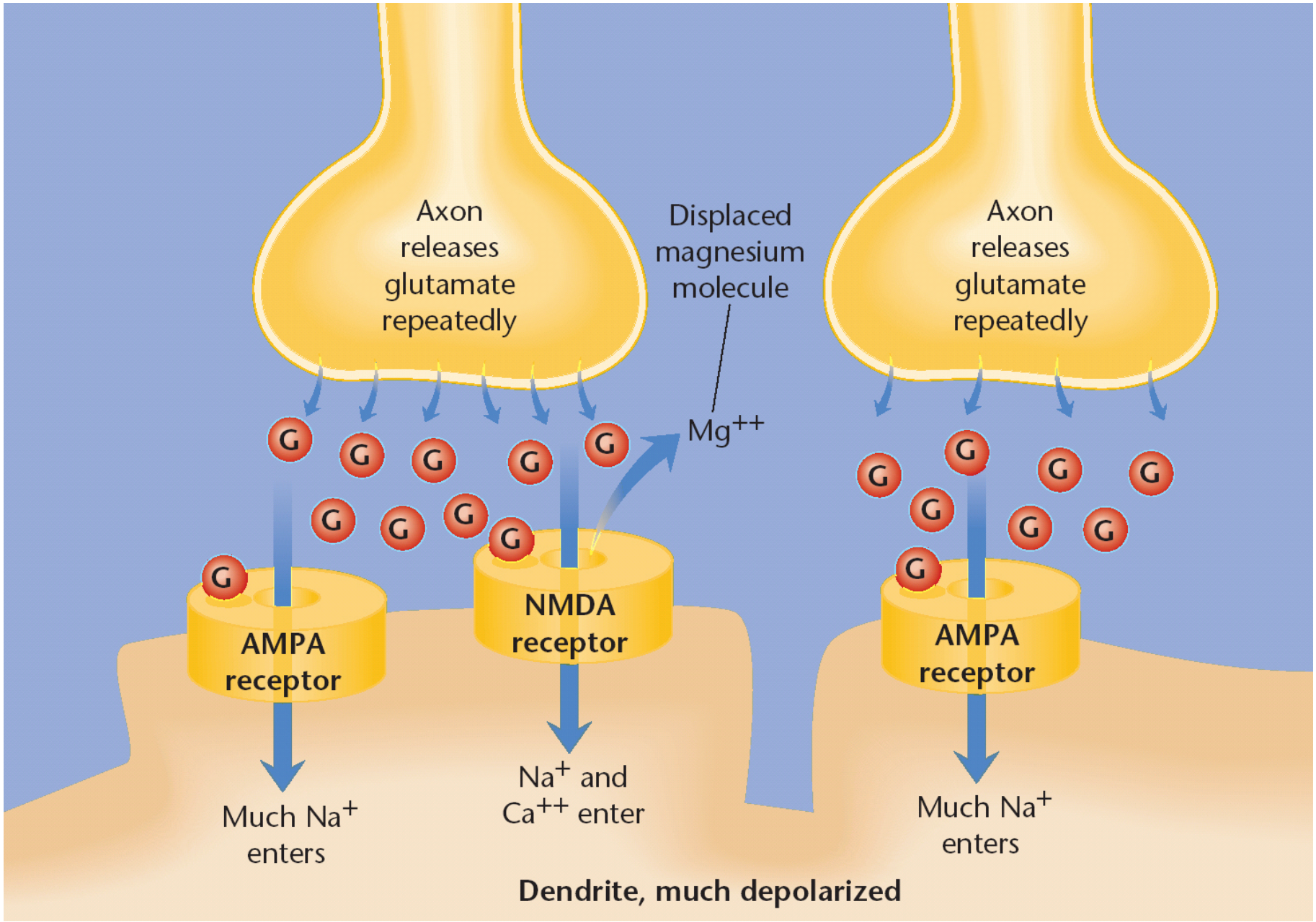


Wake first or sleep first


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


A)
Neuron's synapse is not efficient enough to trigger an action potential.
B)
Heavy simultaneous activity occurs in both neurons
C)
Neuron's synapse, strengthened by this simultaneous activity, triggers an action potential.


