Mechanisms of memory

By Hana Brozka

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‘We are like dwarfs sitting on the shoulders of giants. We see more, and things that are more distant, than they did, not because our sight is superior or because we are taller than they, but because they raise us up, and by their great stature add to ours’

John of Salisbury

Outline

What is memory

Episodic memory

History of memory research

Hippocampus

Memory linking

Memory tagging

Brain-wide memory theories

What is memory

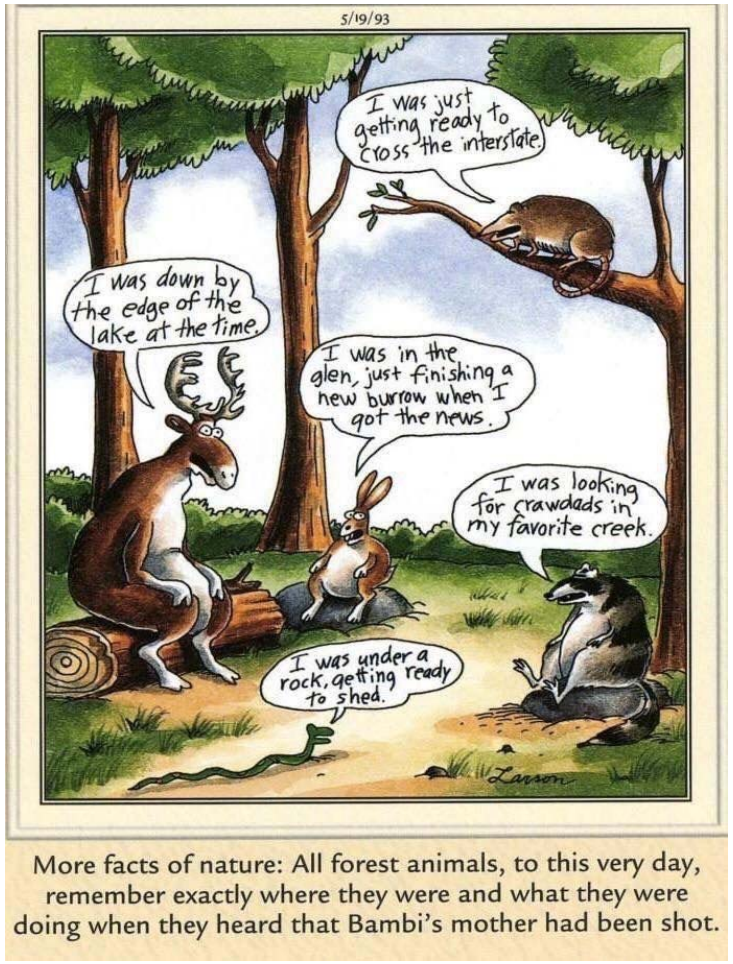
- Ability to retain knowledge
- 3 stage processing model: encoding, storage and retrieval
- Engram = memory trace
  - term for a neural substrate of stored information resulting from a past experience. Usually means set of neurons that are active during memory encoding and retrieval, and when activated they are sufficient to bring back memory
  - ”synaptic engram”

Episodic memory

- Memory of experienced events
- Mental time travel, autonoetic consciousness sense of self, subjective sense of time (Tulving, 1985)
- Do animals posess episodic memory?
- How would you test it?

Behavioral criteria of episodic memory

- What-where-when (or which)
- Integrated content
- Flexibility of behavior
- Incidental learning
- One trial learning
- Unexpected retrieval
- Harnesses long term memory
- Cannot be soved by familiarity
- Free recall
- Threshold retrieval dynamics
- Remember order of things
- Temporal binding



More facts of nature: All forest animals, to this very day, remember exactly where they were and what they were doing when they heard that Bambi's mother had been shot.

History of memory research -Semon

- Richard Wolfgang Semon (1859–1918)
- Started his work with Ernst Haeckel (who coined the phrase “ontogeny recapitulates phylogeny”)
- accomplished zoologist; a species of lizard, the green-blooded skink, Prasinohaema semoni, bears his name (Beolens et al., 2011)
- Had affair with a colleague’s wife, had to resign, and became a private scholar with no university affiliation. He began thinking about memory.
  - Introduced term ‘engram’ as ‘the enduring though primarily latent modification in the irritable substance produced by a stimulus’ - change in a physical substance
  - Learning passed to future generations - dismissed by scientific community (too Lamarckian)

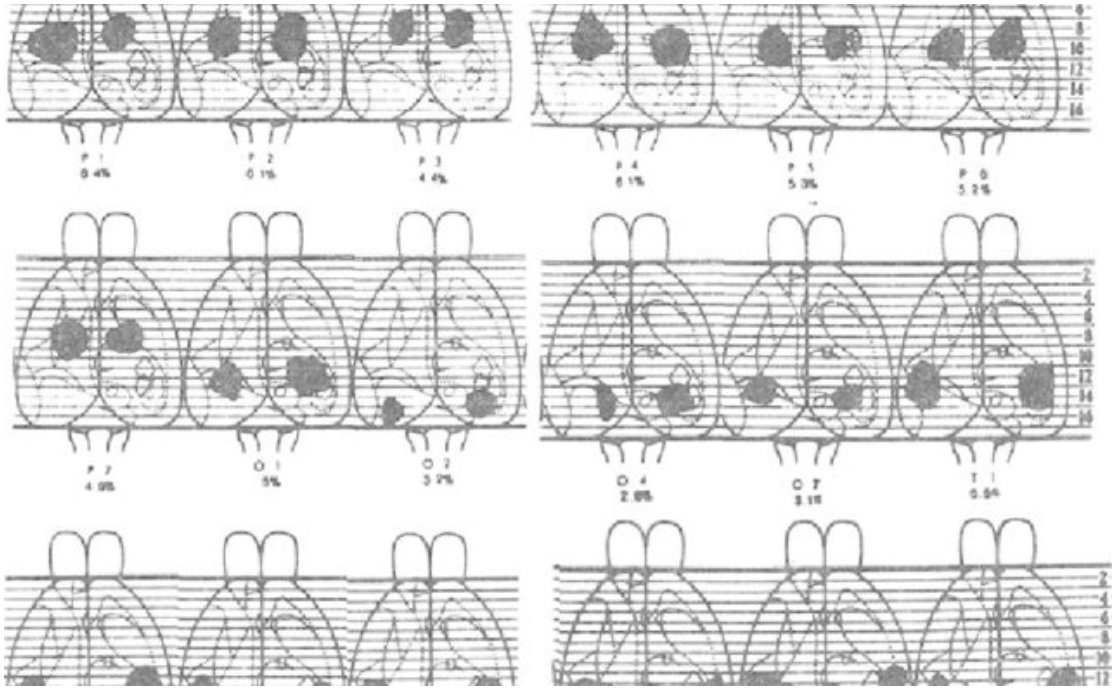
Contributions:

