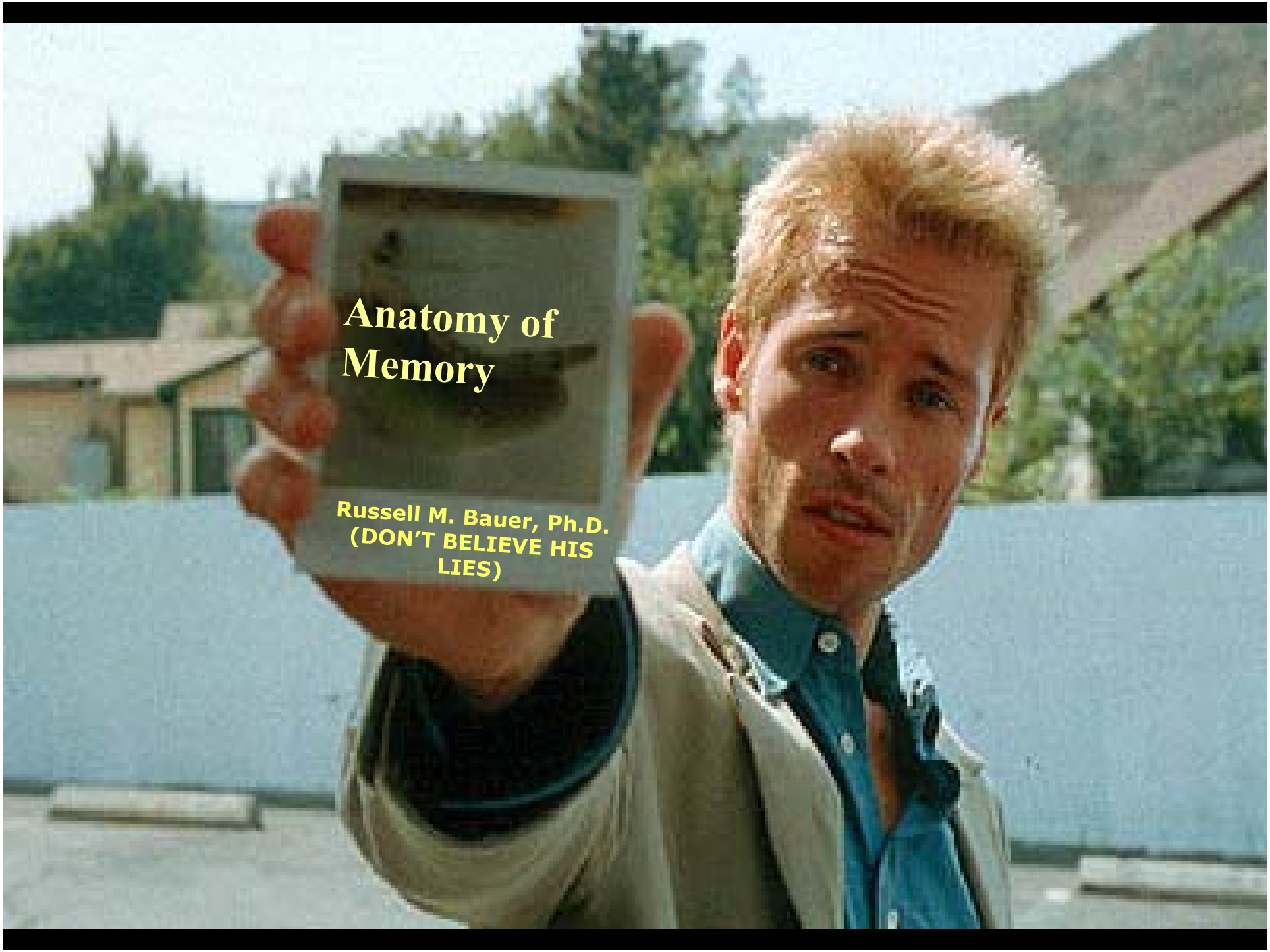
Functional Neuroanatomy of Memory: Three Amnesias or One?

Russell M. Bauer, Ph.D., ABPP/CN
University of Florida
November 11, 2009


Anatomy of Memory
Russell M. Bauer, Ph.D.
(DON'T BELIEVE HIS LIES)

National Academy of Neuropsychology

Presenter Disclosure Information

I have no financial relationships to disclose:

Employee of: University of Florida/State of Florida
Consultant for: DVBIC
Stockholder in: None relevant
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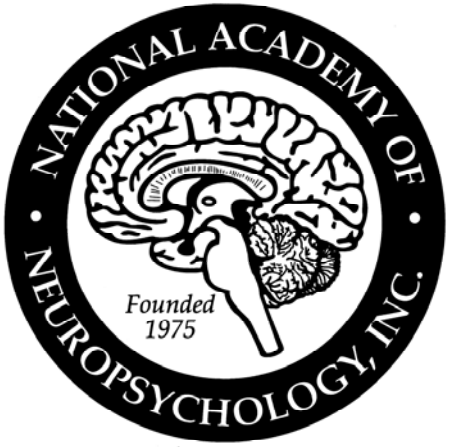
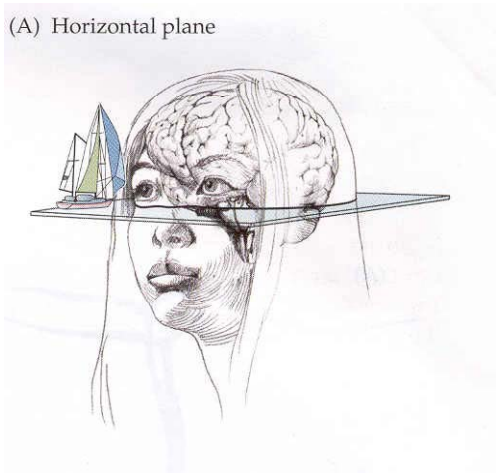


Goals and Learning Objectives

- Describe organization of the human memory system
- Identify principal structures in a distributed system
- Address the question of whether there is a “core” amnesic syndrome
- Apply lesion localization techniques to differential diagnosis

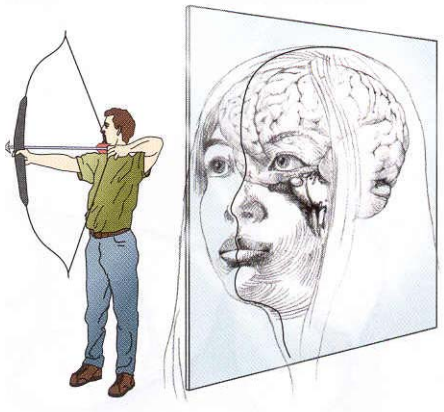
Planes of Section

(A) Horizontal plane



(B) Coronal plane

(C) Sagittal plane

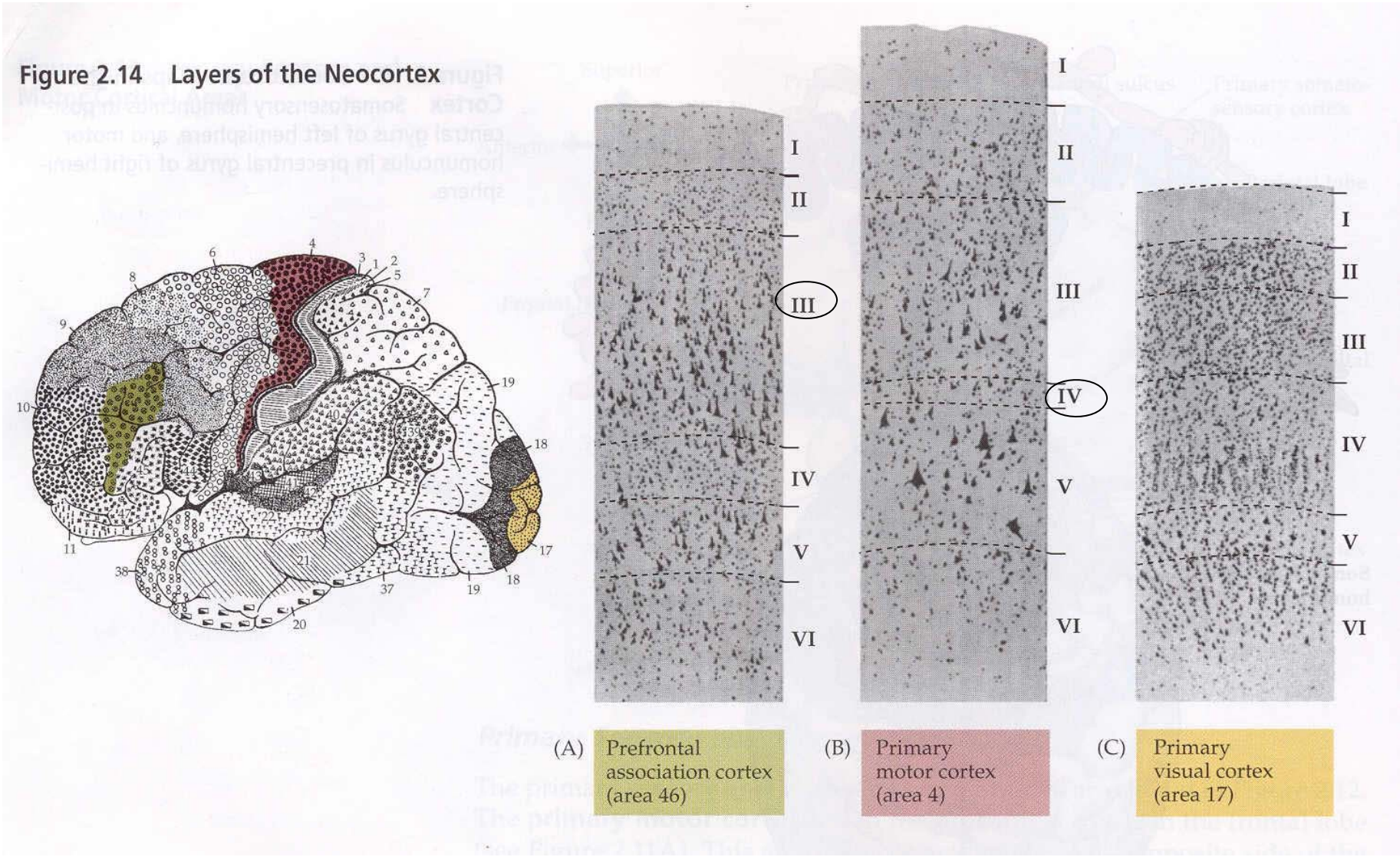


Blumenfeld, 2002

TABLE 2.3 Cell Layers of the Neocortex

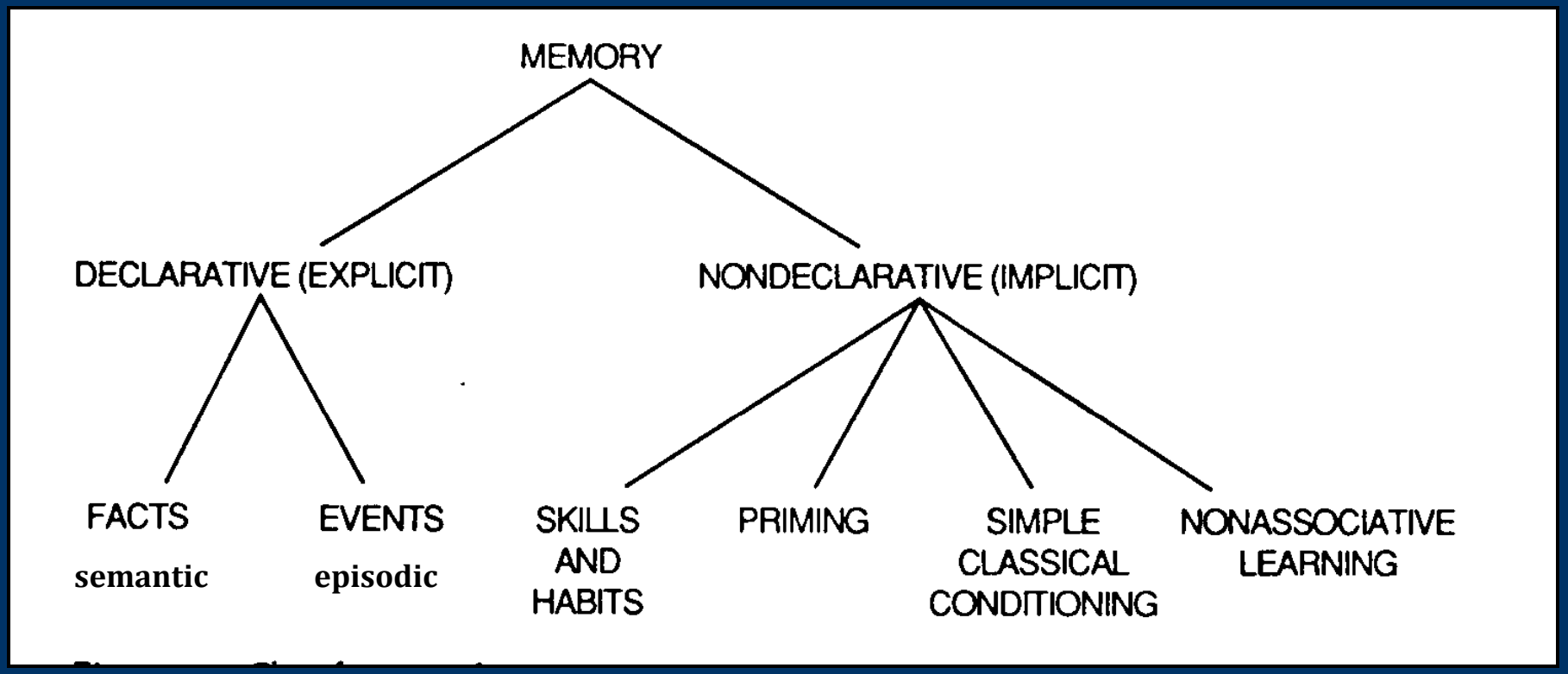
LAYER	NAME	ALTERNATIVE NAME	MAIN CONNECTIONS
I	Molecular layer		Dendrites and axons from other layers
II	Small pyramidal layer	External granular layer	Cortical–cortical connections
III	Medium pyramidal layer	External pyramidal layer	Cortical–cortical connections
IV	Granular layer	Internal granular layer	Receives inputs from thalamus
V	Large pyramidal layer	Internal pyramidal layer	Sends outputs to subcortical structures (other than thalamus)
VI	Polymorphic layer	Multiform layer	Sends outputs to thalamus

Blumenfeld, 2002



Blumenfeld, 2002

Multiple Forms of Memory



CORTEX | HIPP+ | BG+ | CORTEX | AMYG+ | CORTEX

LIMBIC

MOTOR

Human Amnesia: Core Features

anterograde amnesia: defect in new learning

retrograde amnesia/remote memory disturbance: defect in retrieving old memories

spared memory abilities: attention span, psychometric intelligence, nondeclarative memory, “personality”

NOT limited to one modality (visual, tactile)

Clinically Relevant Dimensions of Human Memory Performance

Immediate-recent-remote

Encoding-storage-retrieval

Episodic v. semantic memory

Retrieval mode (deliberate v. nondeliberate)

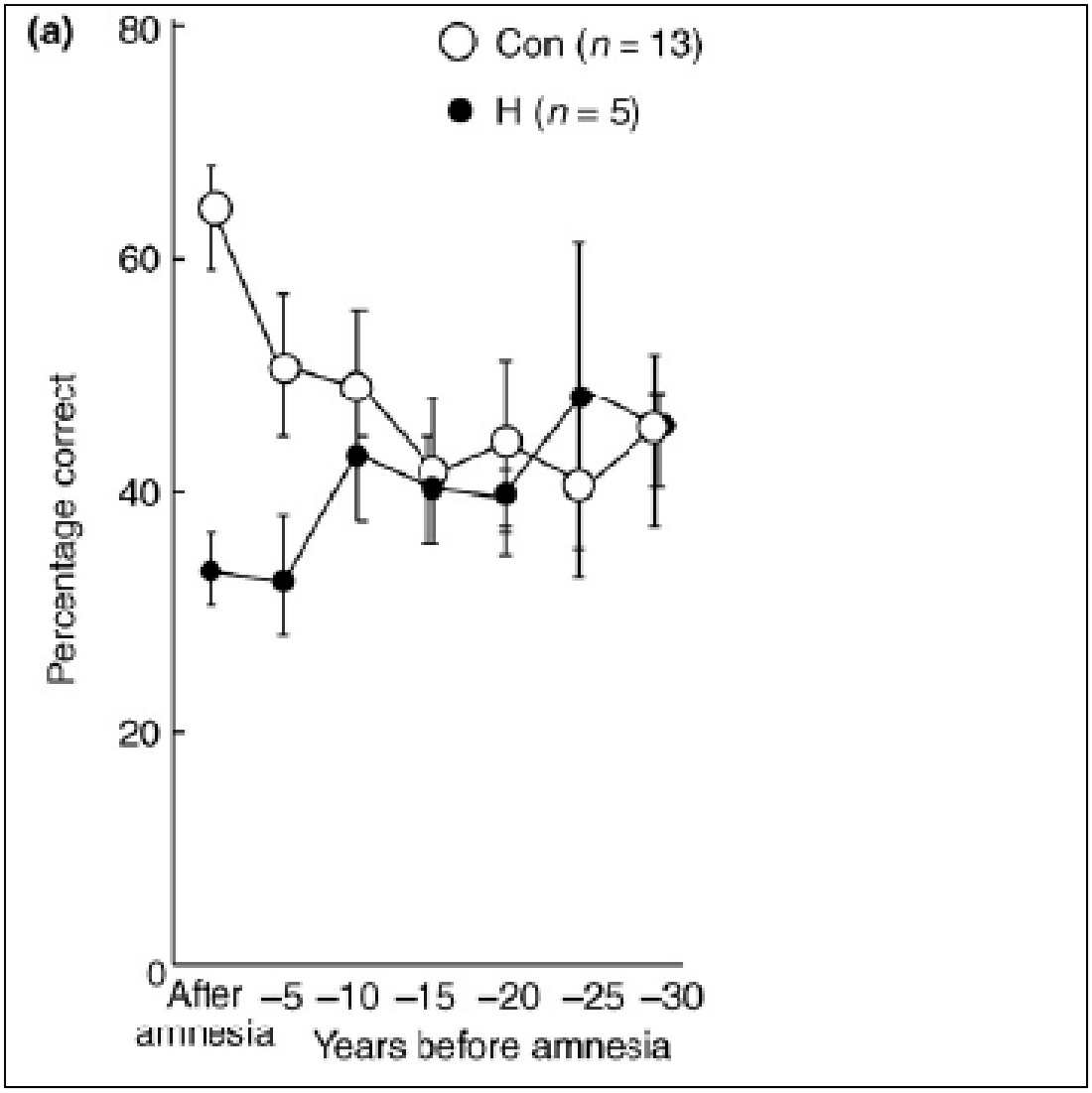
Material specificity

Encoding

- **Definition**: transforming to-be remembered in formation into memorable and retrievable form
  - Encoding I: bringing information-processing capacity to bear on stimuli
  - Encoding II: ability to use the results of E-1 mnemonically
- **When?** during study phase
- **Relevance**: what is remembered is what is processed (levels of processing)
- **Clinical manifestation**: poor immediate (superspan) recall

Consolidation/Storage

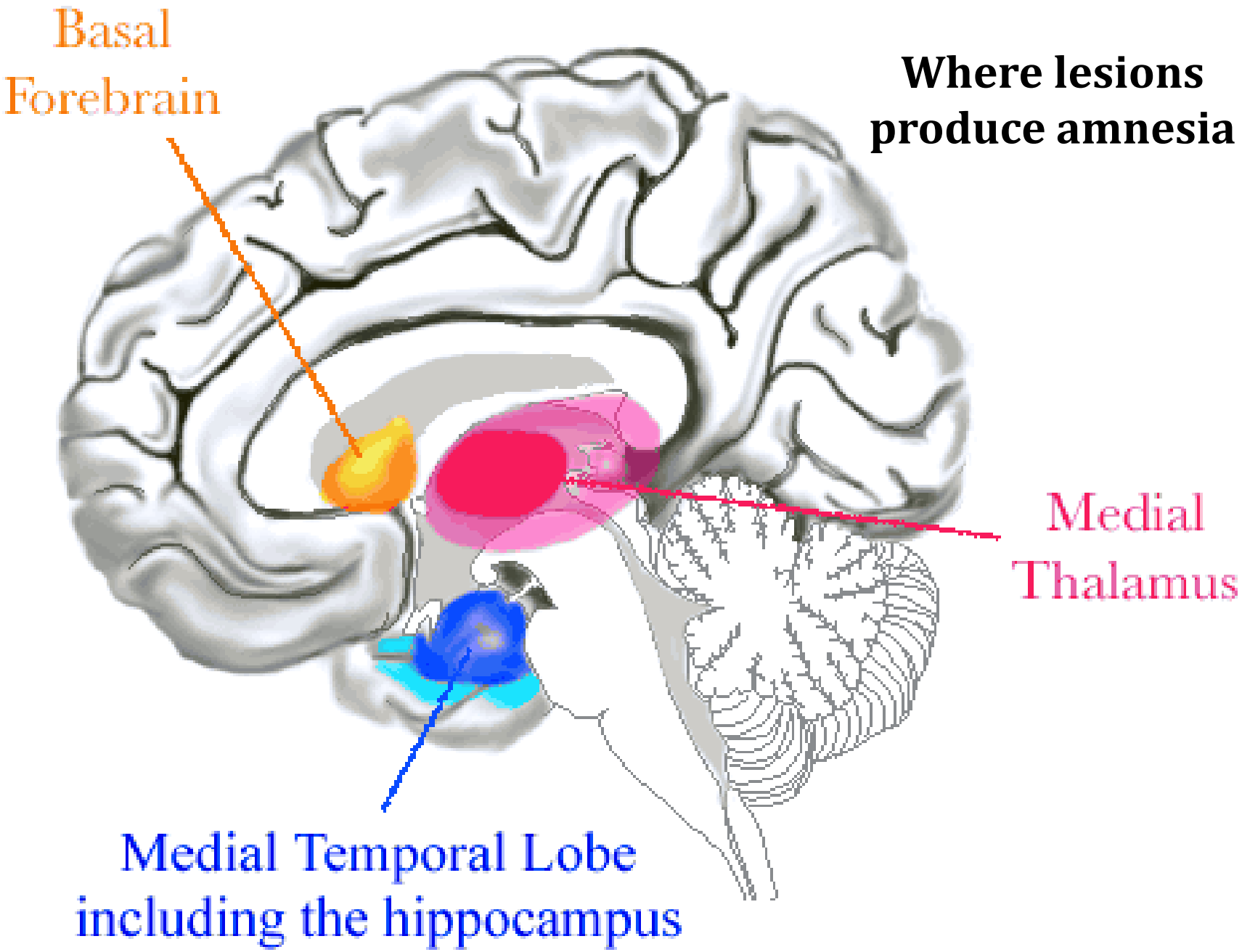
- **Definition:** process of making new memories permanent
- **Basis:** anatomic and physiological changes at cellular level; hippocampal system important
- **When?** during study-test interval
- **Duration:** hours? days? years?
- **Clinical Symptom:** delayed memory << immediate memory (forgetting)



Performance on a test of memory for news stories. From Squire & Bayley, Curr Opin Neurobiol, 2007, 17, 185-196.

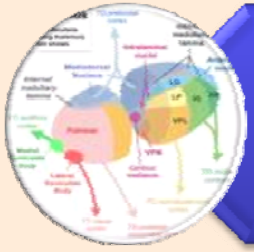
Retrieval

- **Definition**: process of locating, selecting, and activating a memory representation
- **Basis**: re-enactment of processes/neural events occurring at encoding
- **when?** at point of test
- **clinical symptom**: recall << recognition (also true of shallow encoding), inconsistent errors

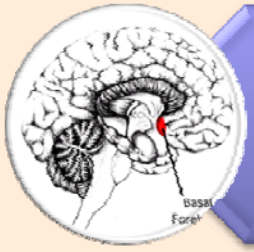

Basal
Forebrain
Where lesions
produce amnesia
Medial
Thalamus
Medial Temporal Lobe
including the hippocampus

The Three Amnesias?

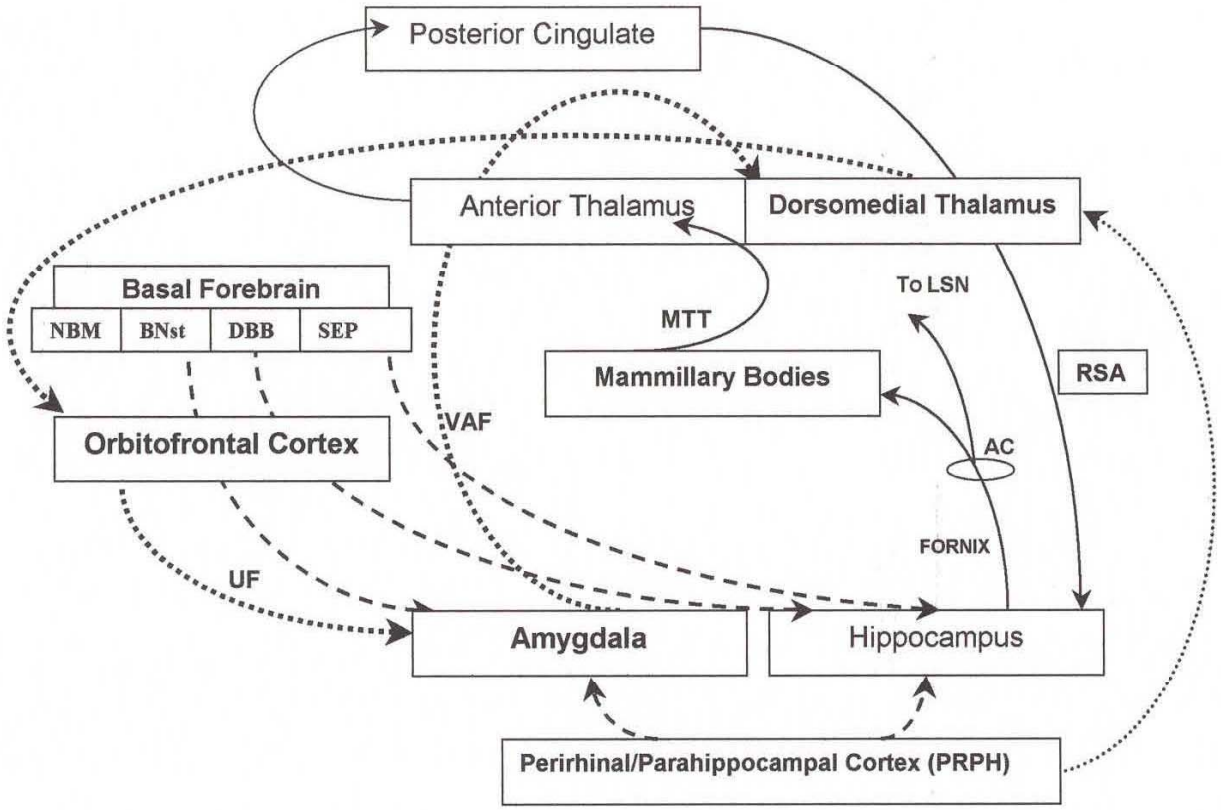
Medial temporal lobe amnesia



Diencephalic amnesia



Basal Forebrain amnesia



Integrated Circuitry Linking Temporal, Diencephalic, and Basal Forebrain Regions

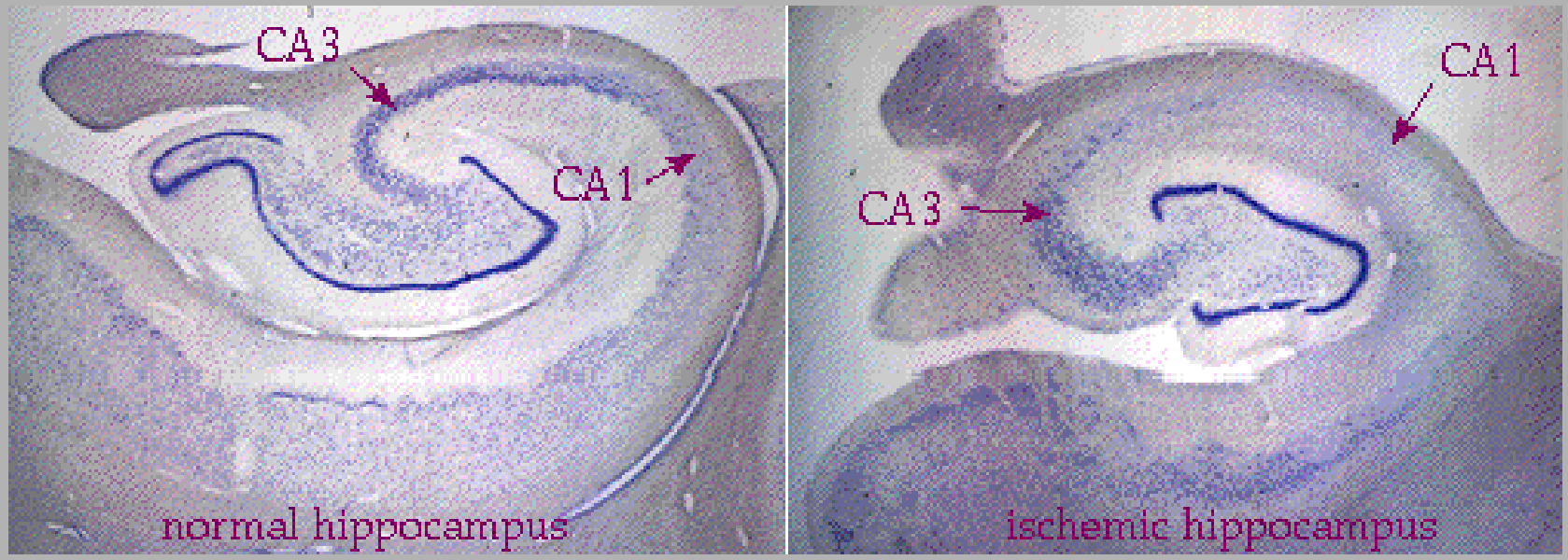
Medial Temporal Syndromes

- Anoxic-hypoxic syndromes
  - cardiac arrest
  - CO poisoning
- Amnesia associated with ECT
- CNS Infections (Herpes)
- MTS and complex-partial epilepsy (material-specific)
- Early AD

