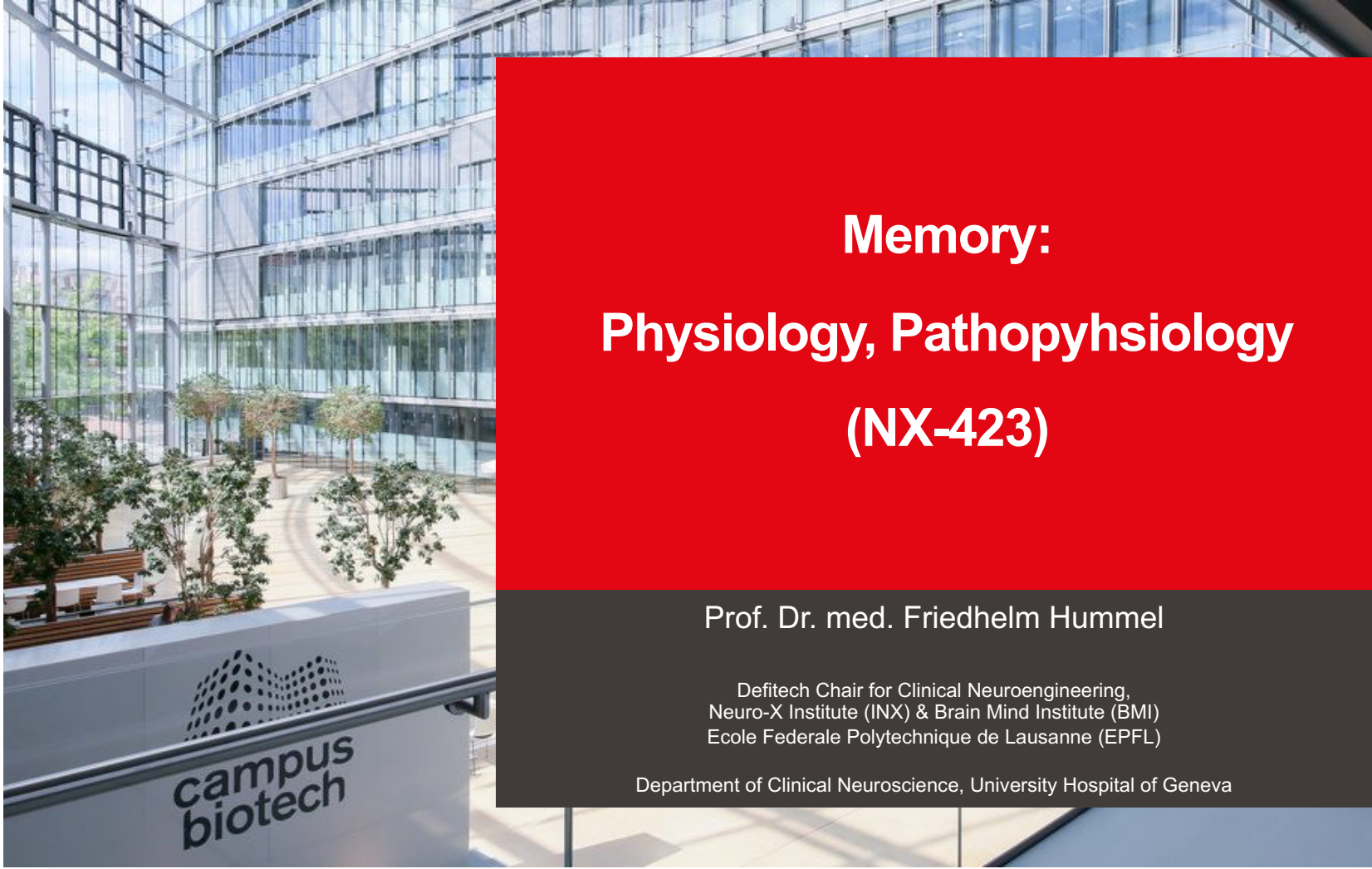
EPFL

Neuro X Institute

HUG Hôpitaux Universitaires Genève

Clinique romande de réadaptation



Memory:

Physiology, Pathopyhsiology

(NX-423)

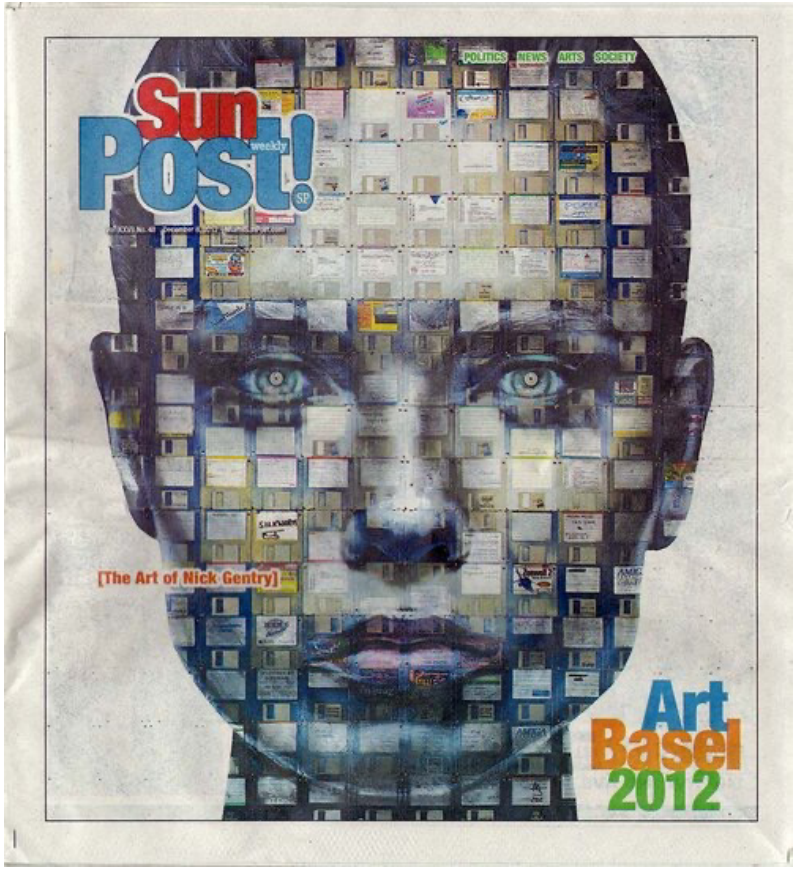
Prof. Dr. med. Friedhelm Hummel

Defitech Chair for Clinical Neuroengineering,
Neuro-X Institute (INX) & Brain Mind Institute (BMI)
Ecole Federale Polytechnique de Lausanne (EPFL)

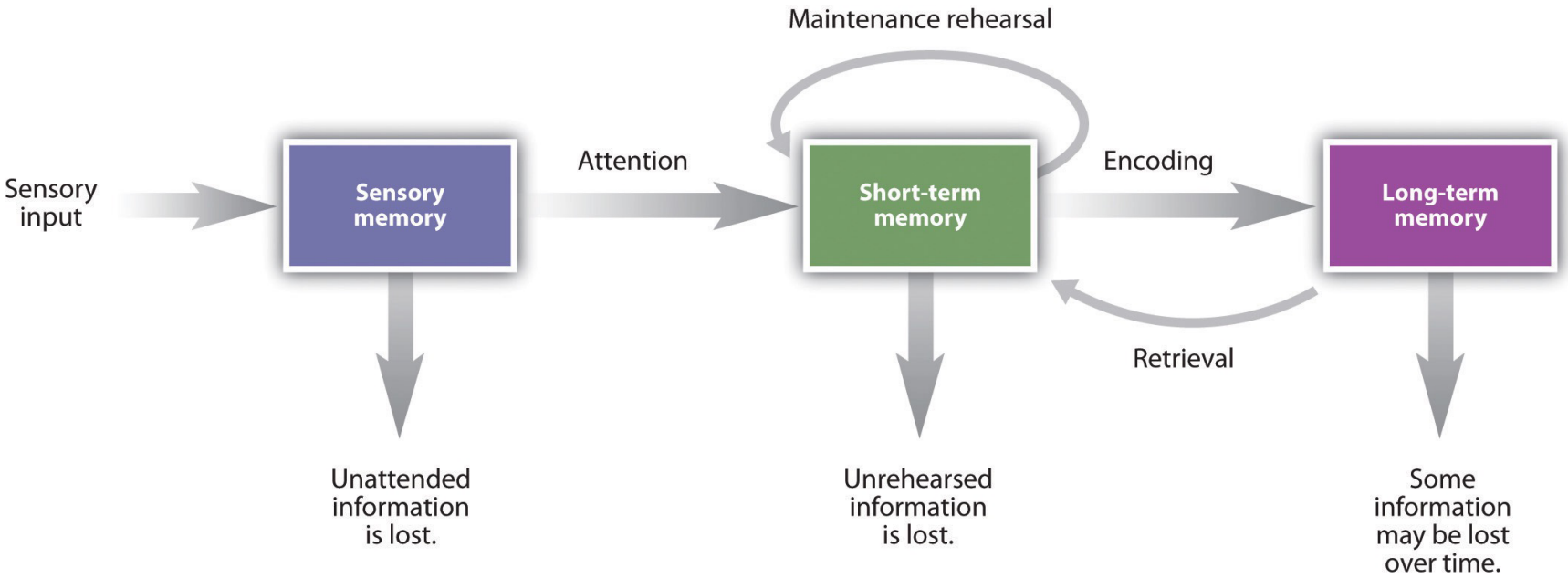
Department of Clinical Neuroscience, University Hospital of Geneva

Neuro-X Master:

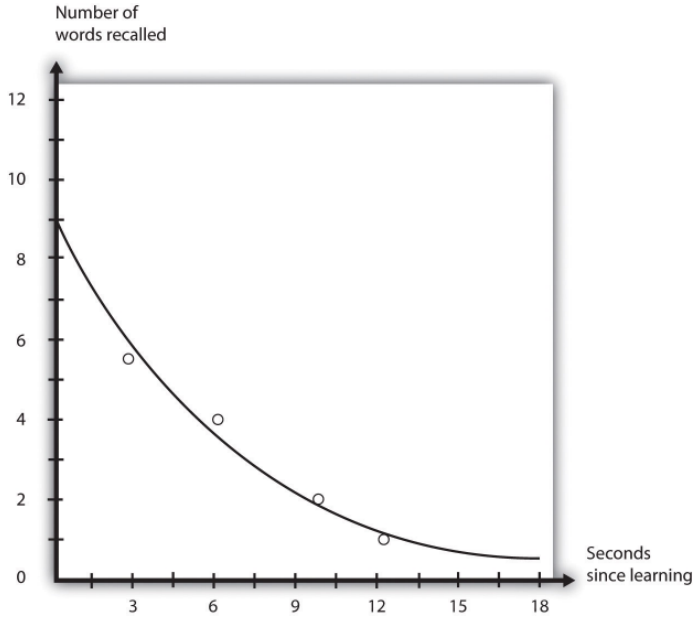
NX-423
Translational neuroengineering


POLITICS NEWS ARTS SOCIETY
Sun
weekly
Post!
SP
[The Art of Nick Gentry]
Art
Basel
2012

Types of Memory



Adapted from Stangor and Walinga, Introduction in Psychology, 2014
Please see also e.g., Kandel *et al.* Mcgraw-Hill 6th Ed, 2021



Peterson and Peterson (1959)

- Allows small amounts of information for a limited time
  - "seven plus or minus two" pieces of information magic number in STM (Miller 1956)
- Fast decay of information in STM (<30-60 sec, Peterson and Peterson (1959); Baddeley, Vallar, & Shallice, 1990)
- Keep (more) information and longer in STM by
  - Chunking of information (797140515 vs 79 714 05 15)
  - Rehearsal

Long-term memory (LTM)

Memory storage that can hold information for days, months, and years.

Capacity of LTM is large, and there is no known limit to what we can remember (Wang et al., 2003).

How perceptions become LTM

Encoding is the process by which we place the things that we experience into memory

Retrieval refers to the process of reactivating information that has been stored in memory.

Storage of information in LTM

- Strengthening connections of neurons that represent the memory
- If pathways in these neural networks are frequently and repeatedly fired, the synapses become more efficient, and these changes create memory.
- Underlying mechanisms long term potentiation (LTD) and Long-term depression (LTP)
- Summarized as consolidation

Long-term potentiation (LTP)

Long-term increase in the excitability of a neuron caused by repeated high-frequency activity of input.

