511-2017-10-27-memory

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Today's Topics

- Learning & memory

Memory capacity of the human brain?

- 1e12 neurons
- 1e3 synapses/neuron
- 1e15 synapses or 1.25e14 bytes
- 1e9 gigabyte, 1e12 terabyte, 1e15 petabyte

http://www.scientificamerican.com/article.cfm?id=what-is-the-memory-capacity

What is learning?

- Q: Acquisition of new or change in existing knowledge, skills, …
- **Non-associative**
  - $A(t+1) = f(A(t))$
  - Habituation ($\dot{f} < 0$), sensitization ($\dot{f} > 0$)
- **Associative**
  - A -> B
  - Classical & operant/instrumental conditioning
  - Sequence, observational, episodic, semantic

What is memory?

- A: Information encoding, storage, retrieval
- Dimensions
  - Short vs. long-term
    - Working memory ~ short-term maintenance for guiding action
  - Explicit (declarative: semantic vs. episodic) vs. implicit (procedural)
  - Retrospective (from the past) vs. prospective (to be remembered)
  - Recognition (familiar or novel) vs. recall

Biological bases of L&M

- Changes in patterns of neural activity
- Changes in connectivity
  - New synapses
  - Altered synapses (strengthened or weakened)
- Computers have separate memory stores; brains store info everywhere

Donald Hebb's Insight

When an axon of cell A is near enough to excite cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficacy, as on of the cells firing B, is increased. (Hebb, 1949, p. 62)

Neurons that fire together wire together. (Lowell & Singer, 1992, p. 211).

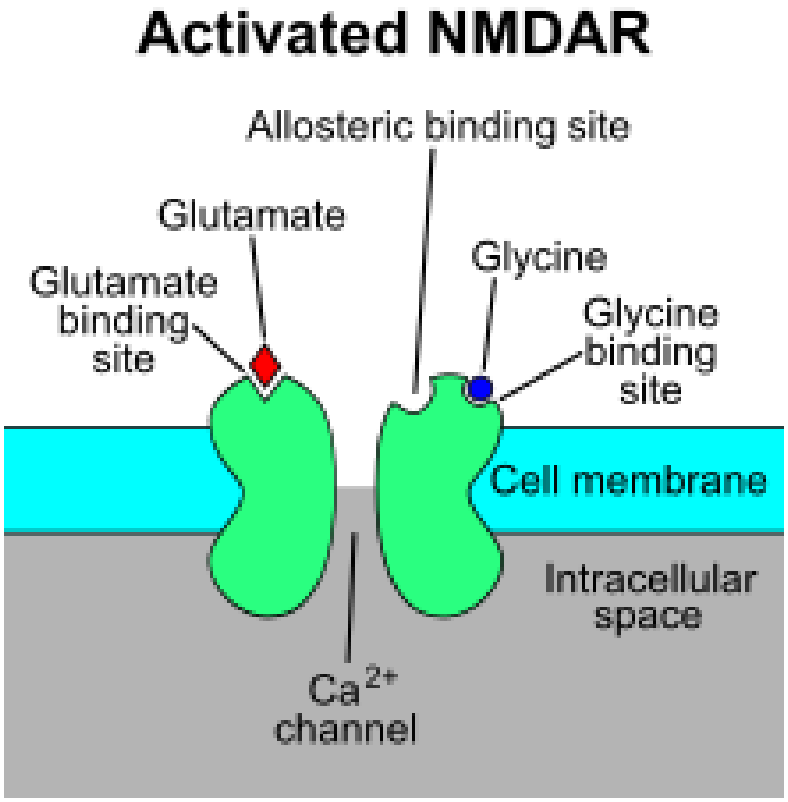
'Hebbian' learning via NMDA receptor

- *N-methyl-D-aspartate* receptor (NMDAR)
- 'Coincidence' detector
  - Sending cell has released NT
  - Receiving cell is/has been recently active

'Hebbian' learning

- Chemically-gated AND
  - Ligand- (glutamate/aspartate + glycine) gated
  - Sending cell active
- Voltage-gated
  - Zn^{++} or Mg^{++} ion 'plug' removed under depolarization
  - Na^{+} & Ca^{++} influx; K^{+} outflux
  - Receiving cell responds

NMDA receptor figure



https://upload.wikimedia.org/wikipedia/commons/thumb/0/00/Activated_NMDAR.svg/220px-Activated_NMDAR.svg.png

NMDA clinical significance

- *Memantine* (Alzheimer's Disease treatment) blocks NMDAR
  - Controls over-activation and Ca^{++} excitotoxicity?
- Implicated in effects of *phencylidine* (PCP)
  - Link to glu hypothesis of schizophrenia?

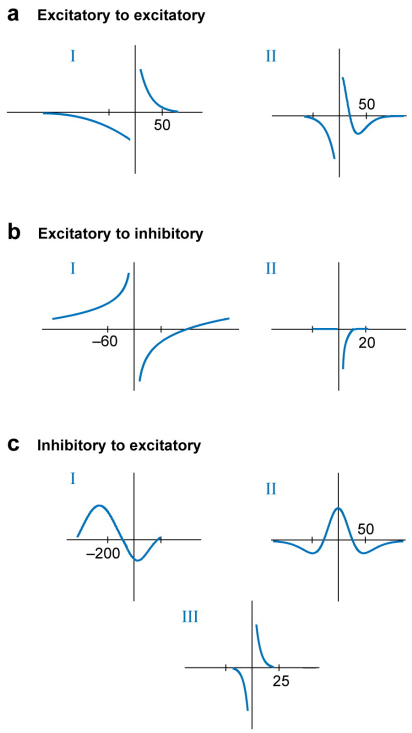
NMDA clinical significance

- *Ketamine* is NMDA receptor antagonist
  - anesthesia, sedation pain relief
  - possible short-term relief for depression
- Analgesic effects of nitrous oxide (laughing gas; NO)
- Ethanol inhibits (Ron and Wang 2011)

But how to learn/remember "causal chains"?