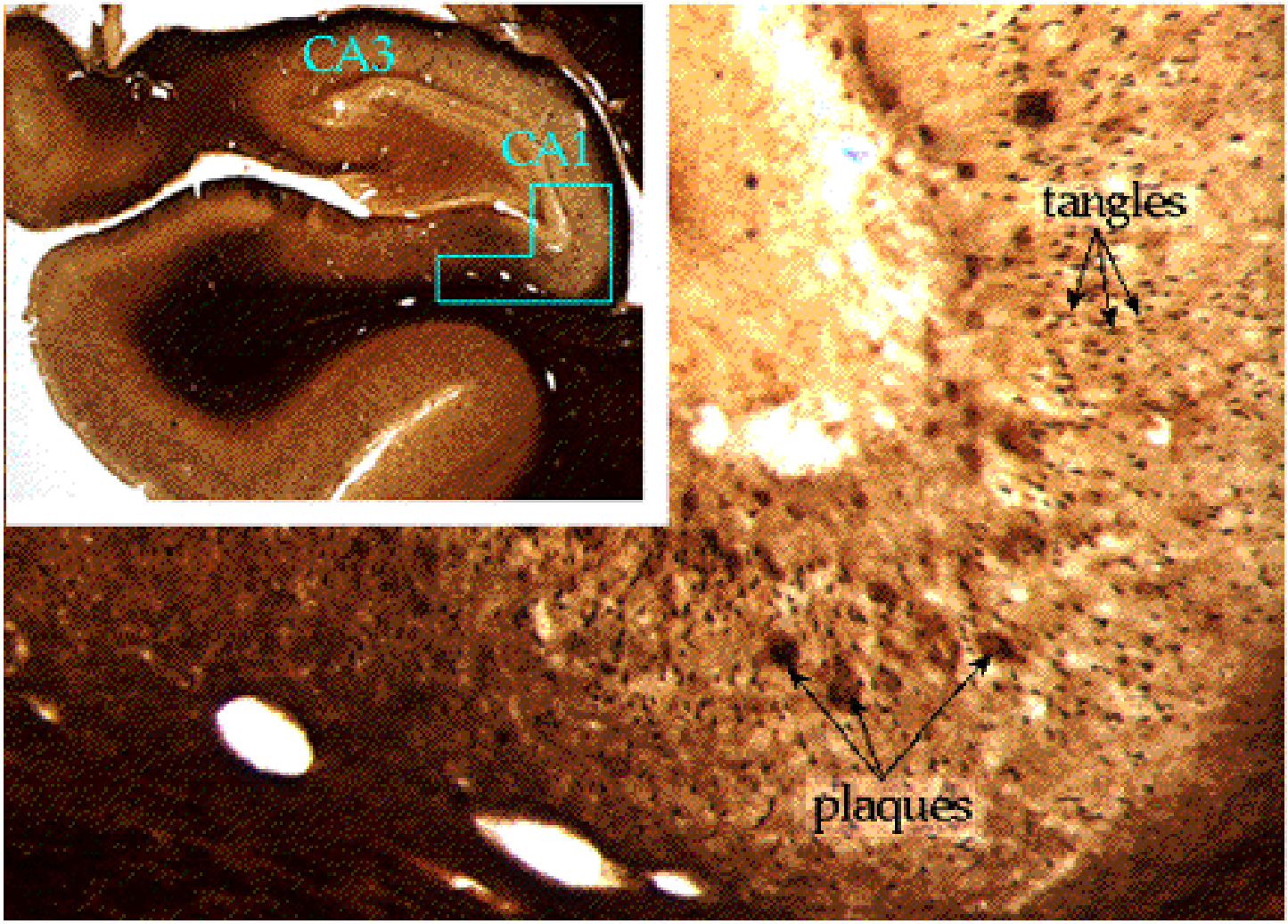
Temporal Lobe Pathology Associated

with Herpes Simplex Encephalitis

FLAIR (Fluid Attenuated Inversion Recovery) in Medial Temporal Sclerosis

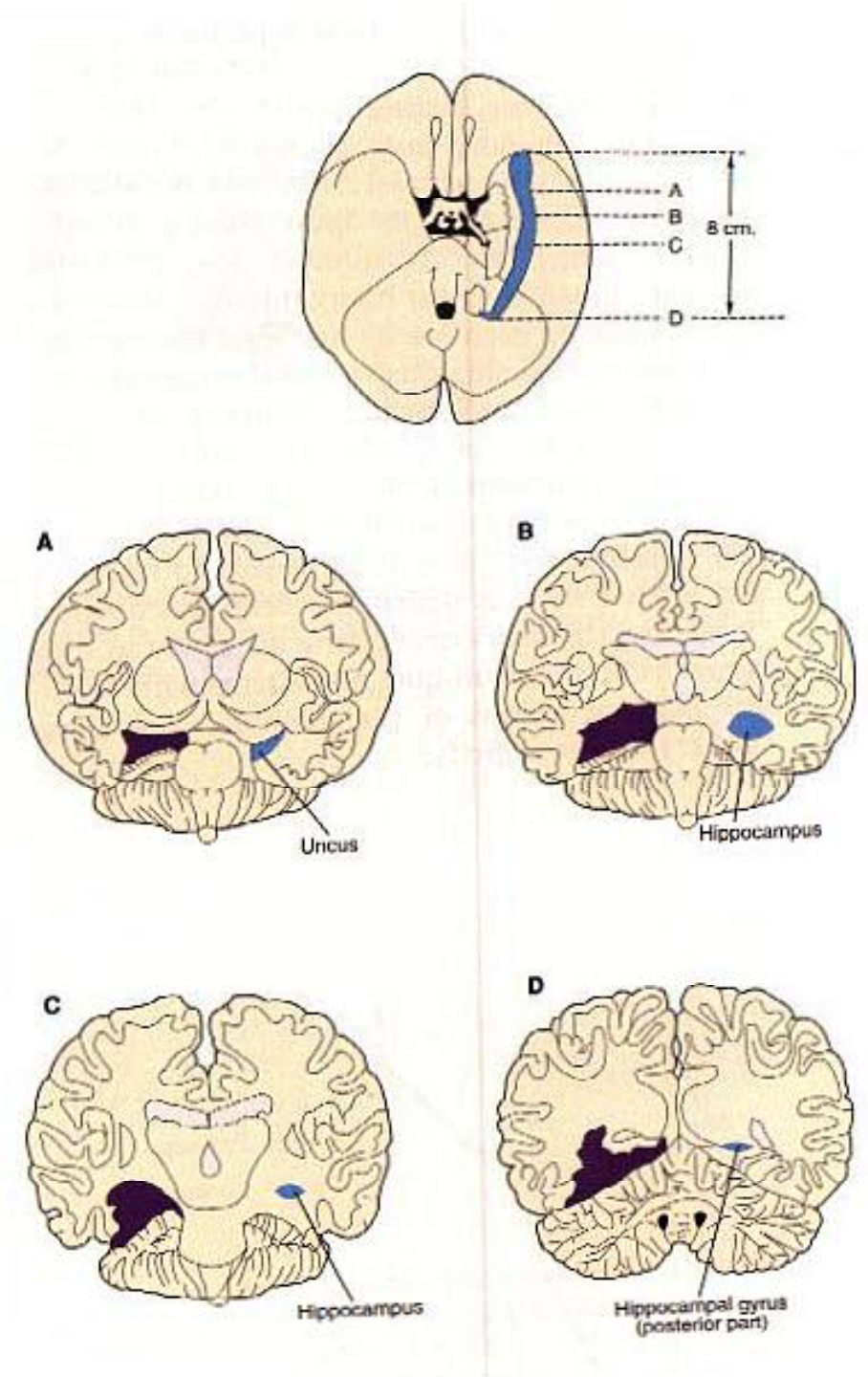


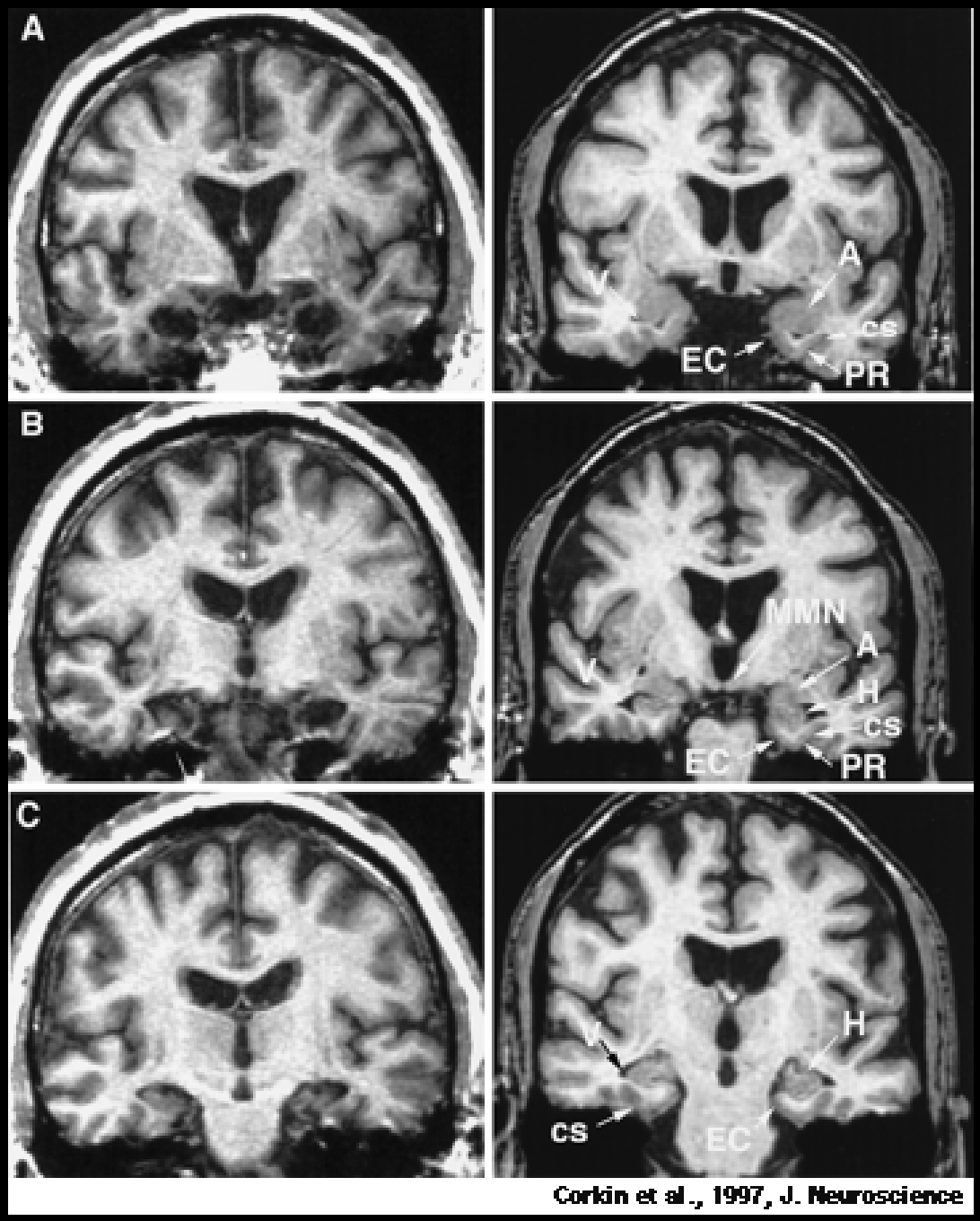
Hippocampus in ischemia



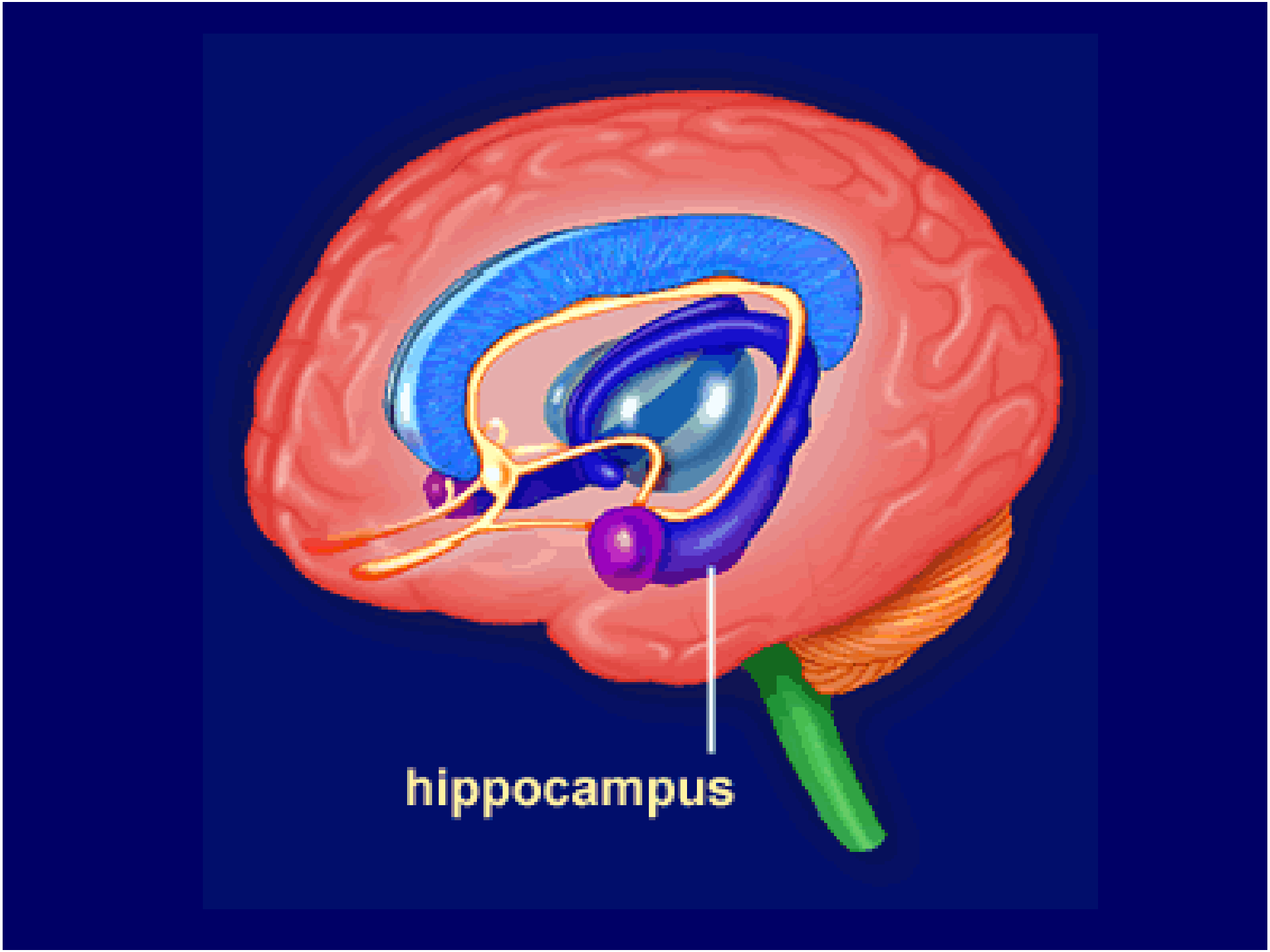
Hippocampus in Alzheimer's Disease

The Case of Henry M (H.M.)

