511-memory

CODE

Rick Gilmore

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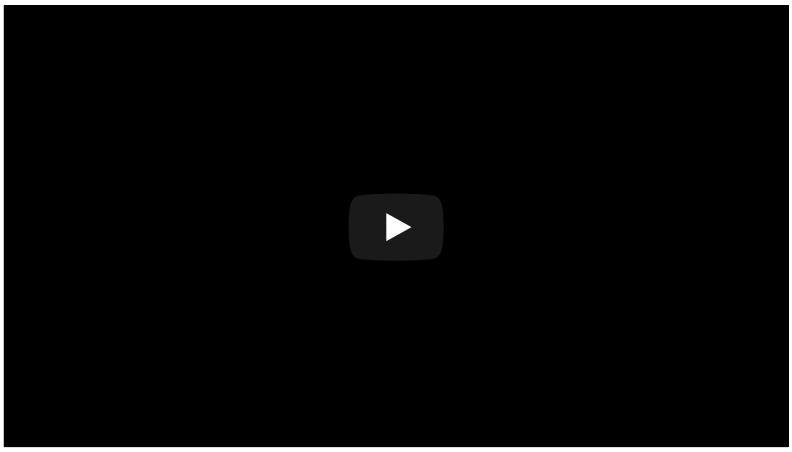
- Fun
- Big picture questions
  - Memory capacity of the human brain?
  - What is learning?
  - What is memory?
  - Are there different types of memory?
  - How do computers and brains compare?
- Biological bases of memory
  - Donald Hebb's Insight
  - Long-term potentiation (LTP) as model of Hebbian learning
    - LTP discovery (Bliss & Lømo, 1973)
    - Mechanisms of LTP plasticity
  - Pathways to plasticity
  - 'Hebbian' learning via NMDA receptor
    - NMDA clinical significance
  - Spike-timing-dependent plasticity
- Memory systems
  - Lashley's search for the 'engram'
  - Modern views
  - Hippocampus
  - Cerebellum
  - Disorders of memory
    - Amnesia
      - Patient HM (Henry G. Molaison)
      - HM's amnesia
      - Other causes of amnesia
      - Patient NA
      - Spared skills in amnesia
      - What does amnesia tell us?
    - Alzheimer's Disease (AD)
      - Progression
      - Treatments
    - The other end of the spectrum…
  - What about working memory? (D'Esposito & Postle, 2015)
- Summary
- References

Fun



Big picture questions

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

What is learning?

https://theelearningcoach.com/learning/10-definitions-learning/ (https://theelearningcoach.com/learning/10-definitions-learning/)

> Learning is the process of acquiring new understanding, knowledge, behaviors, skills, values, attitudes, and preferences. https://en.wikipedia.org/wiki/Learning (https://en.wikipedia.org/wiki/Learning)

- **Non-associative**
  - $A(t+1) = f(A(t))$
  - Habituation ($\dot{f} < 0$), sensitization ($\dot{f} > 0$)
- **Associative**
  - $A \rightarrow B$
  - Classical & operant/instrumental conditioning
  - Sequence, observational, episodic, semantic…learning

What is memory?

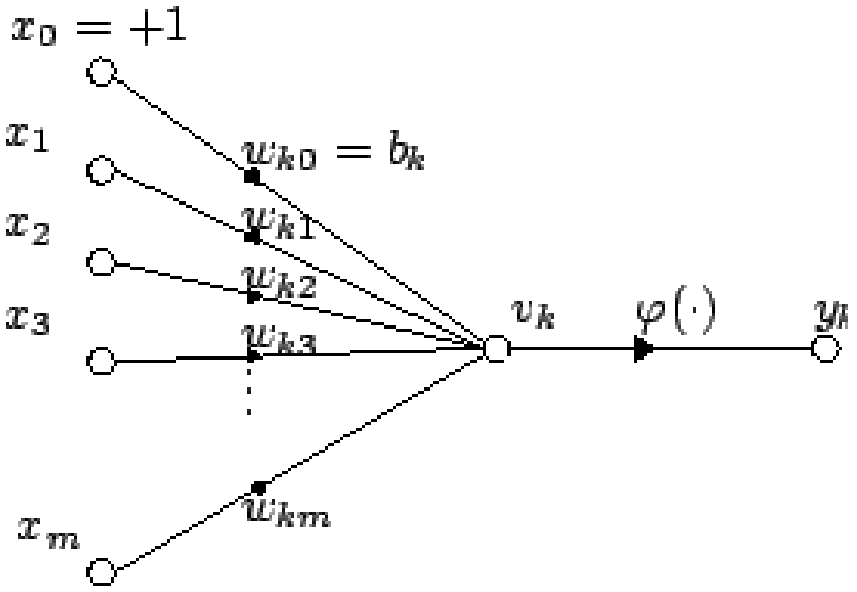
- A: Information encoding, storage, retrieval

Are there different types of memory?

- Facts/events/places/feelings vs. skills
- 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 (judgment of familiarity or novelty) vs. recall

How do computers and brains compare?

Computers	Brains
Computers have separate memory and processing stores	Brains store info everywhere, but there are specialized regions
Computer memory has specific addresses	Brains store in distributed networks
Computer memory is (usually) non-volatile	Memories in brains naturally fade
Computer memory stores all types of information–images, sounds, text, data–as binary sequences, e.g., `01101110`	Human memory stores all types of information in patterns of synaptic connections and ???
Computers render these sequences differently based on information about the *type* of data stored	Brains retrieve or recall different forms of information based on ???
Digital computers were inspired by mathematical models of neurons	Neurons can be simulated by mathematical models implemented in computers



McCulloch-Pitts artificial neuron (https://en.wikipedia.org/wiki/Artificial_neuron)

Biological bases of memory

- Changes in patterns of neural activity
- Changes in connectivity
  - New synapses
  - Altered synapses (strengthened or weakened)

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.*"

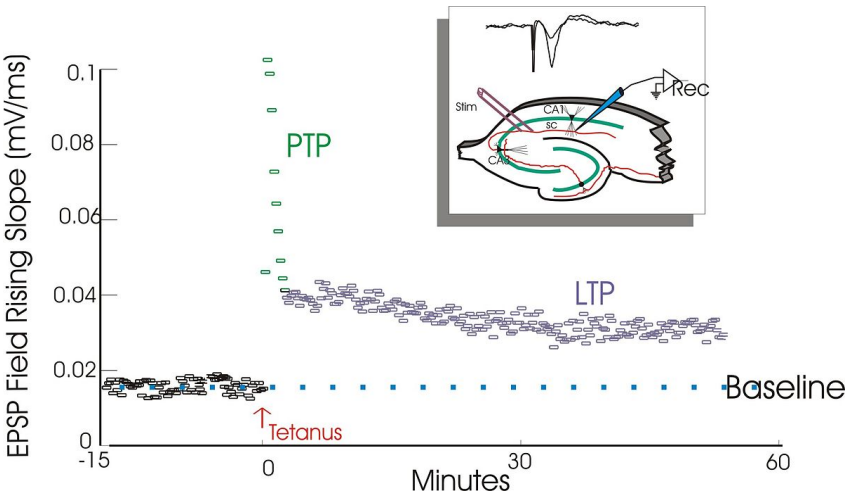
(Lowell & Singer, 1992, p. 211)

