511-2018-10-26-memory

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Prelude

Today's Topics

- Wrap-up on language
- Learning & memory

Memory capacity of the human brain?

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?

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?

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 vs. brains

- Computers have separate memory stores; brains store info everywhere

Donald Hebb's Insight

(Hebb, 1949, p. 62)

(Lowell & Singer, 1992, p. 211).

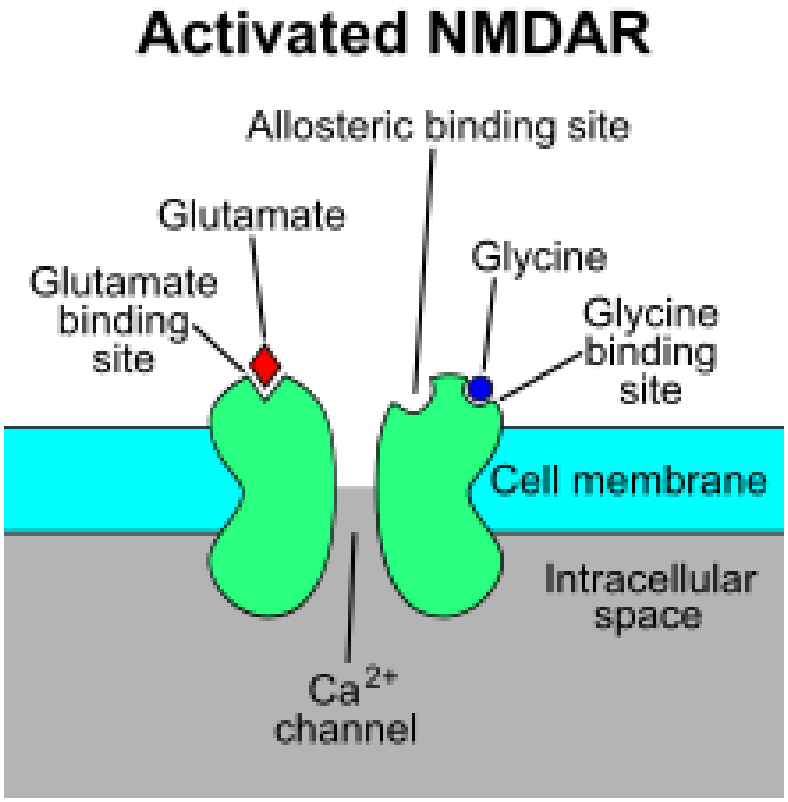
'Hebbian' learning via NMDA receptor

- receptor (NMDA-R)
- '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

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

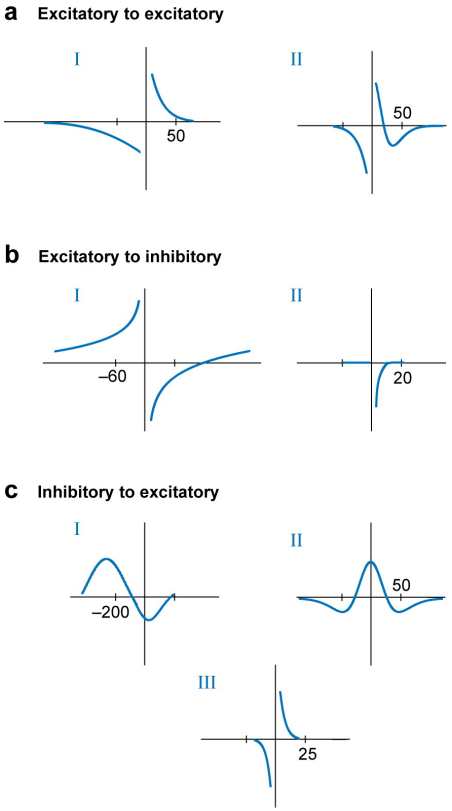
NMDA clinical significance

- 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 & Wang, 2011)

But how to learn/remember "causal chains"?

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

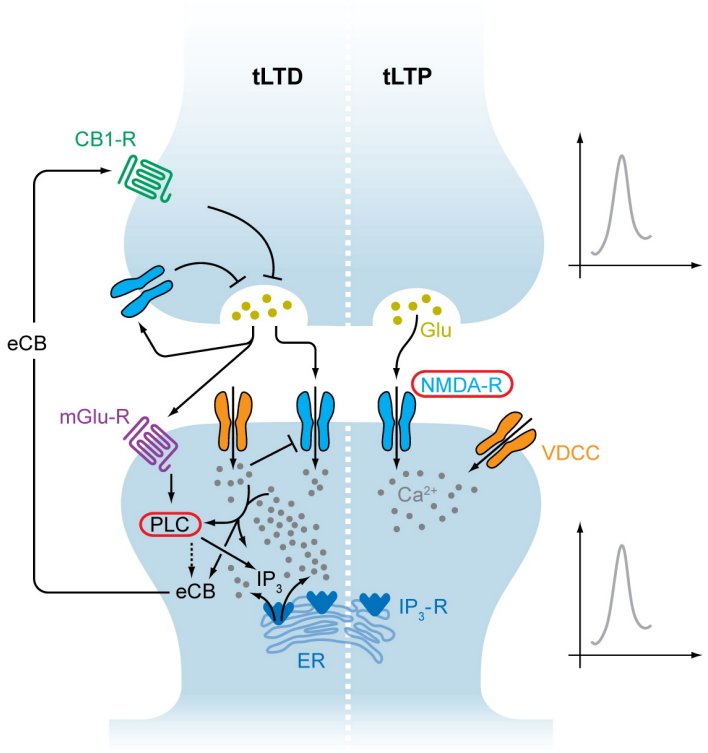
Spike-timing-dependent plasticity



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

(Caporale & Dan, 2008)

