Memory Systems
and
Their Neuronal Underpinnings

FGS, January 2019

First steps:

- What is System
- What is Level in a System
- What is Memory

System:

- A set of units and their interrelationship
- A group of related elements organized for a purpose
- A portion of the universe selected for study

Multiple levels of the brain and its analysis

- Level of organization: structural hierarchy, e.g., from the molecular (angstrom) to the behavioural (meters); lower levels can still be highly complex
- Level of processing: hierarchy of information processing, the highest level being the most distant from the input or the one encoding the most global representation
- Level of analysis: the levels in the operation of a problem-solving system

Levels of Analysis of a Problem-Solving System

- Computational Theory: *The goal of the system, e.g. register, associate*
- Algorithms: *How is the goal obtained step-by-step, e.g. if X do Y then W etc.*
- Hardware implementation: *How is the algorithm implemented in the hardware of the system, e.g. use receptor to detect X, enzyme to do Y, another enzyme to do W*

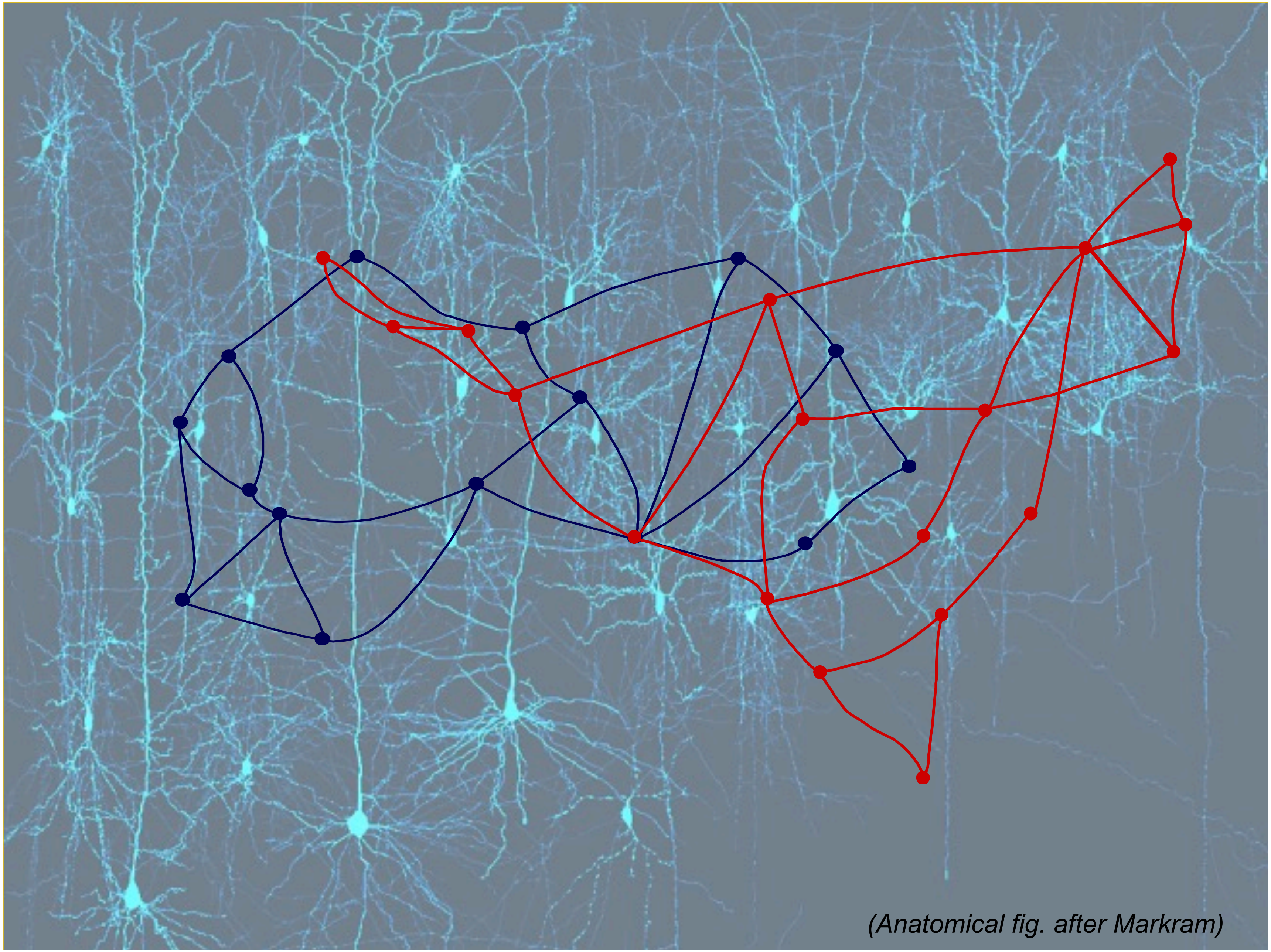
(Marr 1982)

The brain encodes internal representations, which are:

- Maps of event space in neuronal coding space
- Neuronally-encoded structured versions of the world, which could potentially guide behaviour

(Dudai 2002)

Representations are *assumed* to be distributed over spatiotemporal activity patterns of neuronal circuits



Internal representations could be formed in multiple ways:

- By the unfolding of genetic information (innate, a priori), in development
- By individual experience (*instruction*, *selection-'Darwinian'*)
- By the interaction of both