- Focus on retrieval not only on learning
- engram-awakening stimulus need not completely overlap with the original stimulus (present-day ‘pattern completion’ by CA3 area of hippocampus)
- Awakened engram leads to generation of new engram = memory is not static but changes with use (similar to the Multiple trace theory)
- Distributed engram throughout brain

Matthew effect in science

- ‘For unto everyone that hath shall be given, and he shall have abundance: but from him that hath not shall be taken even that which he hath.’ — *Matthew 25:29*
- *(’*The rich get richer and the poor get poorer’)
- More famous scientists get taken more seriously for the same results than unknown ones
- heighten the visibility of contributions to science by scientists of acknowledged standing and to reduce the visibility of contributions by authors who are less well known (Merton, 1968)
- This is positive feedback loop

History of memory research - Lashley

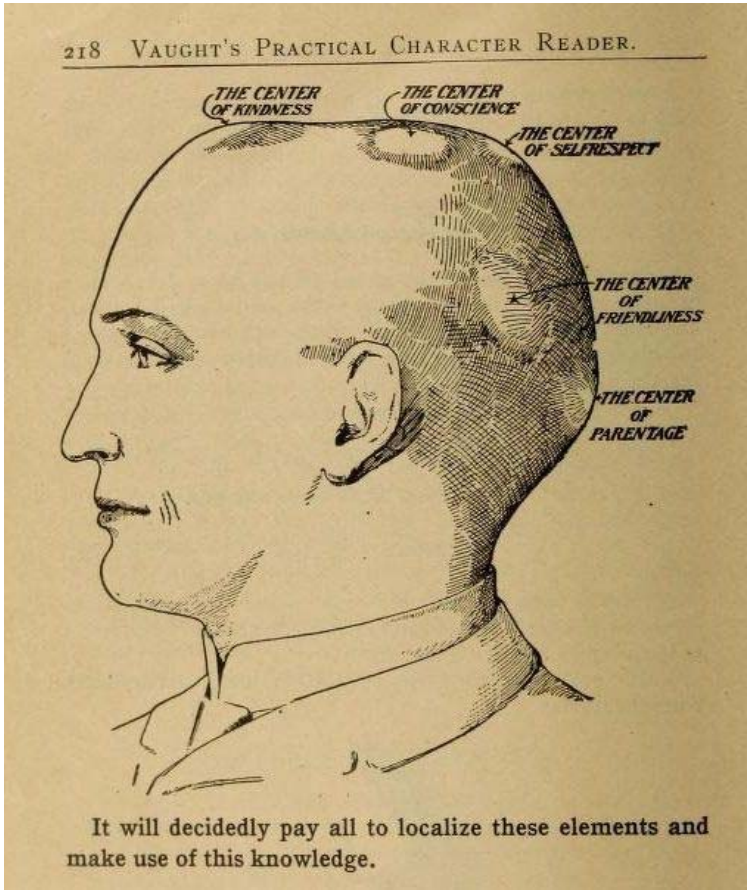


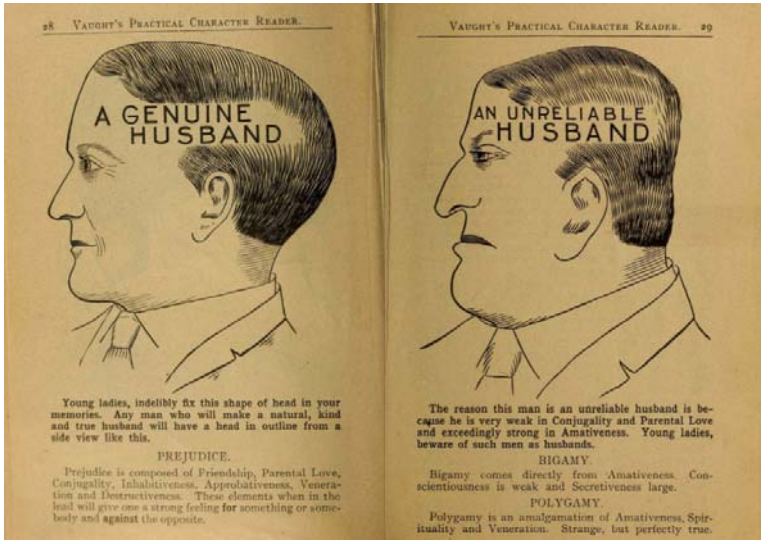
- Karl Spencer Lashley (1890–1958)
- 'inspiring teacher who described all teaching as useless' (Beach, 1961)
- Popularized term 'engram'
- Searched for its localization for more than 30 years
- lesioned some part of the cortex and then trained rats to navigate a maze
- Size but not location correlated with the memory impairment
  - But extent of damage also correlated with the extent of hippocampal damage - Lashley did not realize this
- Engram was everywhere 'the trick, is not to find where the trace is located, but where it is not'

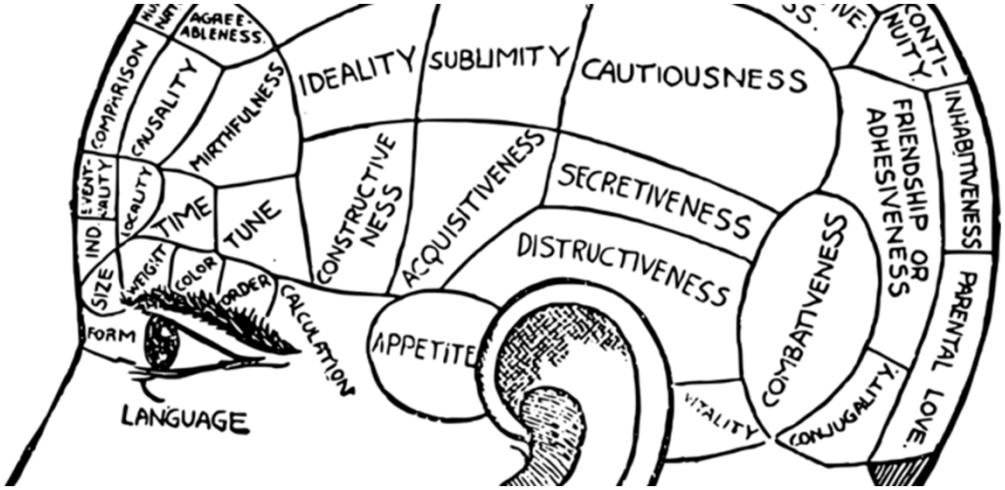
Contributions

- Current methods are very similar to lesions done but Lashley, only more sophisticated
- Modern concept: distributed processing in contrast to 'new phrenology'

