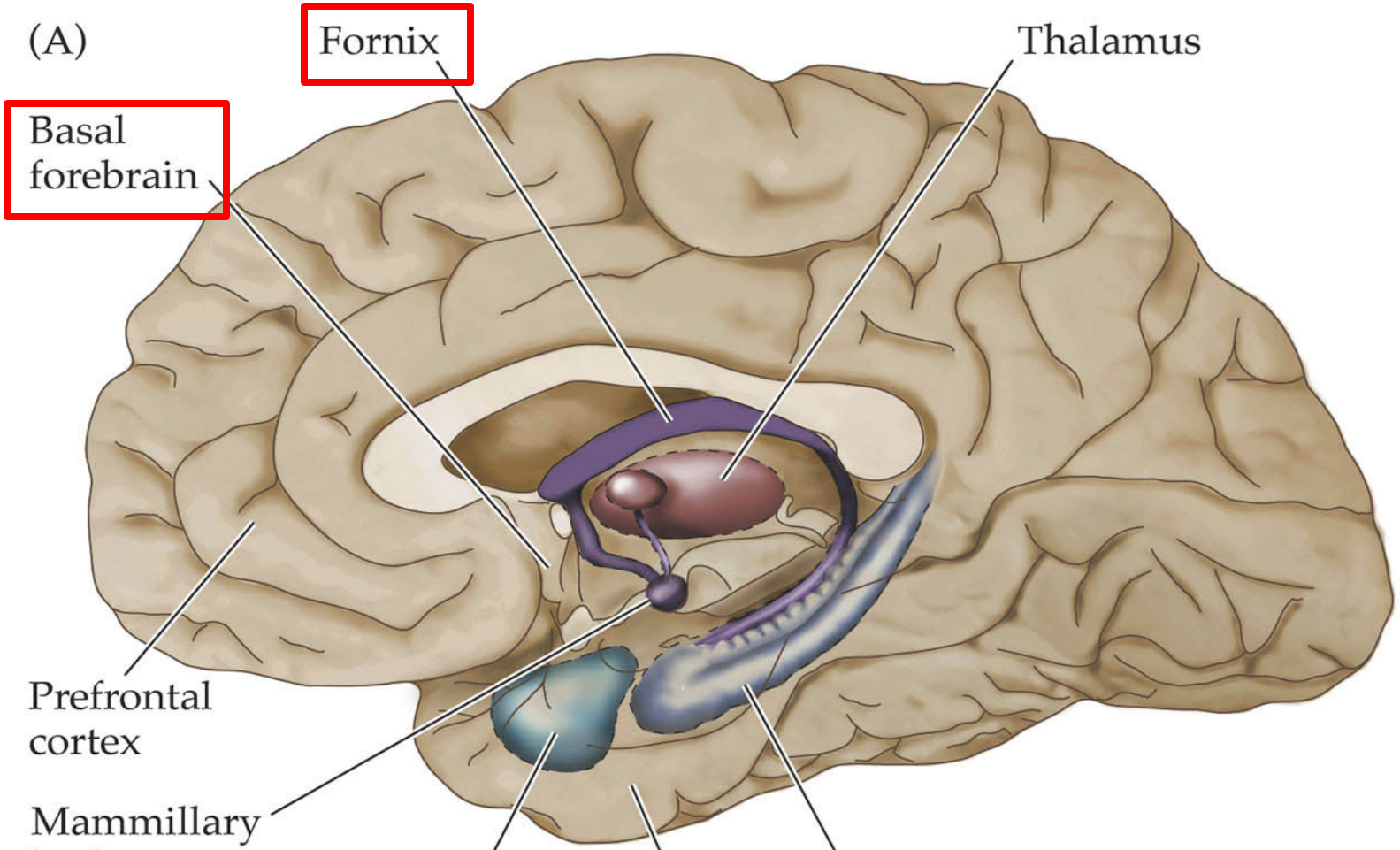
Overview:
- classes of memory
- WM vs. LTM
- DMRs
- LTP in Hippocampus
- Consolidation and MMO
- Associative Memory and AANs
- HM, Memory Deficits and Aging

Of Note:
- WM is very transient
- here LTM refers to enduring memories
  >> one day vs. Daily Memory Records
- Long Term Potentiation is the first step in LTM (long-term) formation
- Overall process is called Consolidation and described by MMO '95 (later slide)
- Auto-Associative Networks store items
- AANs are robust to damage: patient HM did not lose his LTMs

Categories of Memory are Simplifications!

Class-Wide Review:
- post Qs & Topics, study guide
- answer Qs
- camera's on please
- will do "call ons" begin w/ K's

30.6 Brain areas that, when damaged, tend to give rise to declarative memory disorders. (Part 1)



hippo → fornix → mammillary bodies, anterior thalamus → cingulate cortex → rhinal cortex

SEE KEY NOTES

"What is Memory?" – this, perhaps, is not the best question to ask…
"What do I need to Remember?" **-- <u>This</u> is a more pressing matter.**

<u>Examples of</u> *<u>What I Need to Remember</u>*

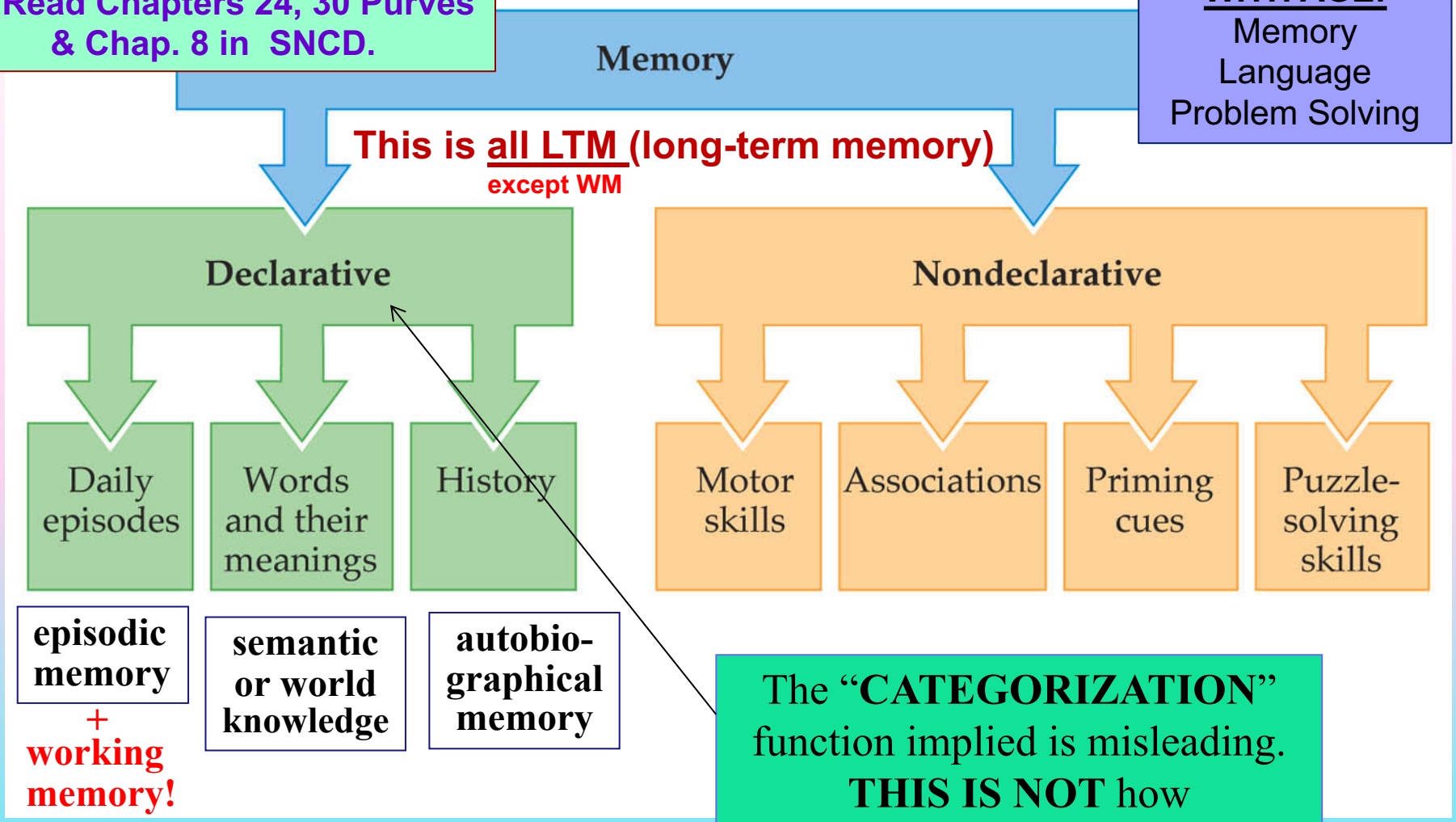
the sequence of words in a sentence (~WM) – so we can make sense of it
the gist of a sentence or topic so we know what to think and do
where I am driving to and how to get there (harder with AlzD)
the meaning of red, yellow and green traffic signals
words and their meanings (acutely lost in Semantic Dementia)
what I want to do today and who I will be interacting with
how to act appropriately in different social venues (see bvFTD)
to get dressed in the morning* and where my I-phone is [& not in laundromats]
to check Facebook, Snapchat, Tinder, LinkedIn and Pinterest before I go out
the passwords to 50 different sites and my lock combination
what neurofibrillary tangles and the hippocampus are
to pay the rent so we do not get evicted
that I am running low on milk, Ramen noodles and marijuana (ADLs)
the name of the person I just met and the phone number I was just given
where the bathroom is
the names of my family members
to take the Quiche out of the oven
to check my pocket calendar so that I do not miss any more meetings

The DETAILS of this list are not testable but the GIST of the list is!

see McGurk below

Read Chapters 24, 30 Purves & Chap. 8 in SNCD.

WHAT WE LOSE WITH AGE:
Memory
Language
Problem Solving



The "**CATEGORIZATION**" function implied is misleading. **THIS IS NOT** how *memory processes work*

ALL declarative memories are excerpts of our **Daily Memory Records!**

WM / working memory ~ STM (short-term memory)?

EM = Episodic Memory (includes daily episodes & LTM)

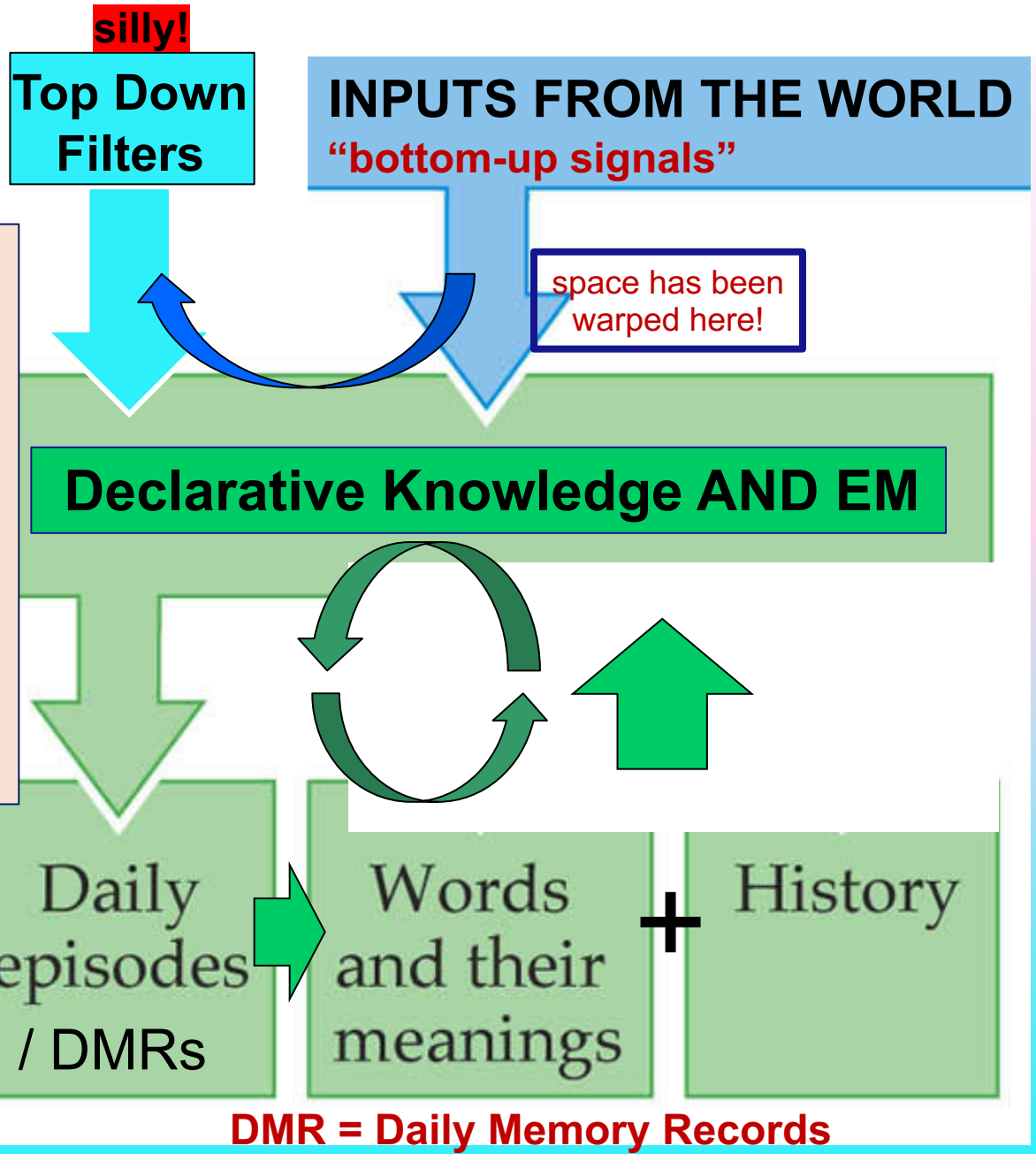
Memories are ACTIVATED NEURONAL REPRESENTATIONS

Formation of Representations *arises from the collision of neocortical Top-Down signals and Bottom-Up inputs from the world*. This results in WM and EM contents. Transient EM (aka DMRs) is a vast store that lasts a day or more. There is a loop between the DMR store and our onboard World-K at both the outset and during consolidation where elements of the DMRs are integrated into our world knowledge; much extraneous context is let go.

See *SNCD* and *MMO-1995* for a deeper dive.

Generation of EEM, enduring EM, is a separate consolidation process from **Knowledge Integration**, and storing *gist* is yet another distinct process

see new notes – 2019, 2021



When Memory, Language, Top-Down and Bottom-Up COLLIDE

https://www.youtube.com/watch?v=2k8fHR9jKVM&t=6s

B B B B B B B F F F F F F F F in 28 seconds

How do I remember things?
two main processes

RT: how good are DMRs in old age & AlzD?

Working Memory – WM chap. 9 *see notes on dichotomy*

7 ± 2 items, effortful, evanescent: **last seconds**

But is WM other processes? much, much more?

counting-memory of bahs, pahs = WM **explaining it later** is DMR

Day-Long / Daily Memory Records - DMRs

thousands of items, effortless, enduring, one-trial

Other Memory Terms: Episodic, Declarative, Autobiographical are all derived from DMRs

context is NOT repeated and so context DISAPPEARS over time:

Episodic Memory → **General Declarative Memory**

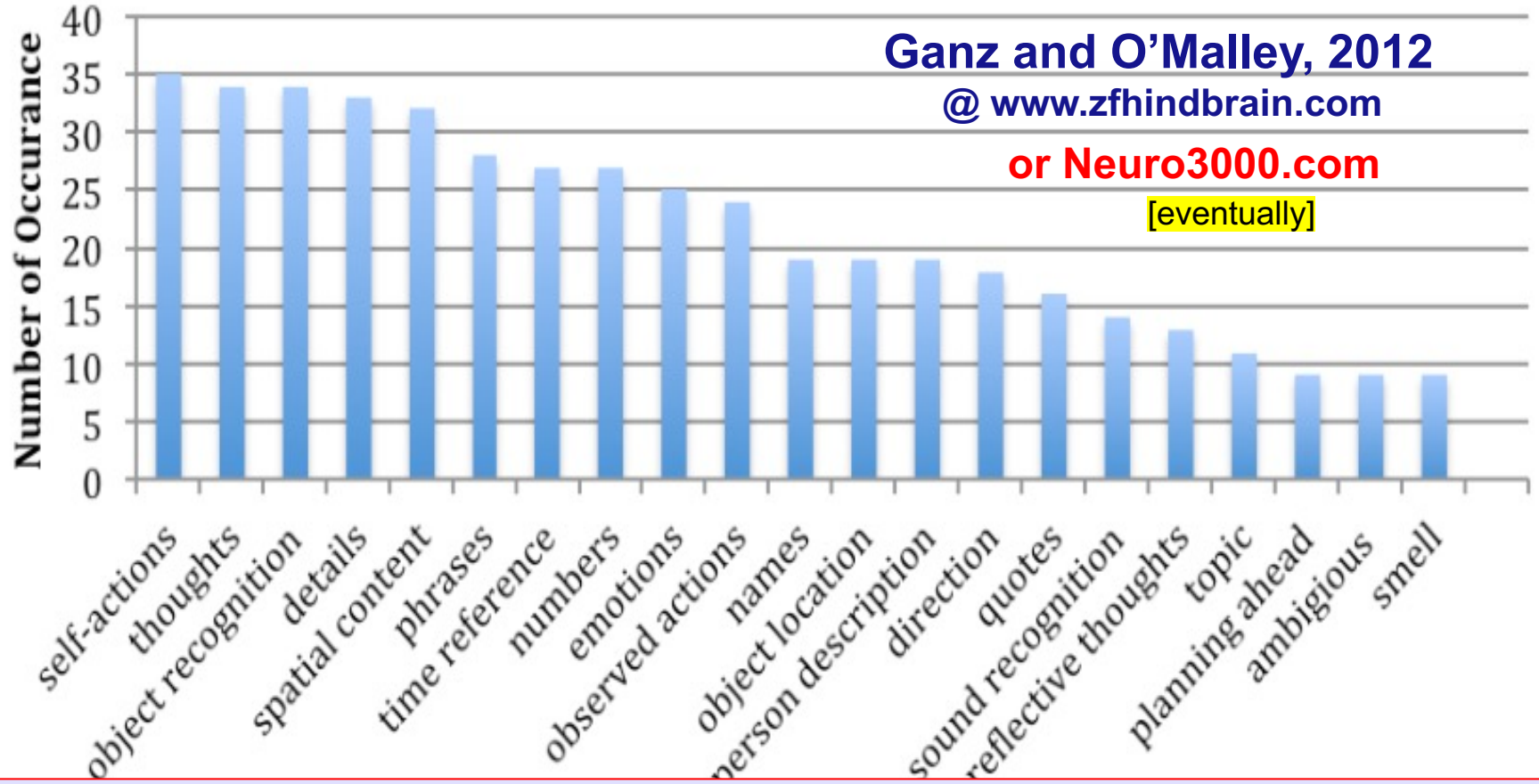
except for particularly notable epochs

For every memory, **context** is the **associated-details** that were present **during the writing of the DMR.**

