

Memories are made of this,  
but what about intellect ?



Professor Keith Kendrick



# Memories are made of this, but what about intellect ?



'Everyone needs memories. They keep the wolf of insignificance from the door.'

Saul Bellow



'Memory is what tells a man that his wife's birthday was yesterday'

Mario Rocca



'The two offices of memory are collection and distribution'

Samuel Johnson

# Neuroscience and the Pharmaceutical industry

## Learning & Memory is big business

The screenshot shows a Microsoft Internet Explorer browser window displaying the Society for Neuroscience website. The browser's address bar shows the URL <http://web.sfn.org/AC3pluh.cfm>. The website header includes the Society for Neuroscience logo and navigation links for Login, Directory, Merchandise, Contact Us, Site Map, and Home. A large banner image depicts a busy meeting scene with the text: "The SfN Annual Meeting is the premier forum for the latest neuroscience research across the field." Below the banner is a navigation menu with links for ABOUT THE MEETING, ABSTRACTS/SYMPOSIA, SESSIONS/EVENTS, HOTEL/TRAVEL, REGISTRATION, ATTENDEE/SPEAKER RESOURCES, and EXHIBITS. The main content area features a vertical sidebar on the left with the text "Annual Meeting" and a main section titled "Neuroscience 2003".

**Neuroscience 2003**

**Record Attendance at Society for Neuroscience 33rd Annual Meeting, New Orleans**

More than 28,800 neuroscientists and their colleagues met in New Orleans for Neuroscience 2003, from Saturday, November 8, to Wednesday, November 12. The Society for Neuroscience Annual Meeting is the premier venue for neuroscientists to meet and exchange the latest discoveries about the brain, spinal cord and nervous system.

SfN preserves the scientific excellence of the meeting while making it more user friendly for attendees. This year featured an increased number of cross-disciplinary lectures; improved Web-based information about the meeting; enhanced capabilities for the CD-ROM Itinerary Planner; and similar science, instrumentation and other

**Neuroscience 2004**

Plan to join us for Neuroscience 2004, SfN's 34th Annual Meeting, in San Diego, October 23-27, 2004.

**October 2004**

S	M	T	W	T	F	S
				1	2	
3	4	5	6	7	8	9
10	11	12	13	14	15	16
17	18	19	20	21	22	23
24	25	26	27	28	29	30
31						

The 2004 meeting starts **Saturday at 1:00 pm** and ends **Wednesday at 5:00 pm**.

**2003 Meeting Information Index**

# Neuroscience and the Pharmaceutical industry

Memory enhancer pills - 'magic bullets'

Licensed: Tacrine  
Aricept  
Exelon®  
Reminyl®  
Mermantine



# Neuroscience and the Pharmaceutical industry

Memory enhancer pills - 'magic bullets'

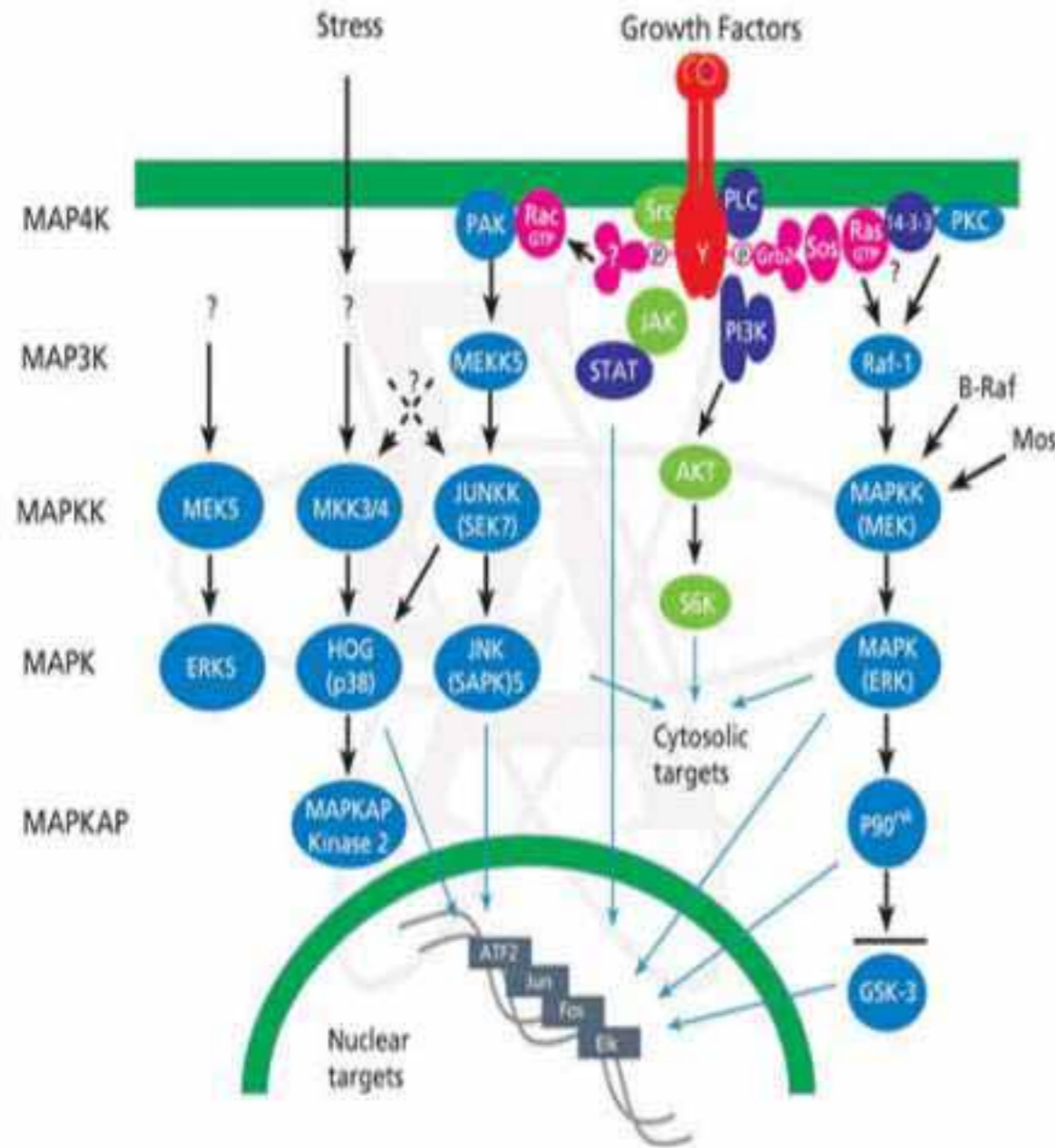
Licensed:	Tacrine	In clinical trials:	CX516 (Ampalex)
	Aricept		MKC-231
	Exelon®		
	Reminyl®		
	Mermantine		

Most only delay cognitive decline or produce mild improvements

They usually have side effects

# Reductionism vs holism

The molecular brain and sub-atomic particles



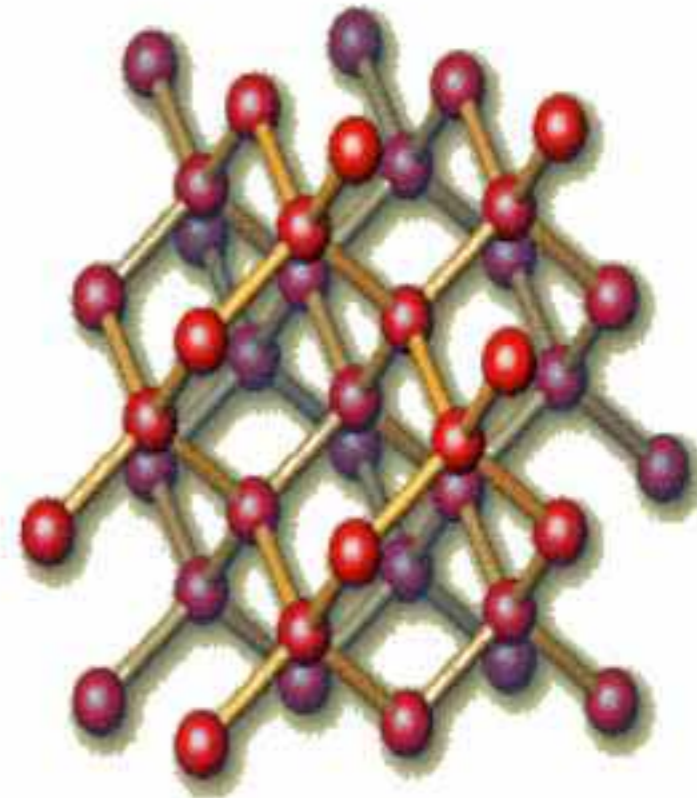
## Elementary Particles

Quarks	$u$ up	$c$ charm	$t$ top	$\gamma$ photon
	$d$ down	$s$ strange	$b$ bottom	
Leptons	$\nu_e$ electron neutrino	$\nu_\mu$ muon neutrino	$\nu_\tau$ tau neutrino	$Z$ Z boson
	$e$ electron	$\mu$ muon	$\tau$ tau	
	I	II	III	
Three Families of Matter				

# Reductionism vs holism

The molecular brain and sub-atomic particles

The search for more holistic explanations of function



# Statistics - the human brain

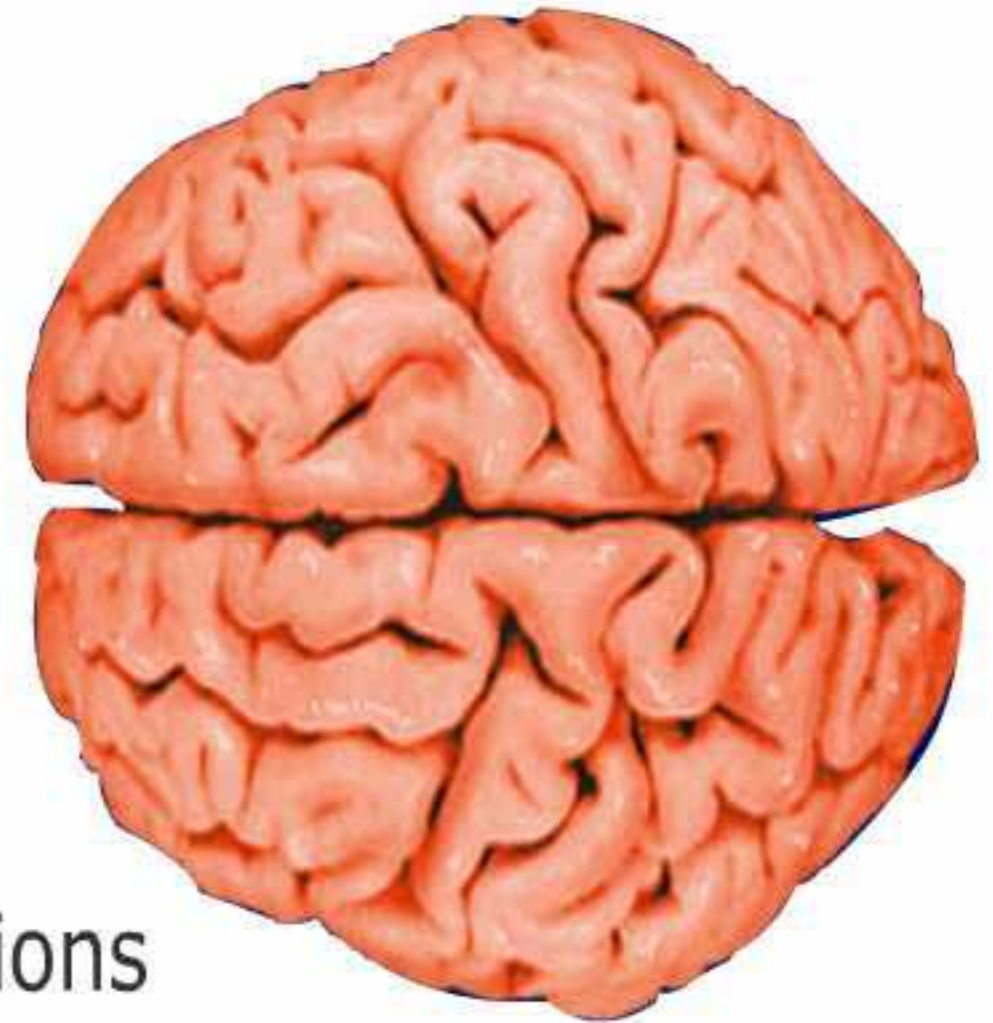
Size - 56 cubic inches

Weight 3lb

100 billion nerve cells ( $10^{11}$ )

1 quadrillion ( $10^{15}$ ) synaptic connections

10 quadrillion ( $10^{16}$ ) synapse operations per second





# Statistics - the human brain

Size - 56 cubic inches

Weight 3lb

100 billion nerve cells ( $10^{11}$ )

1 quadrillion ( $10^{15}$ ) synaptic connections

10 quadrillion ( $10^{16}$ ) synapse operations per second

10 watts !



# Statistics - supercomputers

ASCI Purple (IBM) - US Department of Energy

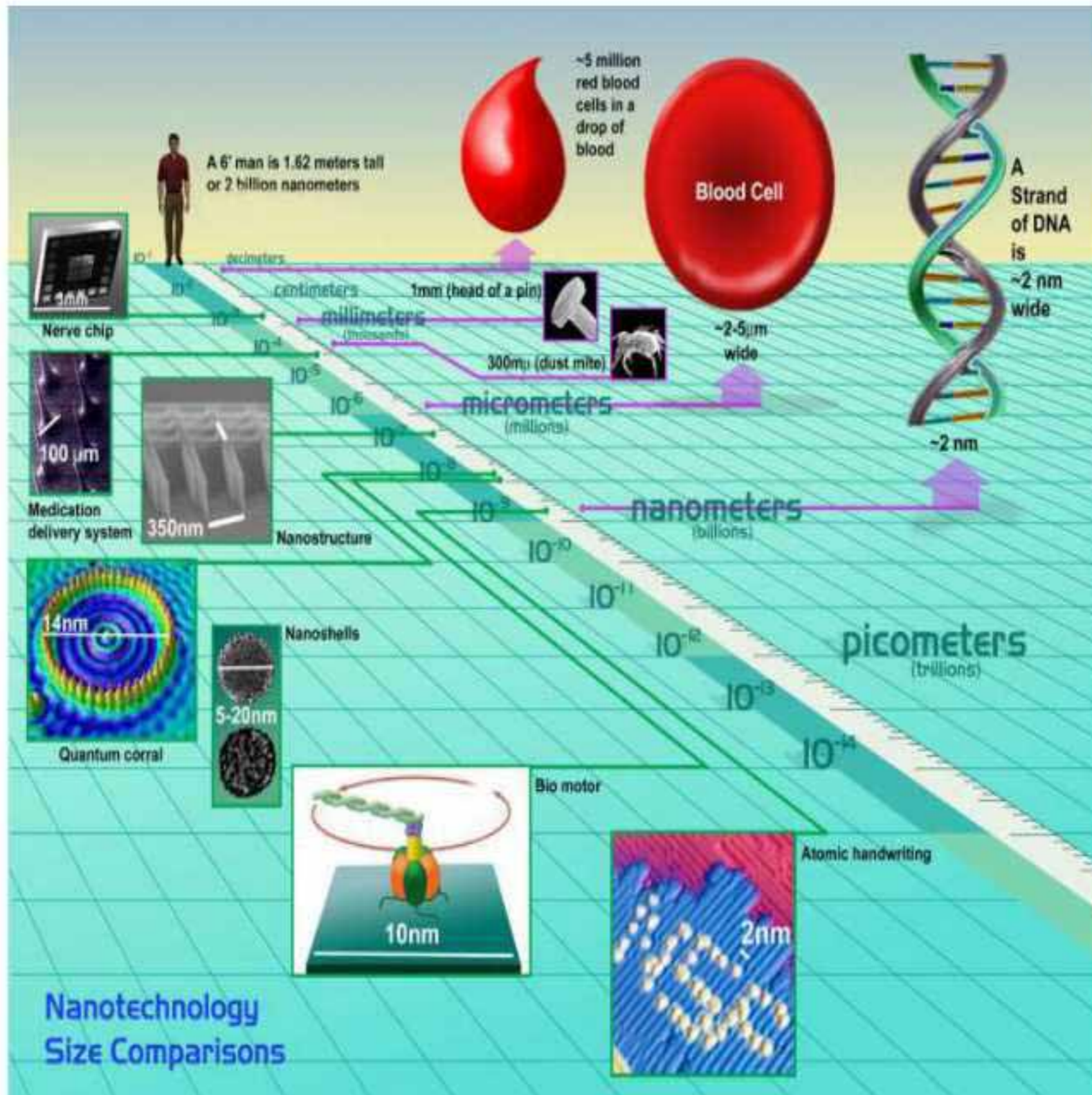
Size 8900 square feet

Weight 197 tons

500 trillion ( $5 \times 10^{14}$ )  
calculations per second



# Statistics - nanotechnology ?



# Statistics - comparisons

Processing power of human brain is considerable -  
information overload ?

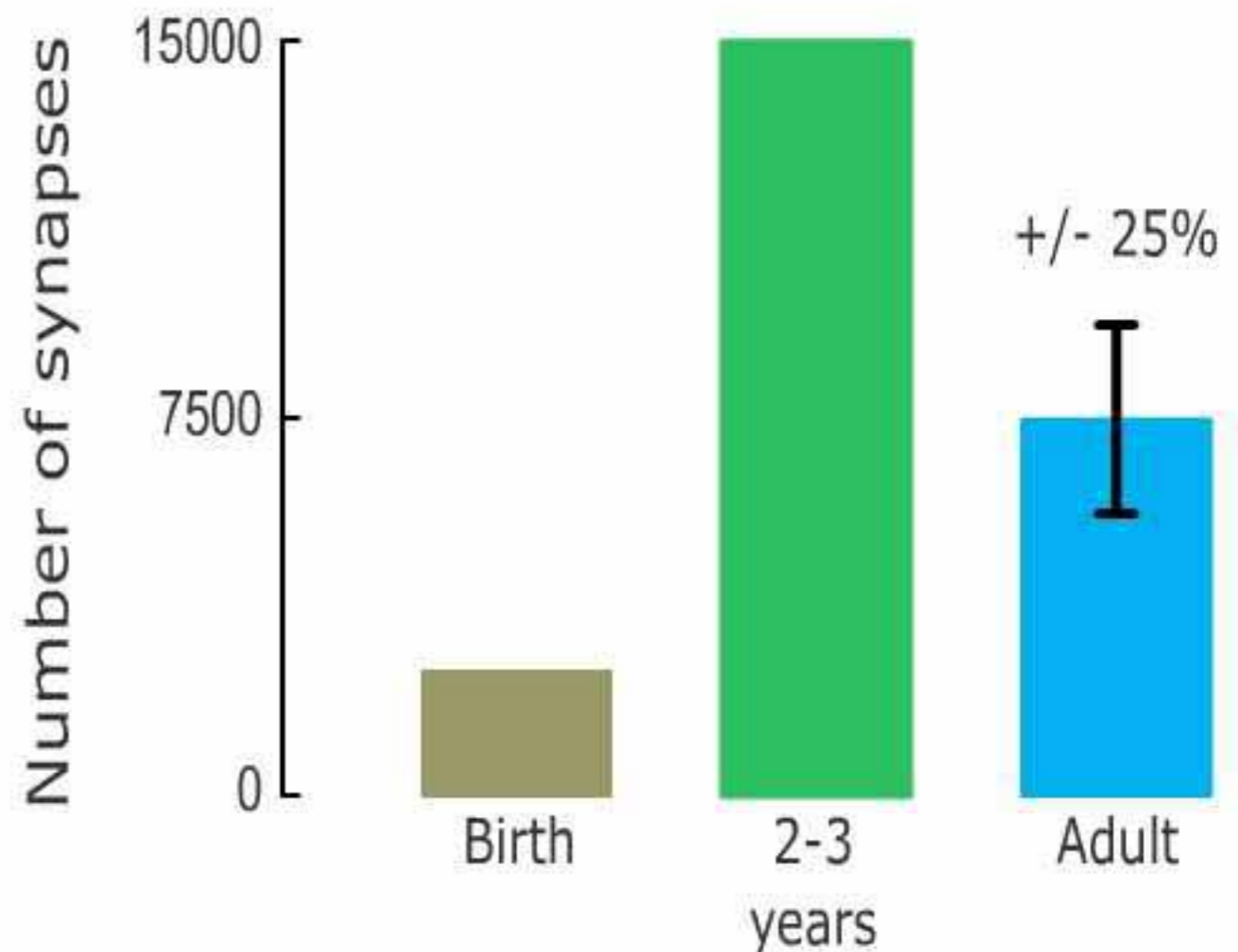


# Statistics - comparisons

Processing power of human brain is considerable - information overload ?

Direct comparisons between brains and computers are not appropriate

Brain development



# Statistics - comparisons

The brain is your own personal organiser:  
seeing the wood not the trees !



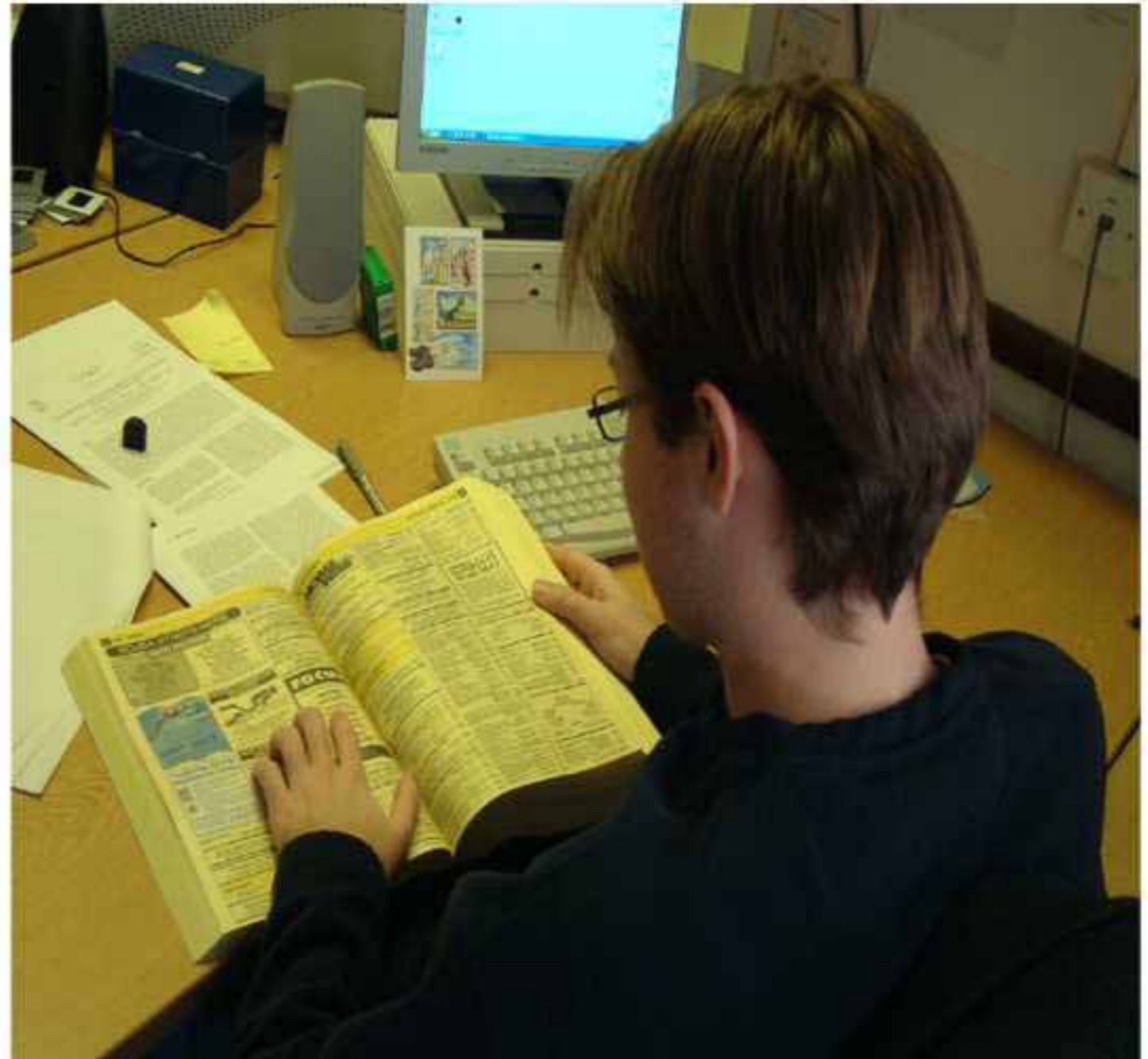
# Statistics - the final word !

Size doesn't matter as much as how you use it !



# What are the key memory processes ?

Short term





# What are the key memory processes ?

Short term

Consolidation

Long term



# Different types of enduring memories

Implicit or procedural



# Different types of enduring memories

Implicit or procedural

Explicit or declarative

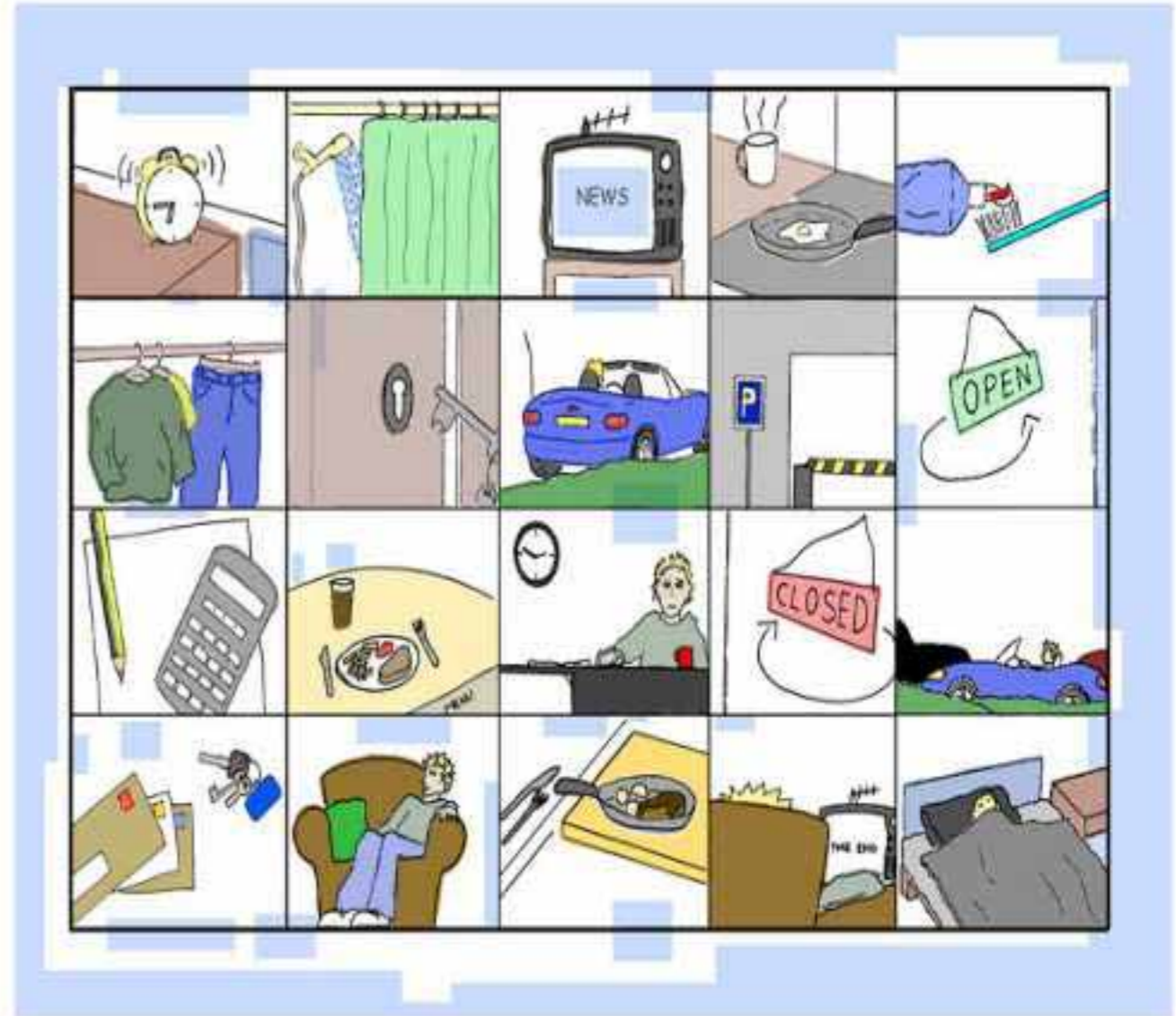


# Different types of enduring memories

Implicit or procedural

Explicit or declarative

Episodic or autobiographical  
- focal content and context



# Different types of enduring memories

Implicit or procedural

Explicit or declarative

Episodic or autobiographical  
- focal content and context

Semantic memory  
-memory representation  
stripped of context

Main Entry: **mem-ory** 🗨️

Pronunciation: 'mem-rɪ, 'me-mɔ-

Function: *noun*

Inflected Form(s): *plural -ries*

Etymology. Middle English *memorie*, from Middle French *memoire*, from Latin *memoria*, from *memor* mindful; akin to Old English *gemimor* well-known, Greek *memōra* care, Sanskrit *smarati* he remembers

Date: 14th century

**1 a** : the power or process of reproducing or recalling what has been learned and retained especially through associative mechanisms **b** : the store of things learned and retained from an organism's activity or experience as evidenced by modification of structure or behavior or by recall and recognition

**2 a** : commemorative remembrance <erected a statue in *memory* of the hero> **b** : the fact or condition of being remembered <days of recent *memory*>

**3 a** : a particular act of recall or recollection **b** : an image or impression of one that is remembered <fond *memories* of her youth> **c** : the time within which past events can be or are remembered <within the *memory* of living men>

**4 a** : a device or a component of a device in which information especially for a computer can be inserted and stored and from which it may be extracted when wanted **b** : capacity for storing information <four megabytes of *memory*>

**5** : a capacity for showing effects as the result of past treatment or for returning to a former condition -- used especially of a material (as metal or plastic)

**synonyms** MEMORY, REMEMBRANCE, RECOLLECTION, REMINISCENCE

## Example of the difference:

snake elephant flamingo hippopotamus human  
rat cat dog horse lion tiger bear

Semantic memory:

Which of these are mammals ?