Spike-timing-dependent plasticity



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Spike-timing-dependent plasticity

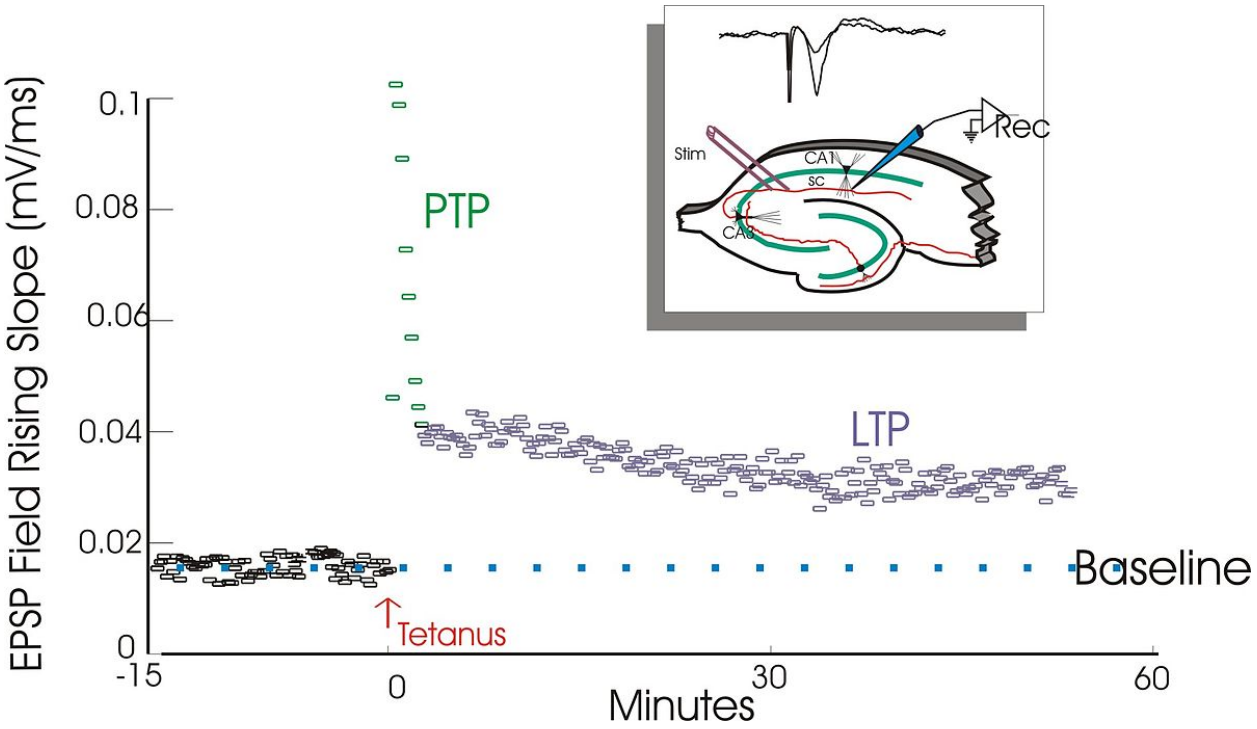
- A before B: strengthen A->B
- A after B: weaken A->B
-
    - Lasting changes in neural firing, connectivity
- NMDA receptor molecular mechanism for implementing LTP and spike-timing-dependent plasticity

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 & Lømo, 1973)

- Granule cell neurons in hippocampus dentate gyrus (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