- e.g., lightning THEN thunder
- unusual food THEN indigestion

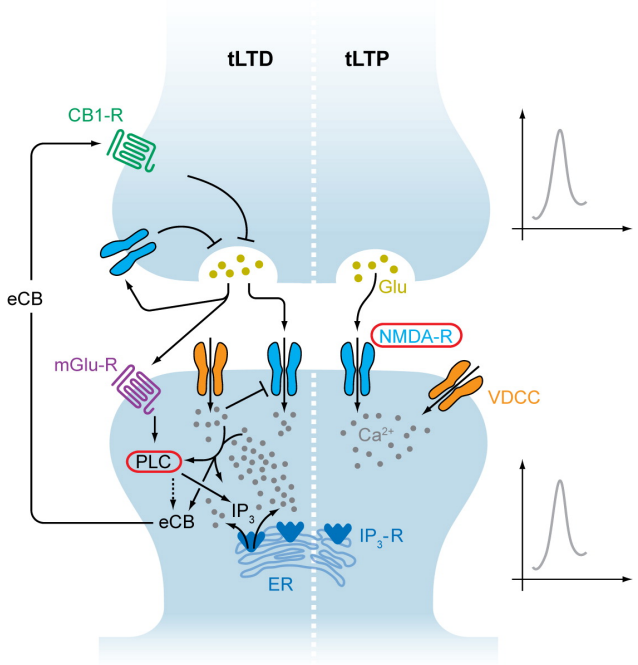
Spike-timing-dependent plasticity



Caporale N, Dan Y. 2008.
Annu. Rev. Neurosci. 31:25–46.

(Caporale and Dan 2008)

Spike-timing-dependent plasticity



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Spike-timing-dependent plasticity

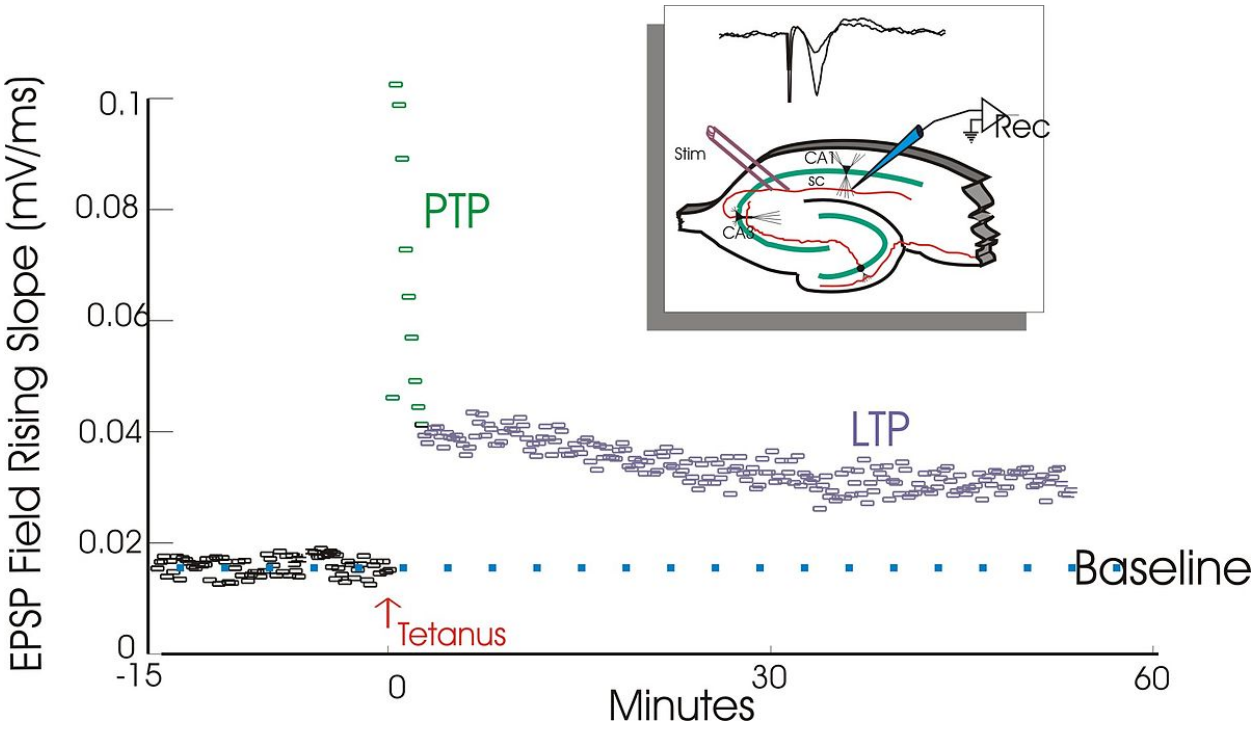
- A before B: strengthen A->B
- A after B: weaken A->B
- *Neural Plasticity*
    - Lasting changes in neural firing, connectivity
- NMDA receptor molecular mechanism for implementing LTP and spike-timing-dependent plasticity

NMDA receptor function may vary by location on neuron

- Long-term potentiation (LTP)
  - Synaptic NMDA receptors
- Long-term depression (LTD)
  - Extrasynaptic NMDA receptors
  - Lowered level of synaptic receptor activation