4. What do DMR epochs look like?

- trans-cortical representations (applies to WM items, tba)
- binding depends gamma, theta and alpha band oscillations
- largely non-linguistic in nature: “knowledge tokens”

DMR Items, Frequency of Item Occurrence

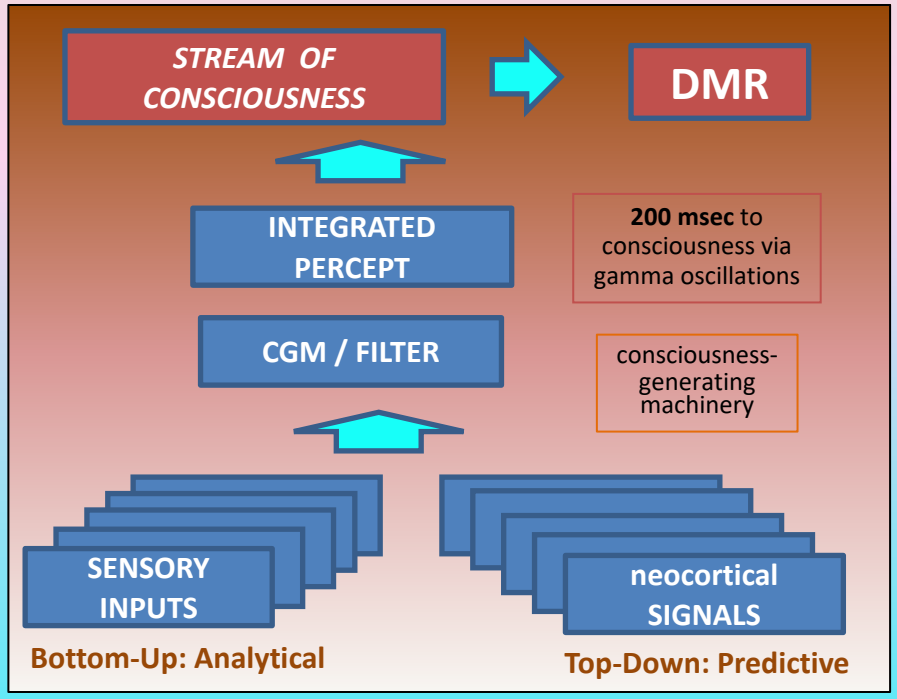


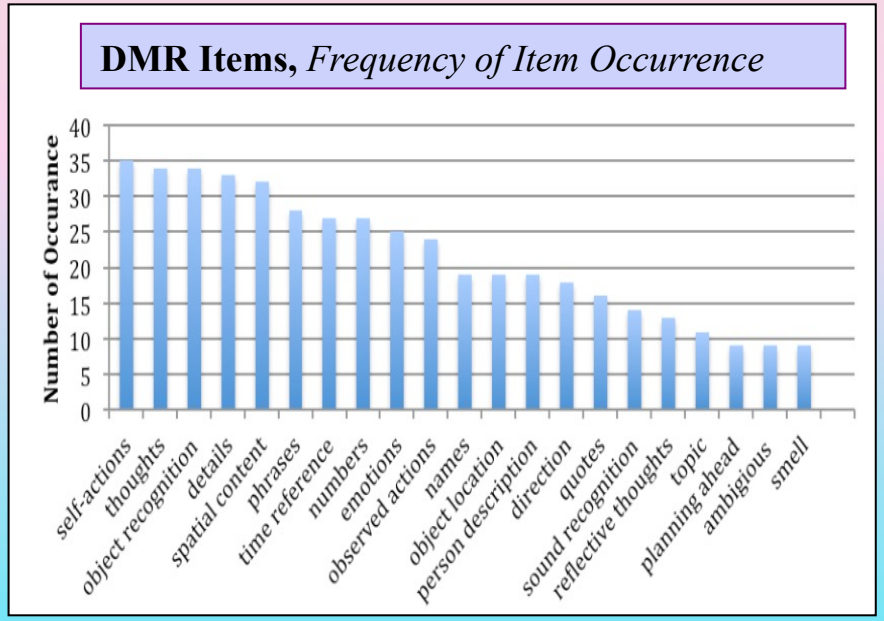
Consc. Epochs see VanRullen & Koch (2003); **Alpha/Gamma** see Ward (2003) in Trends in Cogn. Sciences

HOW does NEW knowledge enter our brains?

Rat Hippocampus
Santiago Ramon y Cajal

Most of the items below are: DIGITAL





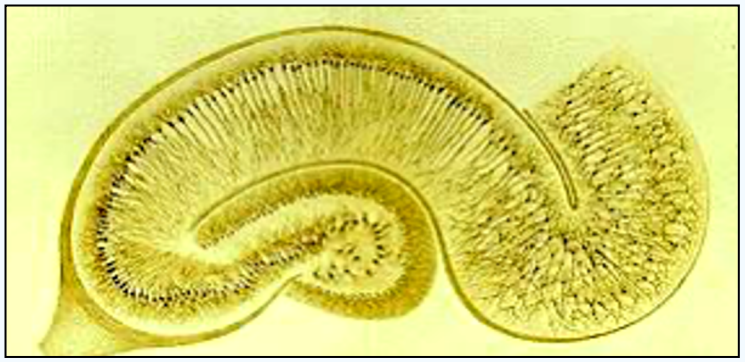
Ganz and O'Malley, 2012 @ www.zfhindbrain.com

see *On Intelligence* (Hawkins, 2004) and Baars & Franklin (2003, 2005, 2007)

actually *On Prediction*

DMR story overlaps 2003 Global Workspace model

LTP happens in the Hippocampus, but where are DMRs stored?



Santiago Ramon y Cajal

LTP also occurs in neocortex, amygdala, basal ganglia and other sites.

Dogma: Working Memory / WM is dominated by PFC (prefrontal cortex)
Dogma: Episodic Memories / EM initially stored in Hippocampus
But: How would you represent the rich, specialized contents of DMRs in hippocampus, vs. the elaborate, massive specialized structures of neocortex?
Alt-M: The initial EM traces (aka DMRs) are stored in neocortex. Hippocampus serves as an indexing system; creates chronology.
After Consolidation: Hippo no longer required; some chrono info is lost.
Prediction: once Hippo is lost, we lose ability to "chronologize" & consolidate

For a heroically Deeper Dive read MMO, 1995…incoming… plus AANs—soon!

Most Simplified Story: UPDATED

PFC = short-term memory aka WM / STM lasts seconds
DMR = stored ~ immediately, lasts for days
LTM = days to decades = surviving elements of DMRs w/ consolidation
LTM is Knowledge + enduring episodic memory

DMR storage = f(specifics)

~ 20 years ago…chatting with Charlie Ellis about genetics, got 1st phonecall…
some details: go home, NU vulnerable; someone: scared, me: angered
"its an attack" [possibly verbatim]

DMR candidate Terms: **Day-Long Memory Record** was *Conscious Record Memory*
immediate EM – seems to be a variant on WM / STM, only 125 hits in Scholar
transient EM – general use is randomized, 178 cites (Oct. 2019)
but Baars & Franklin 2003 specify a decay of hours for *transient EM* which is briefer than DMR; described as "a preconscious representation" and so is totally different from DMRs, and subsequent Declarative Memory

One Possible Future, alas little time:
Discuss WM/STM, DMR, EM, LTM distinction
also LTP in context of STP, STD, PTP, Chapter 24.
add Deco-Rolls STD?

Memory is a Gem with many Facets

Neurotransmitters (NETs) Systems are crucial to learning, memory and cognitive decline. But first we will cover the basics of synaptic plasticity and how LTP can be used to store information in the brain.

Human and Rat Memory Systems rely heavily on Episodic Memory which involves both neocortex and the Hippocampus which has LTP as well as spatial memory mechanisms involving Place, Grid and Head Direction Cells. The Hippocampus is also the place where the Hippopotamus goes to college

Working Memory is very different and in a later lecture we will get deeper into the WM weeds. Then we will be looking more expansively at human memory systems and their degradation with age.

For reference, a 1991 Review on 4 Hypotheses of Memory and Aging is available. This provides many details of the rich history of aging-memory research and could be skimmed; we might mention a few select highlights,

"All memory is associative" …valid claim?

Where do they go to college? ➔

2015, CSHL

Place Cells, Grid Cells, and Memory

Advanced Memory Science!

May-Britt Moser, David C. Rowland, and Edvard I. Moser

Centre for Neural Computation, Kavli Institute for Systems Neuroscience, Norwegian University of Science and Technology, 7489 Trondheim, Norway

The hippocampal system is critical for storage and retrieval of declarative memories, including memories for locations and events that take place at those locations. Spatial memories place high demands on capacity. Memories must be distinct to be recalled without interference and encoding must be fast. Recent studies have indicated that hippocampal networks allow for fast storage of large quantities of uncorrelated spatial information. The aim of the this article is to review and discuss some of this work, taking as a starting point the discovery of multiple functionally specialized cell types of the hippocampal–entorhinal circuit, such as place, grid, and border cells. We will show that grid cells provide the hippocampus with a metric, as well as a putative mechanism for decorrelation of representations, that the formation of environment-specific place maps depends on mechanisms for long-term plasticity in the hippocampus, and that long-term spatiotemporal memory storage may depend on offline consolidation processes related to sharp-wave ripple activity in the hippocampus. The multitude of representations generated through interactions between a variety of functionally specialized cell types in the entorhinal–hippocampal circuit may be at the heart of the mechanism for declarative memory formation.

Memories must Be:
. written quickly
. distinct

Grid Cells Engaged In:
. decorrelation

LTM depends upon
sharp waves
off-line consolidation
specialized cell types

summary: next slide

Deep Thoughts: Do RATS have Declarative Memories?

I smell a rat… or dost a rat smelleth me?

Place Cells, Grid Cells, and Memory

2015 - CSHL

ERC/Hippocampal System: 2nd best studied system in the Mamm. Brain?

May-Britt Moser, David C. Rowland, and Edvard I. Moser

Centre for N
and Technol

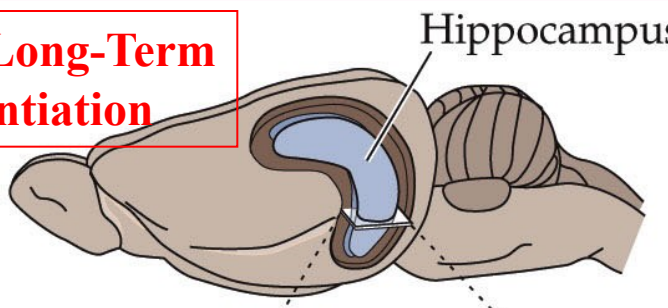
The hippocampal system is critical for storage and retrieval of declarative memories, including memories for locations and events that take place at those locations. Spatial memories place high demands on capacity. Memories must be distinct to be recalled without interference and encoding must be fast. Recent studies have indicated that hippocampal networks allow for fast storage of large quantities of uncorrelated spatial information. The aim of the this article is to review and discuss some of this work, taking as a starting point the discovery of multiple functionally specialized cell types of the hippocampal–entorhinal circuit, such as place, grid, and border cells. We will show that grid cells provide the hippocampus with a metric, as well as a putative mechanism for decorrelation of representations, that the formation of environment-specific place maps depends on mechanisms for long-term plasticity in the hippocampus, and that long-term spatiotemporal memory storage may depend on offline consolidation processes related to sharp-wave ripple activity in the hippocampus. The multitude of representations generated through interactions between a variety of functionally specialized cell types in the entorhinal–hippocampal circuit may be at the heart of the mechanism for declarative memory formation.

mnemonic phone #

This system is required for DMRs & consolidating information into LTM. Relative preservation of the WM system in AlzD suggests that this system is not integral to ongoing WM. Instead WM seems to utilize "consolidated" LTMs that reside throughout neocortex, outside of ERC. I had described hippo as an "indexing" system to enable DMRs to be stored in neocortex (where the representations are) but it is more substantively a contextualizing system that links space and time into a continuum AND all the place/time/context linkages are likely important for neocortex to be able to write DMRs b/c "more linkages". When we use mnemonics to push things from WM into our DMRs (eventually into LTM) we are, methinks, engaging hippo processing resources that normally do not play well with the very evanescent contents of WM.

Figure 24.5 The rodent hippocampus

LTP is Long-Term Potentiation

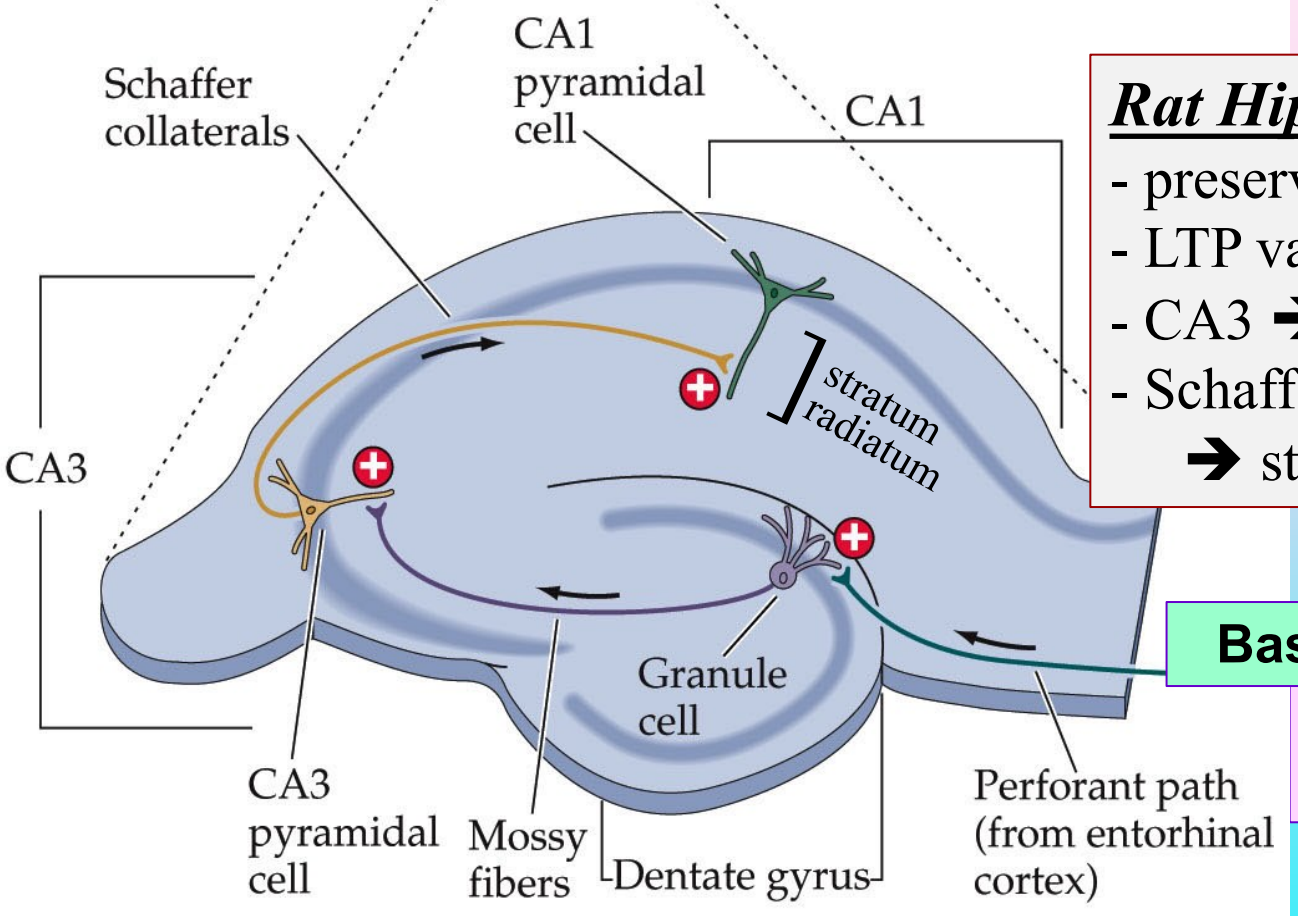


Hippocampus- required for consolidation of long term memory

LTP: discovered in rabbit hippocampus

Lomo & Bliss, 1973 (Per Andersen, Oslo)

LTP/LTD = categories of long-term plasticity



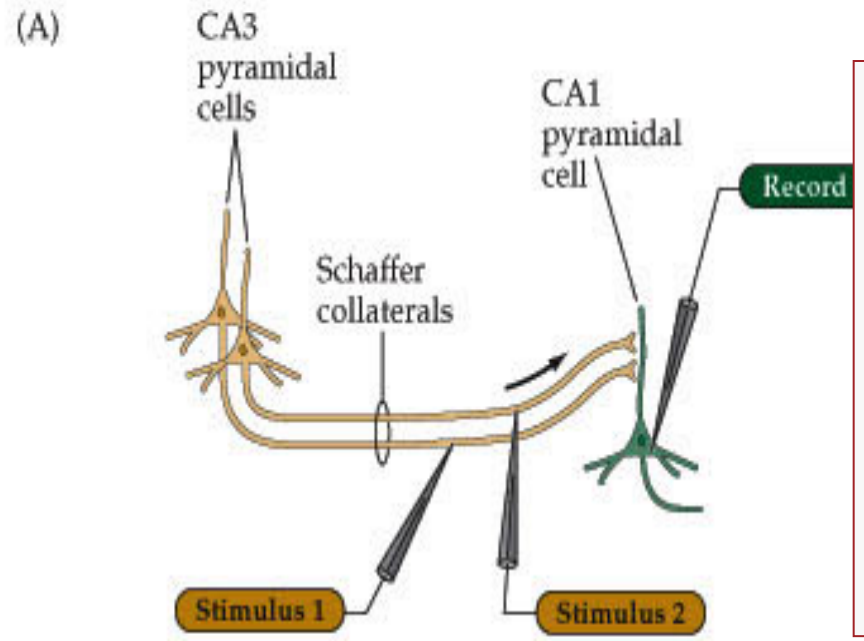
Rat Hippocampal Slice

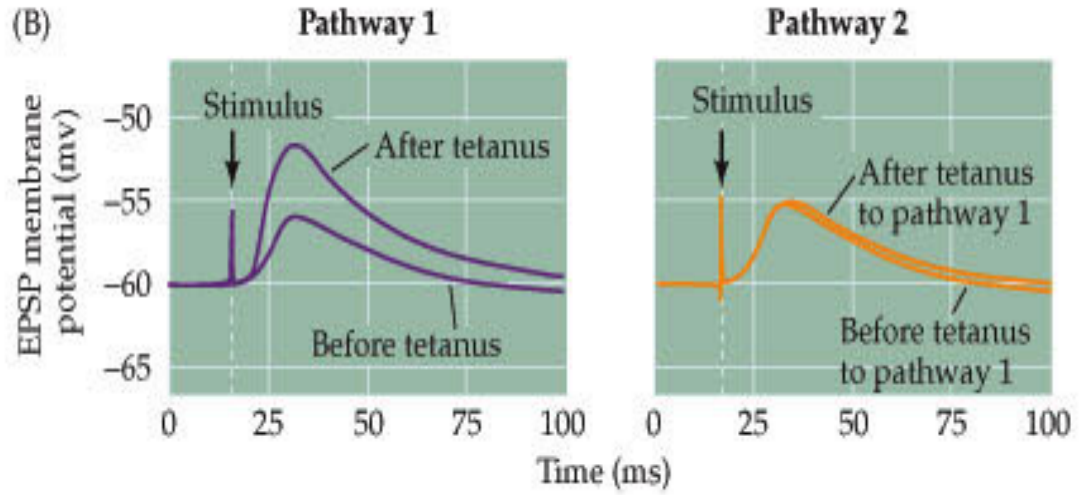
- preserves synaptic connections
- LTP varies at different sites
- CA3 ➔ CA1 = best studied
- Schaffer collaterals (branches) ➔ stratum radiatum