Old Phrenology

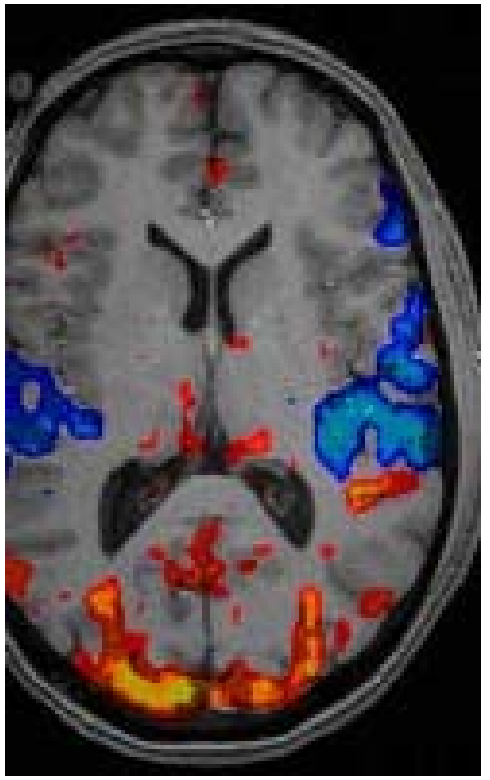






New phrenology

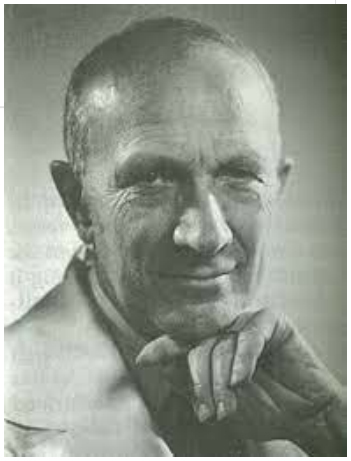
- Modern neurosience boxes: attention, memory, sensation, motivation, emotion, selfhood
- We fit them to different brain regions
  - Hippocampus = memory
  - Amygdala = emotion
  - Insula = selfhood
  - Orbitofrontal cortex = behavioral inhibition
  - dACC = conflict monitoring
  - Prefrontal cortex = planning and motivation
- These boxes were created by psychologists before brain was studies
- Alternative: distributed processing



History of memory research – Donald Hebb

- Donald Olding Hebb (1904–1985)
- Studied English literature and Philosophy
- Lashley's PhD student
- Studied effect of human brain injury on IQ
- Hebb-Williams maze - effect of early life experiences on cognition: believed in early education
- Returned to Lashley, wrote *The organization of behavior: a neuropsychological theory*
- Hebb's cell assembly theory
  - 'neurons that fire together wire together'
  - Recurrent activity between two neurons strengthens the interconnections between them
  - Proposed 'pattern completion'

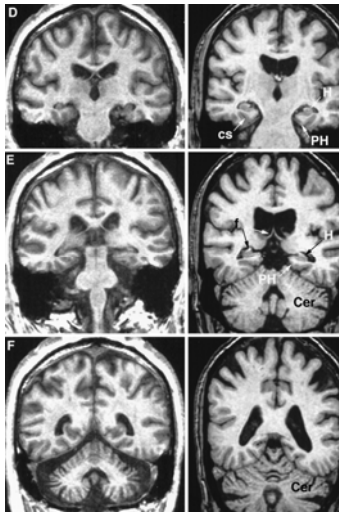
History of memory research – W.G. Penfield



- Wilder Graves Penfield (1891–1976)
- Studied Literature, later MD
- Epilepsy neurosurgeon
- Electrically stimulated different brain regions to determine source of epileptic seizures
- Defined homunculus (Penfield and Boldfrey, 1937)
- Stimulating temporal lobe elicited experiences identified as previously experienced
  - Very memory-like
  - one patient (Case 3, RW) reported: “My mother is telling my brother he has got his coat on backwards. I can just hear them.” When asked if this event actually occurred, RW reported, “Oh yes, just before I came here” (Penfield and Perot 1963)
- Inspired modern engram awakening methods: optogenetic and chemogenetic
- Electrical activity alone can ‘awaken’ engram
- Started a tradition of memory research on epilepsy patients

History of memory research – Brenda Milner

- Brenda Milner (1918-)
- Studied math, then experimental psychology
- Did her PhD under Hebb
- Studied memory impairment in hippocampal damage patients
- Penfield invited her to study Henry Molaison (H.M.) - patient that had both hippocampi removed
- First to show evidence that engram was in fact localized - in the hippocampus
- First to show that there is not 'one' memory (e.g. procedural vs declarative)
- First to show that older memories are spared (older than 3 years) – systems consolidation (However, she said that when transferred, memories lose their episodic nature - became more semantic)

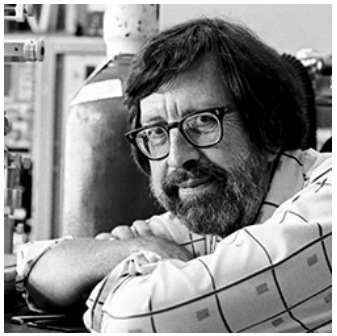


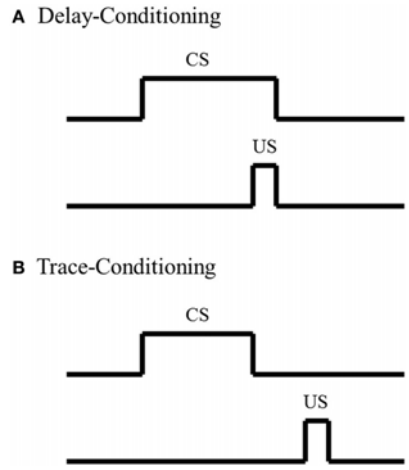
History of memory research – J.V. McConnell

- James Vernon McConnell (1925–1990)
- ‘it seems to me that anyone who takes himself, or his work, too seriously is in a perilous state of mental health’
- Studied cannibalistic flatworms
- Worms formed association between light and shock. McConnell observed conditioned contraction response
- When he split worm in half both halves of worm retained the memory
- Then he crushed the trained worm and fed it to naïve worm – the naïve worm than displayed the conditioned contraction response: claimed to prove that memory is transmitted through RNA
- His work was not replicated at the time. Was poorly designed. He lost prestige and grants
- However, using more automated procedure split worm experiment was replicated (Shomrat and Levin, 2013)
- And indeed, engram appears to be localized in the nucleus and not in synapse - suggesting epigenetic mechanism (i.e. changes in RNA transcription)