LTP discovery (Bliss and Lømo 1973)

- Granule cell neurons in hippocampus DG
- θ band (10–20 Hz) stim for 10–15 sec, or 100 Hz stim for 3–4 sec
- shortened response latency, increased EPSP, increased population response over minutes or hours

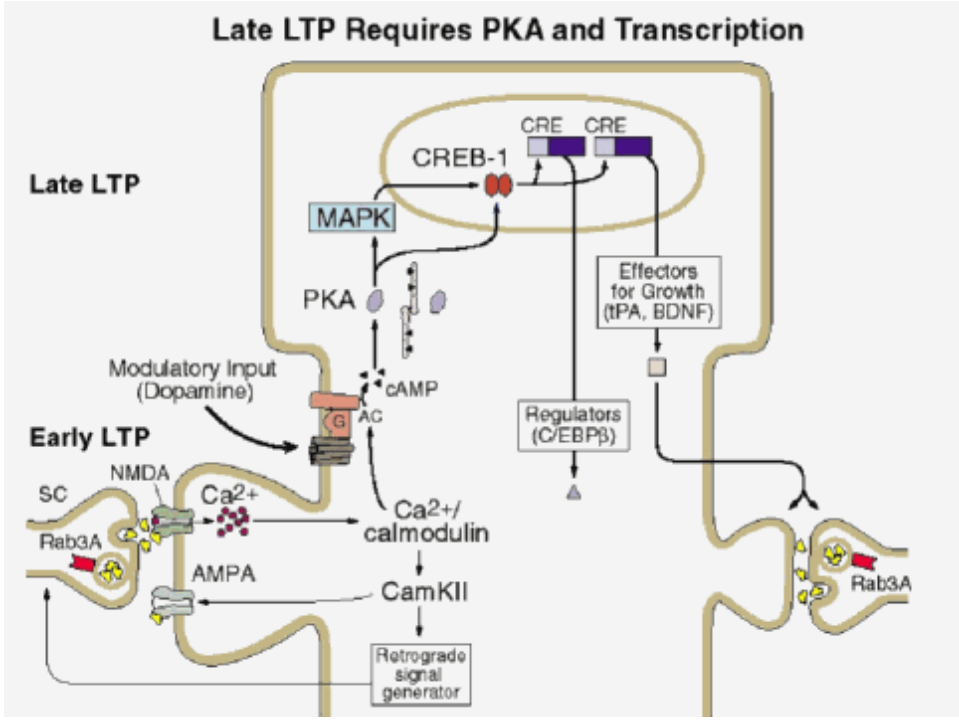

EPSP Field Rising Slope (mV/ms)
0.1
0.08
0.06
0.04
0.02
0
PTP
LTP
Baseline
Tetanus
-15
0
30
60
Minutes
Stim
Rec
CA1
SC
CA3

Mechanisms of LTP plasticity

- number of synaptic receptors
- quantity of NT released
- effectiveness of postsynaptic response

Pathways to plasticity

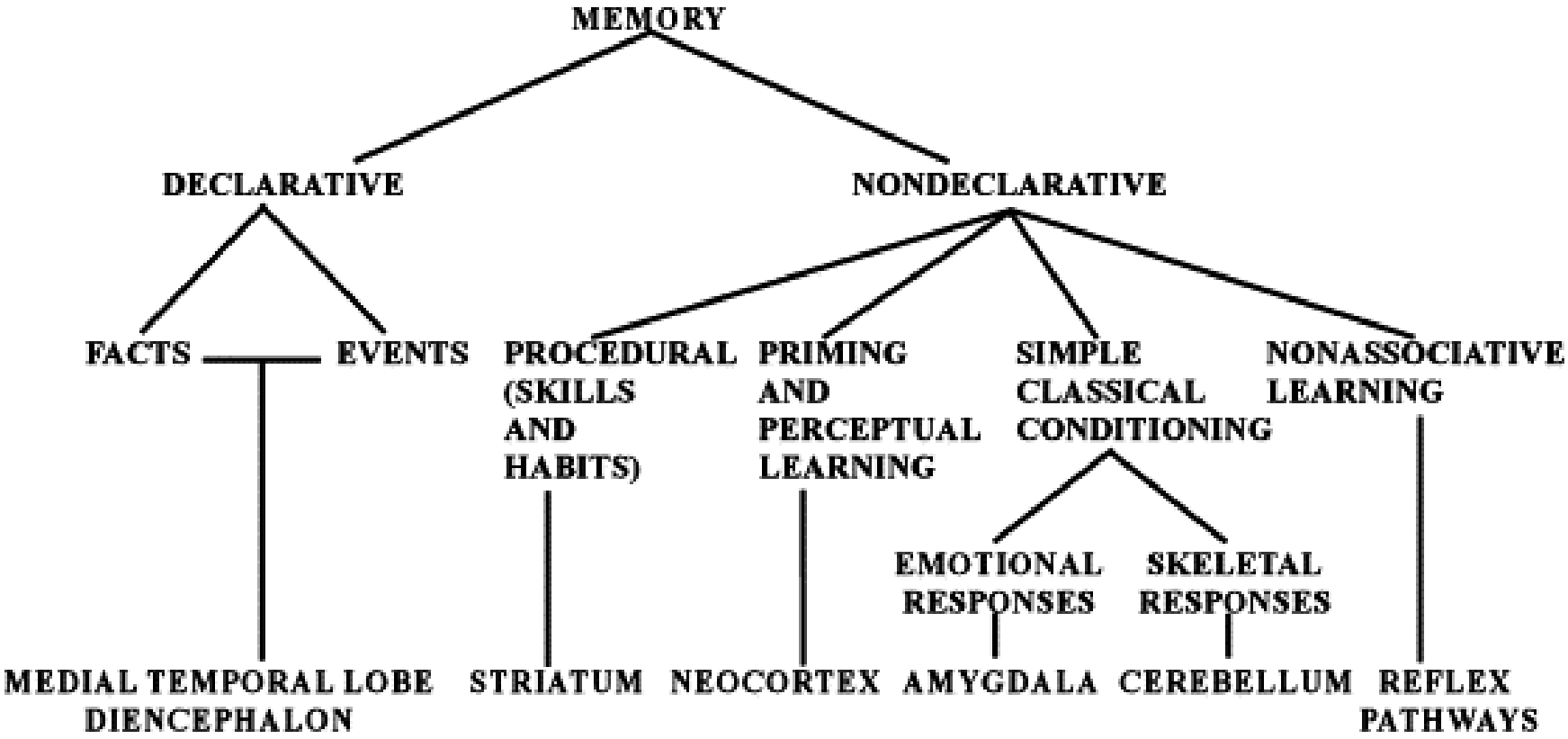
- Ca^{++} entry activates protein kinases (CaMKII and PKAII)
- Early LTP
  - protein kinases *phosphorylate* (add P group to) postsynaptic AMPA receptors
  - Increased current flow through AMPA (glu) receptors
- Late LTP
  - insertion of new receptors into membrane
- Retrograde signal generator influences presynaptic response