Basic Memory Science!

anything repeated is mandatory

Figure 24.6 Long-term potentiation of Schaffer collateral-CA1 synapses





LTP Demonstration

2 stimulating electrodes

1 recording electrode in one CA1 cell

basal responses are same

post- high frequency stim of path 1:

only connection 1 is enhanced

LTP is stimulus dependent

LTP is specific for stimulated pathway

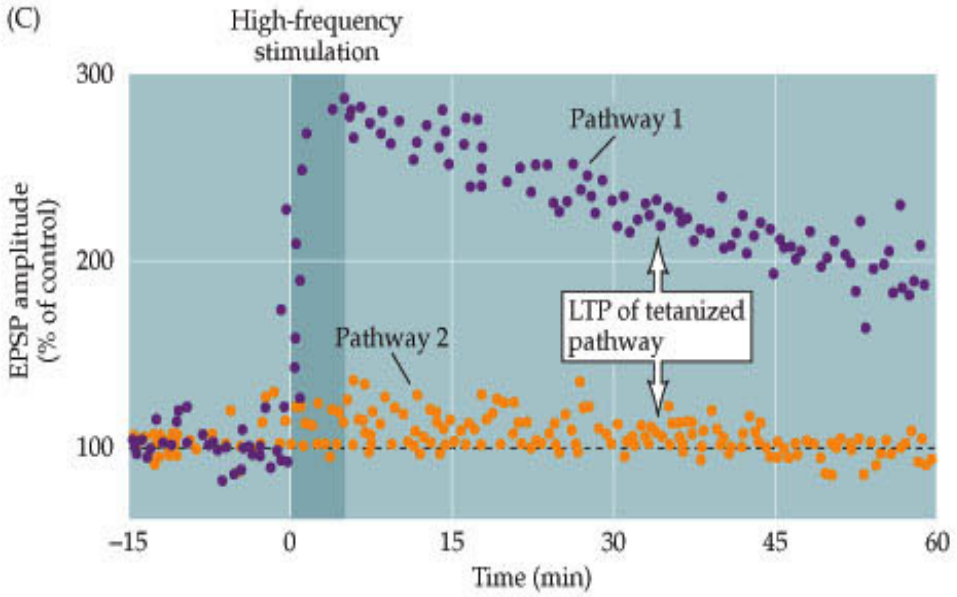
← Snapshots in Time

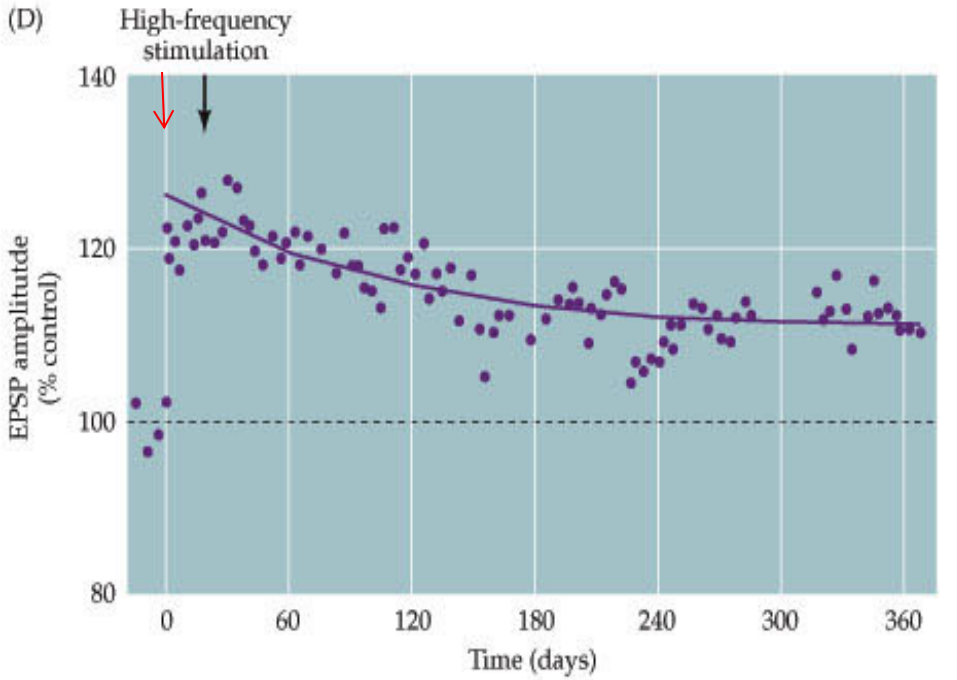
before and after EPSPs

EPSP = excitatory post-synaptic potentials

Purves' Neuroscience 3rd Edition

Figure 24.6 Long-term potentiation of Schaffer collateral-CA1 synapses





← EPSPs not shown here, just the amplitude

Time Course of LTP

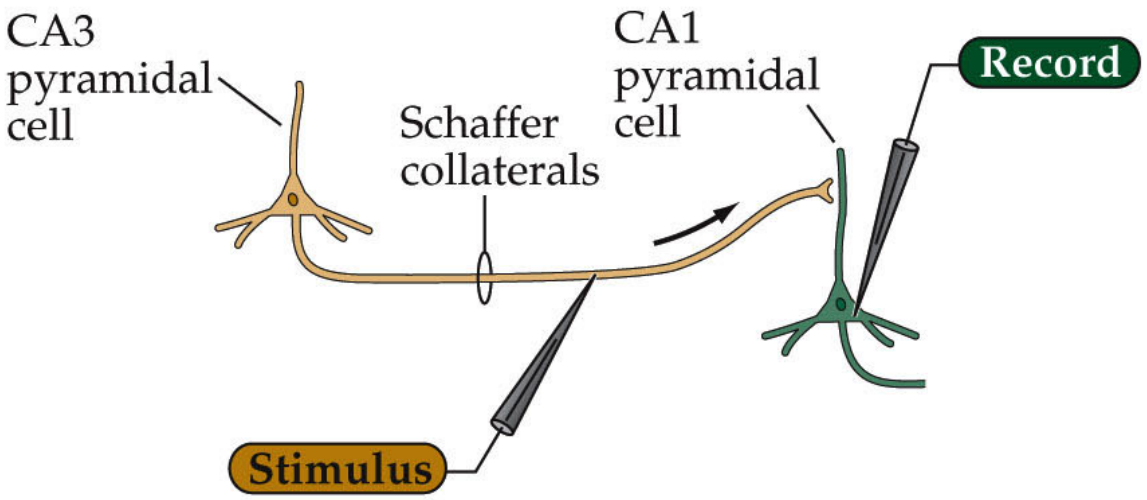
same experiment as previous slide
only pathway 1 was "tetanized"
low-freq. stimul: 2 or 3 shocks/min
has no effect on pathway 2

lower panel

LTP can last for a year or more.
J. Neurosci. 2002
LTP constitutes a form of info. storage

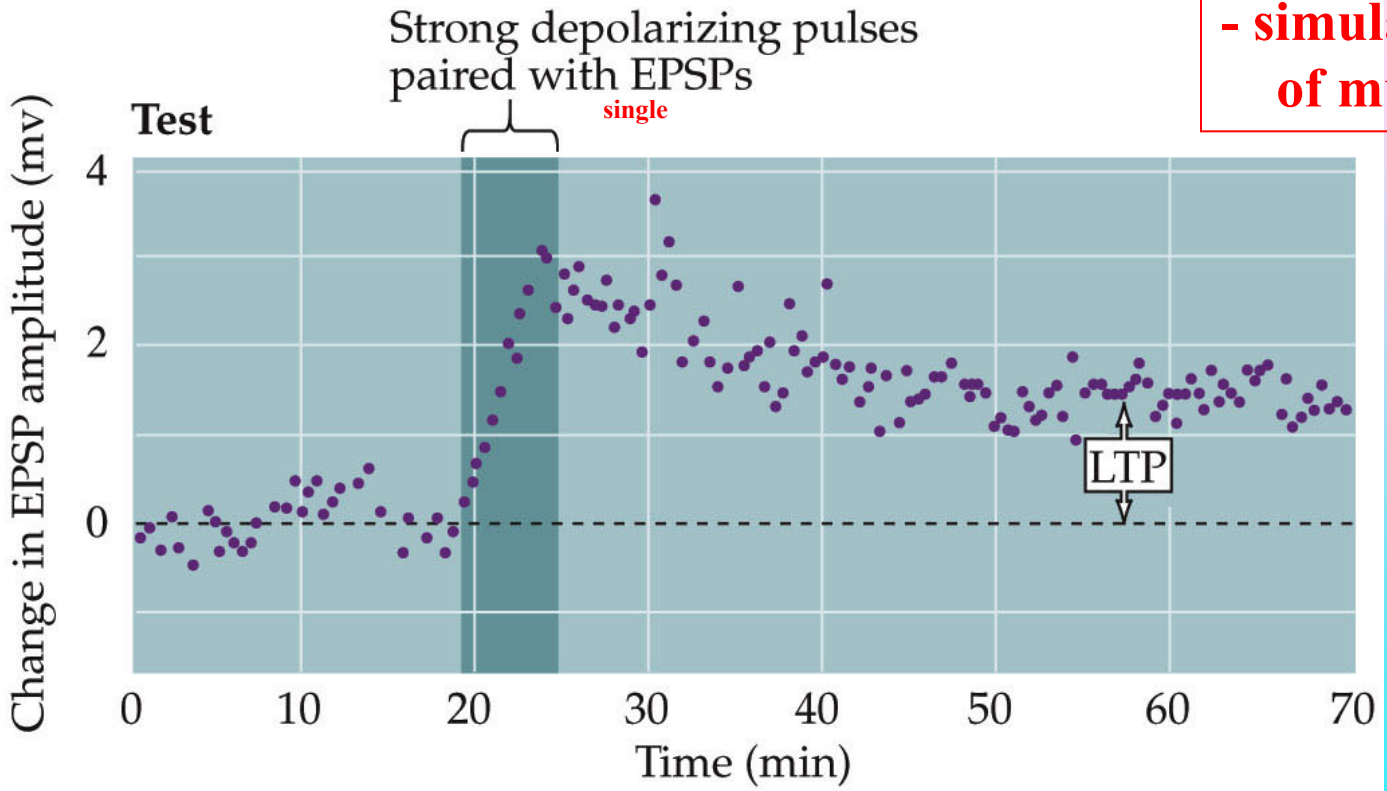
here EPSP = field EPSP recorded from chronic electrode.

Figure 24.7 Pairing presynaptic and postsynaptic activity causes LTP



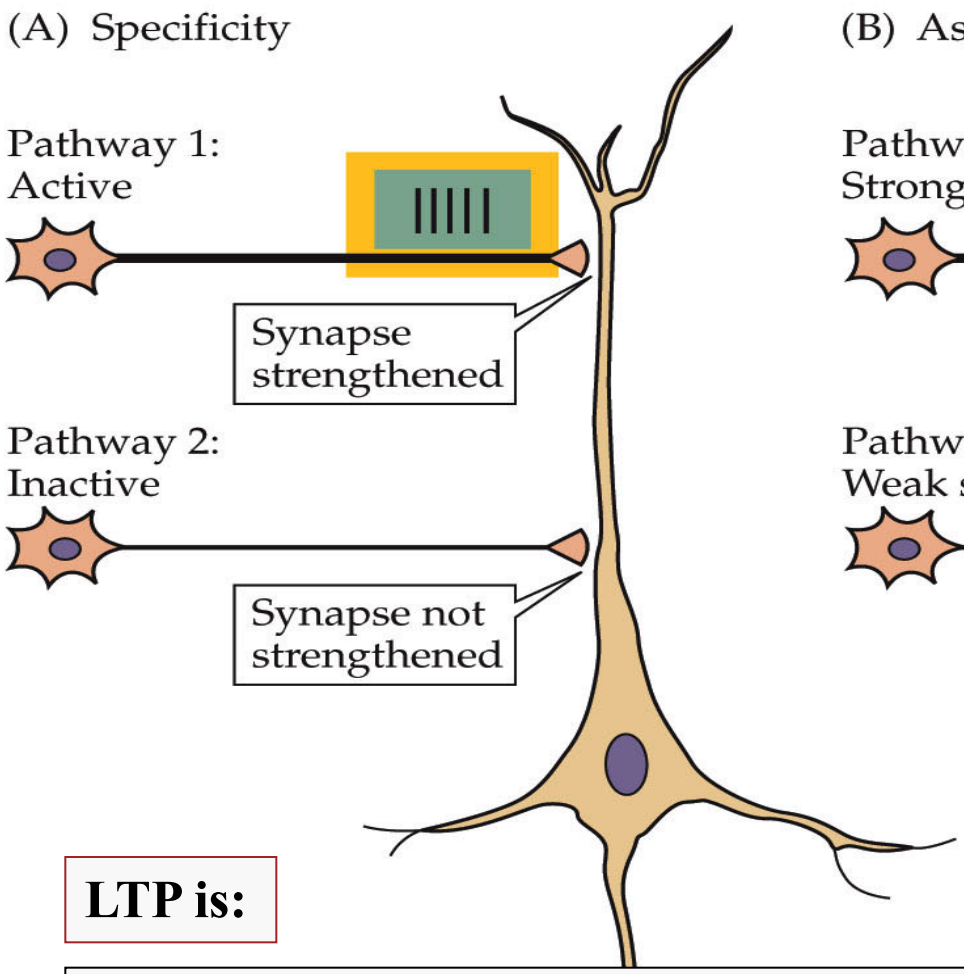
Mechanism of LTP
synaptic stimulation
+ depolarization
= LTP

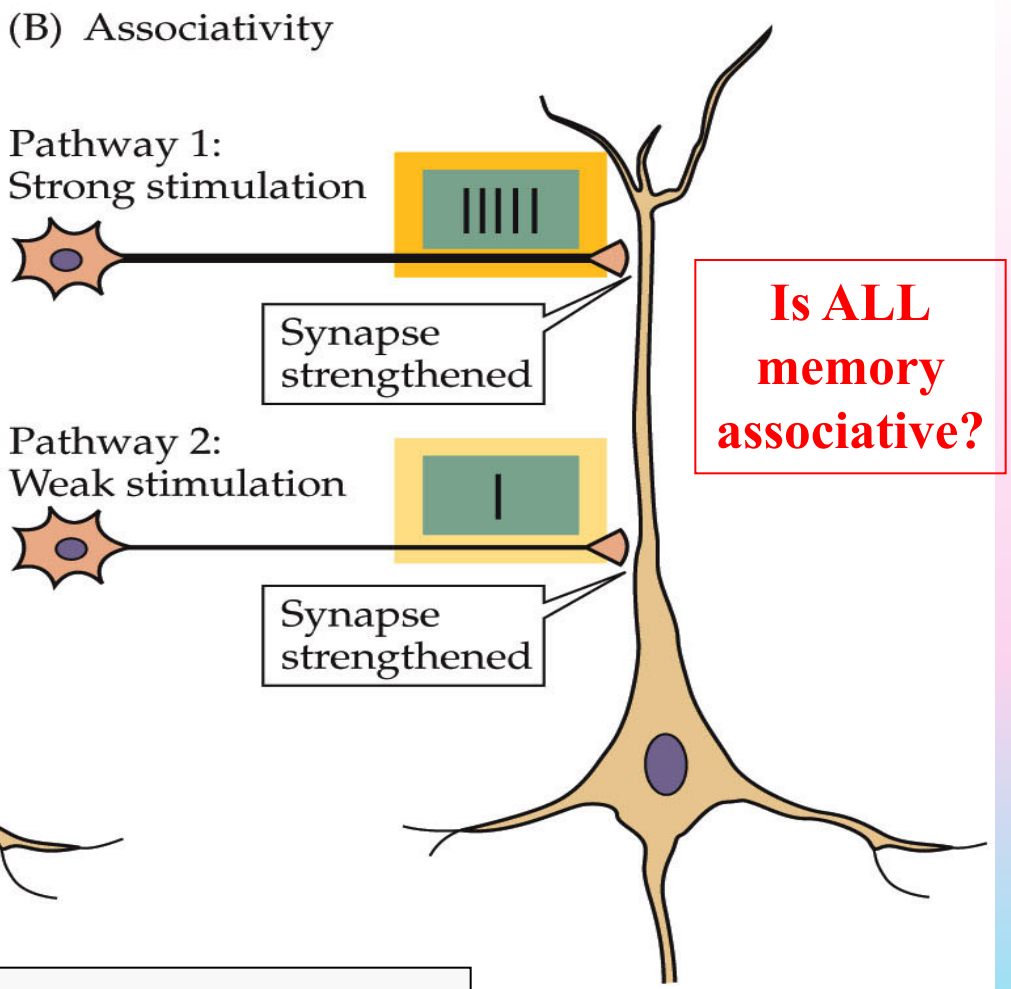
- not high frequency
- more physiological
- **simulates convergence of multiple inputs**



Purves' Neuroscience 3rd Edition

Figure 24.8 LTP at a CA1 neuron receiving inputs from two independent pathways





Is ALL memory associative?

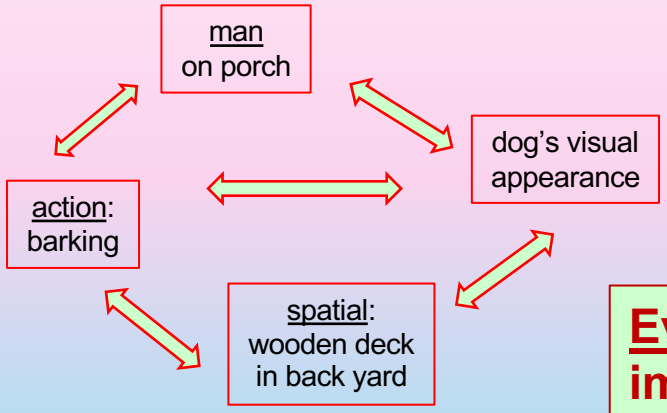
LTP is:

1. state dependent = f(cell ***voltage***)
2. ***specific*** for stimulated pathway
3. ***associative***: Proposed by Donald O. Hebb in *Organization of Behavior* in 1949 ➔ **modern AI!**
4. Takes advantage of 1000-fold connectivity to allow infinite learning flexibility (~connectionism)

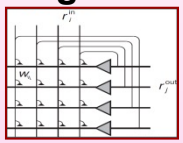
Psychol. Rev. 1995 102:419-457
Why there are complementary learning systems in the hippocampus and neocortex: insights from the successes and failures of connectionist models of learning and memory. MMO: McClelland JL, McNaughton BL, O'Reilly RC.