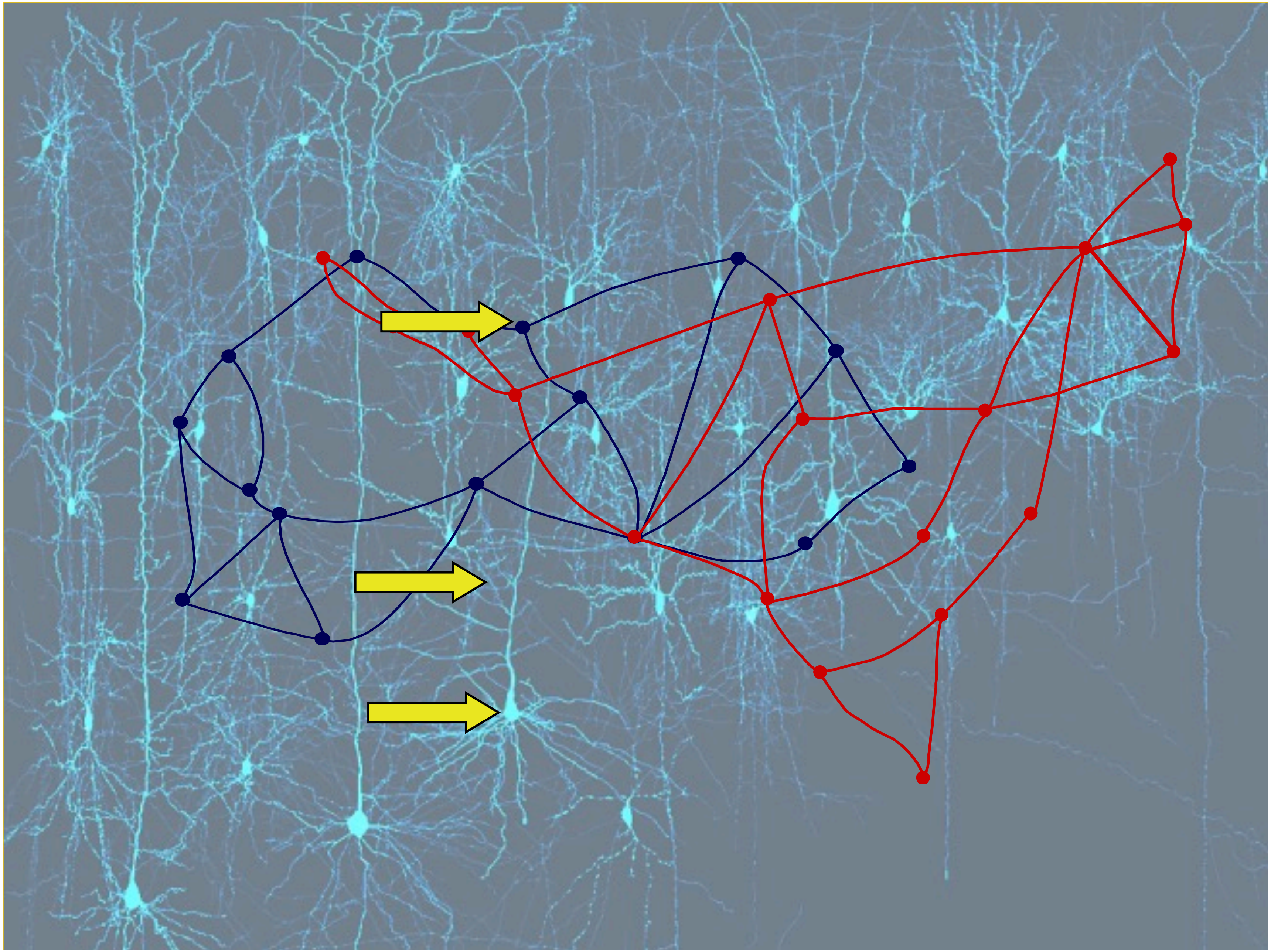
We are now in a position to define learning and memory:

Learning is:

- Induction of an alteration in behavior or in the behavioral potential, which results from the individual's experience (the classical, behvaioural type of definition)
- The acquisition of information, or the reorganization of information that results in new knowledge (the informational type of definition)
- **Experience-dependent generation of enduring internal-representations, or lasting modifications in such representations (the representational, updated type of definition)**

(Dudai 2002)

Changes in representations could be induced by changes in synapses, neurites and cell bodies, including nucleus



Memory is:

- An enduring change in behavior, or in the behavioral potential, which results from the individual's behavioral experience
- The retention over time of learned information
- **The retention over time of experience-dependent internal representations, or the capacity to reactivate or reconstruct such representations**

Note: Learning and memory are multi-level phenomena; they ultimately make sense only if the representational level is considered

(Dudai 2002)

The Synaptic Plasticity and Memory Hypothesis

Activity-dependent synaptic plasticity is induced at appropriate synapses during memory formation, and is both necessary and sufficient for the information storage underlying the type of memory mediated by the brain area in which that plasticity is observed.

(Martin, Grimwood & Morris 2000)

Is this correct? Although a tenet of neurobiology of memory, doubts are now casted. One should dissociate representation from persistence (‘storage’); is the nucleus the key for the latter (‘epigenetics’)?

(Chen…. Glanzman, 2014)

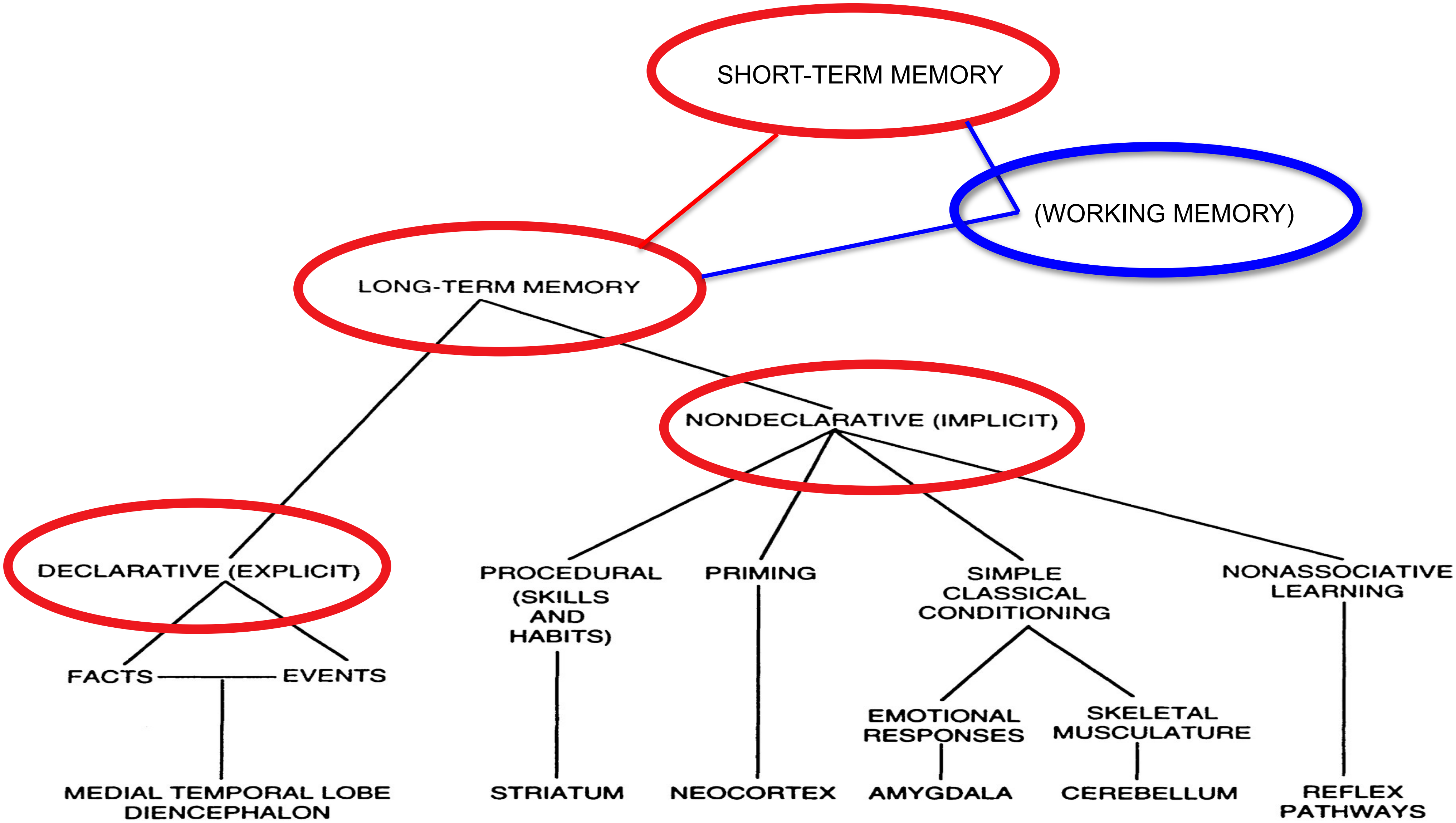
Memory is not monolithic
Multiple taxonomies are possible