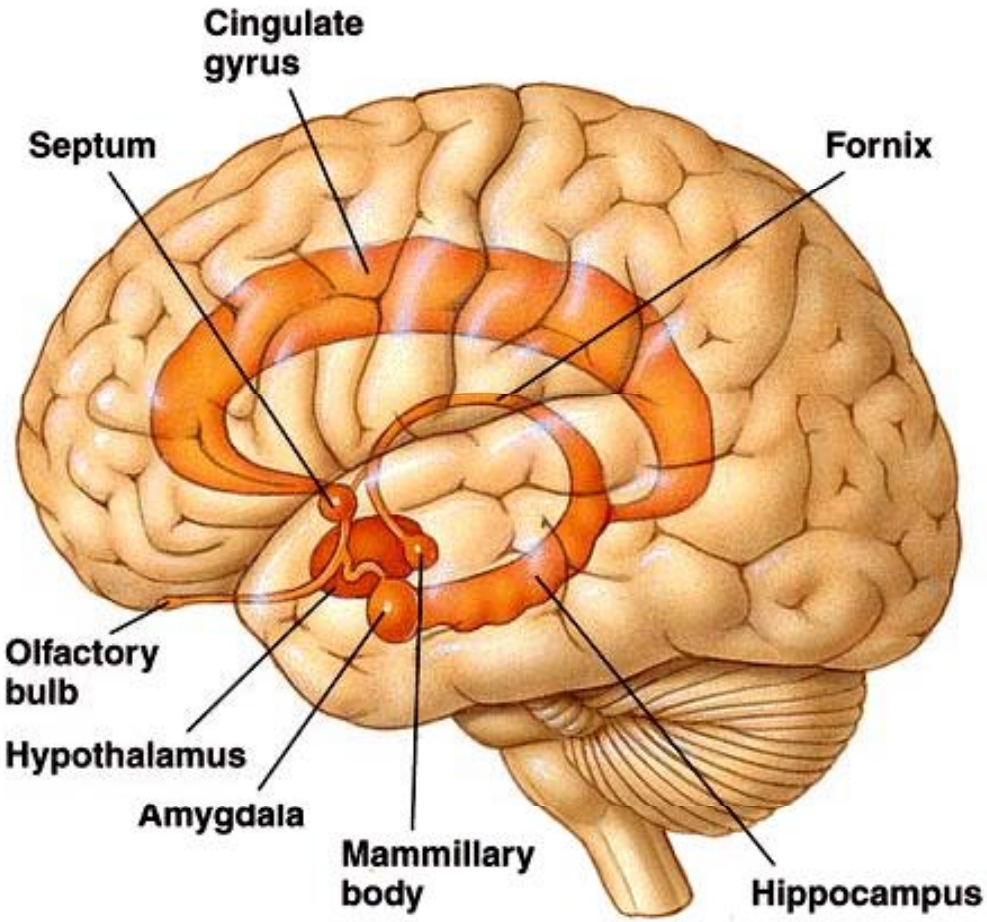


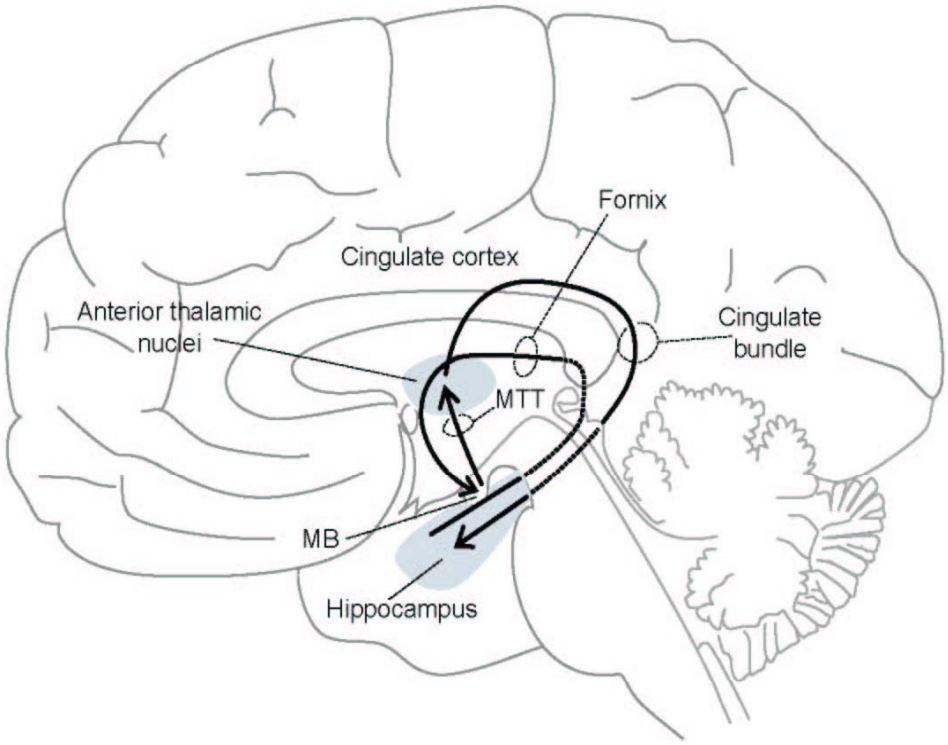


Corkin et al., 1997, J. Neuroscience

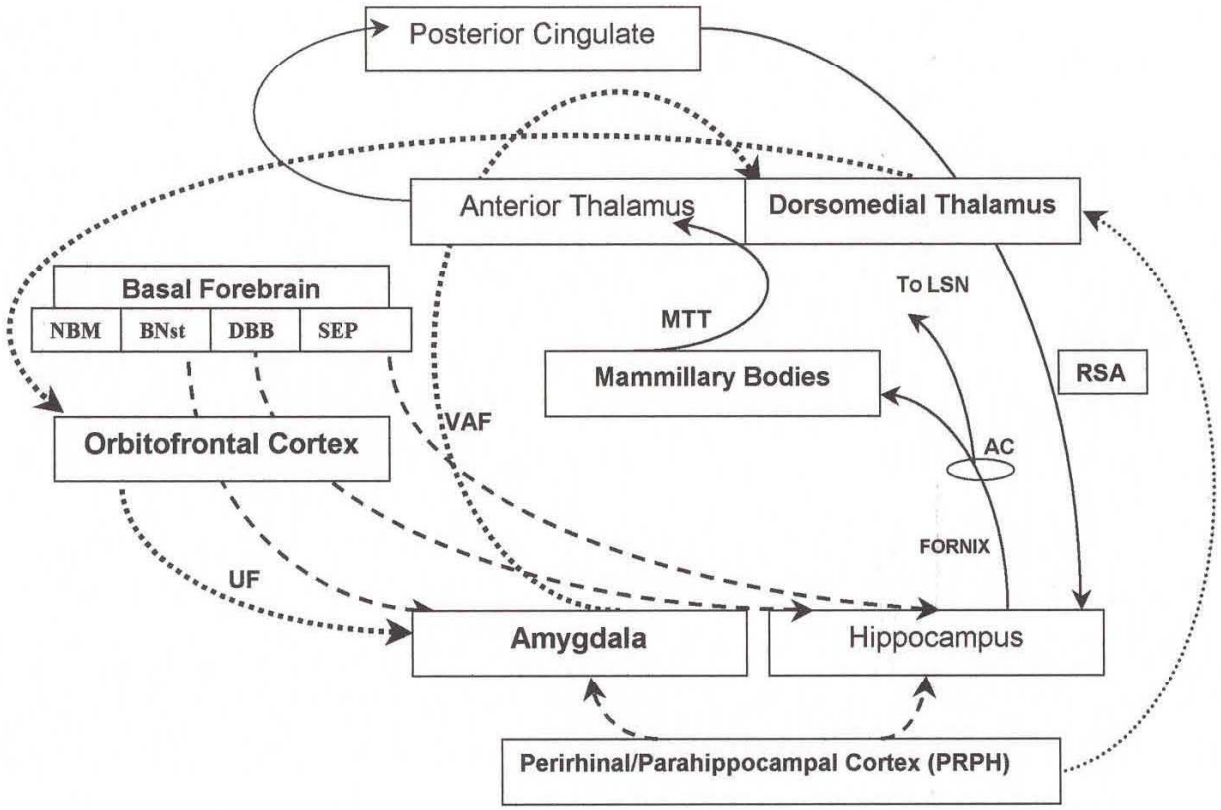

hippocampus

► **Location of Major Limbic System Structures**



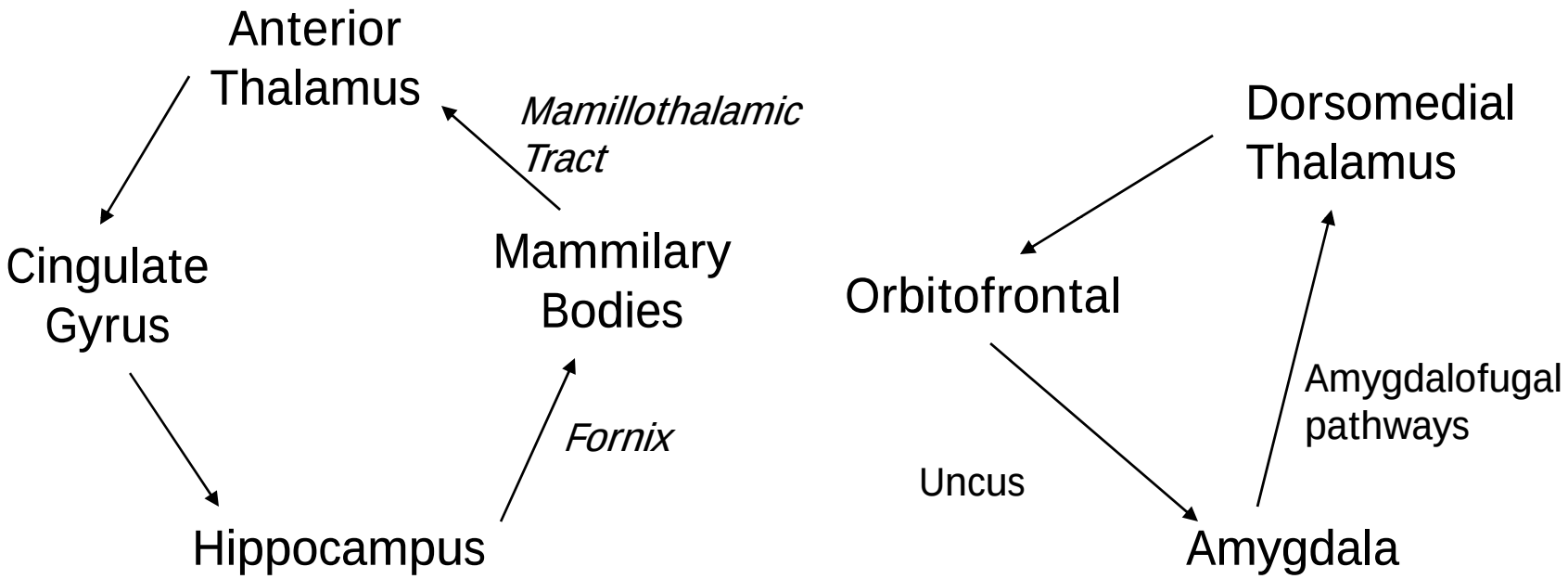


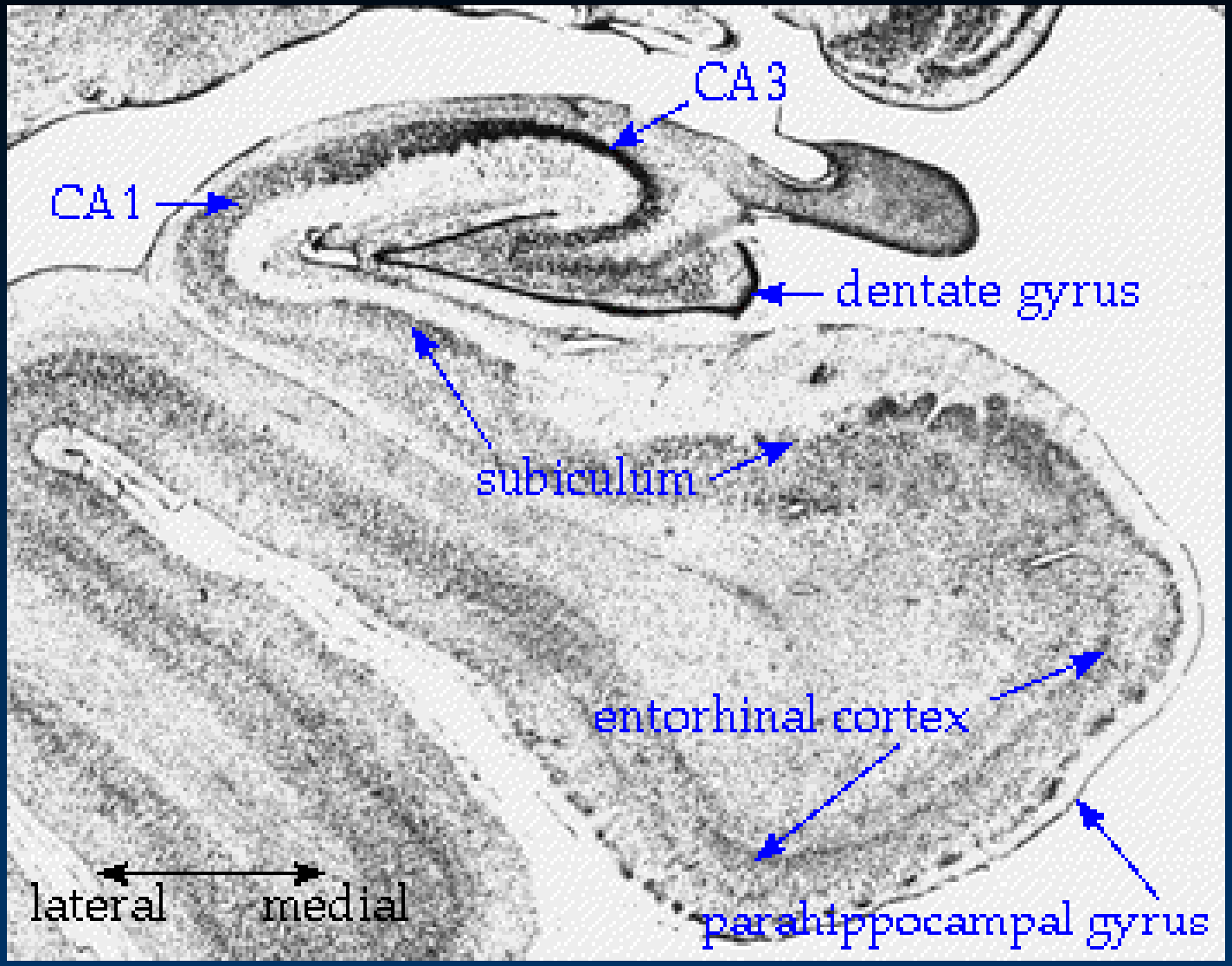
Bauer, Grande, & Valenstein, 2003

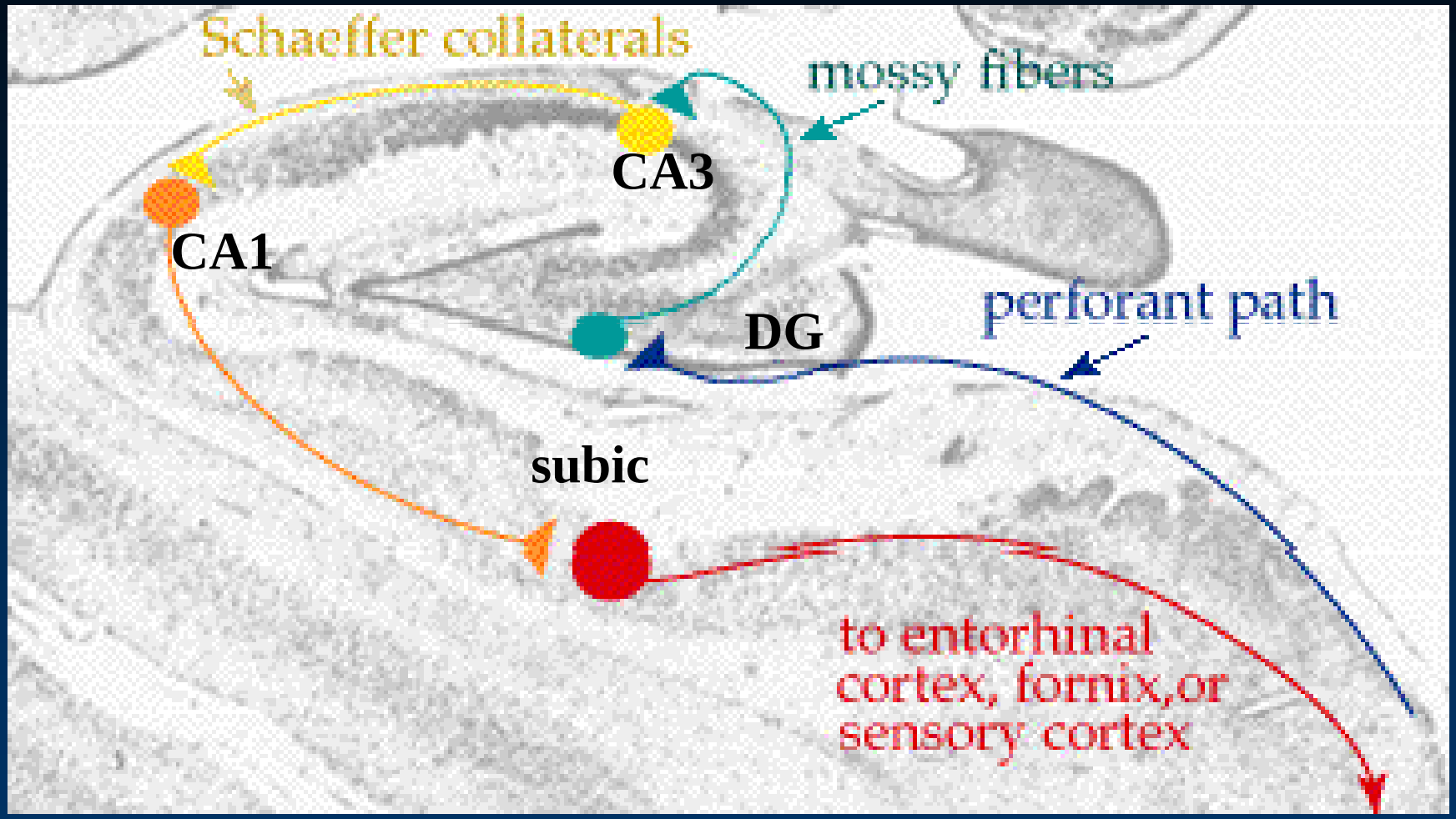


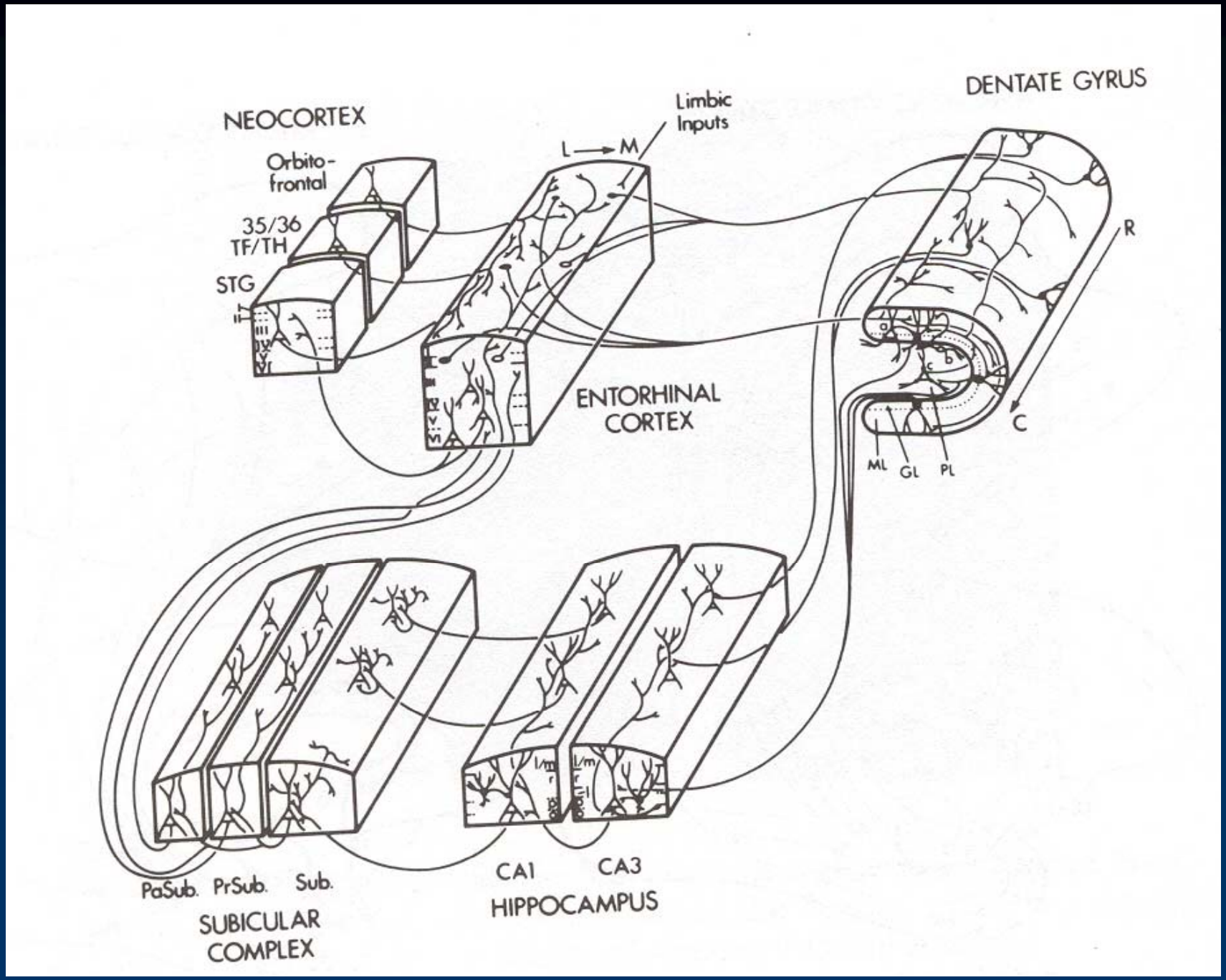
Integrated Circuitry Linking Temporal, Diencephalic, and Basal Forebrain Regions

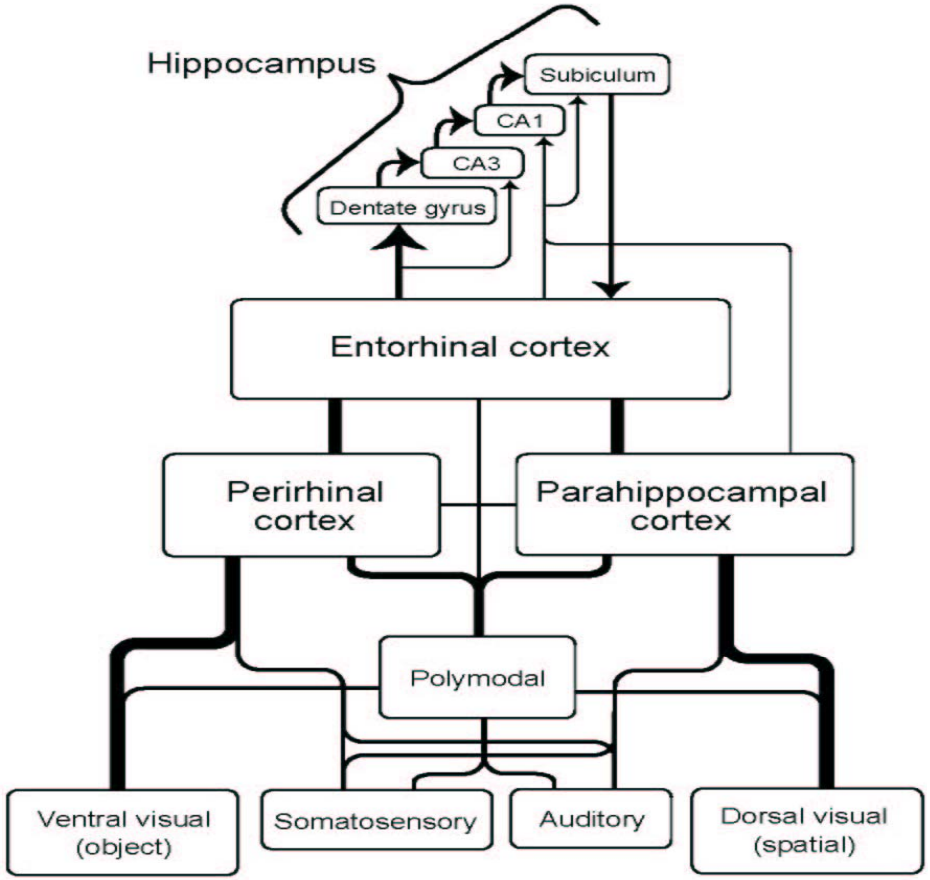
Two Limbic Circuits
(Two-System Theory of Amnesia)

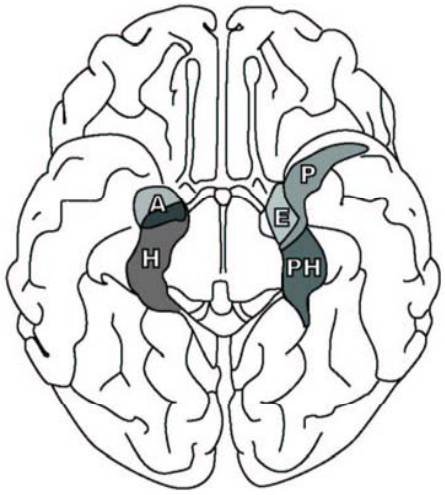



CA3
CA1
dentate gyrus
subiculum
entorhinal cortex
parahippocampal gyrus
lateral
medial


Schaeffer collaterals
mossy fibers
CA3
CA1
DG
perforant path
subic
to entorhinal
cortex, fornix,or
sensory cortex


NEOCORTEX
Orbito-
frontal
35/36
TF/TH
STG
Limbic
Inputs
L → M
ENTORHINAL
CORTEX
DENTATE GYRUS
R
C
ML
GL
PL
PaSub.
PrSub.
Sub.
SUBICULAR
COMPLEX
CA1
CA3
HIPPOCAMPUS

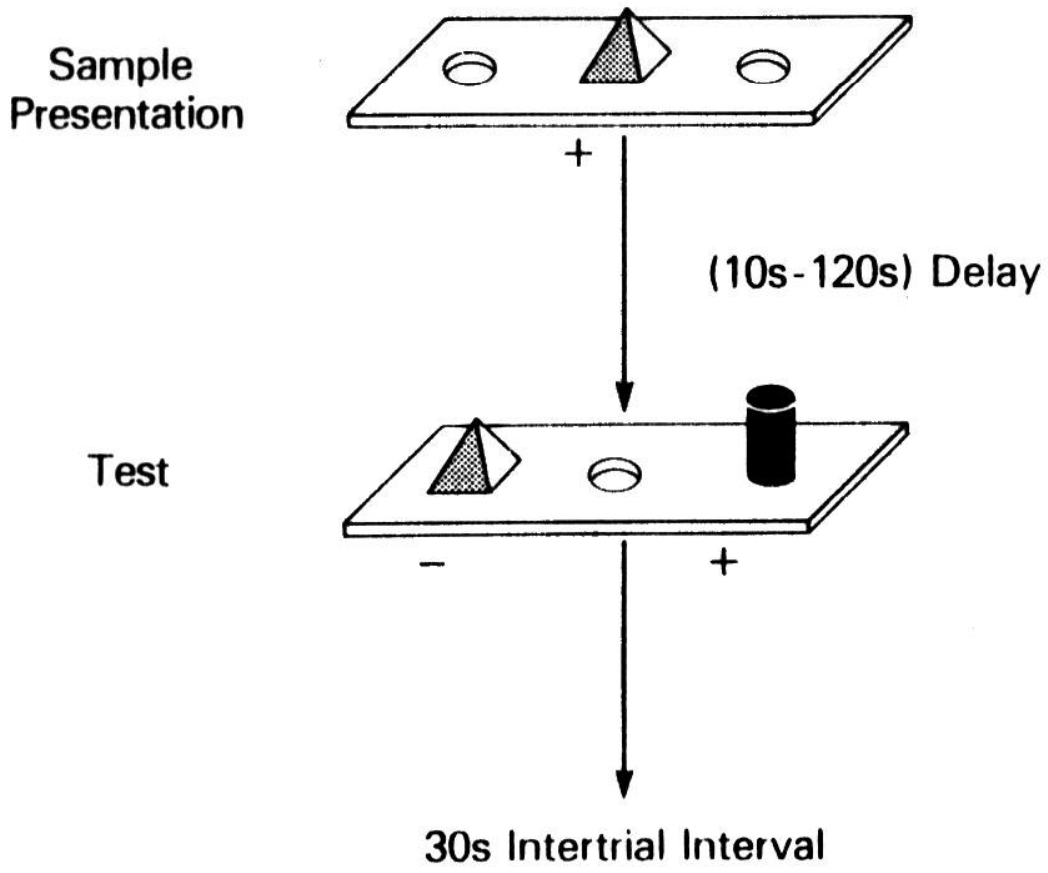




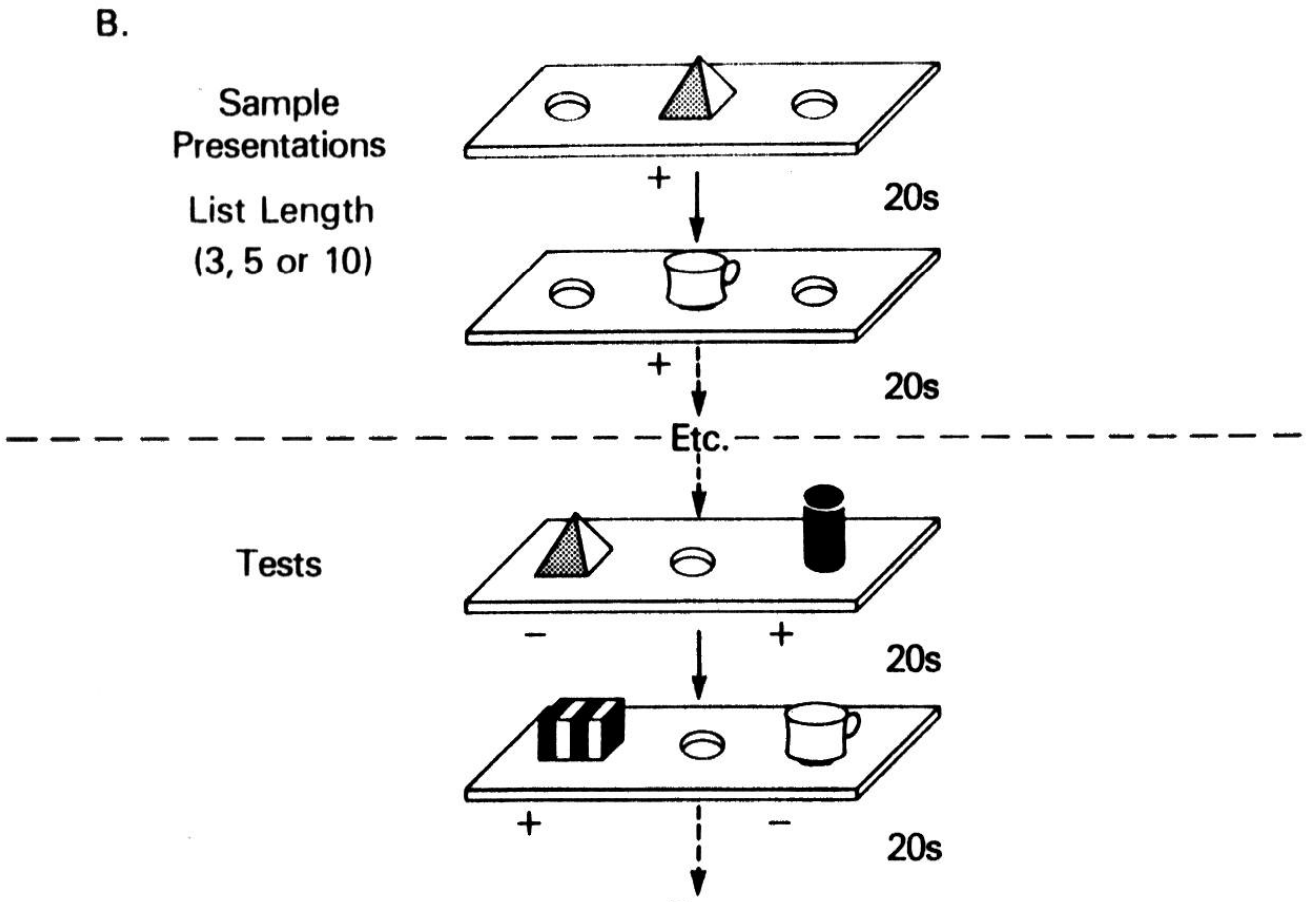
Bauer, Grande, & Valenstein, 2003

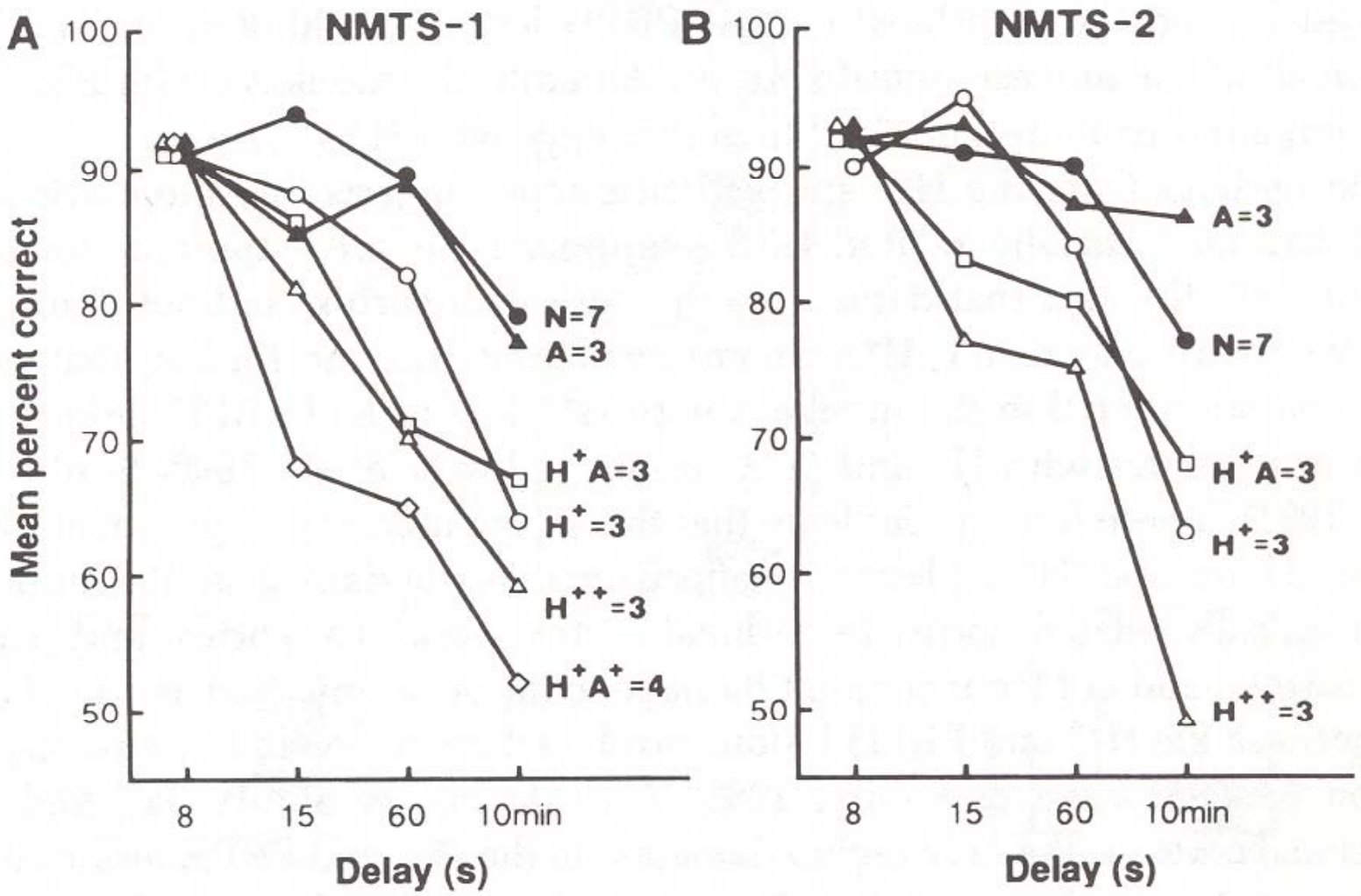
Delayed Nonmatching to Sample

A.



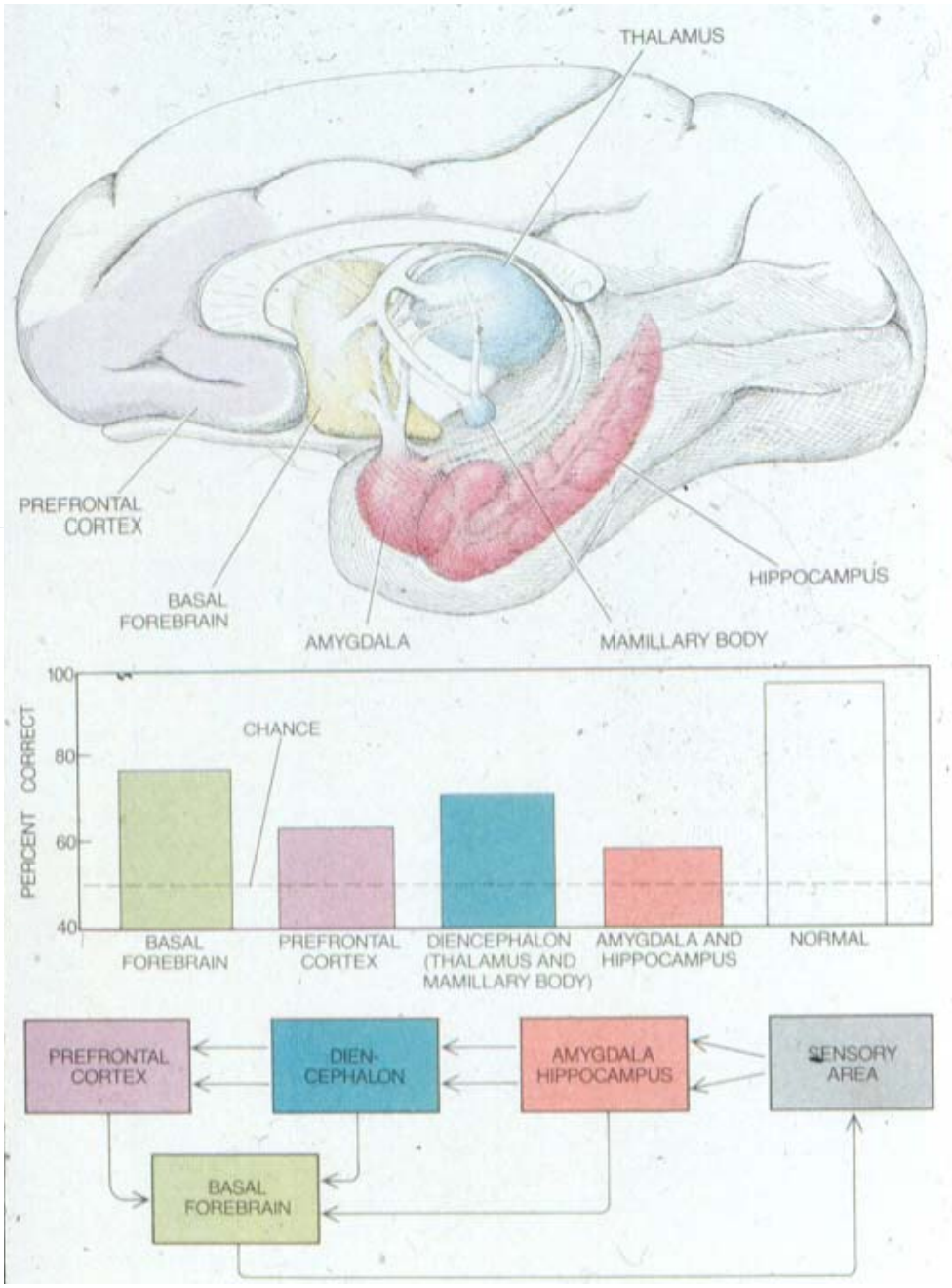
Delayed Nonmatching to Sample, multiple trials, trial-unique objects