Which of them are birds ?

## Example of the difference:

Episodic memory:

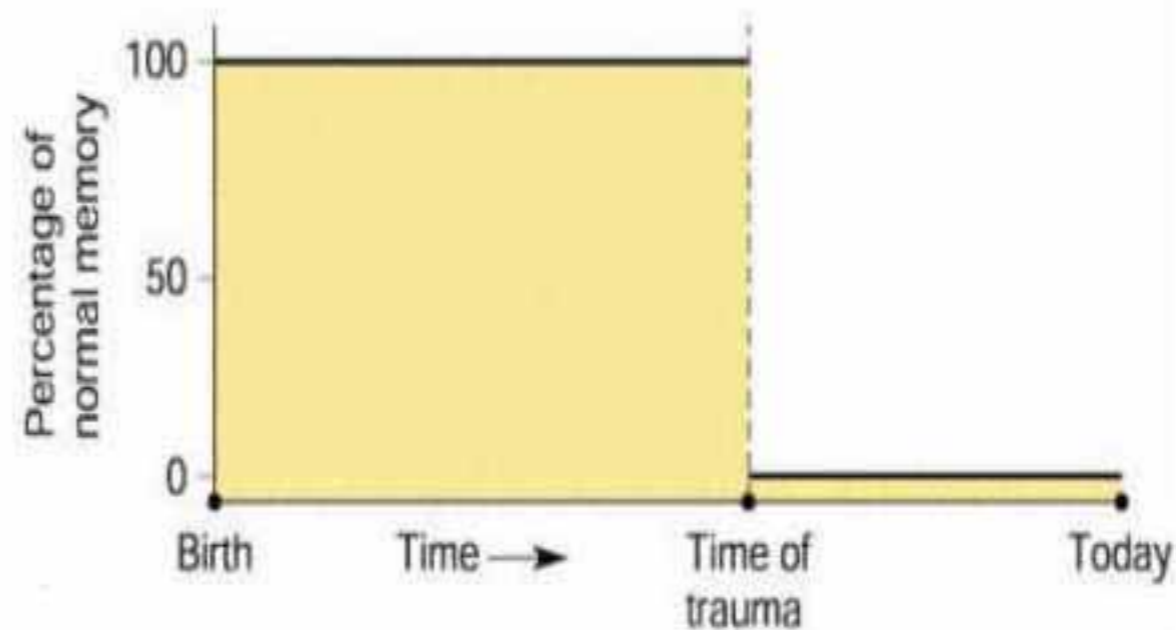
Was the word elephant in the list ?

Was the word giraffe in the list ?

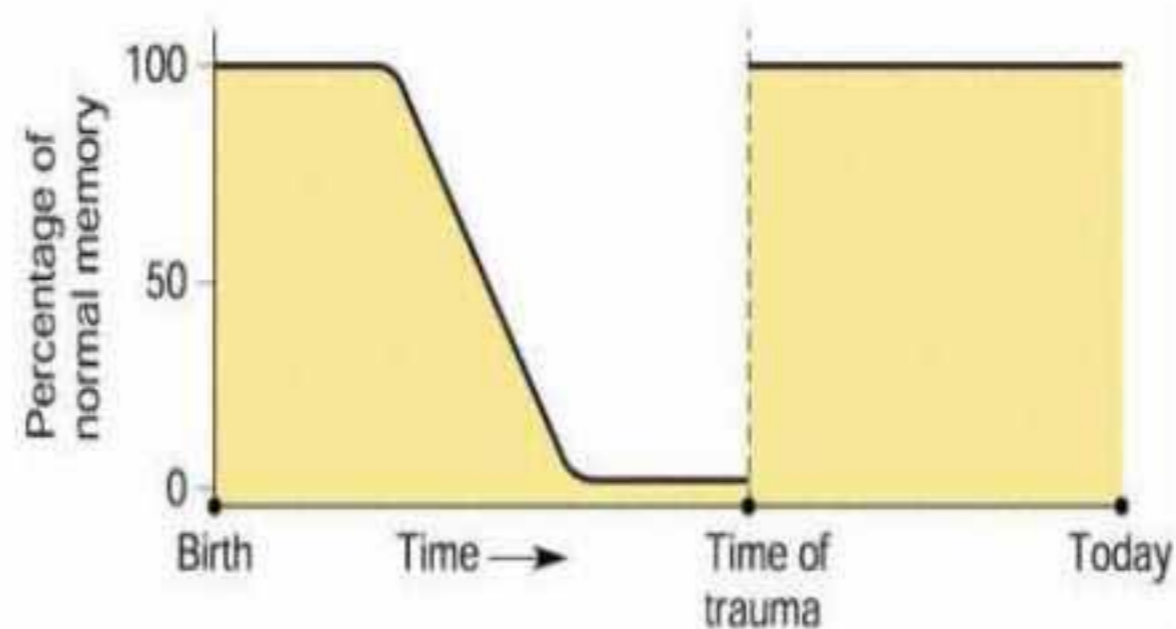
# Amnesia

Electroconvulsive shock - anterograde and retrograde amnesia

Anterograde amnesia



Retrograde amnesia - graded

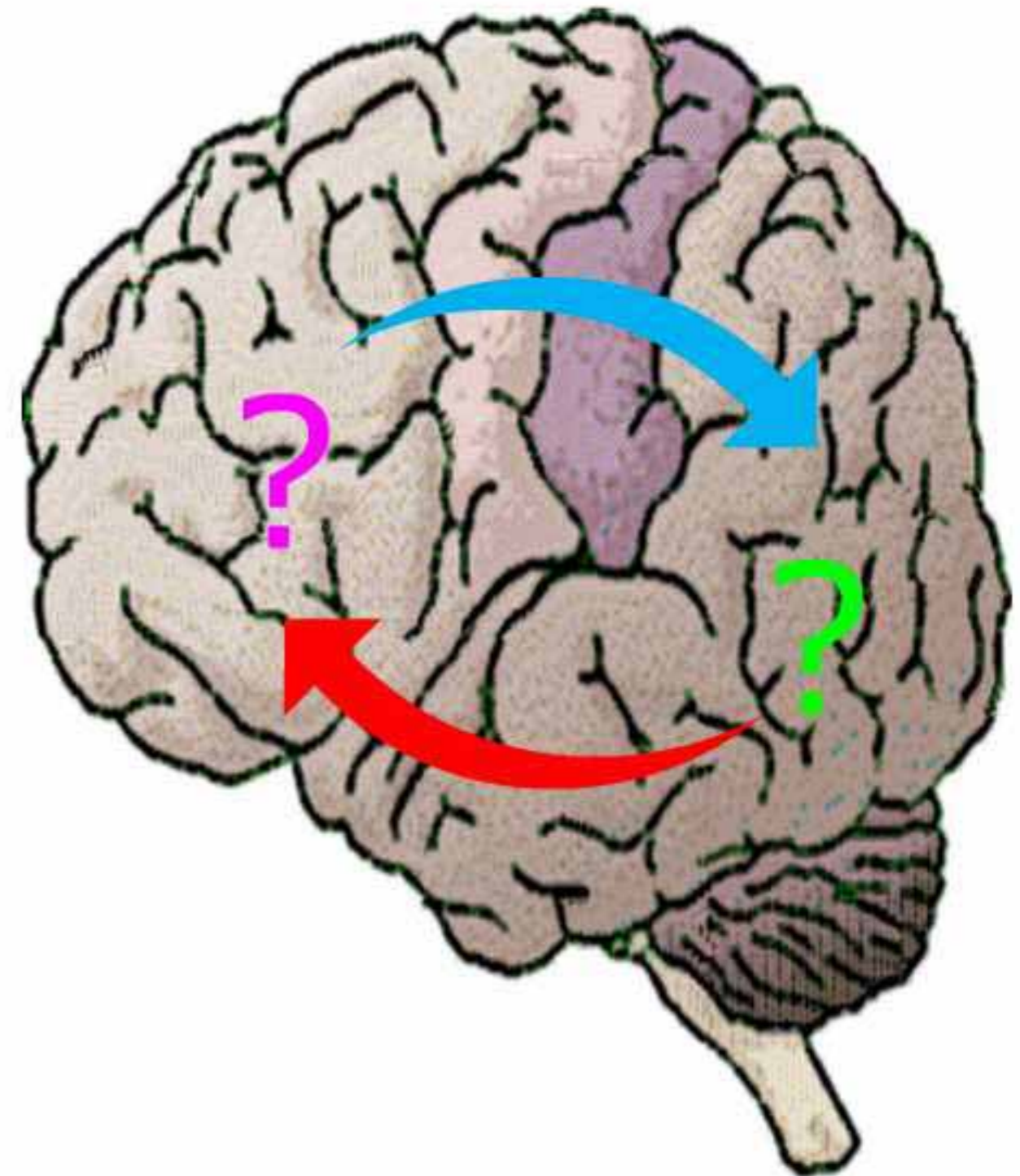




# The search for the engram

Where are the short and long-term memory stores in the brain ?

How does the process of consolidation shift information between them ?

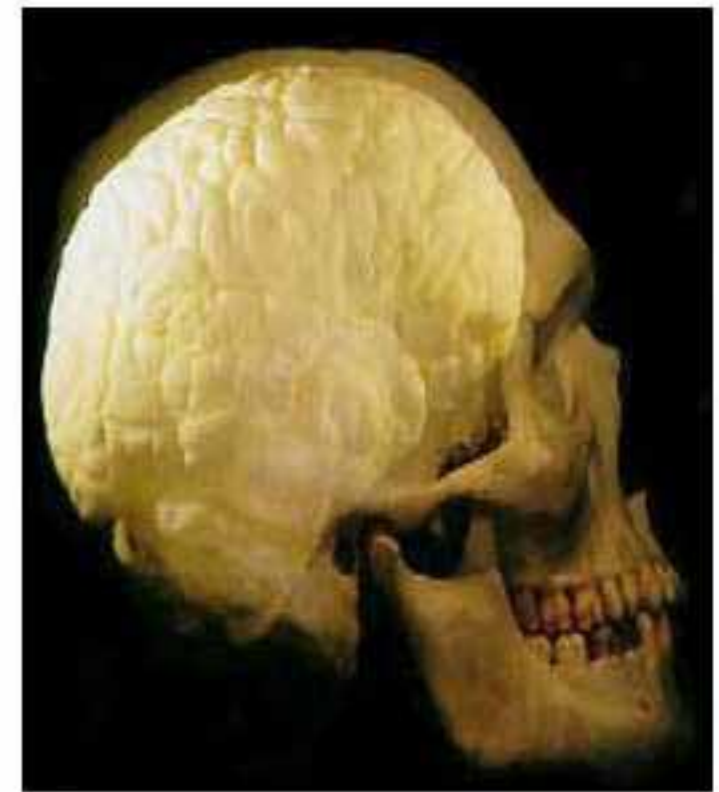


# The search for the engram

Where are the short and long-term memory stores in the brain ?

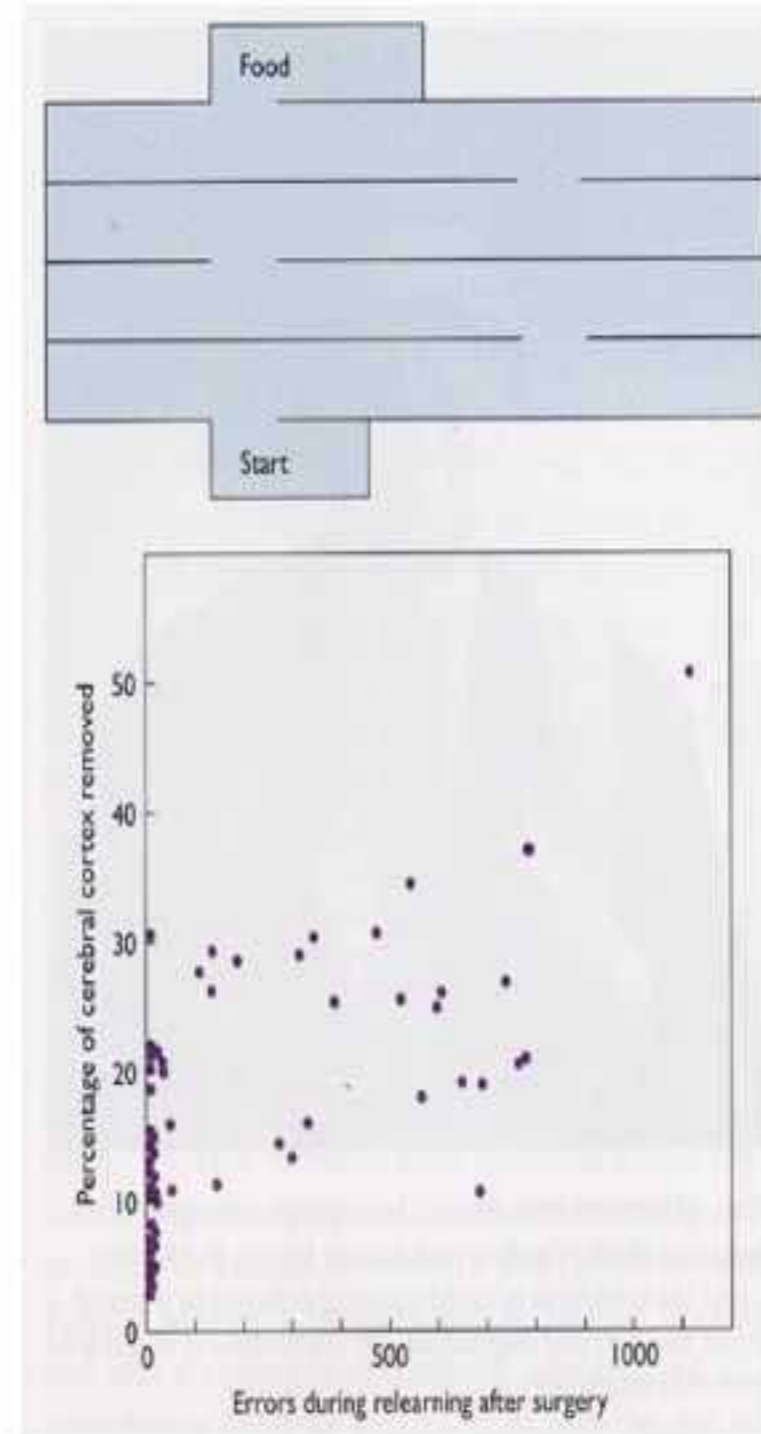
How does the process of consolidation shift information between them ?

The neocortex ?



# The search for the engram

Karl Lashley (1920s) - mass action and equipotentiality



## The search for the engram

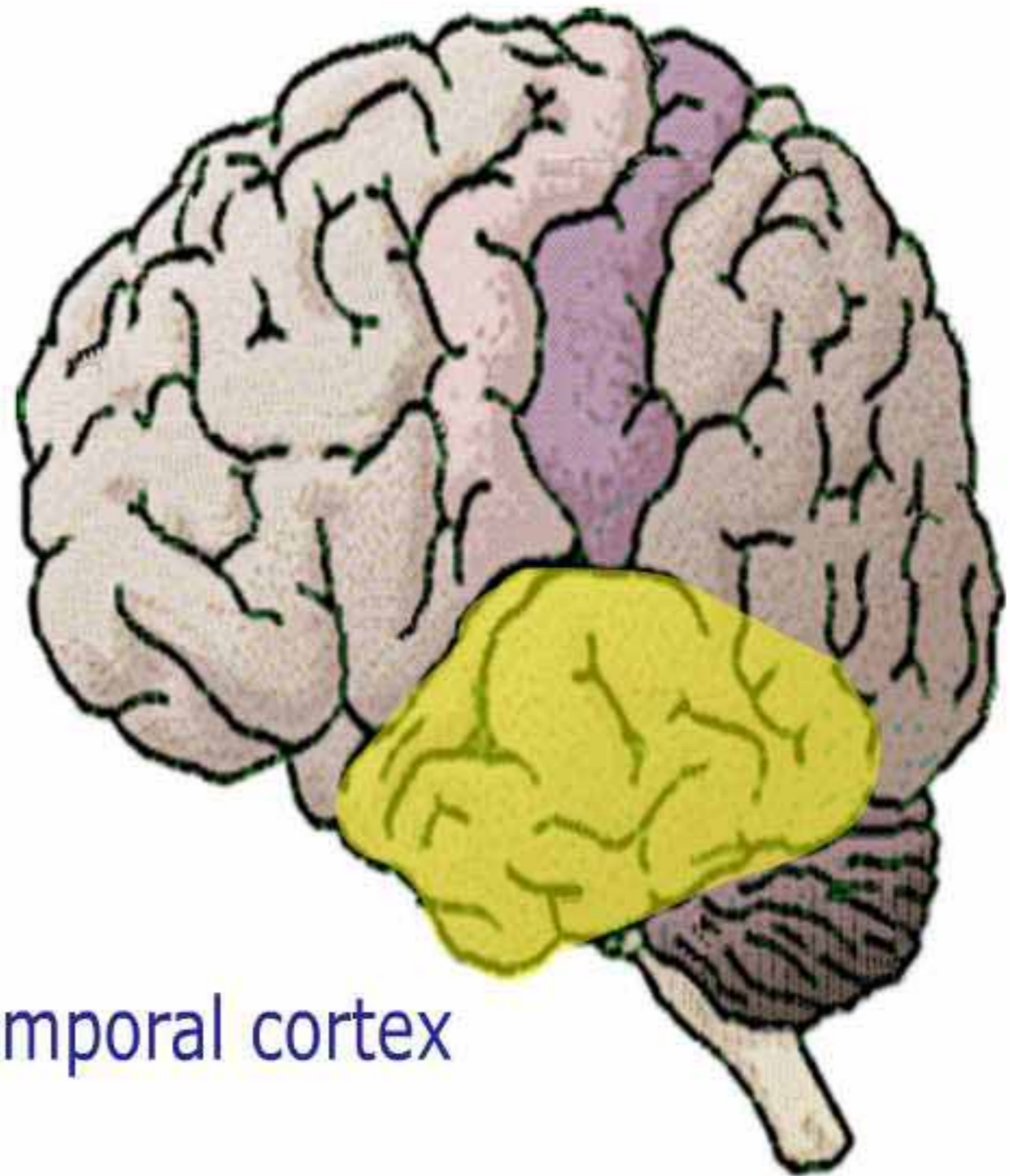
Karl Lashley (1920s) - mass action and equipotentiality



'I sometimes feel, in reviewing the evidence on the localization of the memory trace, that the necessary conclusion is that learning just is not possible' (1950)

# The search for the engram

Wilder Penfield - specific memories in the temporal lobe



Temporal cortex

# The story of HM

Uncontrollable epilepsy from age 9



# The story of HM

Uncontrollable epilepsy from age 9

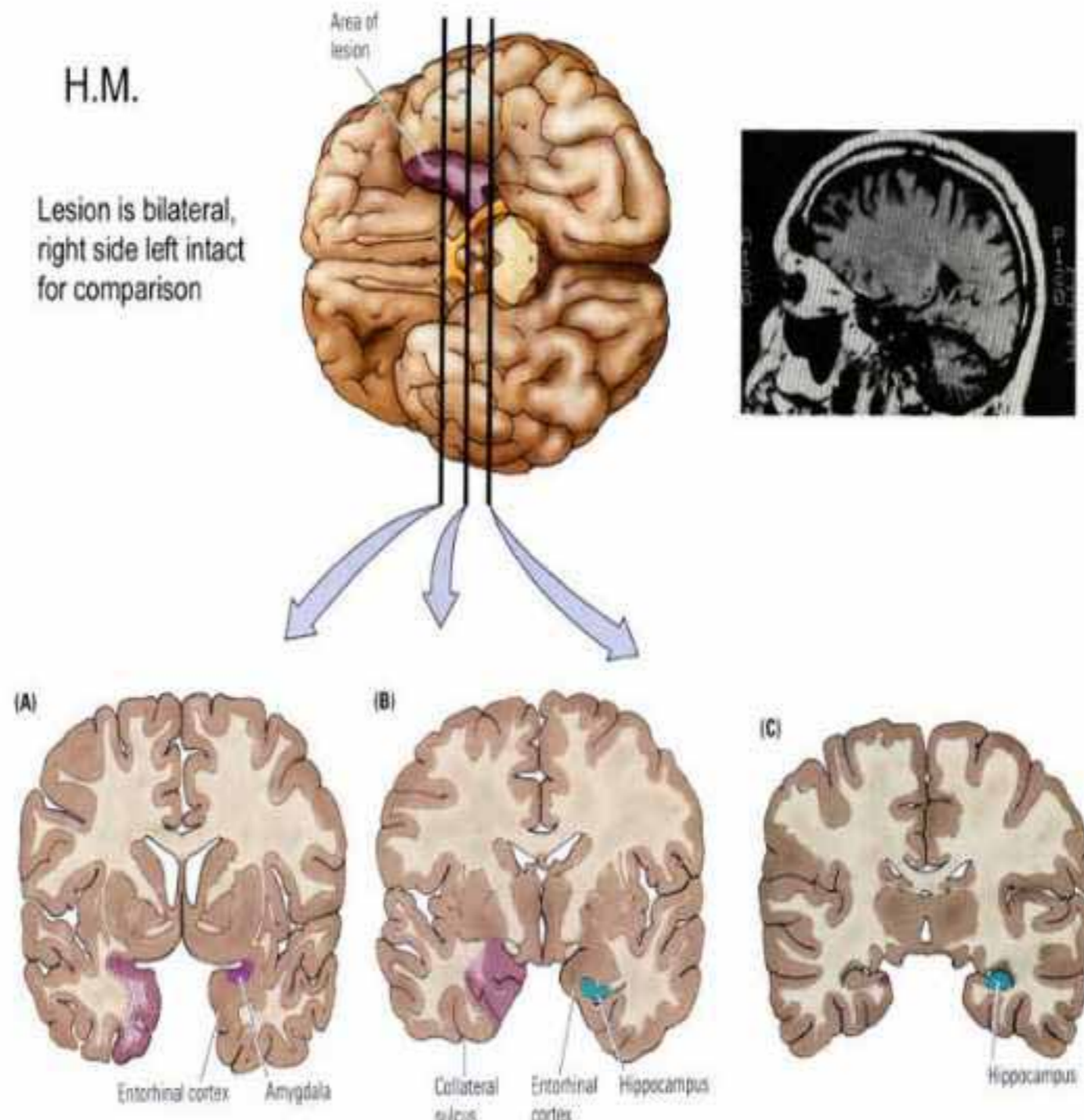
Operated on by William Scoville at age 27



# The story of HM

Removed subcortical components of temporal lobe bilaterally

Epilepsy cured





# The story of HM

Unable to remember new information for more than a few minutes



## The story of HM

Unable to remember new information for more than a few minutes

Memories of events prior to operation intact

# The story of HM

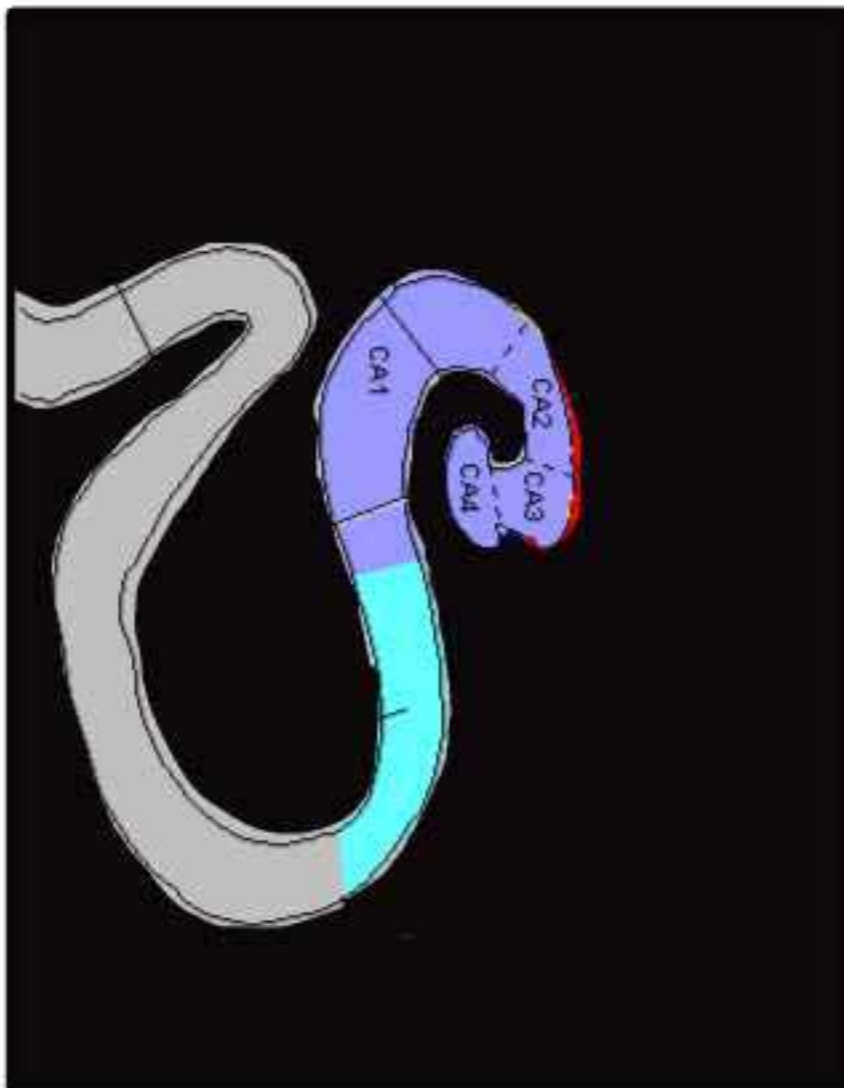
Implicit/Procedural Memories not affected