A Dog and His Man: Dog barking at man on his deck in his backyard

episode:
dog – visual appearance
action – barking at man
location – house on corner



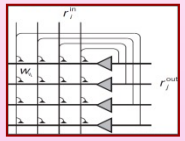
Dog AAN



50 dog types

dog #39 =
brown terrier

Man AAN



75 man types

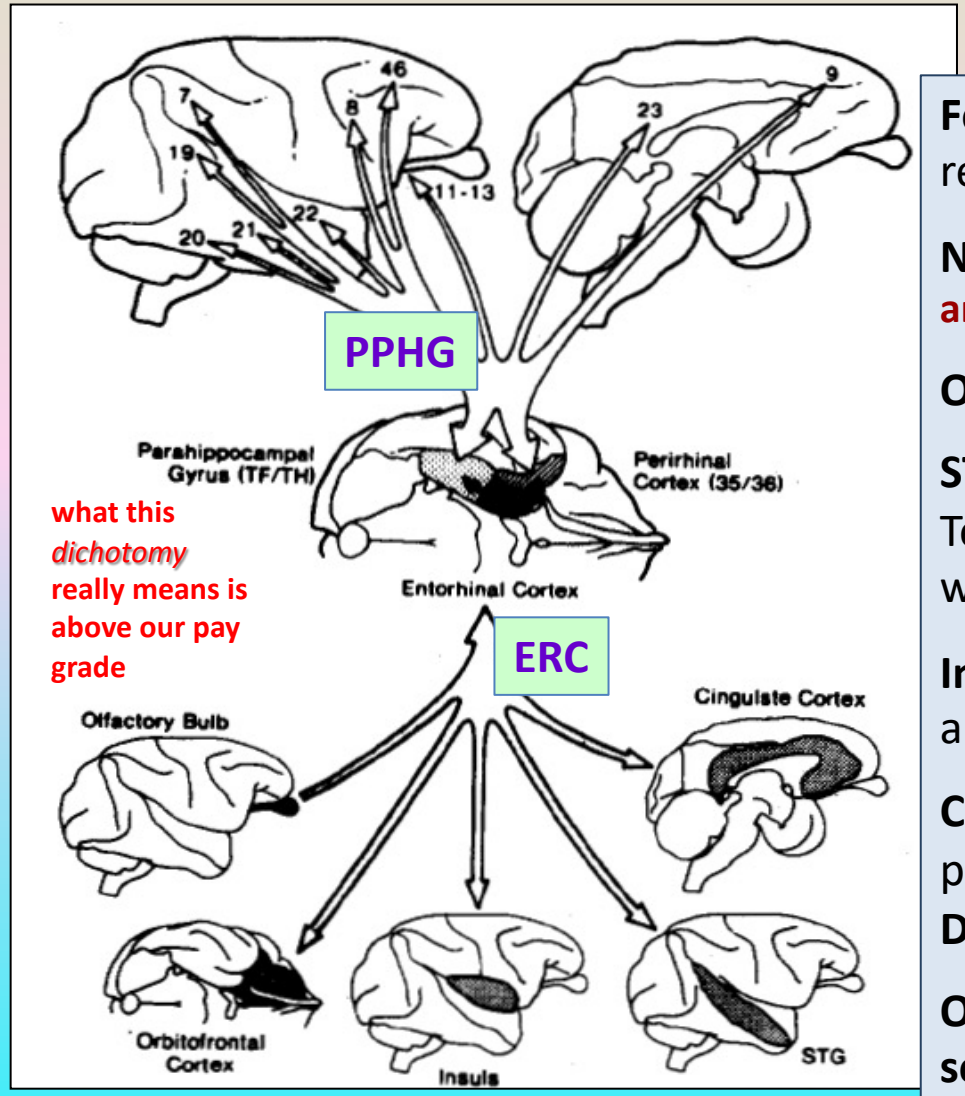
Event: brief episode seen walking to work
impression: normally barky dog being barky
distinct: man on porch ignoring dog
explanation: dog hungry or seeking attention

One small epoch of a DMR. Why does *the brain bother* to save stuff like this? The event seems insignificant. But is there more to the story?

REAL MEMORY SCIENCE IS MESSY ➔

Complementary Learning Systems:
Primate Medial Temporal Connections
McClelland, McNaughton & O'Reilly, 1995 *aka* **MMO**

AlzD: Nature of the Damage
- functional disconnectivity?
- encoding errors / ACh loss?
- damaged stores?



For a deep-dive into Memory Systems. read MMO. Available o.r.

Note that systems converging on ERC are distinct from those onto PPHG (see below)

OFC is part of Frontal Cortex.

STG aka Superior Temporal Gyrus is part of Temporal Lobe and might include face and word areas.

Insula is associated with hypothalamus and physiological functions.

Cingulate cortex is associated with pain, pleasure, reward and motivation AND the **Default Mode Network!**

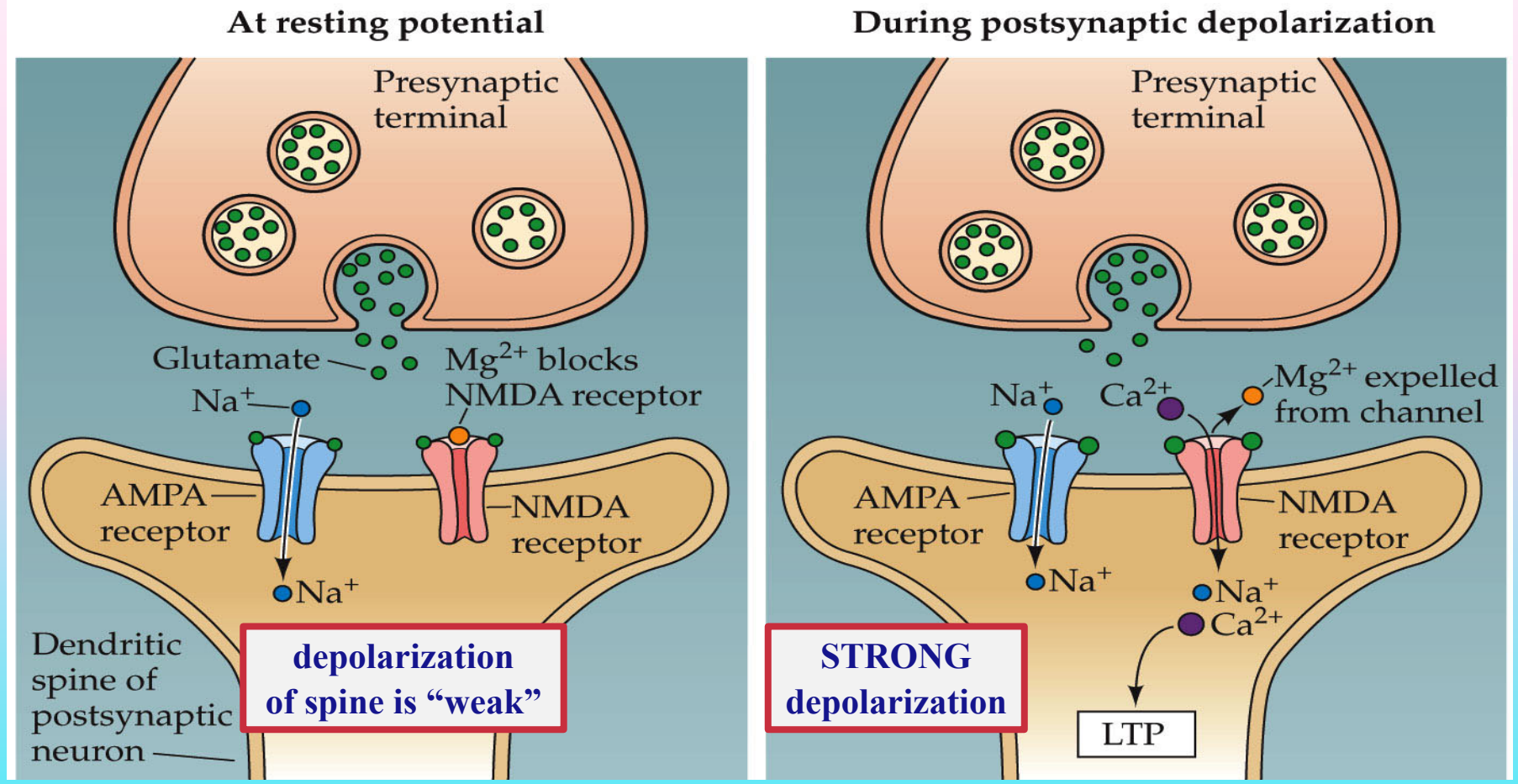
Olfaction is an extremely powerful sensory modality.

Whose Brain is this Brain? ala Whose Boat is this Boat?

Figure 24.9 The NMDA receptor channel can open only during depolarization

Why is *Coincidence Detection* Important for Memories?

coincidence IS associative! ← **"PAIRING" → LTP**



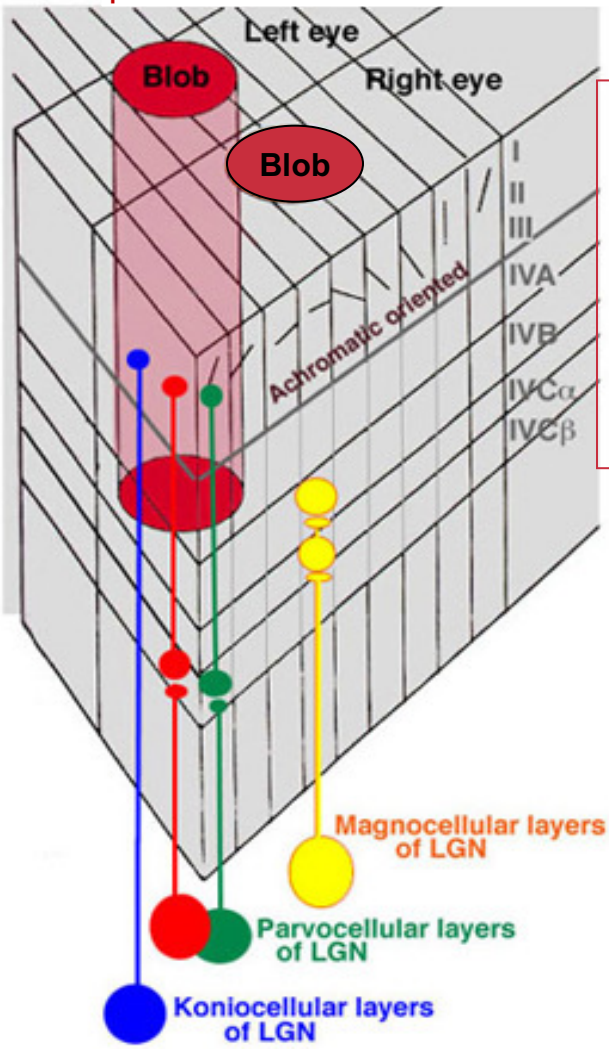
Coincidence-dependent calcium influx; removal of Mg^{++} block. **COINCIDENCE is ASSOC.**
NMDA antagonists: block LTP, have no effect **on responses** to low-frequency stimulation

NEW VERSION OF SLIDE – FOCUS ON DIGITAL!

Is Neocortex Info Processing **Digital** or **Analog**? Relevant to Aging?

What does Digital vs. Analog have to do with Memory or LTP?

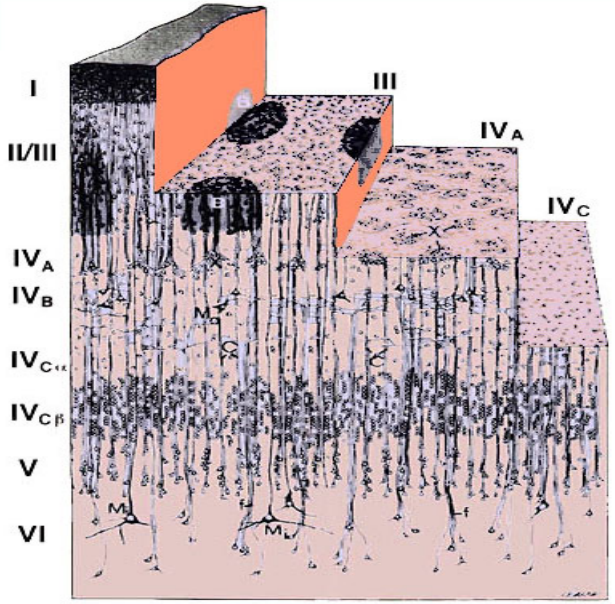
Keep in mind that LTP occurs in such architectures (generally)



corrected image to show "blob" in both left eye & right eye columns.

Interblob = grey matter surrounding blobs.

Why called blobs? see note



blobs stained with cytochrome oxidase

Figure 17. Schematic drawing of the visual ... show neurons, layers, columns and CO blobs.

Objects are **Digital**

Action Potentials are Digital

Words are Digital

"dog" does not morph into "doc"

Analog: EPSPs & IPSPs, Voltage

analog = continuously varying, like waves

digital = discrete items, like fingers, 1s and 0s

How does THIS do digital information processing?

About 49,200 results (0.08 sec)

50,000 results…

Visual Cortex and LTP

Long-term potentiation and NMDA receptors in rat **visual cortex**
A Artola, W Singer - Nature, 1987 - nature.com
... use intracellular recording techniques to show that **LTP** can be induced by high frequency stimulation of the optic radiation in slices of the **visual cortex** of adult ... In most **cortical** neurons t activation of the NMDA mechanism and hence the induction of **LTP** in these ...
☆ 99 Cited by 985 Related articles All 6 versions

Hebbian synapses in **visual cortex**
A Kirkwood, MF Bear - Journal of Neuroscience, 1994 - Soc Neuroscience
... kitten **visual cortex**. In the course of this investigation, we discovered a new method for the demonstration of **LTP** in the neocortex that does not require the use of BMI at all. We found that by stimulating **cortical** layer IV instead of the white matter we could reliably evoke **LTP** in ...
☆ 99 Cited by 425 Related articles All 12 versions

Experience-dependent modification of synaptic plasticity in **visual cortex**
A Kirkwood, MG Rioult, MF Bear - Nature, 1996 - nature.com
... Both in hippocampus" and in **visual cortex** (unpublished observations), LFS produces significar greater LTD in neona ... As an additional test of the sliding-6, hypothesis, **visually** deprived rats we to light for various times, and the effects of LFS were investigated in **visual cortex** ...
☆ 99 Cited by 557 Related articles All 11 versions

Co-regulation of long-term potentiation and experience-dependent synaptic plasticity in **visual cortex** by age and experience
A Kirkwood, HK Lee, MF Bear - Nature, 1995 - nature.com
... 3 Effect of dark-rearing on **LTP** evoked from the white matter in 4–6-week-old rat **visual cortex**. a, Comparison of **LTP** in **visual cortical** slices from 4–5-week-old rats reared in complete darkness with **LTP** in rats reared in a normal lighted environment ...
☆ 99 Cited by 445 Related articles All 12 versions

Synaptic activity and the construction of **cortical** circuits
LC Katz, CJ Shatz - Science, 1996 - science.sciencemag.org

preceding slide:
given what we know about memory and LTP, which brain regions **should not undergo** LTP?
primary sensory?

WHERE AND HOW ARE MEMORIES STORED?
↯
V1…and the REST of Neocortex!
(not to mention MTL)

we're MISSING A FEW DETAILS STILL…

r_i^{in} = *incoming* pattern…aka

Auto-Associative Network in Operation (AAN)

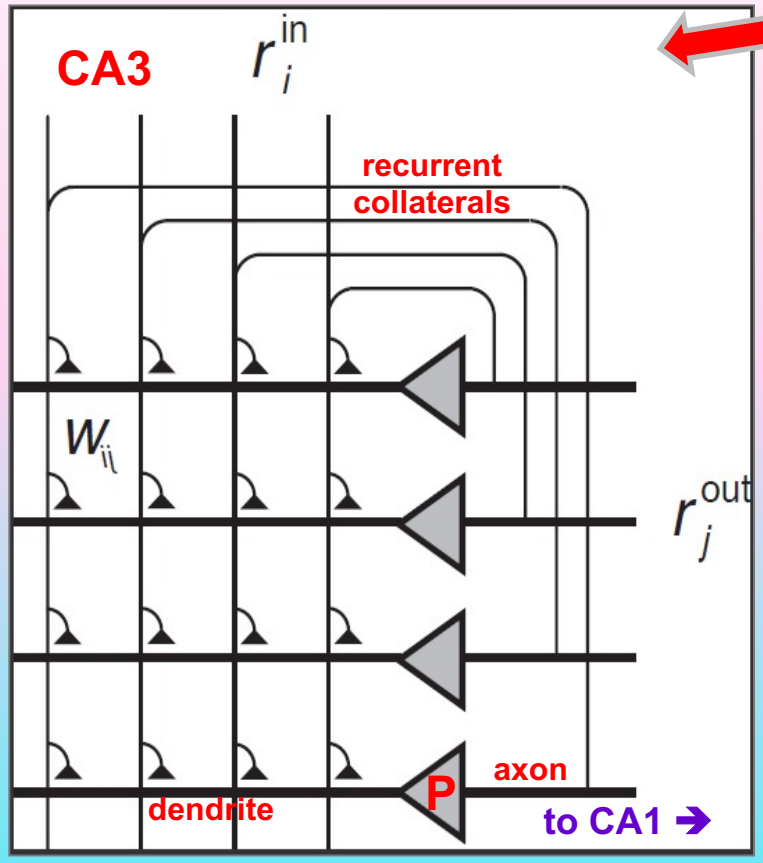
RT: Are AANs *DIGITAL*?

noisy **input vector i**

1
-1
-1

3 features
e.g.
orange
round
smooth

This pattern of features is output to other network nodes e.g. a word AAN that will return the word "nectarine".



r_i^{in} is now an UPDATED pattern:

output vector j

1	-1	1

1	-1	1
-1	1	-1
1	-1	1

This is a cartoon example of the math algorithm used in fixed point attractors: see notes.

output sum: 1 -1 1

sgn (output) 1 -1 1

MEMORY STORAGE:

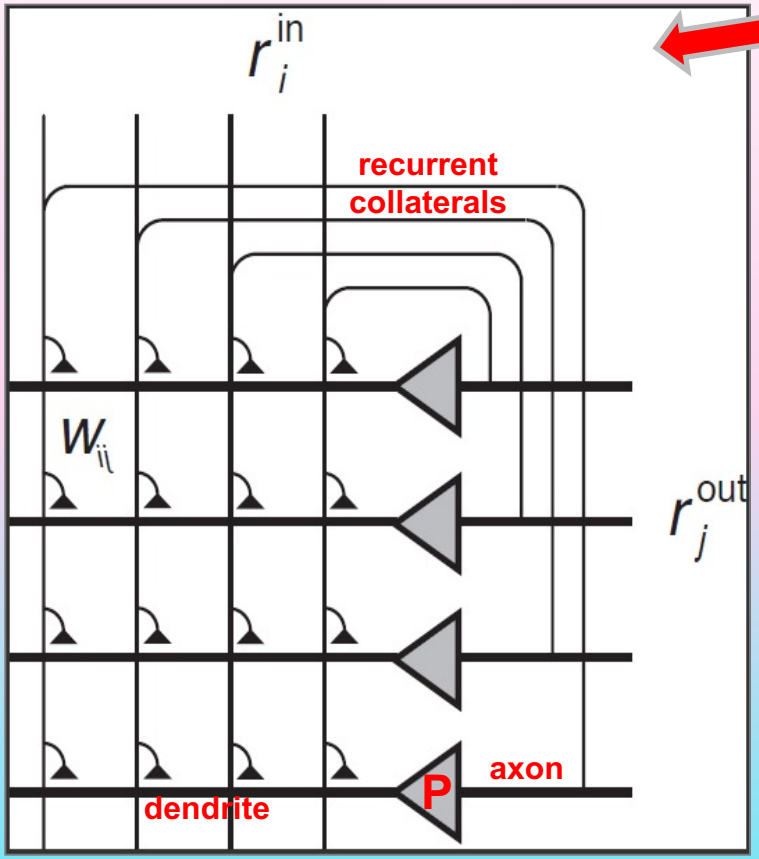
Before you can say *WHERE* you'd like to know *HOW*!