Associative long-term potentiation

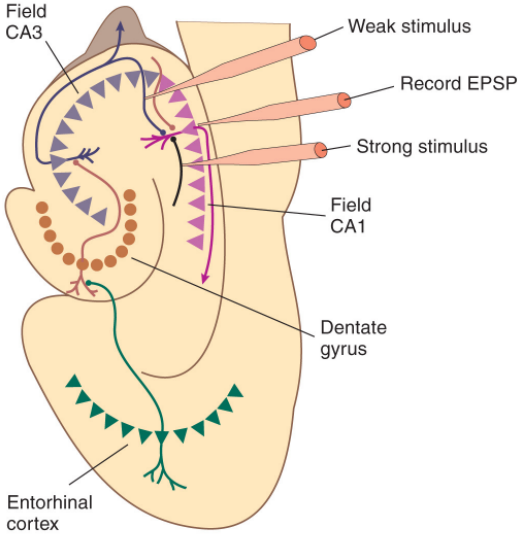
LTP in which concurrent stimulation of weak and strong synapses to a given neuron strengthens the weak ones.

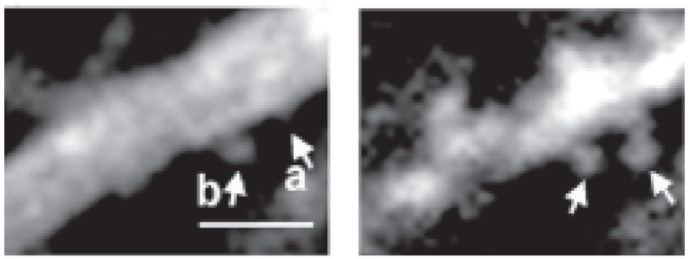
Knowledge, experience, relationship are represented in neuronal networks in the brain

Memory is the reactivation of a specific group of neurons, formed from persistent changes in the strength of connections between neurons'

The answer is synaptic plasticity. This term describes the persistent changes in the strength of connections – called synapses – between brain cells.
These connections can be made stronger or weaker depending on when and how often they have been activated in the past.
Active connections tend to get stronger, whereas those that aren't used get weaker and can eventually disappear entirely.

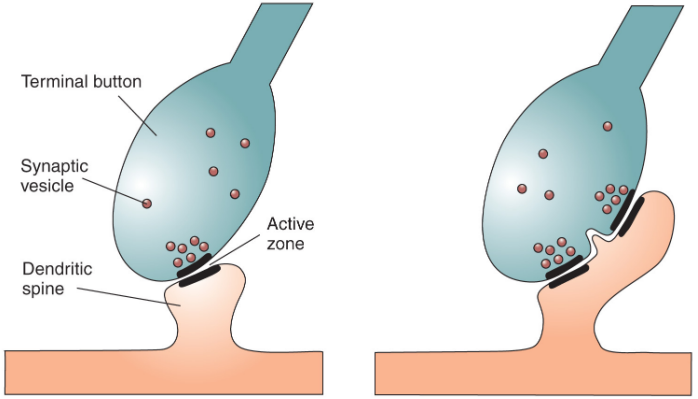
A connection between two neurons becomes stronger when neuron A consistently activates neuron B, making it fire an action potential (spike), and the connection gets weaker if neuron A consistently fails to make neuron B fire a spike.
Lasting increases and decreases in synaptic strength are called long-term potentiation (LTP) and long-term depression (LTD).





Before LTP

After LTP

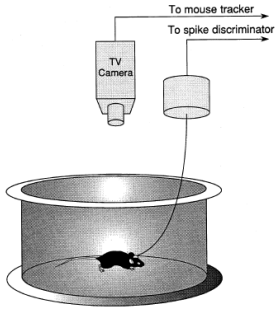


Before long-term potentiation

After long-term potentiation: Generation of a perforated synapse

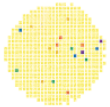
(a)

(b)




Place cell

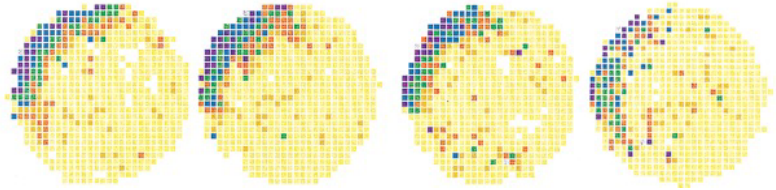

Noisy cell


Silent cell

Place cell stability

Session 1 Session 2 Session 3 Session 4

Wild-type mice



Transgenic mice
(CaMKII mutation – deficit in LTP induction)

Ref.: Rotenberg et al. 1966, Cell.