# The story of HM

Implicit/Procedural Memories not affected

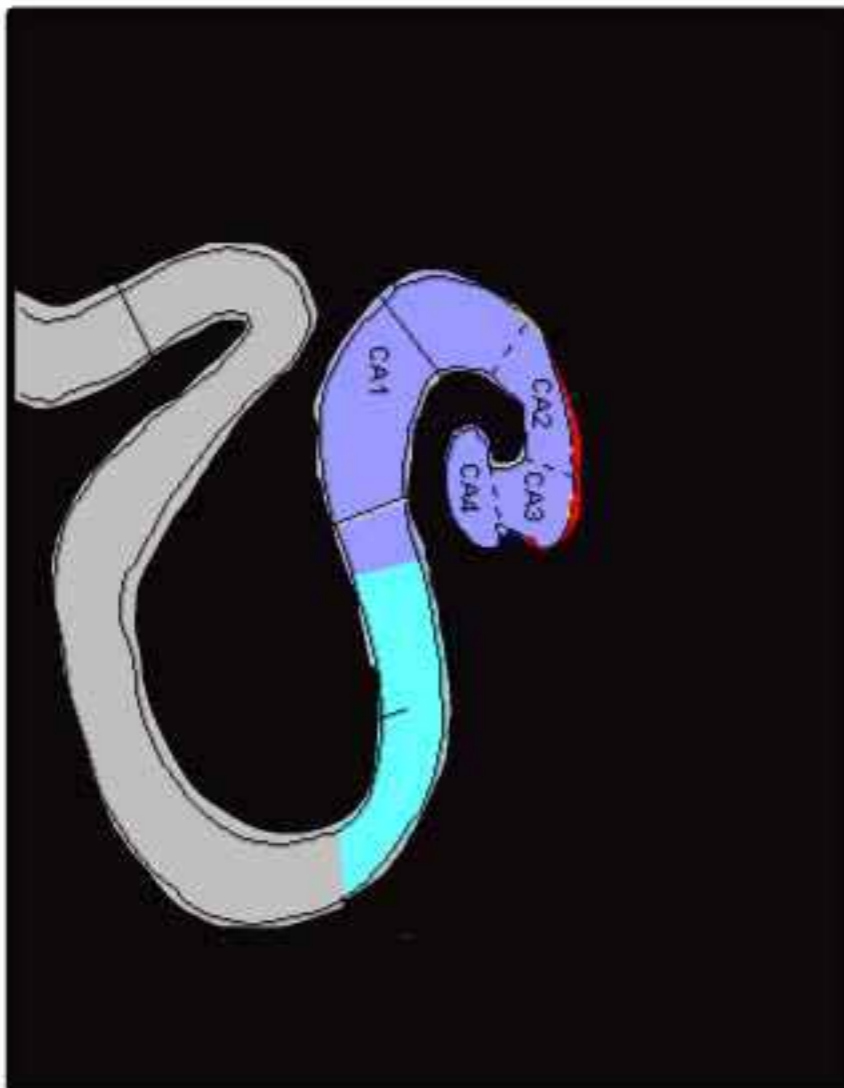
Damage mainly to a brain structure called the hippocampus



# The story of HM

Implicit/Procedural Memories not affected

Damage mainly to a brain structure called the hippocampus



# Hippocampus and spatial memory in animals



# Hippocampus and spatial memory in animals

Food storing animals - enlarged hippocampus



Marsh-tit



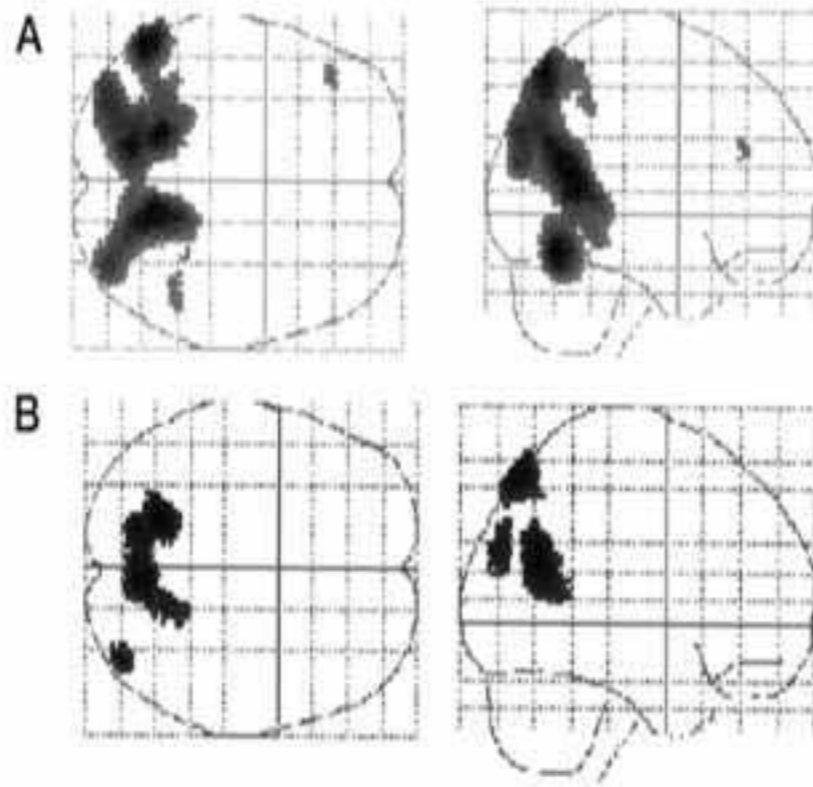
Avian  
hippocampus

# Hippocampus and spatial memory in animals

Food storing animals - enlarged hippocampus

Taxi drivers

(Maguire *et al* 1997)





# Hippocampus and spatial memory in animals

Food storing animals - enlarged hippocampus

Taxi drivers

(Maguire *et al* 1997)

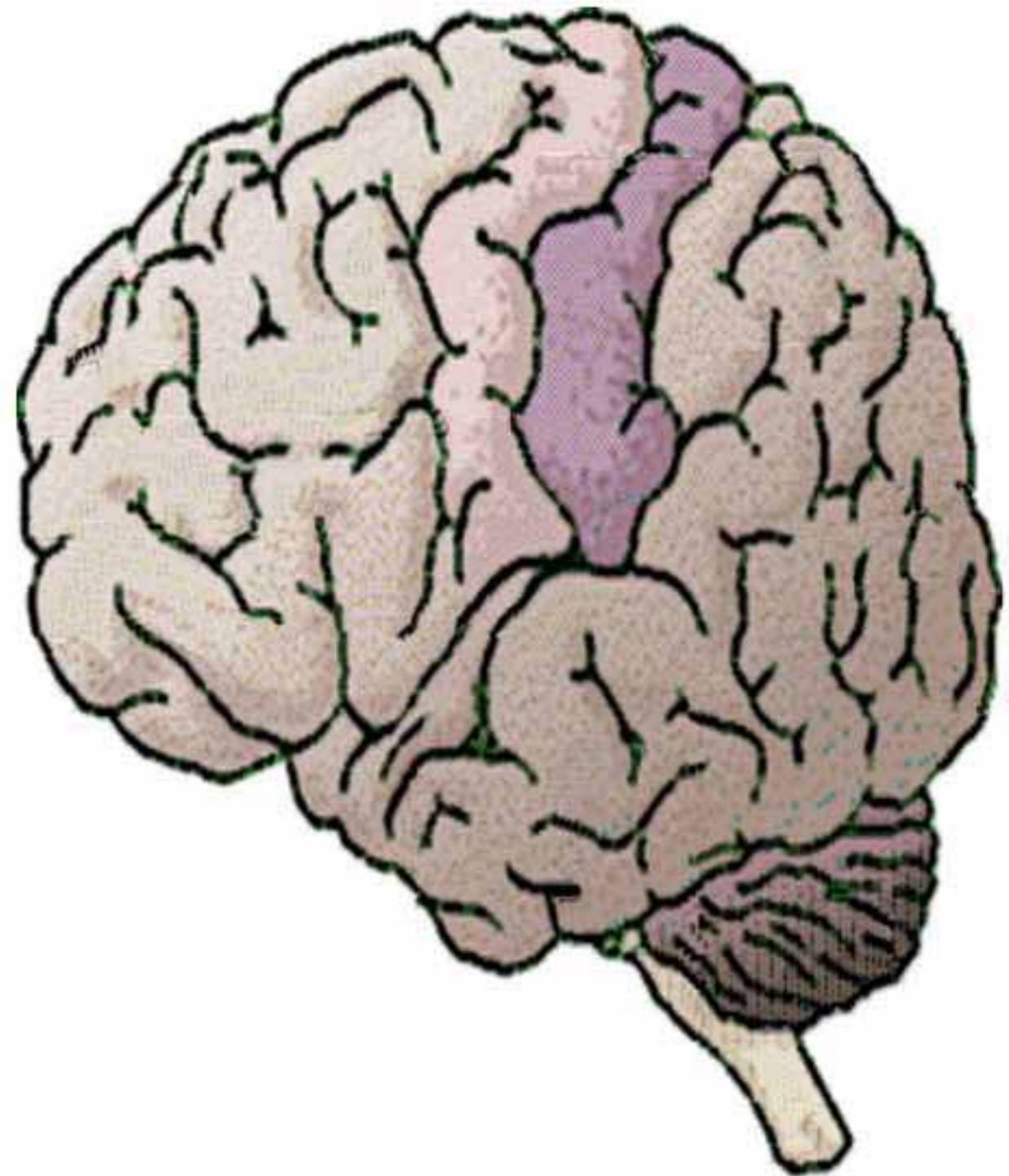
Rat hippocampus is also involved in making learned associations between objects

(Bunsey and Eichenbaum 1996)



# Multiple memory systems in the brain

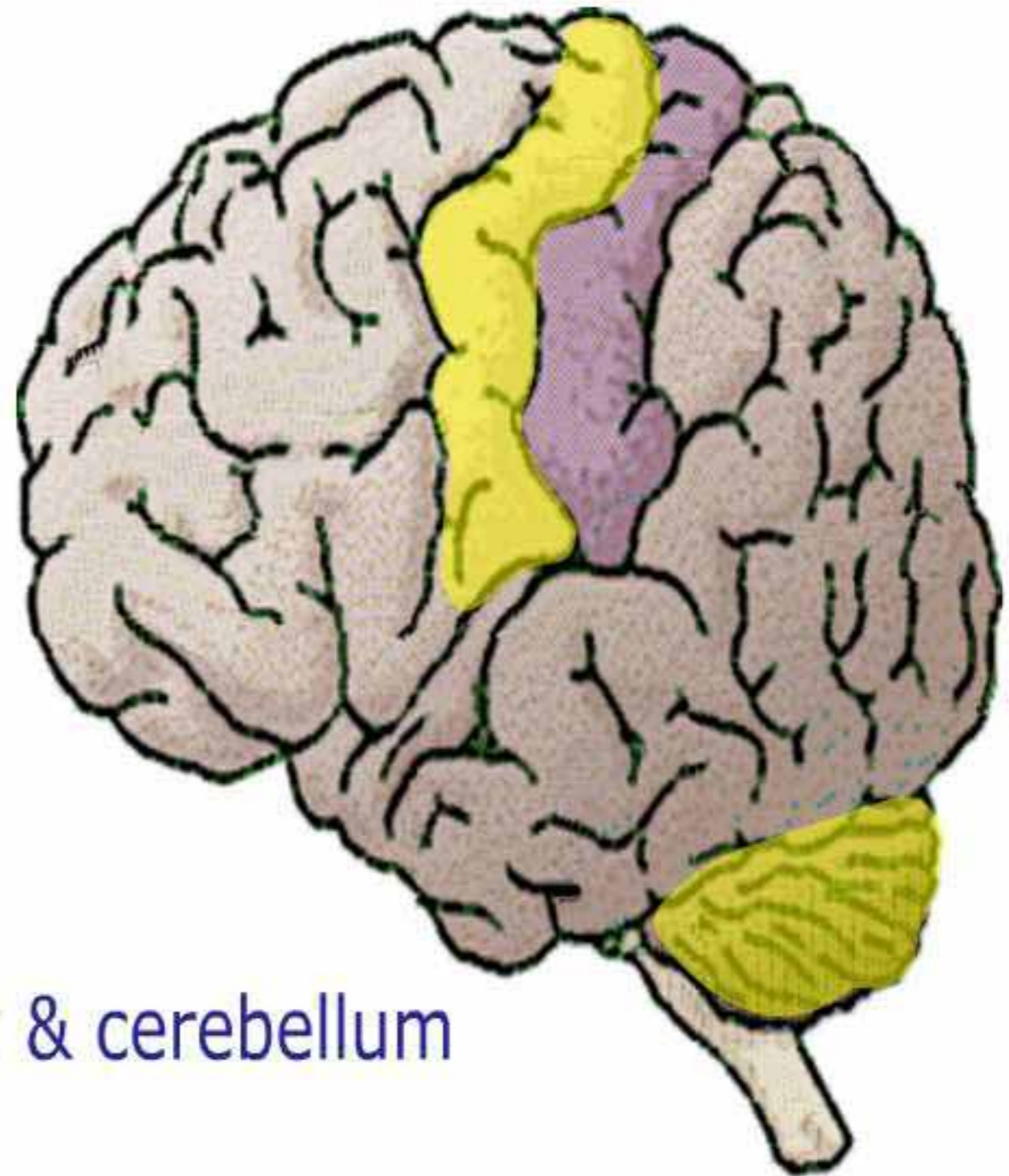
Different brain memory systems for:



# Multiple memory systems in the brain

Different brain memory systems for:

Motor skills



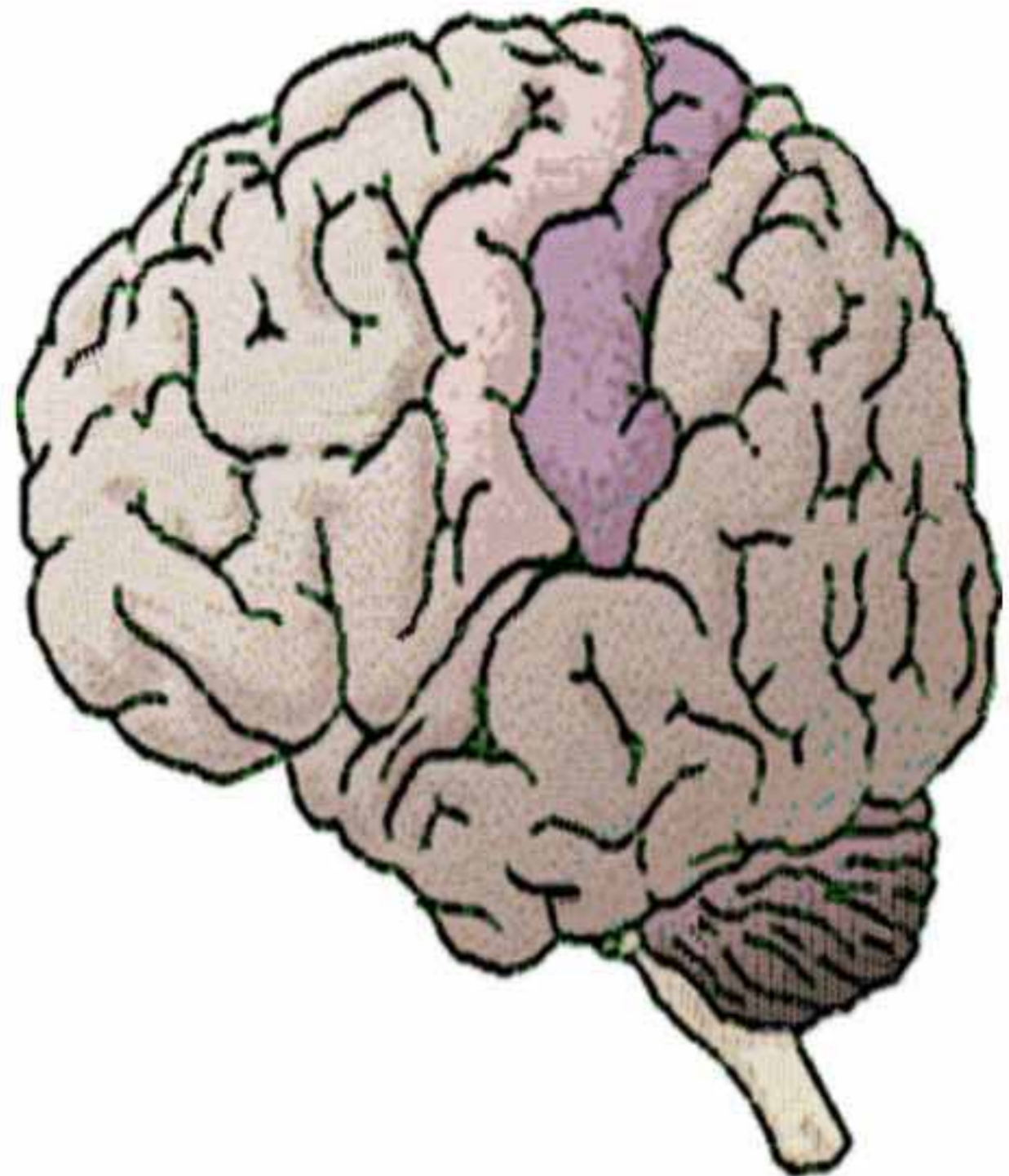
Motor cortex & cerebellum

# Multiple memory systems in the brain

Different brain memory systems for:

Motor skills

Habitual responses



# Multiple memory systems in the brain

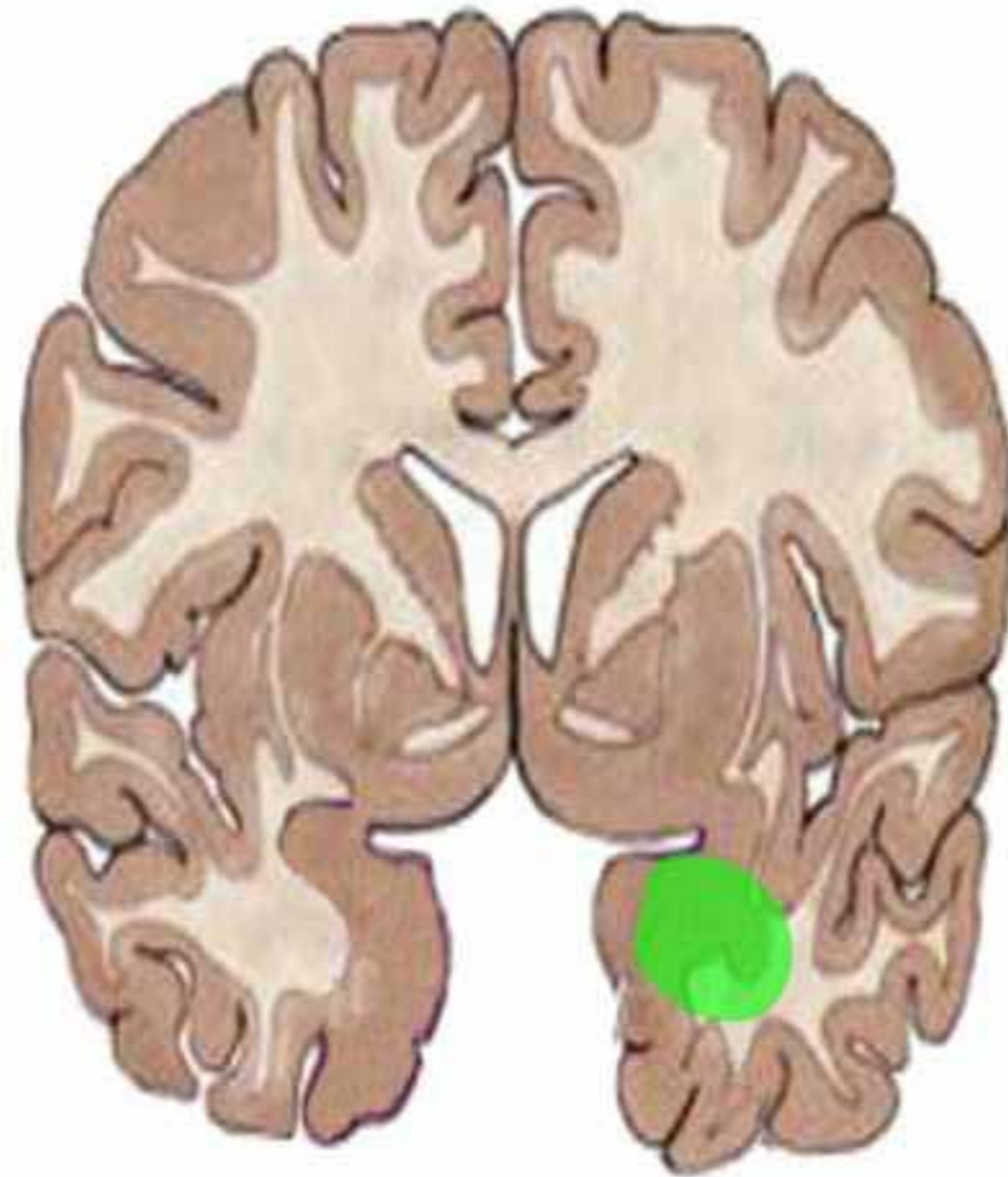
Different brain memory systems for:

Motor skills

Habitual responses

Spatial location

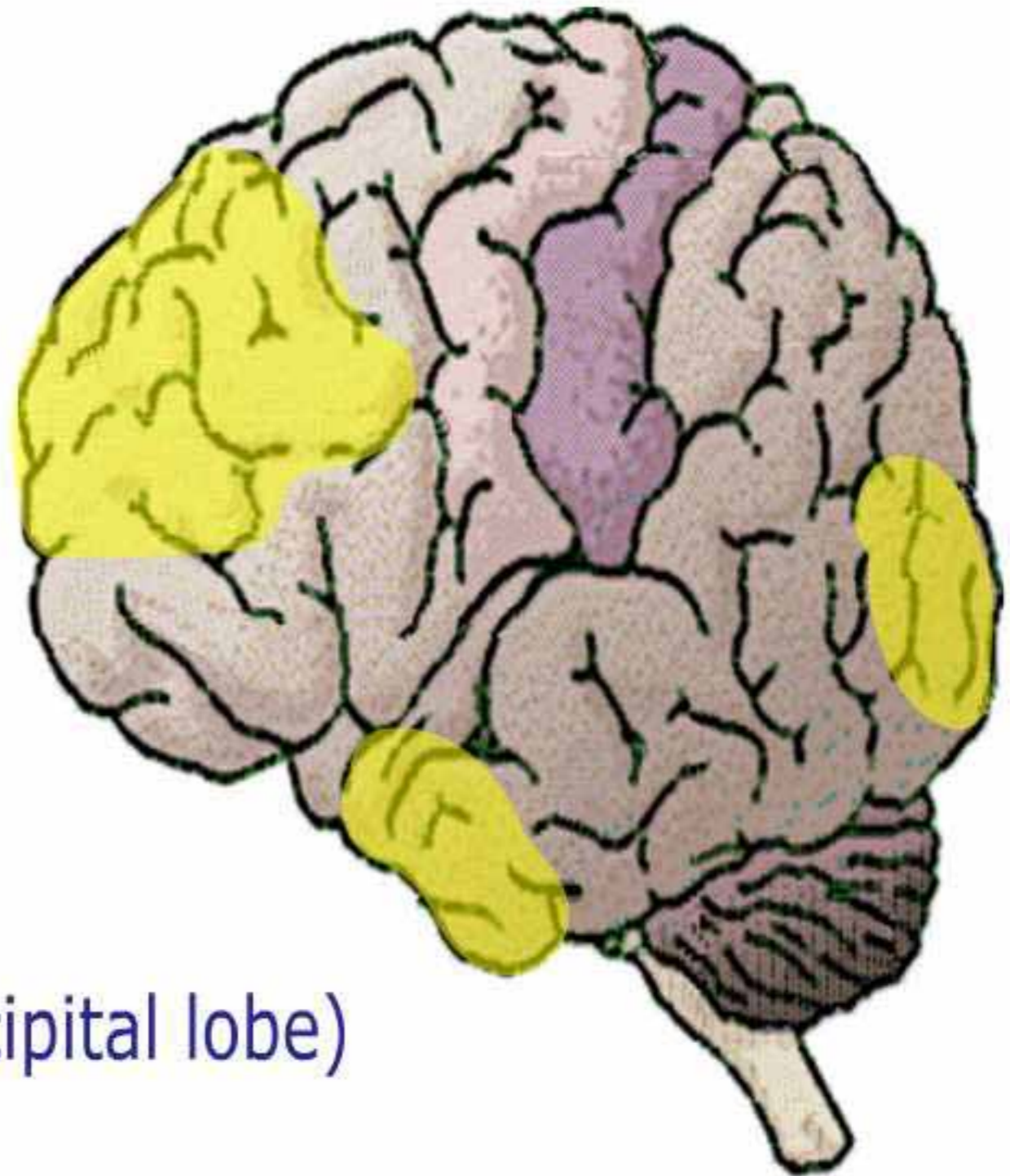
Hippocampus....



# Multiple memory systems in the brain

Different brain memory systems for recognition of:

Visual objects



Frontal cortex

Perirhinal cortex

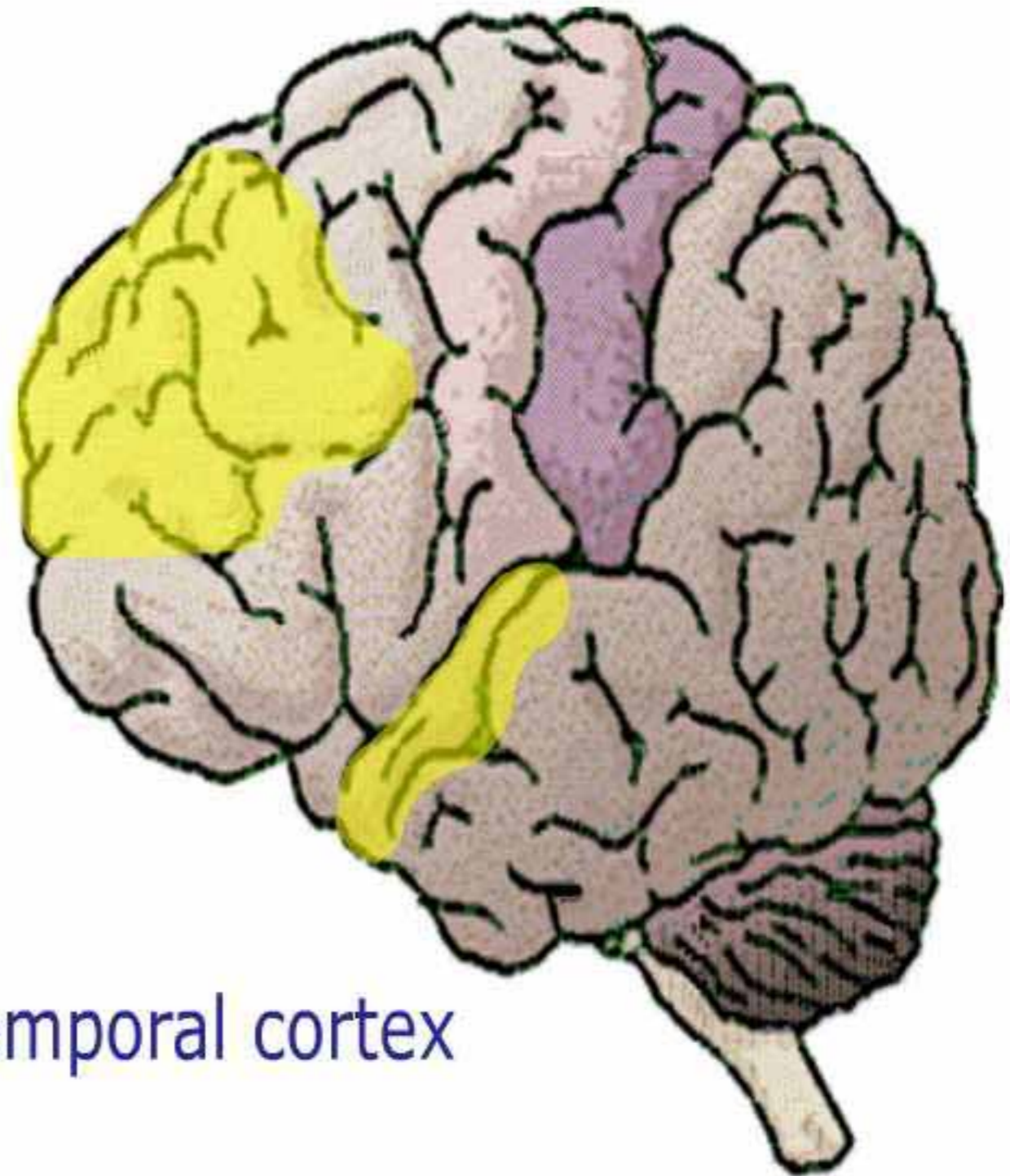
Visual cortex (occipital lobe)

# Multiple memory systems in the brain

Different brain memory systems for recognition of:

Visual objects

Faces



Frontal & temporal cortex

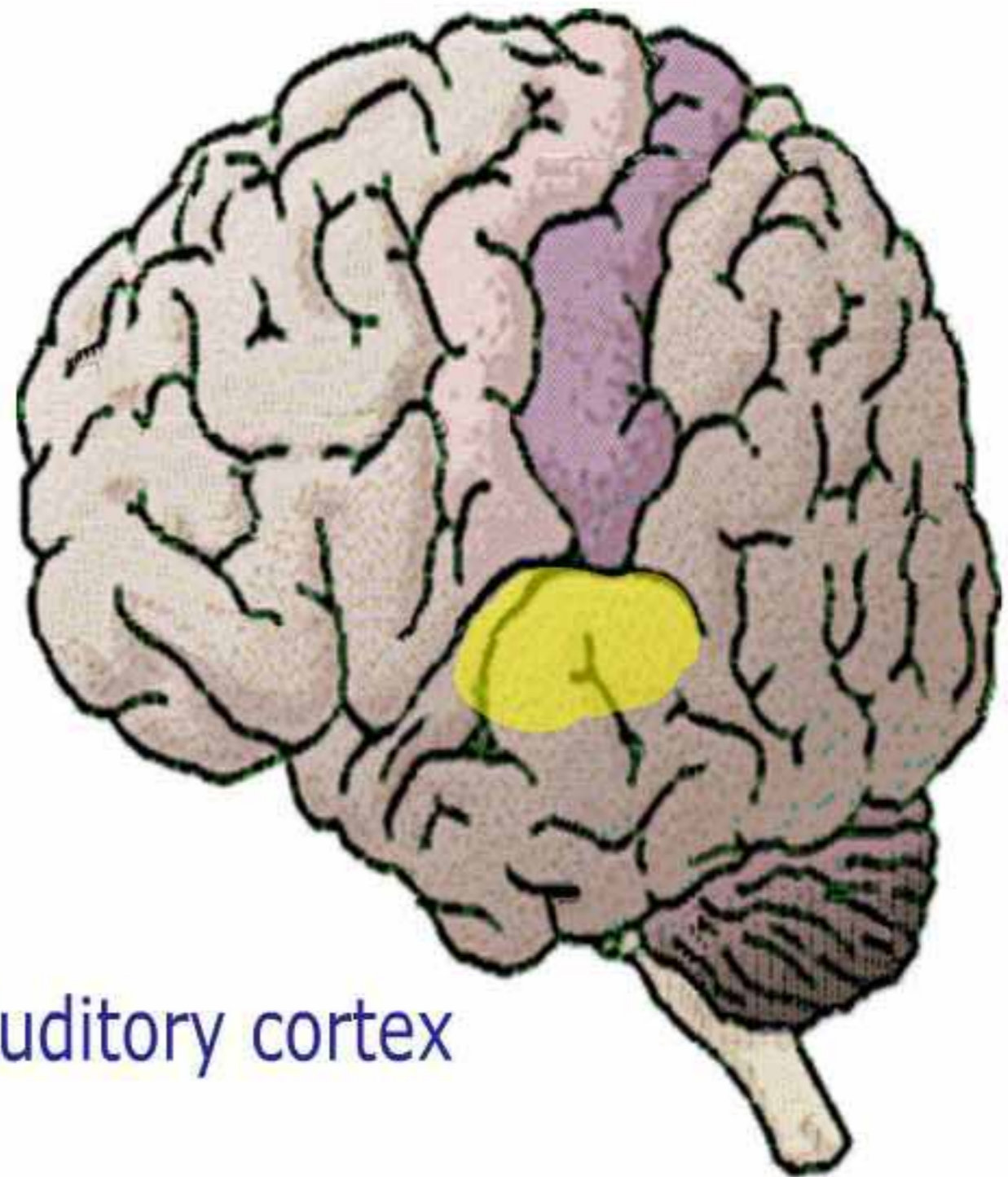
# Multiple memory systems in the brain

Different brain memory systems for recognition of:

Visual objects

Faces

Sounds



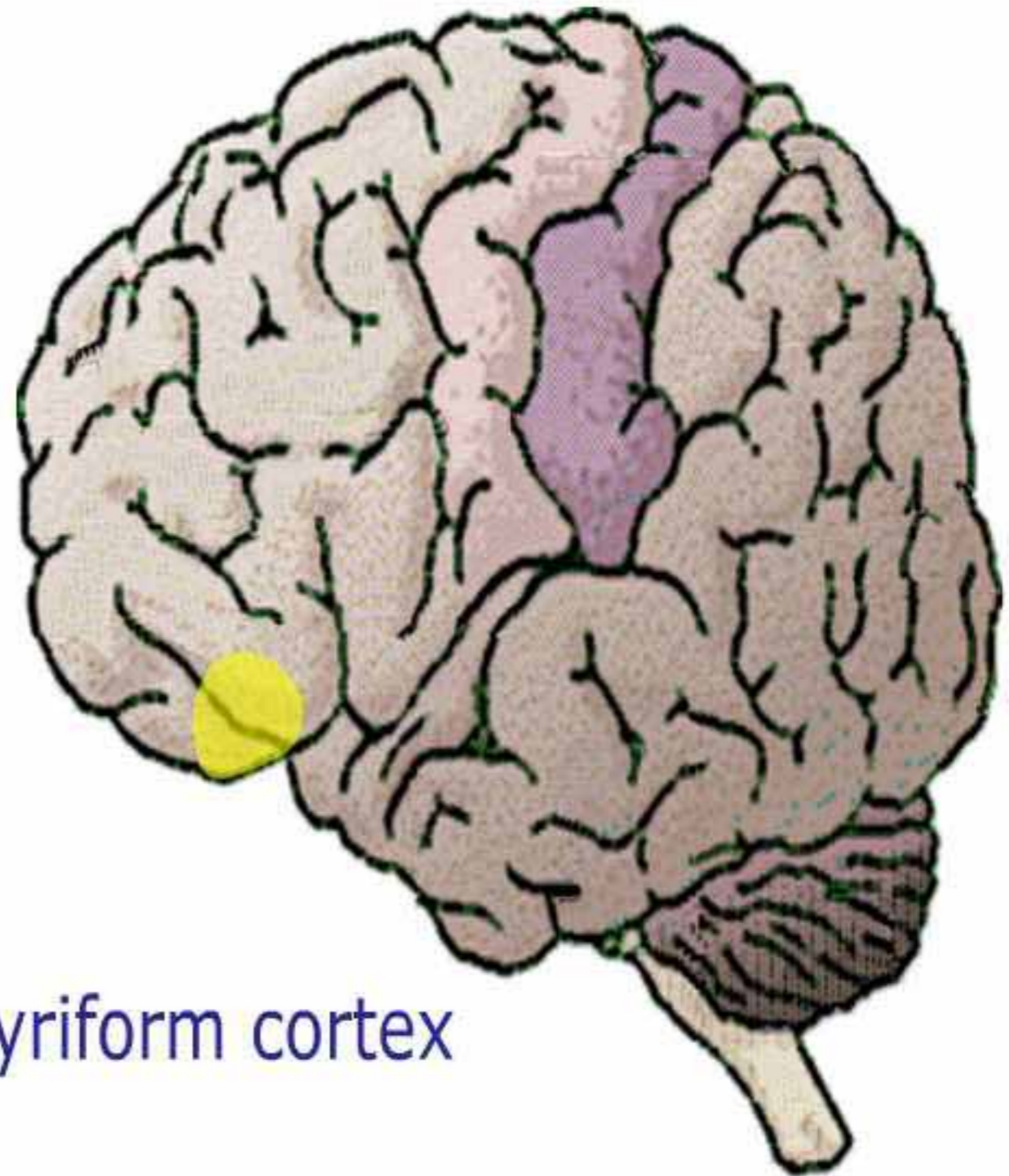
Auditory cortex



# Multiple memory systems in the brain

Different brain memory systems for recognition of:

Smells



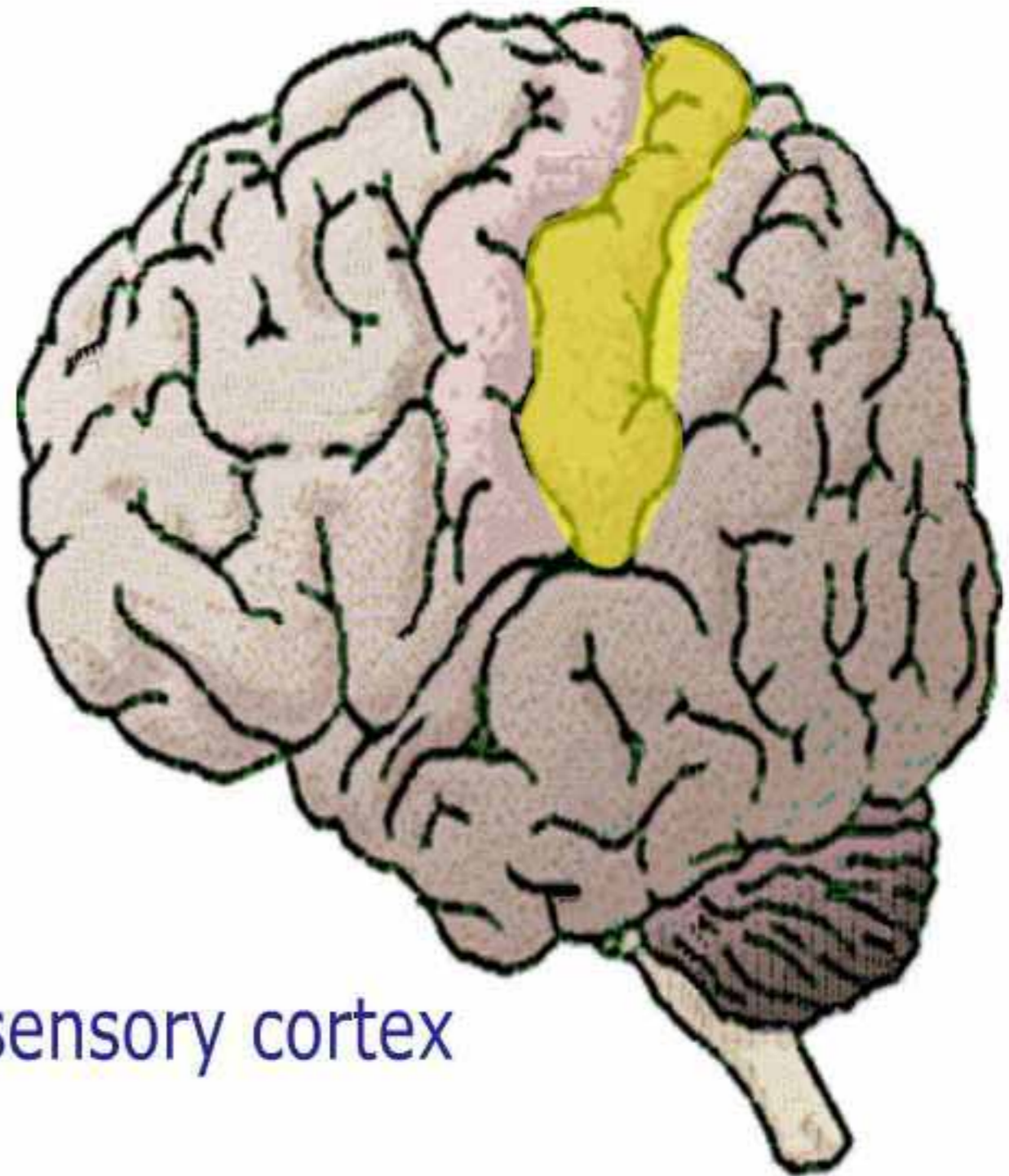
Olfactory bulb & piriform cortex

# Multiple memory systems in the brain

Different brain memory systems for recognition of:

Smells

Touch



Somatosensory cortex

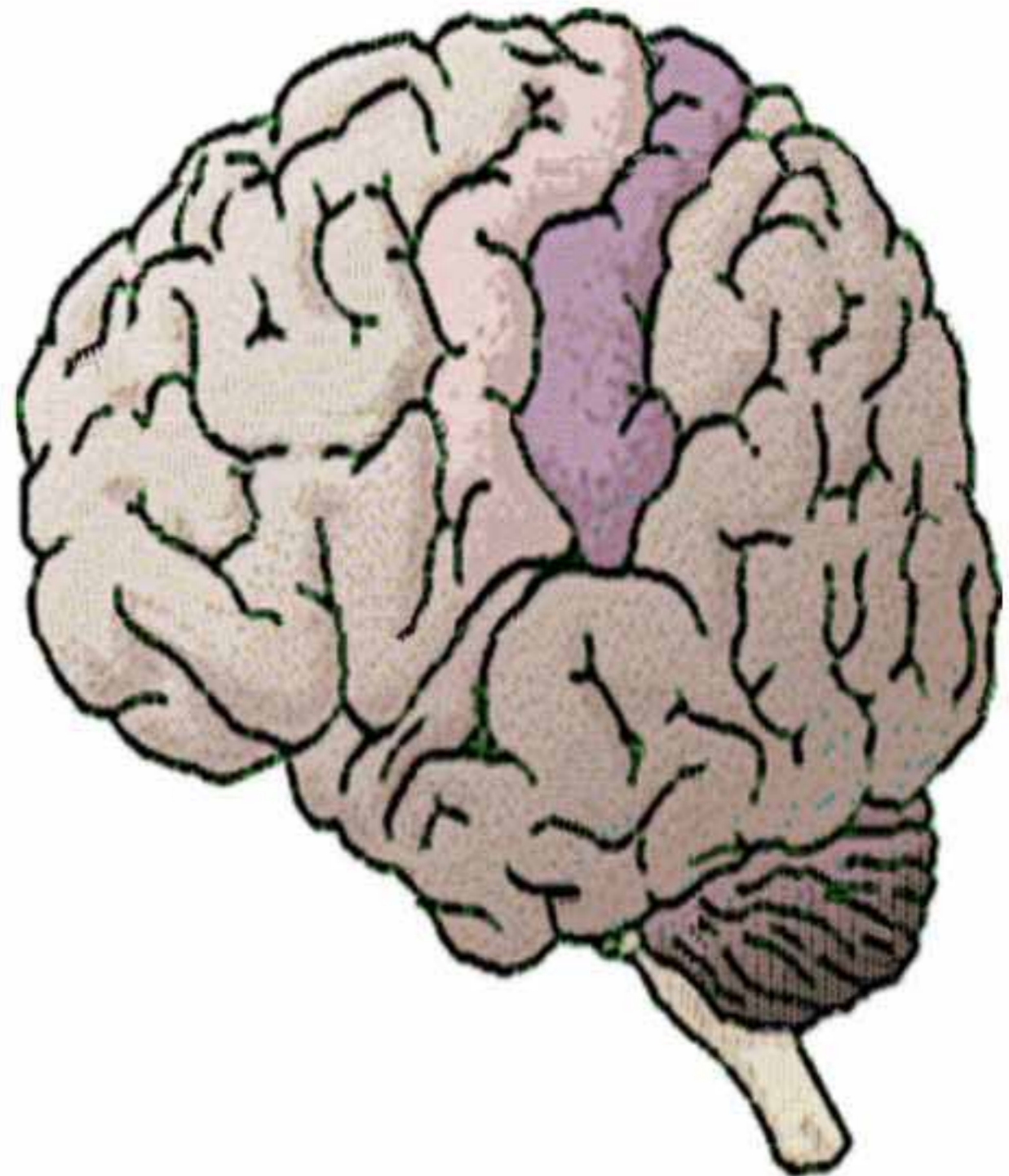
# Multiple memory systems in the brain

Different brain memory systems for recognition of:

Smells

Touch

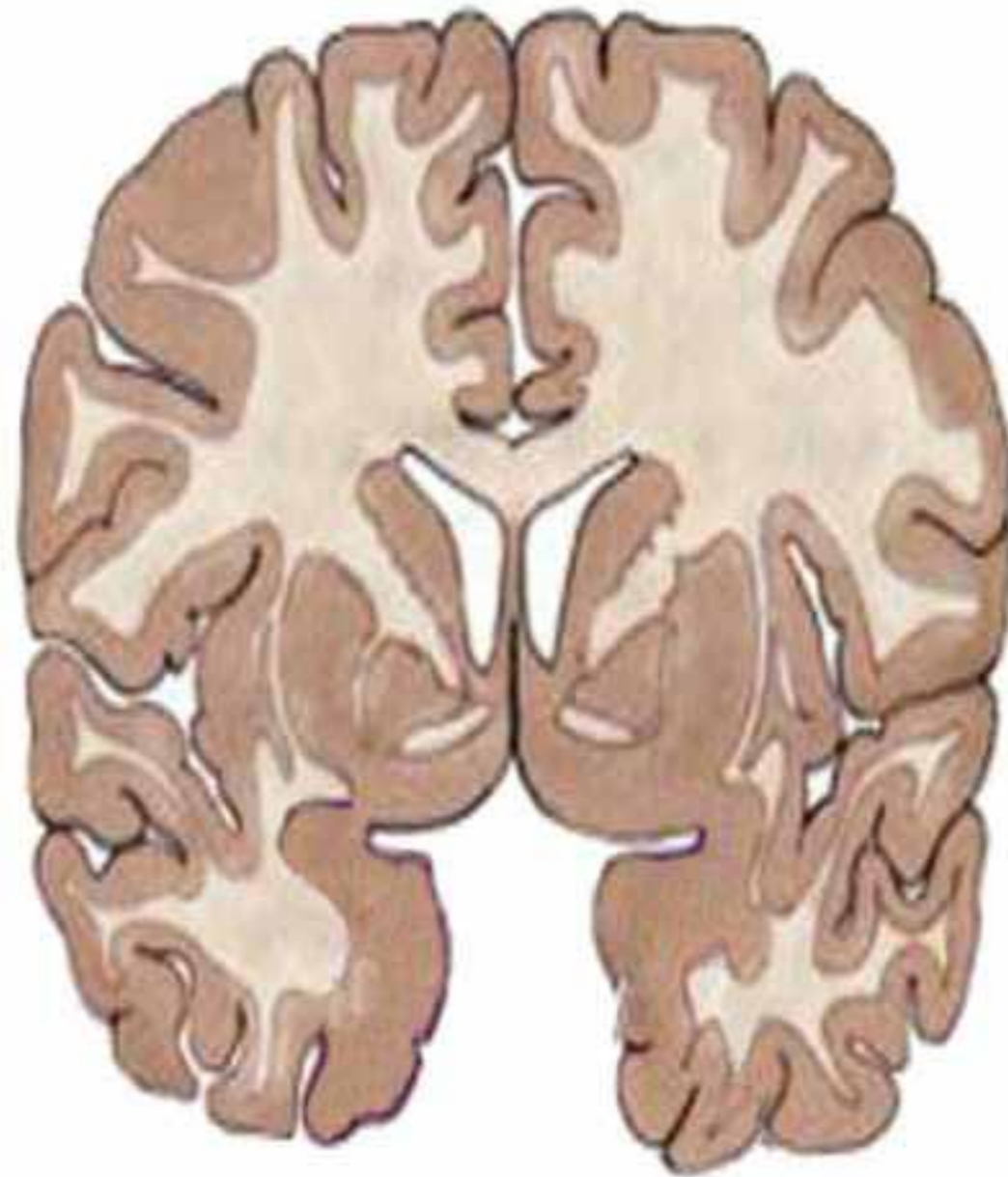
Tastes



# Multiple memory systems in the brain

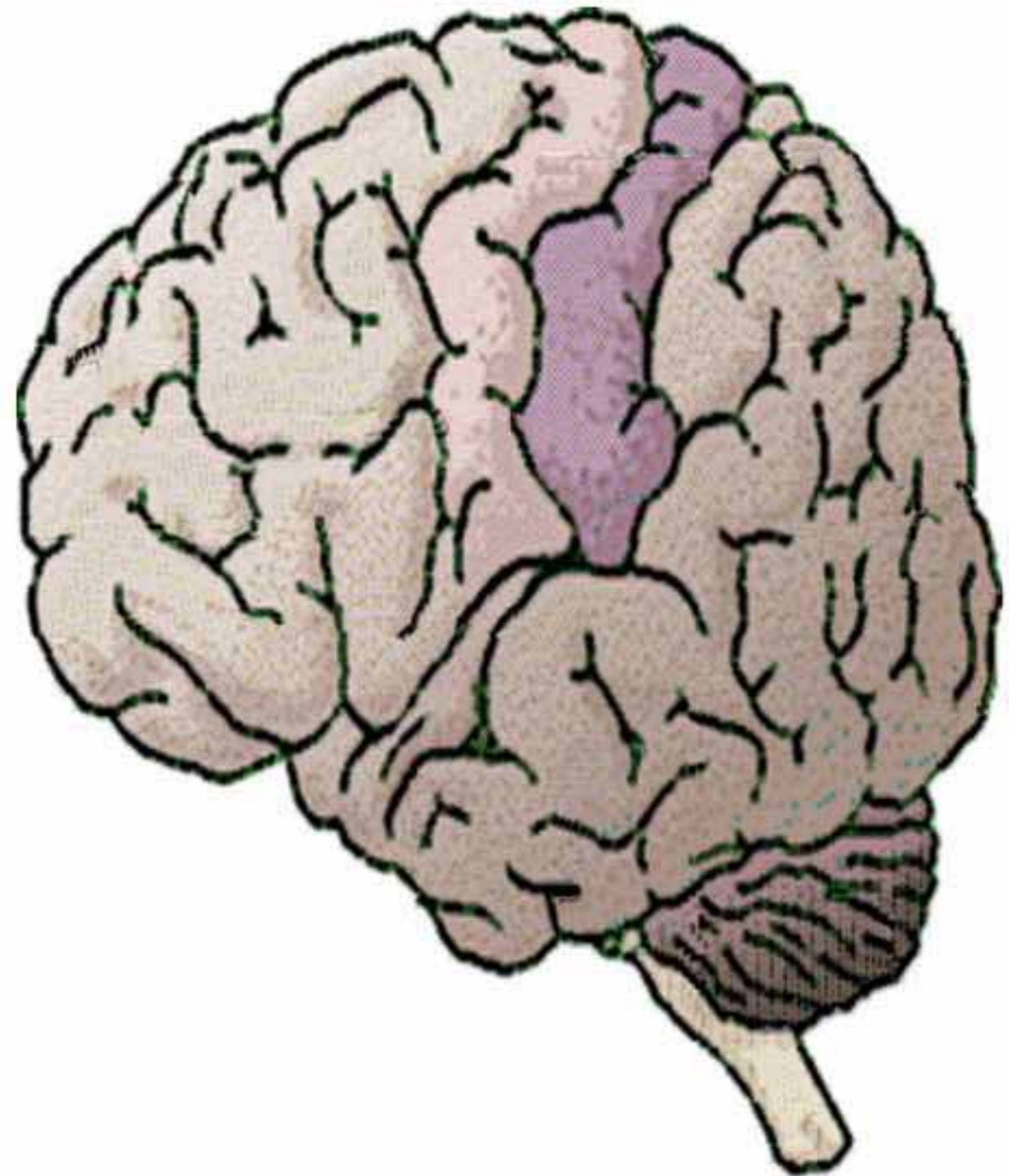
Different brain memory systems for recognition of:

Words



## Multiple memory systems in the brain

'What' things are encoded differently from 'where they are'

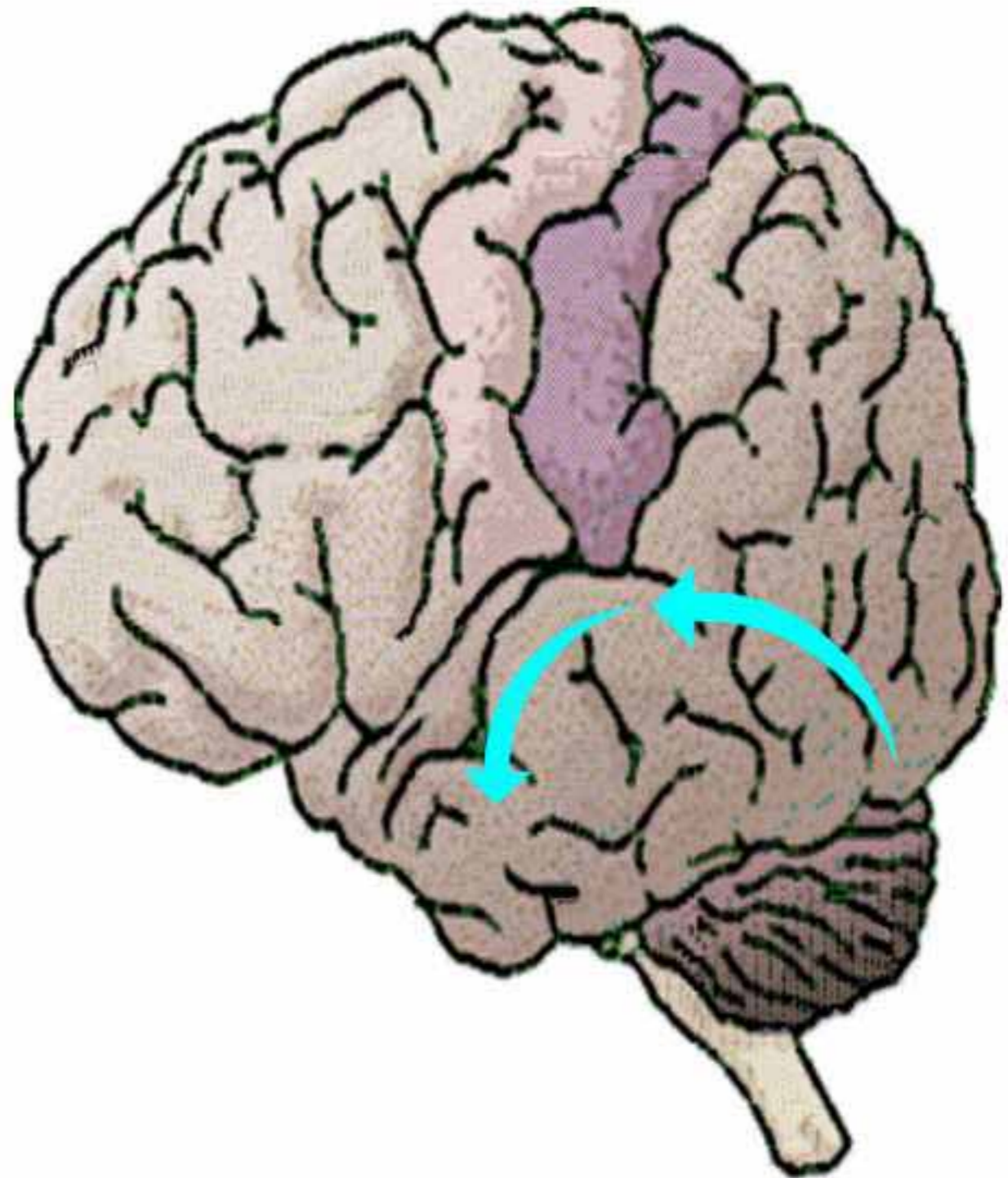


# Multiple memory systems in the brain

'What' things are encoded differently from 'where they are'

What

- Inferior temporal cortex



# Multiple memory systems in the brain

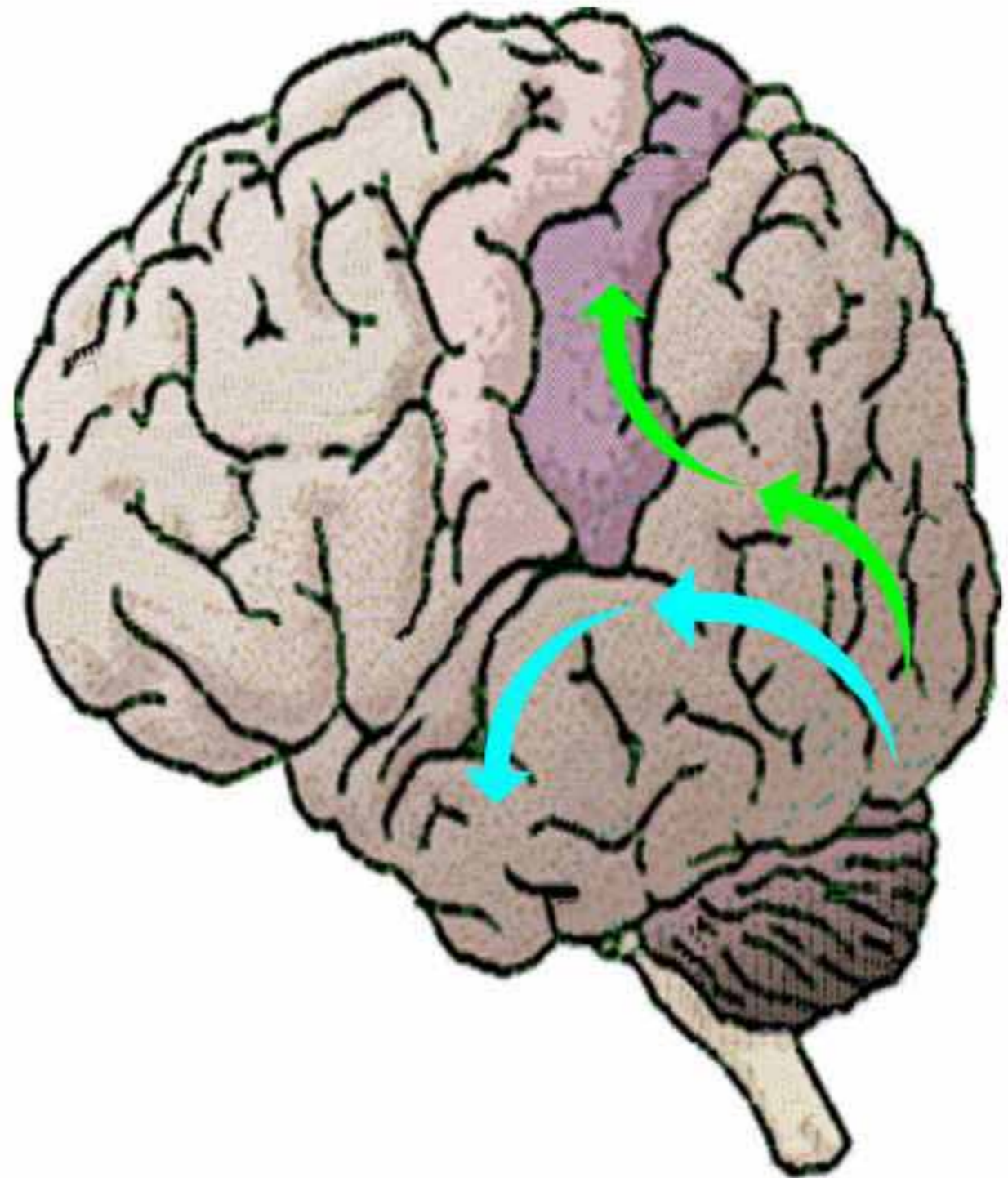
'What' things are encoded differently from 'where they are'