- By time
- By type of acquisition

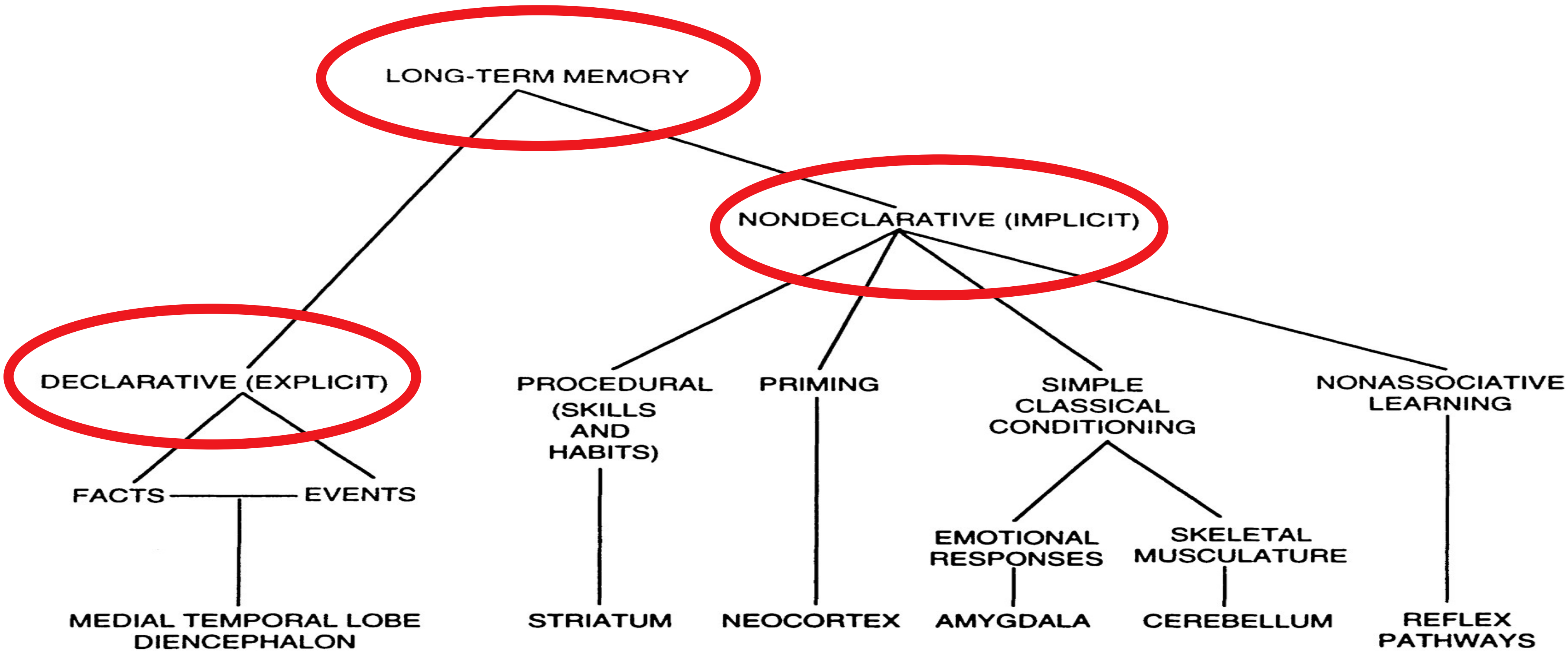
- By type of content
- By purpose

  - and more

Classic Taxonomy of memory systems by type/content



What is the origin of the classification of memory systems by type/content



The rationale was findings from clinical cases of memory loss

The amnesic syndrome

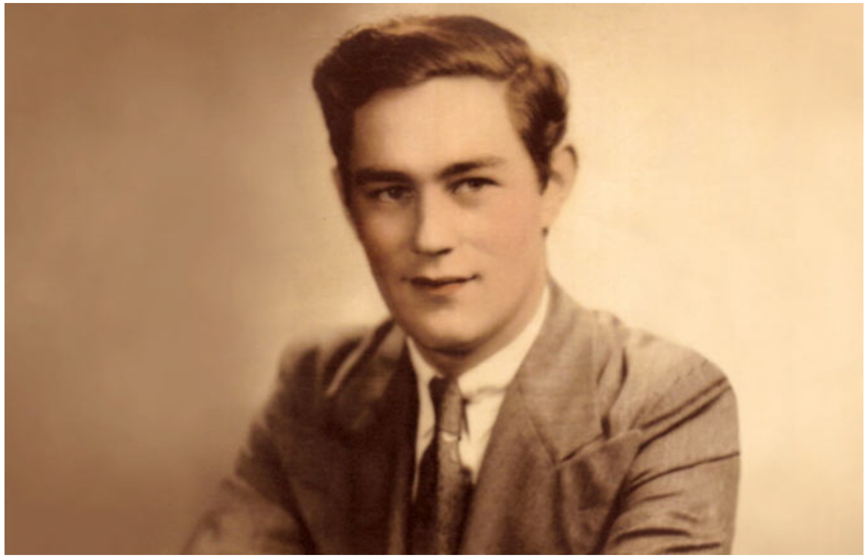
Amnesia:

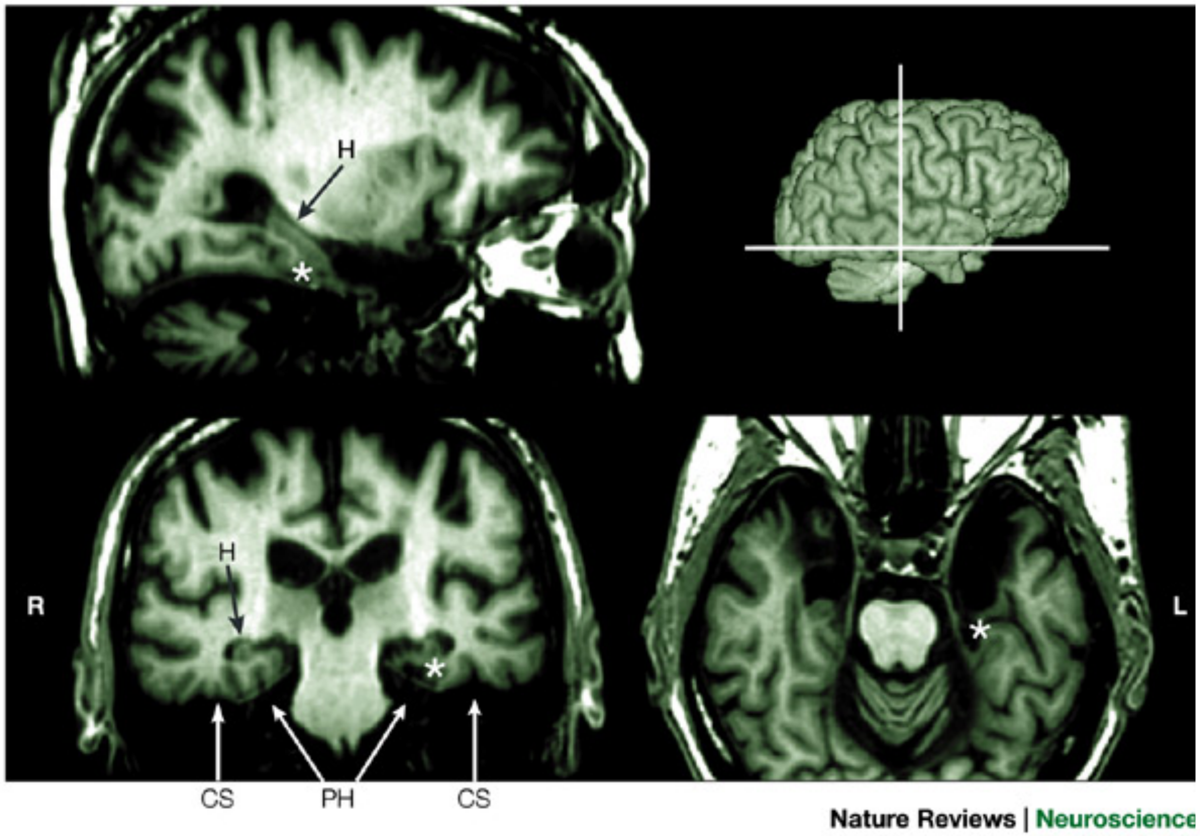
1. The loss or absence of memory.
2. *The amnestic syndrome*: A marked, chronic impairment in memory in the absence of other major cognitive deficits

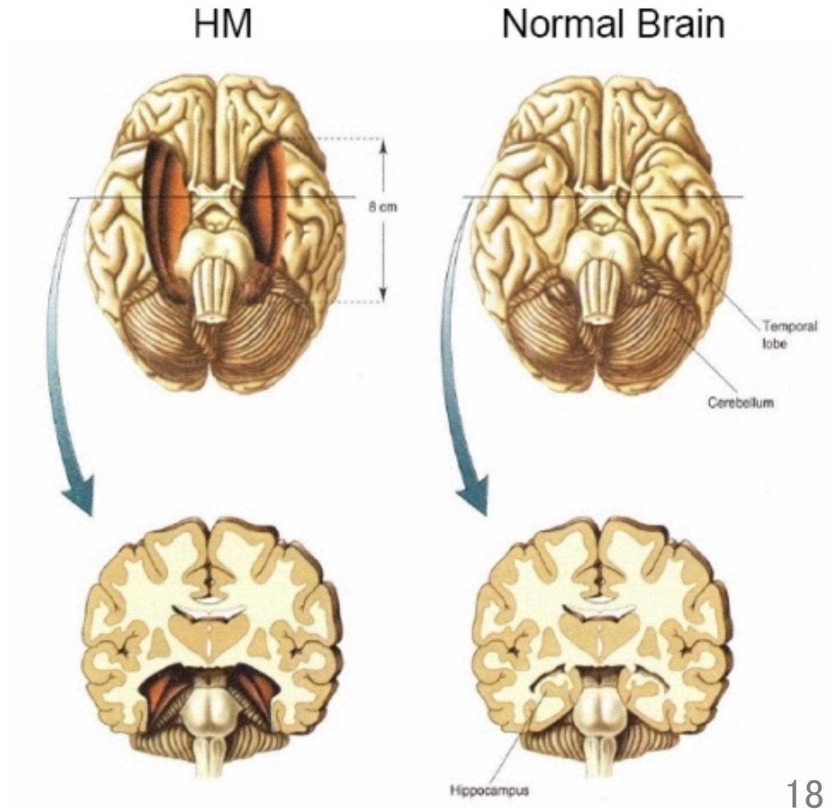
Types of amnesia (by cause):

- Organic amnesia: The consequence of damage to the brain inflicted by injury, disease, or surgical intervention
- Substance-induced amnesia: The consequence of the consumption of certain poisons, drugs (e.g. benzodiazepines), or drugs of abuse
- Functional amnesia: The consequence of severe mental stress or trauma, or of certain affective disorders (pyschogenic or dissociative amnesia)

The 'Classic' Amnesic: H.M. (Henry G. Molaison, 1926-2008)