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


Axon releases glutamate repeatedly
Displaced magnesium molecule
Mg++
Axon releases glutamate repeatedly
G
AMPA receptor
NMDA receptor
AMPA receptor
Much Na+ enters
Na+ and Ca++ enter
Much Na+ enters
Dendrite, much depolarized

Reading scientific research articles

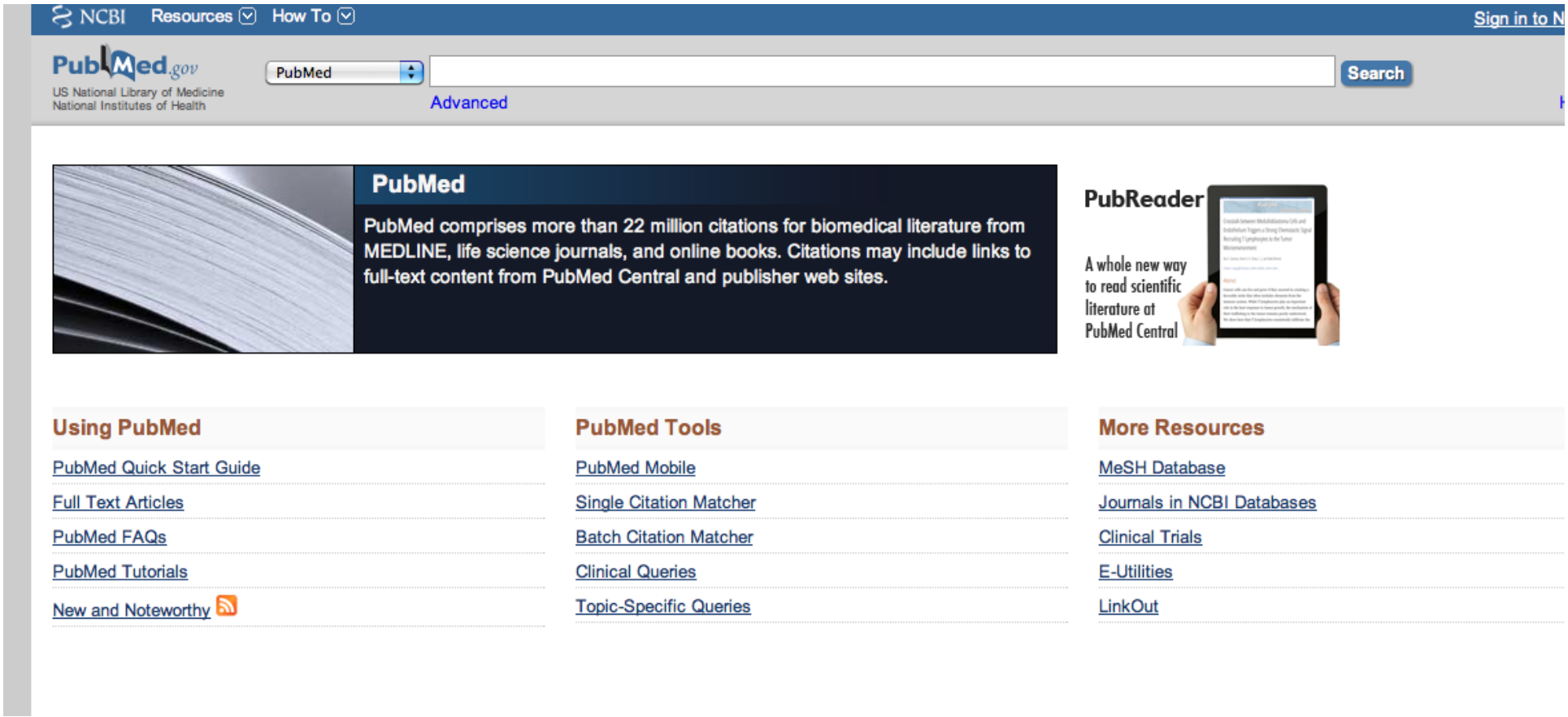
- Abstract
- Introduction
- Methods
- Results
- Discussion
- References

MEMORIZE THIS

www.pubmed.gov

And go to the site!!!

Abstracts on pubmed



SUMMARY

- **Brief tour – ~15 countries in 9 days**
- **Continuity of behavior across animals**
- **Incredible array of techniques for studying brain and behavior**

  Behavioral observation
  Environmental manipulations
  Electrophysiology
  Drug exposure
  Transplants
  Brain lesions
  Neurological patients
  Cell activity
  Gene expression
  fMRI
  Neuroanatomy
  Genetic manipulation
  Comparisons across species
  In vivo and in vitro
  Electrical stimulation

SUMMARY

- Brief tour – ~15 countries in 9 days
- Continuity of behavior across animals
- Incredible array of techniques for studying brain and behavior
- Understanding is cumulative and based on multiple sources of information
- New techniques are not magic bullets
- Incredible amount known!
- Very little known!

- We are incredibly complex creatures
- But we are made of physical parts
- We all have a relevant development past
- We also have an evolutionary past that shapes us

MANTRAS

- Biology is NOT determinism

- Brains produce behavior AND behavior changes brains

- Multiple approaches COMPLETE, don't COMPETE