AANs
mo' details

AAN's enable: **item recognition**, **categorization**, **pattern completion**

r_i^{in} **ORIGINAL:**

noisy input vector i	1
	-1
	-1



r_i^{in} **UPDATED:**

proposed for CA3, Hebbian learning + basis of AI / ML

output vector j

1	-1	1

P = pyramidal cell (in e.g. CA3)

totally arcane:

- **we reach a fixed-point in a single step**
- **new input leads to ➔ new *attractor***
- **otherwise: PNA, tonic firing, du/dt = 0.**

Are AANs *DIGITAL*?

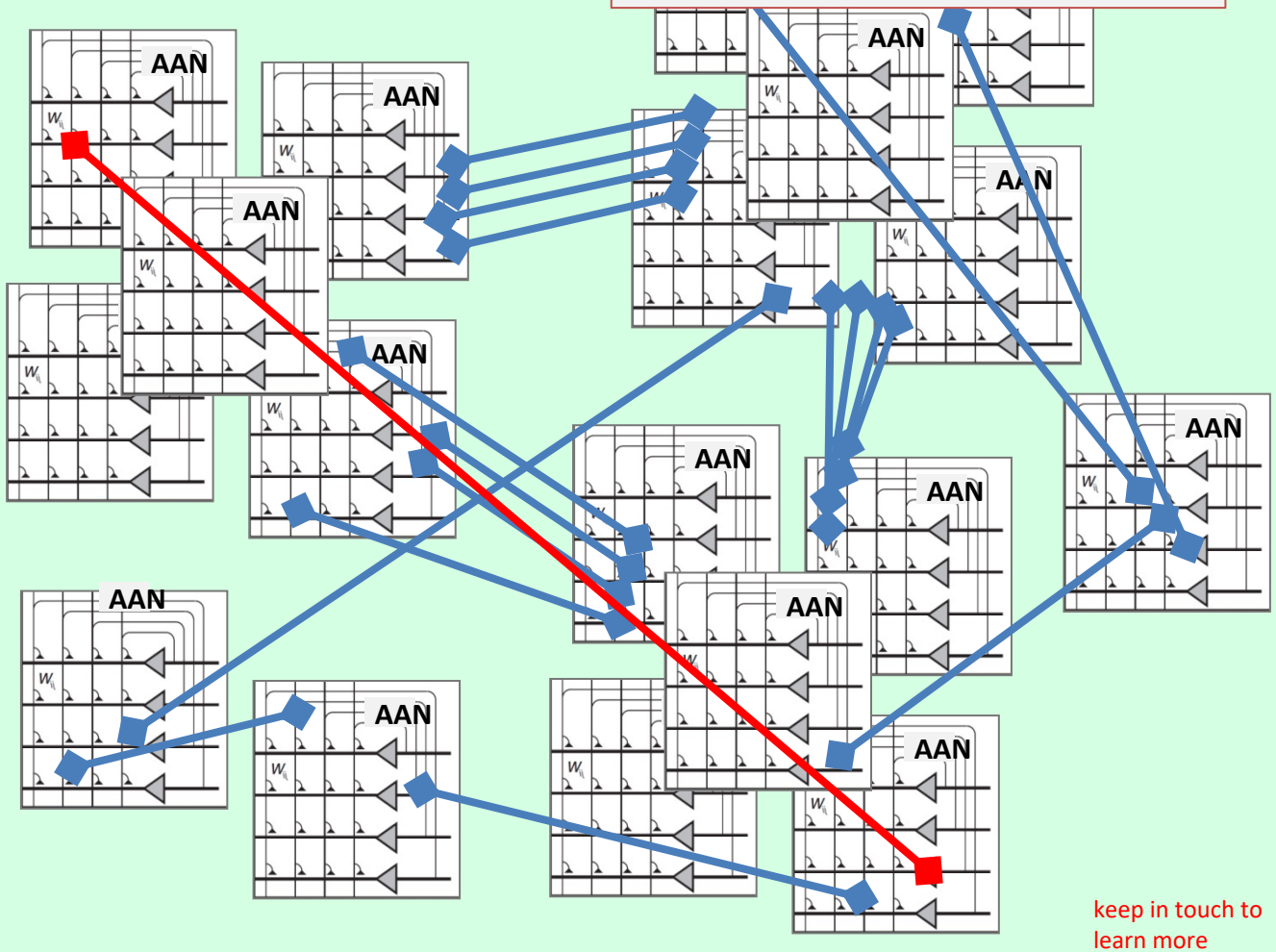
YES! …
and so is WTA activity
[form of Persistent Neural Activity]

What can we say more generally about Neocortical Operations & Breakdowns?

My #2 Question for SysNeuro TODAY remains GP-CPUs or Dedicated Processors?

General Purpose CPU:
- Nelson's Phylogeny
- 6-layer neocortex
~ Synesthesia

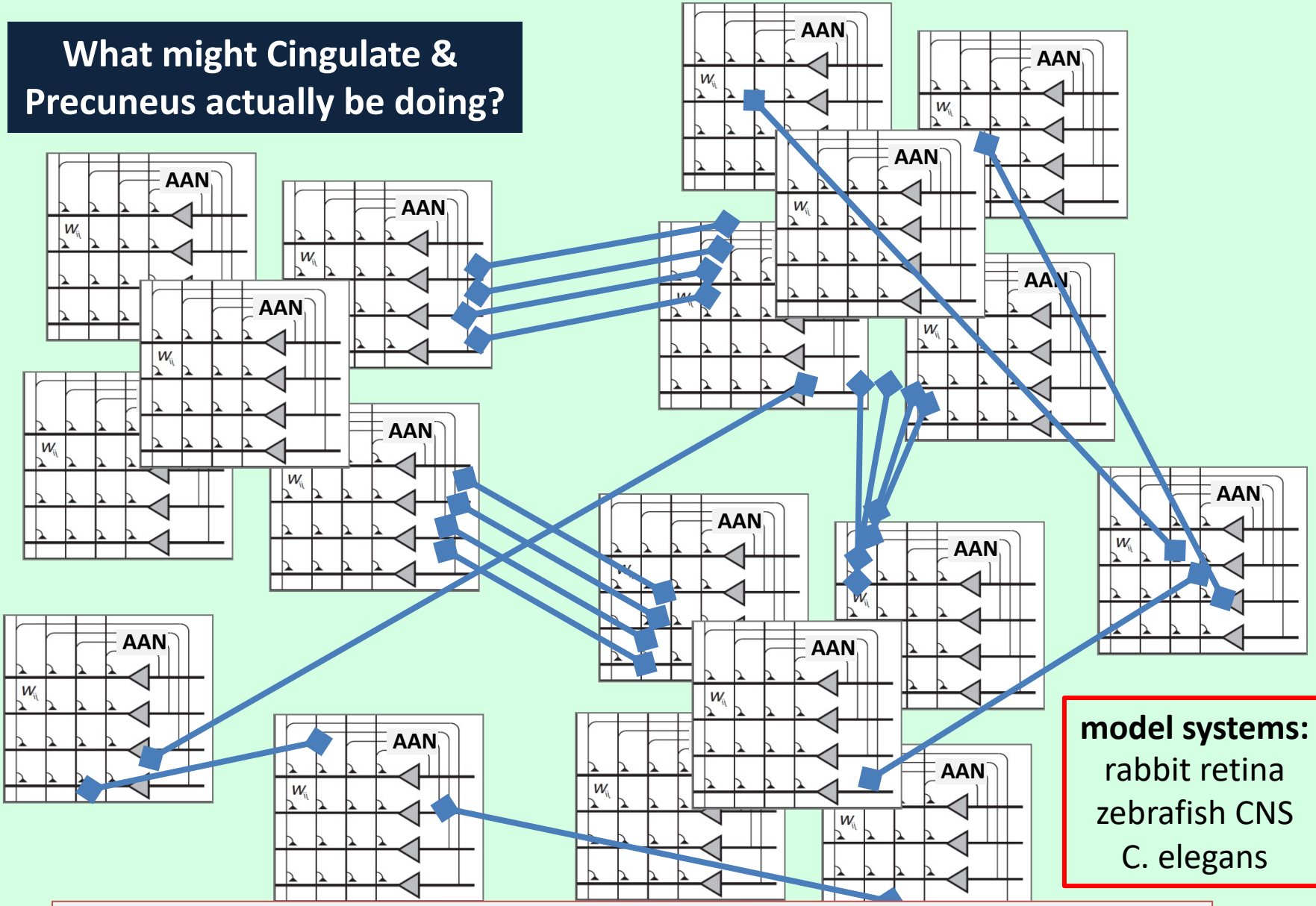
Specialized Processors:
- Brodmann areas
- Innate Operations
  e.g. V1 OS or DS
- Developmental
  Prosopagnosia
- Limitations of Recovery
  after Stroke



keep in touch to learn more

Discussion Items (i) in AlzD is the early damage low cingulate CBF, loss of ACh neurons or ERC-tangles? (ii) How are episodic, autobiographical, semantic and spatial memories laid down? (iii) If this all comes through DMRs, why are different kinds of memories *differentially vulnerable?*

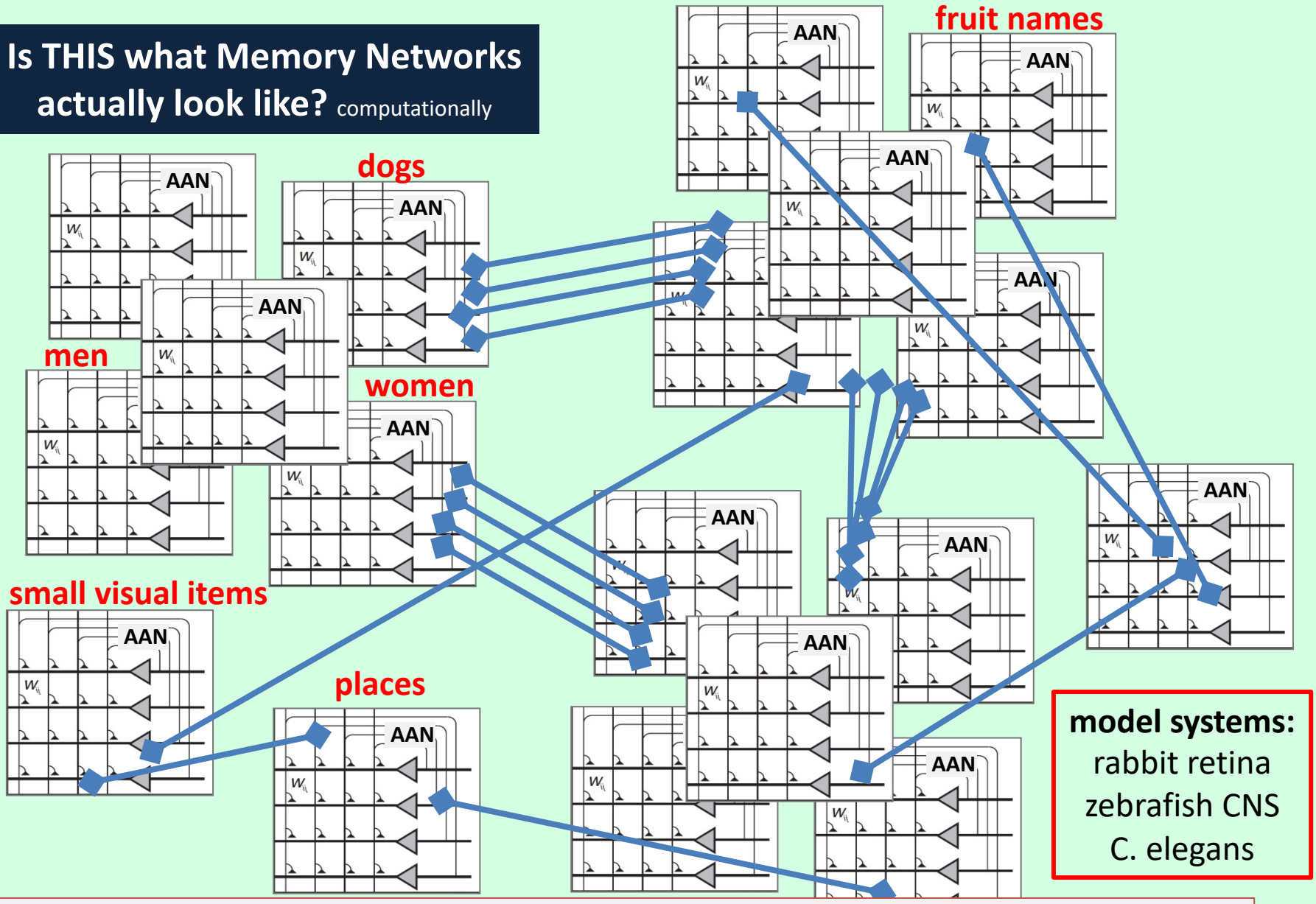
What might Cingulate & Precuneus actually be doing?



model systems:
rabbit retina
zebrafish CNS
C. elegans

What can we say about **changes & operations** of Neocortical Architectures?
"Nothing in Neuroscience makes sense except in the Light of Neuroanatomy"
But what LEVEL of Neuroanatomy do we need to understand?

Is THIS what Memory Networks actually look like? computationally



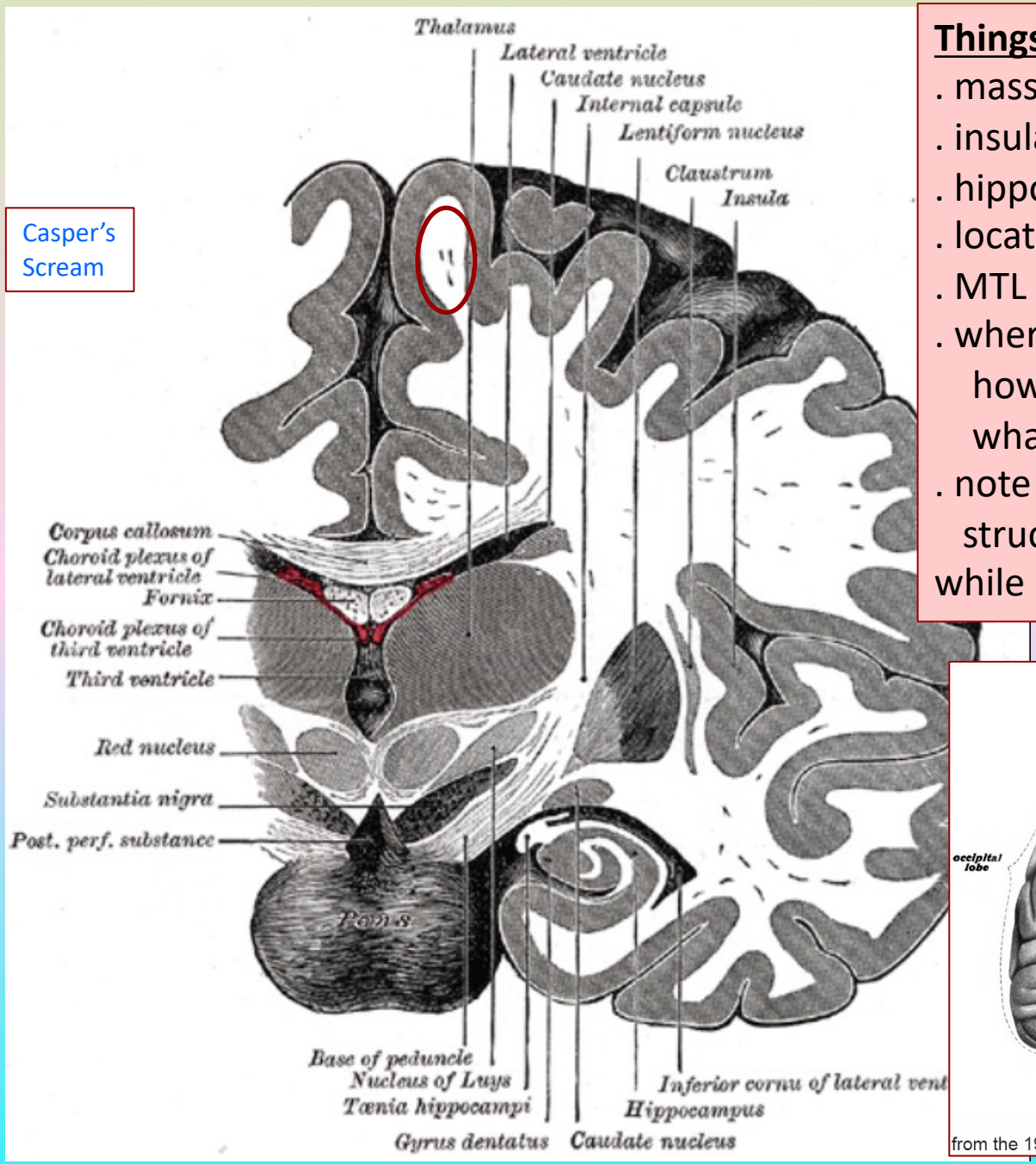
model systems:
rabbit retina
zebrafish CNS
C. elegans

"Nothing in Neuroscience makes sense except in the Light of Neuroanatomy"

But what LEVEL of Neuroanatomy do we need to understand?