Reward

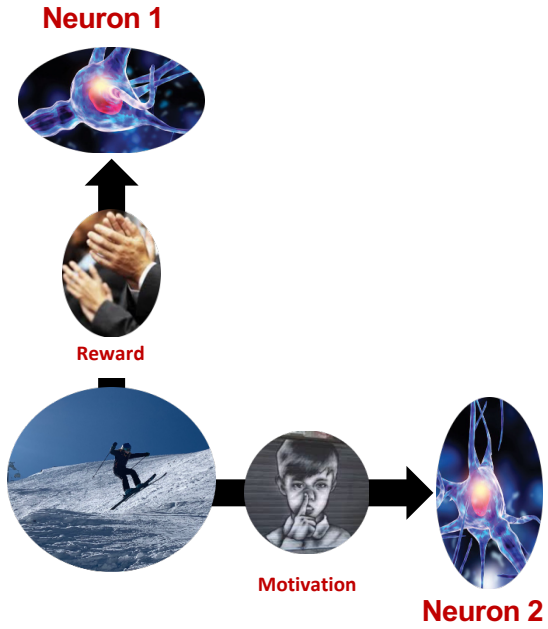
Punishment

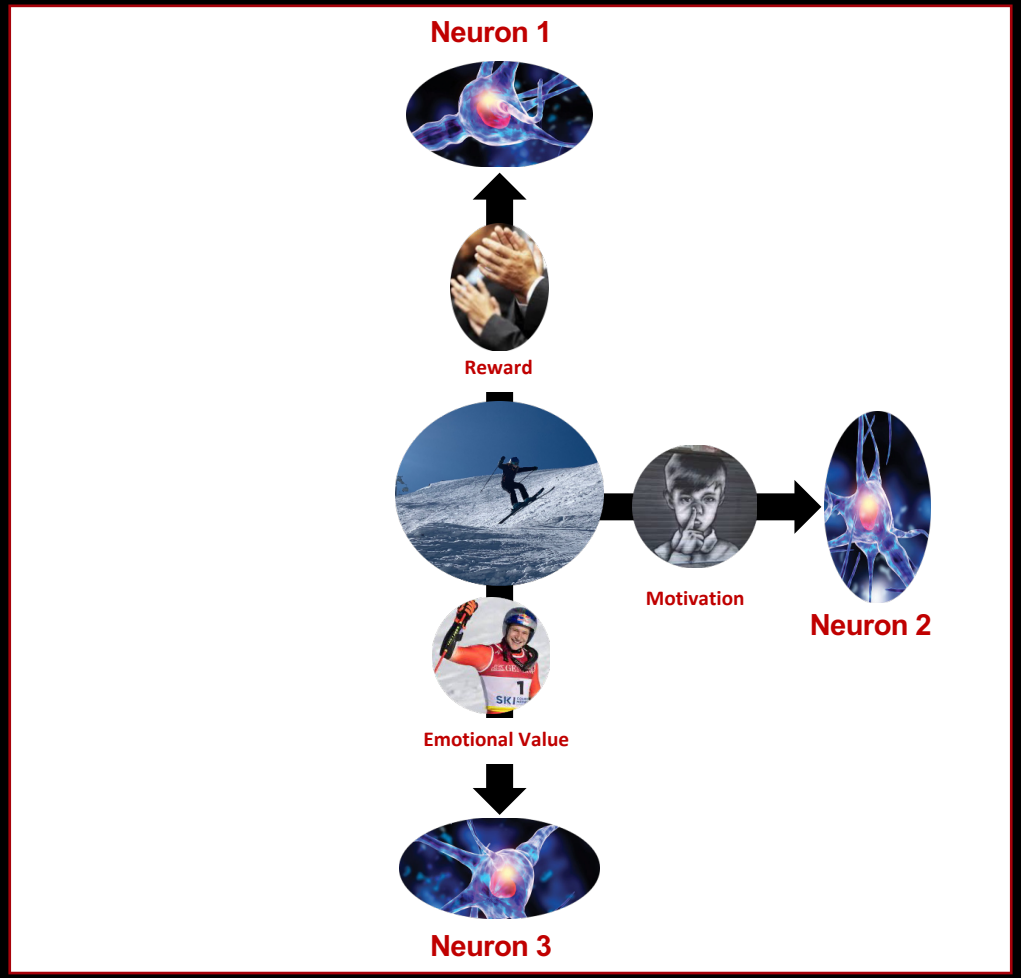
Motivation

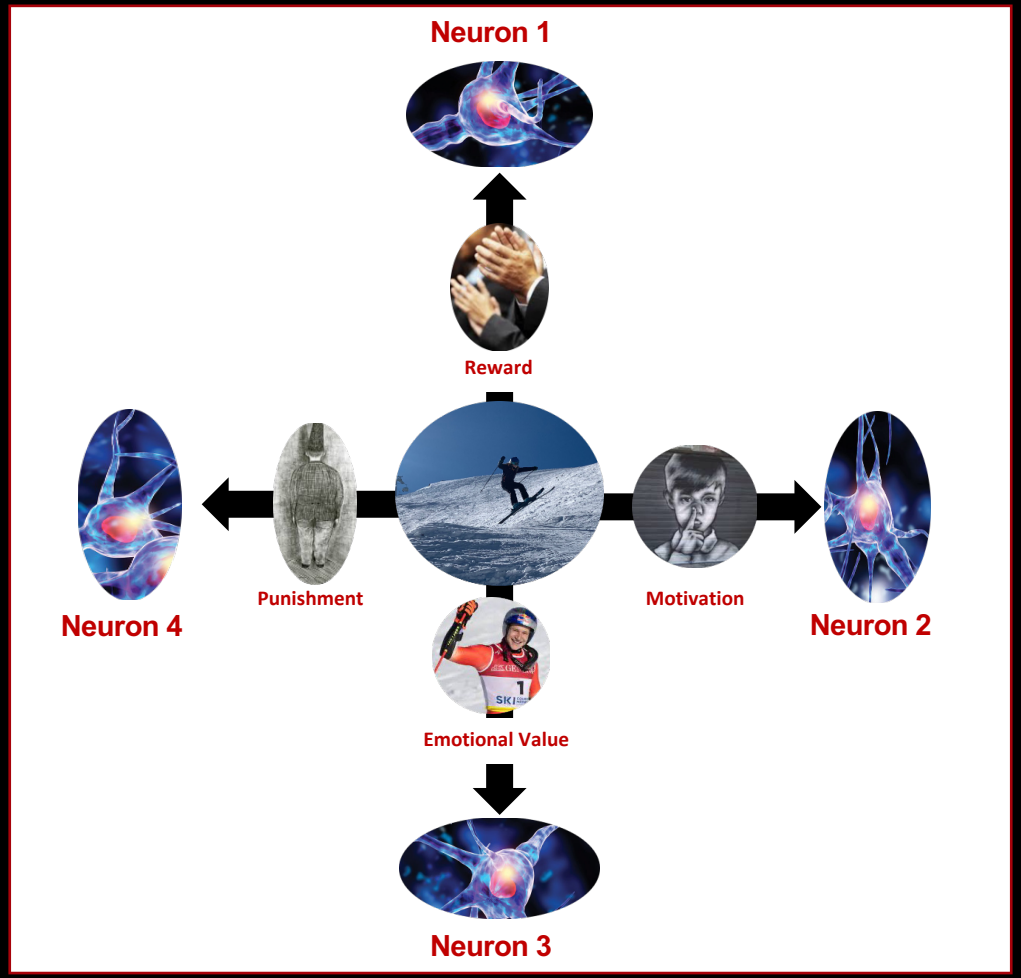
Emotional value

Storing information in the brain

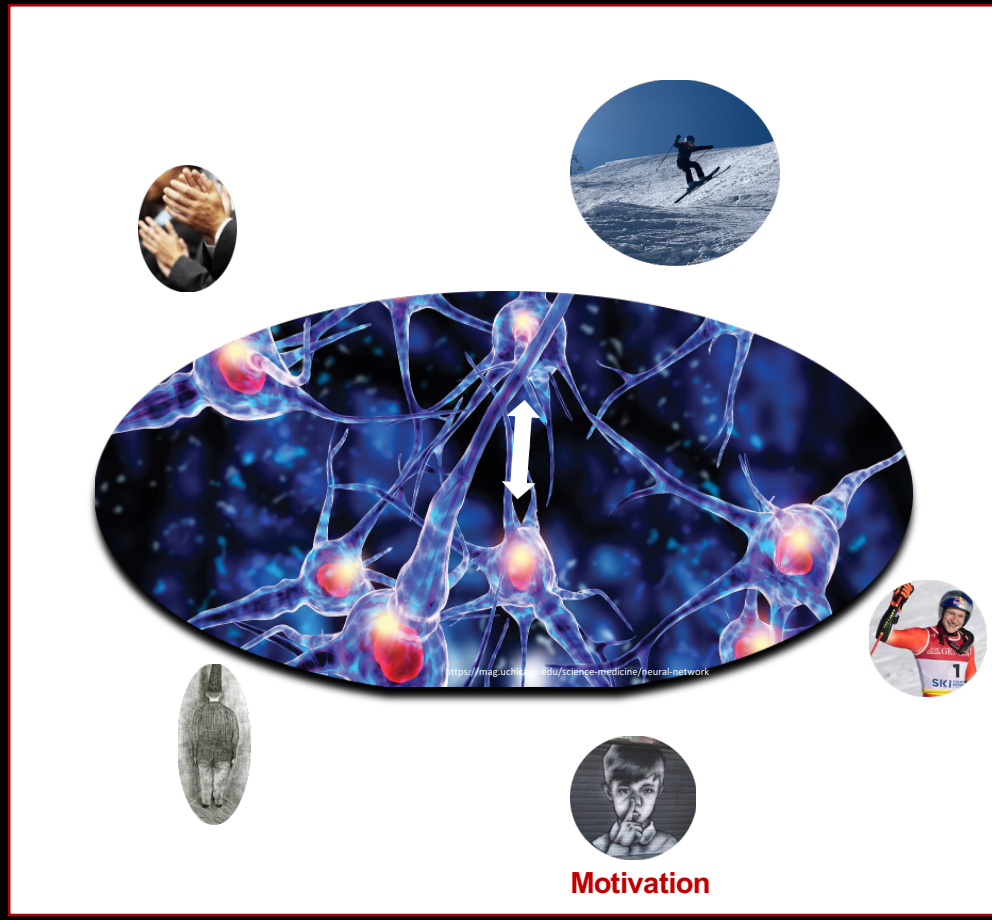
Storing information in the brain




Neuron 1
Reward
Motivation
Neuron 2
Emotional Value
Neuron 3

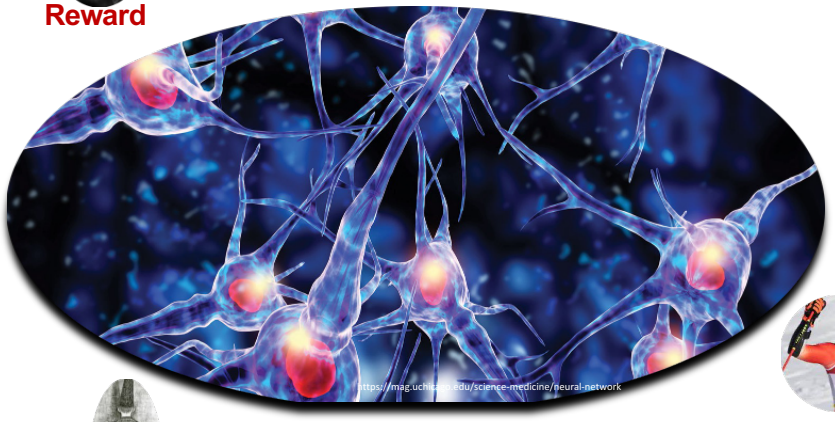

Neuron 1
Reward
Neuron 4
Punishment
Motivation
Neuron 2
Emotional Value
Neuron 3


Reward
https://mag.uchicago.edu/science-medicine/neural-network


https://mag.uchi[illegible].edu/science-medicine/neural-network
Motivation

Storing information in the brain

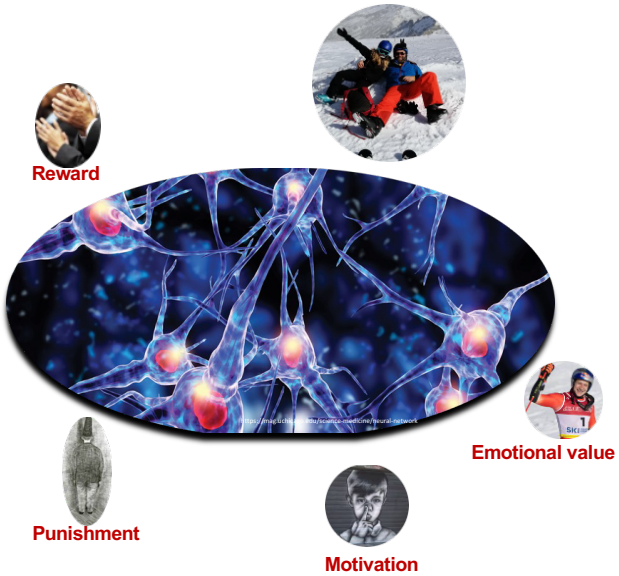
Reward



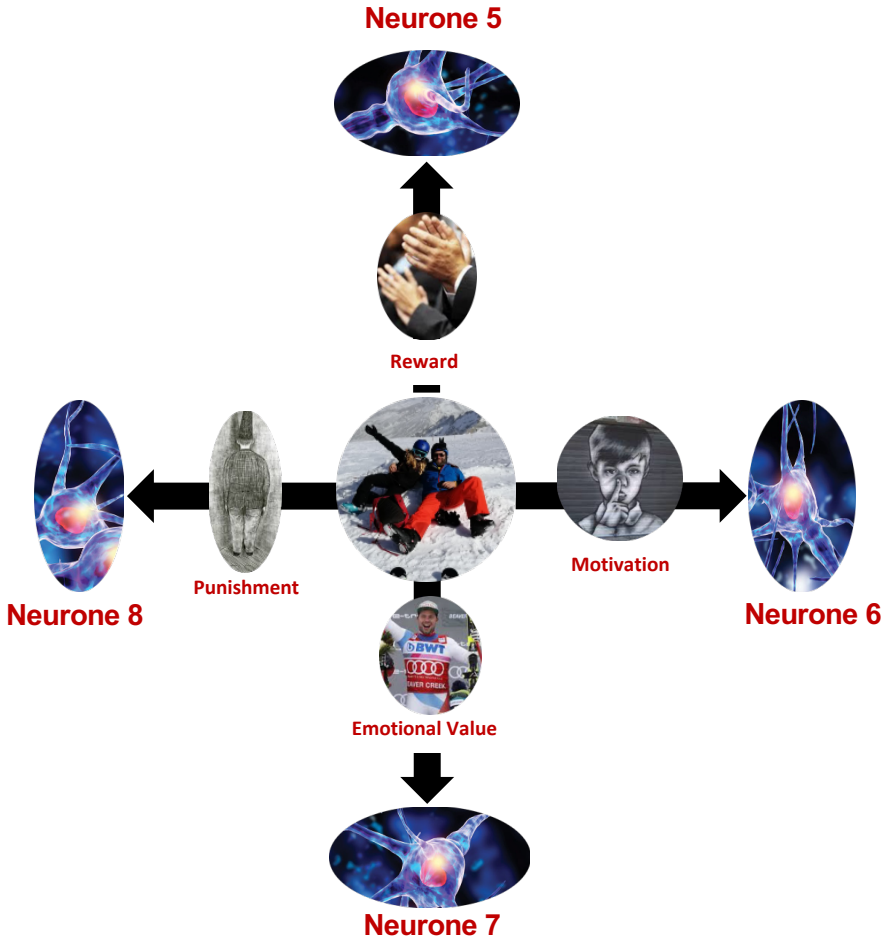
Emotional value

Punishment

Motivation


Reward
Emotional value
Punishment
Motivation

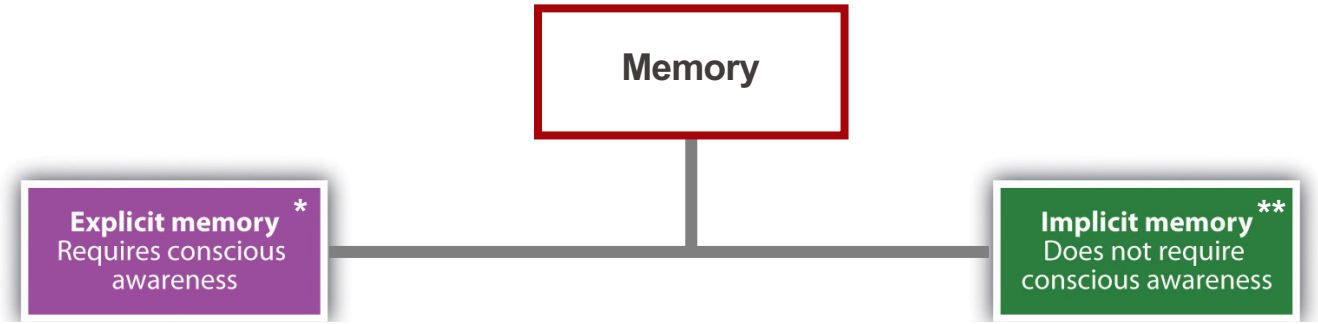
vs.


Neurone 5
Reward
Neurone 8
Punishment
Motivation
Neurone 6
Emotional Value
Neurone 7

https://youtu.be/vcLNNntt6Ts

This animation by Graduate students Julia Hill and Natalia Rozas De O'Laughlin of the Neuroscience Graduate Program at McGovern Medical School at UTHealth explains the concept of synaptic plasticity. It placed third in the 2011 Inaugural Society for Neuroscience Brain Awareness Video Contest.

Memory – Types of Memory

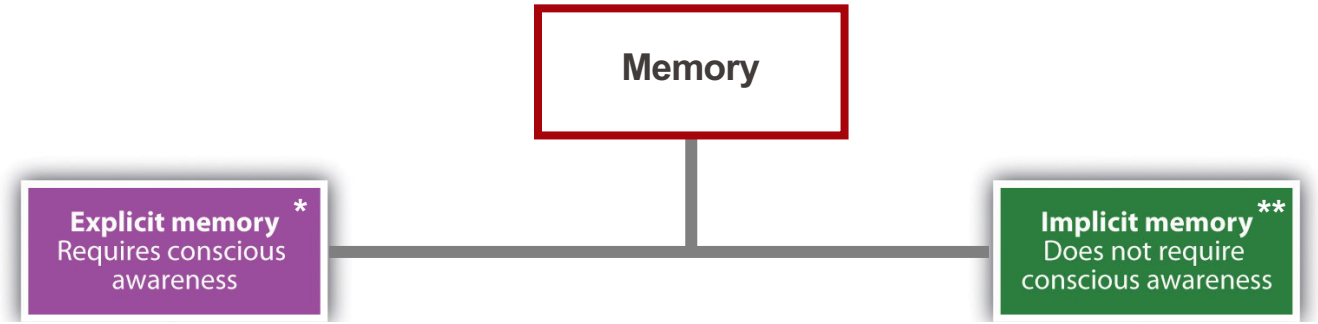


* Declarative

** Non- Declarative

Adapted from Stangor and Walinga, Introduction in Psychology, 2014

Memory – Types of Memory



Recall is Voluntary, Conscious, Verbal (or demonstrable)
Also called **Declarative** memory
Recall or recognition

Involuntary and Unconscious
Require participants to complete a task
Also called **Non-declarative** memory

* Declarative

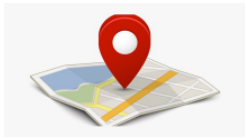
** Non- Declarative

Adapted from Stangor and Walinga, Introduction in Psychology, 2014

Memory – Types of Memory

Memory

- **Explicit memory** * — Requires conscious awareness
  - **Semantic memory** — Facts and general knowledge
  - **Episodic memory** — Personally experienced events
- **Implicit memory** ** — Does not require conscious awareness



* Declarative

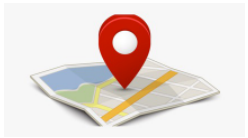
** Non- Declarative

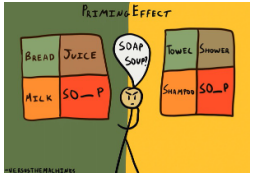
Adapted from Stangor and Walinga, Introduction in Psychology, 2014

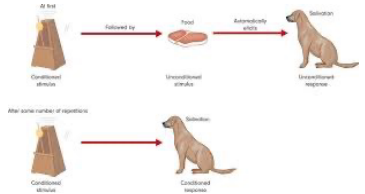
Memory – Types of Memory

Memory

- **Explicit memory** * — Requires conscious awareness
  - **Semantic memory** — Facts and general knowledge
  - **Episodic memory** — Personally experienced events
- **Implicit memory** ** — Does not require conscious awareness
  - **Procedural memory** — Motor and cognitive skills
  - **Priming** — Enhanced identification of objects or words
  - **Learning through classical conditioning**