Long-term potentiation (LTP) as model of Hebbian learning

> "*a persistent strengthening of synapses based on recent patterns of activity. These are patterns of synaptic activity that produce a long-lasting increase in signal transmission between two neurons.[2] The opposite of LTP is long-term depression, which produces a long-lasting decrease in synaptic strength.*" https://en.wikipedia.org/wiki/Long-term_potentiation (https://en.wikipedia.org/wiki/Long-term_potentiation)

LTP discovery (Bliss & Lømo, 1973) (http://doi.org/10.1113/jphysiol.1973.sp010273/full)

- 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

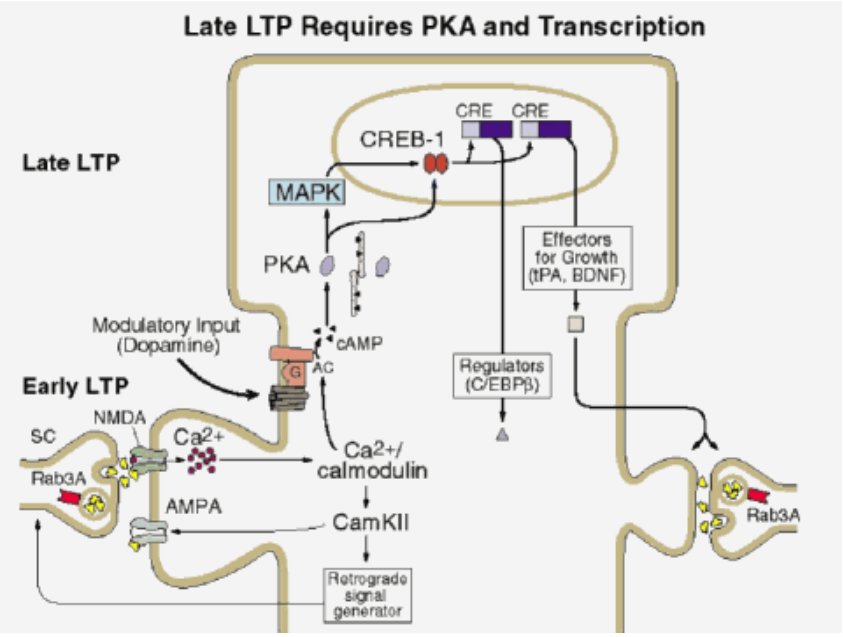


Mechanisms of LTP plasticity

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

Pathways to plasticity

- Glu release activates
  - ionotropic AMPA Glu receptors
  - metabotropic Glu receptors
  - N-methyl-D-aspartate (NMDA) Glu receptors
- Ca^{++} entry via NMDA receptor activates protein kinases (CaMKII and PKAII)
- *Early LTP* (up to few hours)
  - protein kinases *phosphorylate* (add P group to) postsynaptic AMPA receptors
  - Increase current flow through AMPA (Glu) receptors
- *Late LTP*
  - depends on protein synthesis to generate new AMPA receptor
  - insertion of new AMPA receptors into postsynaptic 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

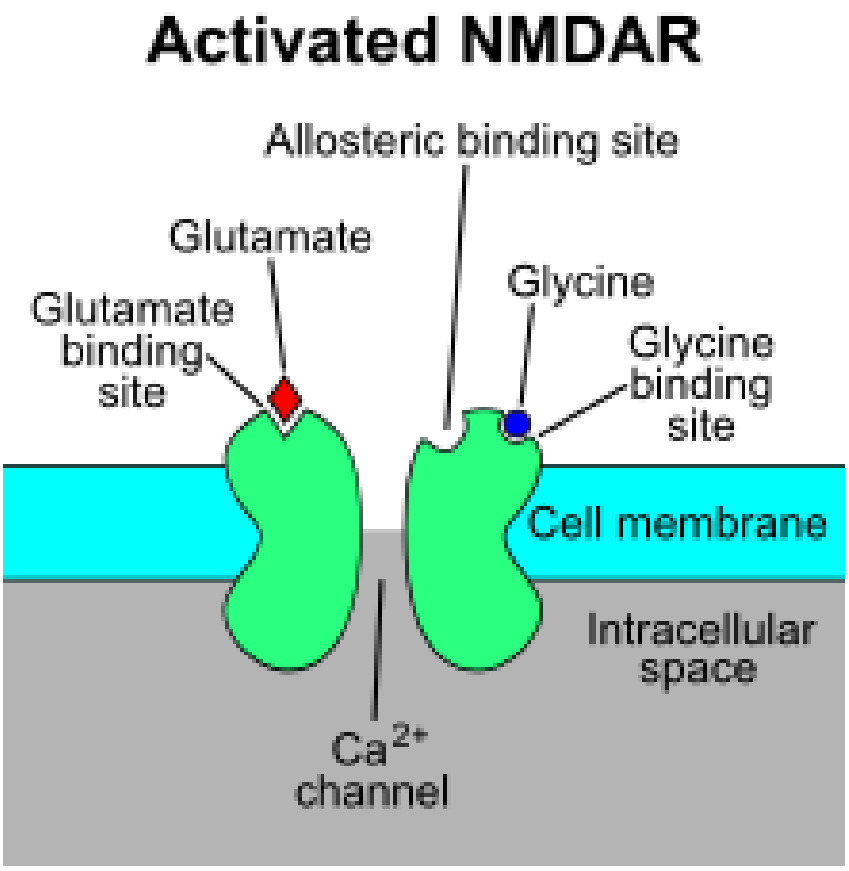
LTP

Eric R. Kandel

‘Hebbian’ learning via NMDA receptor

- *N-methyl-D-aspartate* receptor (NMDA-R) (https://en.wikipedia.org/wiki/NMDA_receptor)
  - Name derived from agonist molecule that selectively binds to the receptor
- ‘Coincidence’ detector
  - Sending cell has released NT
  - Receiving cell is/has been recently active
- 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 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