History of memory research – R.F. Thompson

- **Richard Frederick Thompson** (1930–2014)
- Influenced by Lashley (took his chair in fact)
- First to find an engram in an animal - in cerebellum (McCormick and Thompson, 1984)
- Delay eye-blink conditioning in rabbits
- Two criteria to show that a region is critical for engram
  - Changes in electrophysiological activity in the area during learning
  - Lesion of area causes memory damage
- First, Thompson targeted hippocampus - but no, lesion of hippocampus did not impair delay eye-blink CR (it impairs only trace and contextual conditioning)
- But cerebellum fulfilled both criteria
- He used electrophysiological recordings and lesions: a format copied to present day





Hippocampus

- The region of memory formation
- Pattern separation
- Pattern completion
- Temporal binding
- ‘Indexes’ cortical activity

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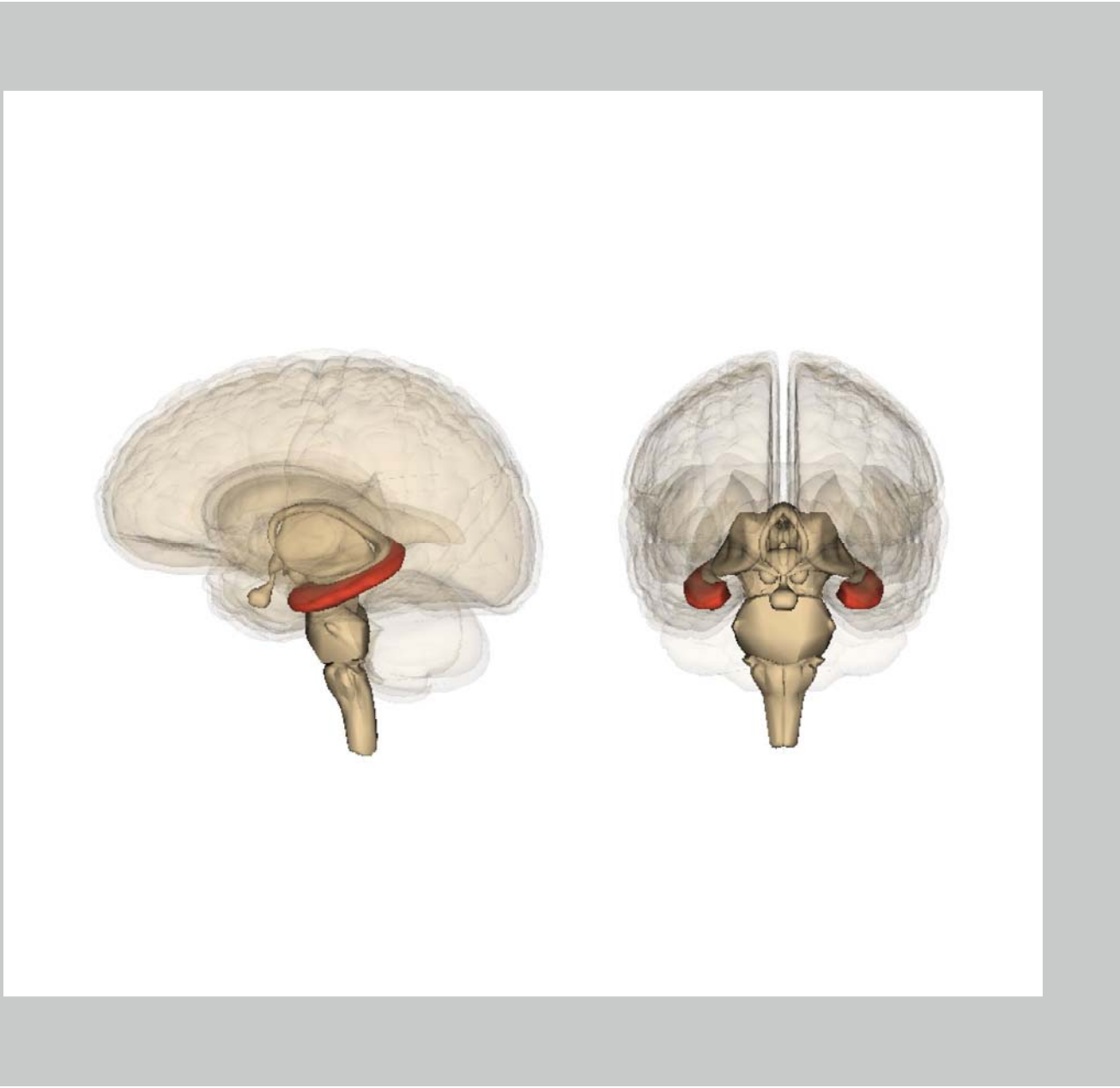
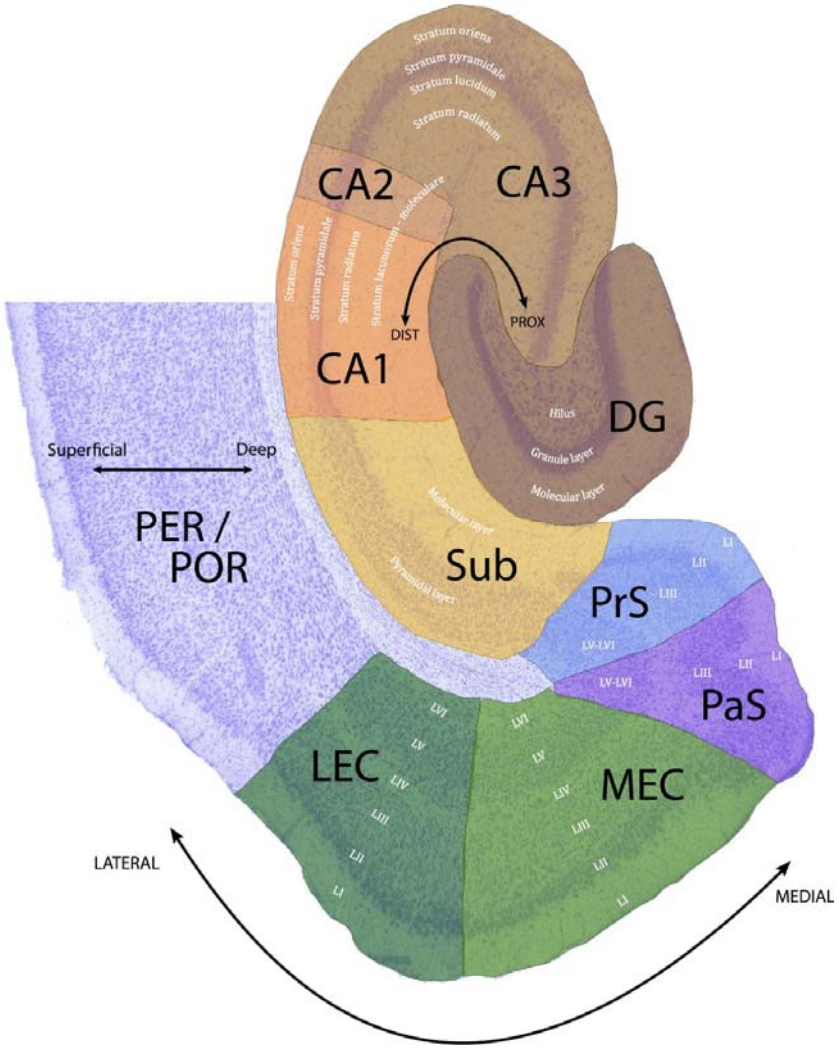
Imagining future and past