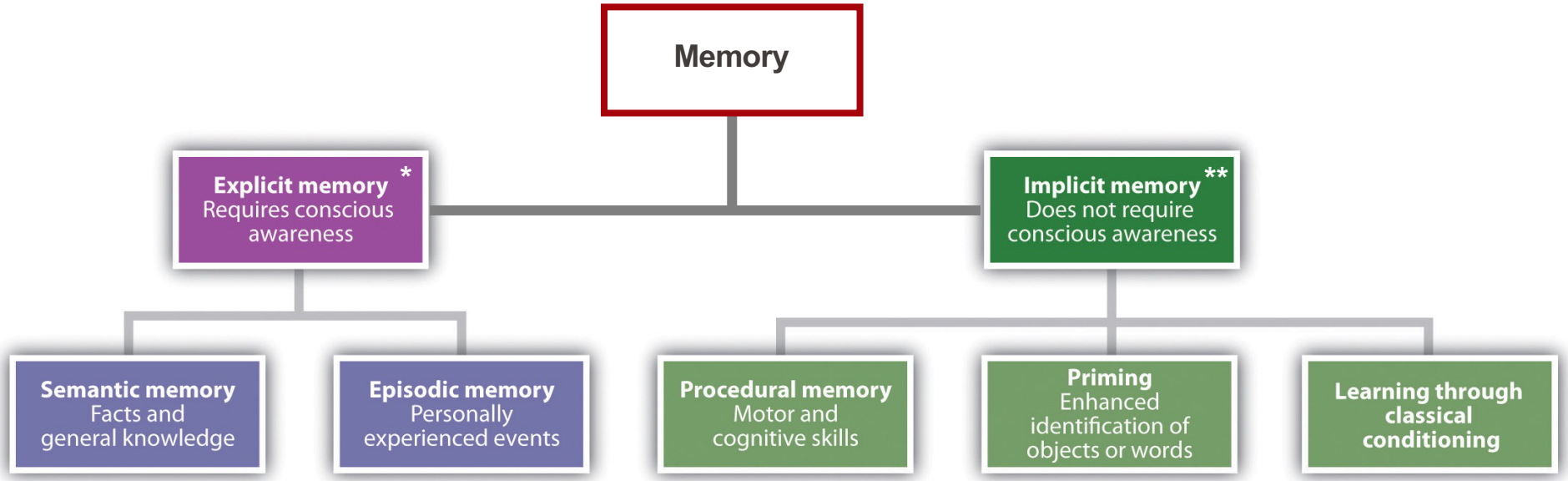


* Declarative

** Non- Declarative

Adapted from Stangor and Walinga, Introduction in Psychology, 2014

Memory – Types of Memory



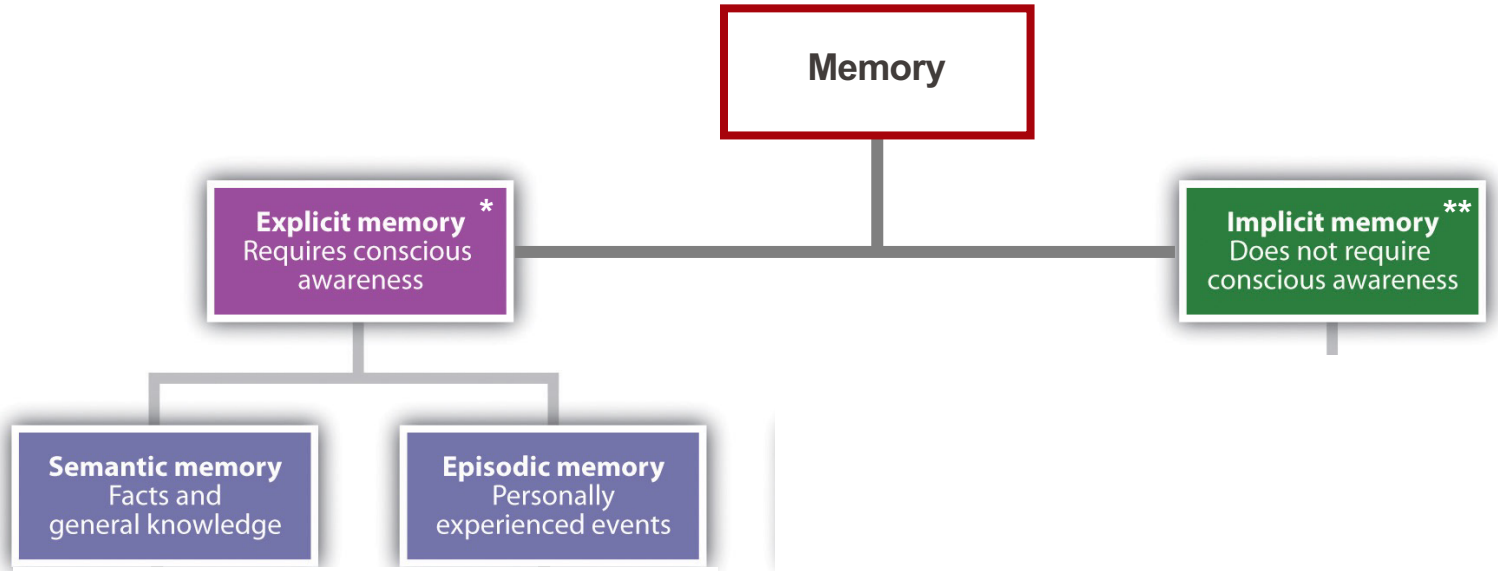
Brain Correlates?

* Declarative

** Non- Declarative

Adapted from Stangor and Walinga, Introduction in Psychology, 2014

Memory – Types of Memory

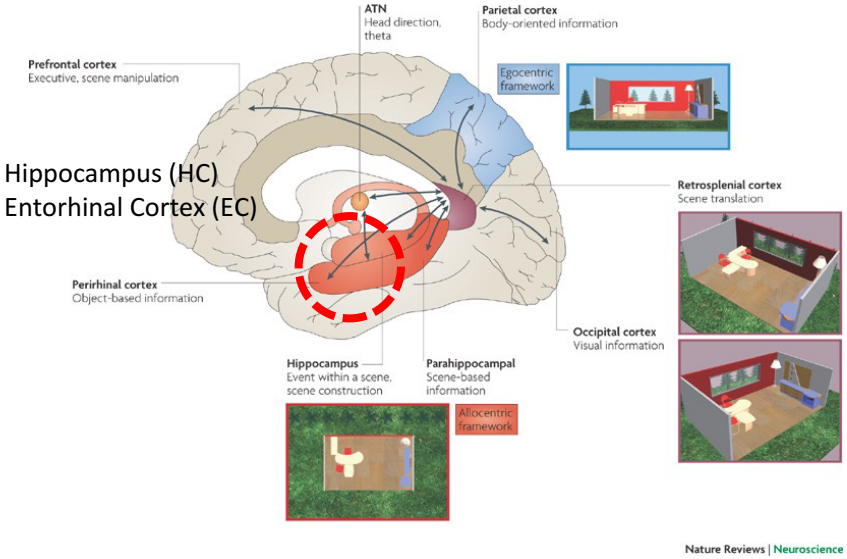


* Declarative

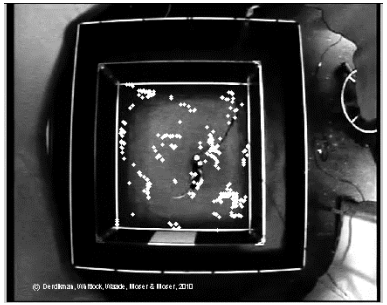
** Non- Declarative

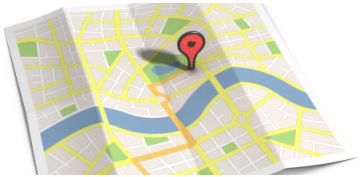
Adapted from Stangor and Walinga, Introduction in Psychology, 2014

Explicit (Declarative) Memory – Animal models



- Grid cells in Entorhinal cortex (EC)



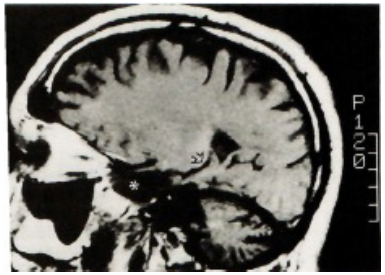


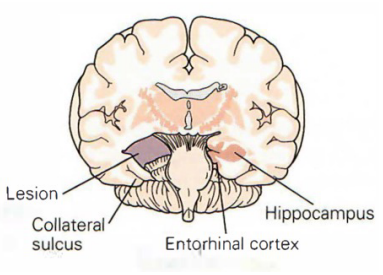
- allocentric spatial representation in the brain
- Spatial navigation
- Memory
- Alzheimer's disease (AD) /MCI

Vann et al., 2009; Moser et al. 2008; Byrne et al. 2007; Kunz et al., 2015

Explicit (Declarative) Memory – Lesion studies

Lesion studies - topographic localization



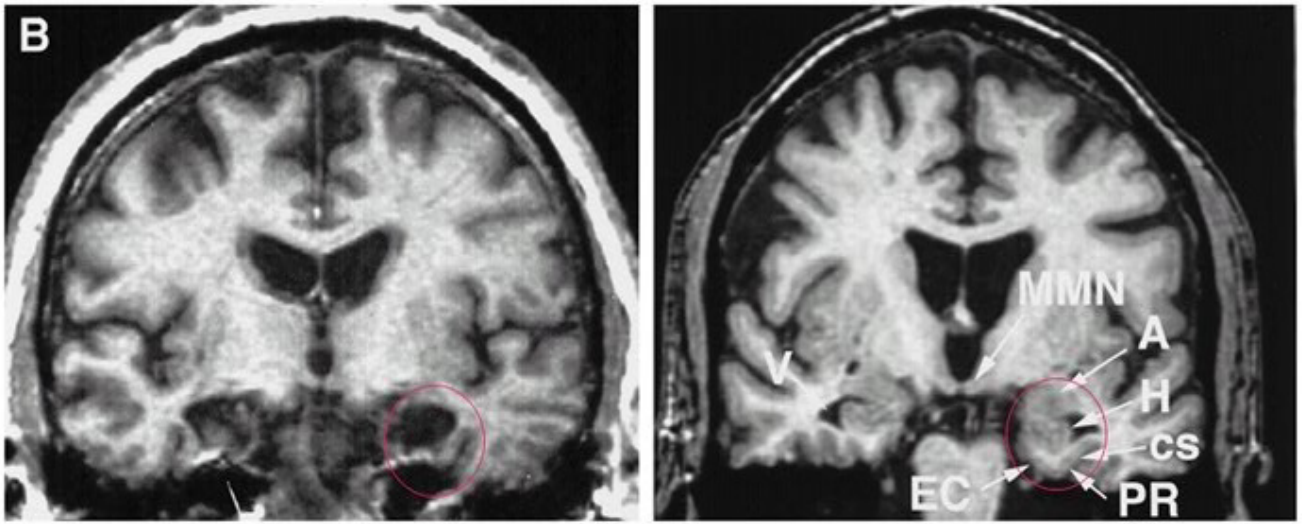


- Patient H.M. (bilateral removal of proportions of the temporal lobe, to treat therapy-resistant epilepsy)
- Deficit in transferring short-term in long term memory, but normal IQ and vocabulary

- *"For several years H.M. saw Milner on an almost monthly basis, yet each time she entered the room H.M. reacted as though he had never seen her before. H.M. had similarly profound difficulty with spatial orientation, It took him about a year to learn his way around a new house."*

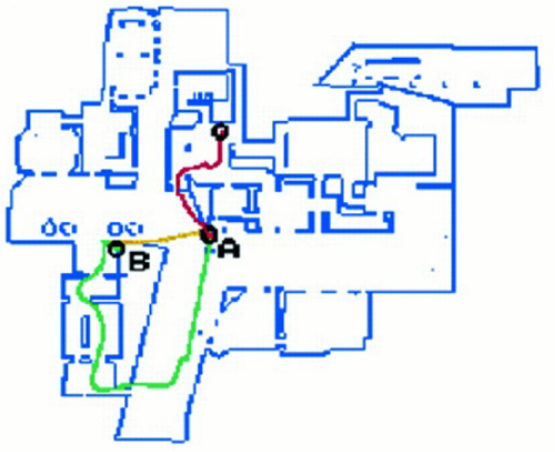
- Ref.: Milner et al. 1968, Neuropsychologia; Kandel et al. 2000, McGraw-Hill.

Patient HM



Bran scans of H.M. (left), and a normal individual (right).