Late LTP Requires PKA and Transcription
Late LTP
CRE
CRE
CREB-1
MAPK
PKA
Effectors
for Growth
(tPA, BDNF)
Modulatory Input
(Dopamine)
cAMP
G
AC
Regulators
(C/EBPβ)
Early LTP
NMDA
SC
Ca2+
Ca2+/
calmodulin
Rab3A
AMPA
CamKII
Rab3A
Retrograde
signal
generator

Dimensions of stored info

- Memory of what or how recalled/recognized
  - Facts/events/places/feelings vs. skills
- Memory of when?
  - Immediate vs. distant past
- Memory for how long?
  - Seconds vs. years

Memory systems in the brain



(Squire 2004)

Hippocampus

https://upload.wikimedia.org/wikipedia/commons/5/5b/Hippocampus_and_seahorse_cropped.JPG

Hippocampus features

- Dense in NMDA receptors
- Central "hub" in network?
  - No, based on anatomical or functional connectivity
  - But yes, when modeling "information flow" (Mišić et al. 2014)

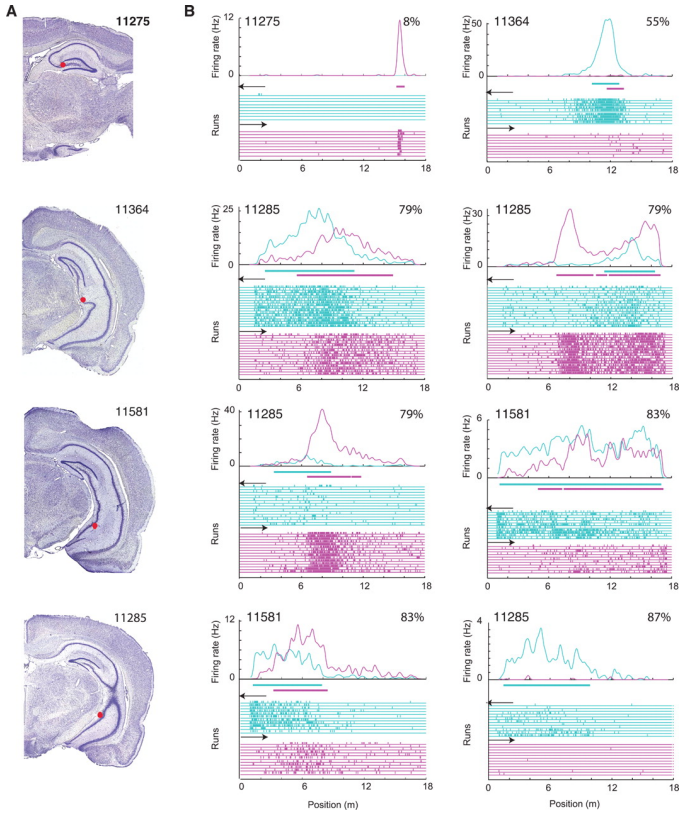
Hippocampus roles

- Formation, storage, consolidation of long-term episodic or declarative memories
- Stores info for later transfer to cortex
    - "Engrams" form in hipp & PFC simultaneously, fade in PFC over time (Kitamura et al. 2017)

Hippocampus roles

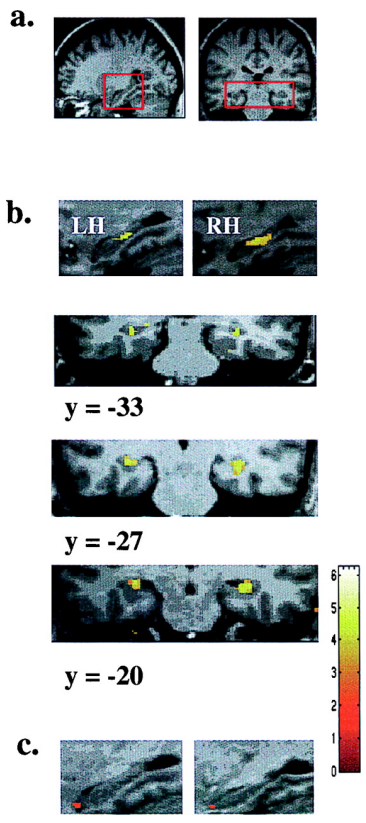
- Spatial navigation
  - Place cells
  - Grid cells
  - Head-direction cells