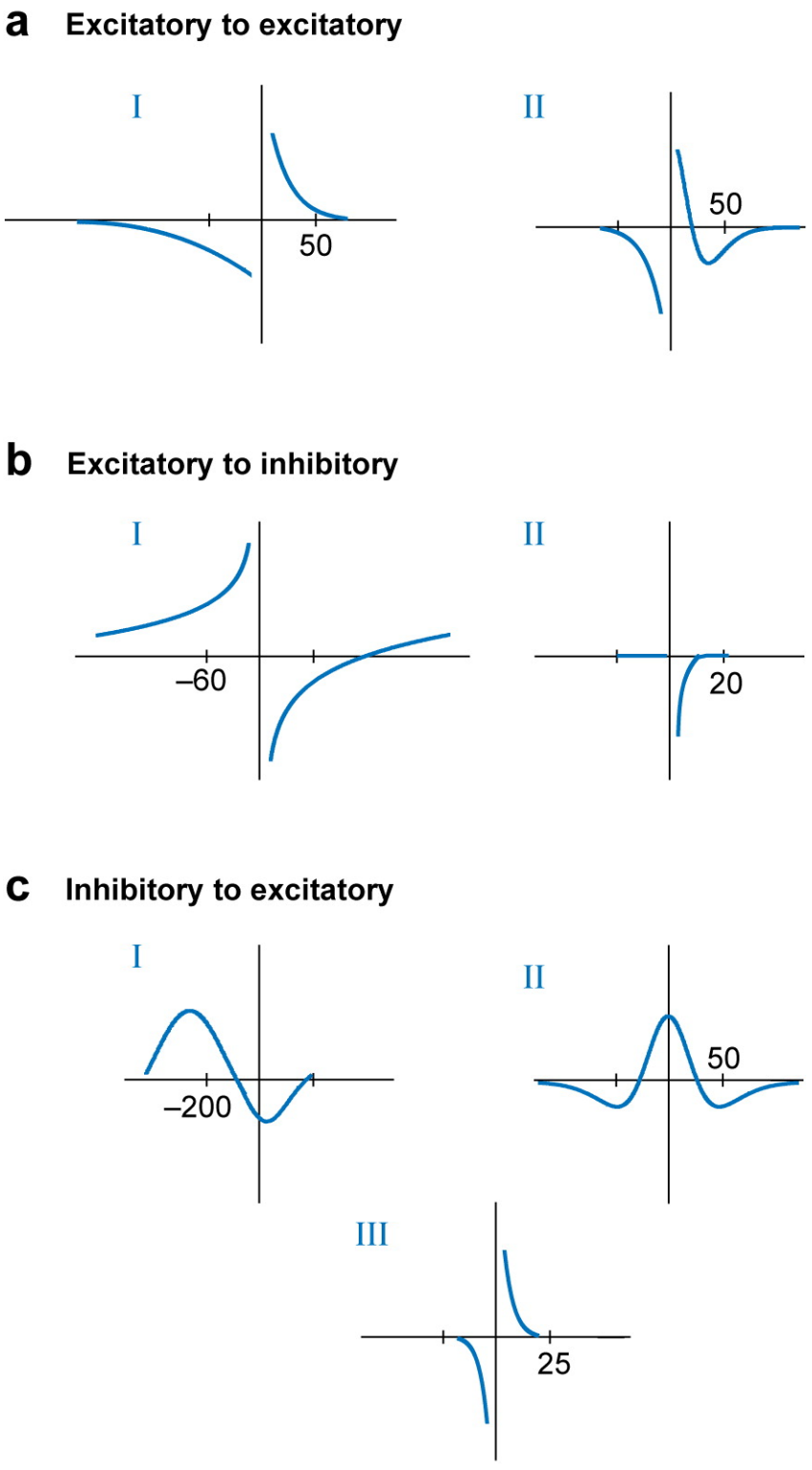
NMDA clinical significance

- *Memantine* (https://medlineplus.gov/druginfo/meds/a604006.html) (Alzheimer's Disease treatment)
  - NMDA-R antagonist
  - Controls over-activation and Ca^{++} excitotoxicity?
- NMDA-R implicated in effects of *phencylidine* (PCP)
  - Link to Glu hypothesis of schizophrenia?
- *Ketamine* is NMDA receptor antagonist
  - anesthesia, sedation pain relief
  - possible short-term relief for depression
- Linked to analgesic effects of nitrous oxide (laughing gas; NO)
- Alcohol (ethanol) inhibits (Ron & Wang, 2011) (https://www.ncbi.nlm.nih.gov/pubmed/21204417)

Spike-timing-dependent plasticity

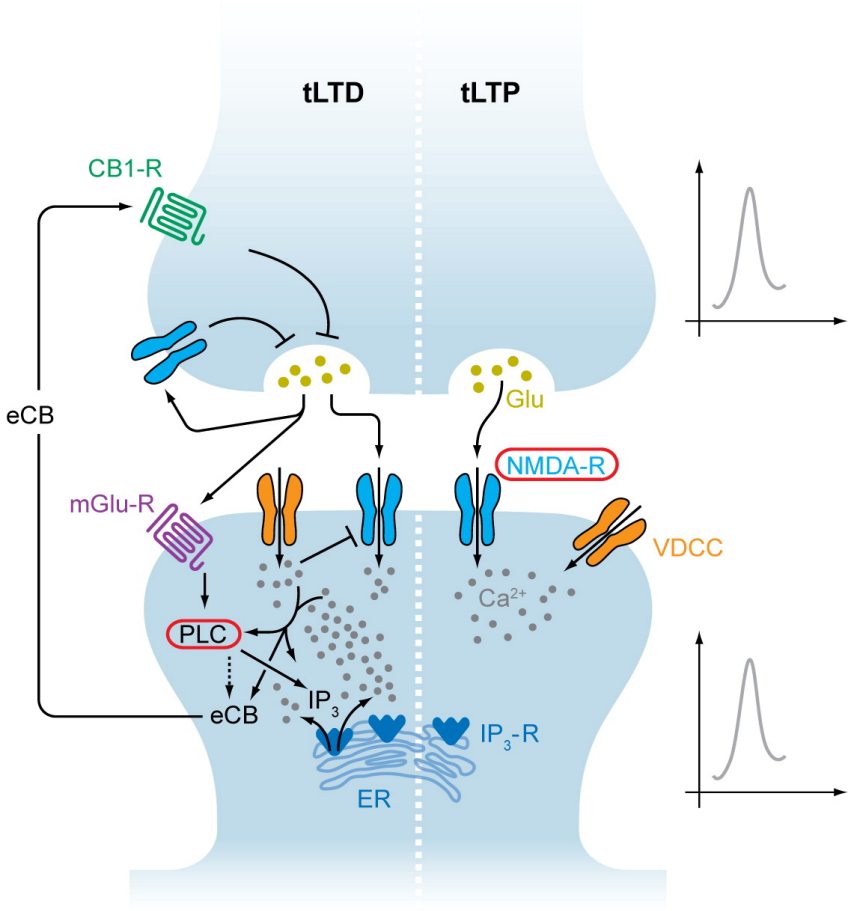
How to learn/remember “causal chains?”