H.M. amnesia was evident on a great variety of tasks

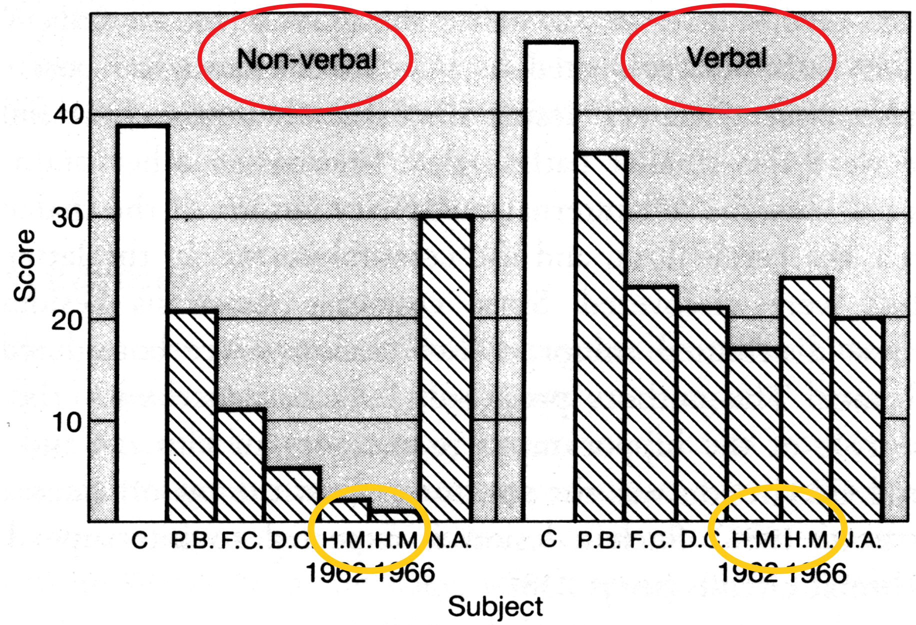
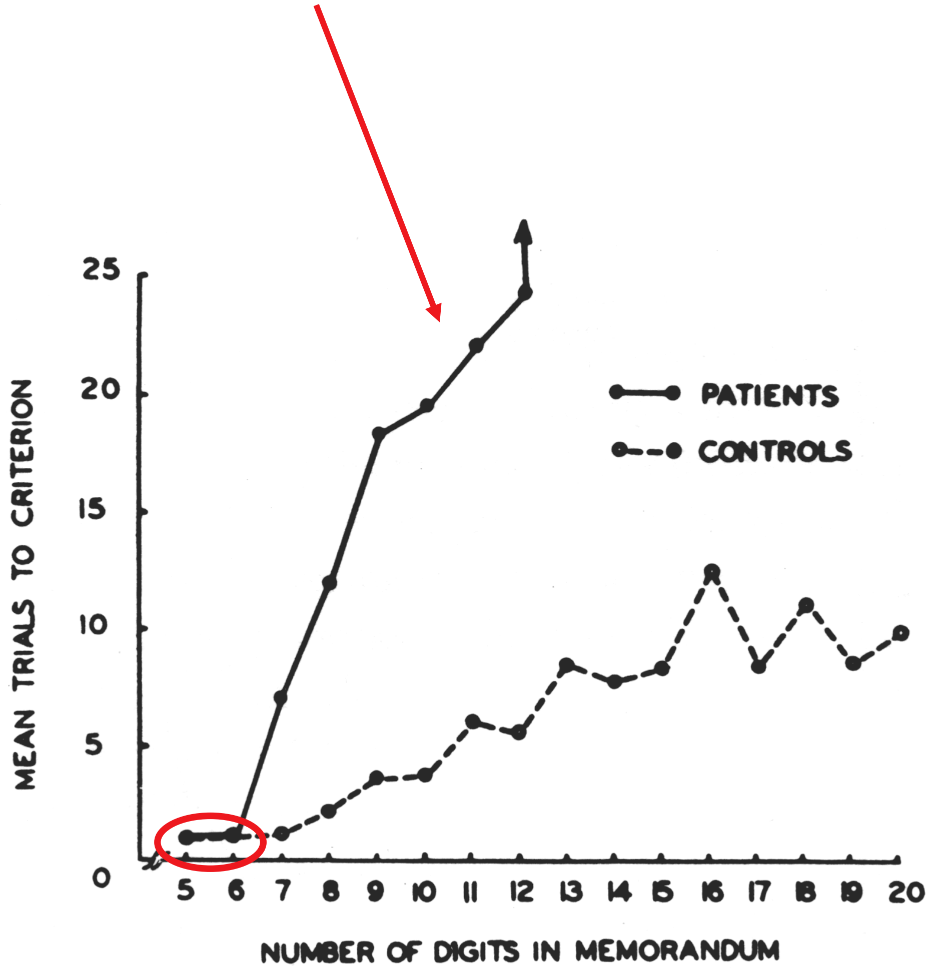


Fig. 15.2. Performance of H.M., N.A., and other amnesics on visual recognition tasks. The subjects had to recognize nonsense designs (non-verbal task), or nonsense syllables, or three-digit numbers (verbal task). For details of the test, see text. C, controls; P.B. and F.C. sustained unilateral left temporal lobectomies; D.C. had a bilateral medial-temporal resection combined with orbitofrontal undercutting. H.M. was tested twice, 9 and 13 years post-surgery. N.A. was tested 4 years post-injury. (From Teuber *et al.* 1968.)

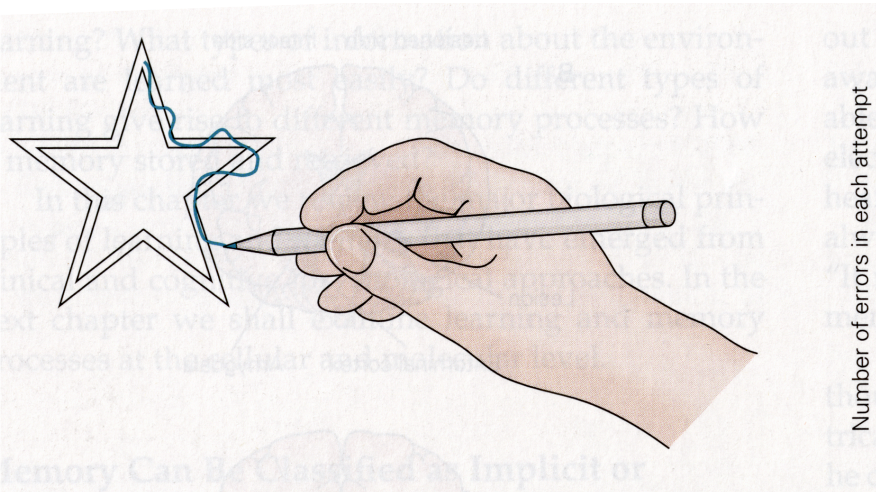
H.M had a normal short-term memory span but failed on long-term memory tests