Spatial precision of place cells



(Kjelstrup et al. 2008)

Human analogue – (Maguire et al. 2000)



(Maguire et al. 2000)

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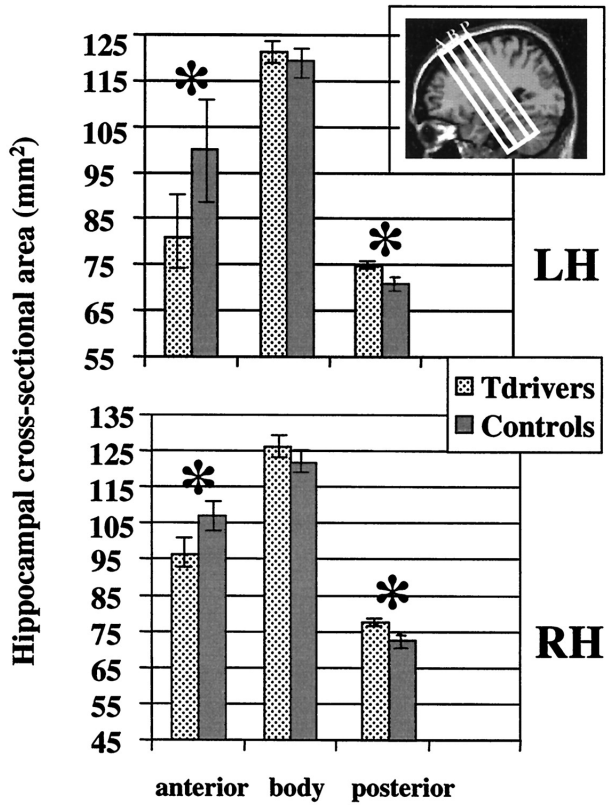

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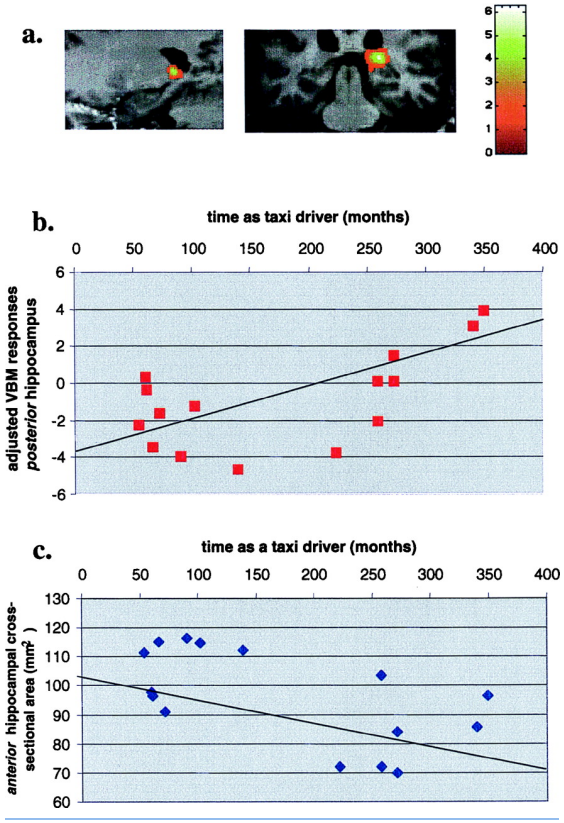


(Maguire et al. 2000)