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



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

(Caporale & Dan, 2008) (http://dx.doi.org/10.1146/annurev.neuro.31.060407.125639)



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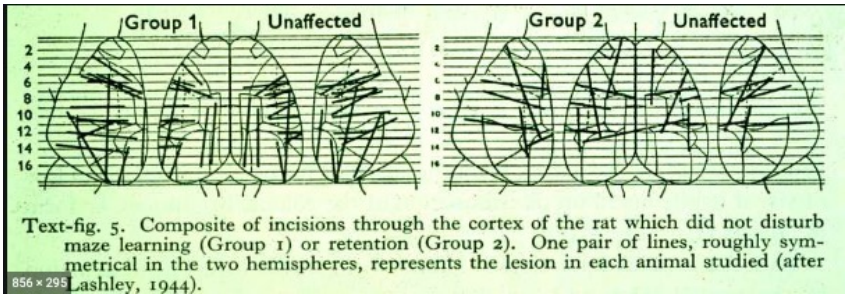
(Caporale & Dan, 2008) (http://dx.doi.org/10.1146/annurev.neuro.31.060407.125639)

- A before B: strengthen $A \rightarrow B$
- A after B: $A \rightarrow B$
- *Neural Plasticity* (https://en.wikipedia.org/wiki/Neuroplasticity)
  - Lasting changes in neural firing, connectivity
- NMDA receptor a molecular mechanism for implementing LTP and spike-timing-dependent plasticity

Memory systems

Lashley's search for the 'engram' (https://en.wikipedia.org/wiki/Engram_(neuropsychology))

- Is memory 'localized' like sensory and motor functions? (Karl S. Lashley, 1944) (https://doi.org/10.1002/cne.900800207)



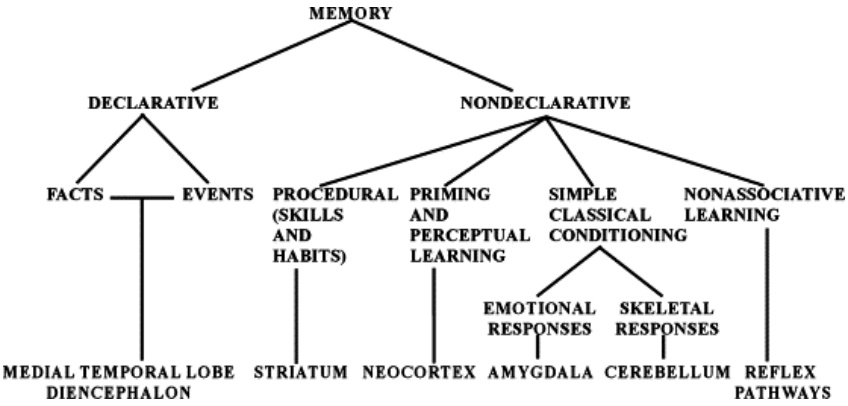
Text-fig. 5. Composite of incisions through the cortex of the rat which did not disturb maze learning (Group 1) or retention (Group 2). One pair of lines, roughly symmetrical in the two hemispheres, represents the lesion in each animal studied (after Lashley, 1944).

> “*“the area subdivisions are in large part anatomically meaningless and misleading as to the presumptive functional divisions of the cortex”*”

(K. S. Lashley & Clark, 1946) (http://dx.doi.org/10.1002/cne.900850207)

Modern views

- Cerebral cortex less central to “engram-like” memory than other areas



(Squire, 2004) (http://dx.doi.org/10.1016/j.nlm.2004.06.005)