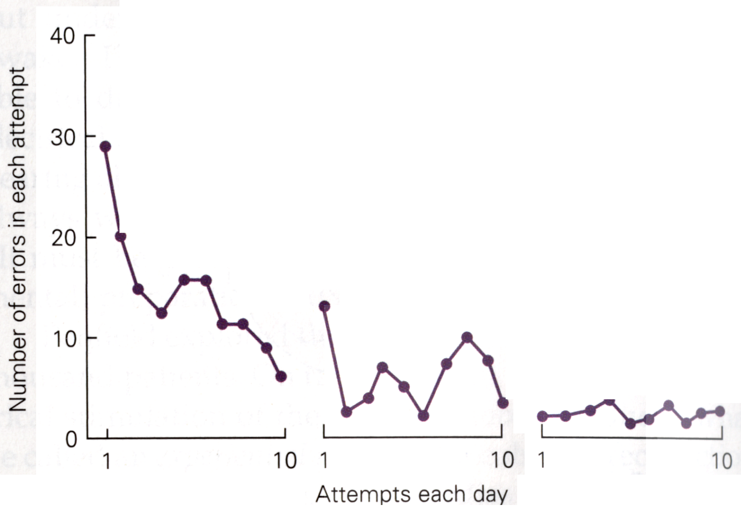


Since H.M. could acquire memory and retain it for a short-while, he is affected in either the consolidation or the storage of long-term memory, or in both

But was H.M. really incapable of mastering new knowledge?

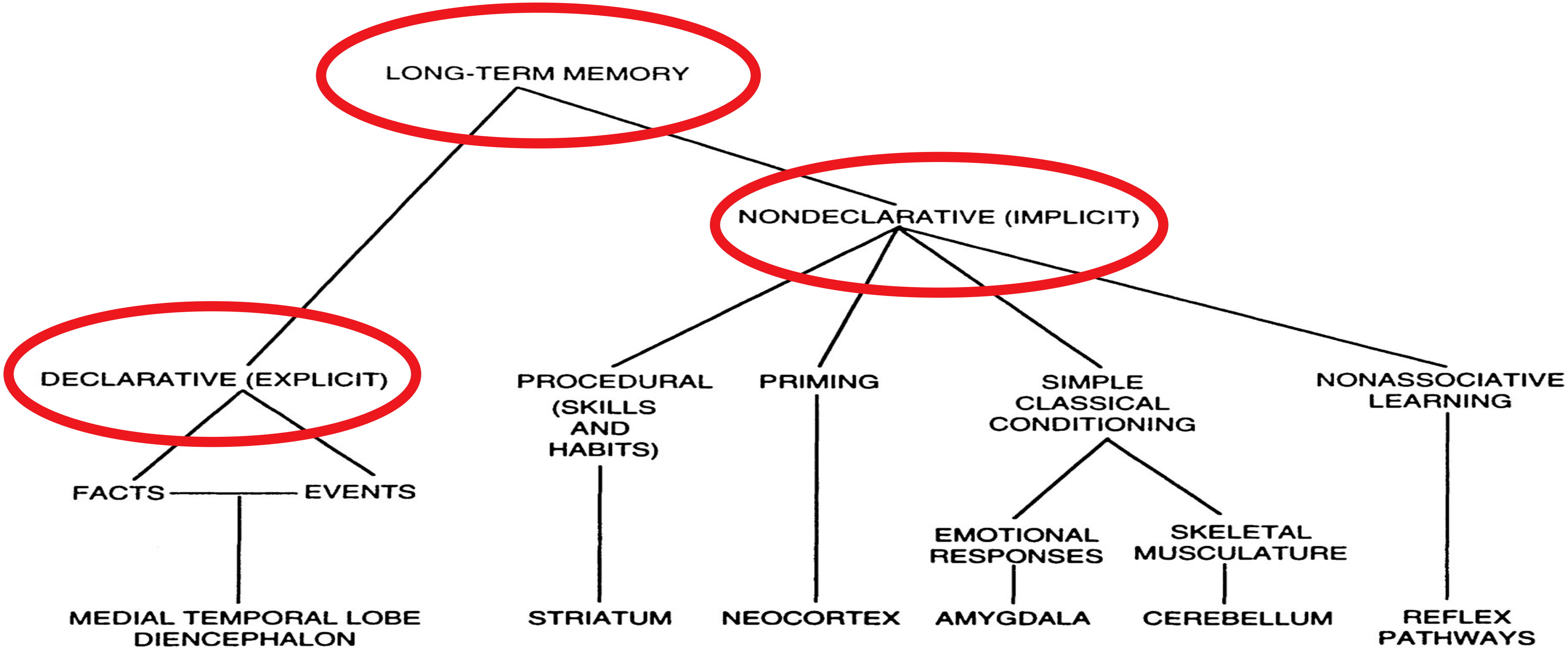
The skill | The memory curve





H.M. and similar patients can master skills
(without ever knowing that have been trained on the task)

This type of finding led to the classification of long-term memory systems into ‘declarative’ and ‘non-declarative’



- <u>Declarative:</u> Conscious awareness required for retrieval
- <u>Non-declarative:</u> Conscious awareness not obligatory for retrieval

System:

- A set of units and their interrelationship
- A group of related elements organized for a purpose
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In recent years data is accumulating that shows that the hippocampus, long considered the hallmark of declarative memory, participates in non-declarative memory as well

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Behavioral/Systems/Cognitive