Hippocampal volume in food-caching birds

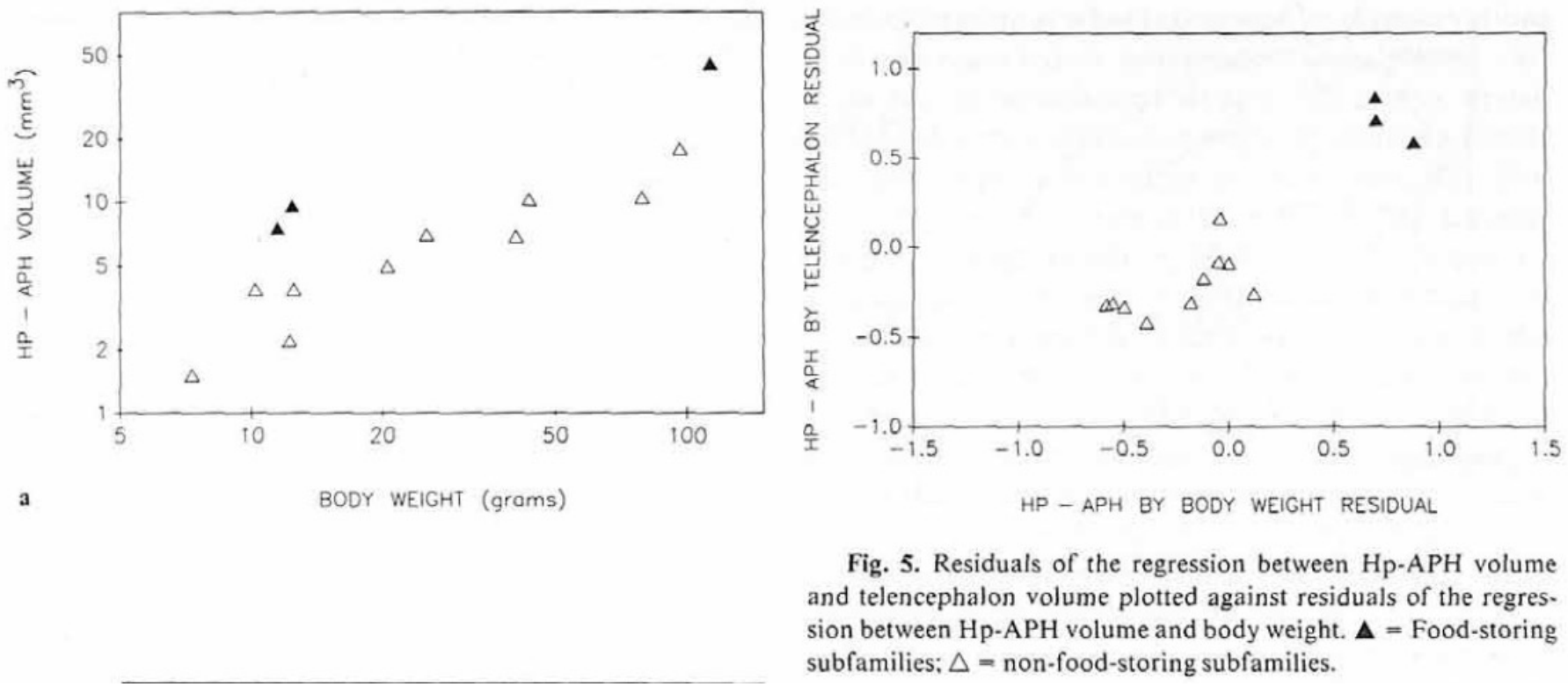


Fig. 5. Residuals of the regression between Hp-APH volume and telencephalon volume plotted against residuals of the regression between Hp-APH volume and body weight. ▲ = Food-storing subfamilies; △ = non-food-storing subfamilies.

(Sherry et al. 1989)

Disorders of memory

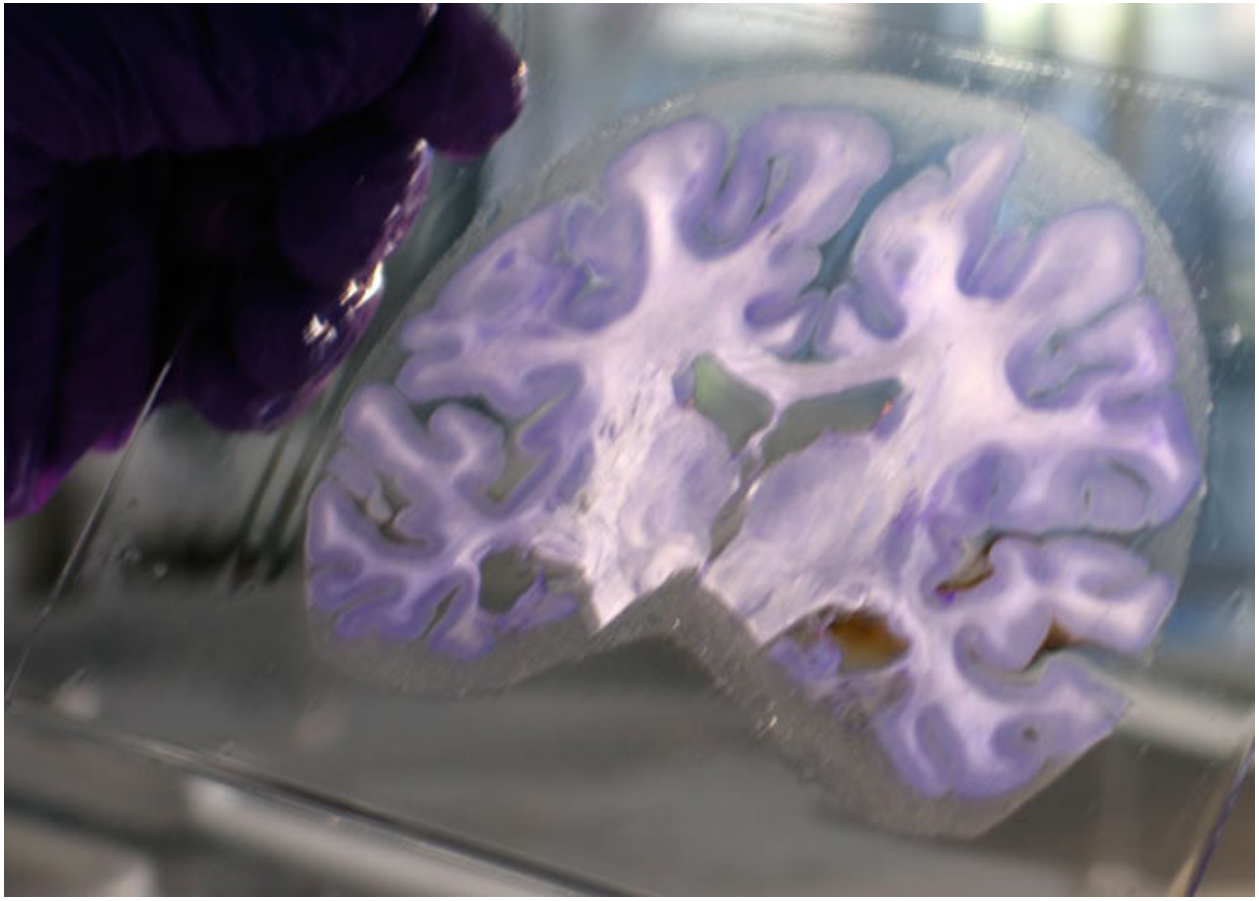
Patient HM (Henry G. Molaison)

- Intractable/untreatable epilepsy
- Bilateral resection of medial temporal lobe (1953)
- Epilepsy now treatable
- But, memory impaired
- Lived until 2008