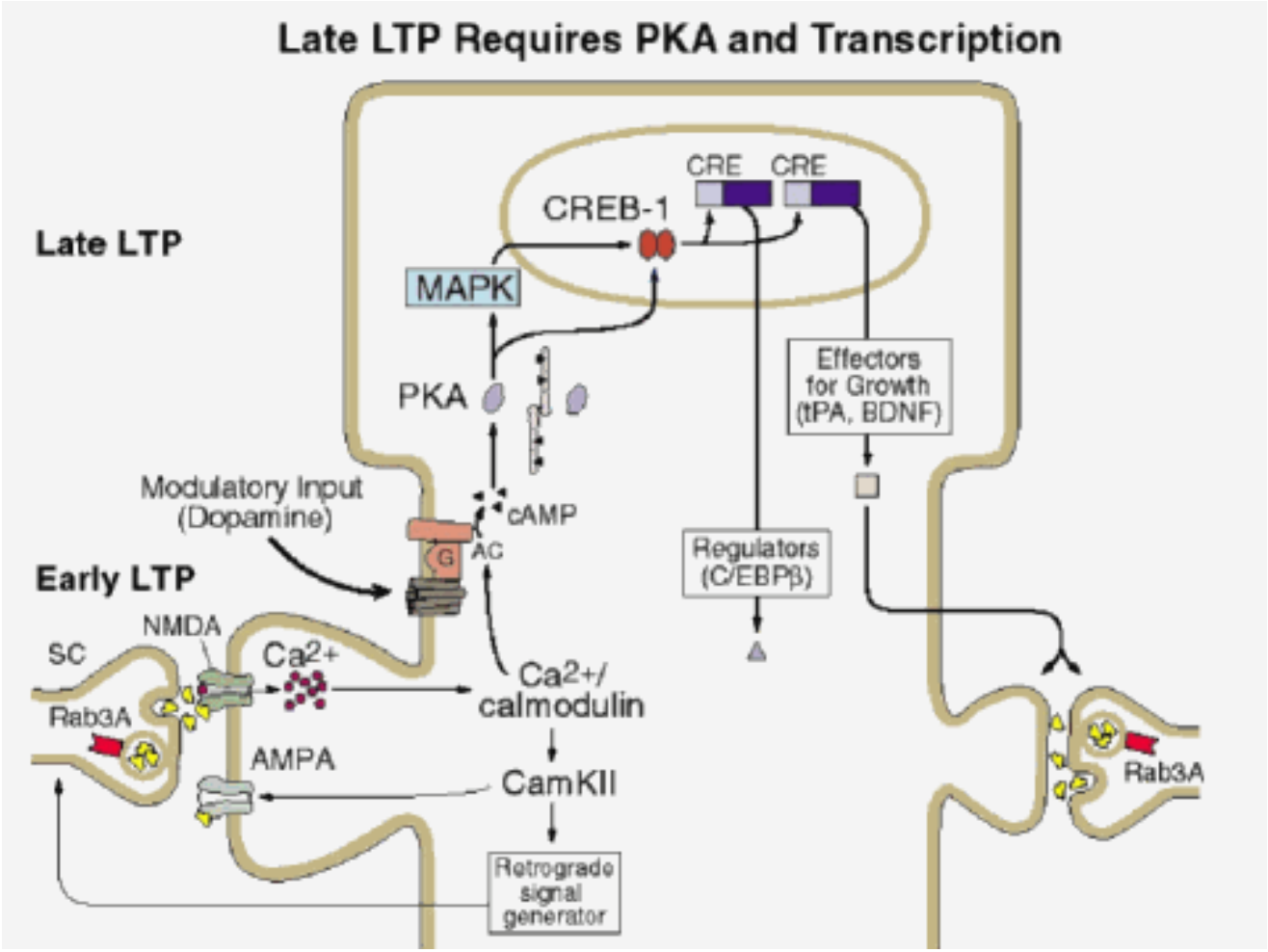

EPSP Field Rising Slope (mV/ms)
0.1
0.08
0.06
0.04
0.02
0
PTP
LTP
Baseline
Tetanus
-15
0
30
60
Minutes
Stim
Rec
CA1
SC
CA3