Unconscious Relational Inference Recruits the Hippocampus

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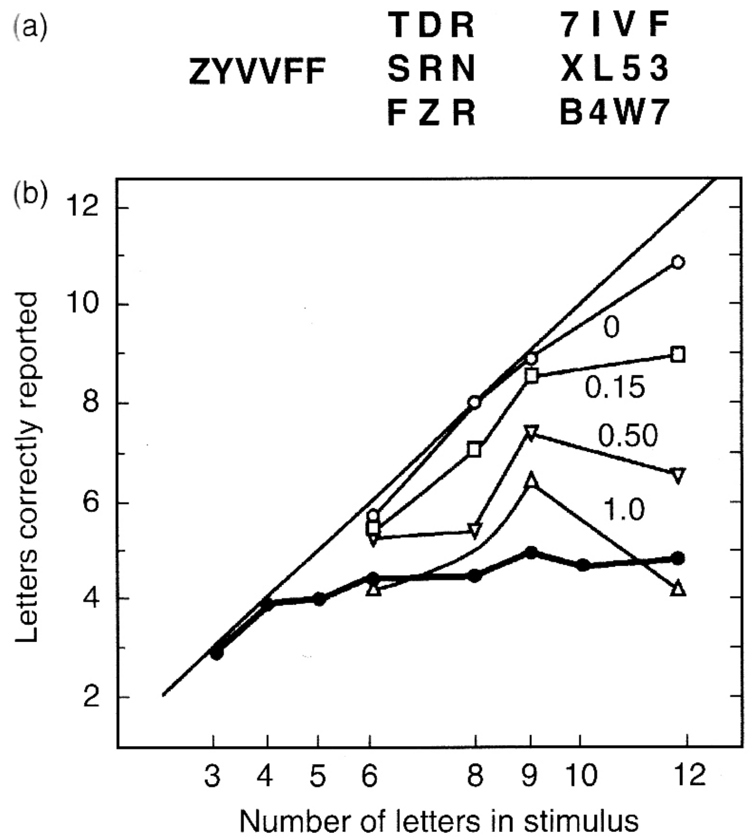
Relational inference denotes the capacity to encode, flexibly retrieve, and integrate multiple memories to combine past experiences to update knowledge and improve decision-making in new situations. Although relational inference is thought to depend on the hippocampus and consciousness, we now show in young, healthy men that it may occur outside consciousness but still recruits the hippocampus. In temporally distinct and unique subliminal episodes, we presented word pairs that either overlapped ("winter–red", "red– computer") or not. Effects of unconscious relational inference emerged in reaction times recorded during unconscious encoding and in the outcome of decisions made 1 min later at test, when participants judged the semantic relatedness of two supraliminal words. These words were either episodically related through a common word ("winter– computer" related through "red") or unrelated. Hippocampal activity increased during the unconscious encoding of overlapping versus nonoverlapping word pairs and during the unconscious retrieval of episodically related versus unrelated words. Furthermore, hippocampal activity during unconscious encoding predicted the outcome of decisions made at test. Hence, unconscious inference may influence decision-making in new situations.

Additional, selected phenomenological properties of memory, that should be assigned mechanistic models, and may cast light on the nature of memory systems:

- Persistence
- Capacity
- Veracitiy

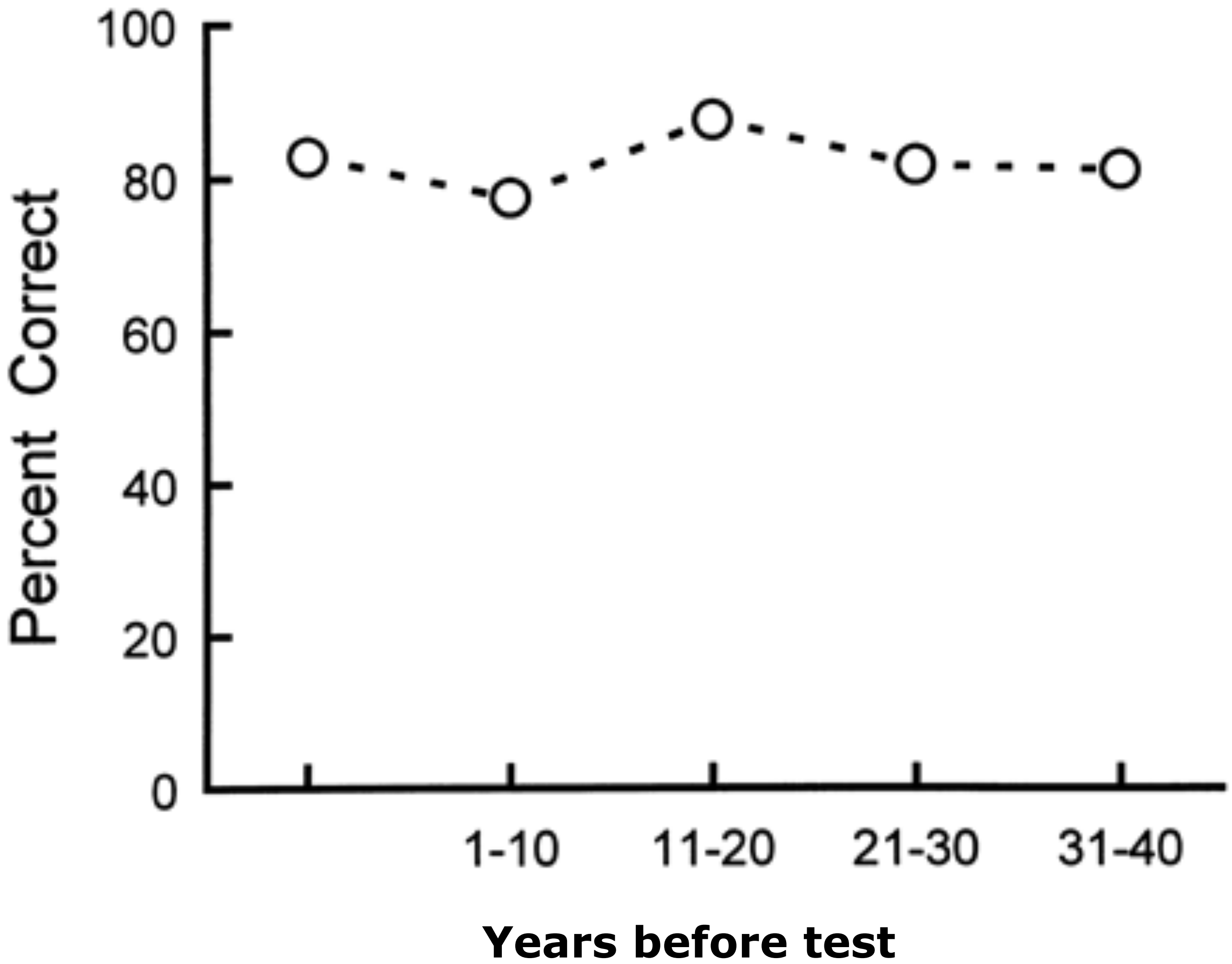
Persistence

The briefest memory: Sensory, e.g. Iconic



Sperling (1960): (a) Nonsense stimuli, each for 50 ms, reported capacity = 4 items
(b) With a preceding tone marking the line, the number goes up much higher, but the information is stored for less than 1 sec.