Where

- Posterior parietal cortex

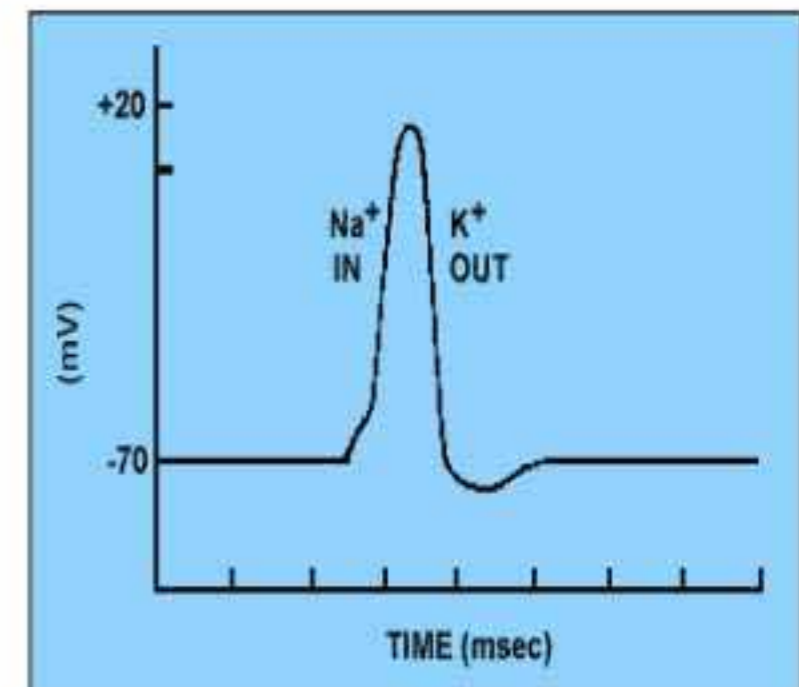
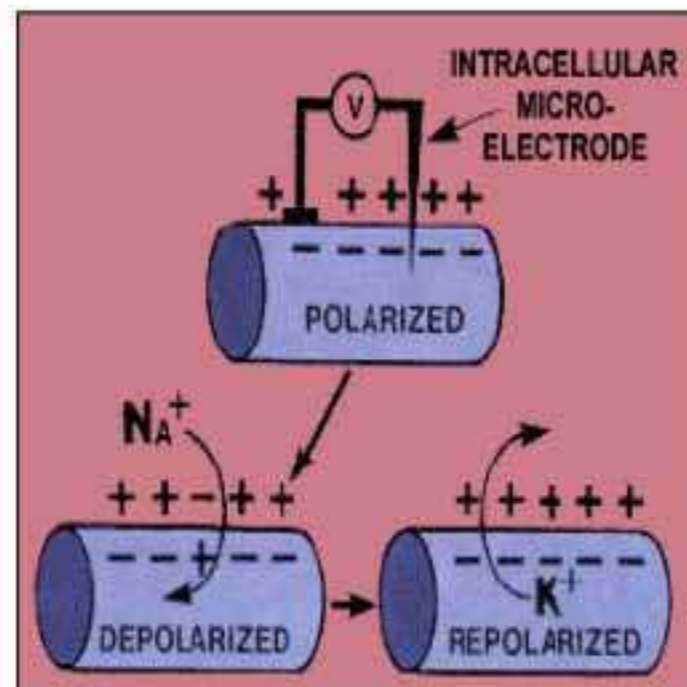
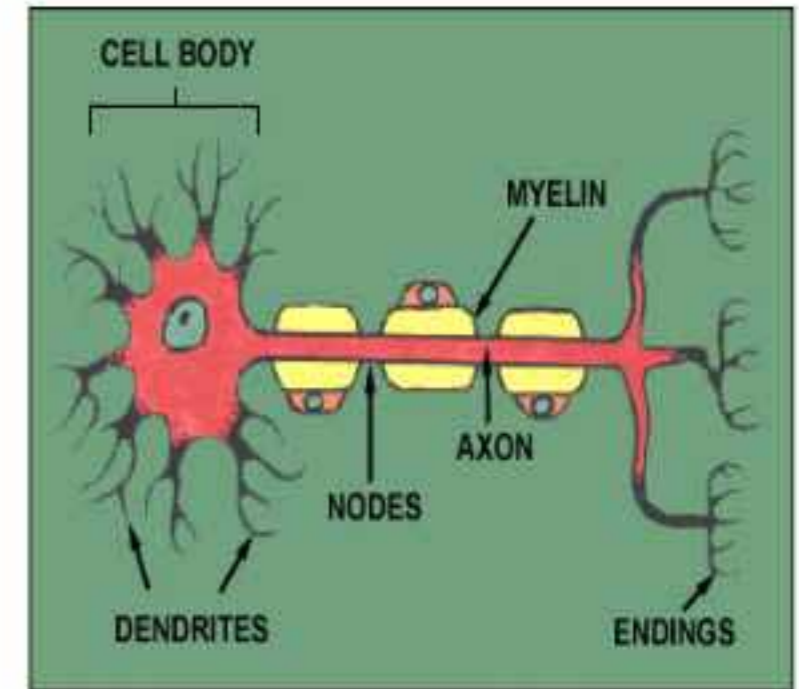
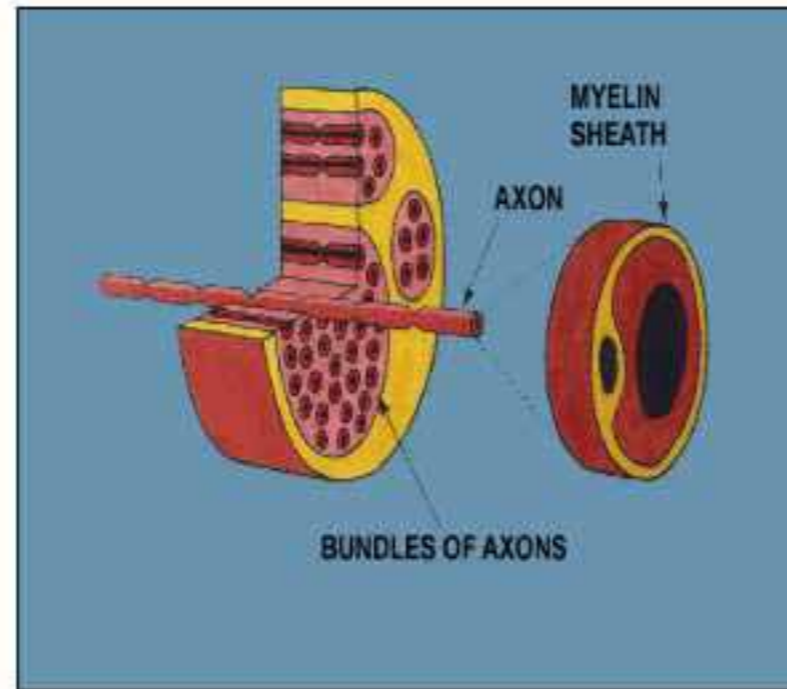
What

- Inferior temporal cortex



# Building blocks for memory

Turning the gain up and down  
in nerve cells

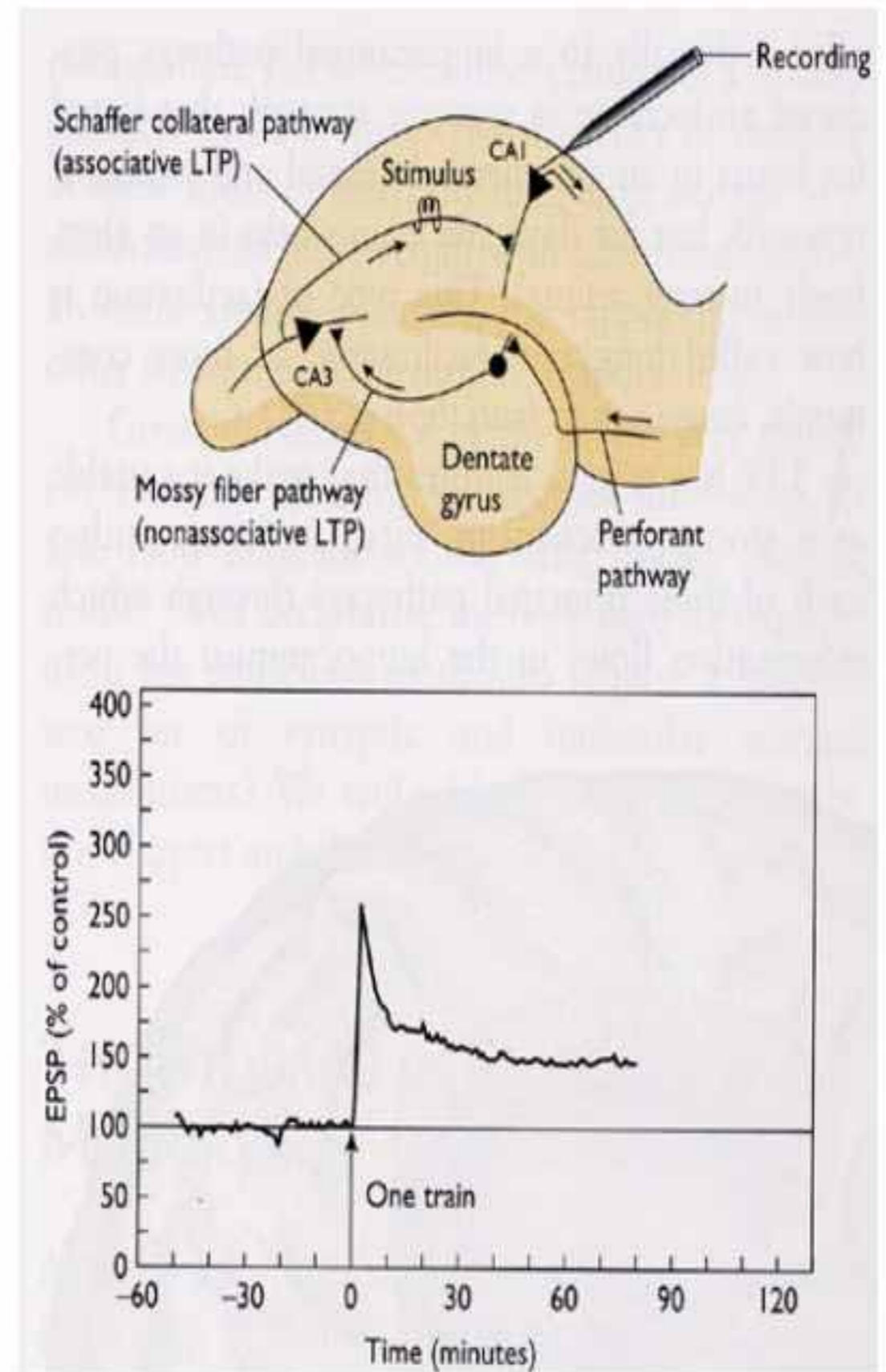




# Building blocks for memory

Turning the gain up and down  
in nerve cells

Long-term potentiation  
Bliss & Lomo 1973



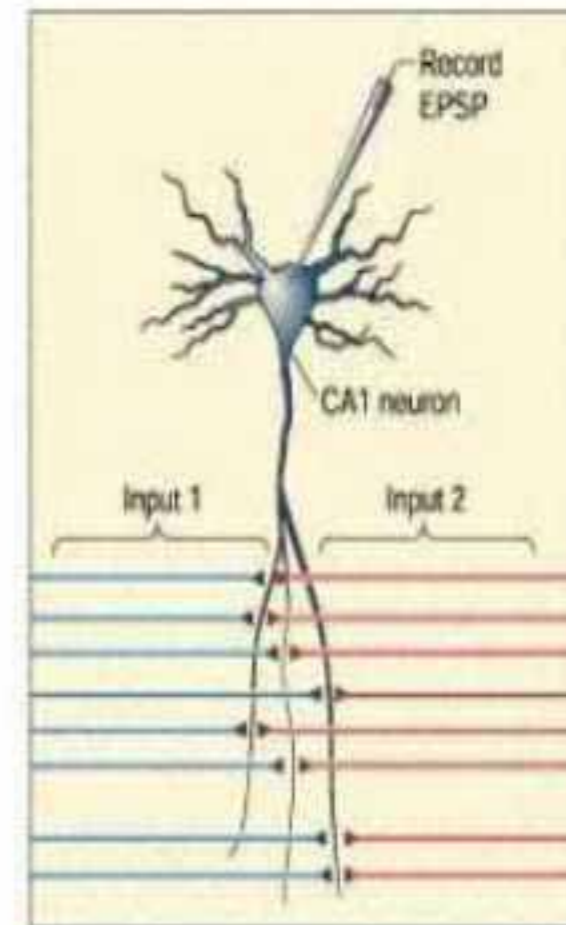
# Building blocks for memory

Turning the gain up and down  
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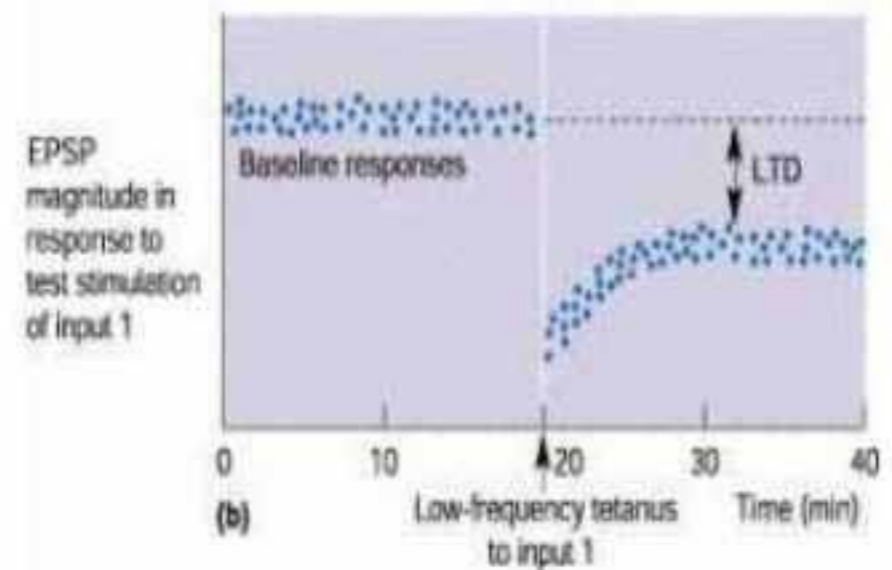
Long-term potentiation

Bliss & Lomo 1973

Long-term depression



(a)



(b)

# Building blocks for memory

Turning the gain up and down  
in nerve cells

Long-term potentiation  
Bliss & Lomo 1973

Long-term depression

Links to memory ?

*Neuron*, Vol. 20, 445–468, March, 1998. Copyright ©1998 by Cell Press

## Cognitive Neuroscience and the Study of Memory

Review

Brenda Milner,<sup>\*</sup> Larry R. Squire,<sup>†</sup>  
and Eric R. Kandel<sup>‡§</sup>

<sup>\*</sup>Montreal Neurologic Institute  
Montreal, Quebec H3A 2B4  
Canada

<sup>†</sup>Veterans Affairs Medical Center  
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San Diego, California 92093

<sup>‡</sup>Center for Neurobiology and Behavior  
College of Physicians and Surgeons  
Columbia University  
Howard Hughes Medical Institute  
New York, New York 10032

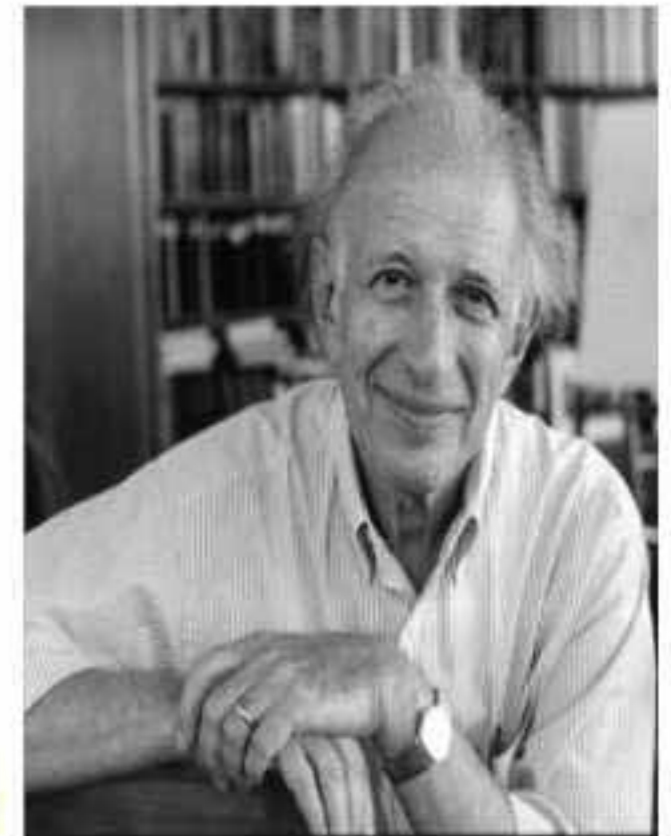
The neurosciences have grown rapidly over the last half century. This growth has been stimulated by two important developments. First, molecular biology has transformed cellular neurobiology and has led to a new conceptual framework for signaling: a molecular framework

that eventually led to the independent discipline of experimental psychology. In its early years, experimental psychology was concerned primarily with the study of sensation, but by the turn of the century the interests of psychologists turned to behavior itself—learning, memory, attention, perception, and voluntary action.

The development of simple experimental methods for studying learning and memory—first in humans by Hermann Ebbinghaus in 1885 and a few years later in experimental animals by Ivan Pavlov and Edgar Thorndike—led to a rigorous empirical school of psychology called *behaviorism*. Behaviorists, notably James B. Watson and Burrhus F. Skinner, argued that behavior could be studied with the precision achieved in the physical sciences, but only if students of behavior abandoned speculation about what goes on in the mind (the brain) and focused instead on *observable* aspects of behavior. For behaviorists, unobservable mental processes, especially abstractions like perception, selective attention, and memory, were deemed inaccessible to scientific study. Instead, behaviorists concentrated on examin-

# So what are the key memory molecules ?

*Alpysia californica* and the Nobel Prize

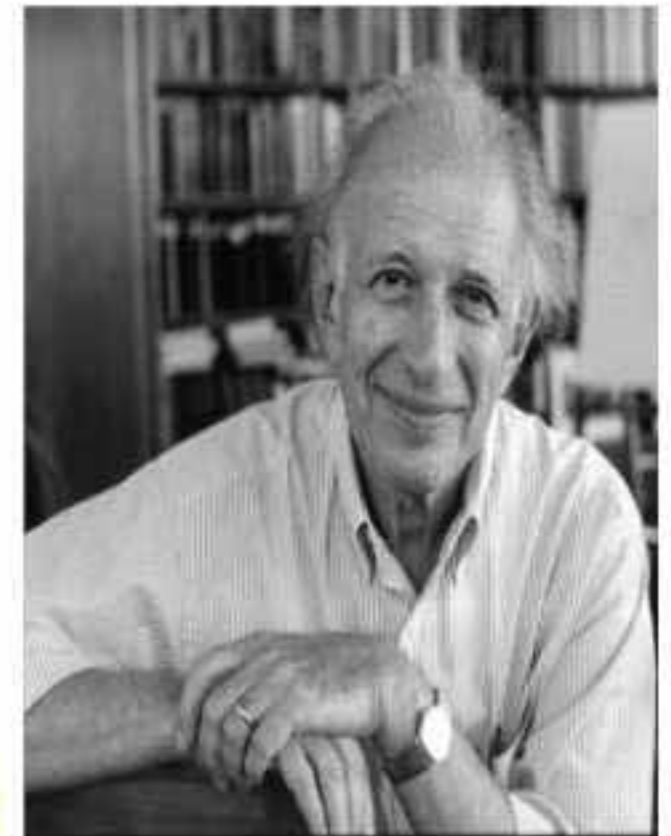


Eric Kandel

# So what are the key memory molecules ?

*Alpysia californica* and the Nobel Prize

How does a cell become more or less sensitive to the same stimulus ?



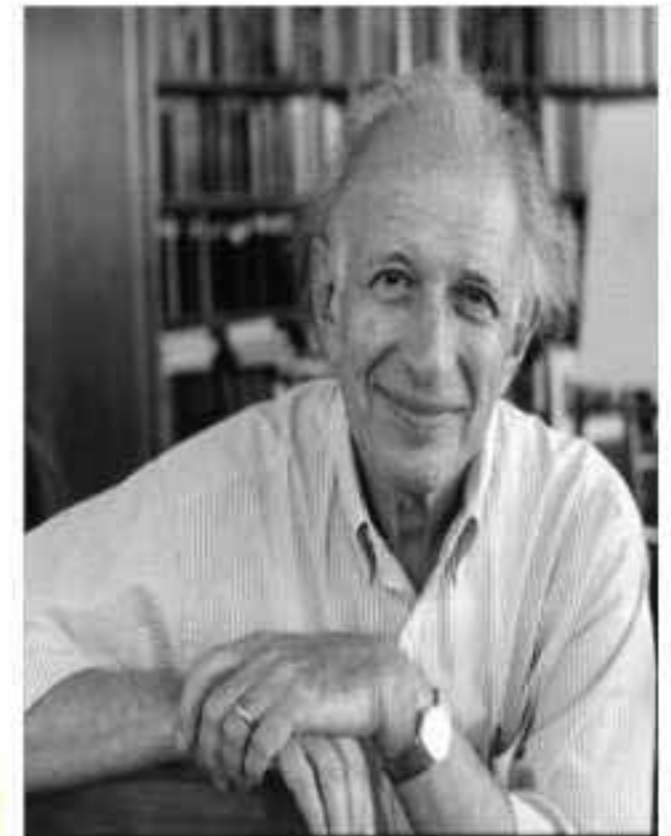
Eric Kandel

# So what are the key memory molecules ?

*Alpysia californica* and the Nobel Prize

How does a cell become more or less sensitive to the same stimulus ?

Changes sensitivities or numbers of synaptic inputs or receptors



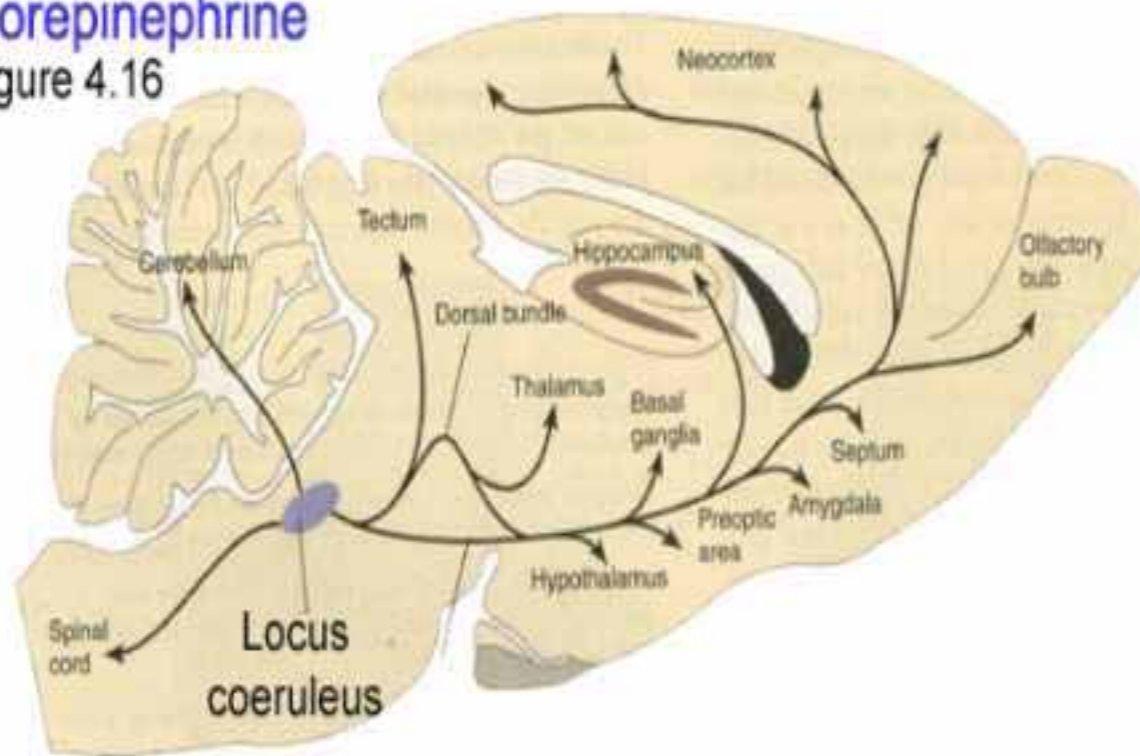
Eric Kandel

# So what are the key memory molecules ?

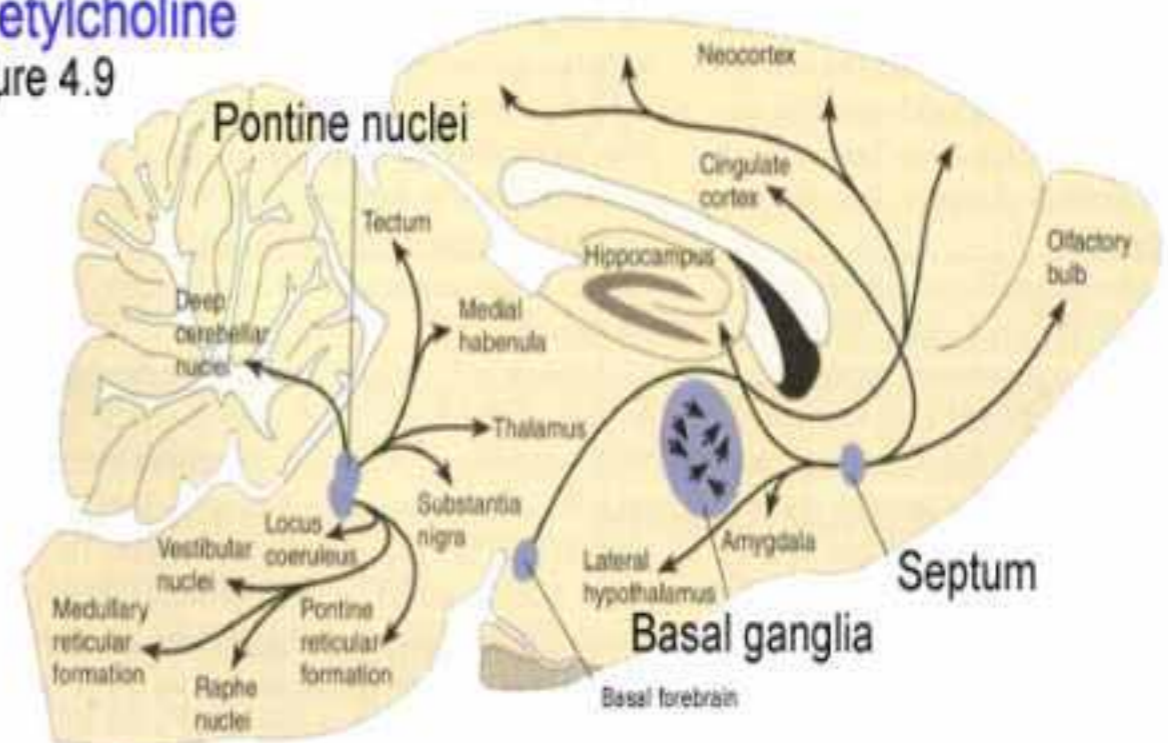
Association and co-incidence

Pay attention while I'm speaking to you !