- Imaging situation that is not in the present
- symmetrical



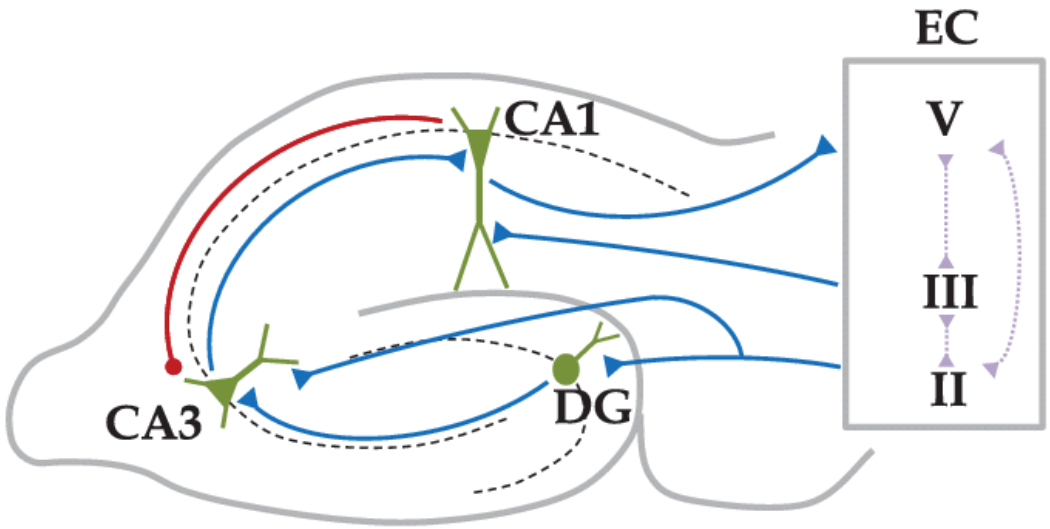
Hippocampus



- https://www.youtube.com/watch?v=k_P7Y0-wgos
- 8:22
- https://www.youtube.com/watch?v=uJ2eoQLTXNo

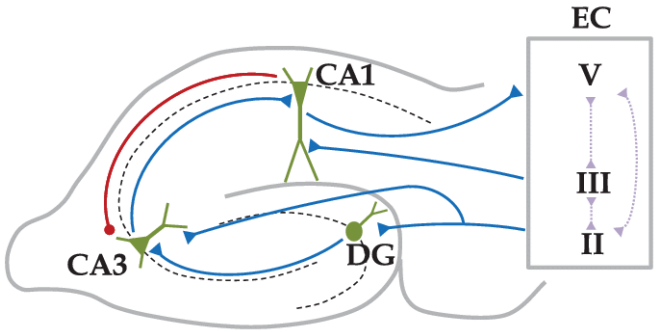
Information flow through hippocampus

- Trisynaptic loop
  - enthorinal cortex (layers 2/3) → **perforant path** → DG → **mossy fibers** → CA3 → **Schaffer collaterals** → CA1 → enthorinal cortex (layer V)

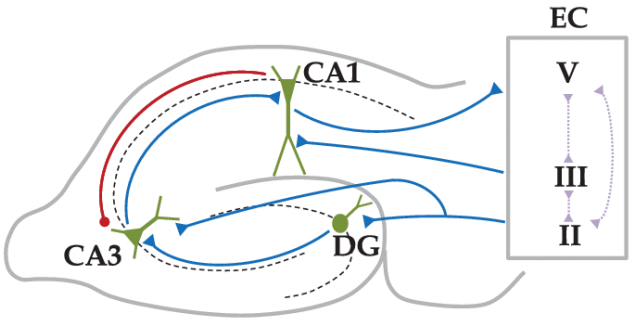


Dentate gyrus

- DG cells: granule cells (GC), Mossy cells (MC), adult born granule cells (newborn GC)
- GCs send a single mossy-fibre (MF) axon to CA3 targeting 10-15 pyramidal cells with 'giant' mossy fibre-synapses (each pyramidal cell in CA3 receives input from about 50 GCs)
- They further contact a similar number of mossy cells via hilar axon collaterals and ~100-150 GABAergic interneurons in the hilus and CA3
- Mossy fibres have low transmission probability at baseline (<1 Hz) but high facilitation when stimulated (> 10 Hz)