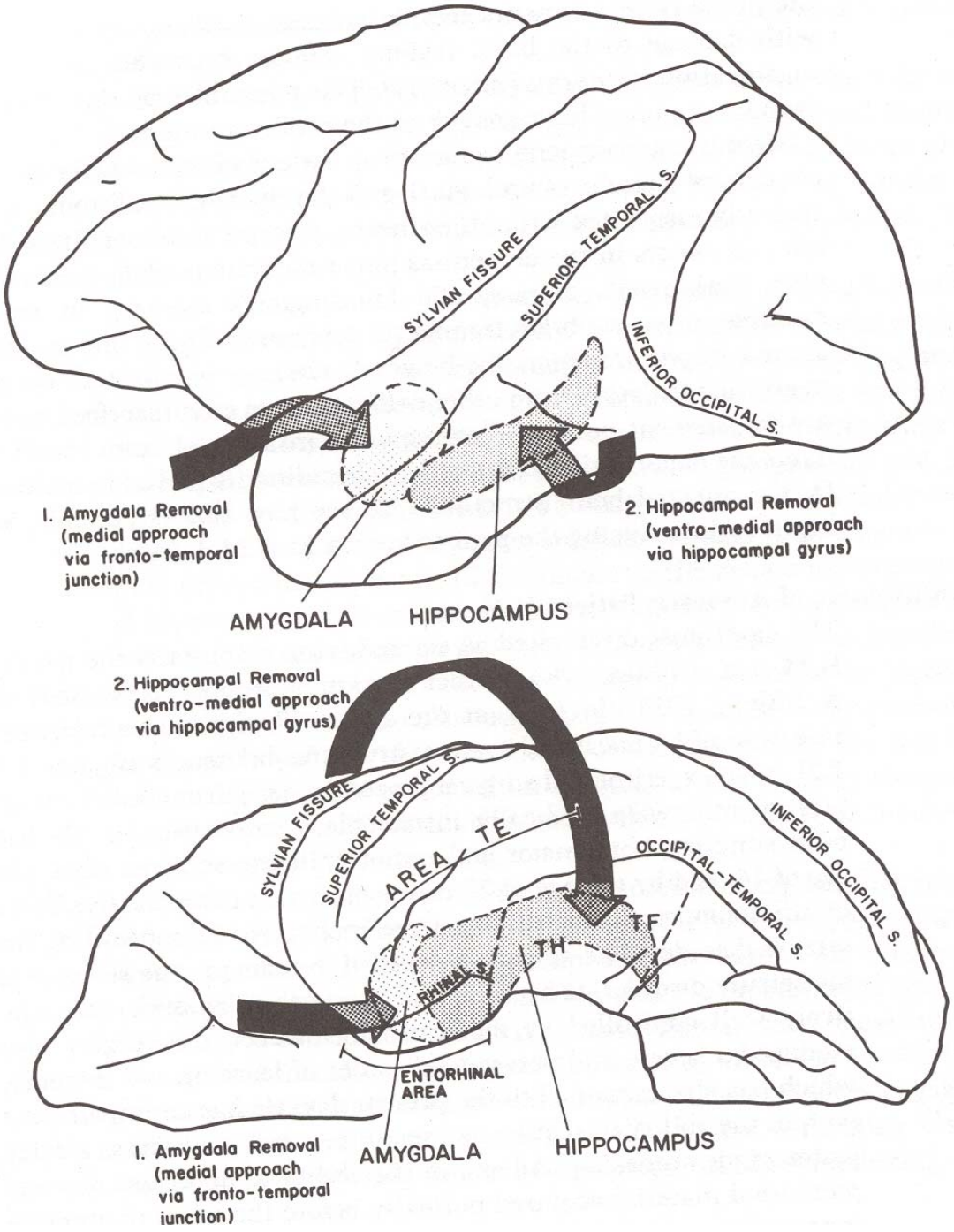


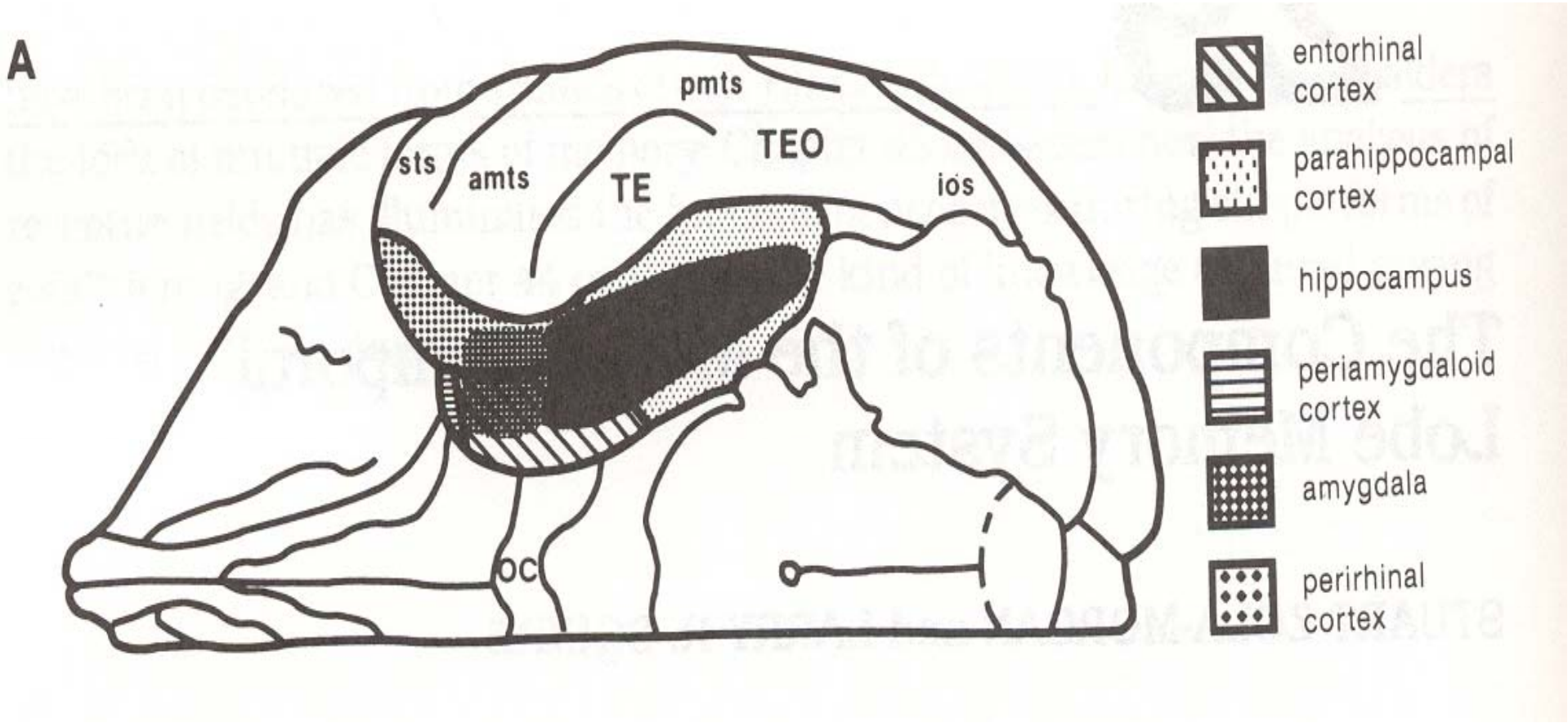


6-8 weeks postsurgery

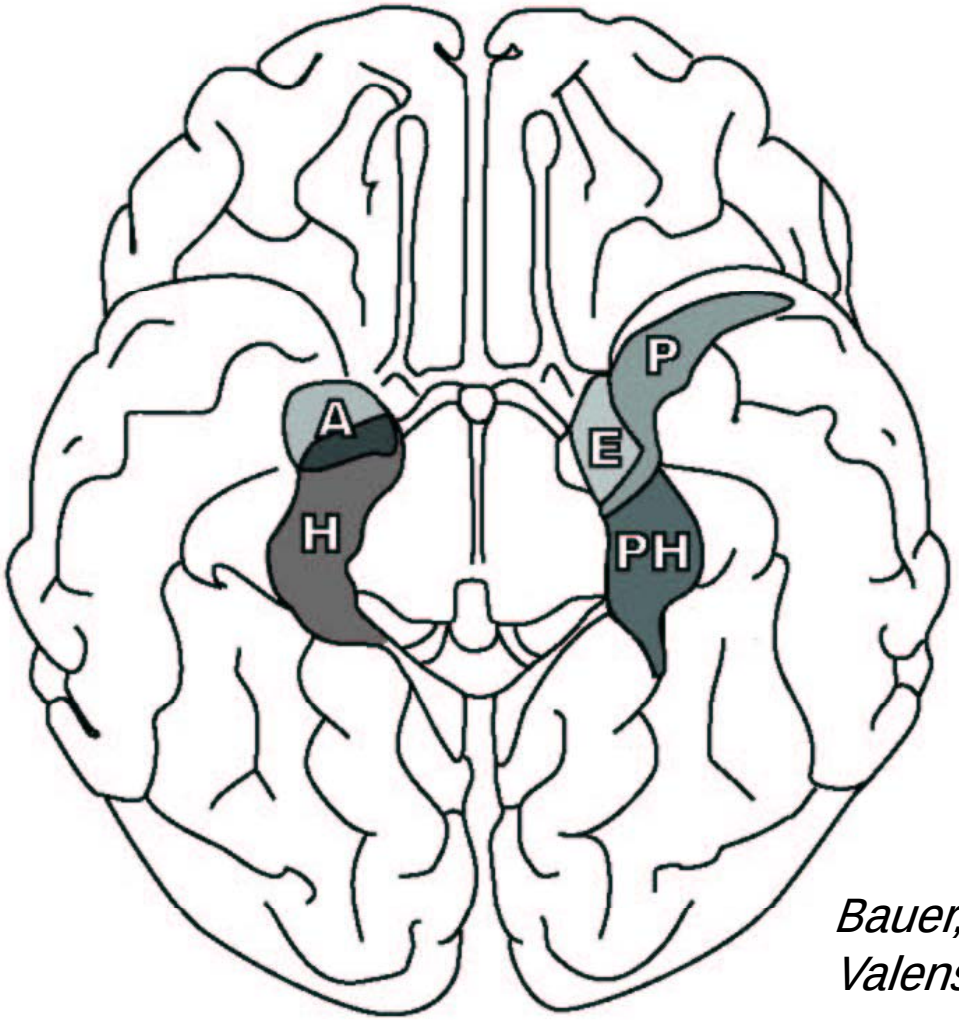
2 years postsurgery


THALAMUS
PREFRONTAL CORTEX
BASAL FOREBRAIN
AMYGDALA
MAMILLARY BODY
HIPPOCAMPUS
PERCENT CORRECT
100
80
60
40
CHANCE
BASAL FOREBRAIN
PREFRONTAL CORTEX
DIENCEPHALON (THALAMUS AND MAMILLARY BODY)
AMYGDALA AND HIPPOCAMPUS
NORMAL
PREFRONTAL CORTEX
DIEN-CEPHALON
AMYGDALA HIPPOCAMPUS
SENSORY AREA
BASAL FOREBRAIN

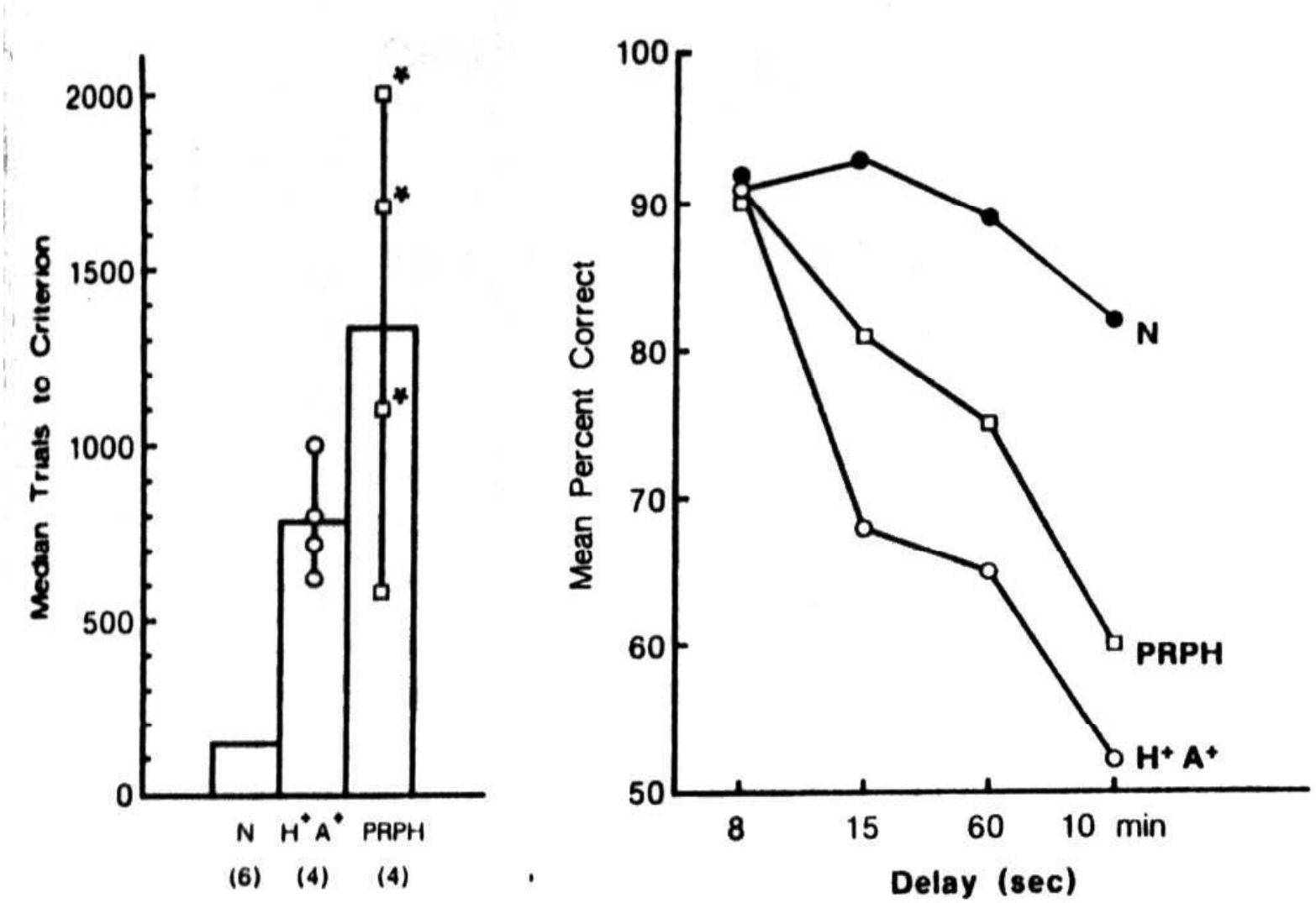

SYLVIAN FISSURE
SUPERIOR TEMPORAL S.
INFERIOR OCCIPITAL S.
1. Amygdala Removal (medial approach via fronto-temporal junction)
2. Hippocampal Removal (ventro-medial approach via hippocampal gyrus)
AMYGDALA
HIPPOCAMPUS
2. Hippocampal Removal (ventro-medial approach via hippocampal gyrus)
SYLVIAN FISSURE
SUPERIOR TEMPORAL S.
AREA TE
OCCIPITAL-TEMPORAL S.
INFERIOR OCCIPITAL S.
TF
TH
RHINAL S.
ENTORHINAL AREA
1. Amygdala Removal (medial approach via fronto-temporal iunction)
AMYGDALA
HIPPOCAMPUS



Zola-Morgan & Squire, 1990

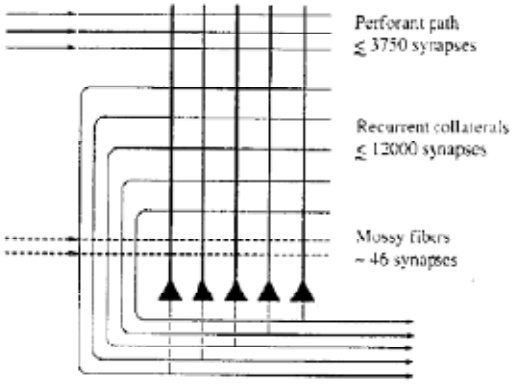


Bauer, Grande, & Valenstein, 2003



Zola-Morgan & Squire, 1990

The hippocampus as an associative memory: anatomy



CA3

CA1

hetero-association

Schaffer collaterals

recurrent collaterals

mossy fibres

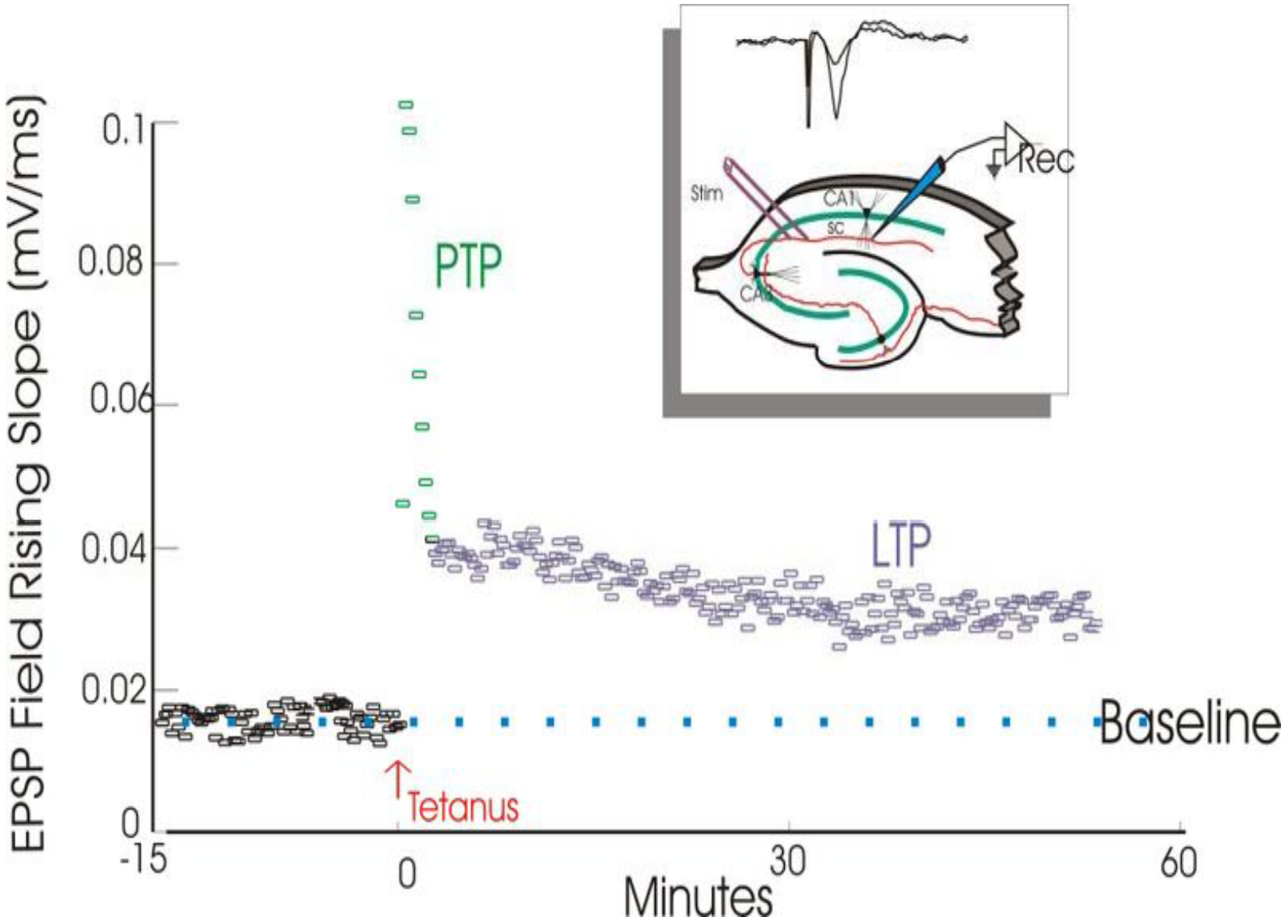
EC

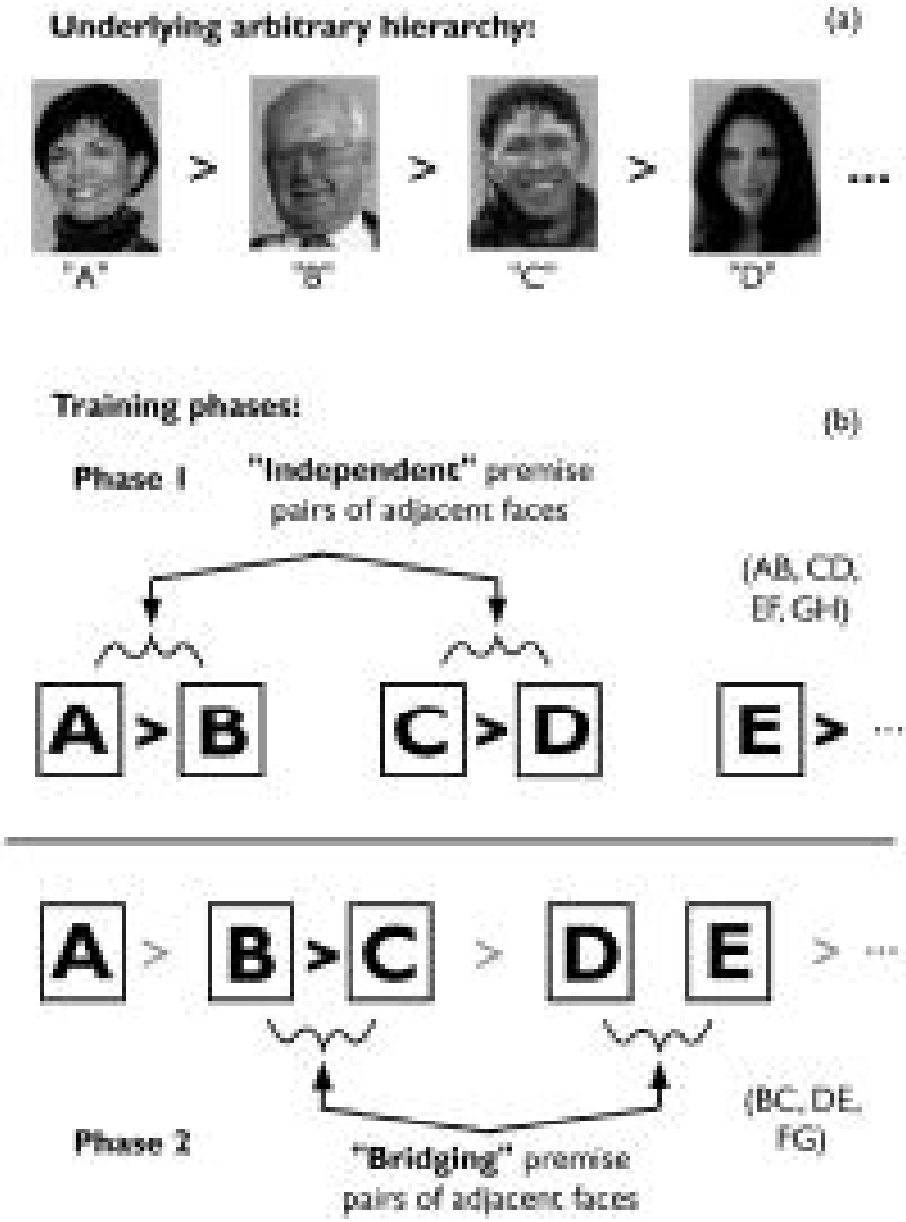
DG

sparse codes

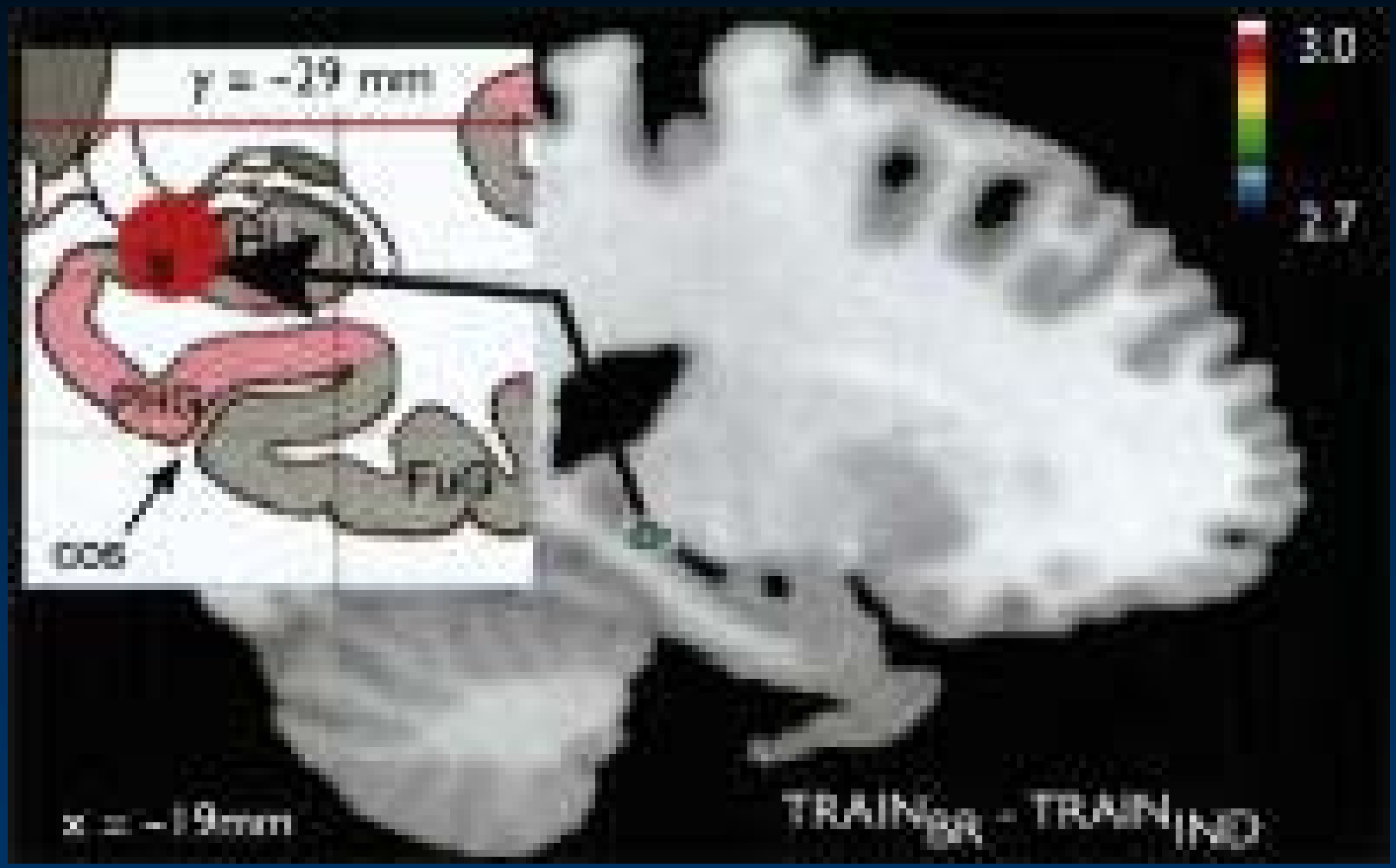
CA3

auto-association

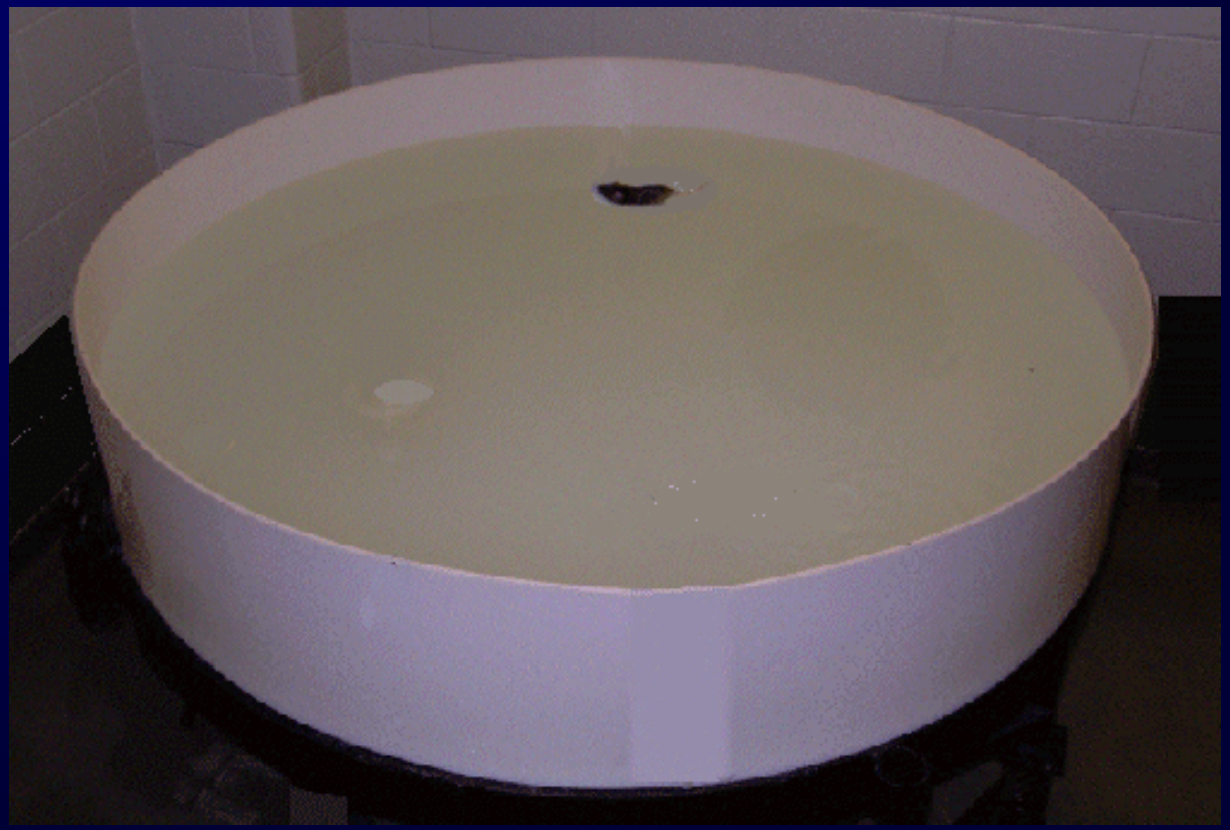

EPSP Field Rising Slope (mV/ms)
0.1
0.08
0.06
0.04
0.02
0
PTP
LTP
Baseline
Tetanus
-15
0
30
60
Minutes
Stim
Rec
CA1
SC
CA3