Hippocampus

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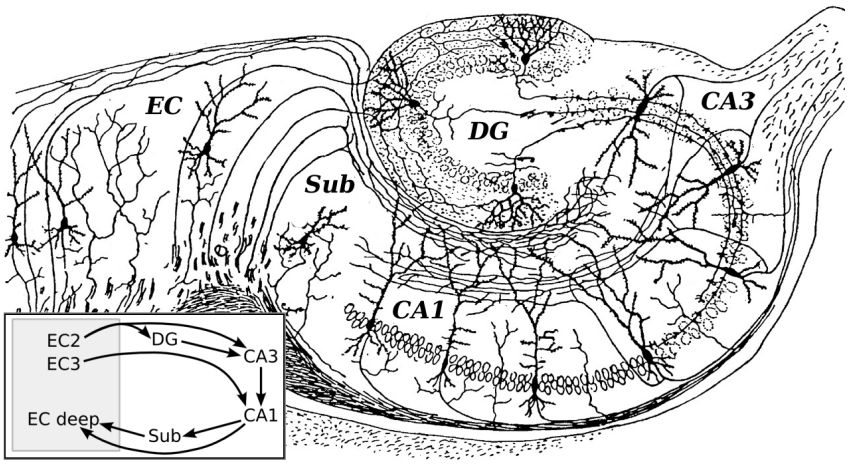
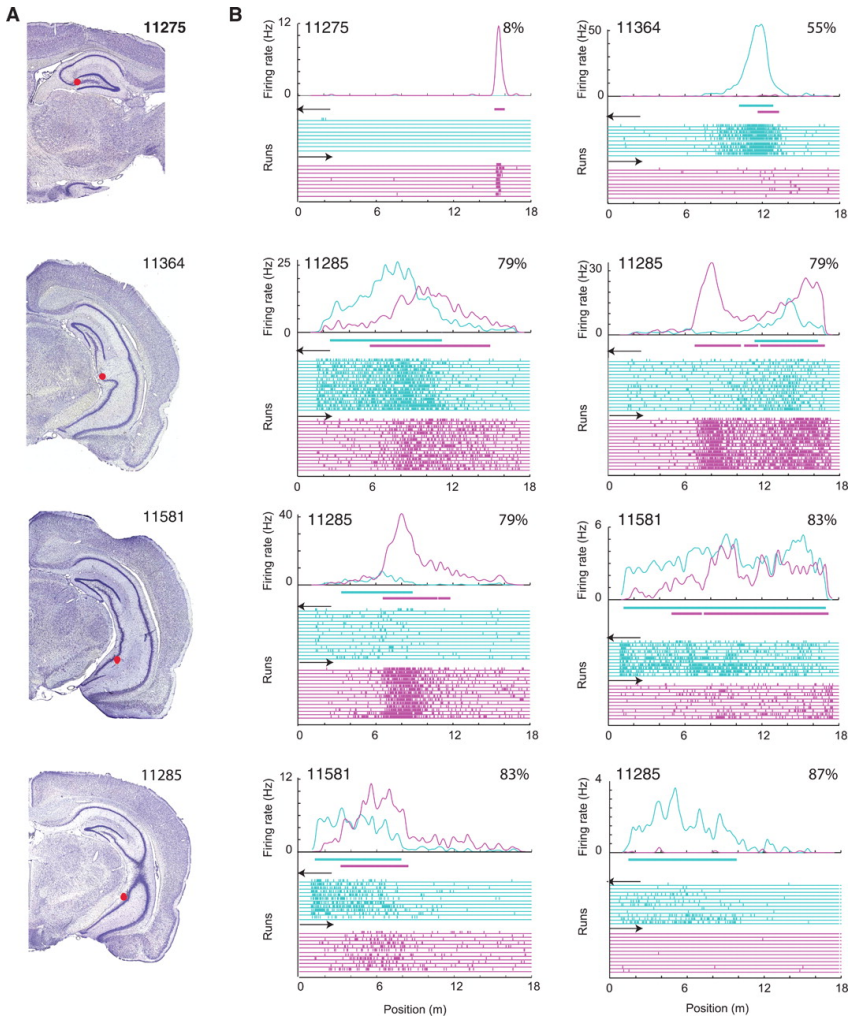
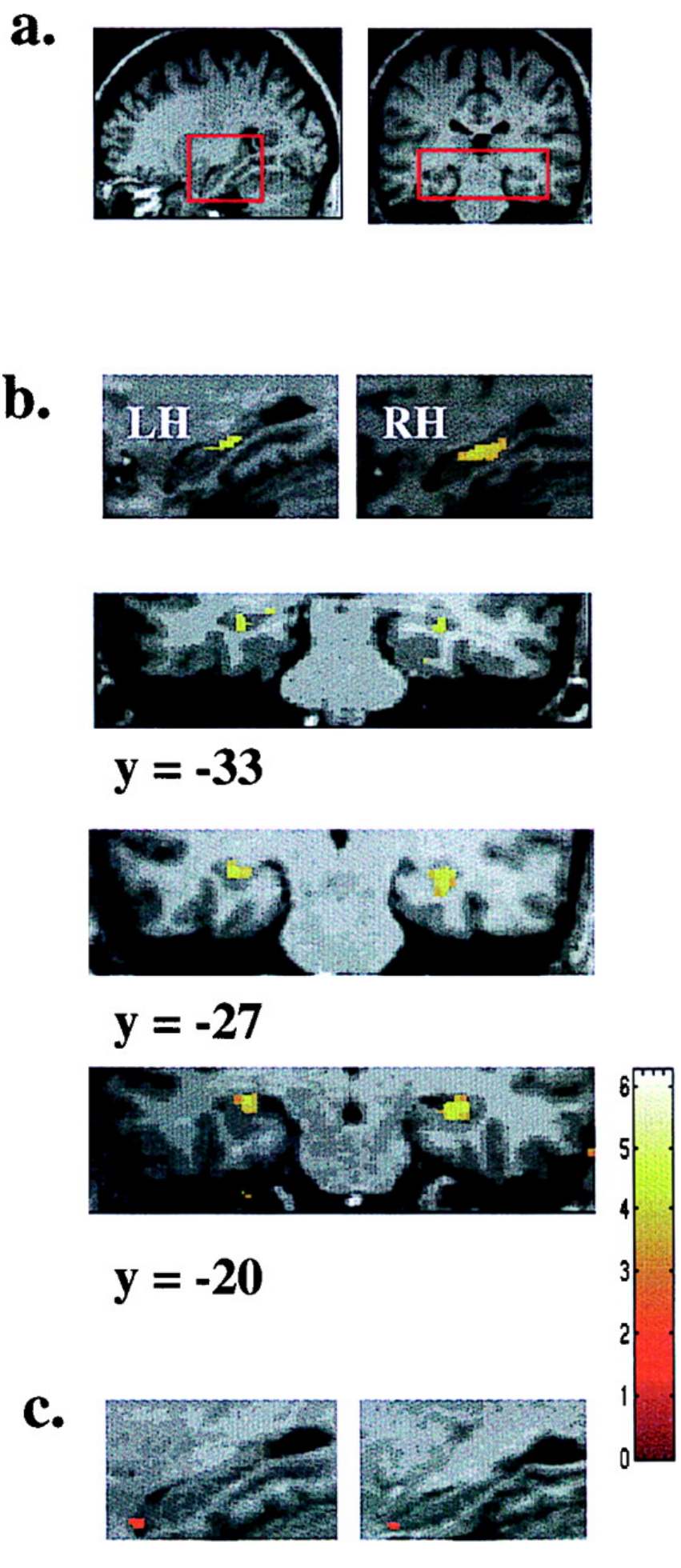