Mechanisms of LTP plasticity

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

Pathways to plasticity

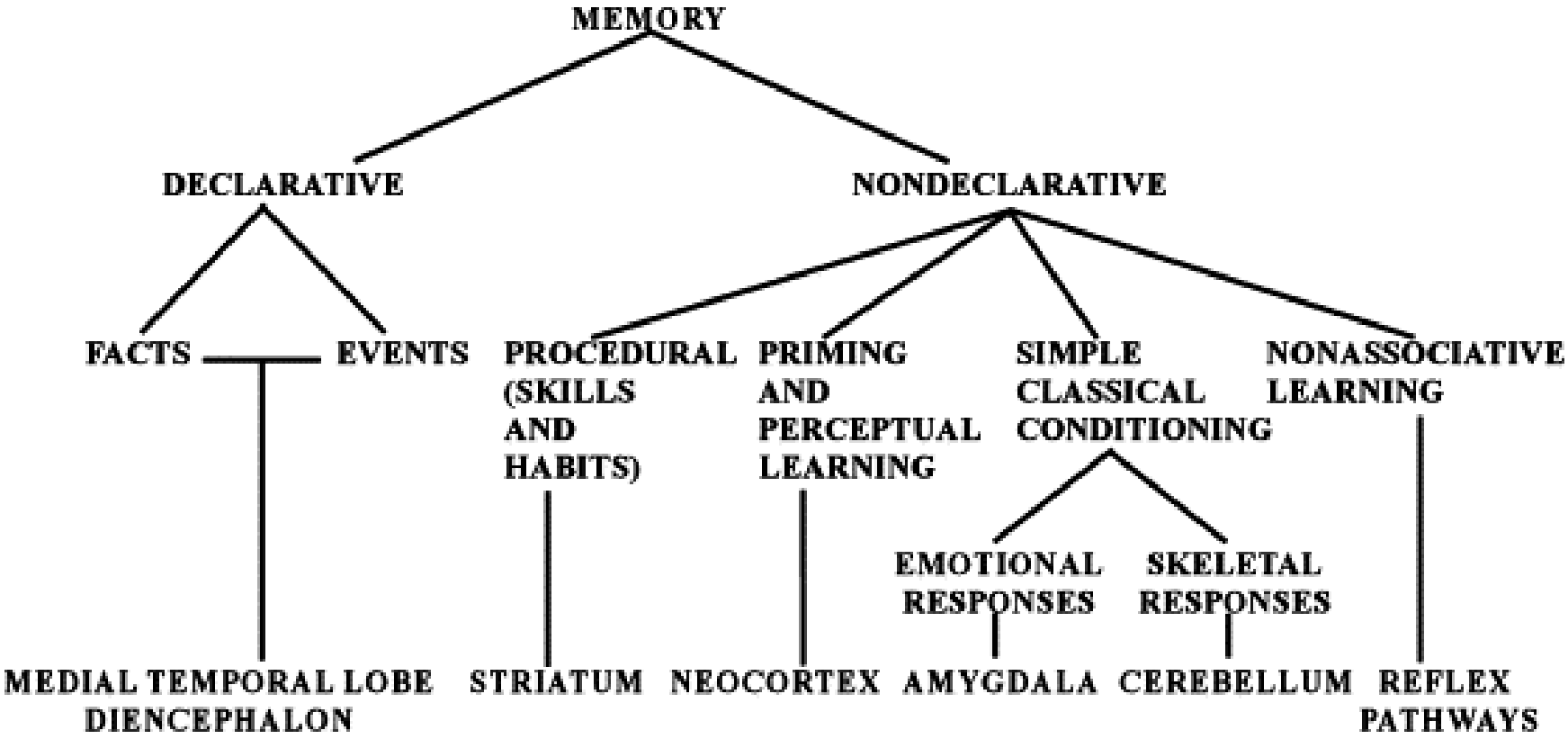
- Ca^{++} entry activates protein kinases (CaMKII and PKAII)
- Early LTP
  - protein kinases (add P group to) postsynaptic AMPA receptors
  - Increased current flow through AMPA (glu) receptors
- Late LTP
  - insertion of new receptors into membrane
- Retrograde signal generator influences presynaptic 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, Goñi, Betzel, Sporns, & McIntosh, 2014)

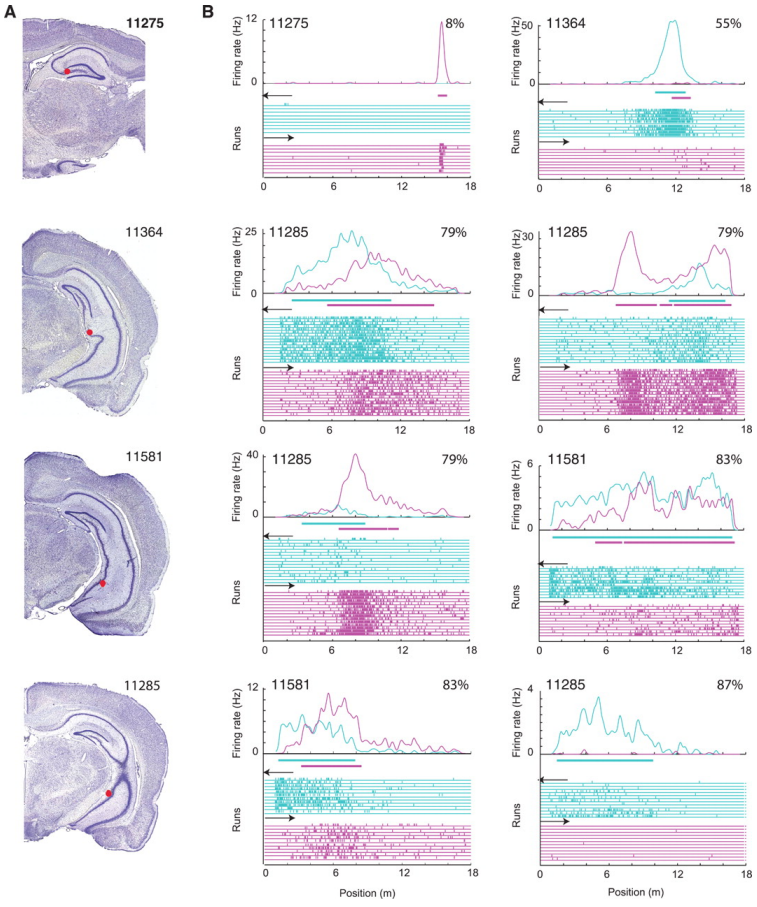
Hippocampus roles

- 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

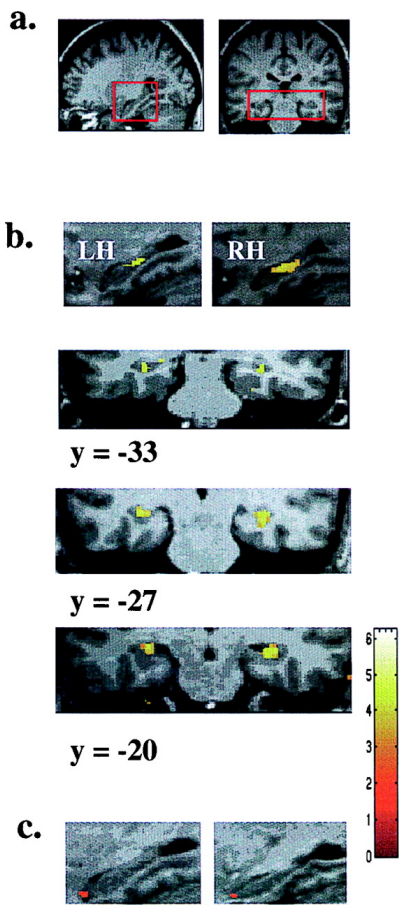
- Spatial navigation
  - Place cells
  - Grid cells
  - Head-direction cells