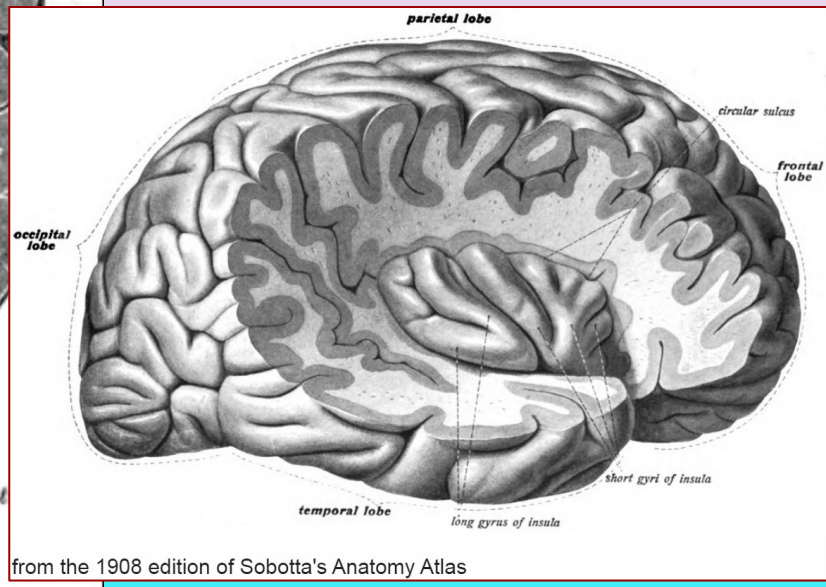
…if we can locate AANs and their connections, we can watch them change with age…

Casper's Scream



Things of Note:

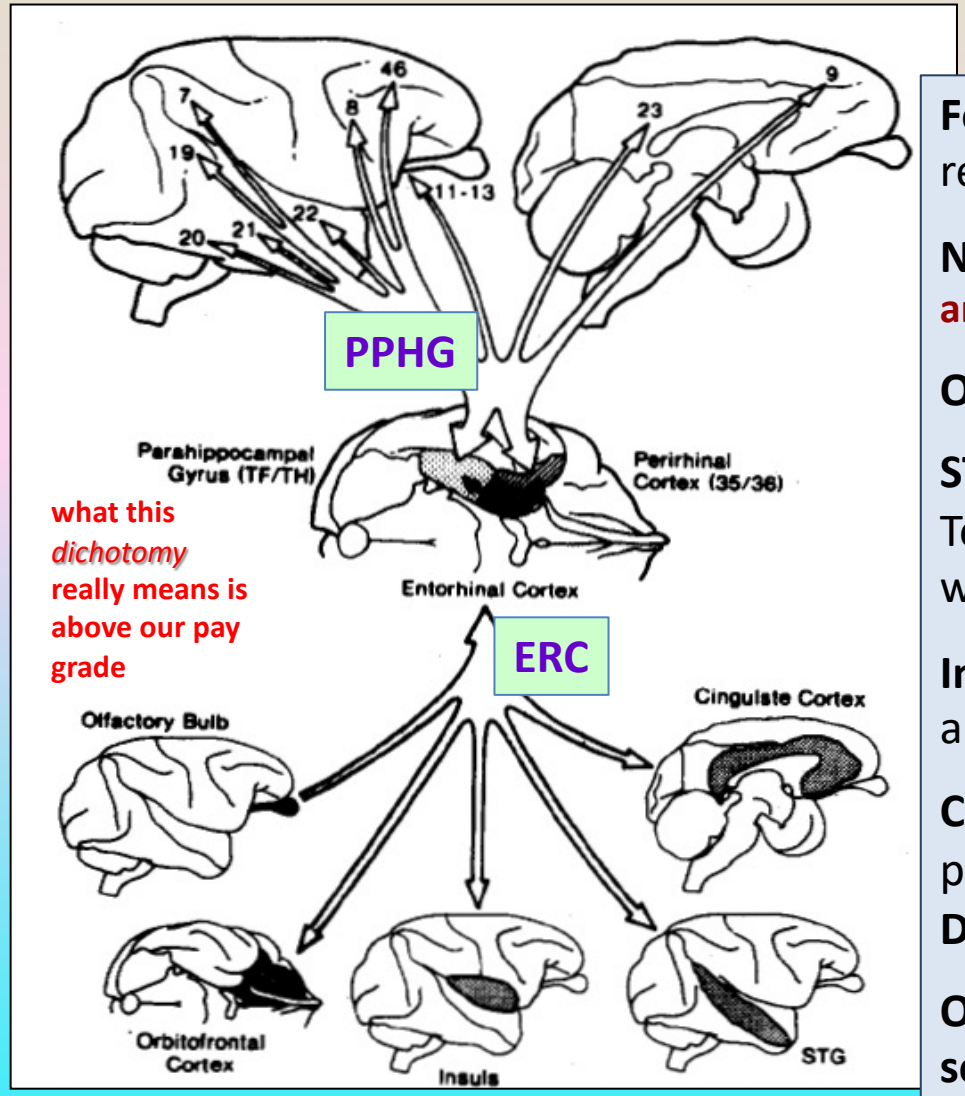
. massive amounts of white matter
. insula (~an internal gyrus)
. hippocampus is small (relatively)
. locate ERC, parahippocampal gyrus
. MTL also a minor part of section
. where is lateral temporal lobe?
how about STG, IPL?
what's on Top?
. note that red nucleus is a midbrain structure, as is Substantia Nigra while caudate is part of basal ganglia



from the 1908 edition of Sobotta's Anatomy Atlas

Complementary Learning Systems:
Primate Medial Temporal Connections
McClelland, McNaughton & O'Reilly, 1995 *aka* **MMO**

AlzD: Nature of the Damage
- functional disconnectivity?
- encoding errors / ACh loss?
- damaged stores?



For a deep-dive into Memory Systems. read MMO. Available o.r.

Note that systems converging on ERC are distinct from those onto PPHG (see below)

OFC is part of Frontal Cortex.

STG aka Superior Temporal Gyrus is part of Temporal Lobe and might include face and word areas.

Insula is associated with hypothalamus and physiological functions.

Cingulate cortex is associated with pain, pleasure, reward and motivation AND the **Default Mode Network!**

Olfaction is an extremely powerful sensory modality.

Whose Brain is this Brain? ala Whose Boat is this Boat?

Shared Functions of Perirhinal and Parahippocampal Cortices: Implications for Cognitive Aging

2018, TINS

PPHG: Peri-Para-Hippocampal Gyrus

This is **beyond the scope** of what we can do this semester, but is essential reading for any would-be ***Memory Mavens***!

Sara N. Burke,[1,2,*] Leslie S. Gaynor
Erik D. Roberson,[8] and Lee Ryan[4,6]

A predominant view of perirhinal cortex (PRC) and postrhinal/parahippocampal cortex (POR/PHC) function contends that these structures are tuned to represent objects and spatial information, respectively. However, known anatomical connectivity, together with recent electrophysiological, neuroimaging, and lesion data, indicate that both brain areas participate in spatial and nonspatial processing. Instead of content-based organization, the PRC and PHC/POR may participate in two computationally distinct cortical–hippocampal networks: one network that is tuned to process coarse information quickly, forming gist-like representations of scenes/environments, and a second network tuned to process information about the specific sensory details that are necessary for discrimination across sensory modalities. The available data suggest that the latter network may be more vulnerable in advanced age.

Highlights

Recent data do not support a content-based dissociation of PRC and PHC function.

We propose a novel process-based model, rooted in anatomy, which contends that the PRC and PHC interact to support two distinct cortical–hippocampal pathways.

One pathway through entorhinal cortex to the dentate gyrus and CA3 supports coarse processing of scenes and environments that quickly form gist-like representations for rapidly informing adaptive behavior.

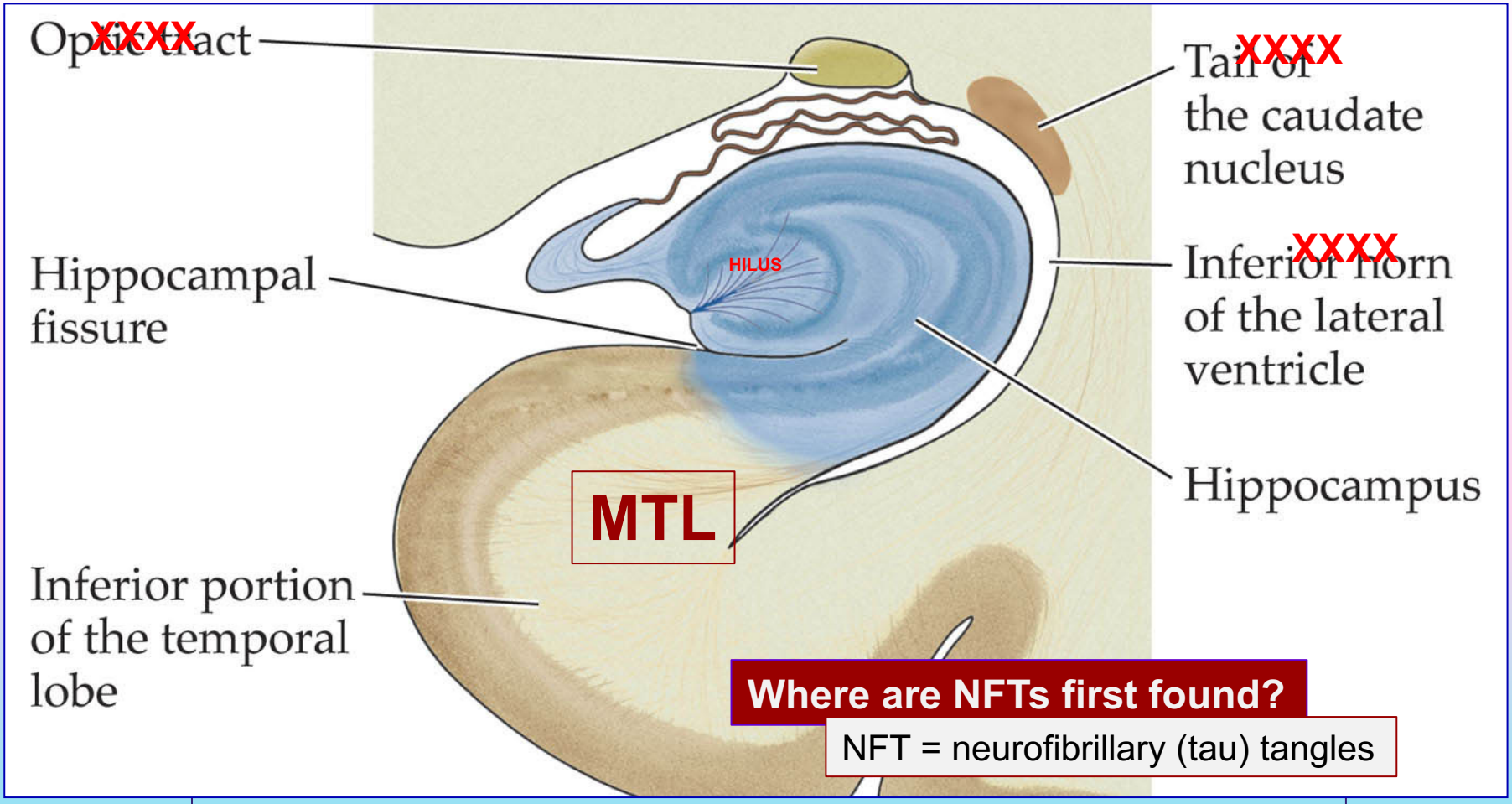
The other pathway is direct from PRC and PHC to CA1, and it enables detailed representations to be associated with gist-like information when a fine-grained analysis is necessary.

Contemporary findings in cognitive aging studies in humans and other

The PRC and PHC Come of Age

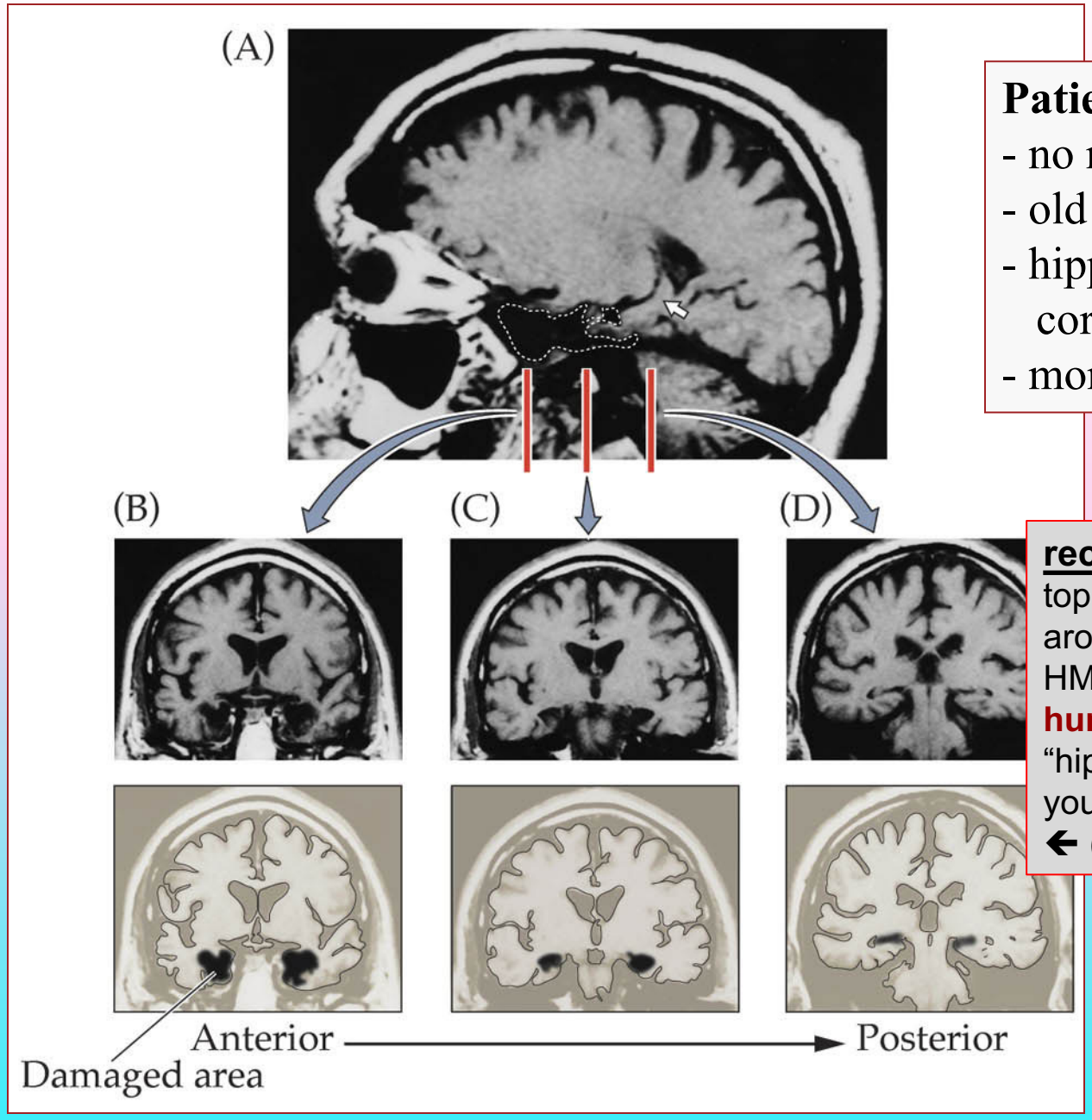
Advanced age is characterized by neurobiological alterations within the medial temporal lobe (MTL) that are linked to cognitive dysfunction in older adults and other animals [1]. While dysfunction within the hippocampus (HPC) and impairments in HPC-dependent behaviors are well documented with age, a debate has emerged regarding age-associated vulnerabilities within other cortical MTL regions. The **perirhinal cortex** (PRC; see Glossary) and **parahippocampal cortex** (PHC) are in the **parahippocampal region** (Figure 1A,B) of the MTL and reciprocally connect with the HPC. The PHC in primates is homologous to the rodent

This is a nice modern (2018) synthesis of Electrophysiology and "Representational" Neuroscience



Patient HM could store no new memories after bilateral removal of his hippocampus along with entorhinal cortex (adjacent to hippo.) and most of the amygdala

Is ERC neocortex? i.e. 6-layered? Maybe. See Notes. Research Topic.



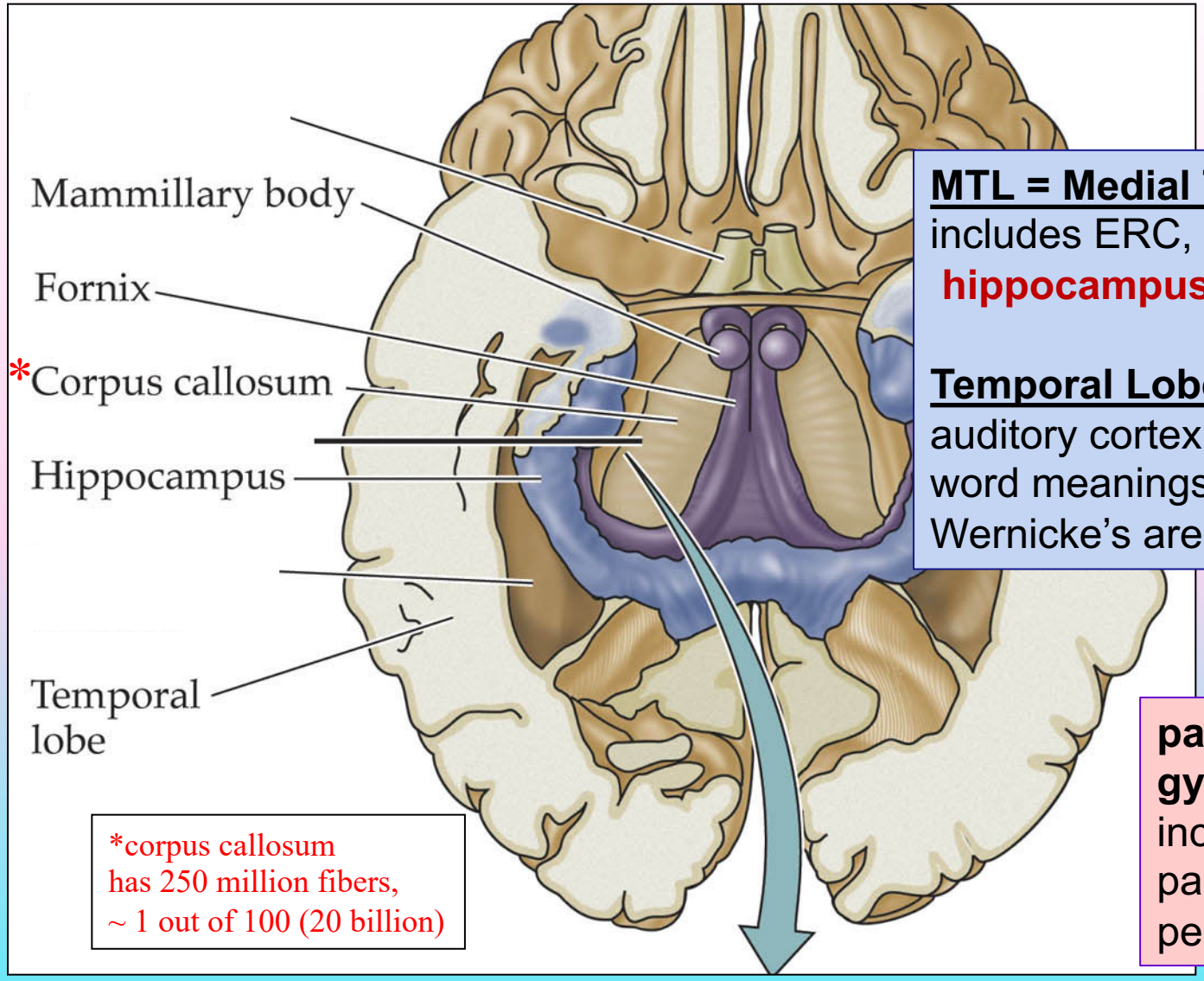
Patients HM, NA and RB:
- no new memories
- old memories OK (sorta)
- hippocampus and associated cortical regions damaged
- more details in Purves

recently noted at BI: 1/31/18 topic of "language effects" on HM arose: Tulving might have taught HM new words, **but it took many hundreds of trials**, absent the "hippocampal/ERC assist" that lets you learn 30 new words a lecture! ← (ballpark guesstimate)

see notes

Purves' Neuroscience 3rd Edition

Purves' Neuroscience 3rd Edition



MTL = Medial Temporal Lobe
includes ERC, hippocampus, PHG.
hippocampus + neocortex = ***IQ***