Santiago Ramon Y Cajal; Source: Wikipedia

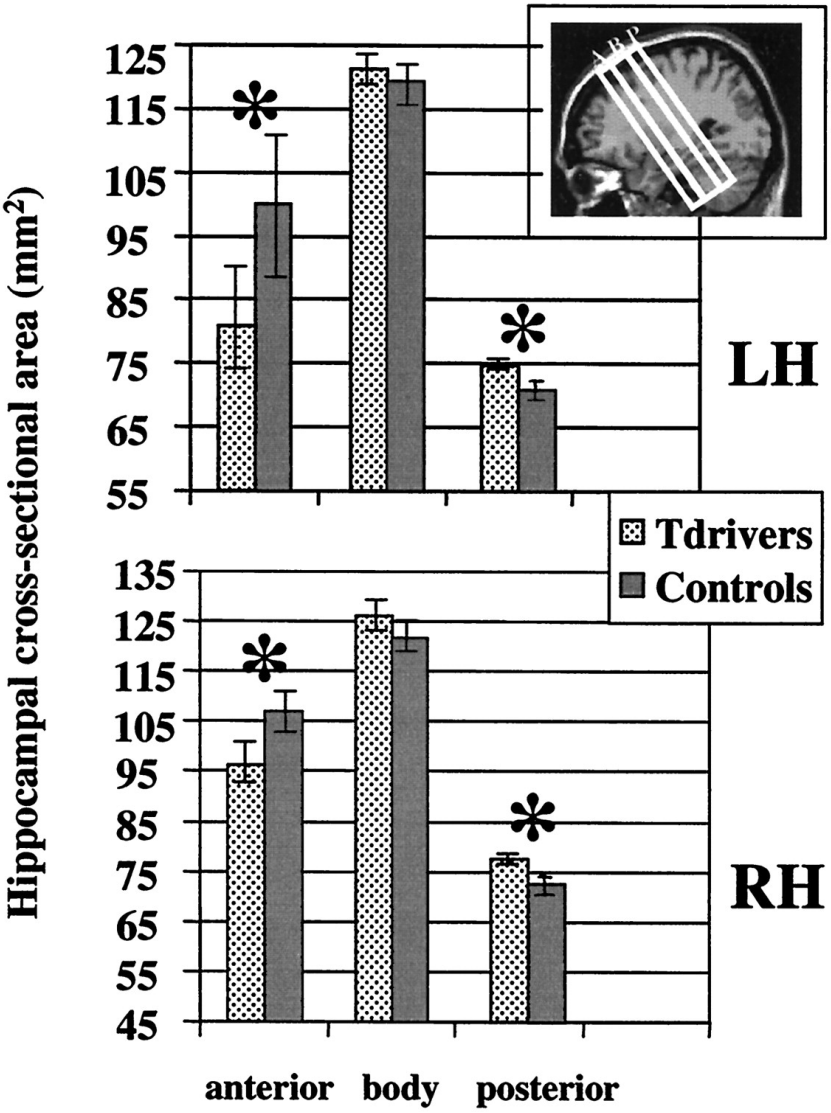
- Dense in NMDA receptors
- Central “hub” in network?
  - No, based on anatomical or functional connectivity
  - But yes, when modeling “information flow” (Mišić, Goñi, Betzel, Sporns, & McIntosh, 2014) (http://doi.org/10.1371/journal.pcbi.1003982)
- Formation, storage, consolidation of long-term episodic 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) (http://doi.org/10.1126/science.aam6808)
- Spatial navigation
  - Place cells (https://en.wikipedia.org/wiki/Place_cell)
  - Grid cells (http://www.scholarpedia.org/article/Grid_cells)
  - Head-direction cells (http://www.scholarpedia.org/article/Head_direction_cells)



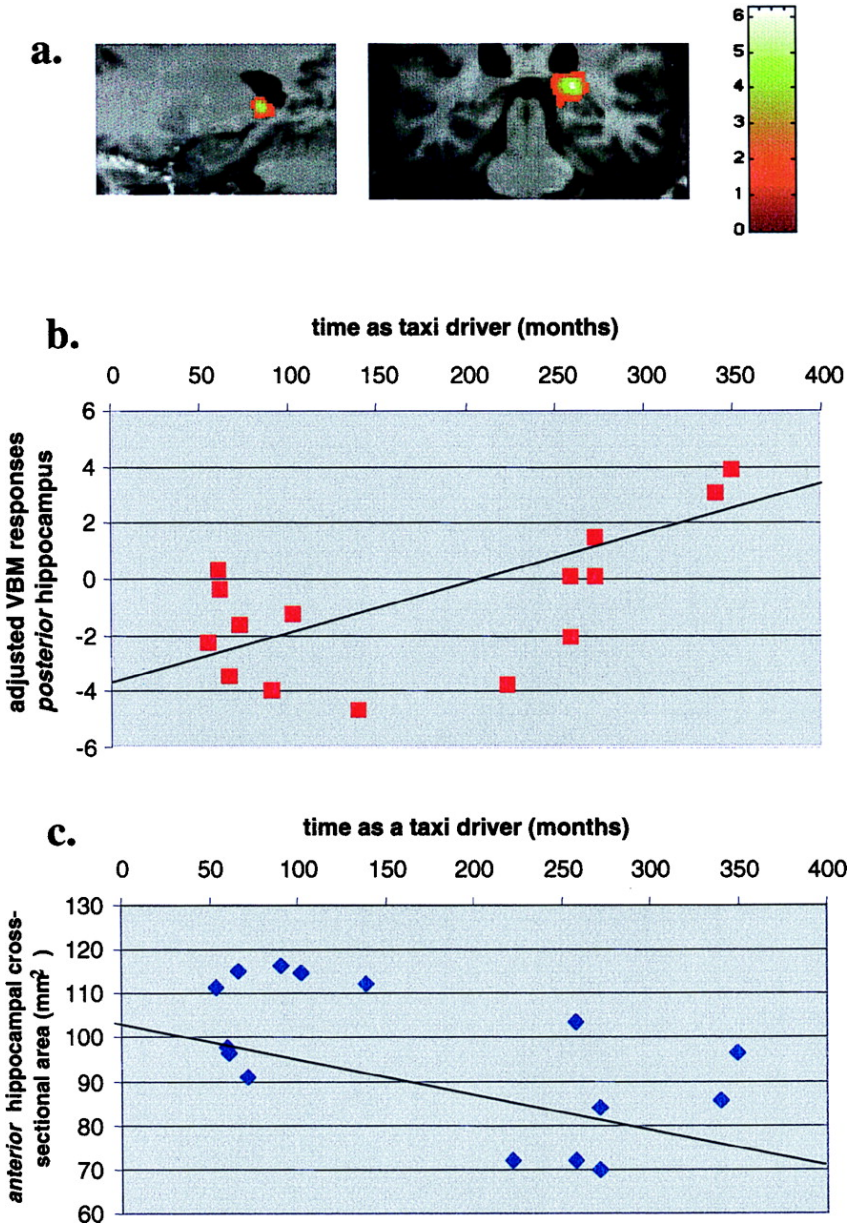
(Kjelstrup et al., 2008) (http://dx.doi.org/10.1126/science.1157086)


a.
b.
LH
RH
y = -33
y = -27
y = -20
c.
6
5
4
3
2
1
0

(Maguire et al., 2000) (http://dx.doi.org/10.1073/pnas.070039597)



(Maguire et al., 2000) (http://dx.doi.org/10.1073/pnas.070039597)



(Maguire et al., 2000) (http://dx.doi.org/10.1073/pnas.070039597)

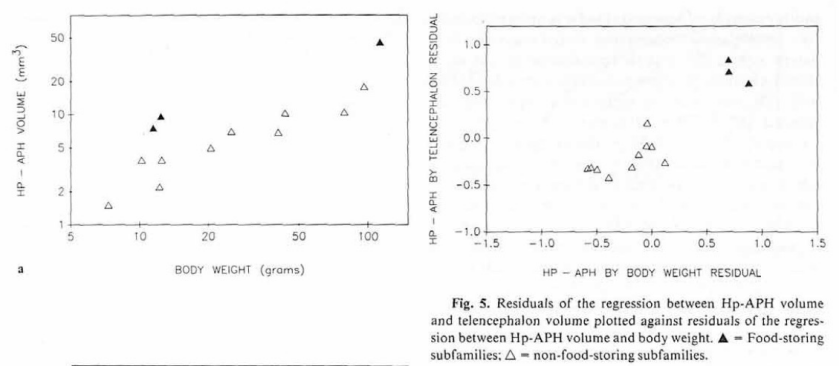


Fig. 5. Residuals of the regression between Hp-APH volume and telencephalon volume plotted against residuals of the regression between Hp-APH volume and body weight. ▲ = Food-storing subfamilies; △ = non-food-storing subfamilies.