Spatial precision of place cells



(Kjelstrup et al., 2008)

Human analogue – (Maguire et al., 2000)



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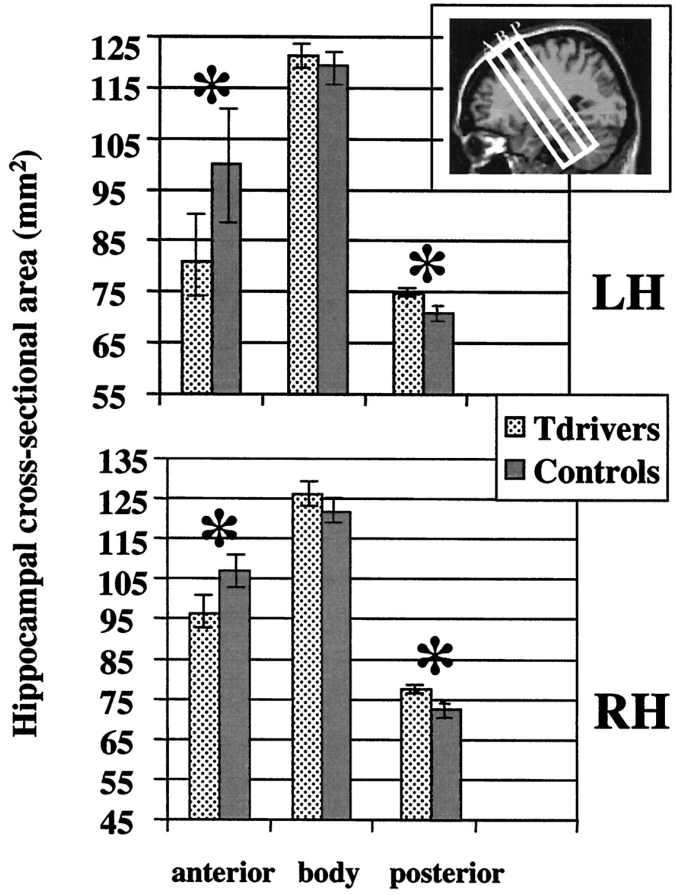

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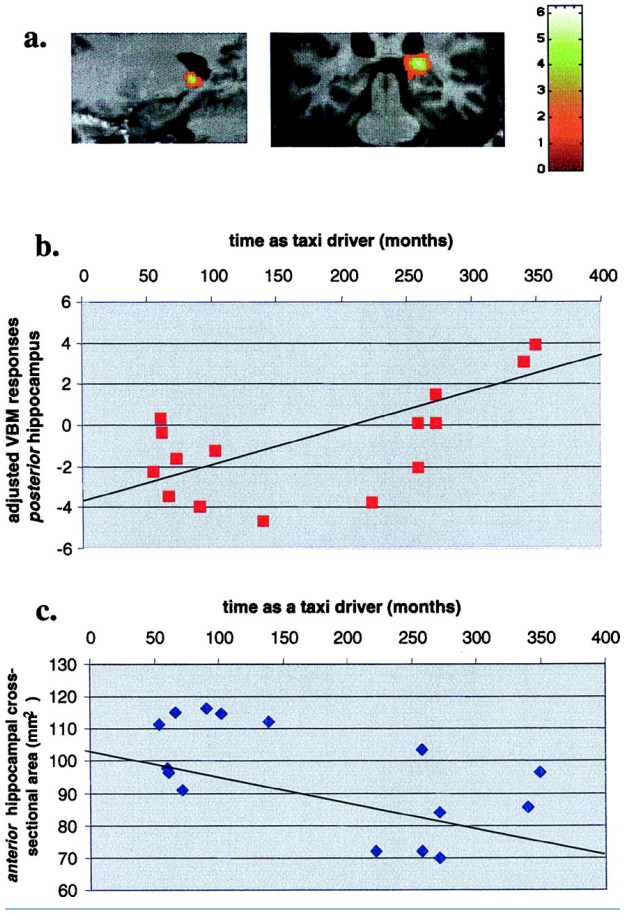


(Maguire et al., 2000)