**Norepinephrine**  
Figure 4.16



**Acetylcholine**  
Figure 4.9



# So what are the key memory molecules ?

Association and co-incidence

Pay attention while I'm speaking to you !

Removing the brakes  
and revving the engine





# So what are the key memory molecules ?

Association and co-incidence

Pay attention while I'm speaking to you !

Removing the brakes  
and revving the engine

Glutamate and calcium  
- the memory superchargers !



# Messenger molecules - turning up the gas !



$\text{Na}^+$

$\text{Ca}^{2+}$

-70mv

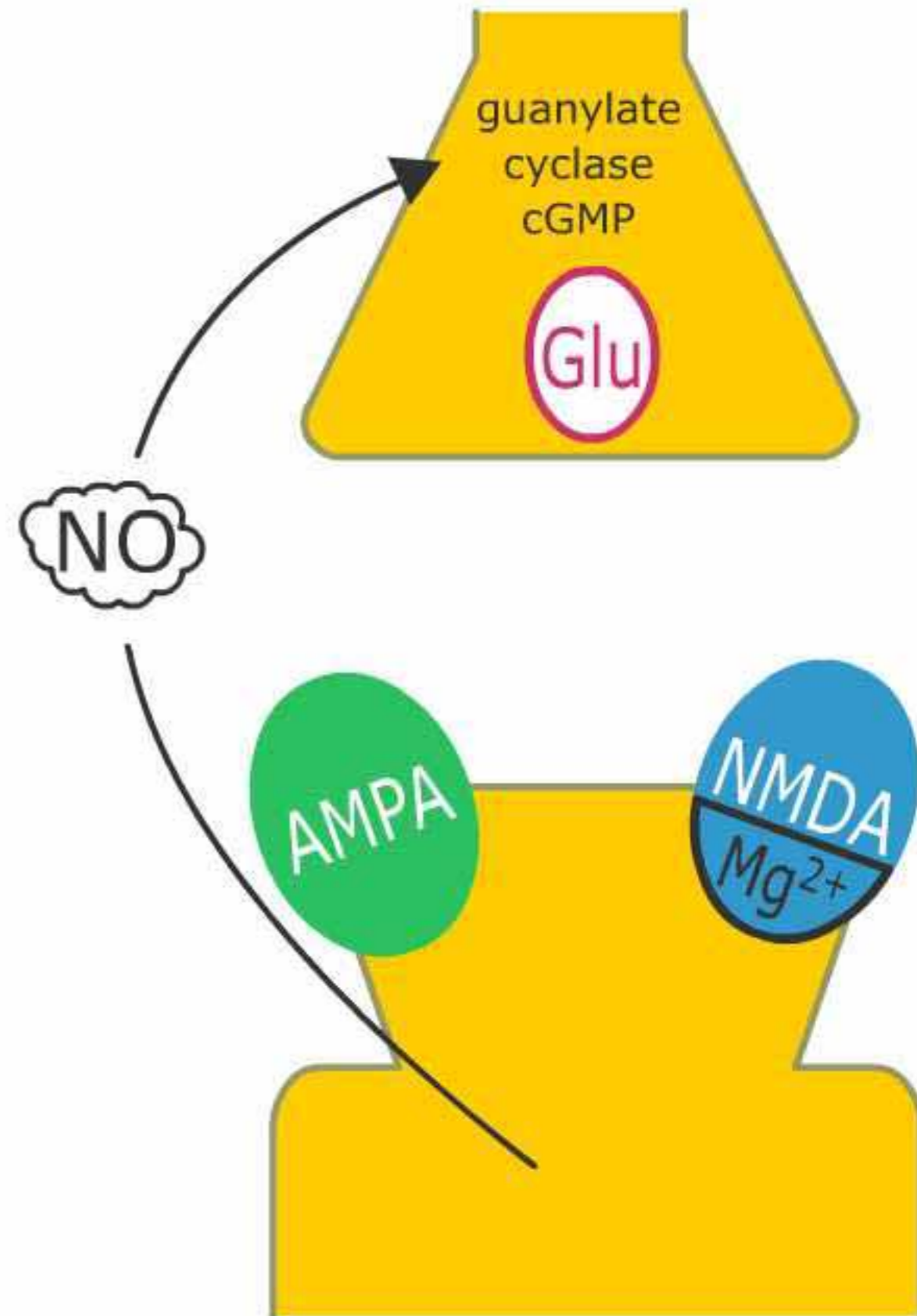


"Hey...step on it !"



# Memory enhancement ?

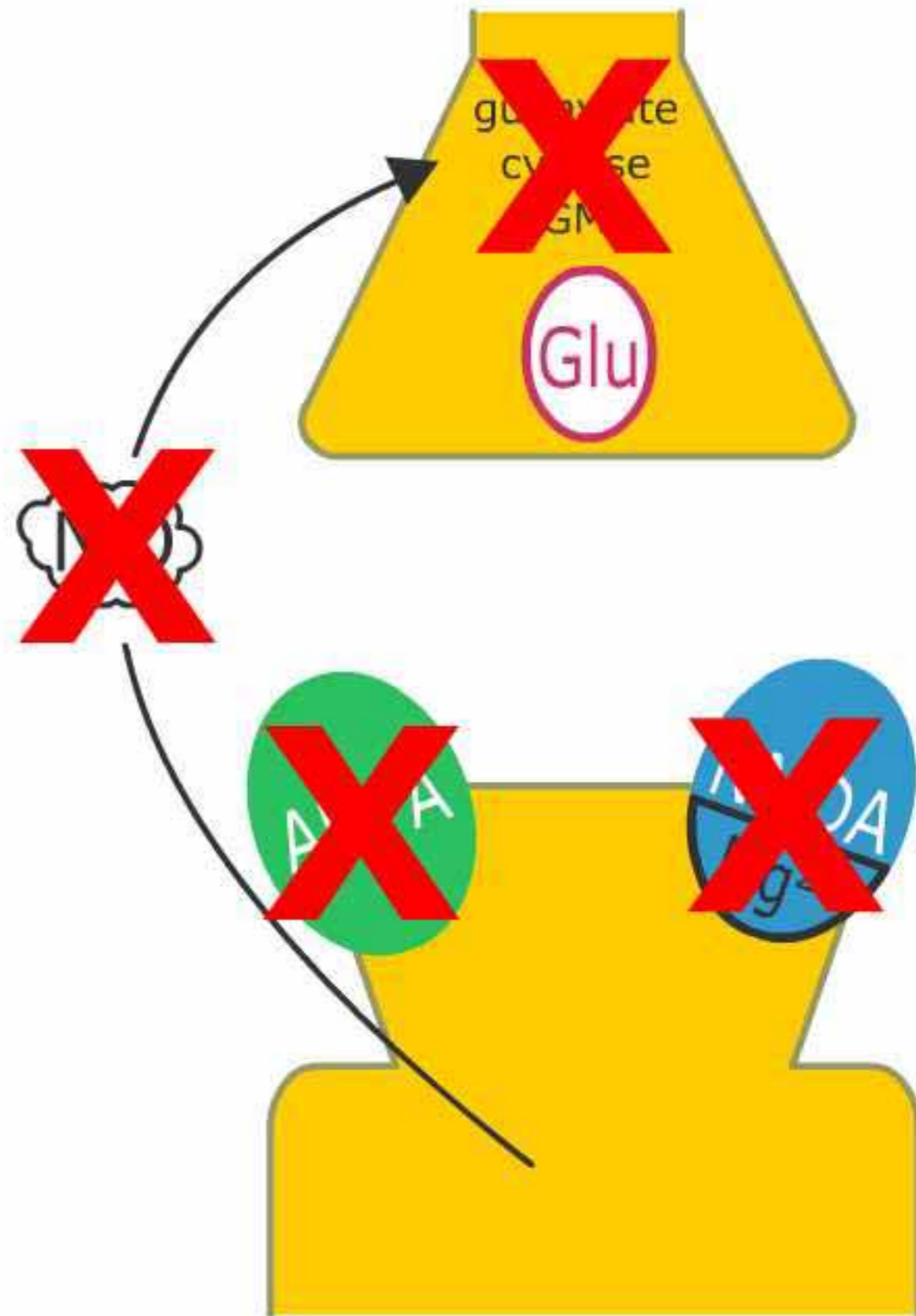
A matter of memory formation rather than recall:



# Memory enhancement ?

A matter of memory formation rather than recall:

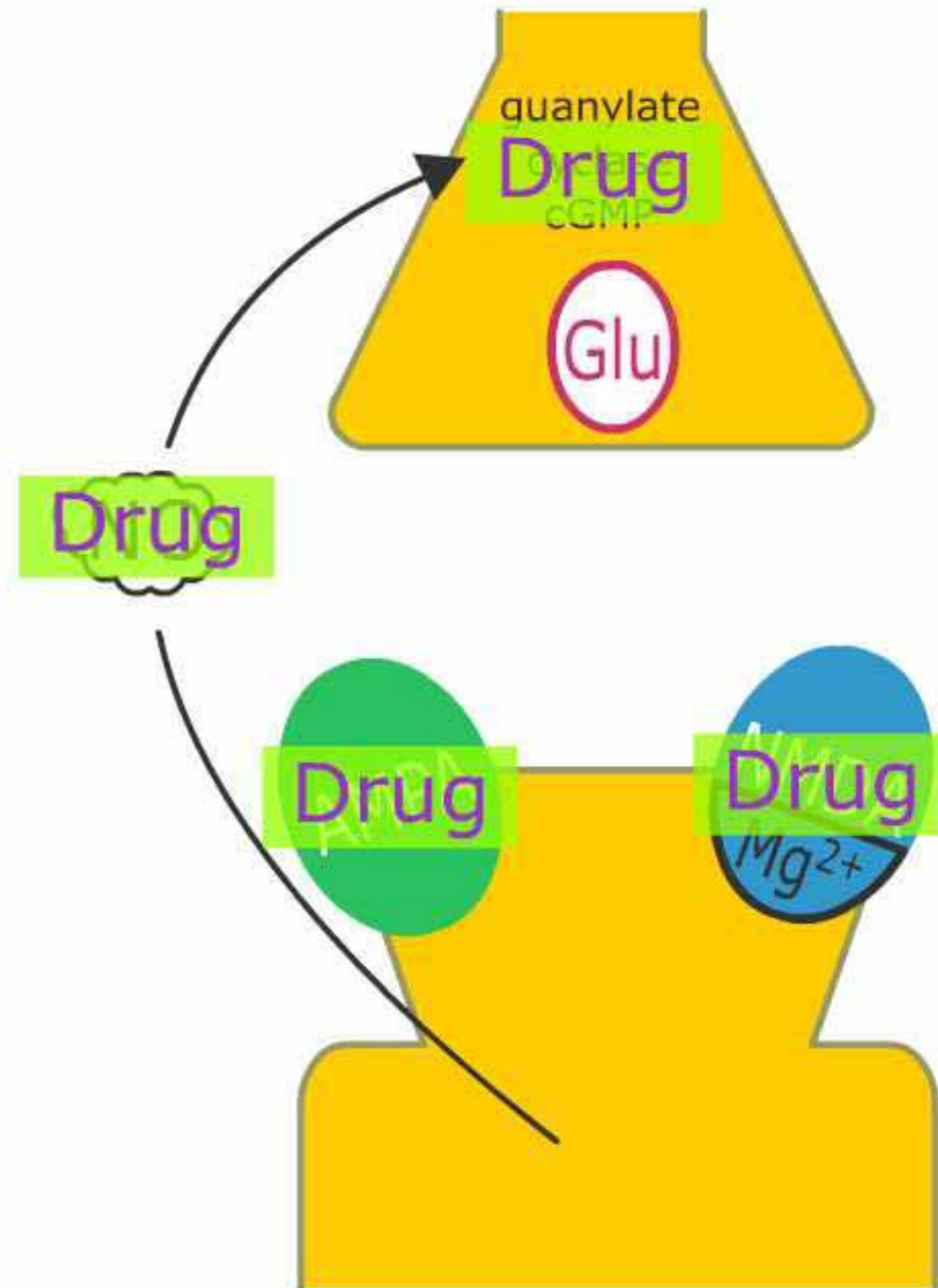
Memory formation ✗



# Memory enhancement ?

A matter of memory formation rather than recall:

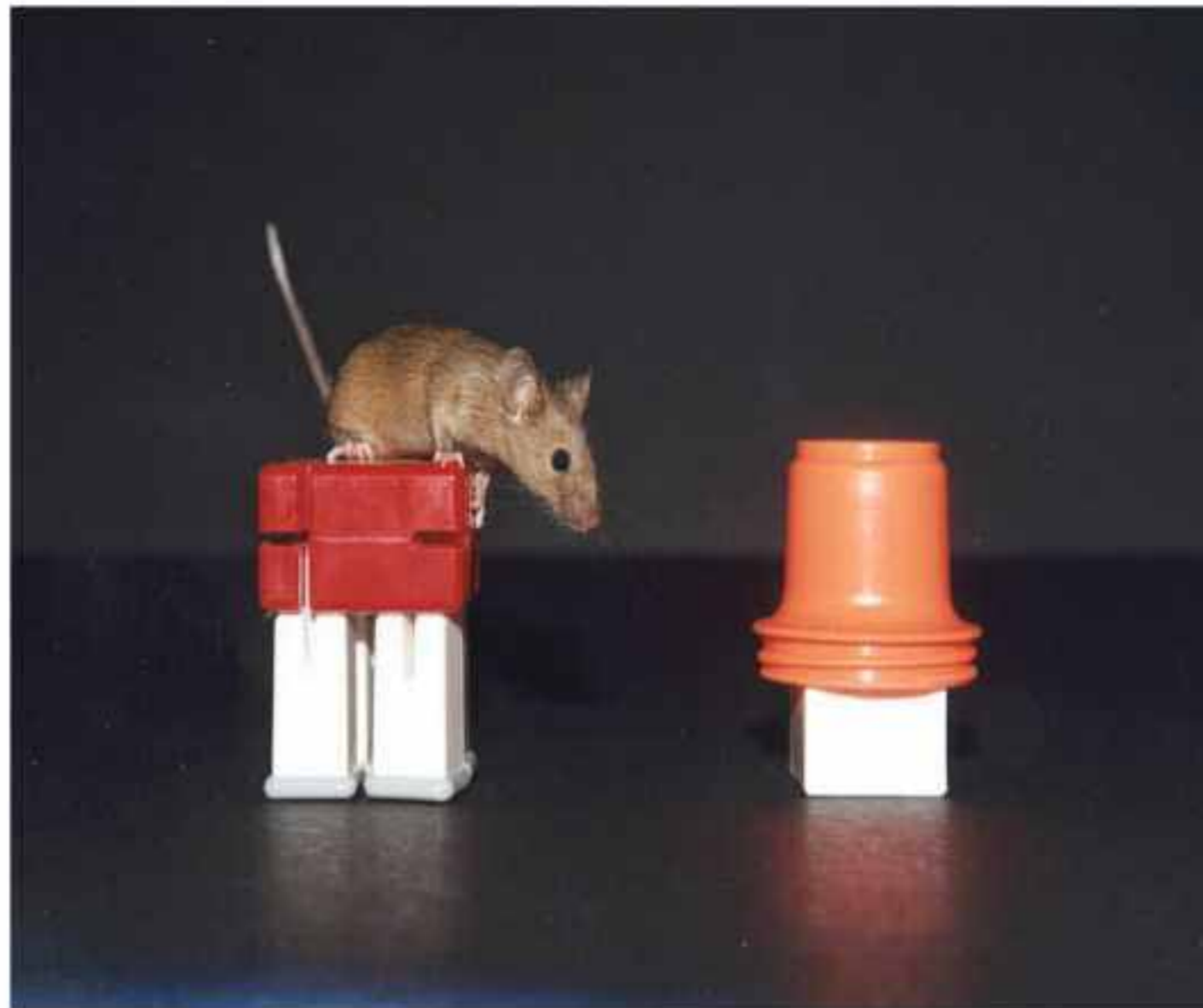
Memory formation ✓



# Memory enhancement ?

More NMDA receptors ?

'2B or not 2B ? - that is the question' (Tang *et al* 1999)



# Molecular switches and structural changes involved in LTM

So how do memories become etched into stone for posterity ?



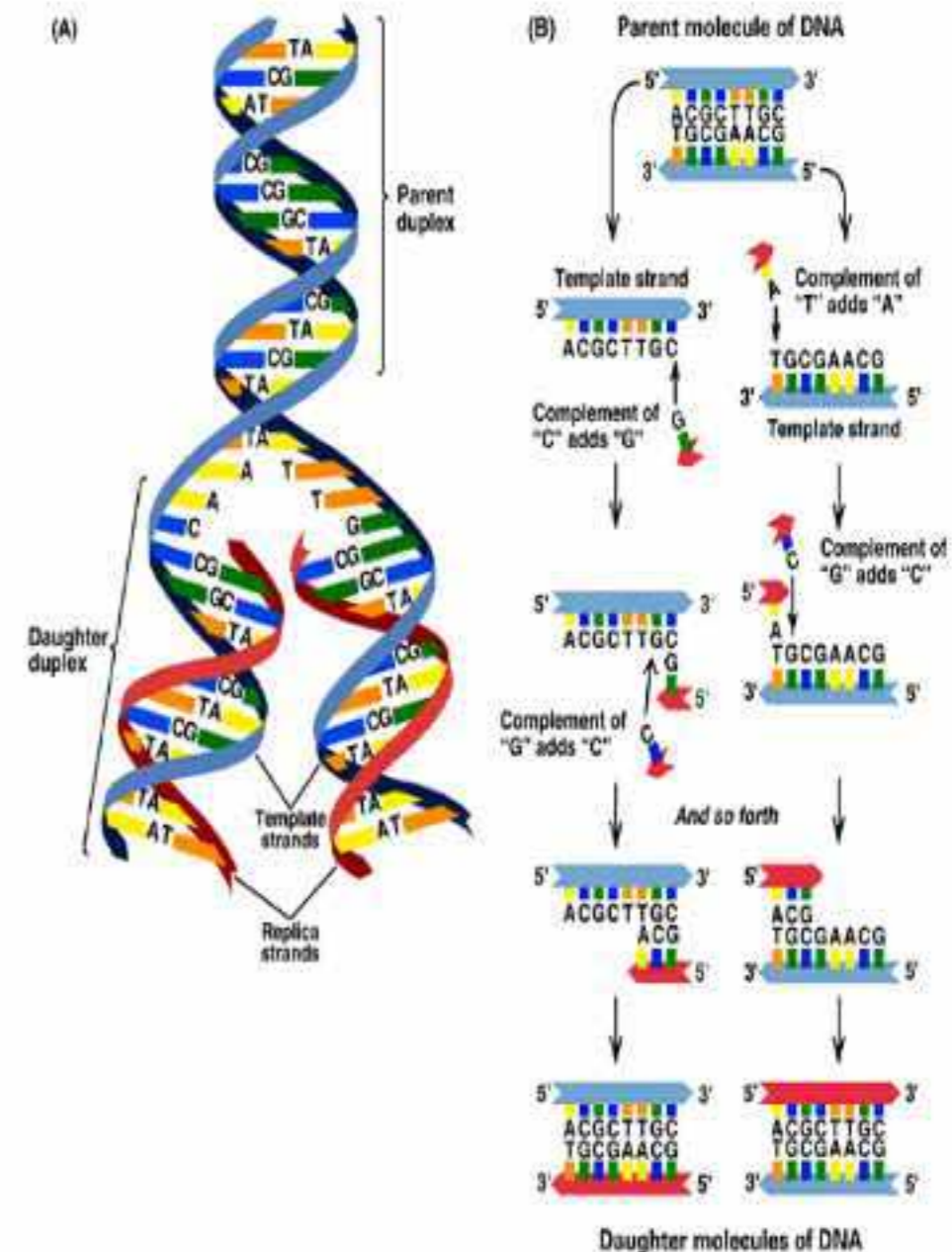
# Molecular switches and structural changes involved in LTM

So how do memories become etched into stone for posterity ?

Altered activity - gene transcription  
- protein synthesis - structural change

Each cell actively expresses 20,000 genes and perhaps 4000 proteins

1000 genes and 200 proteins may be altered when a cells response is potentiated

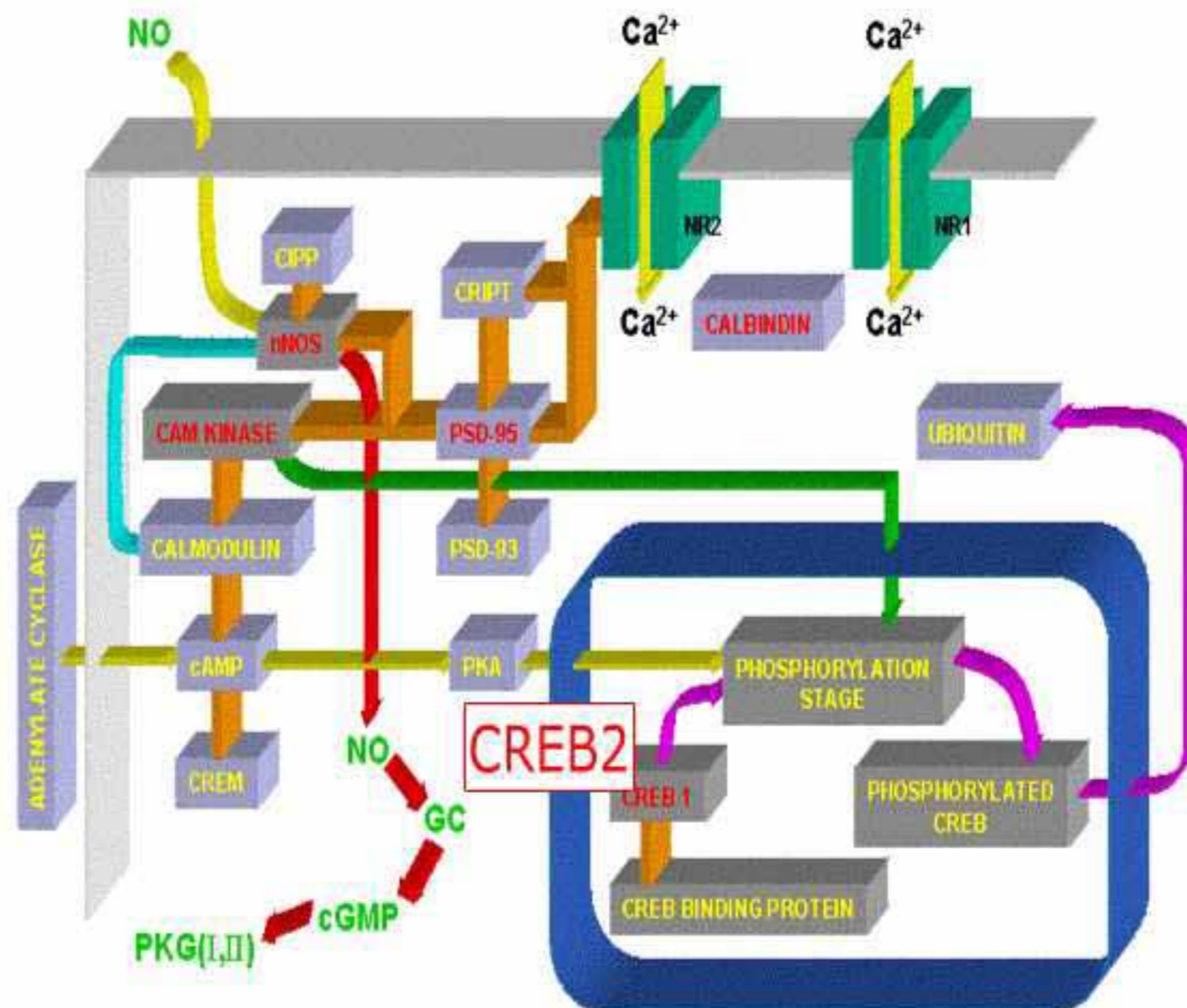




# Molecular switches and structural changes involved in LTM

The long-term memory switch

- kinases, phosphorylation and CREB1



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Repressor elements CREB2 and PP1



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- PP1



- CREB2

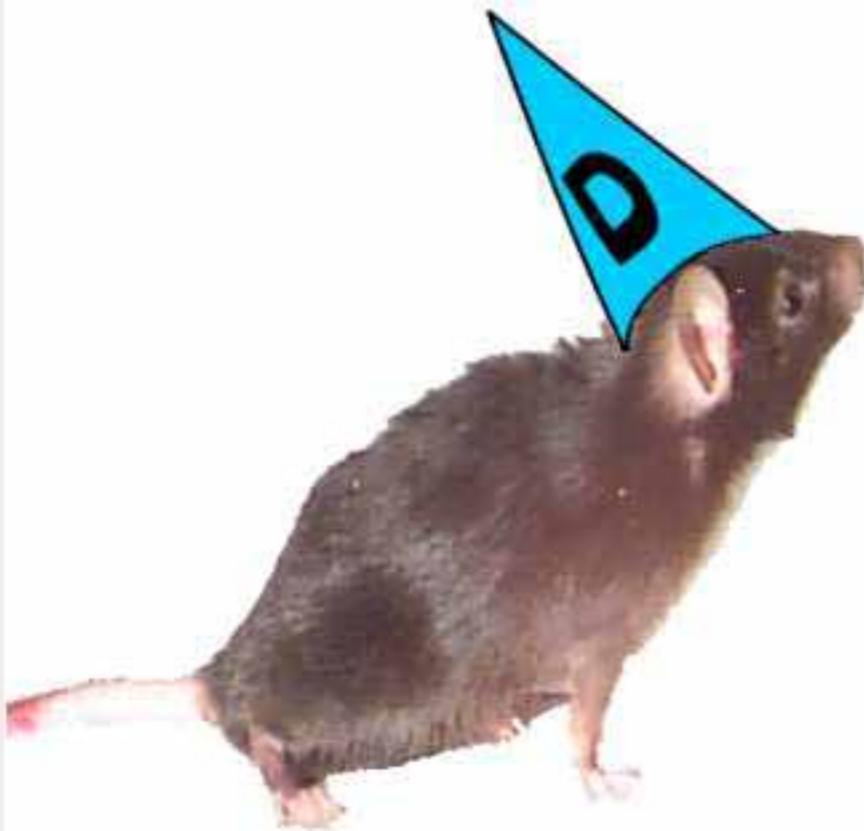


- CREB2

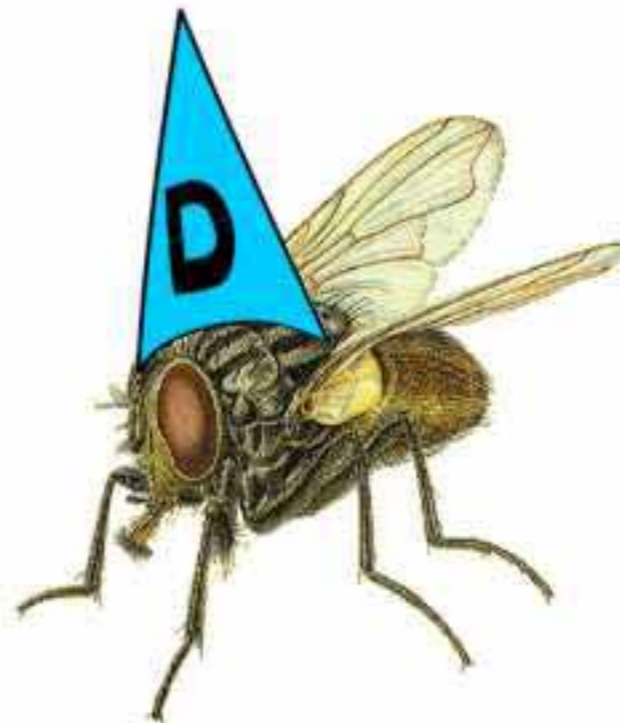
# Molecular switches and structural changes involved in LTM

The long-term memory switch  
- kinases, phosphorylation and CREB1

Repressor elements CREB2 and PP1



+ PP1



+ CREB2



+ CREB2

# Molecular switches and structural changes involved in LTM

The long-term memory switch

- kinases, phosphorylation and CREB1

Repressor elements CREB2 and PP1

Is the 50% genetic contribution to intelligence due to relative differences in CREB1 and 2 ?