(Sherry, Vaccarino, Buckenham, & Herz, 1989) (http://dx.doi.org/10.1159/000116516)

- (Gilmore's view) Humans have repurposed hippocampal system for other cognitive uses, e.g., semantic memory, language

Cerebellum

- response timing, sequences, especially in classical conditioning paradigms (Jirenhed, Rasmussen, Johansson, & Hesslow, 2017) (http://dx.doi.org/10.1073/pnas.1621132114)

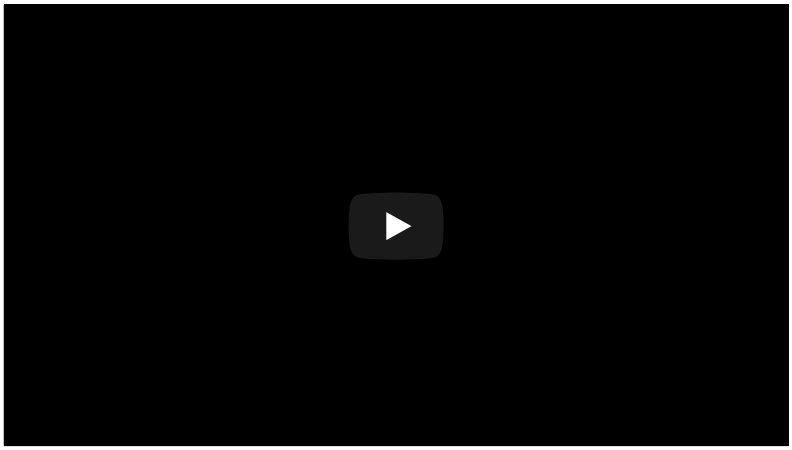
Disorders of memory

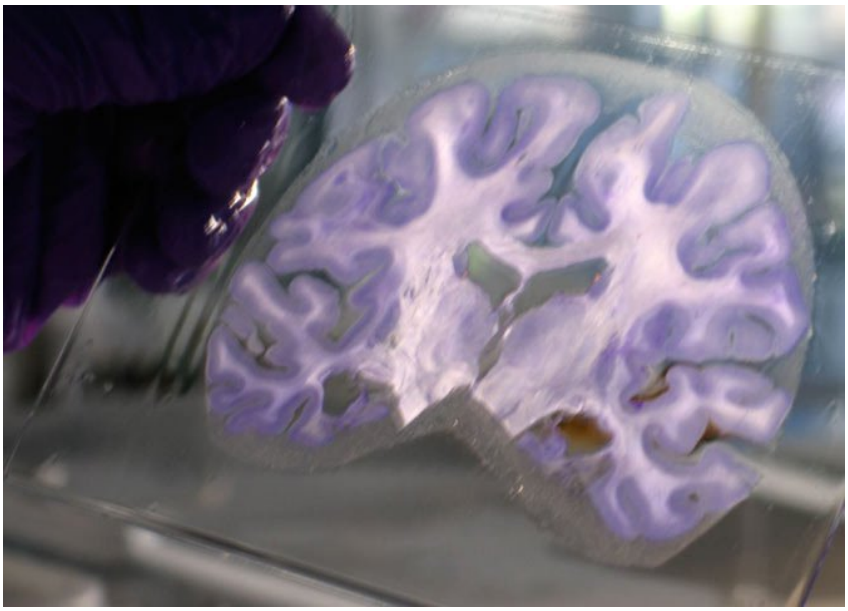
Amnesia

- Acquired loss of memory
- ≠ normal forgetting
- Retrograde (‘backwards’ in time)
  - Damage to information acquired pre-injury
  - Temporally graded
- Anterograde (‘forward’ in time)
  - Damage to information acquired/experienced post-injury

Patient HM (https://www.pbs.org/wgbh/nova/article/corkin-hm-memory/) (Henry G. Molaison)

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



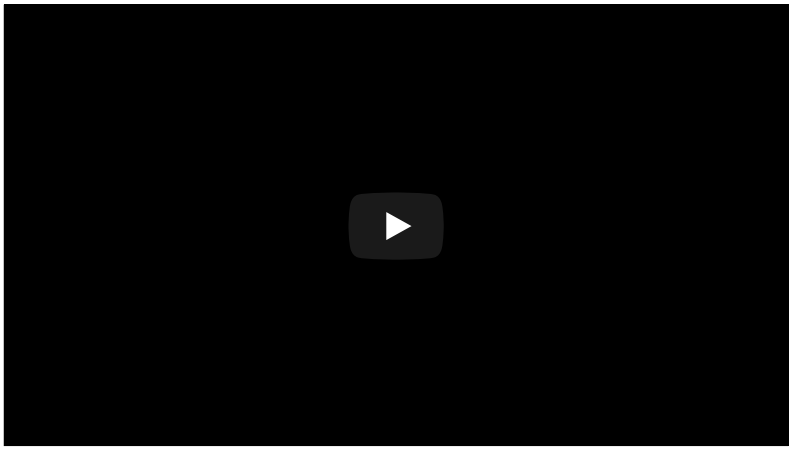


https://www.pbs.org/wgbh/nova/article/corkin-hm-memory/ (https://www.pbs.org/wgbh/nova/article/corkin-hm-memory/)

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

> "*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.*"



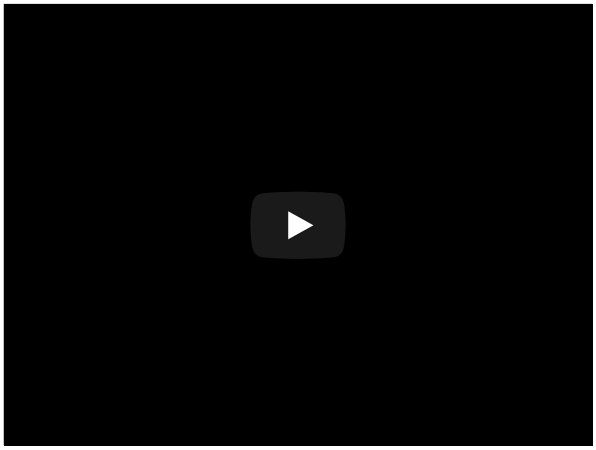
Other causes of amnesia

- Disease

    - Alzheimer's, herpes virus
- Korsakoff's syndrome (https://en.wikipedia.org/wiki/Korsakoff%27s_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?