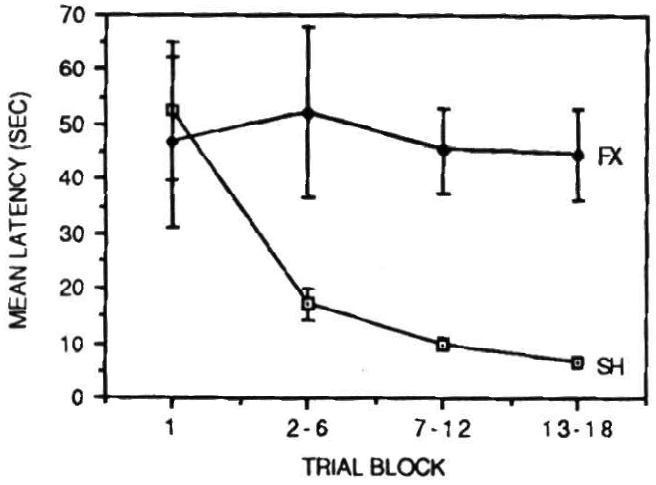
Hippocampus is important in specific types of relational memory (e.g., transitive inference)


y = -29 mm
3.0
2.7
FUS
OCG
x = -19mm
TRAIN_SR - TRAIN_IND

Morris Water Maze



Morris Water Maze

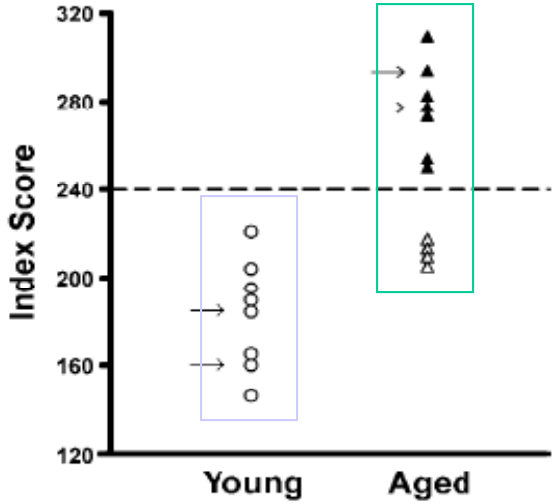


Lesioned rats

Sham operated rats

(Eichenbaum, et al, 1990)

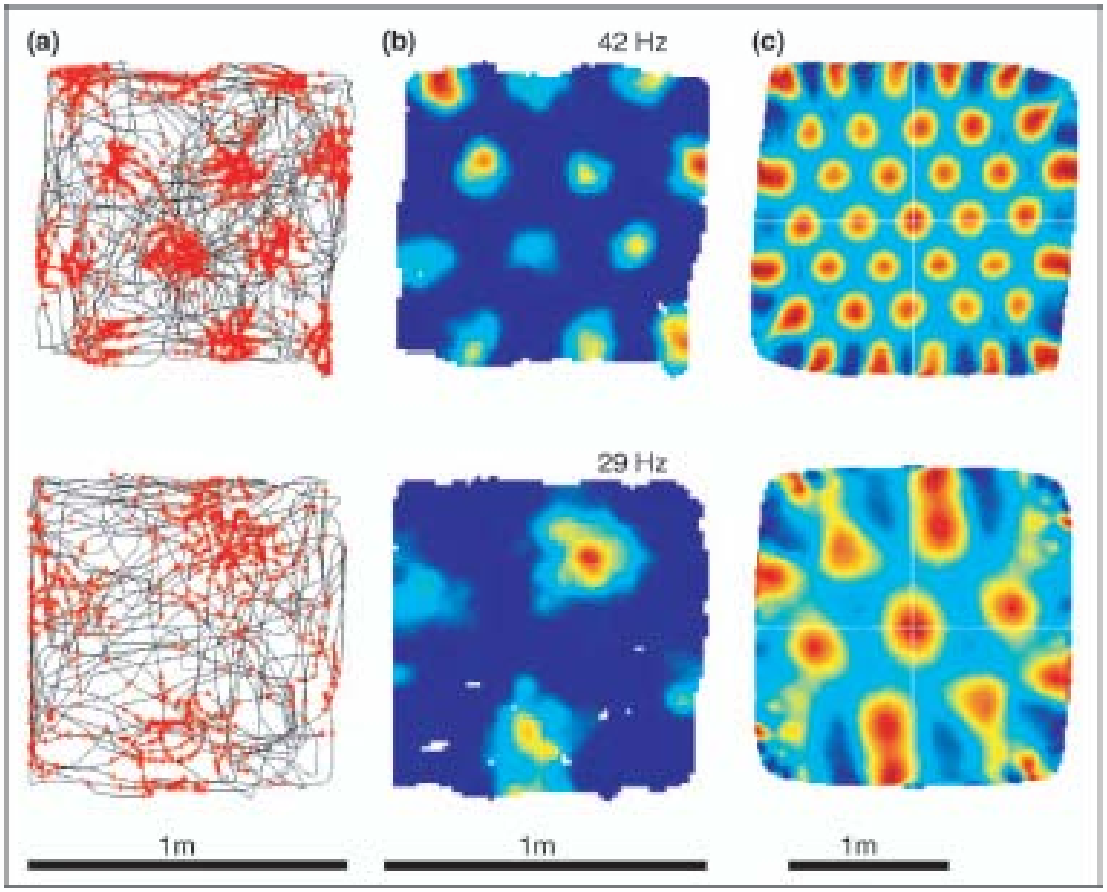
Time to Target



Aged rats

Young rats

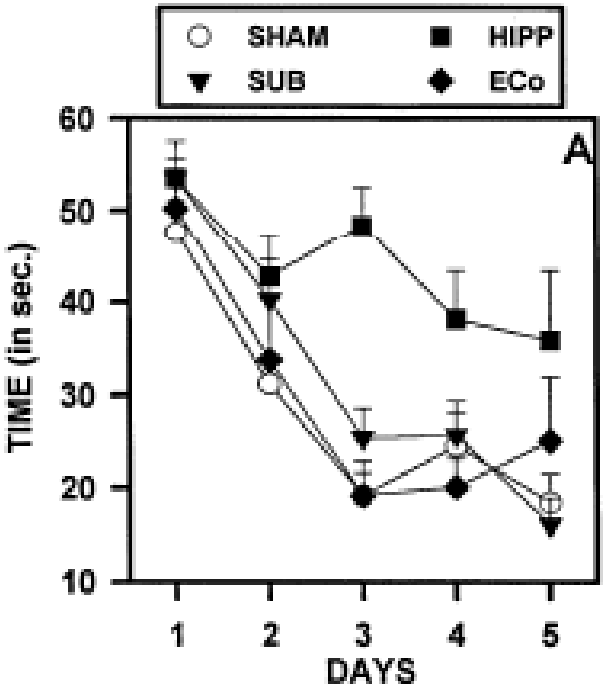
(Gallagher, et al, 1993)



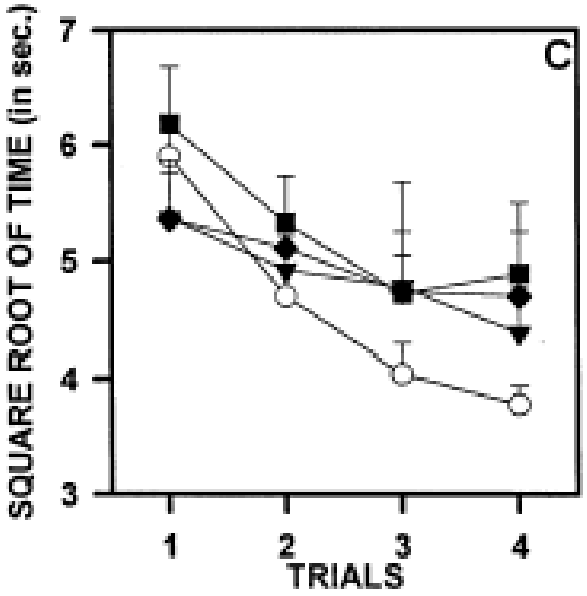
Tessellating firing fields of grid cells in the medial entorhinal cortex. Firing rate distributions are shown for two cells (top and bottom rows, respectively) that were recorded during running in a square enclosure. (a) Trajectory of the rat (black line) with superimposed spike locations (red dots); (b) rate map; (c) spatial autocorrelation for the rate map in (b). Maps in (b) and (c) are colour-coded. In (b), blue is 0 Hz, red is peak rate. In (c), the scale is from blue ($r=-1$) through green ($r=0$) to red ($r=1.0$). Scale bar indicates size of recording enclosure. Note that the distance scale in the autocorrelation diagrams is half of that of the original maps, with points along the perimeter showing correlations between positions spaced by a distance similar to the width of the enclosure. The distributions were recorded from cells located at different distances from the dorsal border of the medial entorhinal cortex; the top cell was most dorsal. Modified, with permission, from [32••].

Leutgeb, et al., Curr Opin Neurobiol, 2005, 15, 738-746.

Hippocampus v. Entorhinal Cortex Lesions and "Reference" vs. "Working" Memory MWM



Reference Memory (H<ECo)



Working Memory (H=Eco=Sub<Sham)

Galani, et al., Behav Brain Res, 1998, 96, 1-12.

Recollection v. Familiarity

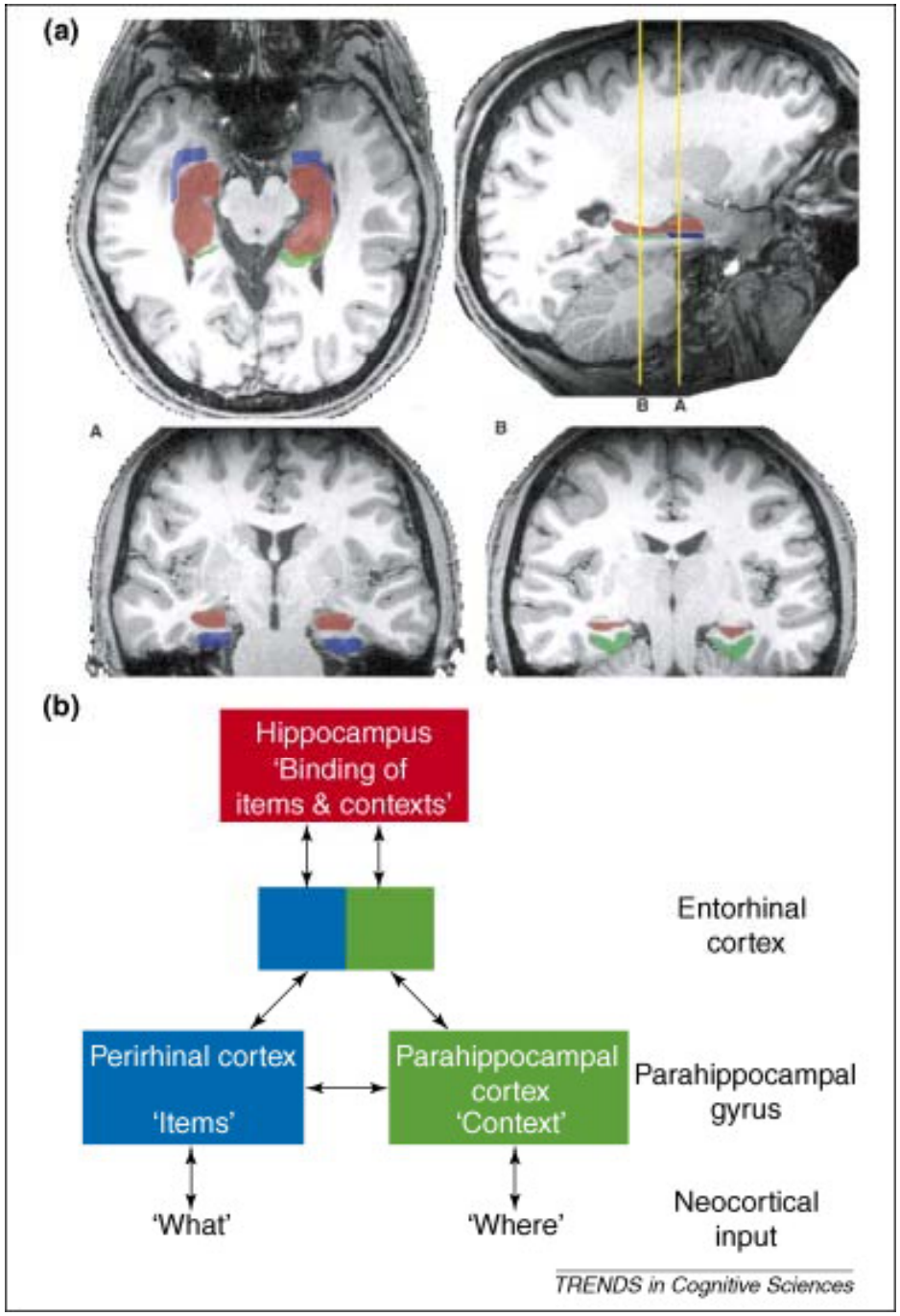
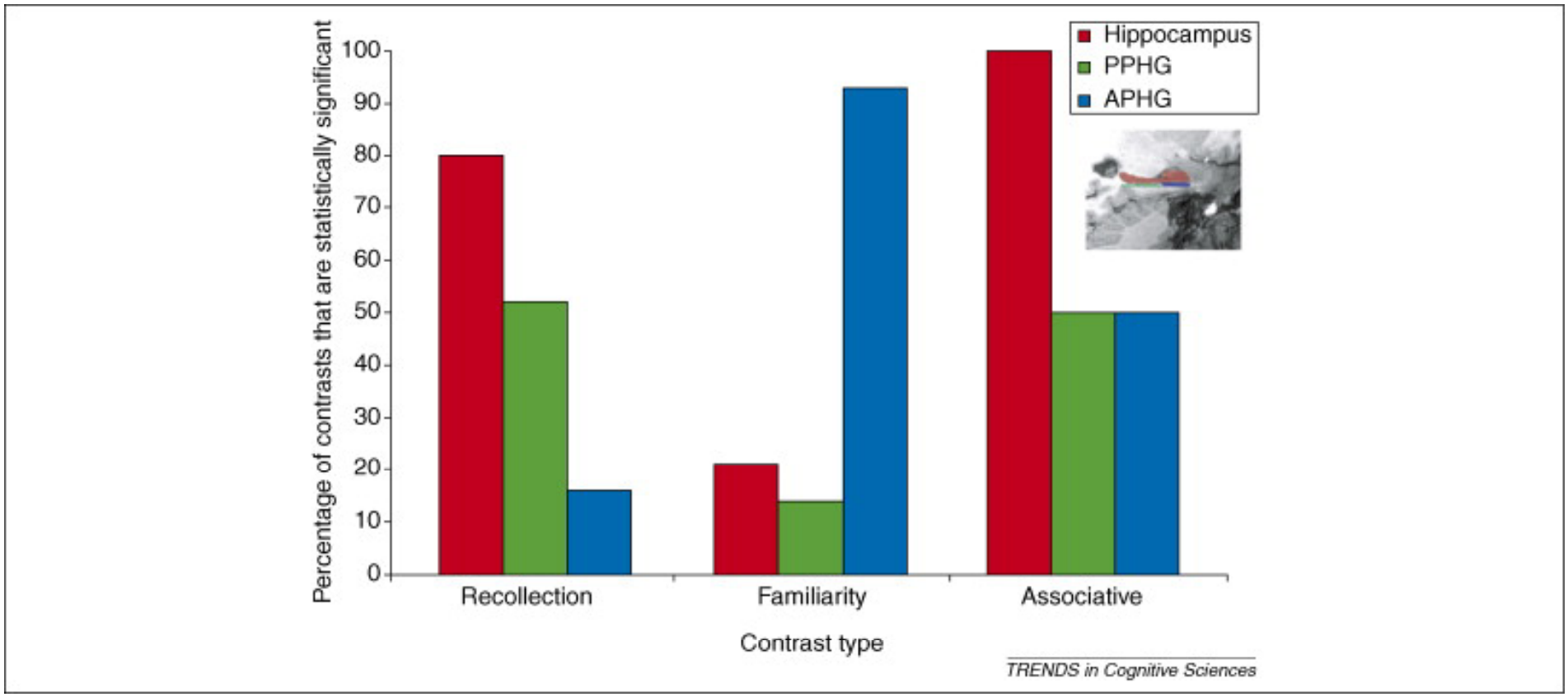


Figure 3. Anatomy of the MTL region. (a) Approximate locations of the hippocampus (red), the PRc (blue) and the PHc (green) shown on T1-weighted magnetic resonance images. (b) Representation of the anatomical connections among, and the proposed roles of, the hippocampus, PRc and PHc in episodic memory according to the BIC model. The arrow between the PRc and PHc indicates the anatomic connection between the two regions; the PRc receives more inputs from the PHc than vice versa. The connections shown here are based on results from anatomical studies of rats and monkeys.

Diana, Yonelinas, and Ranganath, TICS, 2007)

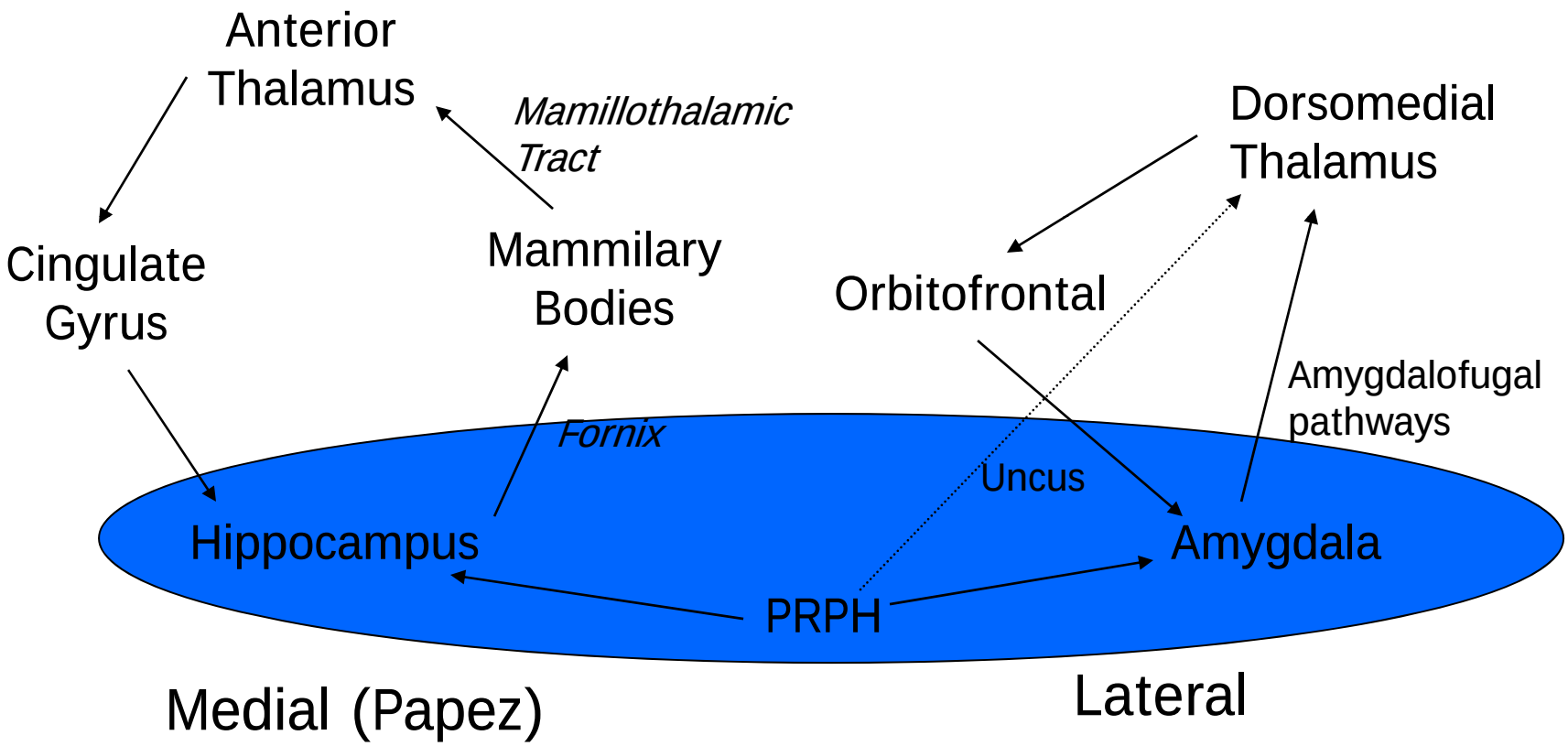
Recollection v. Familiarity

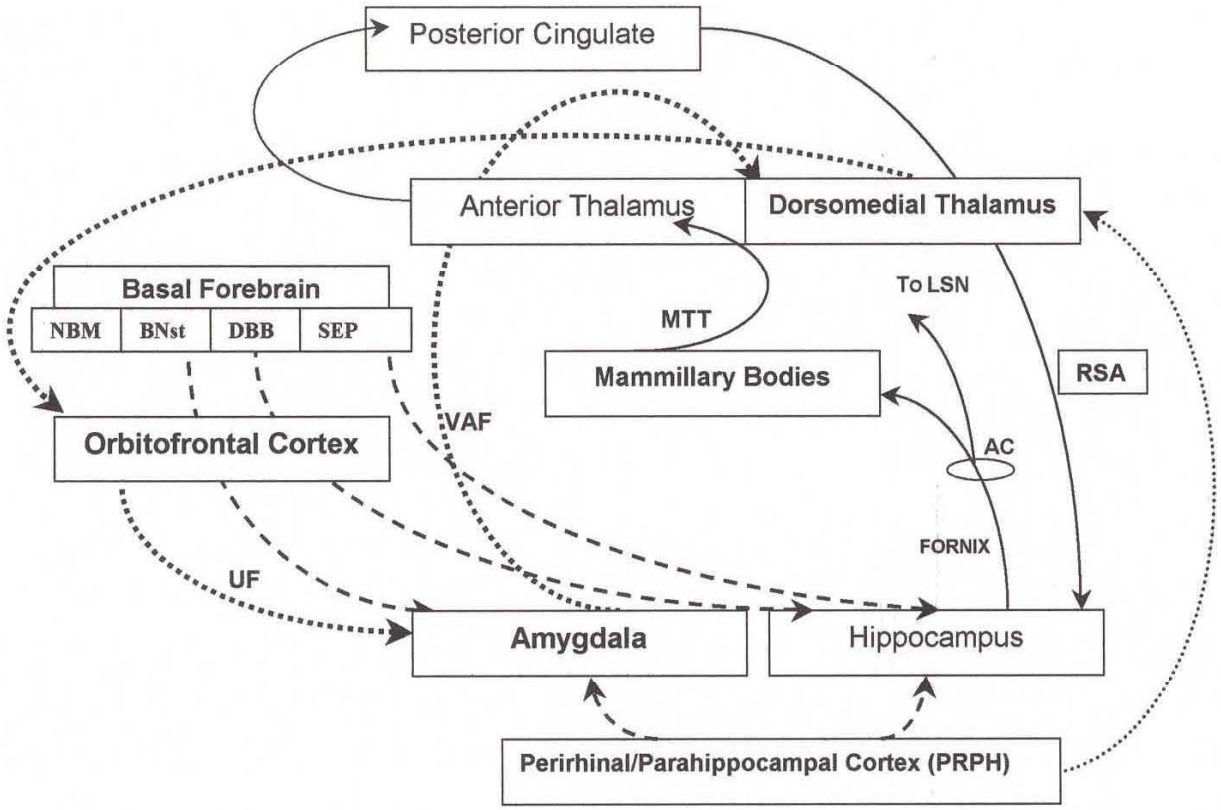


- Figure 1. Activation of MTL subregions in studies of recollection and/or familiarity. Shown is the percentage of contrasts of each type (recollection, familiarity or associative recognition) in which activation was reported for the hippocampus, the posterior parahippocampal gyrus (PPHG) and the anterior parahippocampal gyrus (APHG). Data are summarized from Tables 1 and 2.