Hippocampal volume in food-caching birds

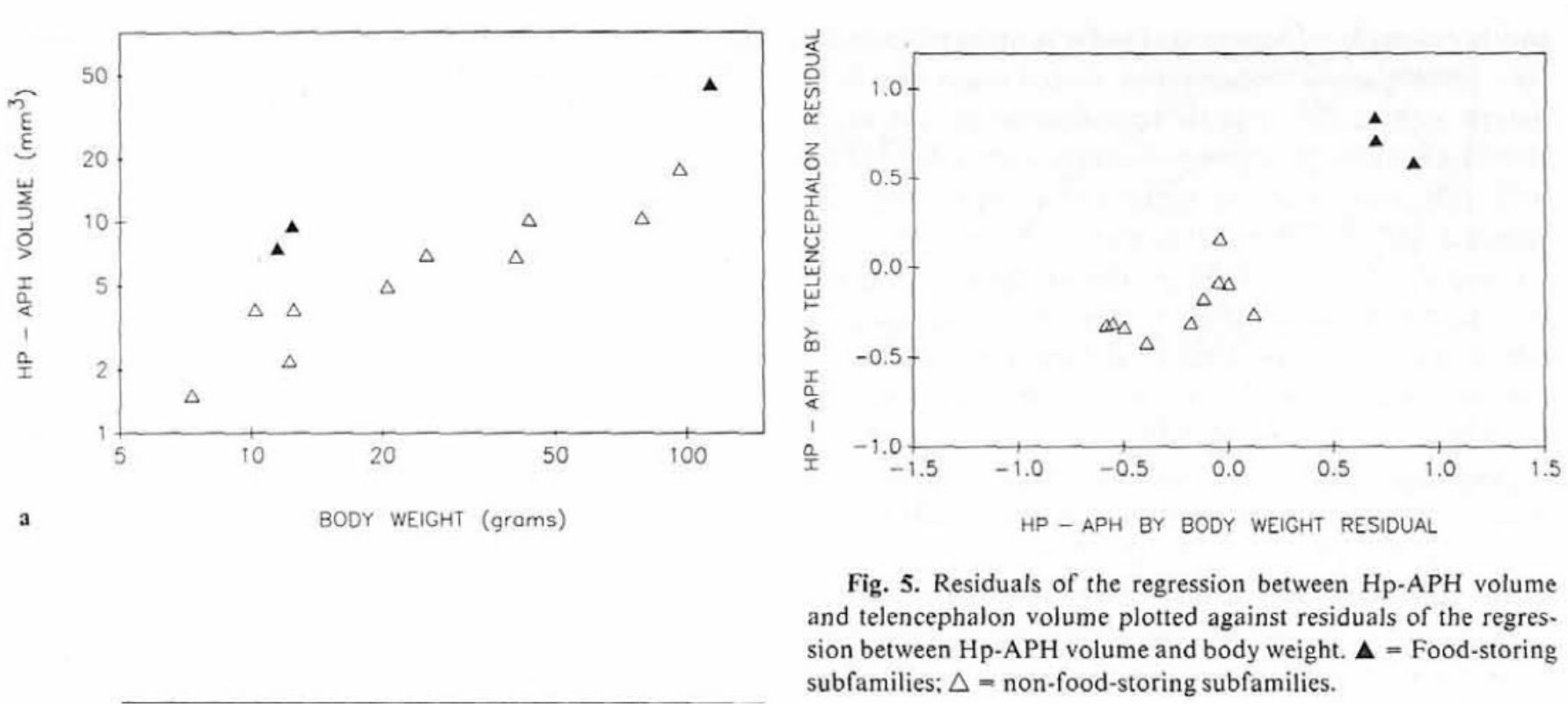


Fig. 5. Residuals of the regression between Hp-APH volume and telencephalon volume plotted against residuals of the regression between Hp-APH volume and body weight. ▲ = Food-storing subfamilies; △ = non-food-storing subfamilies.

(Sherry, Vaccarino, Buckenham, & Herz, 1989)