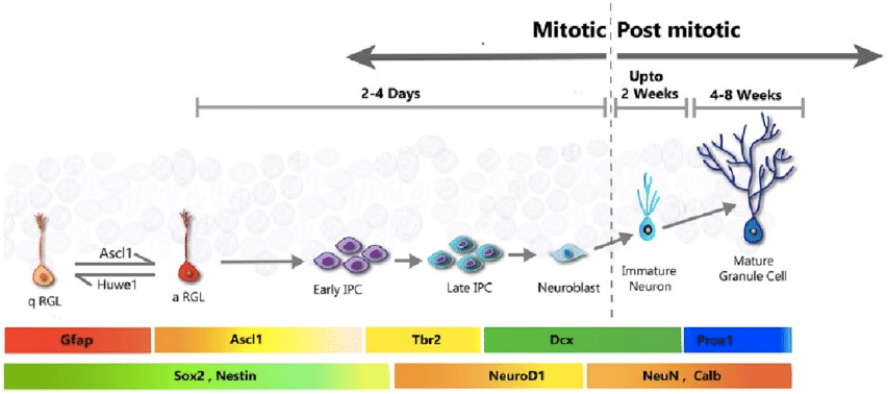
Dentate gyrus

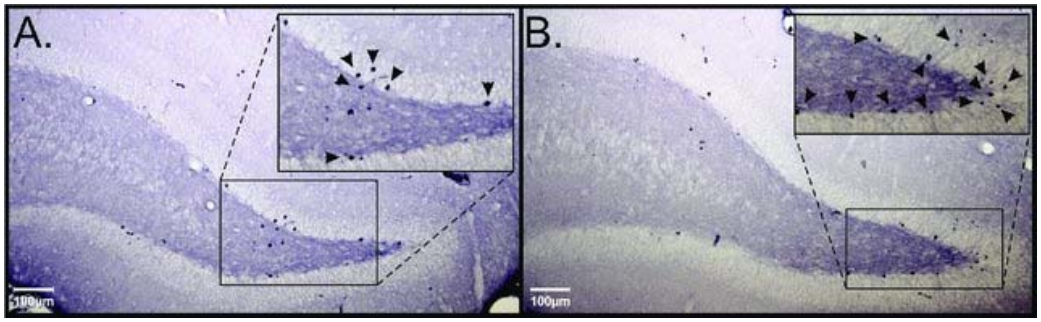


- Inputs
  - Medial enthorinal cortex – MEC (tranditionally ‘where’ stream)
    - border-, head-direction-, object-vector- and grid-cells
  - Lateral enthorinal cortex - LEC (tranditionally ‘what’ stream, maybe ‘when’ stream)
    - Information about objects
  - Acetylcholine inputs
    - Inhibiting acetylcholine in dentate gyrus inhibits learning
    - Activating acetylcholine during sleep impairs memory consolidation
    - Ach has inhibitory effect on GC, mediated by DGs interneuron activation
    - acetylcholine promotes long-lasting potentiation of PP-synapses
  - Dopamine from VTA.
    - Enhances learning by increasing LTP at PP-CG synapses but not esential for learning
- Output
  - CA3
  - Kainate receptor dependant LTP, not NMDA (Petrovic et al., 2017)

Adult neurogenesis in dentate gyrus

- Granule cells
- These cells show increased intrinsic excitability
- Strong responsiveness to external inputs
- Enhanced synaptic plasticity
- Growth:
  - 0-3 weeks: newborn GCs are protected by interneurons and mossy cells, recieve LEC input
  - 3-6 weeks: form mossy fibers, inhibition is delayed, newborn GCs are hyperexcitable but do not distinguish between similar enviroments
  - 6 weeks + : newborn GCs are indistinguishable from mature GCs





Pattern separation function of dentate gyrus

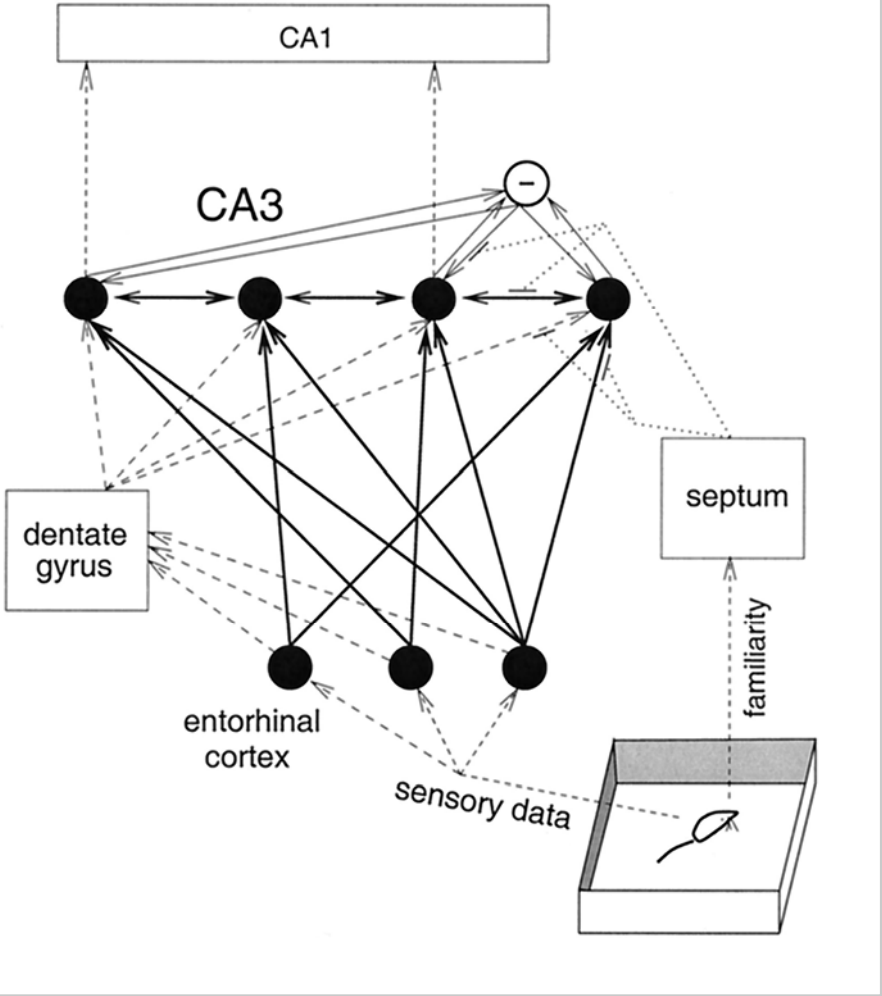
- Distinguishing two similar inputs
- Discrimination of similar experiences
- Very sparce activity of DG, less than 5% of a rodent's GCs are active when it explores a given environment, IEG expression even more sparse
- active GC ensembles may suppress the activation of competing ensembles by recruiting di-synaptic inhibition
- In human MRI imaging entorhinal cortex activity more similar than DG activity when discriminating similar pictures (Bakker et al., 2008)
- Not confirmed beyond doubt

CA3 area of hippocampus: pattern completion

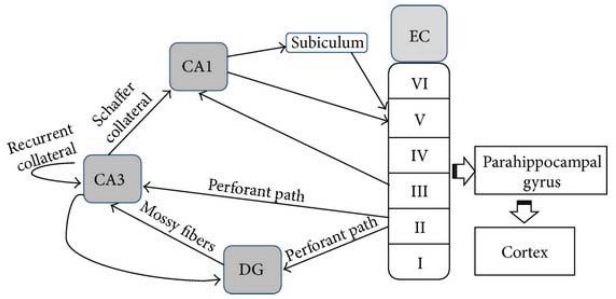
- Pyramidal neurons
- Pattern completion: when we take one or a few details and use them to construct a complete memory
- Recieves input from dentate gyrus via Mossy fibers, and from EC directly via Perforant path
- CA3 neurons react sooner to perforant path stimulation than GC of DG

CA3 as an auto-associative network

- Multitude of recurrent collaterals
- pattern completion
  - reconstruction of complete stored representations from partial inputs that are part of the stored representation
  - holistic retrieval of multidimensional experiences given a cue
  - context dependent memory, partial cues