# Forgetting

So if we suppress the activity of CREB2 and/or PP1 in the brain can we can kiss all of our memory problems goodbye for ever ?



# Forgetting

So if we suppress the activity of CREB2 and/or PP1 in the brain can we kiss all of our memory problems goodbye for ever ?

No - forgetting is an essential part of the brain's memory system

Why ?



# Forgetting

You don't want to be reminded constantly of bad things

Why ?

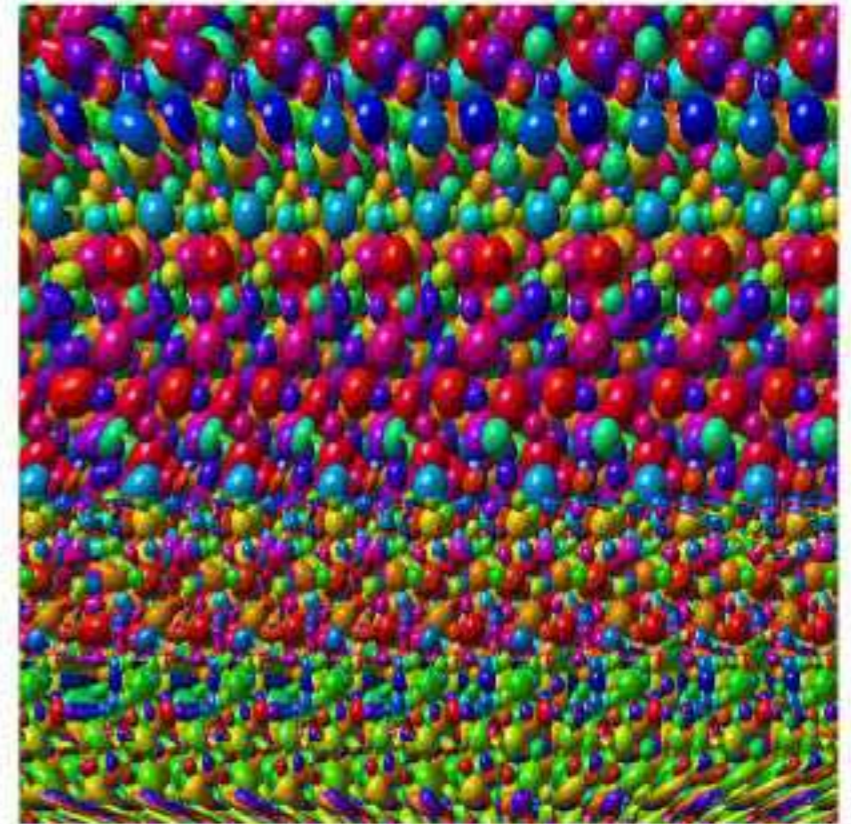




# Forgetting

You don't want to be reminded constantly of bad things

You don't want to be so overloaded with unconnected information that you can't see the wood for the trees



# Forgetting

The case of D.C. Shereshevski



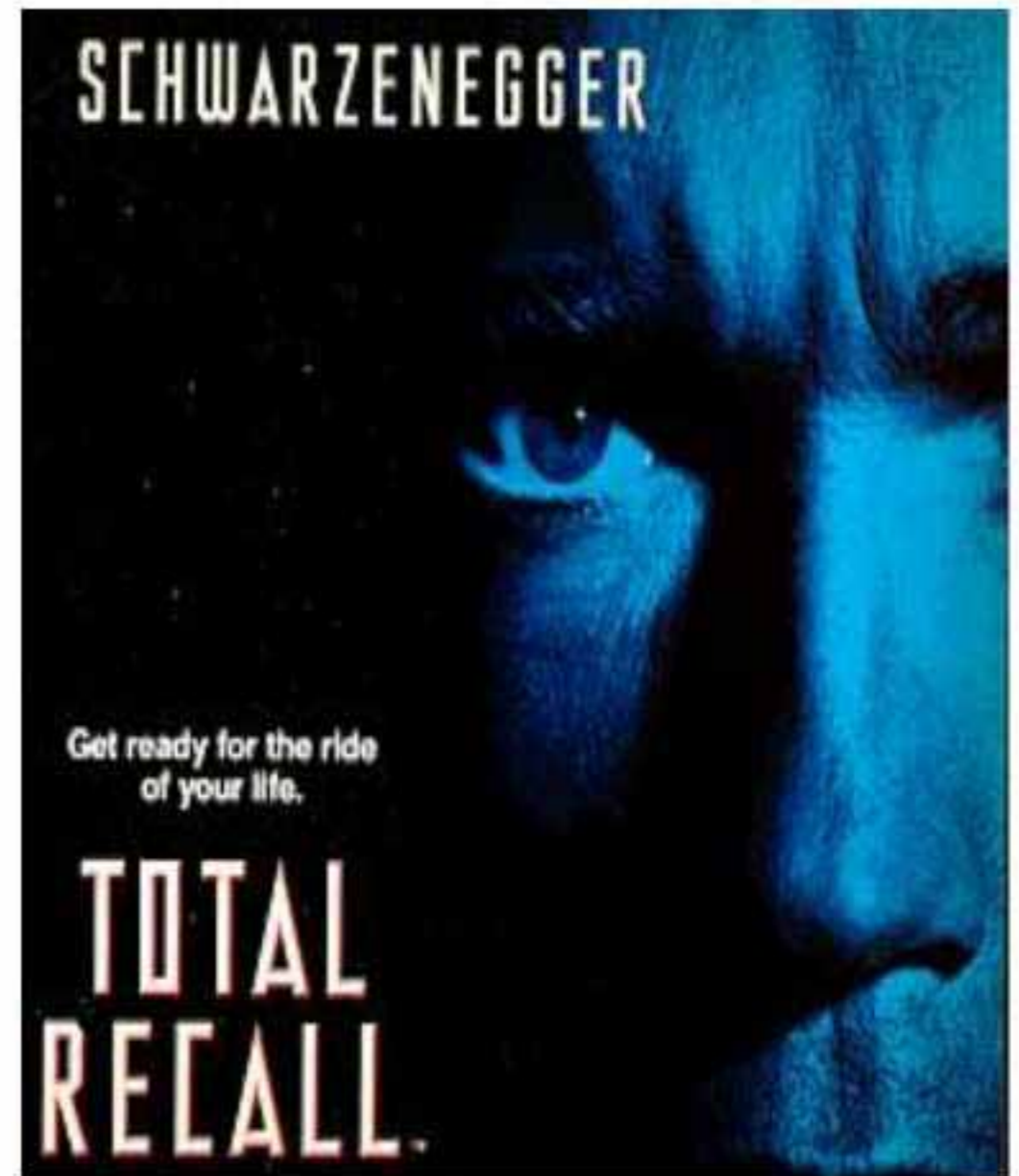
Aleksandr Luria

14	39	12
A	E	123
1492	I	456
K	O	V
1945	54	789
2001	J	B
X	15	H
99	16	W
Q	1066	37
Y	27	C

## So how does forgetting work ?

Everything is stored but we just can't access it - recall problem

Memories fade or are overwritten if not recalled - storage problem

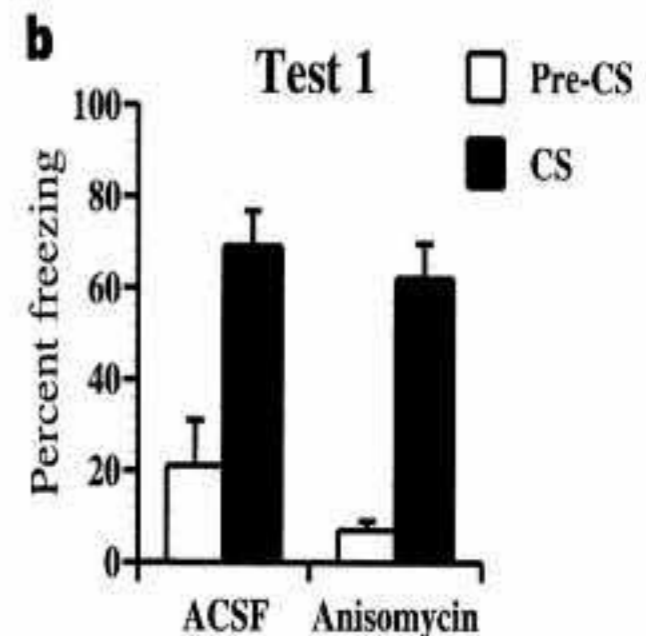
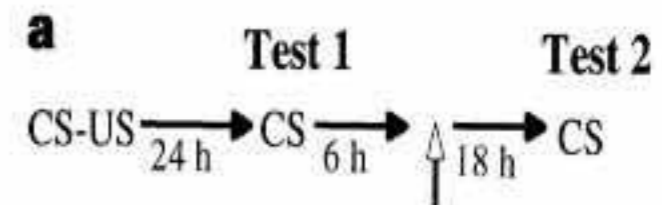
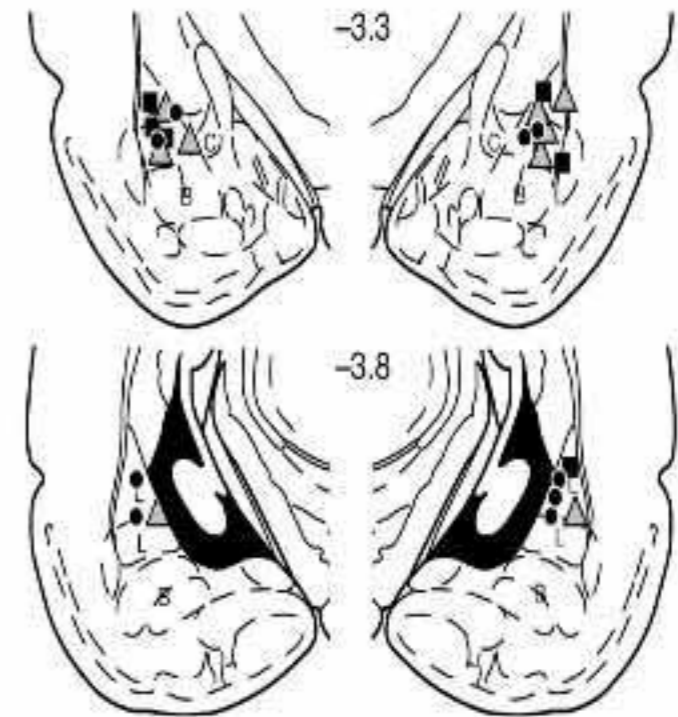


# So how does forgetting work ?

Everything is stored but we just can't access it - recall problem

Memories fade or are overwritten if not recalled - storage problem

The act of remembering also causes protein-dependent changes in the brain  
(Nader et al 2000)



## Memory and hormones

Strong emotional states facilitate the process of memory storage

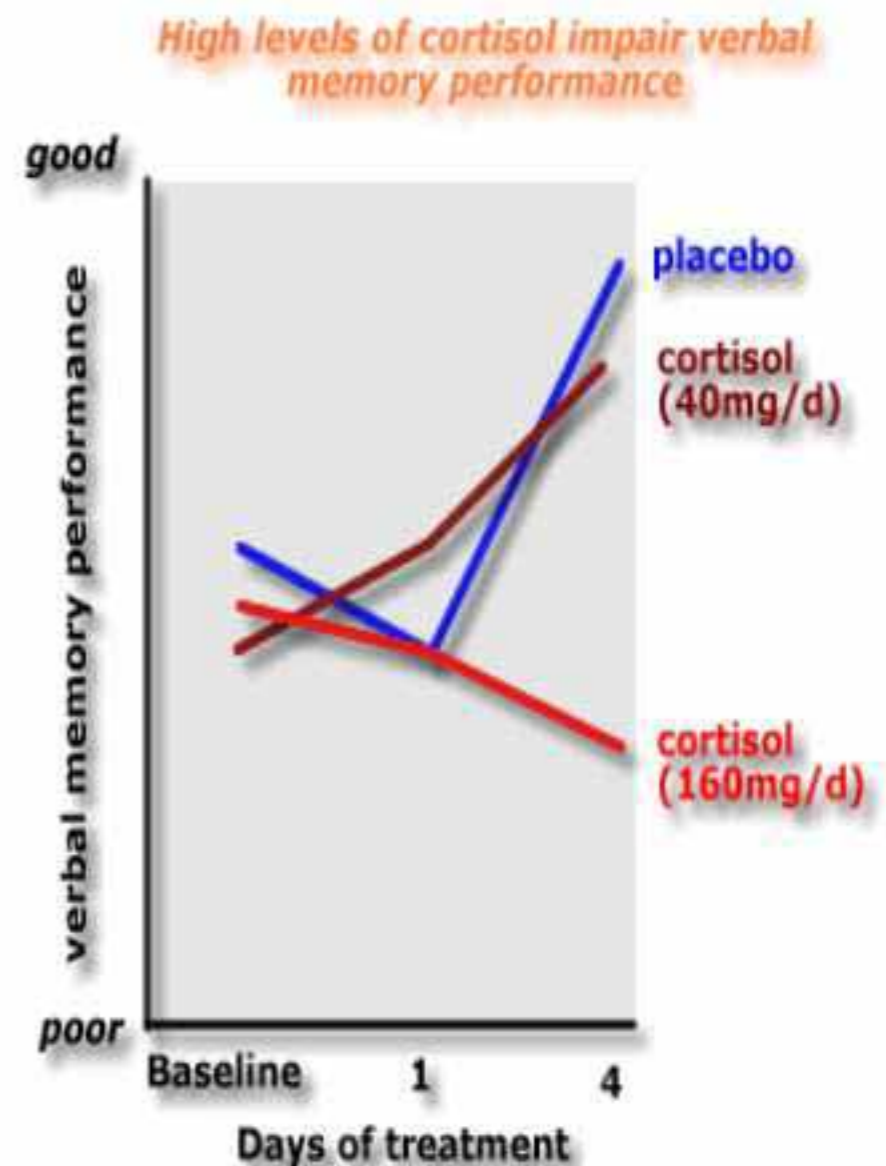


# Memory and hormones

Strong emotional states facilitate the process of memory storage

Stress hormones such as cortisol can, at low levels, facilitate memory processes although at high levels they are very disruptive

Department of Psychology  
University of Plymouth



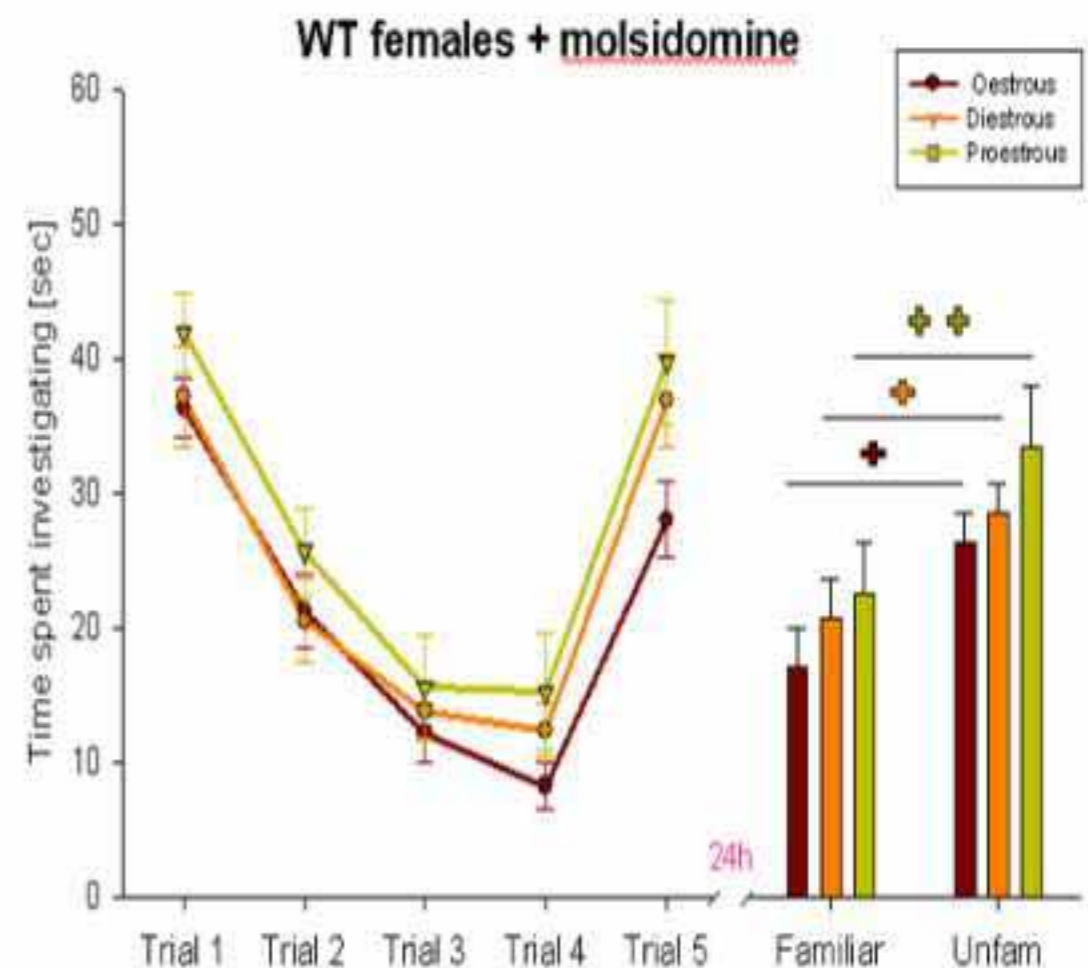
# Memory and hormones

Sex hormones, memory and mate choice - oestrogens

He's only Mr Unforgettable when he can get you pregnant !

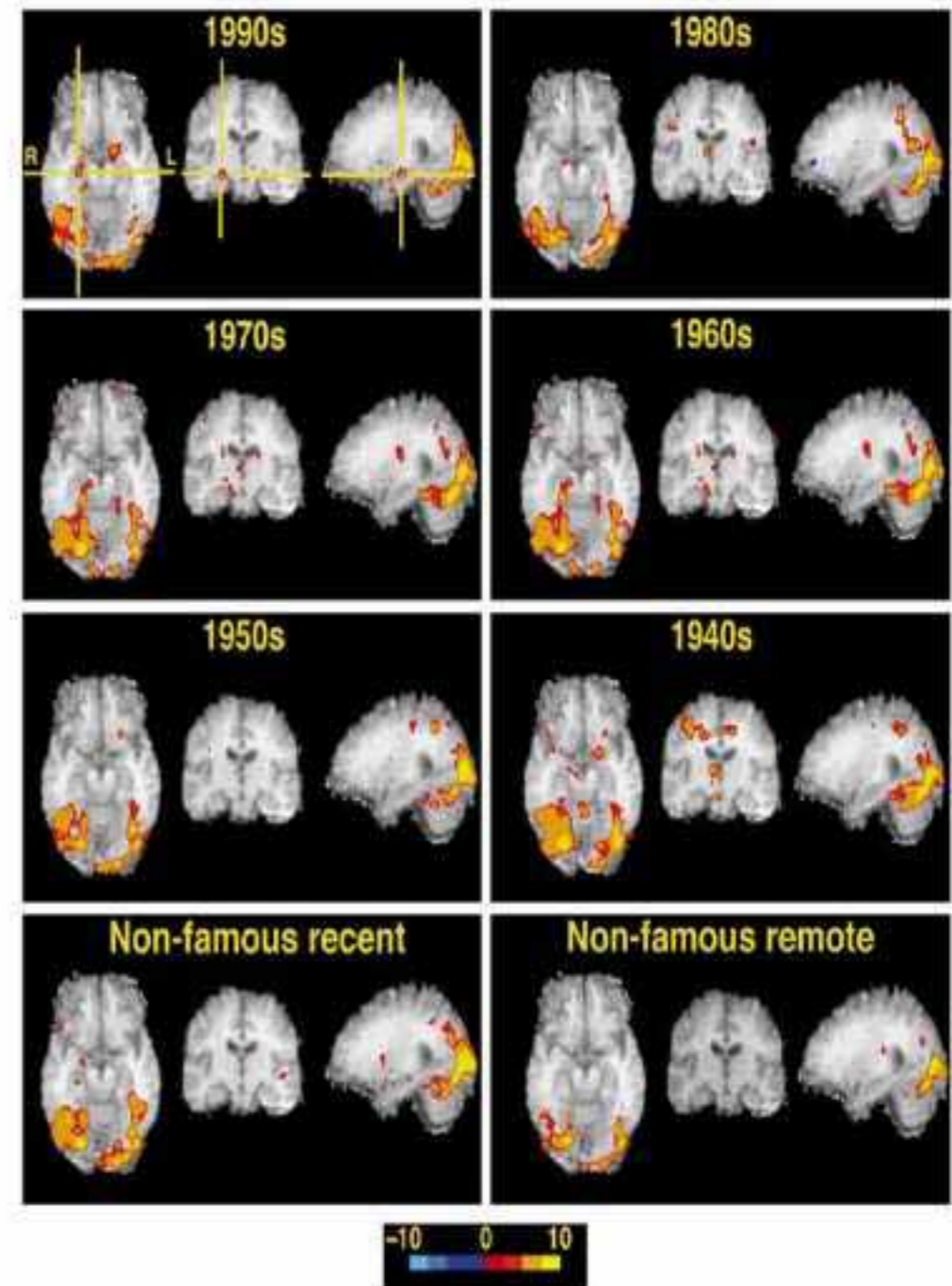
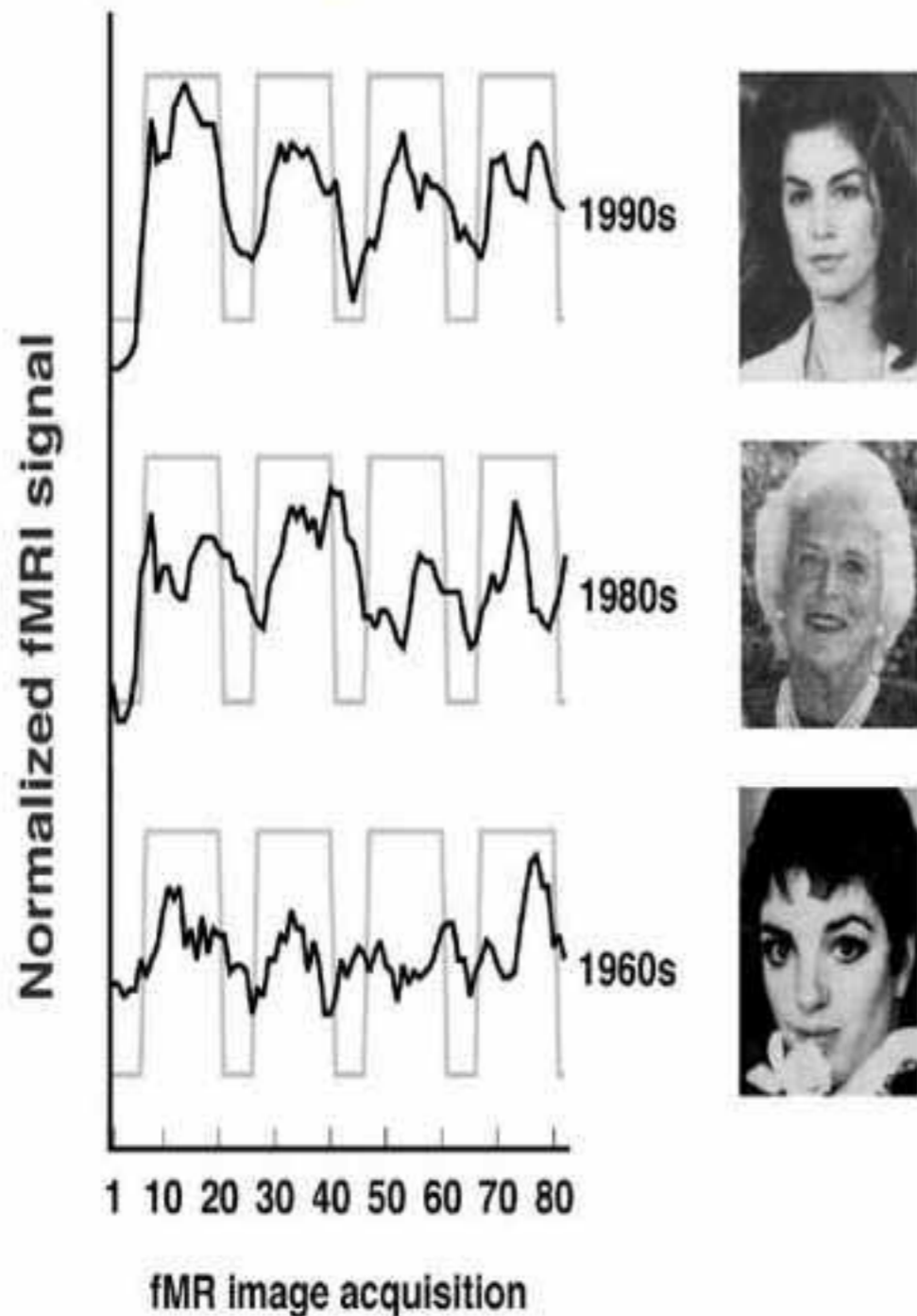
For female mice smell memory is best when they are fertile  
(Sanchez-Andrade and Kendrick 2003)

Possibly caused by oestrogen facilitating NMDA-evoked nitric oxide release



# How are different memories organised ?

## Consolidation of human memory (Haist *et al* 2001)

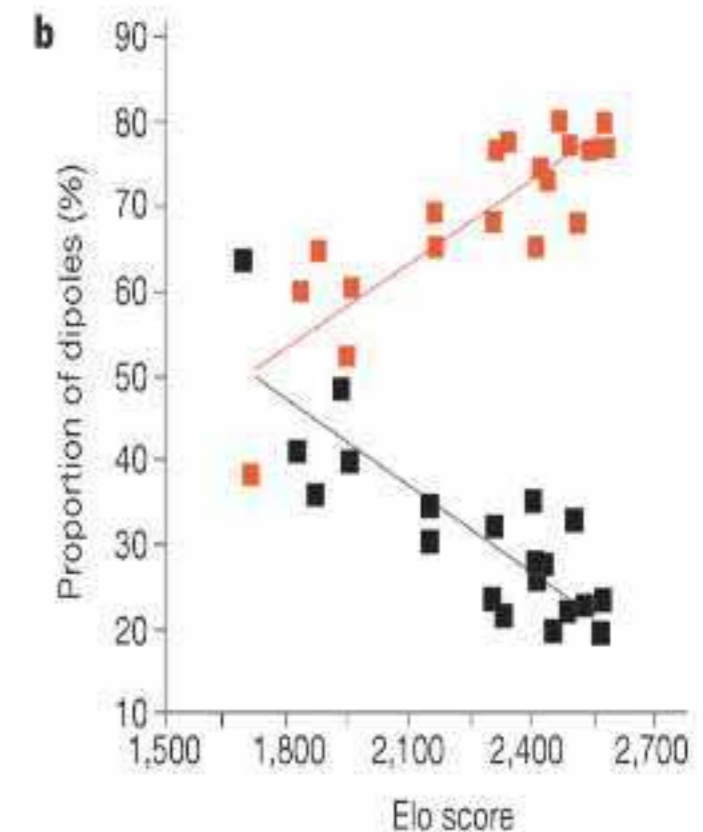
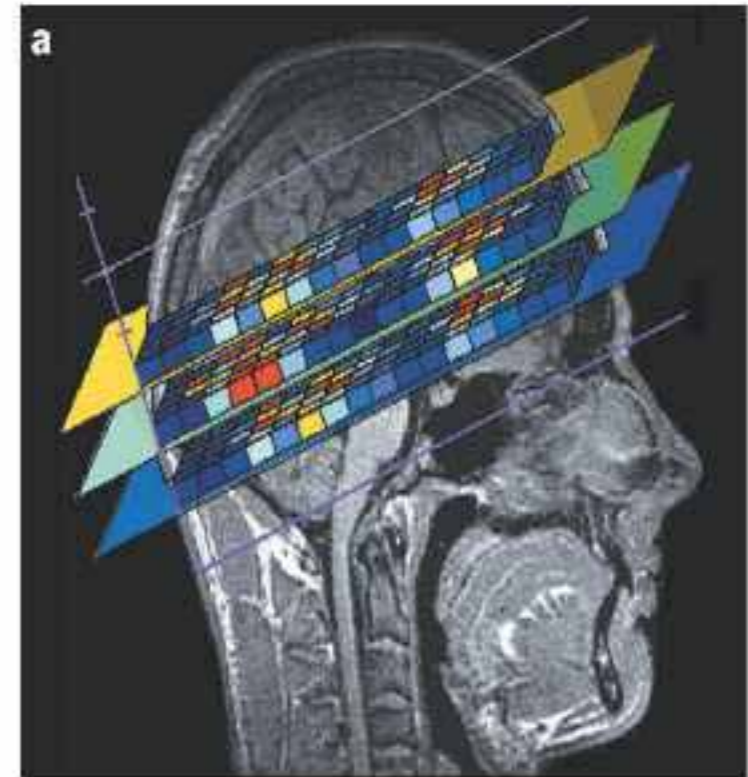