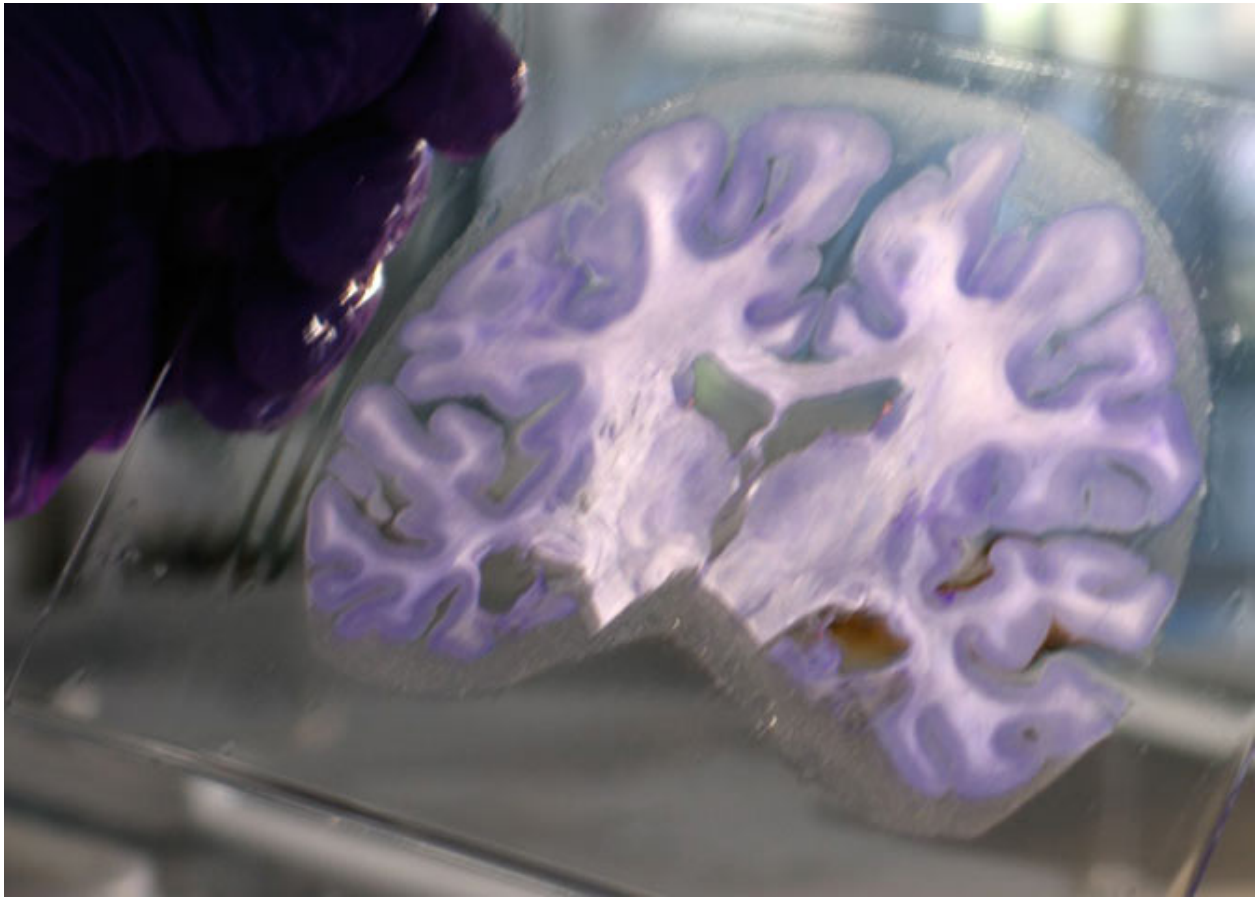
Disorders of memory

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

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

What it's like

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

Spared skills in amnesia

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

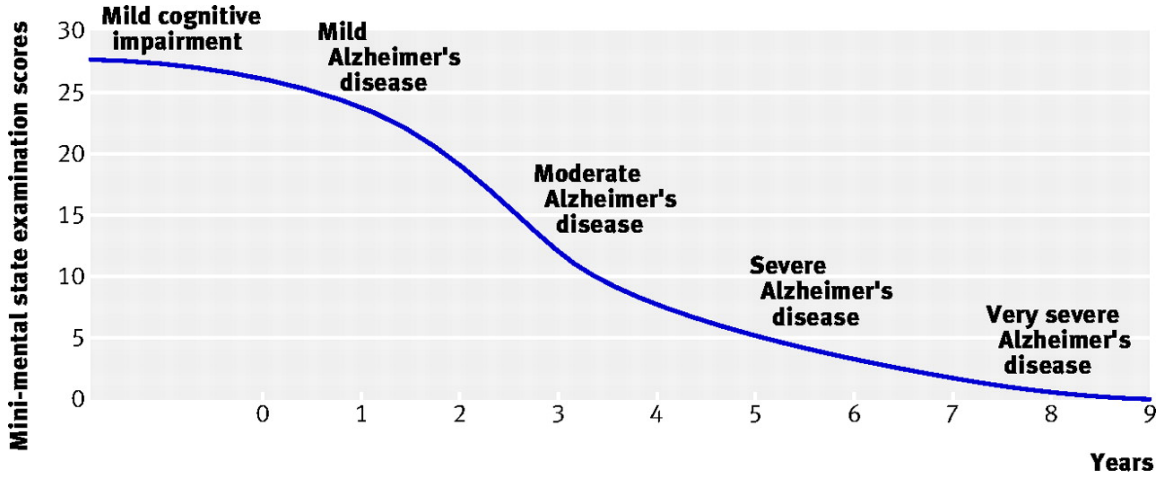
What does amnesia tell us?

- 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 & 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