Spared skills in amnesia

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

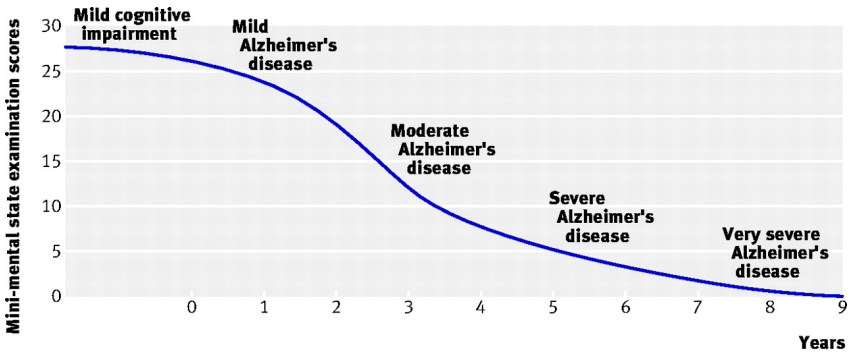
What does amnesia tell us?

- 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) (http://doi.org/10.1136/bmj.b158)

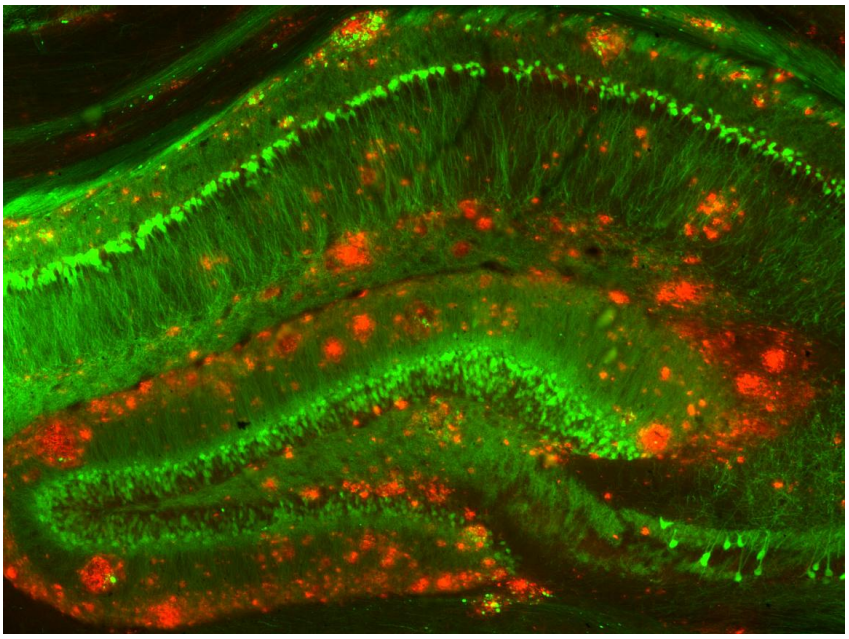
Progression



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) (http://doi.org/10.1136/bmj.b158)

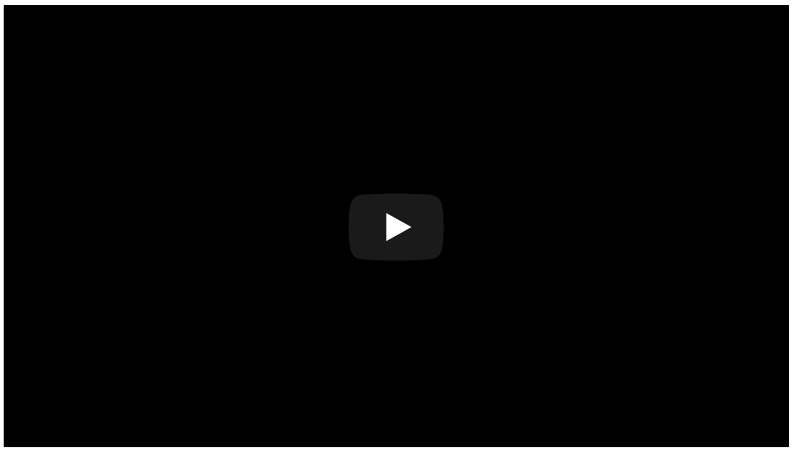
- Post-mortem exams show β amyloid plaques and neurofibrillary tangles



Treatments

- 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 (http://doi.org/10.1016/j.arr.2017.08.005)?

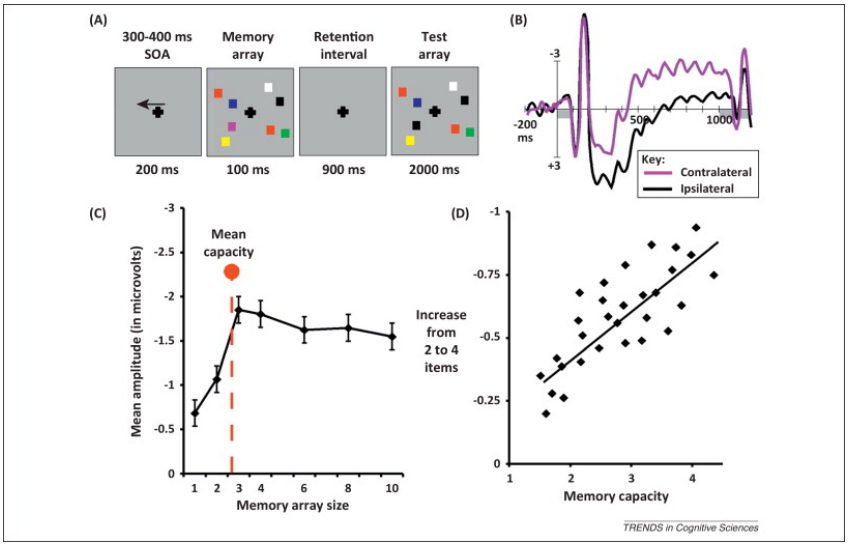
The other end of the spectrum…



What about working memory? (D'Esposito & Postle, 2015) (http://doi.org/10.1146/annurev-psych-010814-015031)

- LTM representations of target items + attention -> elevated activation
  - Semantic items
  - Sensorimotor items
- Capacity for attended items (in Focus of Attention or FoA) limited ~ 4
- Neural basis
  - sustained activation in PFC
  - subthreshold activation in areas where items are stored

Individual differences in visual WM



(Luck & Vogel, 2013) (http://doi.org/10.1016/j.tics.2013.06.006)

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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