CA1 Area of hippocampus



- Main output structure
- Recieves information from CA3 and from EC (layer3)
- Potentially encodes temporal gaps between events
- Projects to EC (layer 5) and to subiculum
- Projection to EC is important during memory encoding, while projection to subiculum is important during memory recall
- Subiculum recruits mamalary bodies that increase stress during recall of fearful memories

Neuronal allocation to the engram

- Neurons with increased excitability are preferentially allocated to the engram
- For example, neurons that cyclic adenosine 3’,5’-monophosphate response element binding protein (CREB) increases neuronal excitability and synaptic efficiency
- Memory engram allocation is bias towards allocation of memory into neurons that express high levels of CREB (amygdala, hippocampus, insula, cortex)
- CREB expression is driven by immediate early gene expression (IEGs)
- However, an artificial increase of CREB in any set of neurons will allocate memory engram there (Yiu et al., 2014)
- Other IEG also affect excitability (such as cFos, Arc, Homer,…)

Linking memories

- Increased excitability of a set of neurons (engram) makes it more likely that it will be a part of another engram if it occurs before the excitability window closes (which is about 5h long)
- This is also what is observed: neurons that part of an engrams of memories that are linked (and ones that occur close together) share some of the population
- Usually then, activating one memory leads to activation of the other
- Degree of the overlap predicts if the association is formed
- Deactivating this common population maintains each separate memory but the association is lost

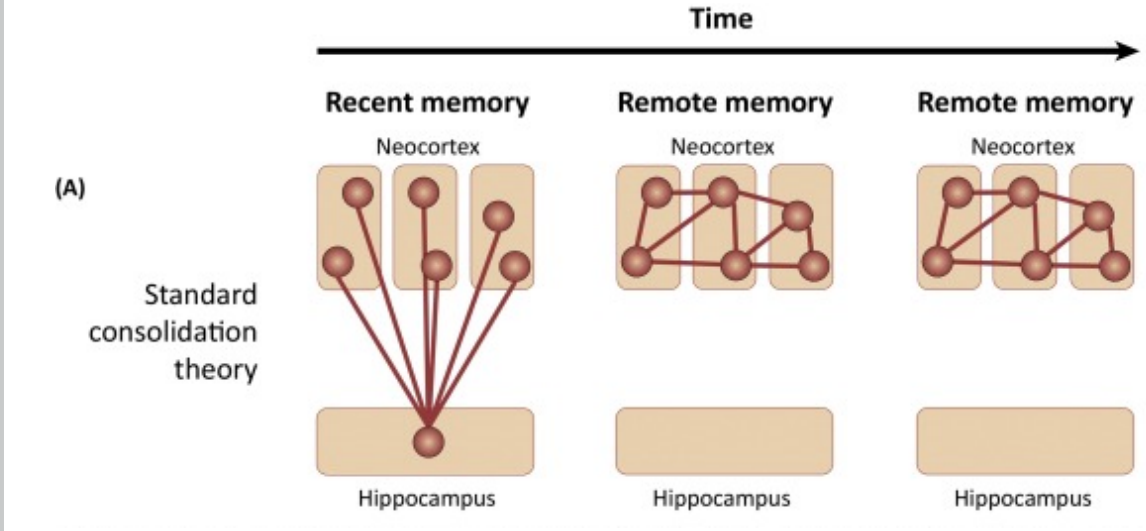
Memory tag and capture

- Initially weak memory can become stabilized in long-term memory by a more salient event
- 1 hour before and 3 hours after (given by decay of early LTP)
- adaptive
- The model proposed is called a sybaptic tag-and-capture" (Frey and Morris, 1997; Dungsmoor et al., 2022)
- Weak potentiation induces a local "tag" at the synapse that is set by glutamate transmission
- Robust potentiation through a strong input to the same neural ensemble upregulates the availability of plasticity-related proteins (PRPs)
- if the PRPs are released while the local tag is still transiently active, the local tag will "capture" the PRPs, thereby strengthening memory
- Behavioral tagging experiments. Salient event is usually novelty, tagging occur by D1/D5 mechanism
- For stronger tagging, dopamine originates from locus coeruleus, for weaker tagging from ventral tegmental area
- Optogenetic activation of LC, but not VTA causes tagging of weak memories
- 'common novelty' and 'distinct novelty' - distinct novelty necessiates formation of new knowledge structures, engages LC