Role of the right hippocampus for spatial navigation



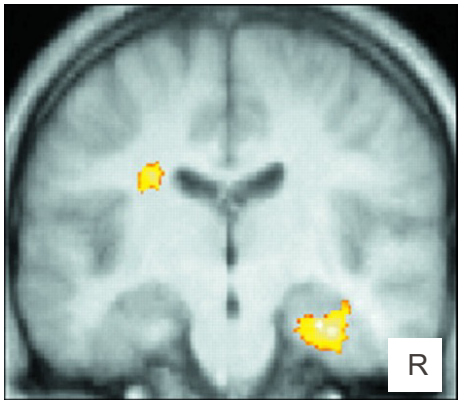
Navigation through a virtual town

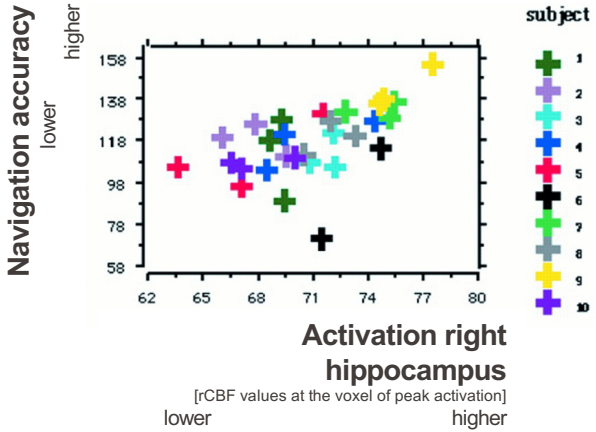
Yellow = accurate trajectory

Green = inaccurate but successful

Red = inaccurate "lost" trajectory

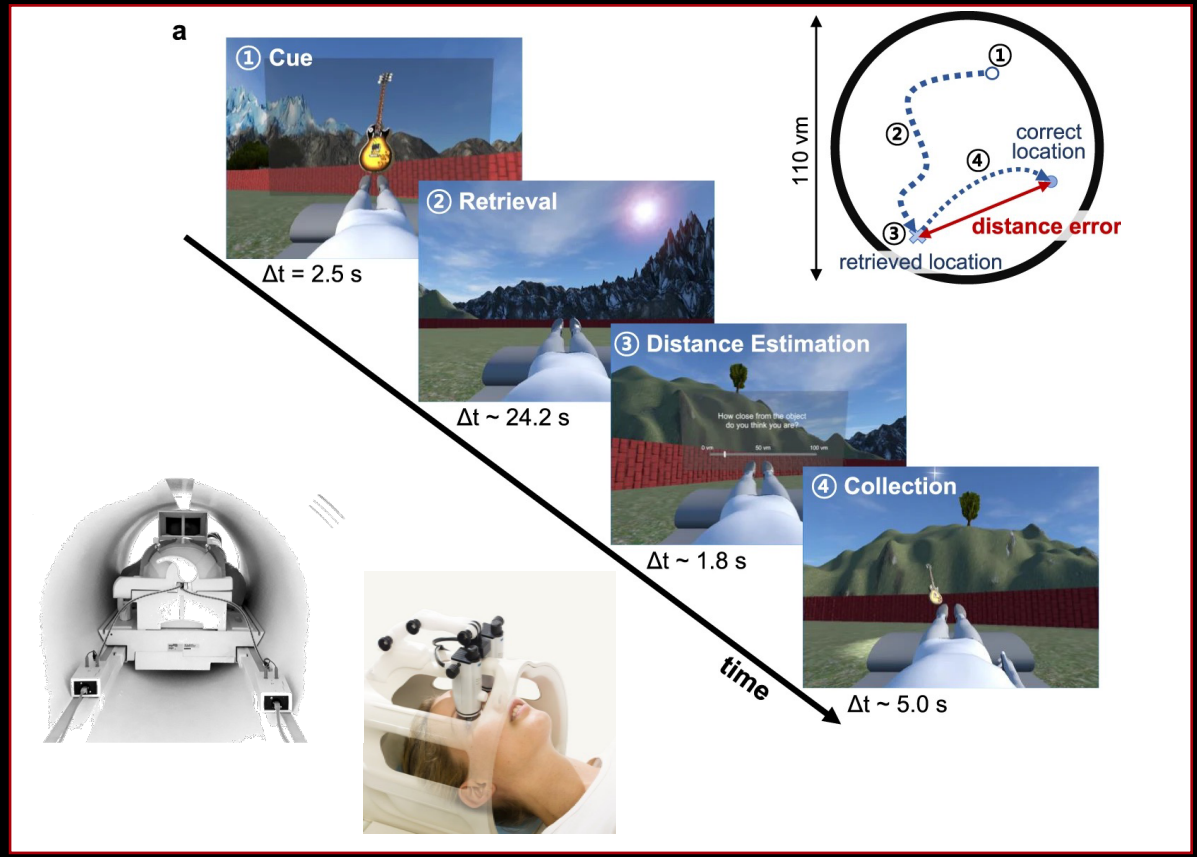
Successful navigation
vs.
control
(following a trail of arrows)





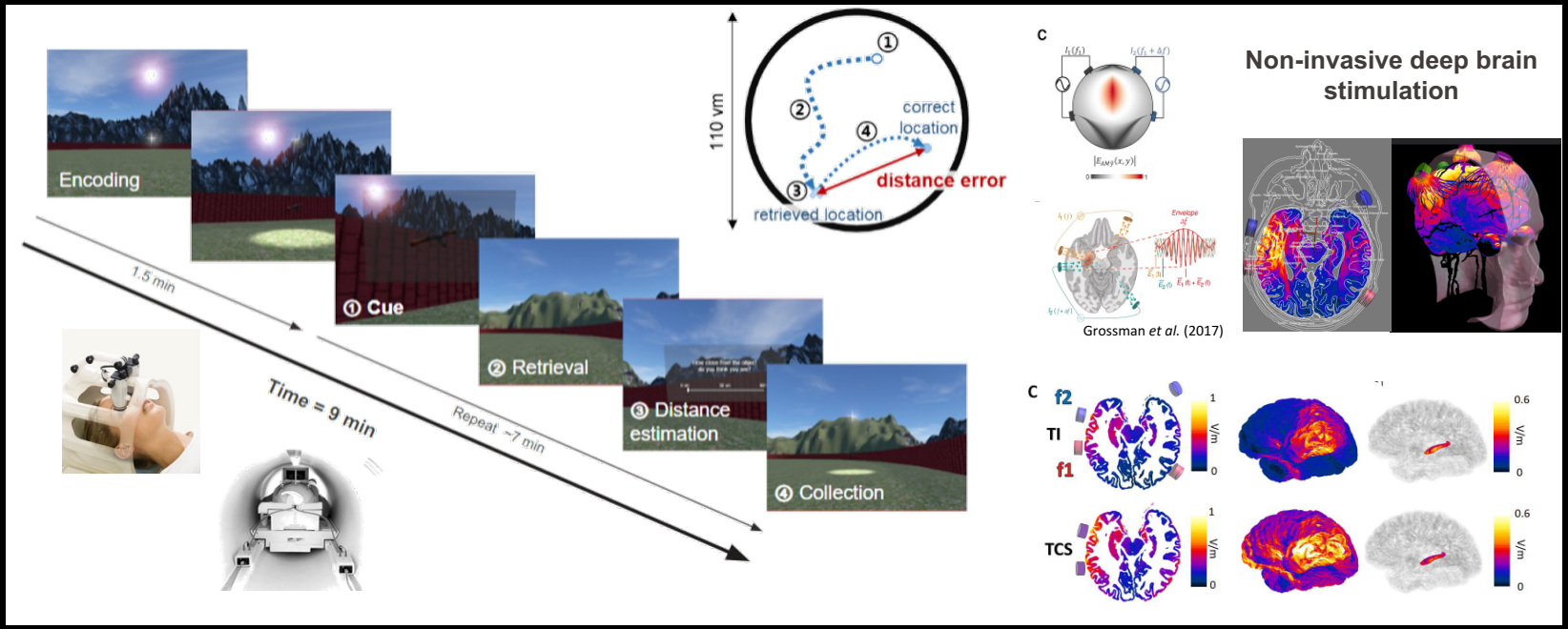
$r = 0.56$, $p < 0.002$

- Ref.: Maguire et al. 1998, Science.

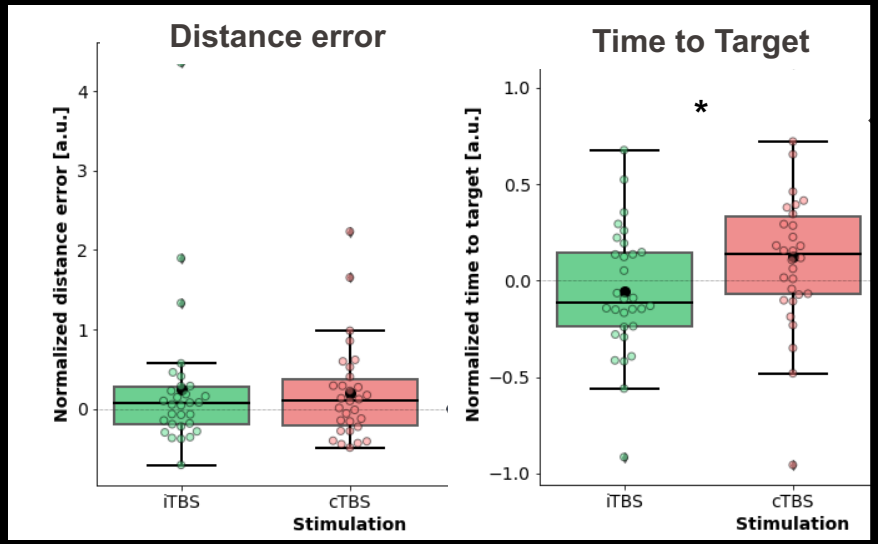


Moon *et al.* Comm Bio (2022)

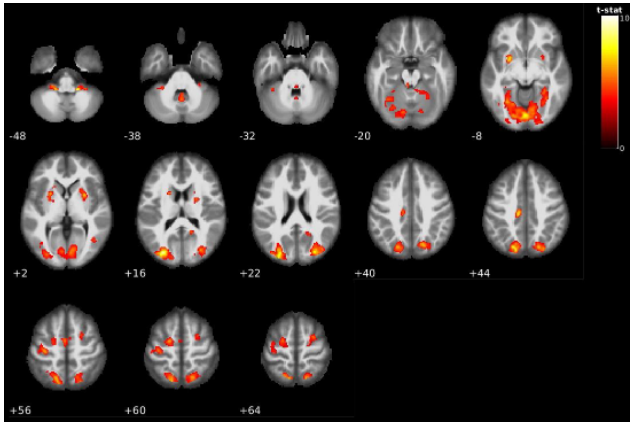
Explicit (Declarative) Memory – VR + Neuroimaging + Neuromodulation

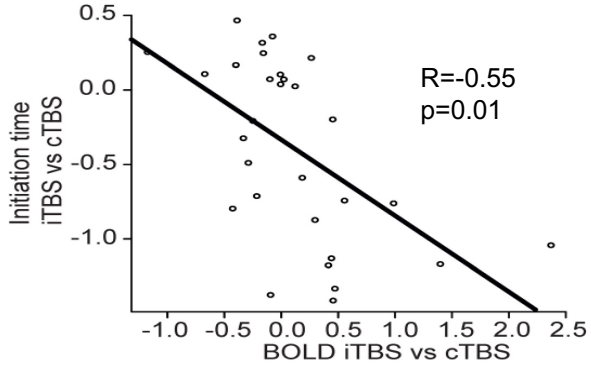


Beanato, Moon *et al.* (in review)



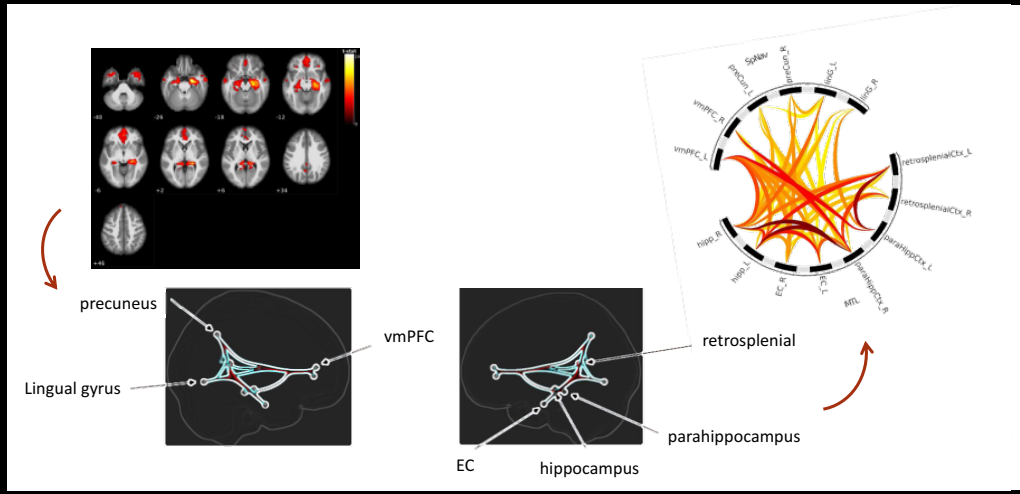
The bigger the hippocampal activity during iTBS vs cTBS the faster subjects retrieve the information about where to go