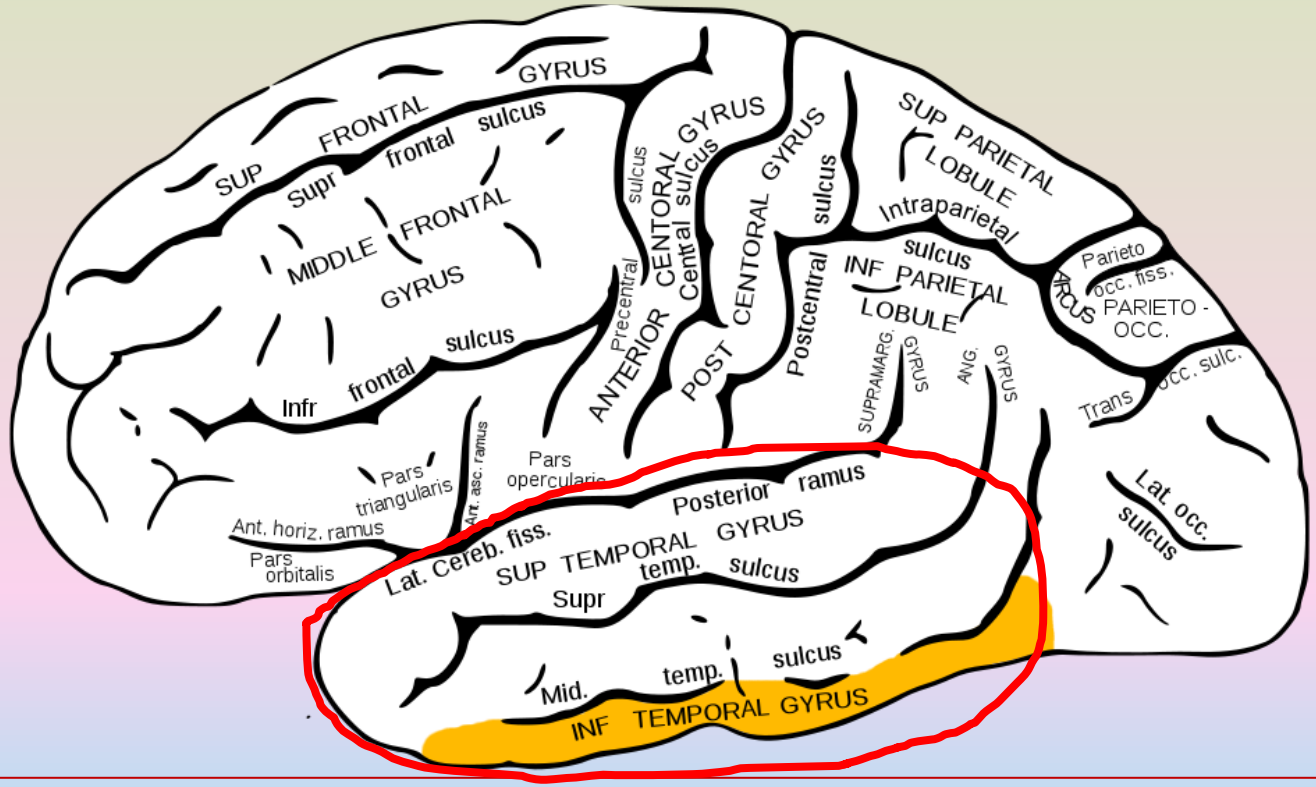
Temporal Lobe ALSO includes:
auditory cortex, object recognition
word meanings, face area,
Wernicke's area, much more.

*corpus callosum
has 250 million fibers,
~ 1 out of 100 (20 billion)

para-hippocampal gyrus = PHG,
includes:
parahippocampal AND
perirhinal cortices

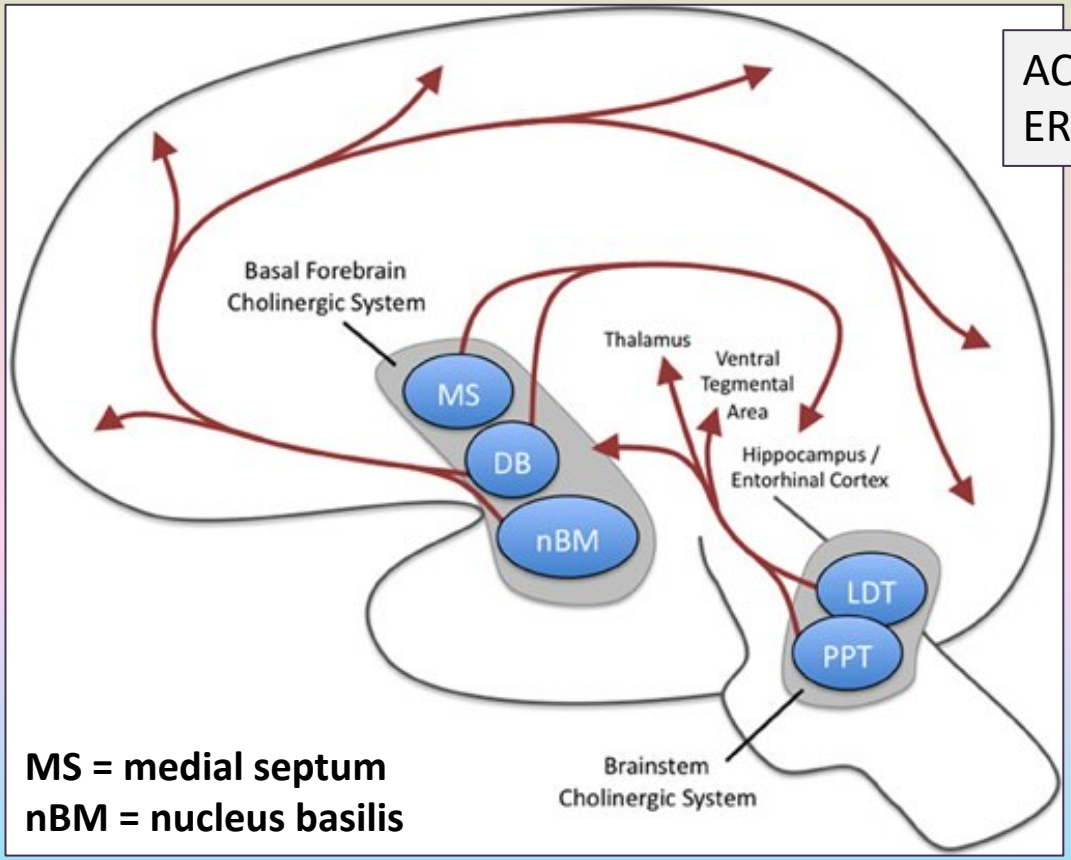
another view of major memory, limbic structures:
novelty and salience are conjoined imperatives

Lateral View of Neocortex



MTL or medial temporal lobe lies "inside" the **lateral portion of temporal lobe** (shown here in red). The MTL includes ERC and para/peri hippocampal cortices as well as the hippocampal formation proper (which has 3 layers and so is NOT called neocortex). The significance of the HM slide/notes was that removal in patient HM of the hippocampus/amygdala/ERC not only removed (or damaged) those regions BUT ALSO disconnected ACh fibers from their lower temporal lobe targets, presumably including the inferior temporal gyrus highlighted in the diagram above (Easton cited Horel-1978 as making this claim). This means that HM's "dense amnesia" might be more due to a loss of encoding, possibly outside of the hippocampus *[very speculative],* and this could have major ramifications for EM, DMRs, memory storage and memory consolidation; stay tuned for updates.

cholinergic system in human brain



ACh = acetylcholine.
ERC = entorhinal cortex

Chapters 10 and 11

MS = medial septum
nBM = nucleus basilis

Two Main Systems: (i) Basal Forebrain, (ii) Cholinergic brainstem nuclei
BF system projects throughout neocortex and is neuromodulatory
brainstem nuclei also project to Hippo, ERC. IGNORE subnuclei labels.

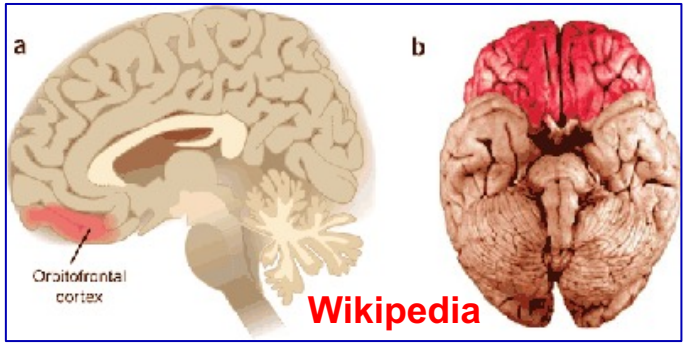
https://www.researchgate.net/figure/227180210_fig1_Figure-1-Major-cholinergic-projections-of-the-central-nervous-system-Two-groups-of

Cerebral Cortex, 2000

Orbitofrontal Cortex Pathology in Alzheimer's Disease

Gary W. Van Hoesen[1,2], Josef Parvizi[2] and Ching-Chiang Chu[2]

[1]Department of Anatomy and Cell Biology, University of Iowa and [2]Division of Cognitive Neuroscience, Department of Neurology, University of Iowa Hospitals and Clinics, Iowa City,



cortical disconnection syndrome!
- at "end-stage" AlzD illness.
- NFTs in perirhinal, then ERC!

The orbitofrontal cortex has been examined in Alzheimer's disease (AD) from the viewpoint of neurofibrillary tangle (NFT) pathology, its laminar distribution and topography. NFT pathology in the orbitofrontal cortex is extensive in AD. In cases with extensive cortical pathology, NFTs extend from the pole of the frontal lobe to the orbitoinsular junction. In lesser affected cases, the anterior granular part of the orbital cortex is less invested by NFTs. Layers III and V contain the greatest density of NFTs and these are most dense in the dysgranular areas, posterior to the transverse orbital sulcus. Posterior and medial orbitofrontal areas, forming area 13 and the posterior tip of the paraolfactory gyrus, are the most severely damaged, as are the smaller agranular fields that surround the olfactory tract and cortex. The widespread orbitofrontal damage in AD affecting projection neurons suggests that this pathology may contribute heavily to the many non-memory-related behavior changes observed in this disorder.

AD cortical pathology at end-stage illness is analogous to a cortical disconnection syndrome (Hyman *et al.*, 1984; Hof *et al.*, 1990; Hof and Morrison, 1994; Hof, 1997).

Topographically and quantitatively, the greatest cellular changes in AD occur in the temporal lobe, followed closely by the limbic lobe. These pathological observations resonate well with the memory-related cognitive changes in AD. For example, AD pathological changes in the form of NFTs are observed first in the perirhinal cortex (Brodmann's area 35), followed closely by entorhinal cortex (Brodmann's area 28) and the regio inferior (CA 1/subicular) zones of the hippocampal formation (Kemper, 1978; Hyman *et al.*, 1984; Braak and Braak, 1985, 1991; Arnold *et al.*, 1991). Quantitatively these can be extensive in cognitively normal humans (Price and Morris, 1999) but reach a critical number in time and correlate with recent memory changes. Additional NFTs, neuritic plaques and amyloid burden in ad-

MEMORY AND AGING: FOUR HYPOTHESES IN SEARCH OF DATA

Leah Light, 1991
Ann. Rev. Psychol.

What is WRONG with these four HYPOTHESES?

a lot, iaw LL

free recall ≠ recog. memory

← **Topic of 2010 Divided Attn. Paper**

I just re-read this article (Fall, 2019) and was surprised at how little our real understanding has changed over the past 30 years! The breadth and depth of this 1991 report is striking and equally striking is the extent to which it overlaps the many topics we've encountered this semester and the many questions that remain unanswered. While this PDF is "testable" many items in here have been presented and so this is well worth the read for context and highlighting key concepts and findings.

Of DMRs, EM, HM, MMO, LTM and Consolidation: a RECAP

Recap: (1) MMO has nothing to do with WM (working memory)
(2) Episodic Memory (EM) is created "instantly" in a chrono DMR
(3) Surviving EM is termed "Enduring EM" and **is written by** hippo + neocortex
(4) LTM includes words, knowledge, eEM and ABM
(5) Neocortex-MTL-Hippo interplay: its complicated (see SNCD Chapter 8)
(6) Patient HM, others fit with multiple scenarios; more in MMO

Much more on these topics at zfhindbrain.com:

- From *Stream of Consciousness* (SoC) we **RECORD** *excerpts* into DMRs
- *Excerpts* of DMRs are **SAVED** into Long Term Memory (LTMs) [consolidation]
- Most learning/memory is **Hebbian**, which requires coincident firing
- Multiplexing/concurrent rhythms is a computational multiplier, BUT …
  ARE rhythms computations? [as opposed to mere carrier bands; *see notes; new 2019*]

Absent a read of this paper, a considerable part of frontier of consciousness / neocortical operations / memory formation will be missing.

How conscious experience and working memory interact

Bernard J. Baars[1] and Stan Franklin[2]

[1]The Neurosciences Institute, San Diego, California 92121, USA
[2]Institute for Intelligent Systems, The University of Memphis, Memphis, Tennessee 38152, USA

Active components of classical working memory are conscious, but traditional theory does not account for this fact. Global Workspace theory suggests that consciousness is needed to recruit unconscious specialized networks that carry out detailed working memory functions. The IDA model provides a fine-grained analysis of this process, specifically of two classical working-memory tasks, verbal rehearsal and the utilization of a visual image. In the process, new light is shed on the interactions between conscious and unconscious aspects of working memory.

This is the closest thing that I can find in the literature to DMRs, but it is more about the generation of consciousness via perception (moreso than WM). But it does propose a **Transient EM** that persists for hours (clearly NOT WM!) and addresses processes that bring the sensory world into consciousness. But it is not about the writing of consc. experience into DMRs or at least it's not formulated that way…

I should consult w/ them!

All active components of cognitive working memory (WM) are accurately reportable: for example, perceptual input, rehearsal, recall, and the act of responding with a recalled item. But accurate report is also the standard operational

Global Workspace theory

Global Workspace theory is a cognitive architecture with an explicit role for consciousness (Fig. 2). It makes minimal assumptions:

FROM: "Orbitofrontal Cortex Pathology in AD". OFC mentioned by McClellan.

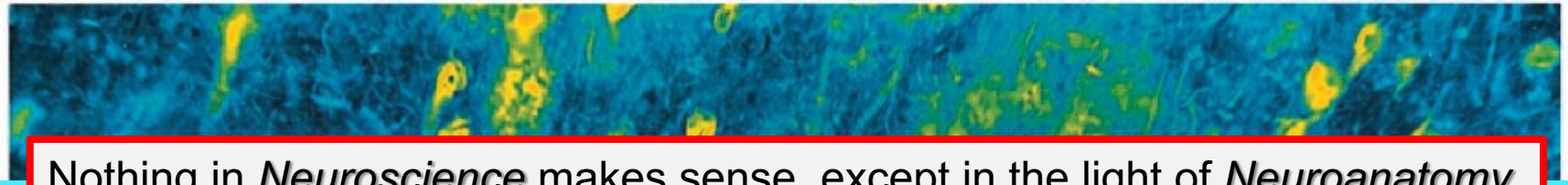
Tangles are Us

this involves a widening of sulci and a flattening and atrophy of gyri. Posteriorly and medially it is not unusual to observe a discoloring of the cortex. Microscopically, most of the orbitofrontal cortex contains NFTs in layers III and V in cases with heavy pathology, and with pathological staining these form dense ribbons anteriorly to posteriorly and laterally to medially. Layer V is especially prominant for its number of NFTs and for paired helical filaments that extend for long distances into the apical dendrites of these large pyramidal neurons (Fig. 6). The anterior and medial granular orbitofrontal cortex, corresponding to Brodmann's areas 10 and 11, and the anterior half of the paraolfactory gyrus in some AD cases, may be relatively spared, with only occasional NFTs in layers III and V. However, all of the cases we have studied contained NFTs in the dysgranular posterior and medial orbitofrontal cortex. The lateral and posterior parts of the orbitofrontal dysgranular cortex, corresponding to what we have termed area 47p, had variable degrees of pathology. Hof *et al.* (Hof *et al.*, 1995) have pointed out that the transverse orbital sulcus is a limiting sulcus roughly dividing the orbital cortex into granular areas anteriorly and dysgranular areas posteriorly. We agree with this observation since this sulcus in AD often seemed to divide a more modest quantity of NFTs in granular cortex anteriorly from a greater quantity of NFTs in dysgranular cortex posteriorly. However, within the latter, posterior and medial dysgranular orbitofrontal cortices had highly dense quantities of NFTs.

The high quantity of NFTs in layers III and V corresponds well with observations in other cortical association areas in AD. As pointed out by Hof and Morrison (Hof and Morrison, 1994, 1996), these pyramidal neurons are the origin for many neural systems of the cerebral cortex, including intra- and interhemispheric corticocortical association systems and corticofugal systems that course to the pons and to the striatum. The heavy involvement of posterior and medial orbitofrontal cortices in AD would suggest also that the ventral striatum and magnocellular nuclei of the basal forebrain would also be deprived of orbitofrontal cortex input (Mesulam and Mufson, 1984; Haber *et al.*, 1995).

In addition to the pathways mentioned above, a number of recent investigations in non-human primates have clarified the organization of the cortical connections of the amygdala and hypothalamus (Amaral and Price, 1984; Barbas, 1988, 1993; Barbas and De Olmos, 1990; Carmichael and Price, 1995; Price *et al.*, 1996; Öngür *et al.*, 1998; Rempel-Clower and Barbas, 1998). Many of these neural systems involve the posterior and medial parts of the orbitofrontal cortex and the pyramidal neurons that in humans have NFTs in AD. In view of the high mean density of NFTs in these orbitofrontal areas in all cases

Do not sweat the details, but since orbitofrontal is involved in so many things it is of note.