Theories of brain-wide memory formation

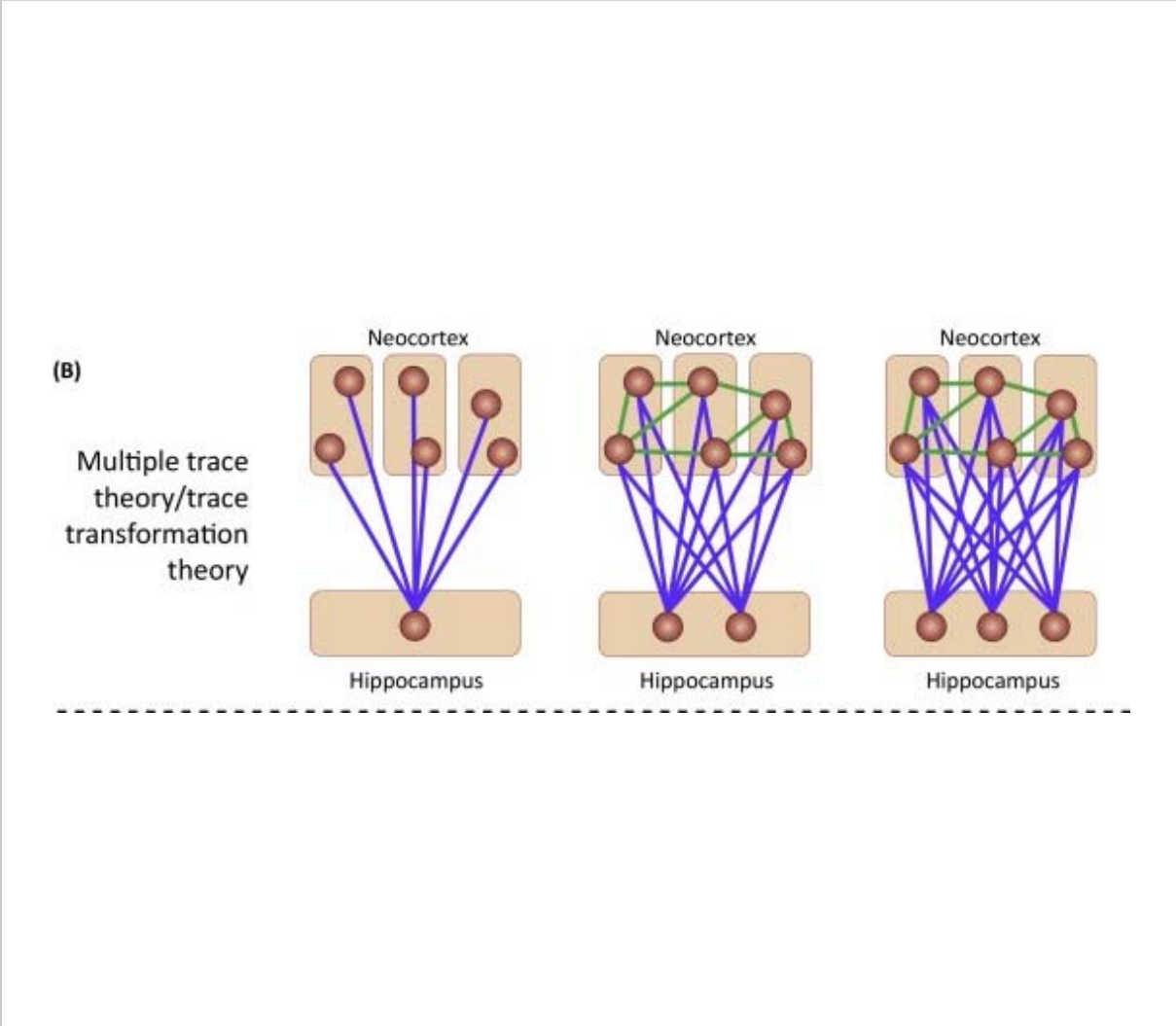
Systems consolidation theory

- Based on H.M.'s ability to retrieve old memories.
- Memories are only transiently dependent on hippocampus
- Memories will be forgotten if they are not fully represented in neocortex
- Extra-hippocampal sites mature and interact to retrieve a memory hippocampaus is no longer needed
- Notion that hippocampus has a limited capacity
- Time course of memory transfer is not specified
- During sleep- replay of events by hippocampus to neocortex
- Milner - what is remembered is probably coded by neocortex but is of more general (less episodic nature)
- Consolidation in animal studies takes place in hours/days, while in humans it takes years



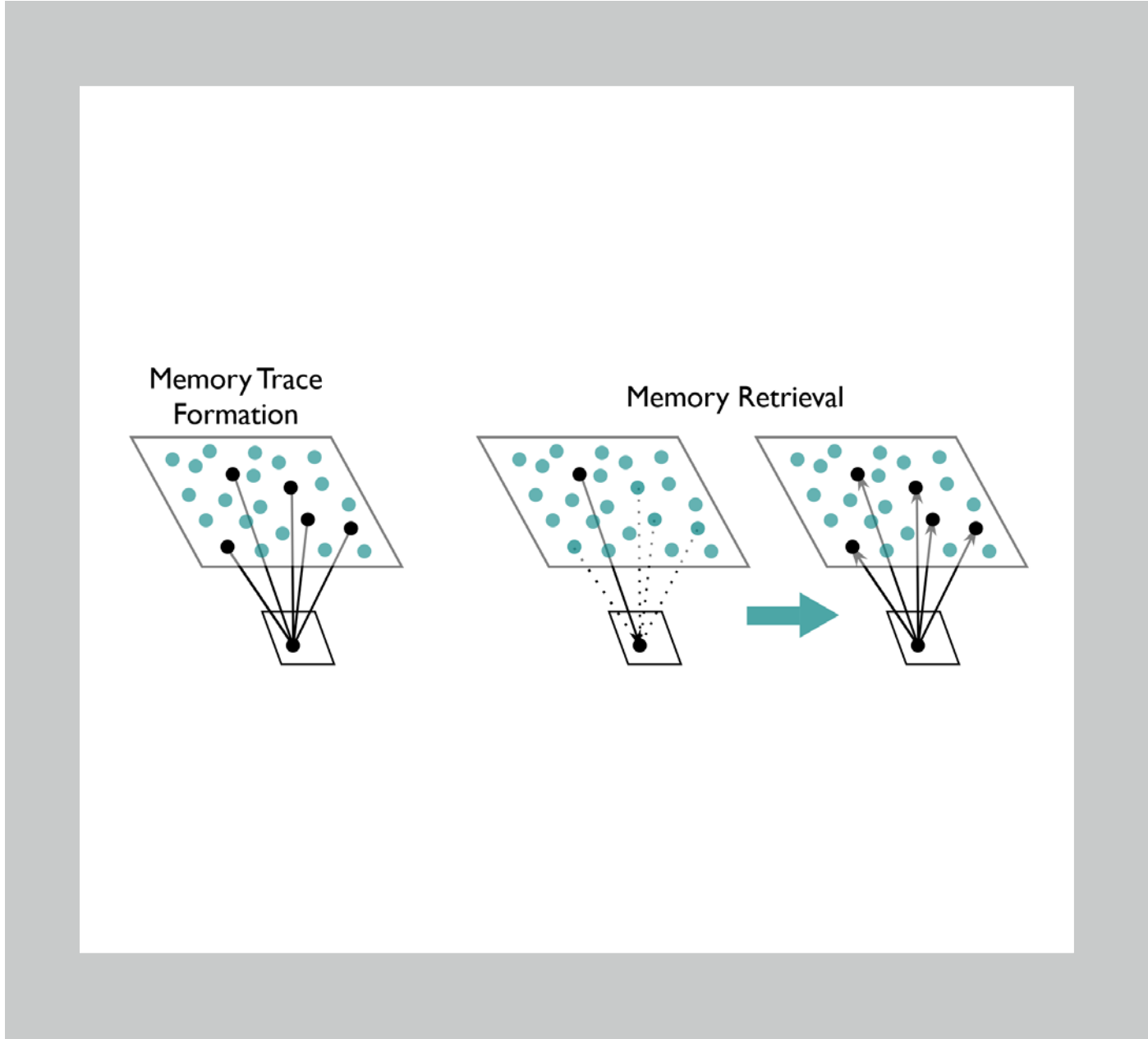
Multiple trace theory

- **Multiple trace theory** (Nadel & Moscovitch, 1997)
  - Older memories are experienced more often and each new recollection leaves new memory trace
  - Memory trace is still dependent on the hippocampus
  - Predictions:
    - Full damage of hippocampaus will lead to full retrograde amnesia
    - Partial hippocampal damage will spare older memories because they are ‘overrepresented’ in hippocampus



Memory ‘index’theory

- Teyler and DiScenna,1986
- Hippocampus does not store memories but creates an ‘index’ of cortical activity
- Reciprocal connections of hippocampus with most neocortical areas
- During memory retrieval hippocampus reproduces activity in neocortex that was present during encoding



Thank you for your attention!

See you on my next presentations

- Neurotransmitters and behavior
- Advanced techniques in the study of learning and memory