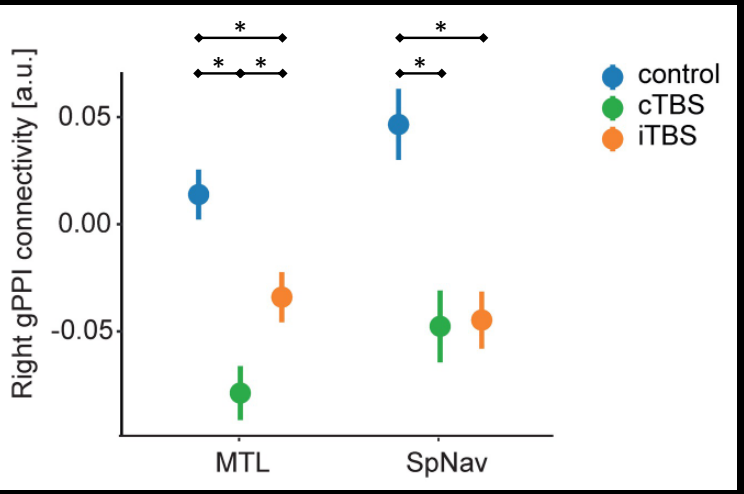




Beanato, Moon *et al.* (in review)

generalized Psychophysiological Interaction (gPPI)



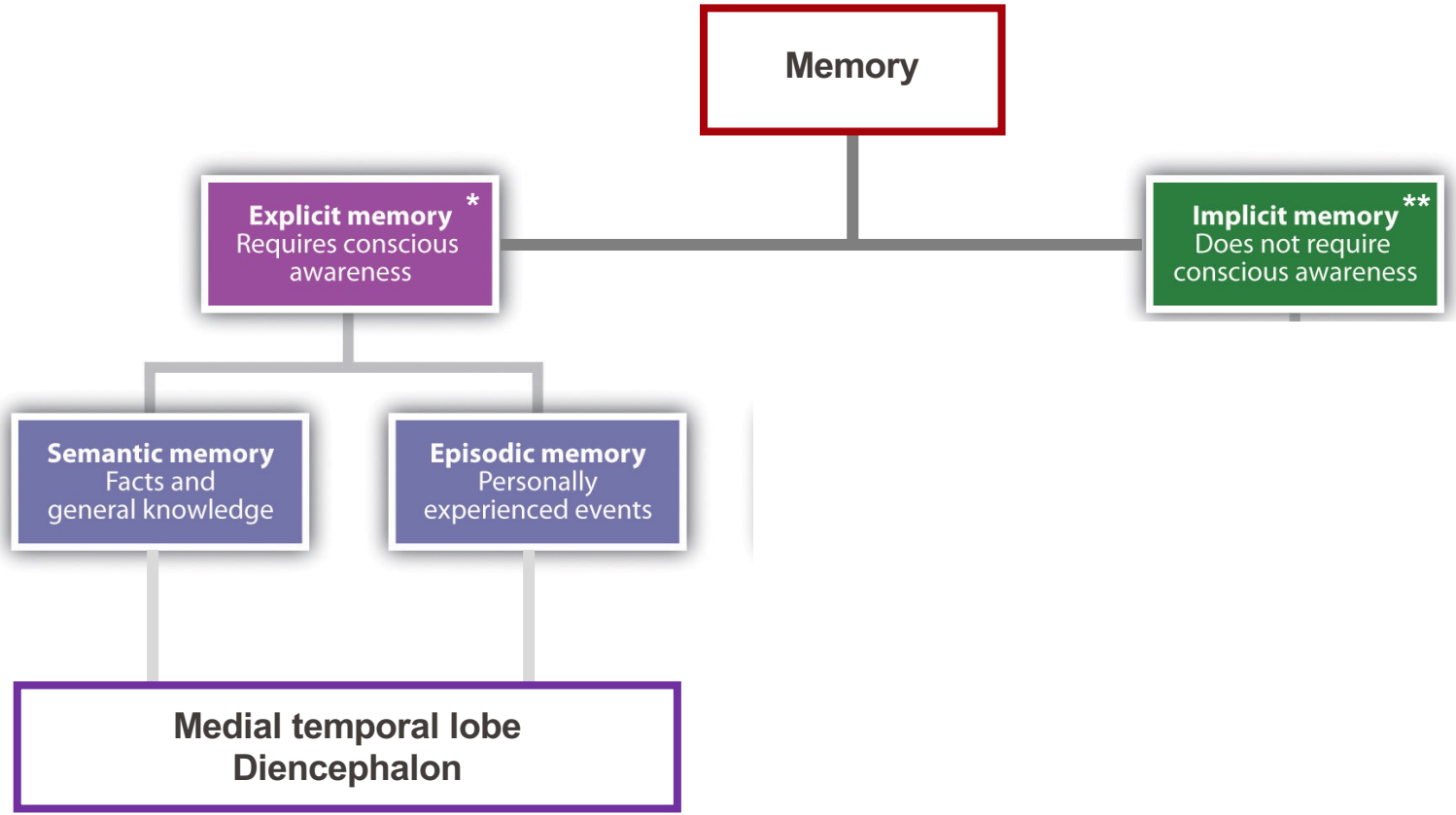


General effect of theta bursts on hippocampal connectivity

Focal effect of **iTBS** versus cTBS within the **right hippocampal connectivity** within the right **MTL**

Beanato, Moon *et al.* (in review)

Memory – Types of Memory

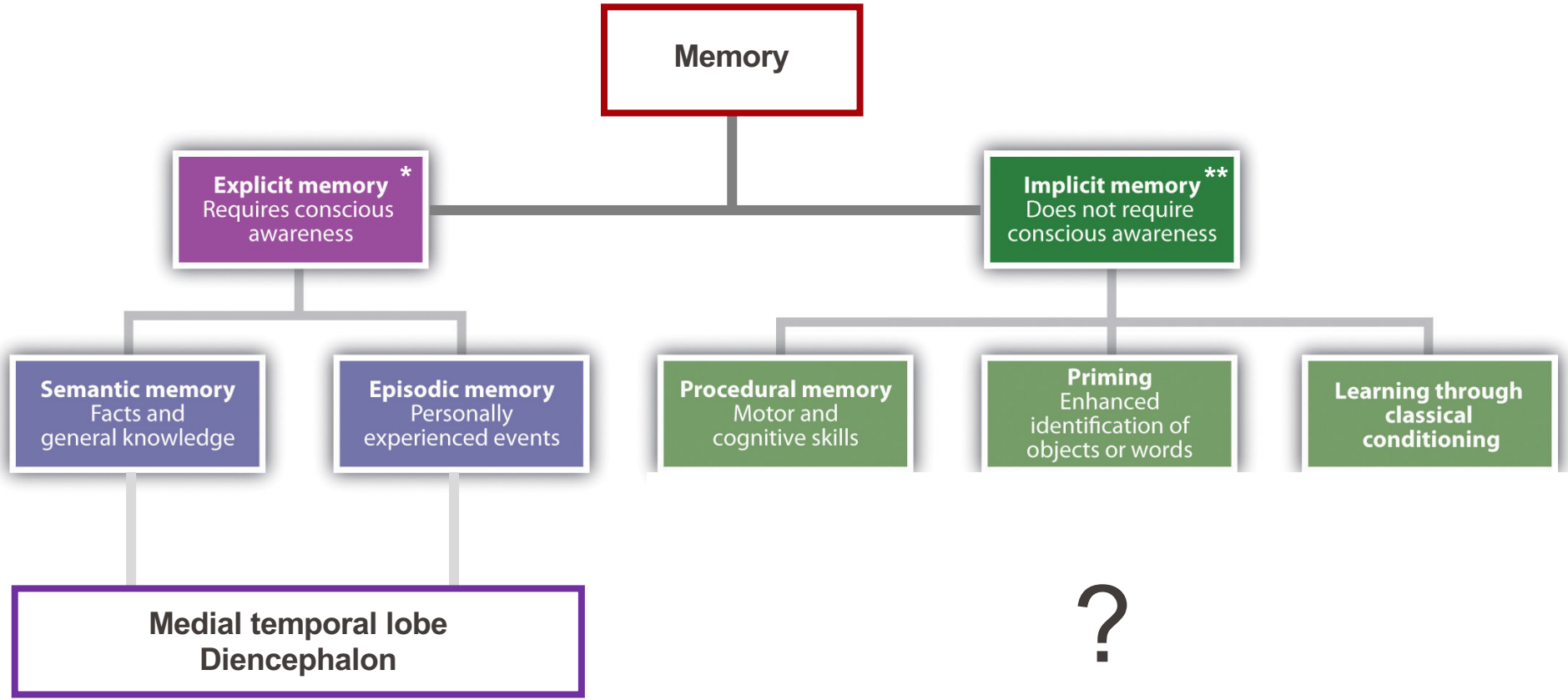


* Declarative

** Non- Declarative

Adapted from Stangor and Walinga, Introduction in Psychology, 2014

Memory – Types of Memory



* Declarative

** Non- Declarative

Adapted from Stangor and Walinga, Introduction in Psychology, 2014

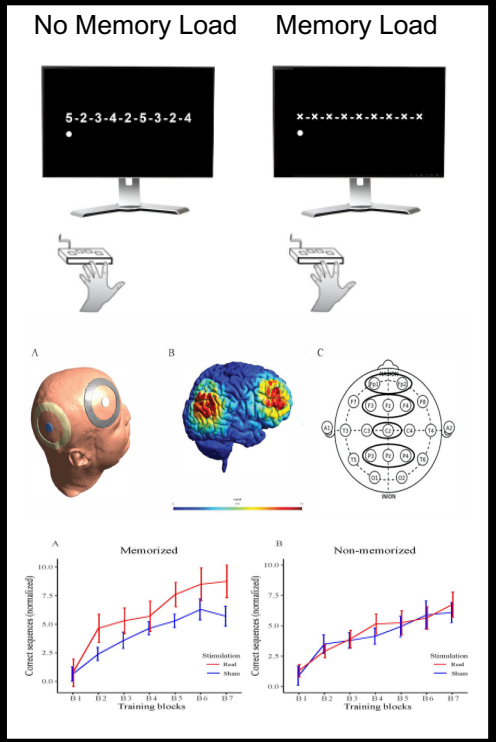
Implicit (Non-Declarative) Memory – Procedural Memory

Implicit (Non-Declarative) Memory – Neuroimaging

M1, PMd, PMv, SMA, **Basal ganglia**, Cerebellum, FPN

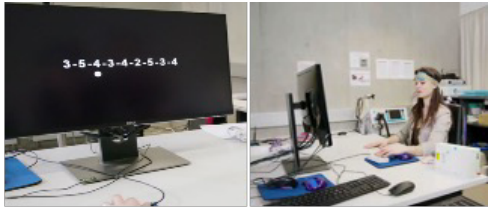
(for review Dyon *et al.* 2009; Diedrichsen & Kornysheva 2015; Krakauer *et al.* 2019)

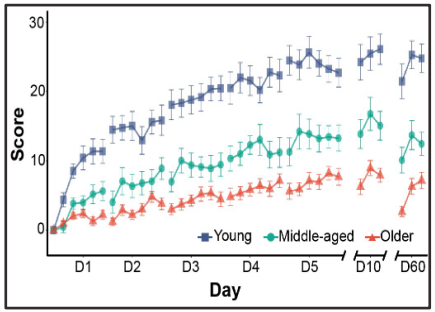
Implicit (Non-Declarative) Memory – Neuromodulation