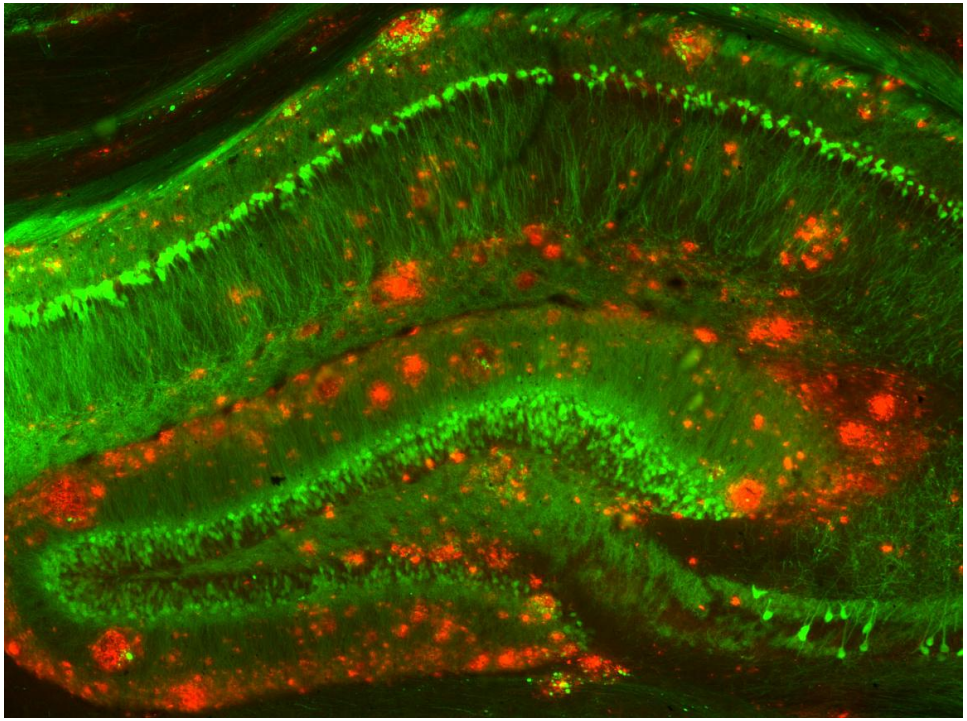
Severe Alzheimer's disease: Agitation, altered sleep patterns, assistance required in dressing, feeding, bathing, established behavioural and psychological symptoms of dementia

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

(Burns & Iliffe, 2009)

AD

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



AD treatments include

- Acetylcholinesterase (AChE) inhbitors (e.g. Aricept)
- NMDA-R partial antagonists (e.g., Memantine)
- Drugs that address amyloid β don't work especially well
- AD the result of disordered immune response?

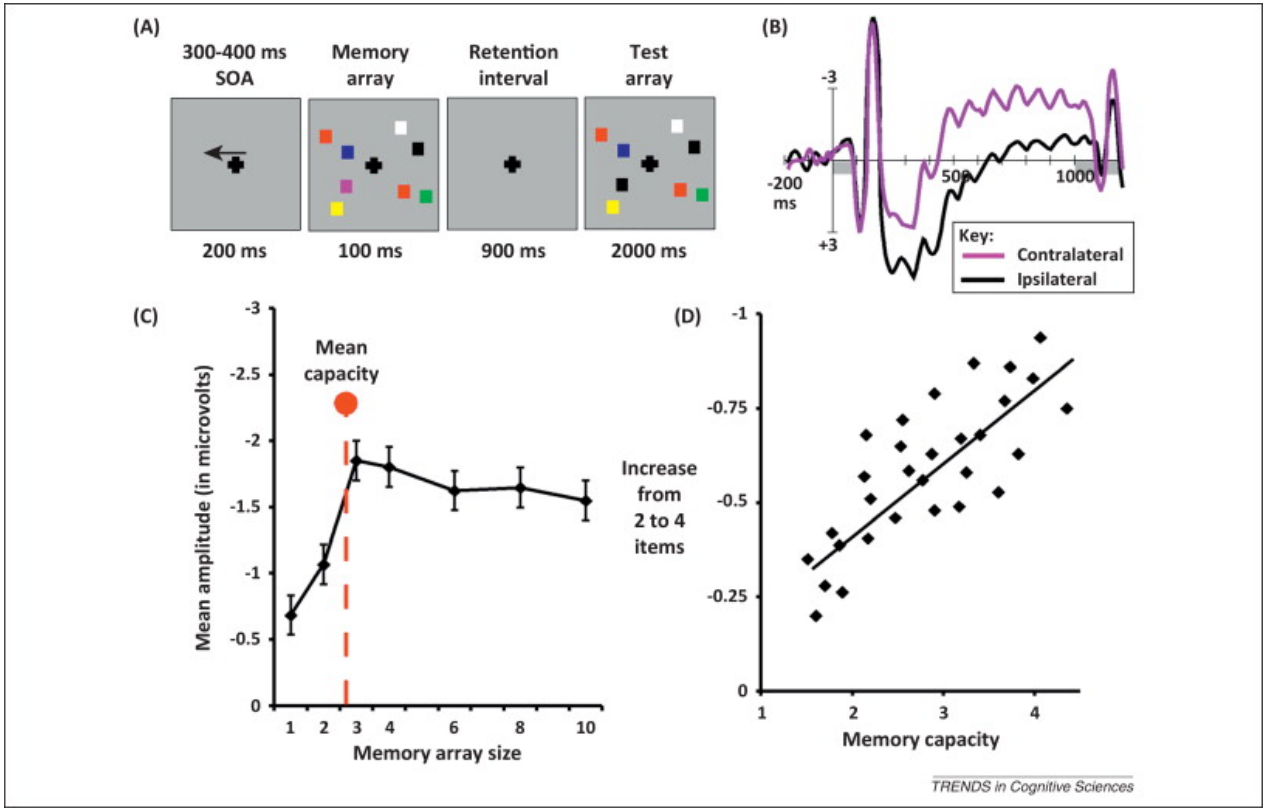
What about working memory? (D'Esposito & Postle, 2015)

- 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 & Postle, 2015)

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

Individual differences in visual WM (Luck & 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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