Diana, Yonelinas, and Ranganath, TICS, 2007)

Two Limbic Circuits and the Two-system theory of amnesia





Integrated Circuitry Linking Temporal, Diencephalic, and Basal Forebrain Regions

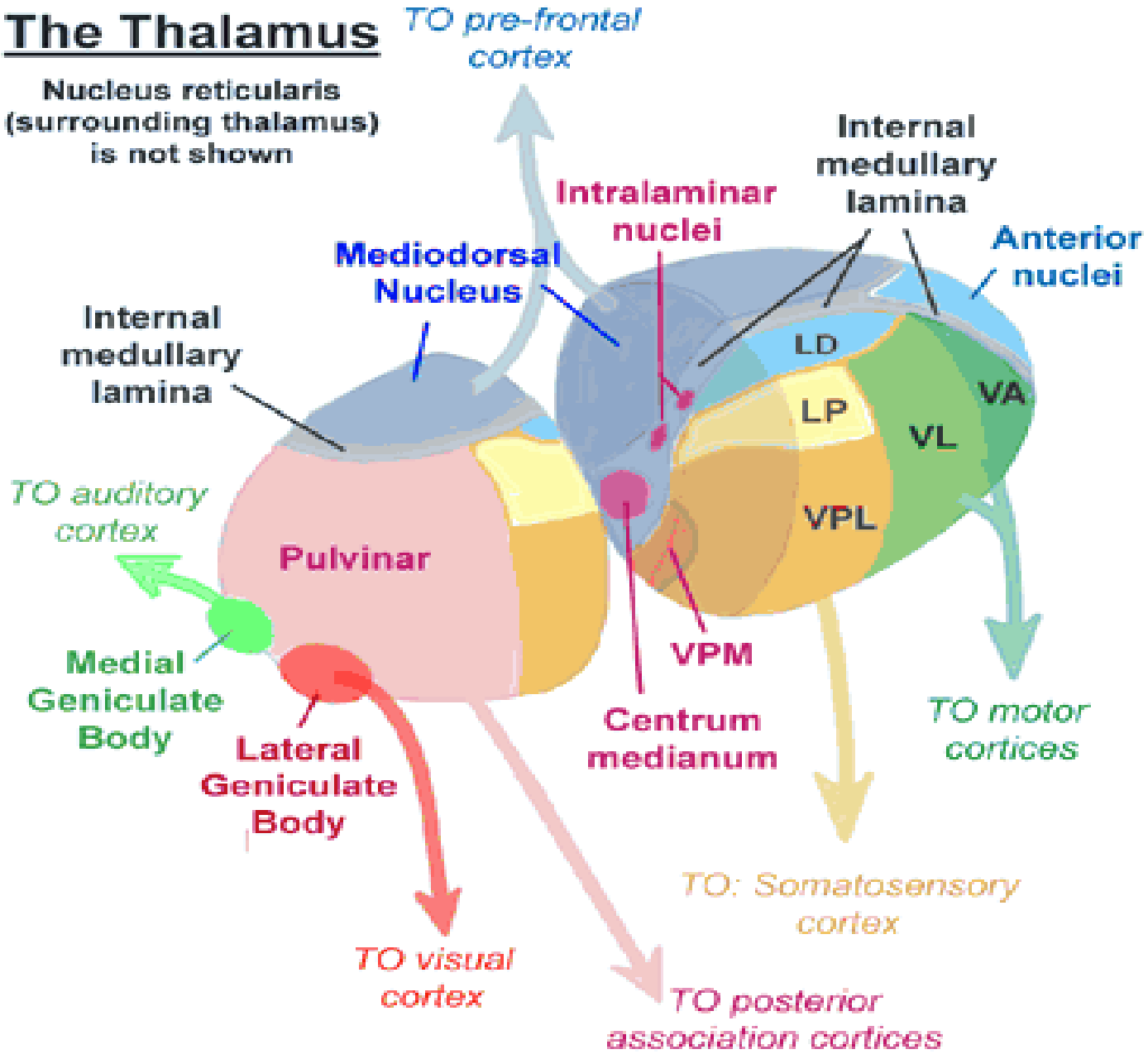
Diencephalic Syndromes

- Korsakoff Syndrome associated with ETOH abuse or malabsorption
  - prominent encoding deficits
  - role of frontal pathology
- Vascular disease
- Thalamic trauma

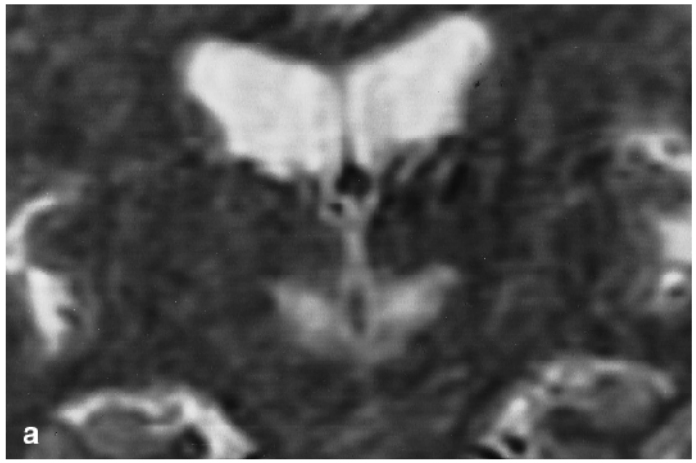
Mammillary Body Lesions in a case of Korsakoff's Disease

The Thalamus

Nucleus reticularis (surrounding thalamus) is not shown



MRI in paramedian thalamic stroke



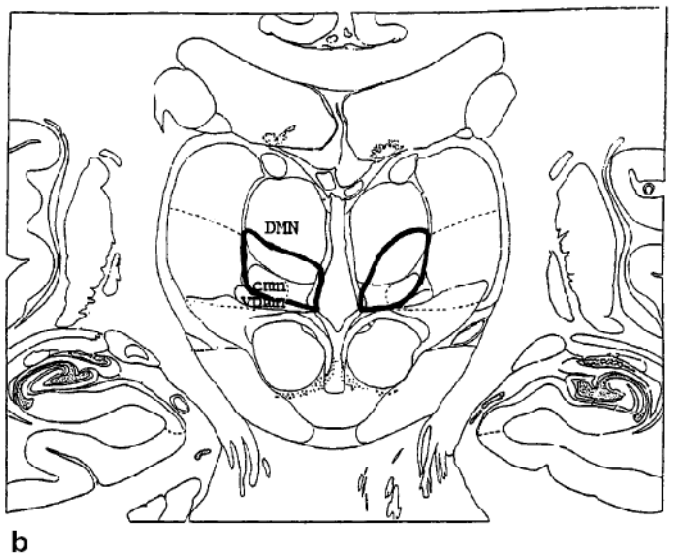
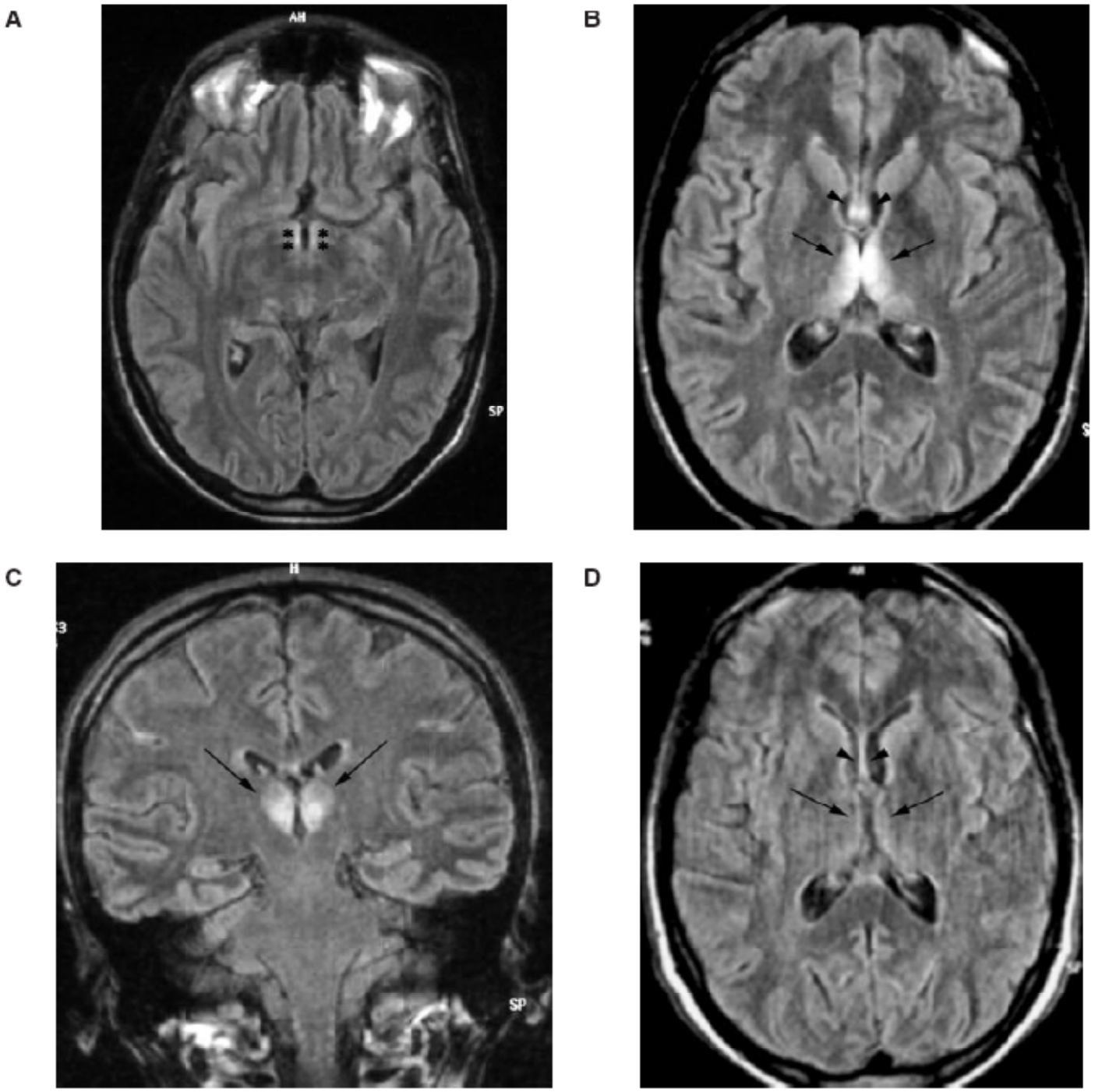


Fig. 1 Patient 1. **a,b** Coronal T2-weighted image through the paramedian thalamus. Bilateral, symmetrical ischaemic lesions in the dorsomedial (DMN) and caudomedial (CMN) nuclei. **c,d** Axial T2-weighted image through the paramedian thalamus. The ischaemic lesions affect the DM, CM, VPLN (ventroposterolateral) and VPMN (ventroposteromedial) nuclei bilaterally in an almost symmetrical manner (*CMN* centromedian nucleus, *DMN* dorsomedial nucleus, *VPLN* ventroposterolateral nucleus, *VPMN* ventroposteromedial nucleus, *S* subthalamic nucleus)

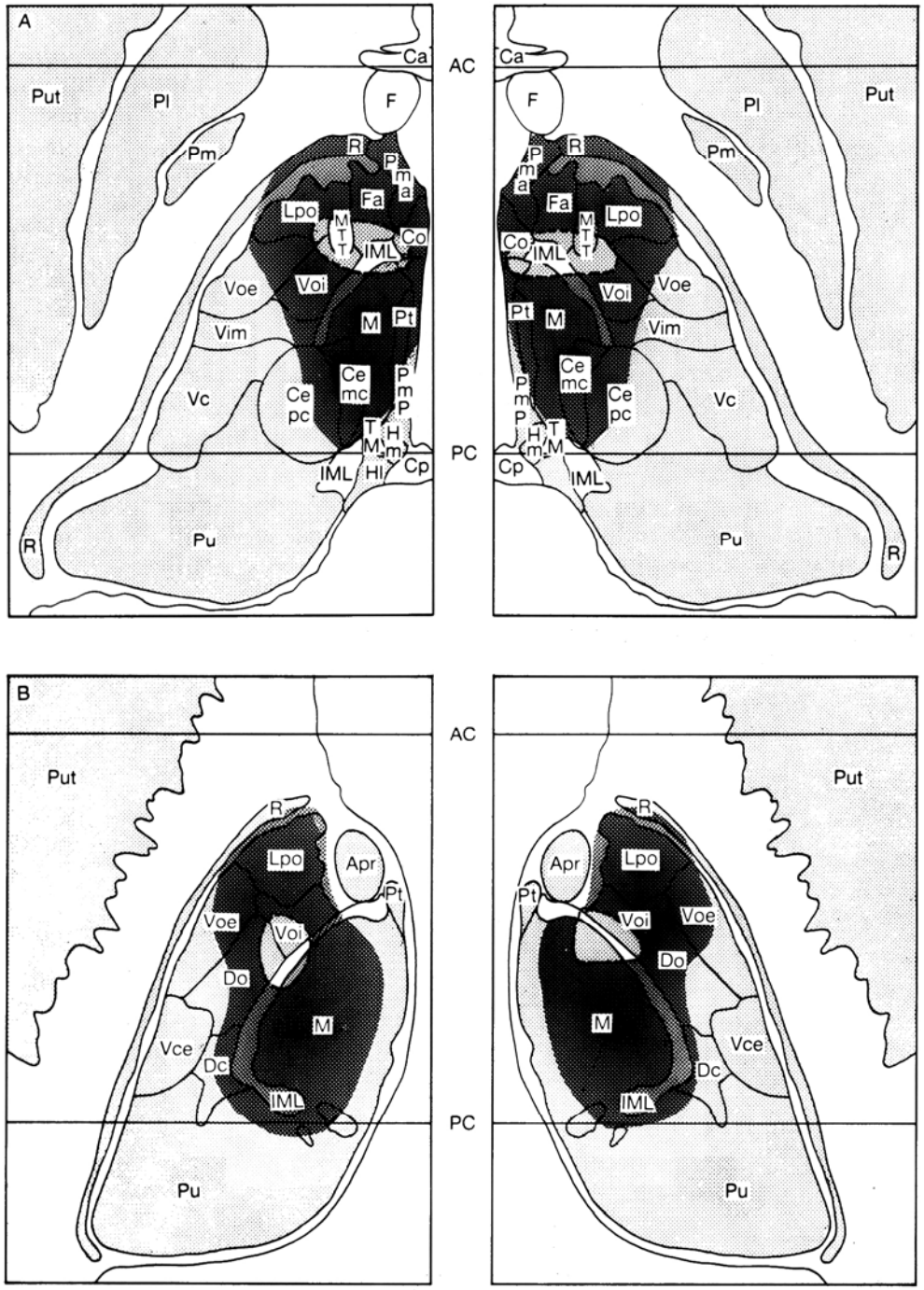
Lövblad, et al (1997)

Neuroradiology, 39, 693-698.



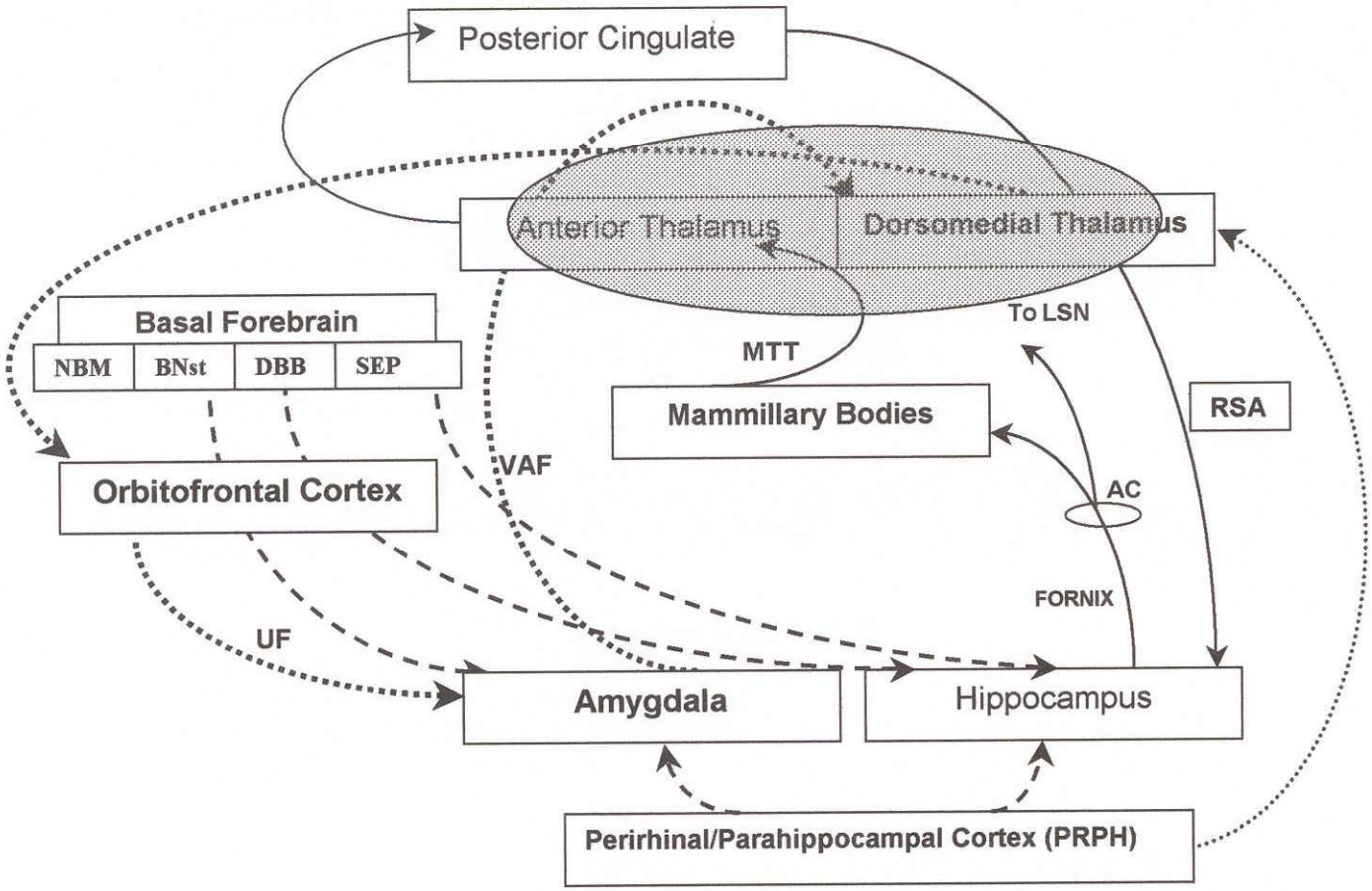
Mammillary body (a), medial thalamic (arrows in B,C) and fornix (arrowheads in B) damage in a case of Alcholic Korsakoff syndrome. D shows resolution of signal changes after 5 months of abstinence.

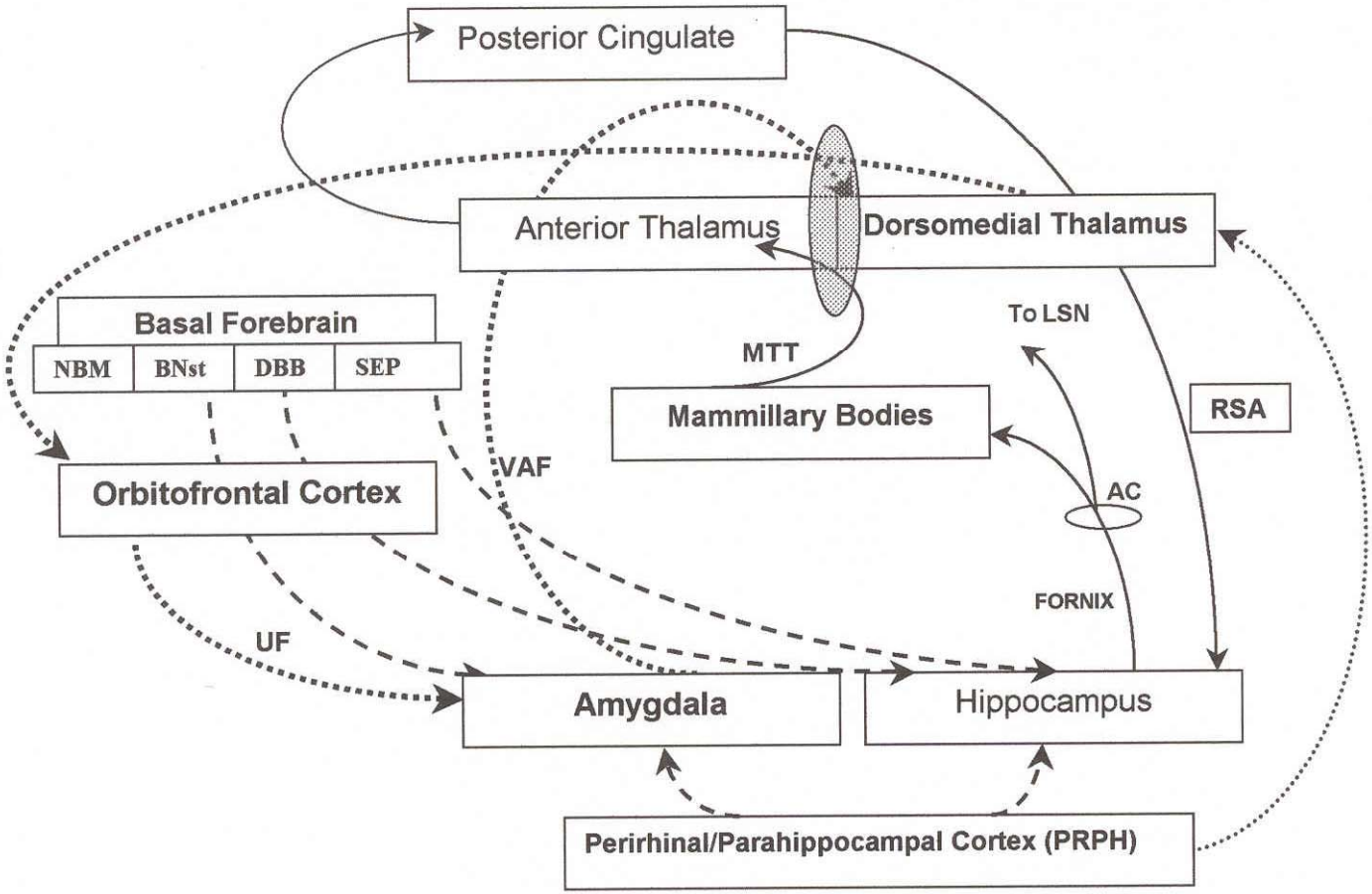
Caolo, et al (2005). Brain, 128, 1584-98



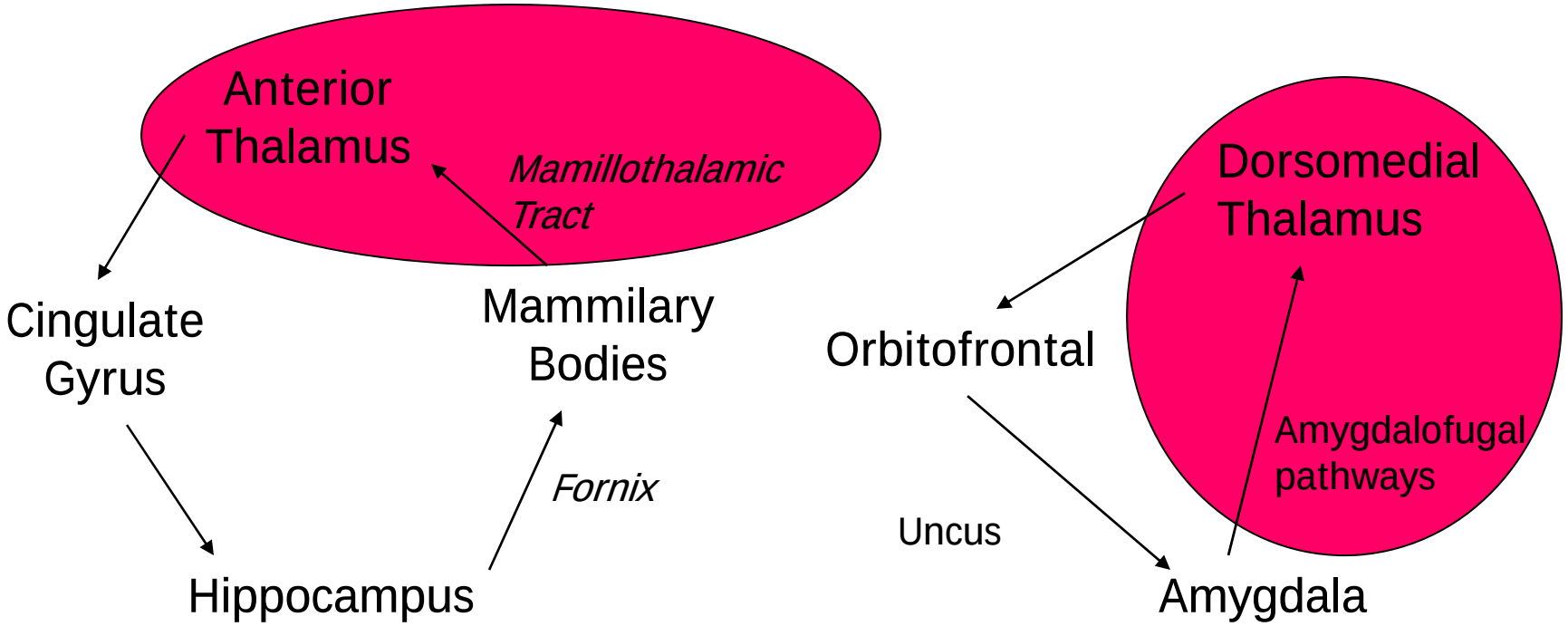
Anterior thalamic lesions affecting the MTT and VAF pathways produce persistent amnesia, posterior lesions do not

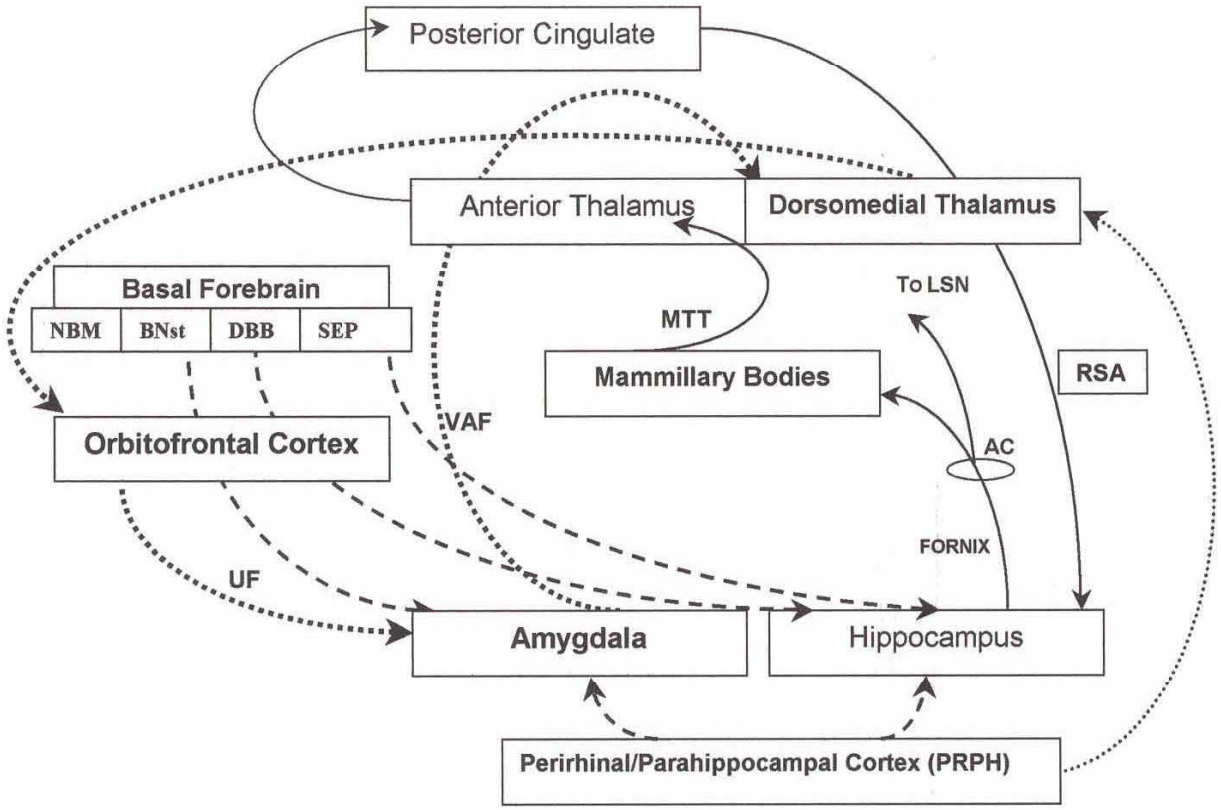
Graff-Radford, et al (1990). Brain, 113, 1-25.