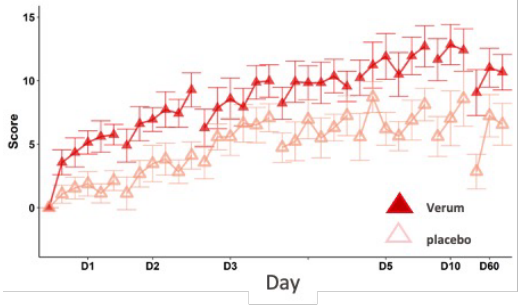
Draaisma *et al.* 2022

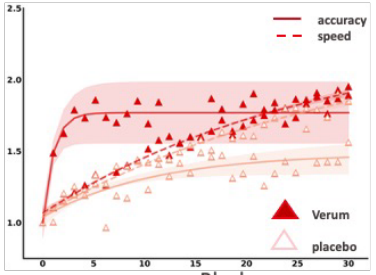
Motor sequence learning



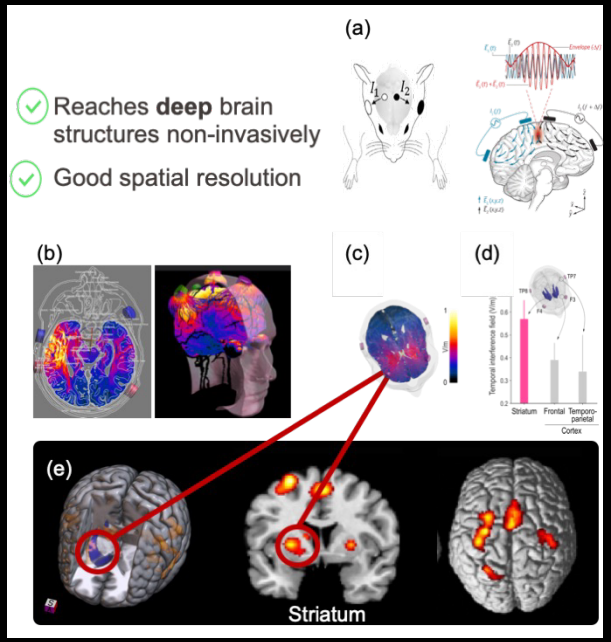


Motor cortex modulation

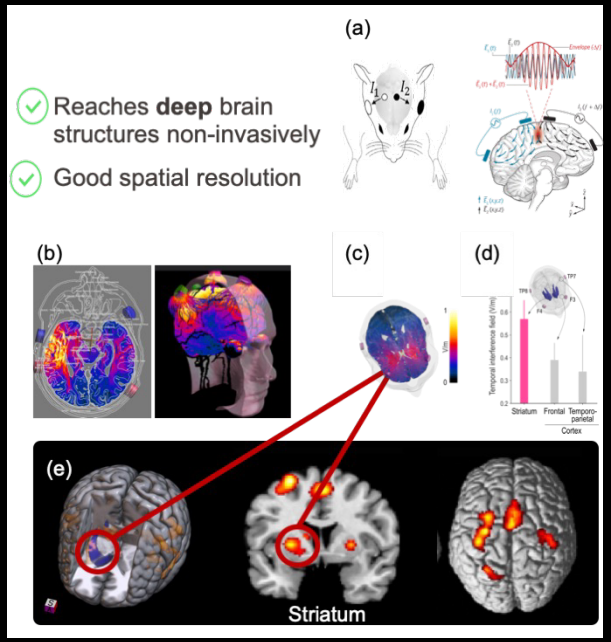


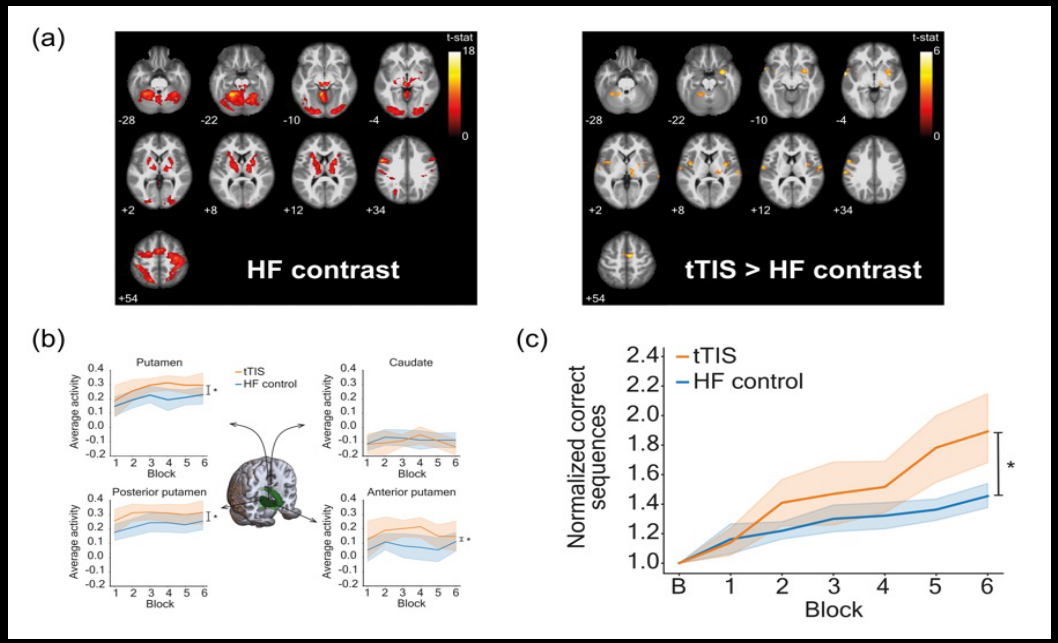


Maceira-Elvira *et al.* 2022



Causal link between human **striatum** and procedural learning and memory?



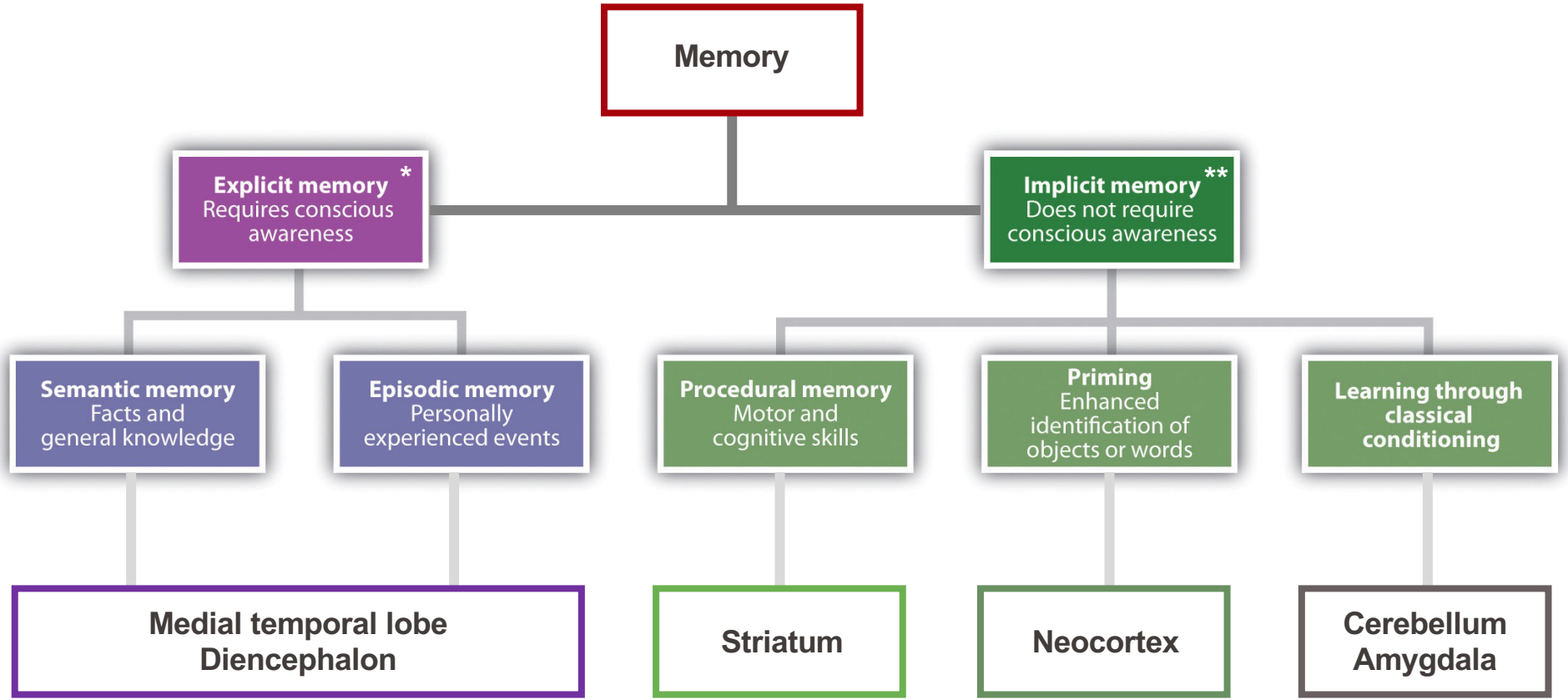


Wessel, Beanato et *al.* Nature Neuroscience 2023

Causal link between human **striatum** and procedural learning and memory

(Please see also e.g., Kandel *et al.* Mcgraw-Hill 6th Ed, 2021; Squire *et al.* 2004; Krakauer *et al.* 2019)

Memory – Types of Memory



* Declarative

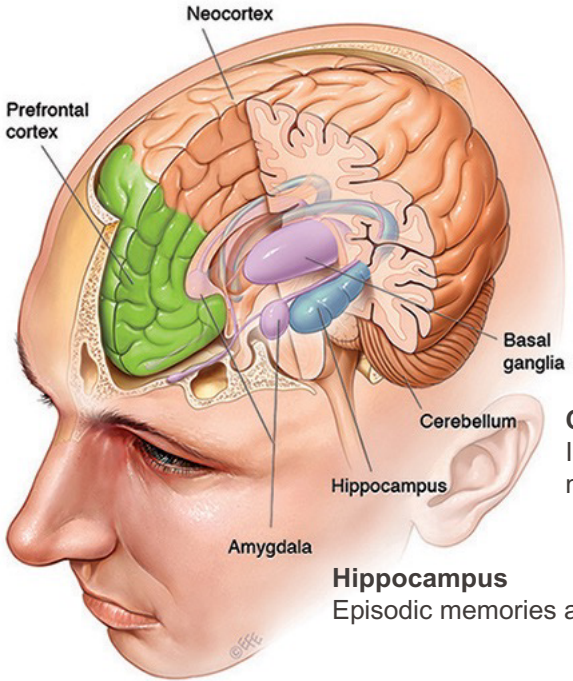
** Non- Declarative

Adapted from Stangor and Walinga, Introduction in Psychology, 2014

In Sum: Memory networks

Friedhelm C. Hummel

Neocortex
Involved in higher cognitive functions (sensory perception, motor commands, spatial reasoning, language…). Transfer, consolidation processes in interaction with the hippocampus



Basal ganglia
Involved in multiple cognitive processes such as emotion, reward processing, habit formation, procedural (motor) learning and memory.

Prefrontal cortex
Involved in many complex cognitive functions.
Short-term/working memory (left more verbal WM, right more spatial WM.

Cerebellum
Involved in motor control and procedural (motor learning and memory processes).

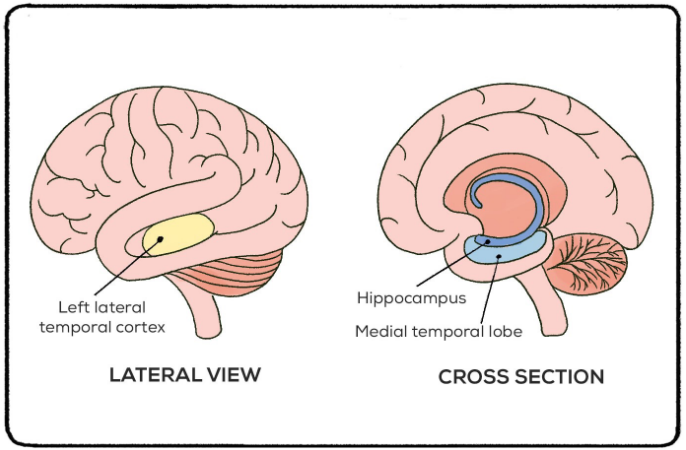
Hippocampus
Episodic memories are formed and stored for later access

Amygdala
Emotional aspects of memory (fear, joy, shame, love). Particularly important strong emotional memories difficult to forget (e.g., PTSD).