Nothing in *Neuroscience* makes sense, except in the light of *Neuroanatomy*

see Q. in note

PREVIEW of CHAPTER 9

SUMMARY -- The Cognitive Neuroscience of Working Memory, Annual Rev. Psych, 2015

1. An enduring principle of the multiple-component model of working memory (Baddeley and Hitch, 1974) is that the short-term retention of information **(a.k.a. "working memory storage") and the control of how that information is used to guide behavior are subserved by distinct processes.** With regard to the former, however, earlier ideas of specialized buffers have been largely superseded by state-based models.

2. Although state-based models of working-memory storage are often categorized as "activated LTM" models or "sensorimotor recruitment" models, all are grounded in the idea that **the attentional selection of mental representations brings them into working memory,** and that the consequences of attentional prioritization explain such properties as capacity limitations, proactive interference from no-longer-relevant items, and so on.

3. Recent research applying multivariate pattern analysis (MVPA) to **fMRI and EEG data has provided compelling neural evidence for state-based models of working memory storage…according to Brad and Mark.**

4. Some recent findings from computational modeling, extracellular electrophysiology, fMRI, and EEG, suggest that working memory storage may depend on **the transient reorganization of synaptic weights, rather than on sustained, elevated activity**. PNA aka **Persistent Neural Activity** is sustained elevated activity: see SNCD.

5. The PFC likely represents higher-order information, such as task rules, goals, or abstract representations of categories, as compared to feature- and stimulus-specific representations in posterior cortex. Moreover, a critical mechanism for working memory function is the **synchronization of PFC activity with activity** in other brain regions.

6. One dimension of functional organization of PFC is **a hierarchical caudal-to-rostral gradient of the level of abstraction** of the rules and goals that guide behavior.

7. Top-down control signals emanating from PFC likely take at least two forms: signals that modulate gain by either enhancing task-relevant information or suppressing task-irrelevant information, and signals that can modulate the selectivity of information represented in posterior cortical regions.

8. Dopamine plays a critical role in working memory function. The complex interplay of midbrain dopamine in prefrontal and striatal circuits underlies "tonic maintenance" and "phasic gating" functions that govern the balance between cognitive flexibility and stability.

Too many structures! But a major experimental manipulation of the ACh systems is to cut the Fornix.

Fornix (neuroanatomy)

Where is 3D navigation of basic Neuroanatomy?

Research databases exist but teaching tools lag; check with Bob Sikes!

From Wikipedia, the free encyclopedia

The **fornix** (Latin: *arch*) is a C-shaped bundle of nerve fibers in the brain that carries signals from the hippocampus to the mammillary bodies and then to the anterior nuclei of thalamus. The fornix is part of the limbic system. While its exact function and importance in the physiology of the brain is still not entirely clear, it has been demonstrated in humans that surgical transection – the cutting of the fornix along its body – can cause memory loss. There is some debate over what type of memory is affected by this damage, but it has been found to most closely correlate with recall memory rather than recognition memory. This means that damage to the fornix can cause difficulty in recalling long-term information such as details of past events, but it has little effect on the ability to recognize objects or familiar situations.

Contents [hide]

Path of cholinergic fibers not mentioned
Role in Memory Emphasized
Fornix projects to thalamus, mamm. bodies might connect L/R hippocampus?

Easton: the fornix (is) the route of subcortical communication with the hippocampus, including cholinergic connections in monkeys.

Fornix

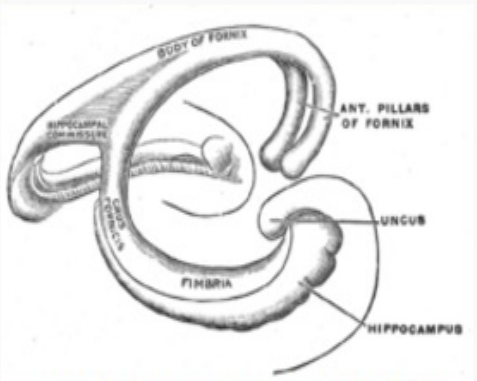
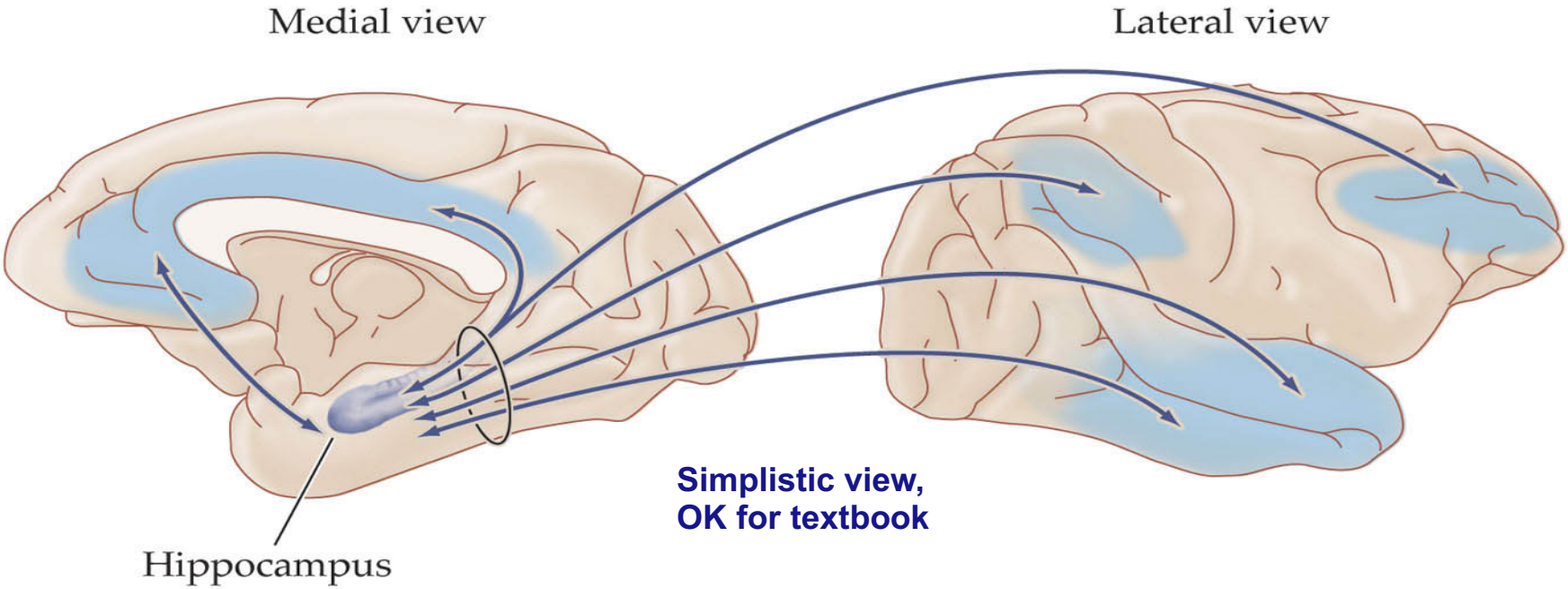


Diagram of the fornix. Right=anterior

Details	
Identifiers	
Latin	*Fornix*
MeSH	*A08.186.211.577.265*
NeuroNames	*hier-250*
NeuroLex ID	*Fornix*
TA	A14.1.08.949

30.8 Connections between the hippocampus and possible declarative memory storage sites.



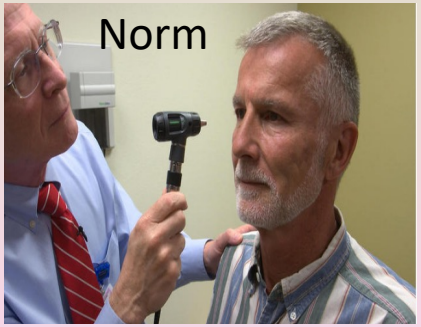
The connections are actually from **association cortices** to entorhinal, perihippocampal and parahippocampal cortex. **Entorhinal cortex (ERC)** has direct reciprocal connections with the hippocampus, but distant cortices project to ERC.

Which neocortical region should NOT undergo LTP?

"What is Memory?" – is not the question…
"What do I need to Remember?" **-- THIS is the question**

For Example

the words in a sentence– so we can make sense of the sentence
the gist of the sentence to know what to think and do
where I am driving to, how to get there **[confusion will be my epitaph]**
the meaning of red, yellow and green traffic signals
what I want to do today and who I will be interacting with
how to act appropriately in different ***social venues*** -more habit, basal ganglia, specific neocortical modules
to get dressed in the morning and where my I-phone is
to check Facebook, Snapchat, Tinder, Instagram, Twitter before I go out
the passwords to 50 different things and my lock combination
what neurofibrillary tangles and the hippocampus are
to pay the rent so we do not get evicted ← if this pops back in mind 10 min from now is it WM or LTM?
that I am running low on marijuana, milk and Ramen noodles
the name of the person I just met and the phone number I was just given
where the bathroom is In a bar this is called "problem solving"!
the names of my family members
to take the Quiche out of the oven
to check my pocket calendar so that I do not miss any meetings



Norm, who could not remember woman was his wife, was socially PERFECT, very nice guy, **not Tim Apple**

REAL Systems Neurobiology: Life in Prefrontal Cortex

Bruno Averbeck & Moonsang Seo, 2008

PLoS Computational Biology

Are DMRs stored in the temporal / parietal / prefrontal cortices?

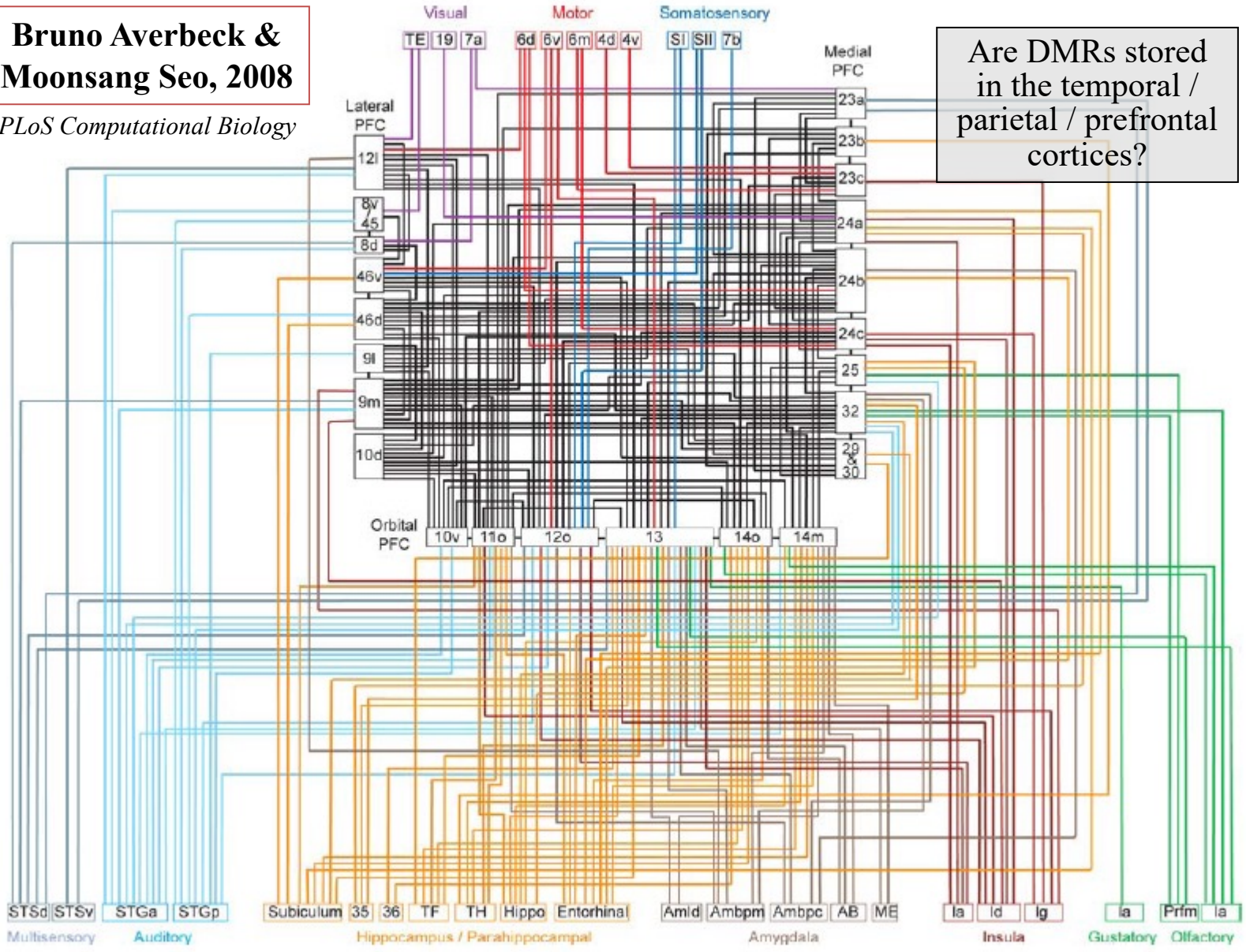


Figure 1. Connectivity diagram showing interconnections of frontal reward and decision-making networks with sensory, limbic, and motor systems. In this diagram, for clarity, only intermediate and strong projections to the frontal cortex are shown.

models: we can agree that the Hippocampus and ERC are crucial to human cognition!

ELSEVIER

Neuropsychologia

Thanks to Jamie Bunce & Shezal Padani; White Paper due out soon

2012 **Great Review of role of ACh in Hippocampal Function, Encoding and (not) Retrieval.**

A specific role for septohippocampal acetylcholine in memory?

Alexander Easton*, Vincent Douchamps, Madeline Eacott, Colin Lever*

Department of Psychology, University of Durham,

This concerns episodic memory (EM) not Working Memory (WM)

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ABSTRACT

Acetylcholine has long been implicated in memory, including hippocampal-dependent memory, but the specific role for this neurotransmitter is difficult to identify in human neuropsychology. Here, we review the evidence for a mechanistic model of acetylcholine function within the hippocampus and consider its explanatory power for interpreting effects resulting from both pharmacological anticholinergic manipulations and lesions of the cholinergic input to the hippocampus in animals. We argue that these effects indicate that acetylcholine is necessary for some, but not all, hippocampal-dependent processes. We review recent evidence from lesion, pharmacological and electrophysiological studies to support the view that a primary function of septohippocampal acetylcholine is to reduce interference in the learning process by adaptively timing and separating encoding and retrieval processes. We reinterpret cholinergic-lesion based deficits according to this view and propose that acetylcholine reduces the interference elicited by the movement of salient locations between events.

- **nice history** documenting manipulation of cholinergic system
+ **gory details** of hippocampal encoding, retrieval and nested oscillators
- **not technically** on “aging” but all aging/ACh/memory loss is ~built on this

Disruption of cholinergic neurotransmission exacerbates Aβ-related cognitive impairment in preclinical Alzheimer's disease

Yen Ying Lim [a], Paul Maruff [b,c], Rachel Schindler [d], Brian R. Ott [a], Stephen Salloway [a], Don C. Yoo [e], Richard B. Noto [e], Cláudia Y. Santos [f], Peter J. Snyder [a,f,g,*]

an ACh, Memory and AlzD study: an intense research area

Disruption in cholinergic neurotransmission is one of the earliest neuropathological changes in preclinical Alzheimer's disease (AD) and may be associated with abnormal beta-amyloid (Aβ) accumulation. Therefore, disruption of cholinergic neurotransmission with scopolamine may unmask otherwise undetectable cognitive deficits in preclinical AD. To compare the effects of low-dose (0.20 mg s.c.) scopolamine on cognition between Aβ+ and Aβ− cognitively normal (CN) older adults using the Groton Maze Learning Test (GMLT). CN older adults completed the GMLT predose and then received scopolamine (0.20 mg) subcutaneously. Participants were reassessed 1-, 3-, 5-, 7-, and 8-hours post dose. All participants underwent positron emission tomography neuroimaging for Aβ using ^{18}F-florbetapir within 6 weeks of their baseline visit. Rhode Island Hospital Clinical Research Center, Providence, USA. CN older adults (n = 63), with a family history of AD and subjective memory complaints were enrolled (15 were classified as Aβ+ and 48 were classified as Aβ−). Cognition was assessed using the computerized GMLT at all predose and post-dose time points. At 5-hours post dose, the Aβ+ group performed significantly worse than the Aβ− group on all measures of learning efficiency and working memory and/or executive function (Cohen's d = 1.13–1.56). When participants were classified as having an abnormal response to scopolamine (based on change score at 5-hours post dose >0), 100% were correctly classified as Aβ+ and 67% as Aβ−. The results of this study suggest that diminished cholinergic tone likely occurs in preclinical AD, and as such, the use of a cholinergic stress test to perturb an already compromised neurotransmitter system may be an effective way of identifying CN older adults who are in this preclinical stage of AD.

Neurobiology of Aging (2015) 2709-2715

Groton Maze Test on CN older adults

CN = cognitively normal

-includes AB+ and AB- individuals

-scopolamine was given to block ACh

-AB+ did worse on EM, WM, Exec. functions

- "cholinergic stress test" might help ID preclinical stage of AlzD = huge research area!

theory: ACh inputs to Hippocampus promote encoding of new info.

blocking ACh hinders encoding AND promotes retrieval, qed:

scopolamine is Truth Serum!

- Scopolamine promotes CA3-AAN activity

“All memory is associative”. valid claim?
ignore older verbiage below...skipping most of this

Neurotransmitters (NETs) Systems are crucial to learning, memory and cognitive decline. But first we will cover some articles relating to memory -- we will sample some material from a few background PDFs on memory and then examine some cognitive deficits associated with aging.

For upcoming Memory Lecture, we are going to sample content from 5 different PDFs – more info TBA. Might read whatever is most interesting to you.

For reference, a 1991 Review on 4 Hypotheses of Memory and Aging might be provided.

We can then see how those ideas have played out in the *2015 Review on the Cognitive Neuroscience of Working Memory* (which is not about aging per se, but we can see its 2015 implementation).

Working Memory is very different than Episodic Memory which relates to the 2015 Article I labeled as HippoReview is actually narrowly focused on Place Cells, Grid Cells and Memory and provides some background for animal studies of brain aging. [That's Hippocampus, not Hippopotamus].

We get deeper in the weeds with the **2015 PLoS article on Working Memory in Aging Brain Networks.**

Finally, there is a compact but highly pertinent article on **Aging, Memory, Attention and Context,** which we will try to cover or might not: situation in flux. The title is: "Psychol Aging. 2010. Effects of aging and divided attention on memory for items and their contexts."

What is memory? plus PFC diagram, plus Neuro slides

CASE STUDY: **76 year old woman**

referred by neurologist b/c: memory issues.

NeuroPsych TESTS:

- MMSE = 19 out of 30 [bad]
- could not copy simple cube
- could not draw clock face with hands
- repeated her own sentences w/in a few minutes (during interview)
- during testing could "repeat back" sentences
- but poor performance on word generation
- poor performance on complex trails (confused)
- ExecFxg decline = bad b/c why? [DQ]
  - inquired about resuming driving
  - companion tearful on exit summation
  - no scans available, diagnosis: MCI? other?

Before we can think about *the nature of her damage*, we first need to consider how memory normally works!

MMSE = mini mental status exam

F(x) = Function … Fxg = functioning