Posterior Cingulate
Anterior Thalamus
Dorsomedial Thalamus
Basal Forebrain
NBM
BNst
DBB
SEP
MTT
To LSN
Mammillary Bodies
RSA
VAF
Orbitofrontal Cortex
AC
FORNIX
UF
Amygdala
Hippocampus
Perirhinal/Parahippocampal Cortex (PRPH)


Posterior Cingulate
Anterior Thalamus
Dorsomedial Thalamus
Basal Forebrain
NBM
BNst
DBB
SEP
MTT
To LSN
Mammillary Bodies
RSA
VAF
Orbitofrontal Cortex
AC
FORNIX
UF
Amygdala
Hippocampus
Perirhinal/Parahippocampal Cortex (PRPH)

Two Limbic Circuits and the Two-system theory of amnesia

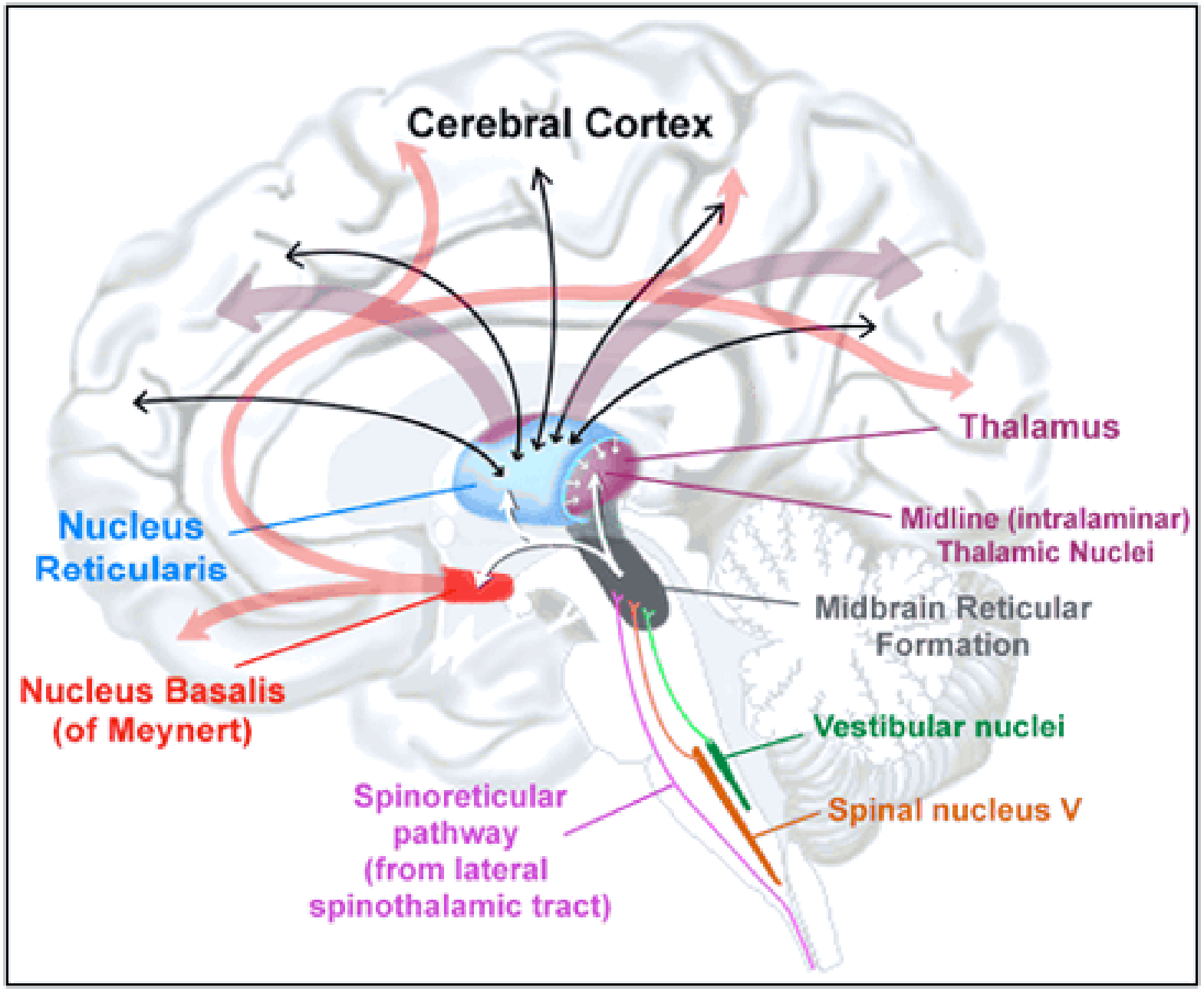




Integrated Circuitry Linking Temporal, Diencephalic, and Basal Forebrain Regions

Basal Forebrain Syndromes

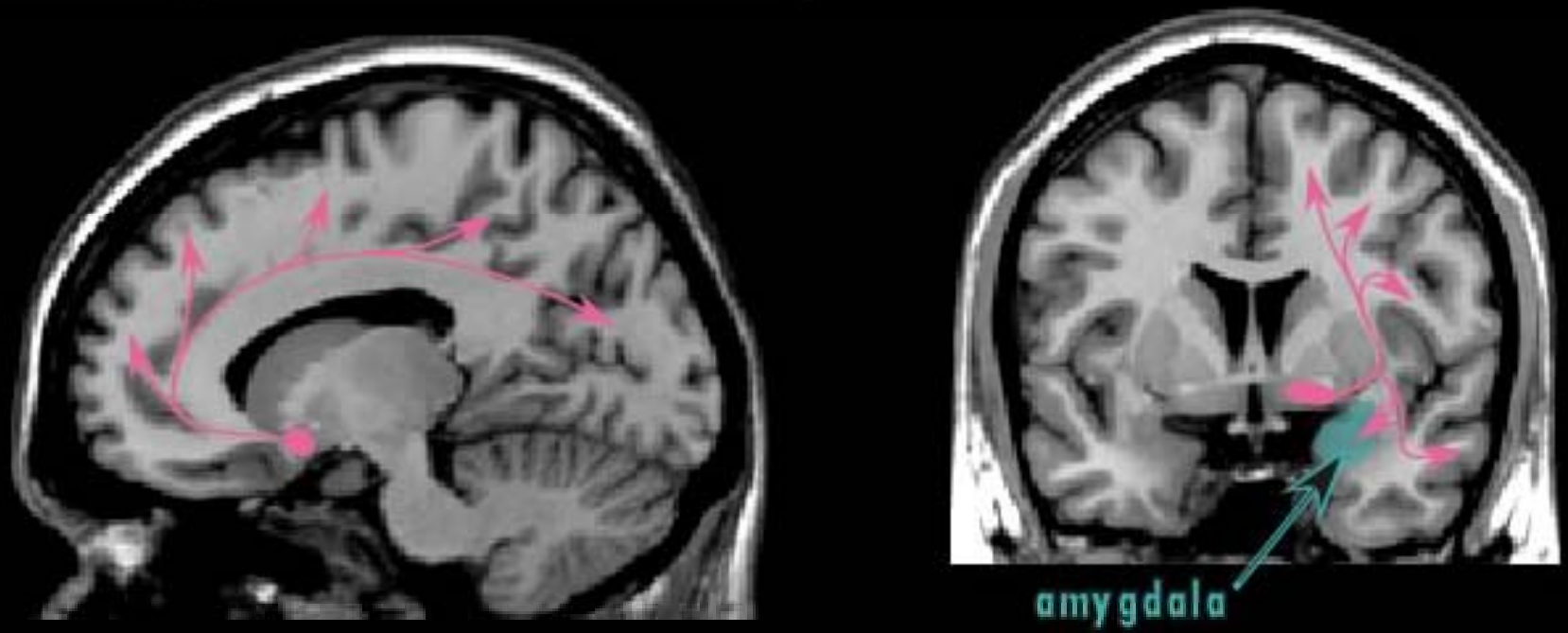
- Anterior Communicating Artery (ACoA) infarctions
  - prominent anterograde, variable retrograde amnesia
  - prominent confabulation
  - frontal extension of lesions
- Basal forebrain and cholinergic projections to hippocampus

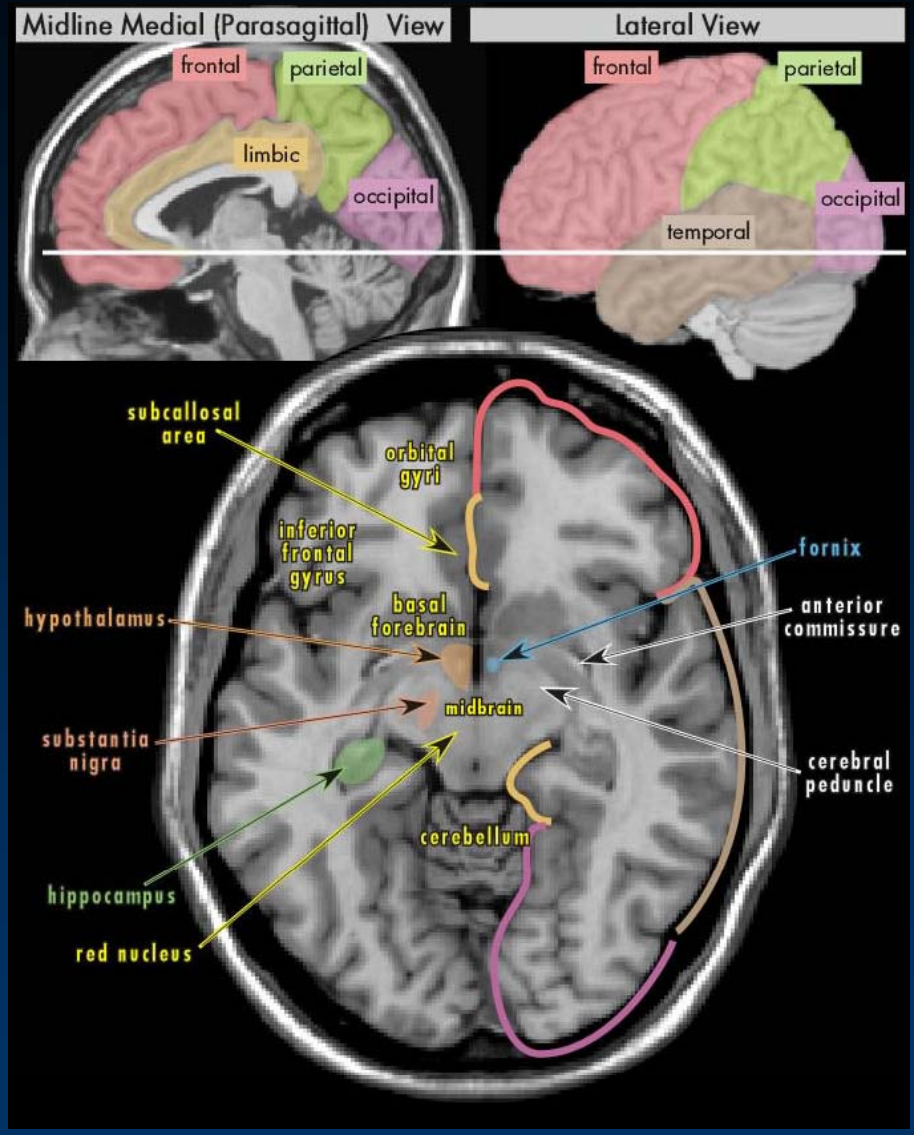

Cerebral Cortex
Thalamus
Midline (intralaminar)
Thalamic Nuclei
Nucleus
Reticularis
Midbrain Reticular
Formation
Nucleus Basalis
(of Meynert)
Vestibular nuclei
Spinal nucleus V
Spinoreticular
pathway
(from lateral
spinothalamic tract)

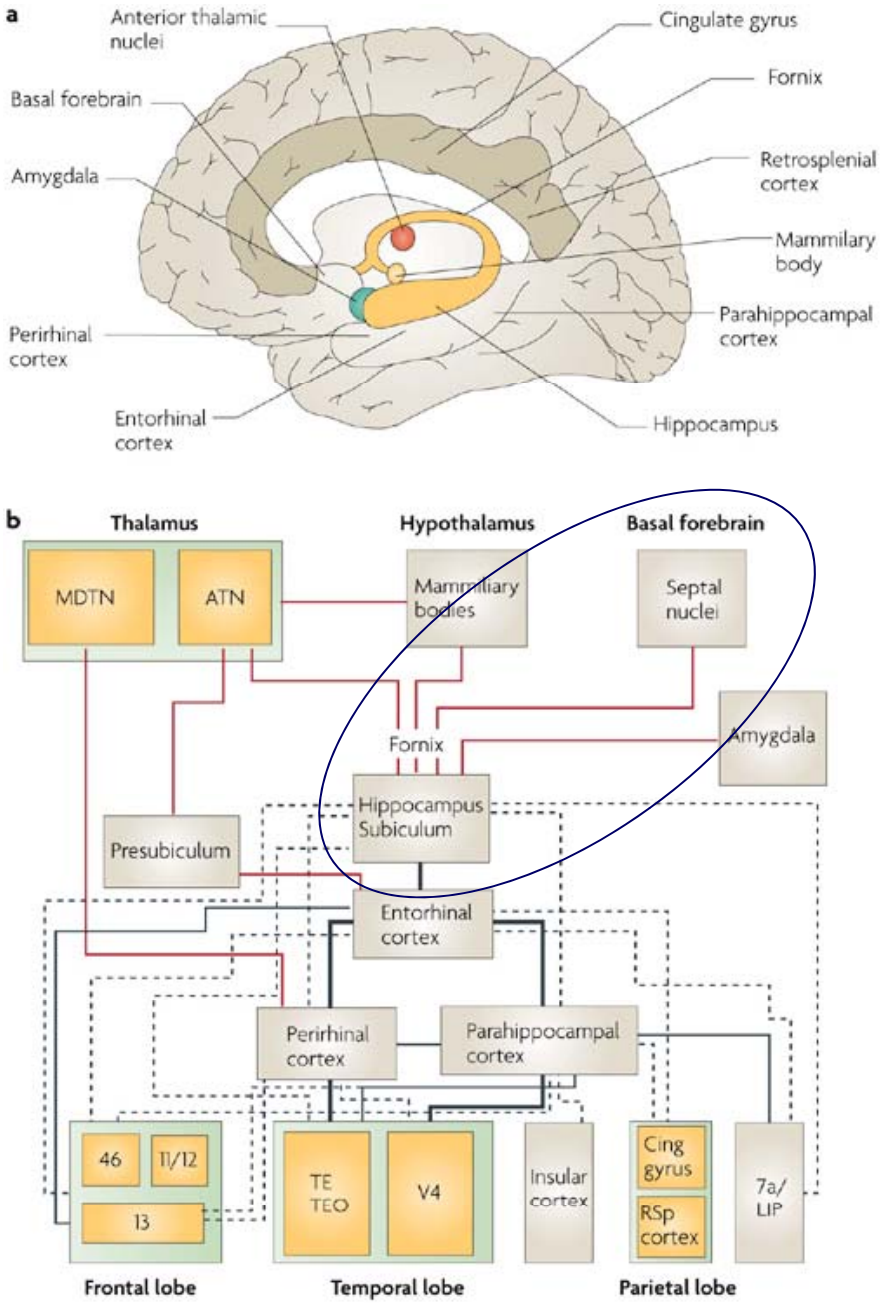
Basal Forebrain

The basal forebrain area (basal nucleus of Meynert, nucleus of the diagonal band, septal nuclei) contains many cholinergic neurons. The general location of this important region and its projections to cortical and subcortical areas are indicated on sagittal and coronal magnetic resonance images (used with permission Mid-Atlantic Mental Illness Research, Education, and Clinical Center).

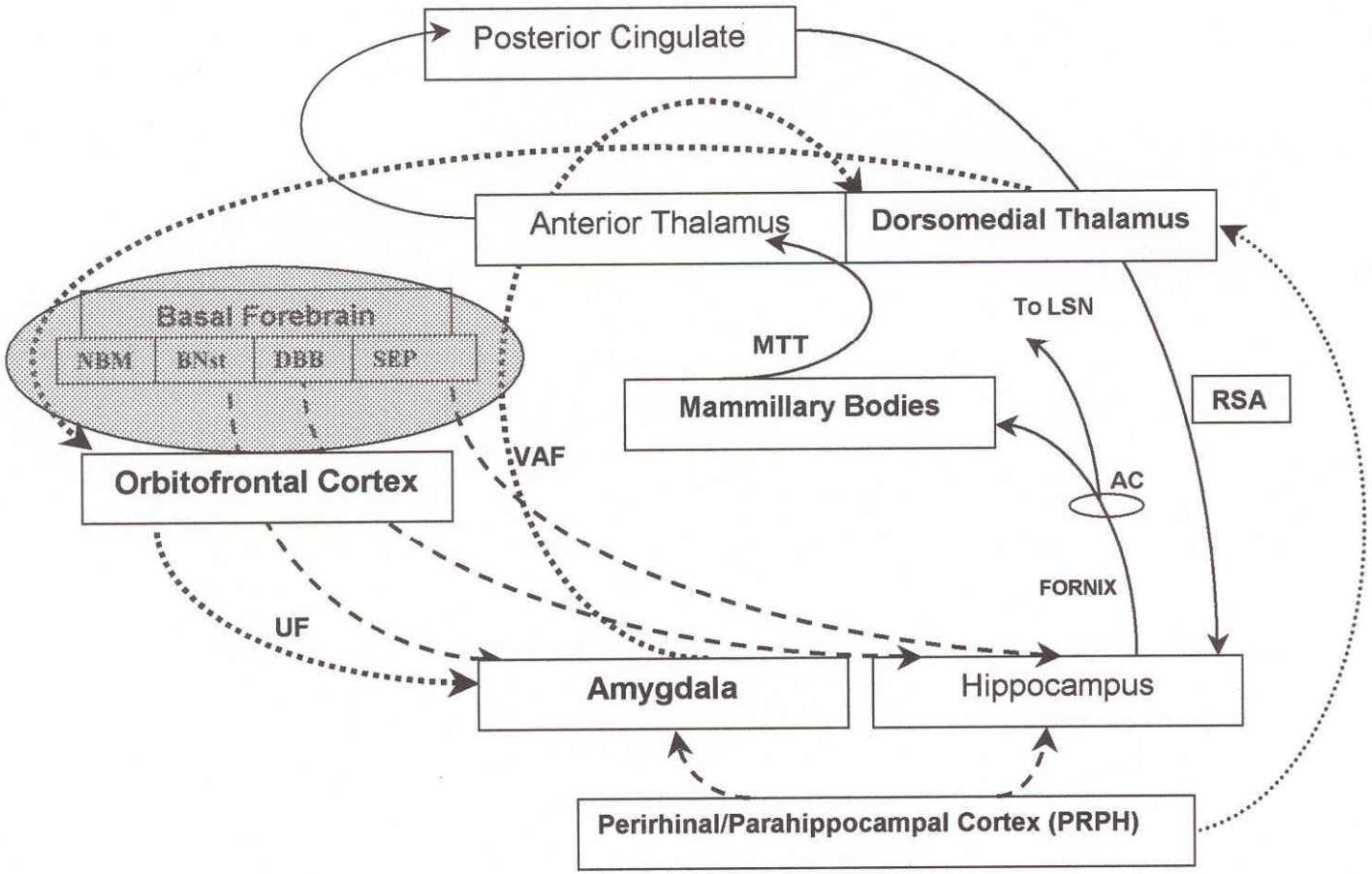
Sagittal Brain Section	Coronal Brain Section

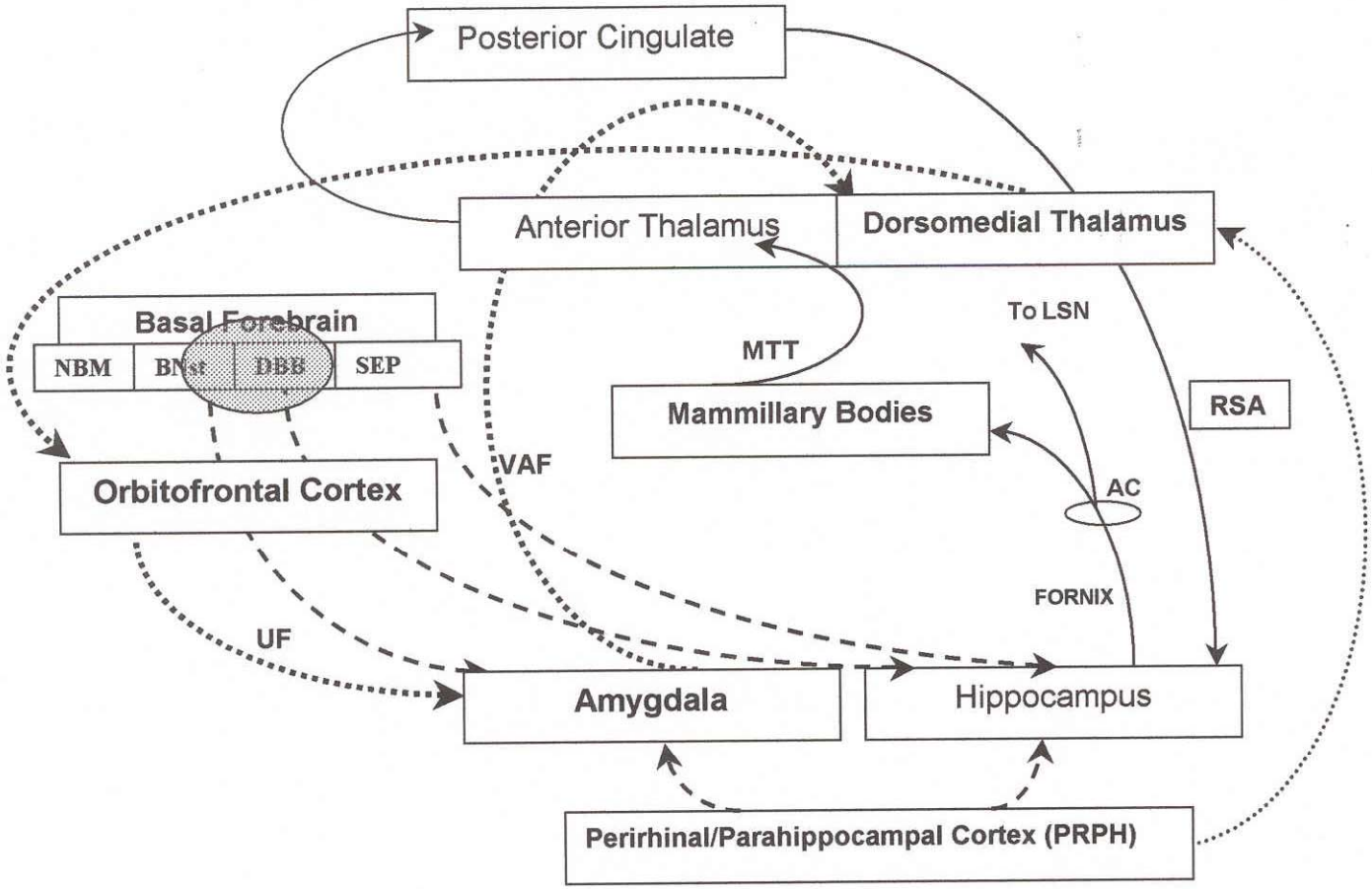



Midline Medial (Parasagittal) View
frontal
parietal
limbic
occipital
Lateral View
frontal
parietal
occipital
temporal
subcallosal area
orbital gyri
inferior frontal gyrus
fornix
anterior commissure
hypothalamus
basal forebrain
midbrain
substantia nigra
cerebral peduncle
cerebellum
hippocampus
red nucleus



Bird & Burgess, 2008, Nature Reviews Neuroscience


Posterior Cingulate
Anterior Thalamus
Dorsomedial Thalamus
Basal Forebrain
NBM
BNst
DBB
SEP
MTT
To LSN
Mammillary Bodies
RSA
VAF
Orbitofrontal Cortex
AC
FORNIX
UF
Amygdala
Hippocampus
Perirhinal/Parahippocampal Cortex (PRPH)


Posterior Cingulate
Anterior Thalamus
Dorsomedial Thalamus
Basal Forebrain
NBM
SEP
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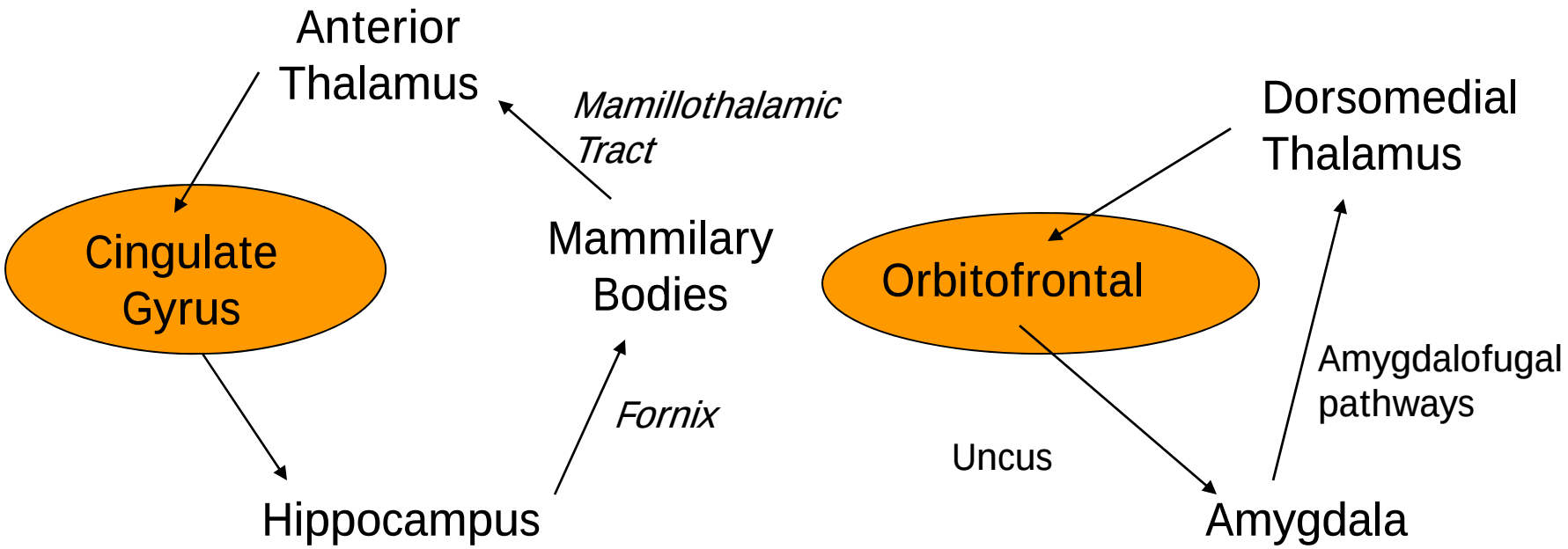
MTT
To LSN
Mammillary Bodies
RSA
VAF
Orbitofrontal Cortex
AC
FORNIX
UF
Amygdala
Hippocampus
Perirhinal/Parahippocampal Cortex (PRPH)

Two Limbic Circuits

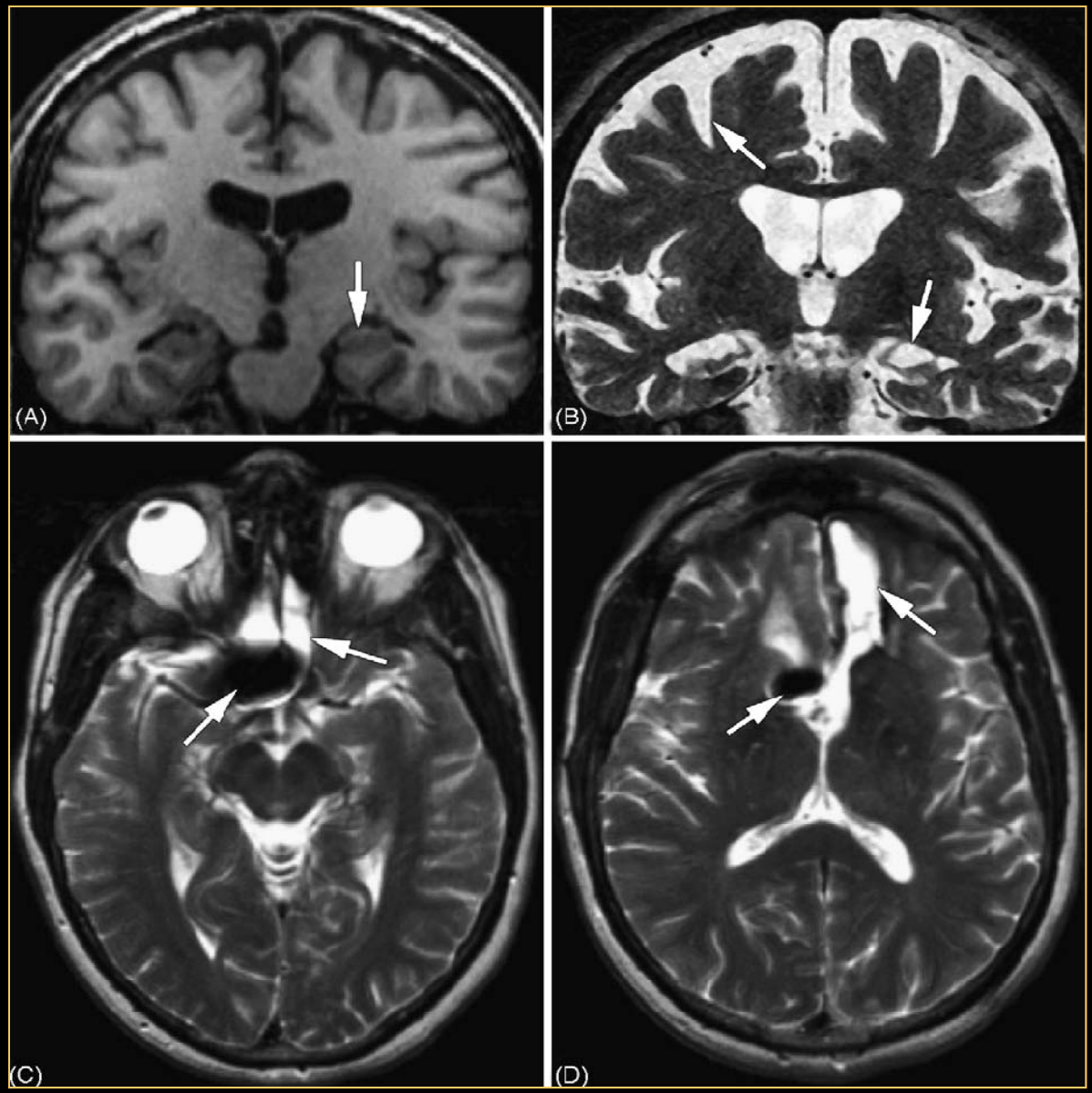


Medial (Papez)

Lateral

Three Amnesias or One?