Clinical Case

accomplished musicologist, keyboardist, conductor, music producer, and professional tenor (Westminster Cathedral)

- Brain infection (herpes encephalitis)
- Affecting especially the parts of his brain concerned with memory (hippocampus bilaterally erased)
- Memory span of only seconds
- Anterograde amnesia and retrograde amnesia
- ‘30 seconds clive’
- ‘feeling/love’ for wife and musical expertise remained



Oliver Sacks, 2007, The New Yorker
Pract Psych 2022

'…His ability to **perceive** what he saw and heard was **unimpaired**. But he did **not** seem to be able to **retain** any impression of anything for more than **a blink**. Indeed, if he did **blink**, his eyelids parted to reveal a **new scene**. The view before the blink was utterly forgotten. Each blink, each glance away and back, brought him an entirely new view. I tried to imagine how it was for him. . . . Something akin to a film with bad continuity, the glass half empty, then full, the cigarette suddenly longer, the actor's hair now tousled, now smooth. But this was real life, a room changing in ways that were physically impossible…'

'…It was as if **every waking moment** was the **first** waking moment. Clive was under the constant impression that he had just emerged from unconsciousness because he had no evidence in his own mind of ever being awake before. . . .
"I haven't heard anything, seen anything, touched anything, smelled anything," he would say. "It's like being dead." …'

(Deborah Clive's wife; 2005, "Forever Today")

Oliver Sacks, 2007, The New Yorker

'…holding something in the palm of one hand, and repeatedly covering and uncovering it with the other hand as if he were a magician practising a disappearing trick. He was holding a chocolate. He could feel the chocolate unmoving in his left palm, and yet every time he lifted his hand he told me it revealed a brand new chocolate.

"Look!" he said. *"It's new!"* He couldn't take his eyes off it.

"It's the same chocolate," I said gently.

"No . . . look! It's changed. It wasn't like that before . . ." He covered and uncovered the chocolate every couple of seconds, lifting and looking.

"Look! It's different again! How do they do it?"

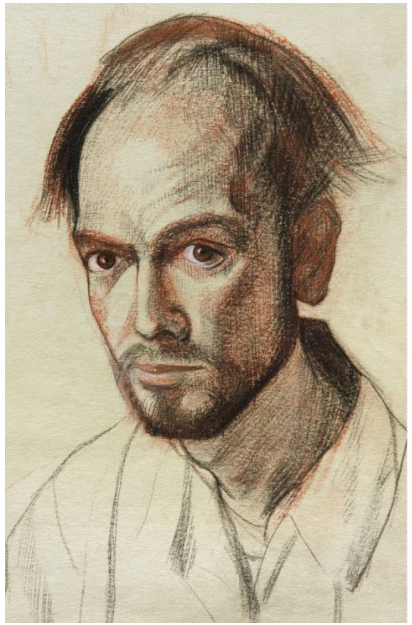
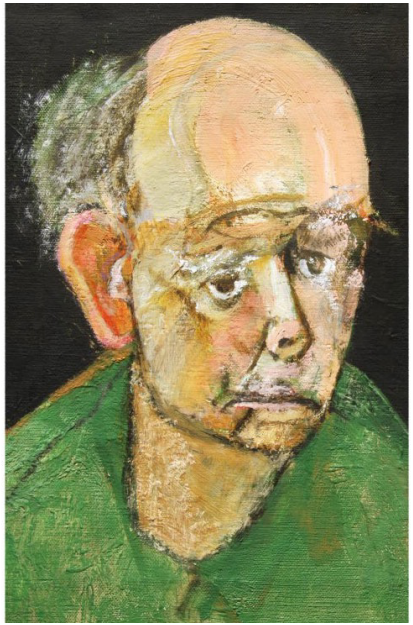
'…The only times of feeling alive were when Deborah visited him. But the moment she left, he was desperate once again, and by the time she got home, ten or fifteen minutes later, she would find repeated messages from him on her answering machine: *"Please come and see me, darling—it's been ages since I've seen you. Please fly here at the speed of light.""*

(Deborah Clive's wife; 2005, "Forever Today")

Oliver Sacks, 2007, The New Yorker

- **Memory** refers to the ability to **store** and **retrieve** information over time.
- **Explicit** memory refers to experiences that can be **intentionally** and **consciously** remembered, and
- it is measured using **recall**, **recognition**, and **relearning**.
- **Explicit** memory includes **episodic** and **semantic** memories.
- **Implicit** memory refers to the influence of **experience** on behaviour, even if **not aware** of those influences.
- The three types of implicit memory are **procedural memory**, **classical conditioning**, and **priming**.
- Information processing begins in **sensory** memory, moves to **short-term** memory, and eventually moves to l**ong-term** memory.
- The **capacity** of long-term memory is **large**, and there is no known limit to what we can remember.
- **Defined brain** regions involved in specific aspects of memory
- **LTP/LTD** one of the core underlying mechanism

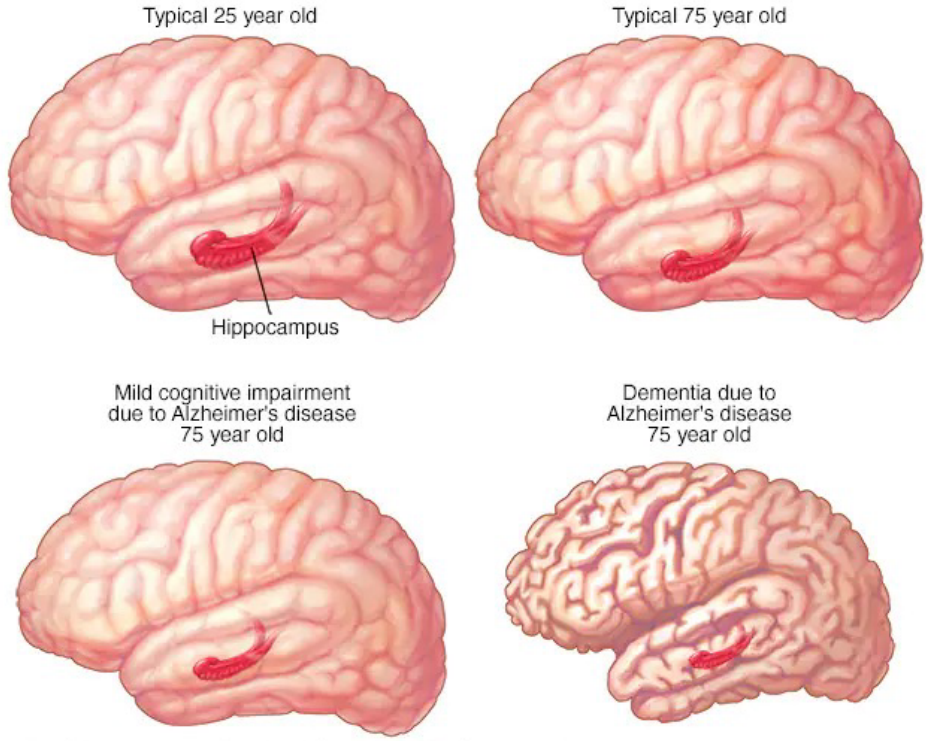
Questions?


https://www.boredpanda.com

Healthy Aging vs. Minimal cognitive impairment vs. Dementia

Memory disorders

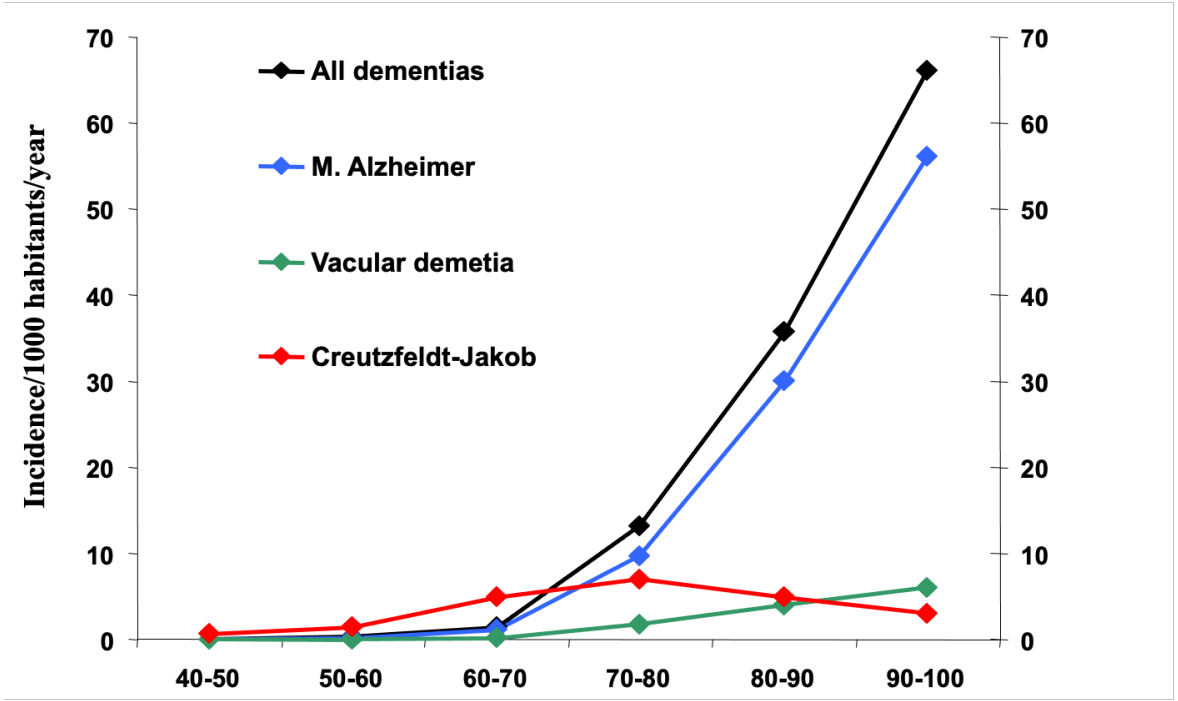


Dementia

- Umbrella term for symptoms complex (memory, perception, behaviour, language, and personality)
- Different underlying pathologies (not a single disease)
- Brain areas degenerate progressively

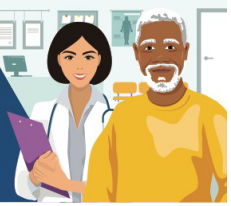
Alzheimers disease international

Dementia

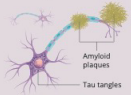
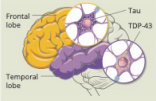
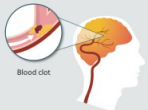

Incidence/1000 habitants/year
70
60
50
40
30
20
10
0
All dementias
M. Alzheimer
Vacular demetia
Creutzfeldt-Jakob
40-50
50-60
60-70
70-80
80-90
90-100

Understanding Different Types of Dementia

As we age, it's normal to lose some neurons in the brain. People living with dementia, however, experience far greater loss. Many neurons stop working, lose connections with other brain cells, and eventually die. At first, symptoms can be mild, but they get worse over time. Read on to learn more about four different types of dementia.



TYPES OF DEMENTIA

Alzheimer's Disease	Frontotemporal Dementia	Lewy Body Dementia	Vascular Dementia
What Is Happening in the Brain?*			
Abnormal deposits of proteins form amyloid plaques and tau tangles throughout the brain. 	Abnormal amounts or forms of tau and TDP-43 proteins accumulate inside neurons in the frontal and temporal lobes. 	Abnormal deposits of the alpha-synuclein protein, called "Lewy bodies," affect the brain's chemical messengers. 	Conditions, such as blood clots, disrupt blood flow in the brain. 
*These changes are just one piece of a complex puzzle that scientists are studying to understand the underlying causes of these forms of dementia and others.			
Symptoms			
Mild • Wandering and getting lost • Repeating questions **Moderate** • Problems recognizing friends and family • Impulsive behavior **Severe** • Cannot communicate	**Behavioral and Emotional** • Difficulty planning and organizing • Impulsive behaviors • Emotional flatness or excessive emotions **Movement Problems** • Shaky hands • Problems with balance and walking **Language Problems** • Difficulty making or understanding speech *There are several types of frontotemporal disorders, and symptoms can vary by type.*	**Cognitive Decline** • Inability to concentrate, pay attention, or stay alert • Disorganized or illogical ideas **Movement Problems** • Muscle rigidity • Loss of coordination • Reduced facial expression **Sleep Disorders** • Insomnia • Excessive daytime sleepiness **Visual Hallucinations**	• Forgetting current or past events • Misplacing items • Trouble following instructions or learning new information • Hallucinations or delusions • Poor judgment
Typical Age of Diagnosis			
Mid 60s and above, with some cases in mid-30s to 60s	Between 45 and 64	50 or older	Over 65

Diagnosis

Symptoms can be similar among different types of dementia, and some people have more than one form of dementia, which can make an accurate diagnosis difficult. Symptoms can also vary from person to person. Doctors may ask for a medical history, complete a physical exam, and order neurological and laboratory tests to help diagnose dementia.

Treatment

There is currently no cure for these types of dementia, but some treatments are available. Speak with your doctor to find out what might work best for you.

Living with dementia can be challenging, but there are ways to manage it. To learn more about these types of dementia and other conditions that can cause dementia, visit **www.nia.nih.gov/health/what-is-dementia**.

NIH National Institute on Aging

More Details week 3!