Brenda Milner tells the story

Brenda Milner, Neuropsychologist

HM's surgery



Amnesia

- Acquired loss of memory
- ≠ normal forgetting
- Note: computers don't forget

HM's amnesia

- Retrograde amnesia
  - Can’t remember 10 yrs before operation
  - Distant past better than more recent
- Severe, global anterograde amnesia
  - Impaired learning of new facts, events, people
- But, skills (mirror learning) intact

Types of amnesia

- Retrograde ('backwards' in time)
  - Damage to information acquired pre-injury
  - Temporally graded
- Anterograde ('forward' in time)
  - Damage to information acquired/experienced post-injury

What it's like

Every day is alone in itself, whatever enjoyment I've had, and whatever sorrow I've had…Right now, I'm wondering, have I done or said anything amiss? You see at this moment, everything looks clear to me, but what happened just before? That's what worries me. It's like waking from a dream. I just don't remember.

What it's like

Memento Original 35 mm Anamorphic Trailer (HD) (CC)

Other causes of amnesia

- Disease
  - Alzheimer's, herpes virus
- Korsakoff's syndrome
  - Result of severe alcoholism
  - Impairs medial thalamus & mammillary bodies

Patient NA

- Fencing accident
- Damage to medial thalamus
- Anterograde + graded retrograde amnesia
- Are thalamus & medial temporal region connected?

Patient NA

Larry Squire's Amnesic Patient NA

Spared skills in amnesia

- Skill-learning
- Mirror-reading, writing
- Short-term memory
- “Cognitive” skills
- Priming

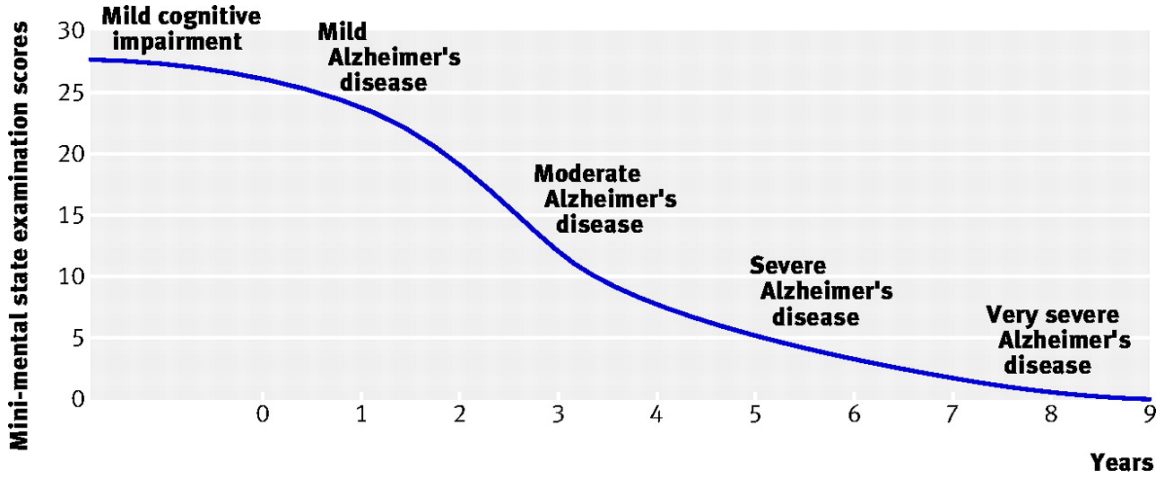
What does amnesia tell us?

- Long-term memory for facts, events, people
- ≠ Short-term memory
- ≠ Long-term memory for “skills”
- Separate memory systems in the brain?

Alzheimer's Disease (AD)

- Chronic, neurodegenerative disease affecting ~5 M Americans
- Cognitive dysfunction (memory loss, language difficulties, planning, coordination)
- Psychiatric symptoms and behavioral disturbances
- Difficulties with daily living
- (Burns and Iliffe 2009)

AD progression



Mild cognitive impairment: Complaints of memory loss, intact activities of daily living, no evidence of Alzheimer's disease

Mild Alzheimer's disease: Forgetfulness, short term memory loss, repetitive questions, hobbies, interests lost, impaired activities of daily living

Moderate Alzheimer's disease: Progression of cognitive deficits, dysexecutive syndrome, further impaired activities of daily living, transitions in care, emergence of behavioural and psychological symptoms of dementia