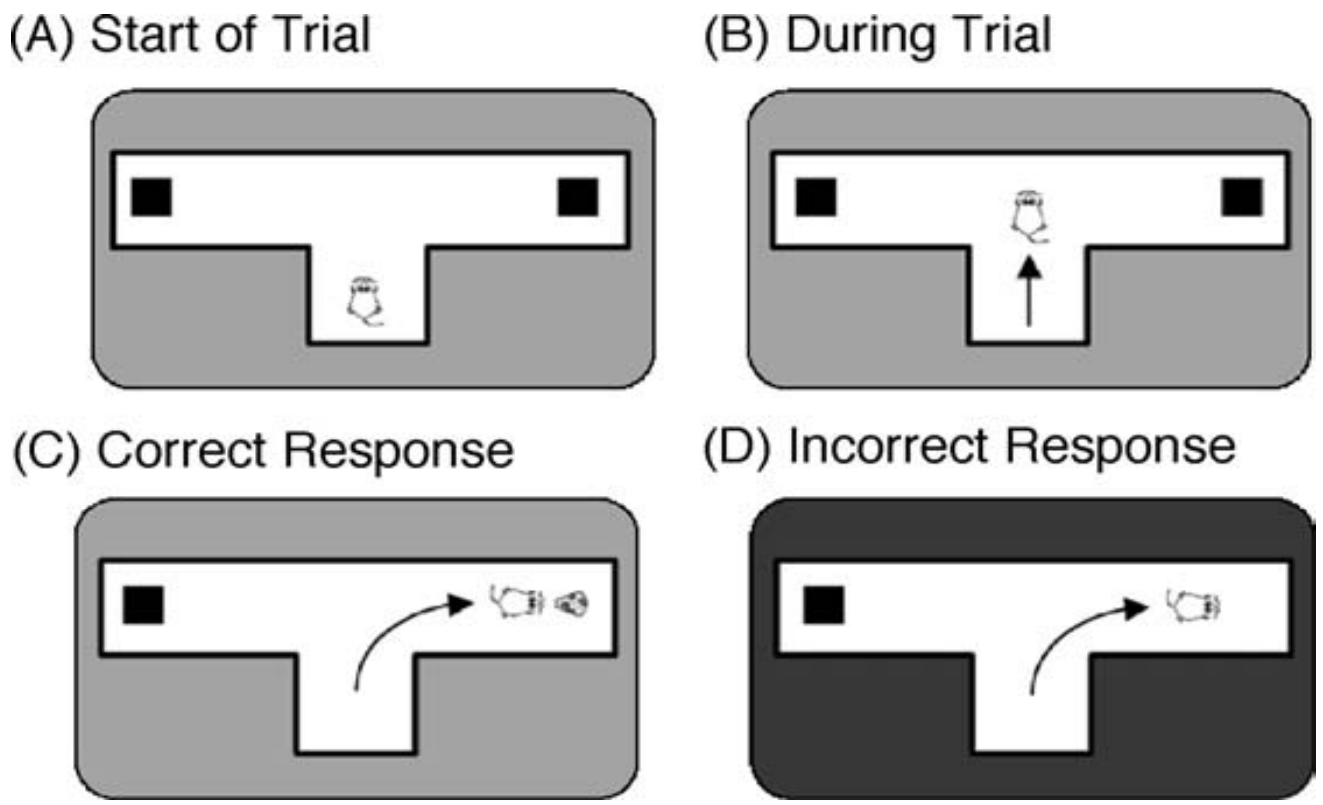
Locus of Processing Defect	Presence of Confabulation	Deficits Supposedly Unique to Diencephalic Amnesia	Pattern of Remote Memory Disturbance
Temporal: Consolidation (rapid forgetting)	Temporal: No	Interference susceptibility	Temporal: time-limited
Diencephalic: Encoding	Diencephalic/BF: Maybe/yes	Metamemory defects	Diencephalic: temporally graded



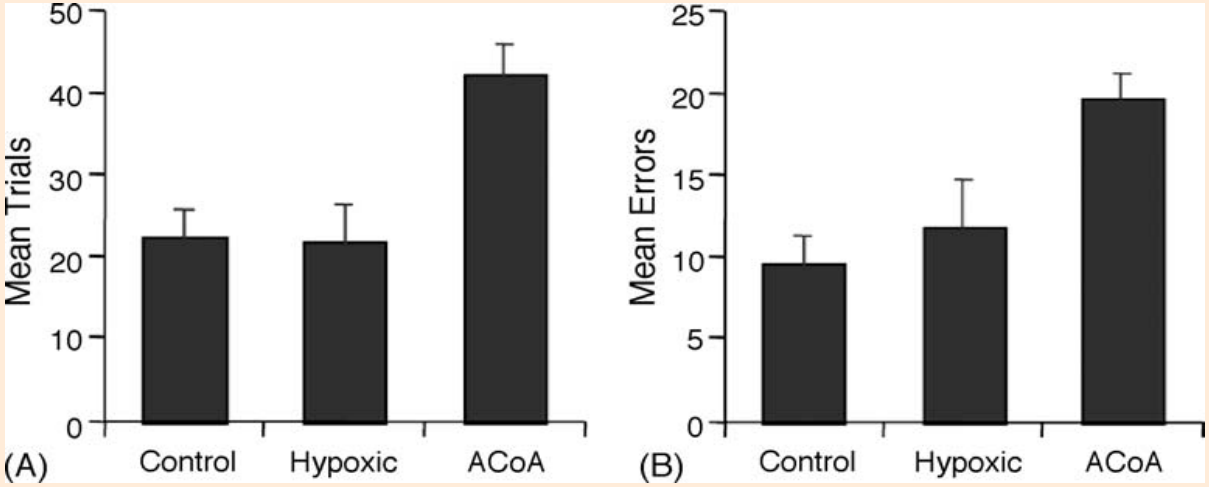
MTL

Basal Forebrain

Myers, et al. (2006)

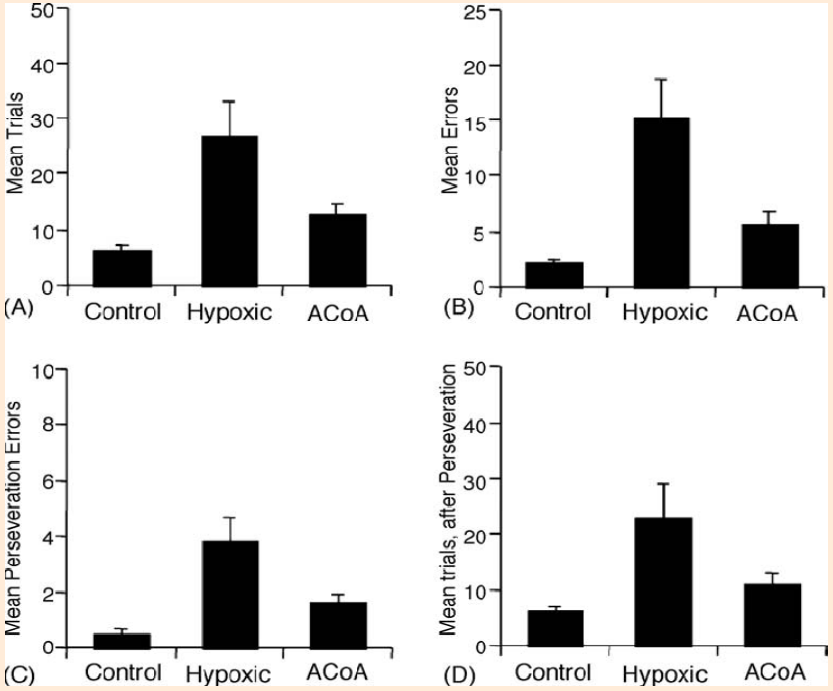


Myers, et al. (2006)



Learning

AcoA < H



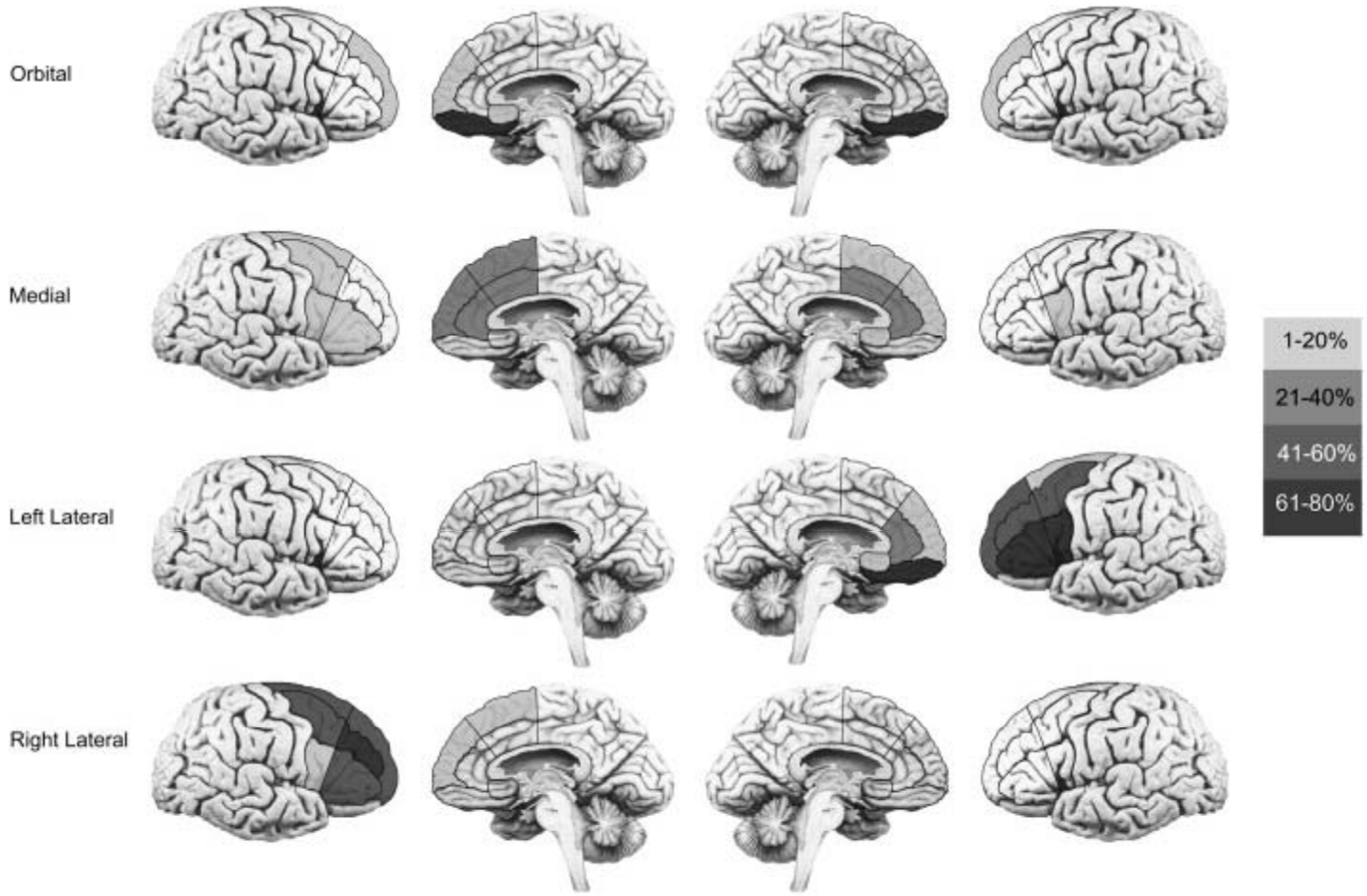
Reversal

H < AcoA

Myers, et al. (2006)

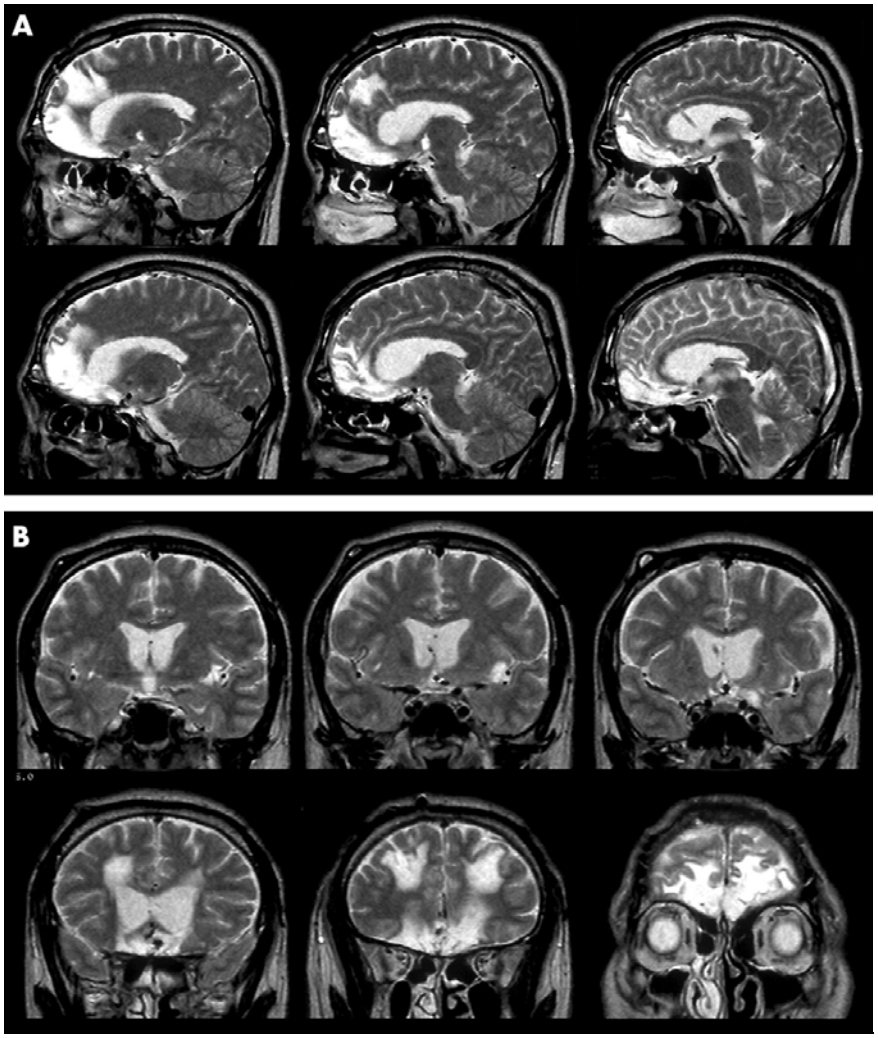
Confabulation

- "Spontaneous" or "persistent" confabulation
  - Extensive frontal damage seems to be necessary in addition to damage to BF structures
  - Severe anterograde amnesia + dysexecutive syndrome
- "Provoked" or "transient" confabulation:
  - Can result from lesions restricted to BF or OFC



Orbital/medial/L lateral: confabulation of personal episodic memories
Orbital/medial/R lateral: confabulation of orienting in time
High confabulators had OFC or inferior cingulate lesions
Memory disorder was necessary for confabulation to occur

Turner, Cipolotti, Yousry, & Shallice, 2008, Cortex, 44, 637-648

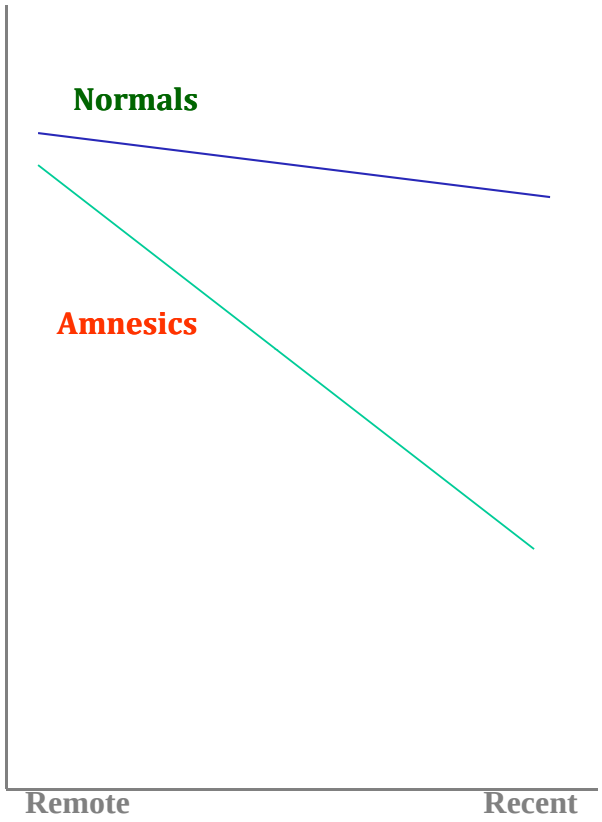


Fujii, T et al. J Neurol Neurosurg Psychiatry 2005;76:1309-1310

Patient with orbitofrontal lesions sparing BF:

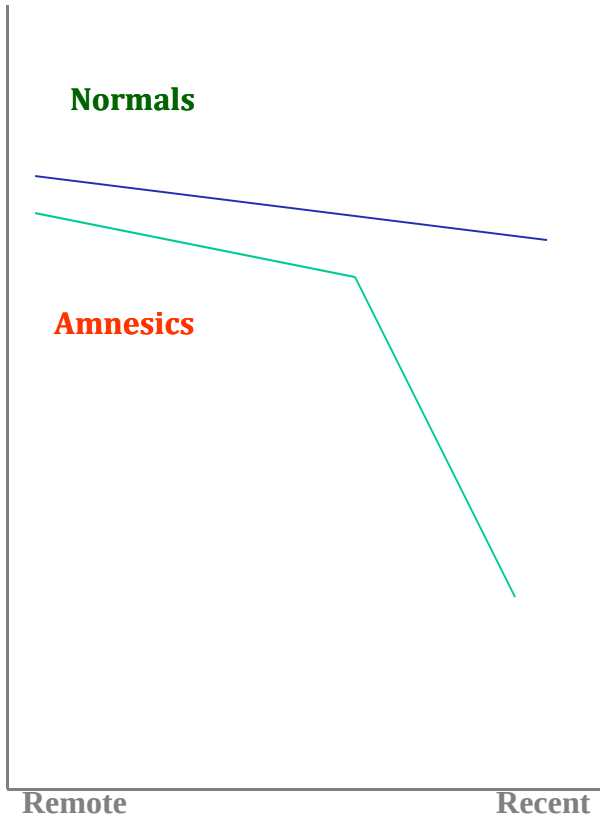
-no amnesia
-no confabulation

Patterns of Retrograde Amnesia



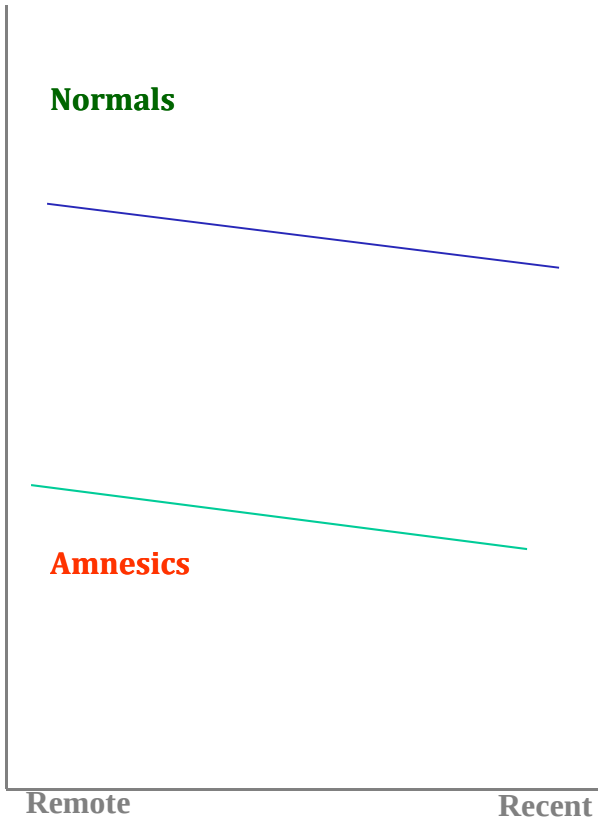
Temporally-Graded RA

Seen in AK



Temporally-Limited RA

Seen in MTL



Decade-Nonspecific RA

Seen in Basal Ganglia (HD) disease

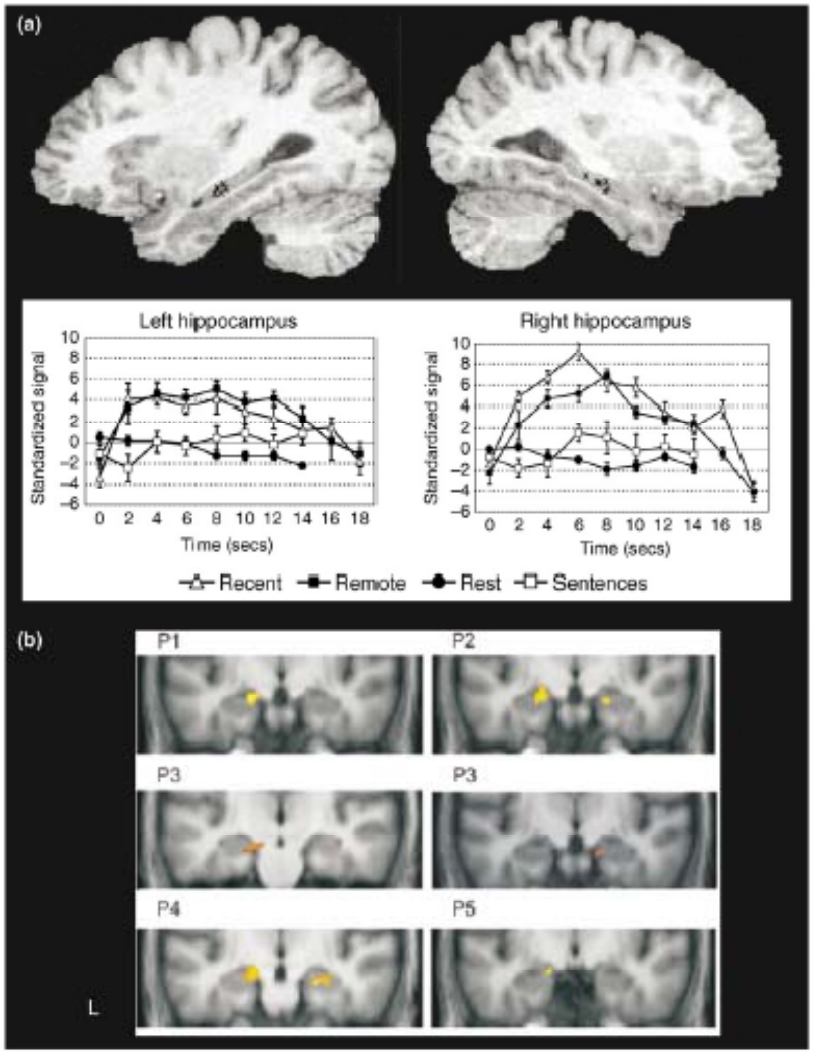
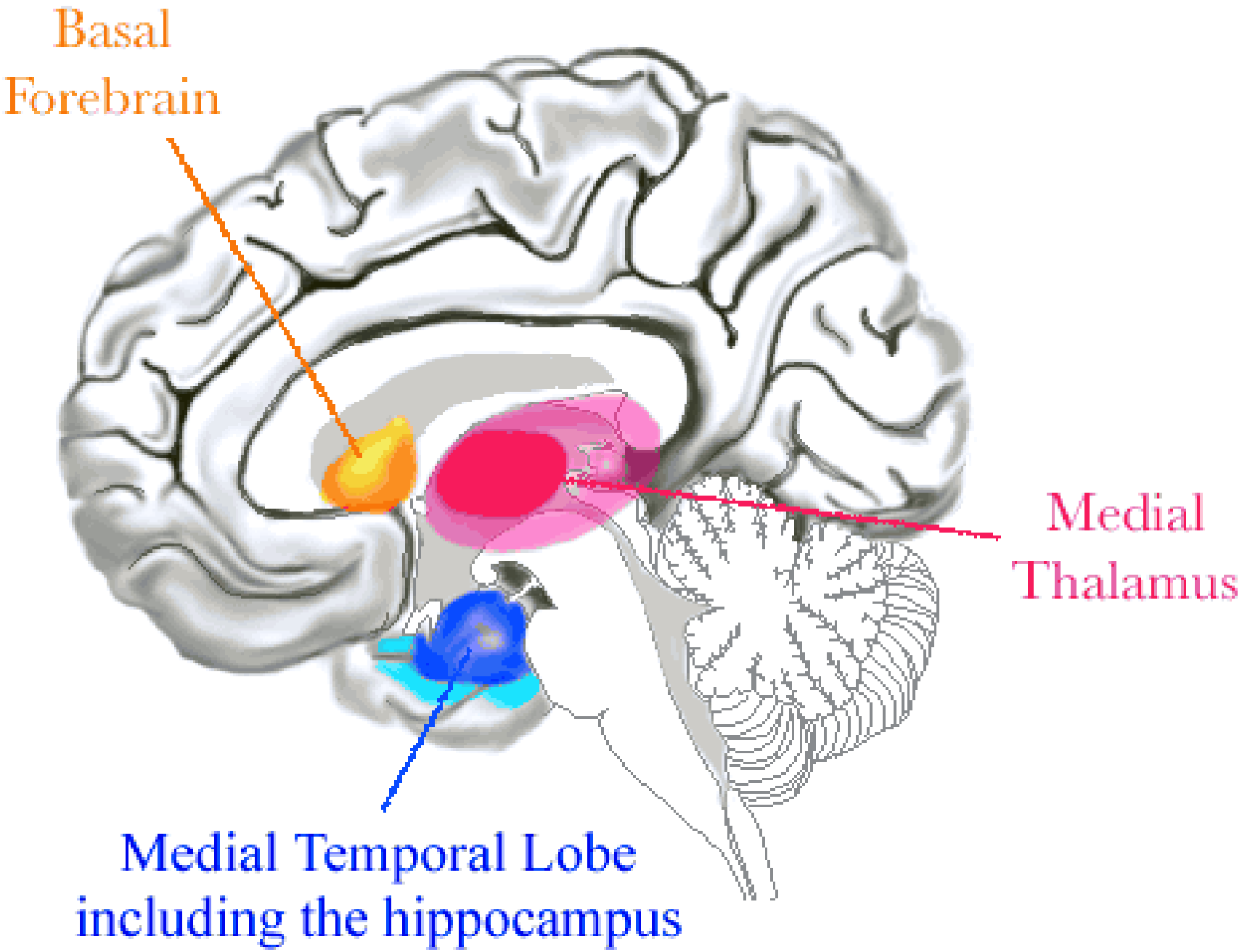


Figure 3. Support for the multiple trace theory (MTT) is suggested by evidence for hippocampal involvement in both recent and remote time periods during AM retrieval. (a) An example of equivalent activity in the hippocampus for both recent and remote AMs, which did not differ on ratings of vividness, emotional intensity, importance or the number of details [51]. Mean activity in right and left hippocampi for recent AMs (<4 years old), remote AMs (>20 years), a sentence completion task and rest. Center of activation per individual is indicated (X). Reprinted, with permission, from Ref. [51]. (b) Hippocampal activity, following small volume correction, for AMs from recent to remote time periods [52]. P1 = 0–17 years; P2 = 18–30 years; P3 = >31 years, except for the past 5 years; P4 = past 5 years, except the past 12 months; P5 = past 12 months. Reprinted from Ref. [52], with permission from Oxford University Press.

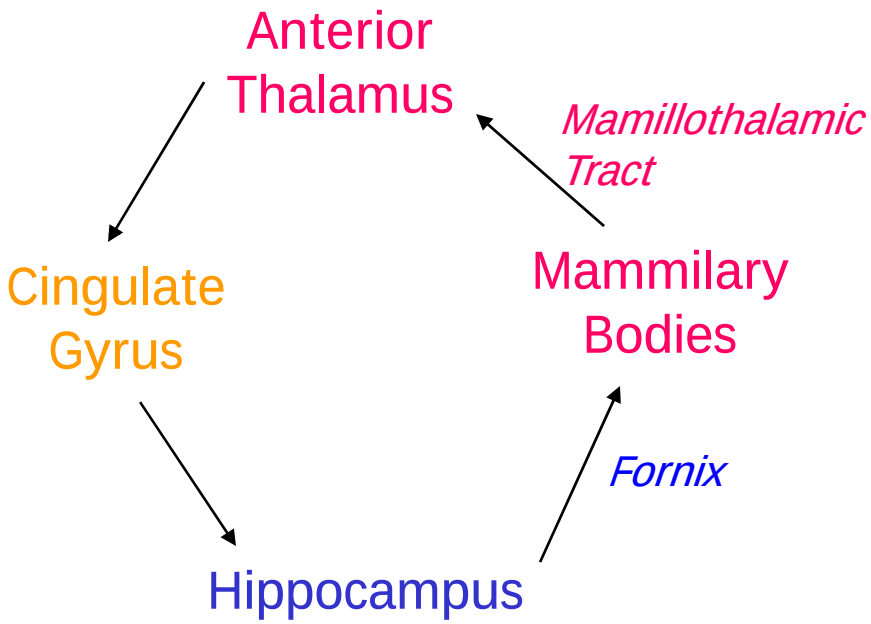
Cabeza & St. Jacques, 2007

Conclusion: One Amnesia

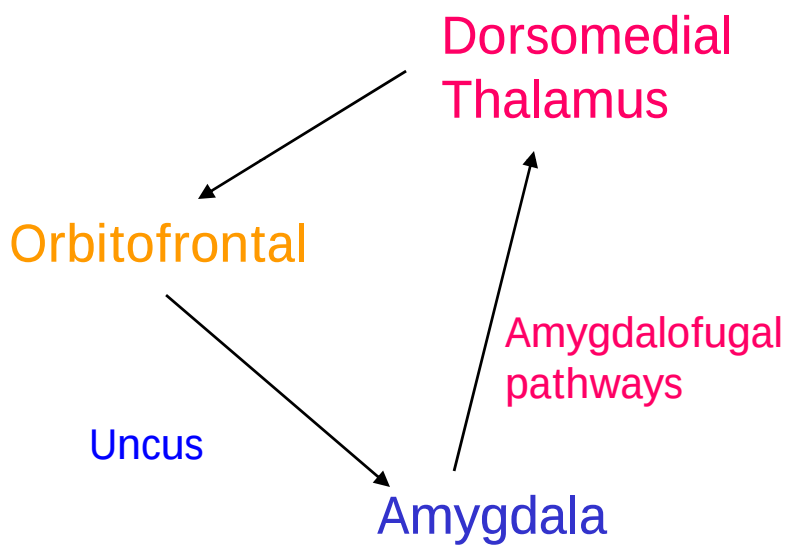
- No compelling data suggesting different "core" amnesic syndromes for MTL, diencephalic, and basal forebrain amnesia
- Behavioral differences attributable to "neighborhood" damage
- It is likely, however, that different structures/systems contribute different things to the memory process


Basal
Forebrain
Medial
Thalamus
Medial Temporal Lobe
including the hippocampus

Two Limbic Circuits



Medial (Papez)



Lateral

Bauer, Grande, & Valenstein, 2003

Key Points

- Extended memory system including hippocampus, amygdala, and basal forebrain
- We (basically) understand anatomy, now we need to understand computation
- Notion of distinct subtypes of amnesia generally less favorable now than 10 years ago
- Certain structures are 'wired' for associational processing; these structures are reciprocally connected to cortical processors