# How are different memories organised ?

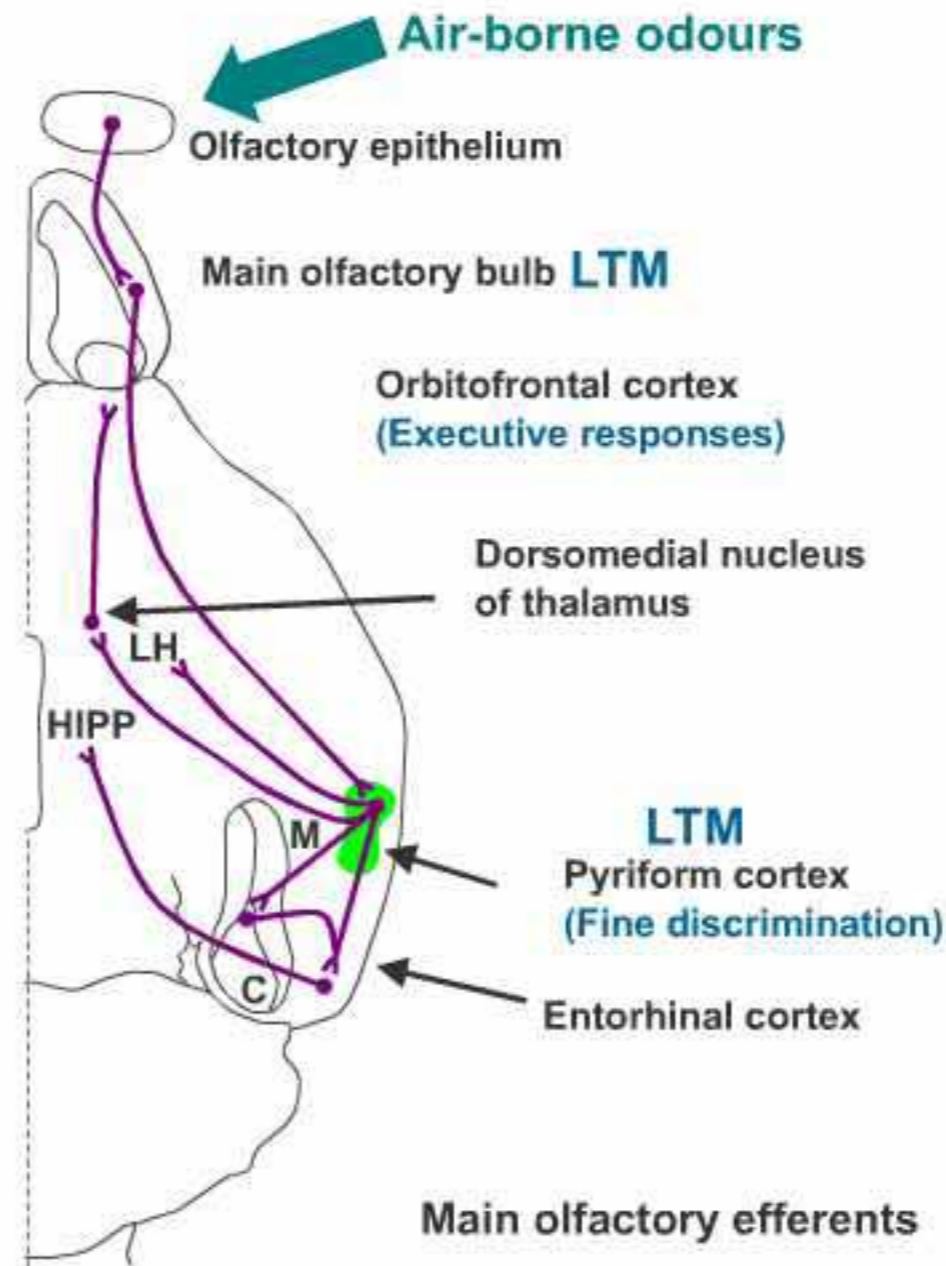
Consolidation of human memory  
(Haist *et al* 2001)

Chess experts vs chess amateurs  
(Amidzic *et al* 2001)



# How are different memories organised ?

Mother sheep identifying the smells of their lambs

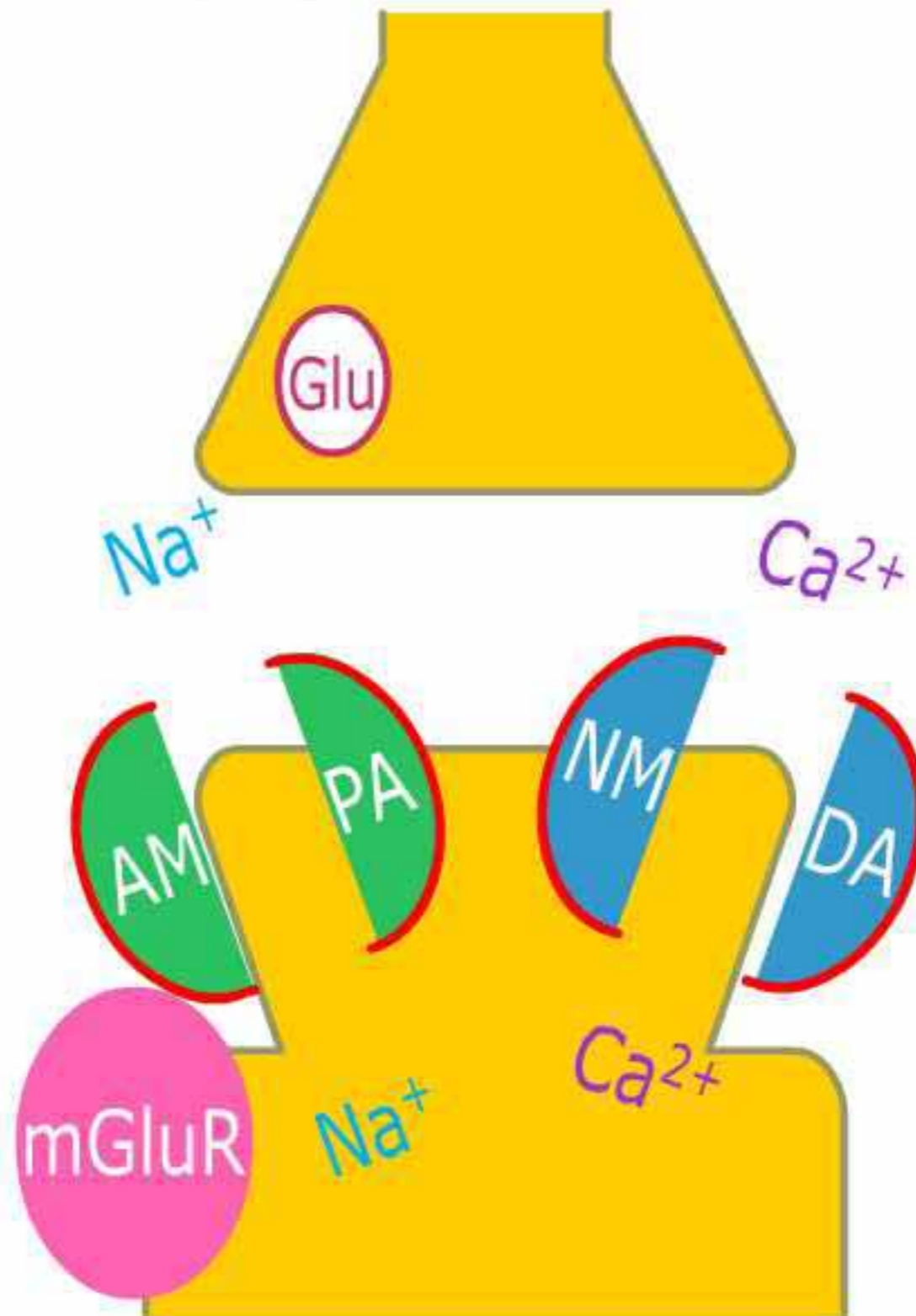


(da Costa *et al* 1997 Mol. Brain Res.)

# How are different memories organised ?

Mother sheep identifying the smells of their lambs

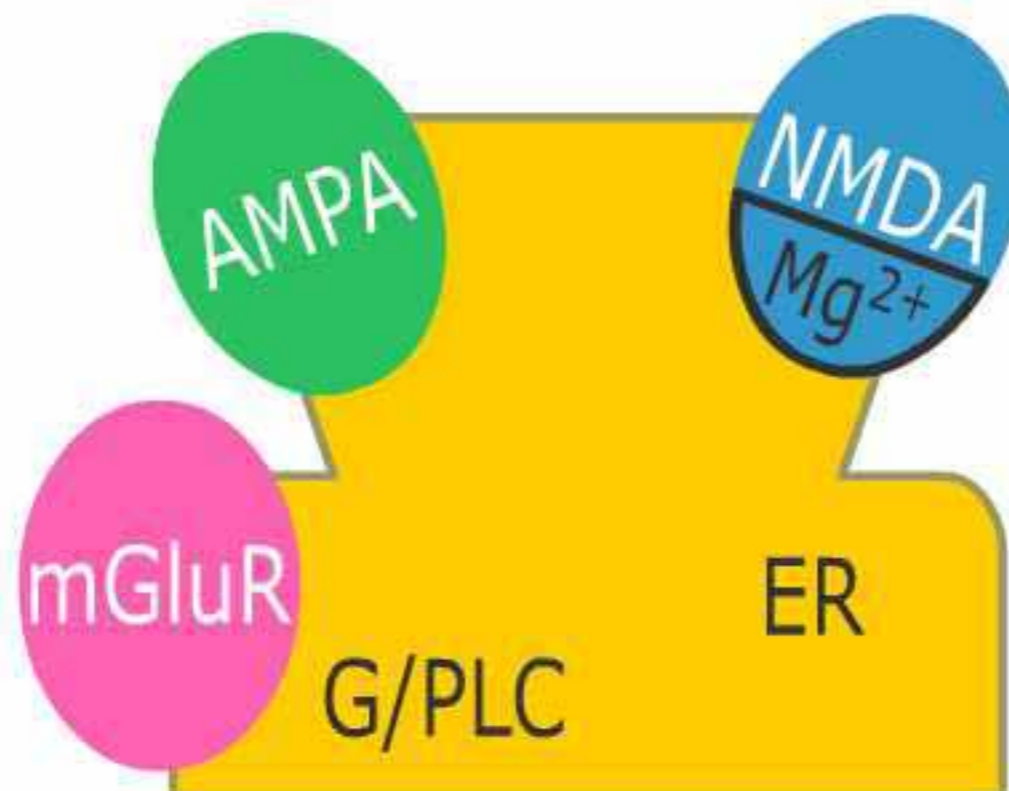
Short term:  
AMPA/NMDA  
sensitisation



# How are different memories organised ?

Mother sheep identifying the smells of their lambs

Long term:  
mGluR  
activation



# Some general principles of brain information storage

The size of a memory representation decreases with time

Sparse encoding through specialisation

The 'Granny cell' trap



## Some general principles of brain information storage

The size of a memory representation decreases with time

Sparse encoding through specialisation

The 'Granny cell' trap

Memories are distributed representations capable of filling in gaps



# Some general principles of brain information storage

Generate as extensive and flexible representations of new information as possible

The screenshot shows a website for 'Information Technology' with a search results page for 'Computer Accessories/Consumables'. The page features a navigation menu, a search bar, and a grid of product listings. The products listed include:

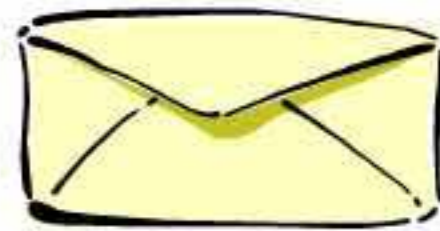
- Fuji Diskettes
- Imation 3.5in. Neon Diskettes
- Imation Diskettes
- Imation Rainbow Diskettes
- Neato Floppy Disk Labels
- Sony Diskettes
- Verbatim Diskettes
- Imation 3490E/3590 Tape Cartridges
- Fuji DG 90 4mm Data
- HP DDS Data Cartridges
- Imation 4mm & 8mm Data Tapes
- Sony 4mm & 8mm Data

The website interface includes a search bar, a 'Go' button, and a 'Next Page' link. The page number is 11, and there are 12 pages in total. The navigation menu includes links for 'RS Home', 'About RS', 'Products', 'Search', 'Orders', 'InfoZone', 'Register', 'Help', and 'Log-In'.

# Some general principles of brain information storage

Generate as extensive and flexible representations of new information as possible

Find ways to piggy back the new onto the old

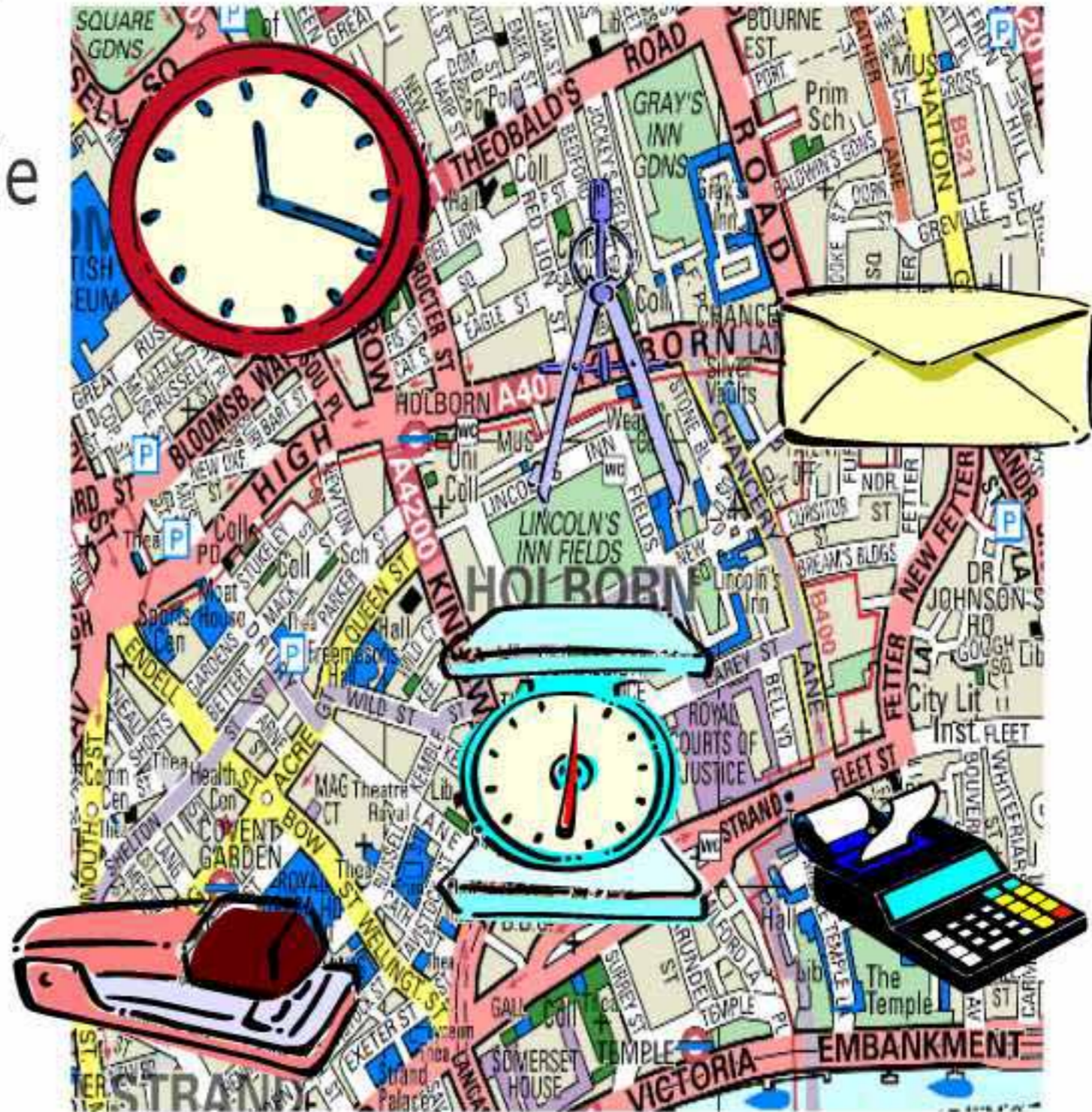




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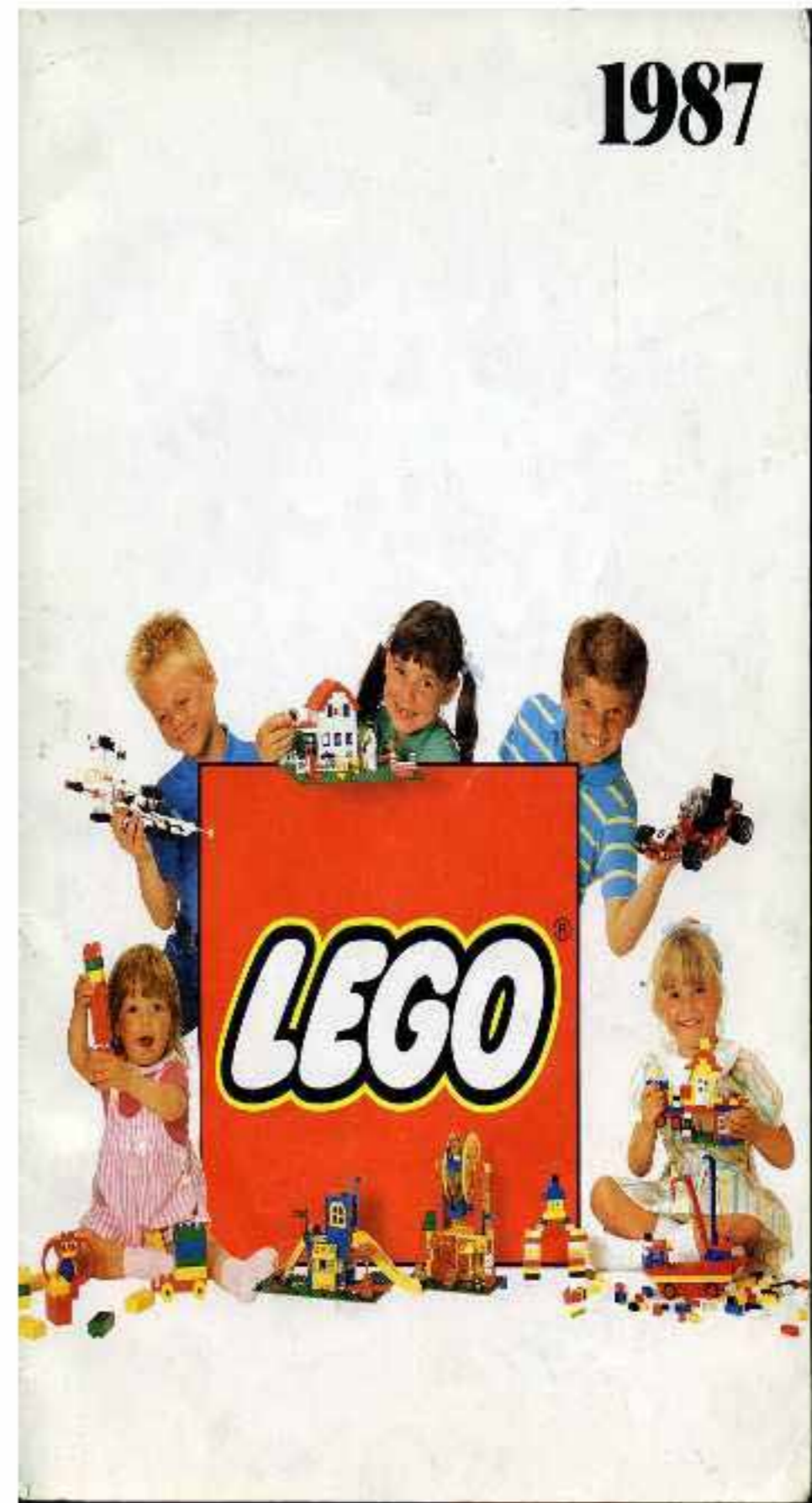


# Some general principles of brain information storage

Generate as extensive and flexible representations of new information as possible

Find ways to piggy back the new onto the old

Use more than one information access route



# Intelligence: language, rules and rhythms

Increased size of brain neocortex

- consciousness, awareness and long-term memories



# Intelligence: language, rules and rhythms

Increased size of brain neocortex

- consciousness, awareness and long-term memories

Symbolic representations improve organisation

- language, numbers etc.

Learning and application of rules and formulae



# Intelligence: language, rules and rhythms

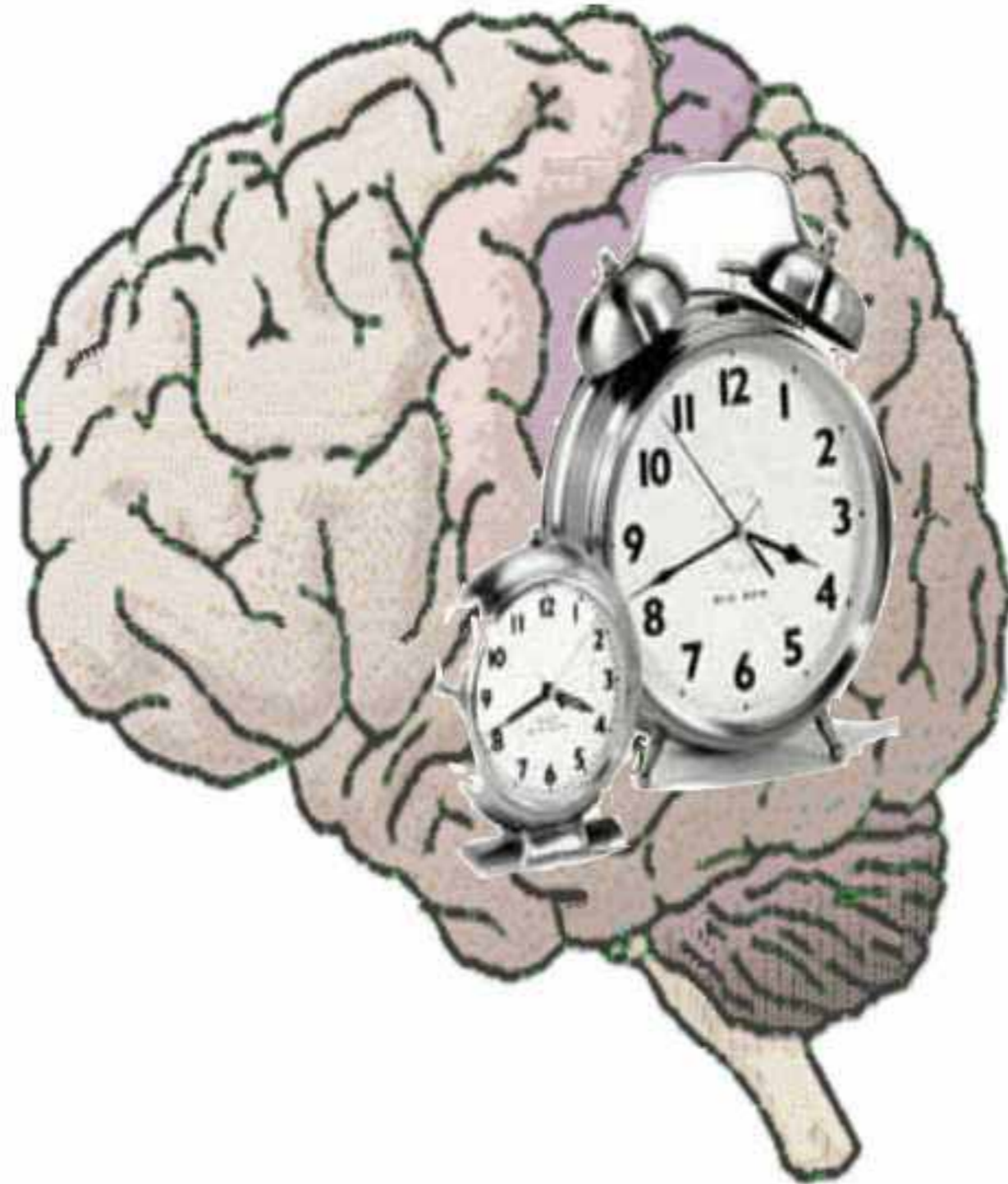
How does the brain link up and integrate information from different sensory modalities and memory systems to both derive and apply general rules ?

It's all a matter of juxtaposition and timing !



# Intelligence: language, rules and rhythms

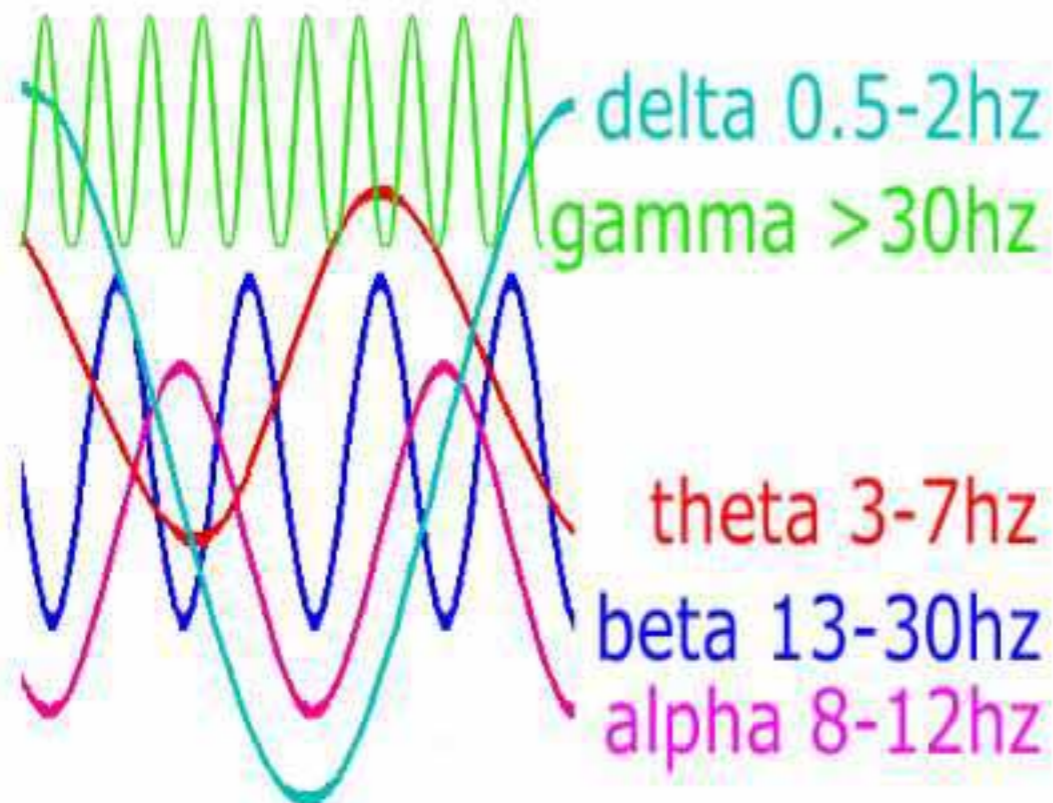
Time is the dimensional aspect of brain function we need to understand



# Intelligence: language, rules and rhythms

Time is the dimensional aspect of brain function we need to understand

The importance of synchrony, correlations and rhythms for binding information



Cambridge Philharmonic Orchestra

## Cognitive enhancement

So where do the next generation 'cognitive enhancer bullets' come from ?

Targeted drug delivery to specific brain regions will reduce unwanted side effects

Drugs targeting molecular repressors CREB2 or PP1

Learning how to induce patterns of brain activity that facilitate memory



# Conclusions

Memories start in short-term labile form that can become consolidated into a long-term one

The brain has multiple memory systems

Designed primarily to integrate not just to store

The hippocampus plays a key role in consolidating memories

## Conclusions

Good knowledge of the molecular control of memory formation and consolidation

Less known about global organisational principles

To be best organised we need to be able to forget

# Conclusions

Intelligence: organisation through language and consciousness and neocortex size

Cognitive enhancer bullets targeted drugs and tuning into rhythms

# Conclusions

In the meantime the best advice is:

Use it or lose it !