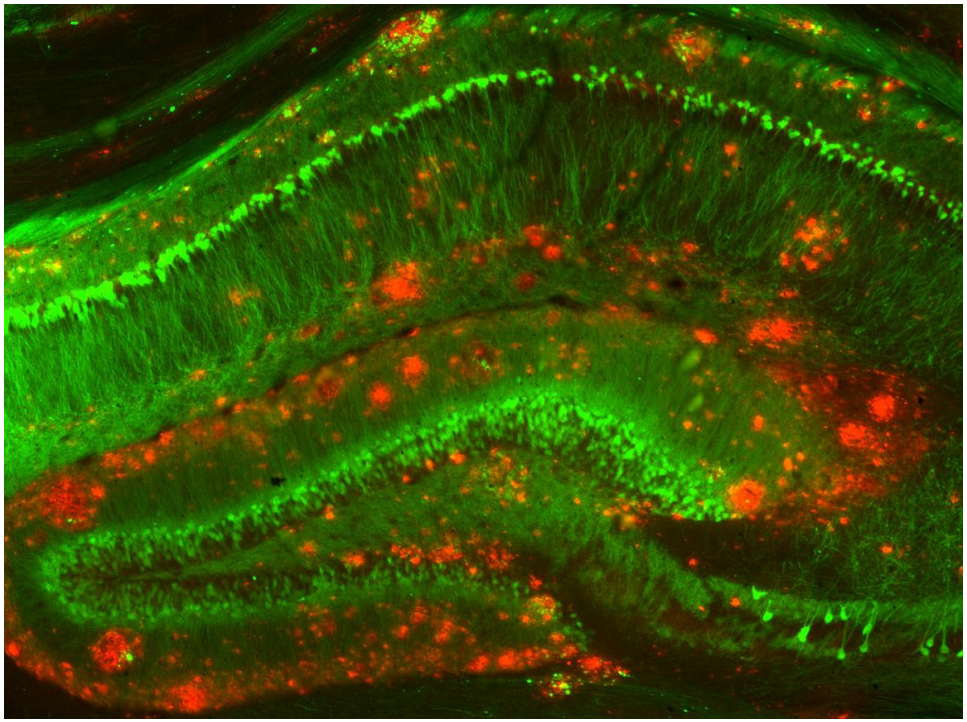
Severe Alzheimer's disease: Agitation, altered sleep patterns, assistance required in dressing, feeding, bathing, established behavioural and psychological symptoms of dementia

Very severe Alzheimer's disease: Bedbound, no speech, incontinent, basic psychomotor skills lost

(Burns and Iliffe 2009)

AD

- Post-mortem exams show beta amyloid plaques and neurofibrillary tangles



AD treatments include

- Acetylcholinesterase (AChE) inhbitors (e.g. Aricept)
- NMDAR partial antagonists (e.g., Memantine)

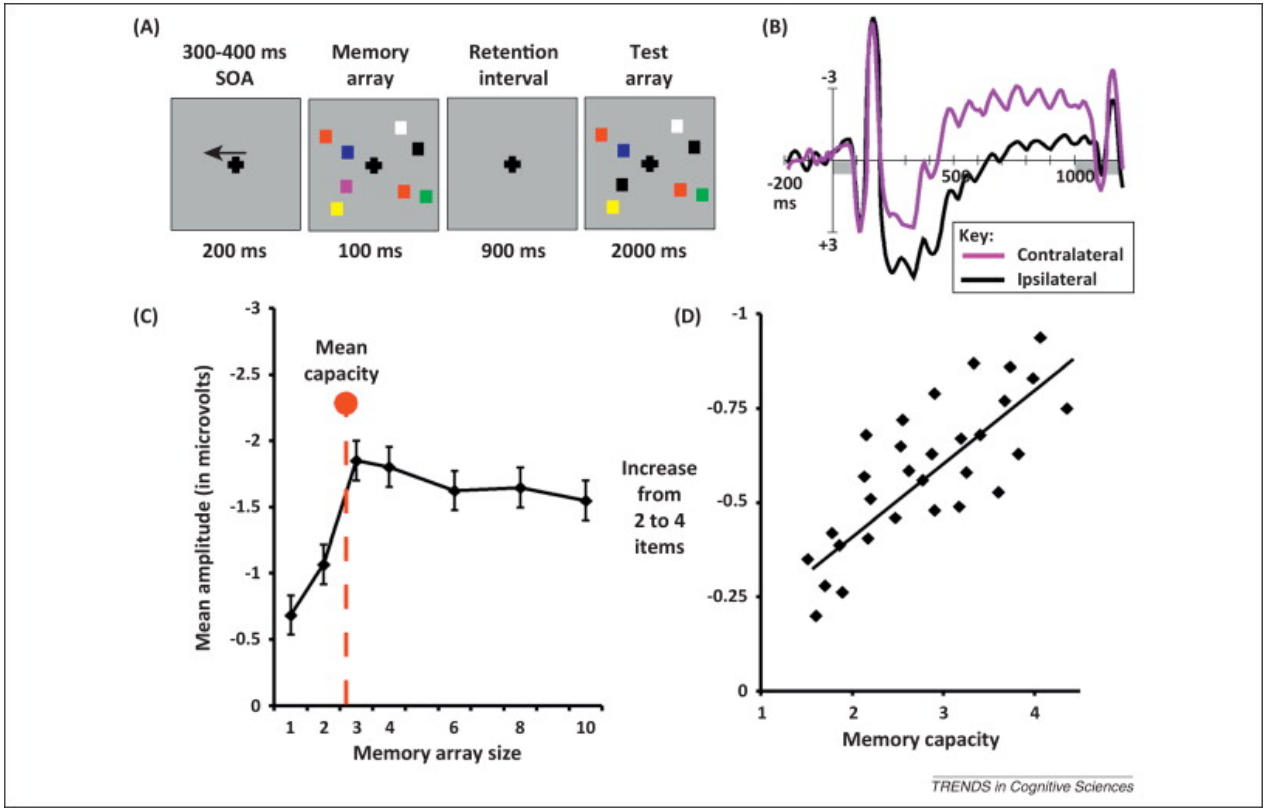
What about working memory? (D'Esposito and Postle 2015)

- LTM representations of target items + attention -> elevated activation
  - Semantic items
  - Sensorimotor items
- Capacity for attended items (in Focus of Attention or FoA) limited ~ 4

What about working memory? (D'Esposito and Postle 2015)

- Neural basis
  - sustained activation in PFC
  - subthreshold activation in areas where items are stored

Individual differences in visual WM (Luck and Vogel 2013)



Summary

- Multiple types of learning & memory
- Learning & memory distributed across the brain
- Hippocampus + PFC critical areas binding together sensory/semantic info stored elsewhere
- Changes in synaptic #, strength, connectivity provide cellular basis

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