The longest memory: A life time



(Reed and Squire 1998)

Some other memories decline with normal ageing

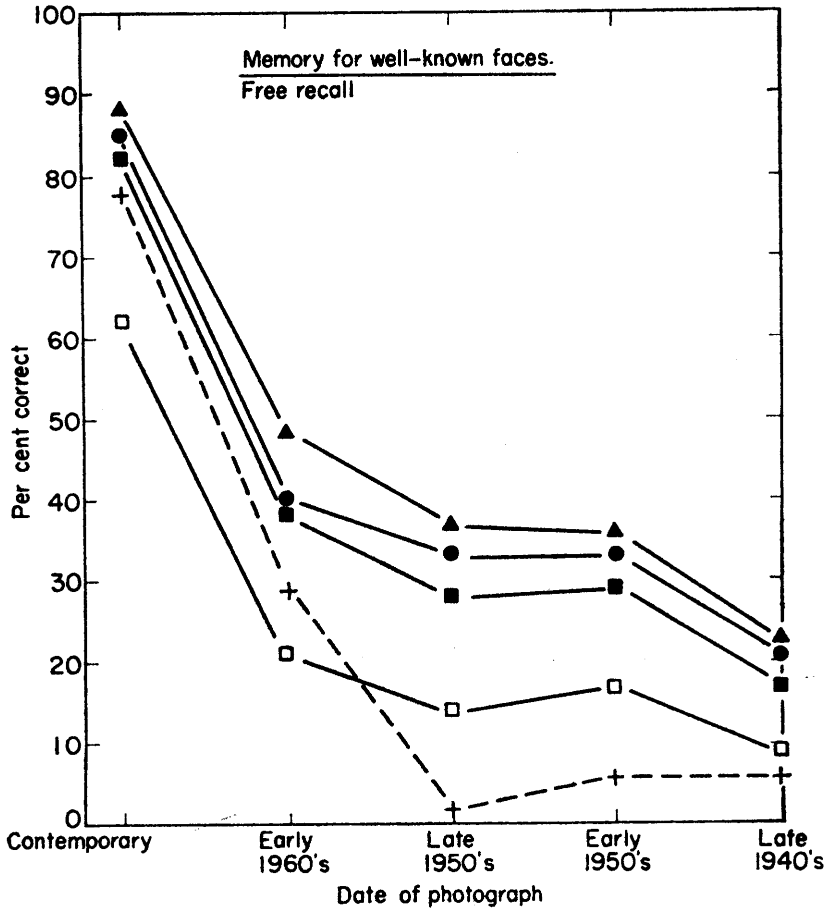


FIGURE 3. Memory for well-known faces. Free recall. ▲ 40s ● 50s ■ 60s □ 70s-80s + Average 16 yrs. 11 mths.

(Warrington and Sanders 1971)

Infantile amnesia: No episodic memory for events before the age of three

Forgetting curves of episodic memory are not monolithic

The reminiscence effect or *bump:* Higher probability
To recollect episodes from adolescence and early adulthood
than personal events from other lifetime periods.

Table 1
Questions Presented to Respondents

1. At some point in their life, many people have experienced an extremely happy event that they recall with much happiness and warmth. If you have at least one very happy memory from your life, how old are you in your happiest memory?
2. At some point in their life, many people have experienced an extremely sad event that they recall with much sadness and sorrow. If you have at least one very sad memory from your life, how old are you in your saddest memory?
3. At some point in their life, many people have had an extremely important experience which made big changes in their life or outlook and which they recall as an epoch-making event. If you have at least one memory of an epoch-making event, how old were you when your most epoch-making event took place?
4. At some point in their life, many people have experienced a traumatic event in which they or someone else was seriously injured, maybe their own life or the life of someone else was in serious danger, and they were feeling deeply shocked, helpless, very afraid, and did not know what to do. For example, traumas may include serious accidents, assaults, abuse, the sudden death of somebody, life-threatening diseases, military combat, torture, etc. Please look back upon your life and consider whether you have ever experienced an event that was traumatic to you. If you have at least one traumatic memory, how old are you in your most traumatic memory?
5. Sometimes a memory about our past suddenly pops up in our mind with no preceding attempts at remembering. The memory may seem to arise from nothing or it may come as an association to, for example, a sound, or a smell, or a song on the radio, etc. Some sudden memories may deal with old experiences, others with things that have happened recently. How often does it happen to you that memories suddenly pop up by themselves?
6. Try to remember the last time you noticed a memory that suddenly popped up by itself. How old were you in the event that this memory was dealing with?
7. Try to remember the last time you noticed a memory that popped up by itself. Was this memory dealing with a happy or sad event in your life?

(Berntsen & Rubin 2002)

The reminiscence bump:

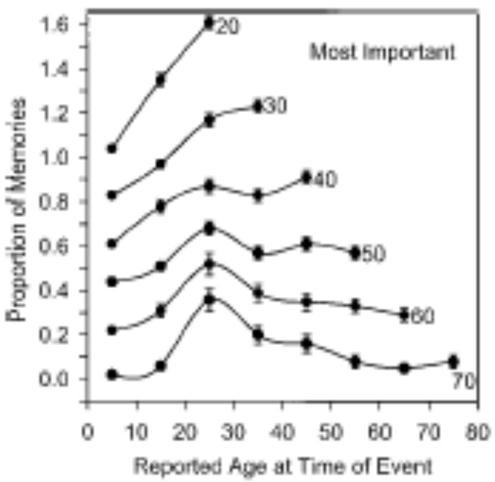


Figure 2. The distribution of most important autobiographical memories. Each decade age group is labeled by the youngest age included and is offset by 0.20 from the next oldest age group to make all plots visible. Standard errors are shown for all plots.

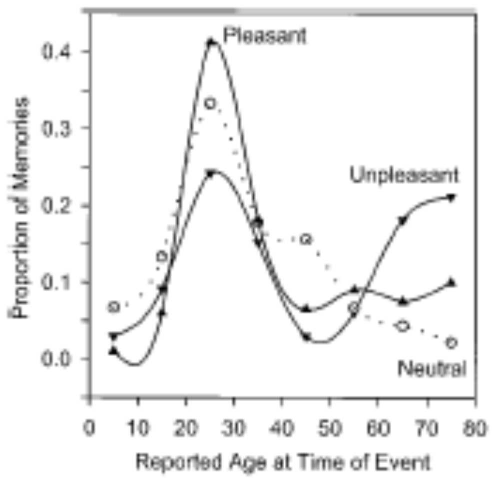


Figure 12. The distribution of pleasant, neutral, and unpleasant important autobiographical memories of 60 participants tested in a laboratory setting reanalyzed from Rubin and Schulkind (1997a).

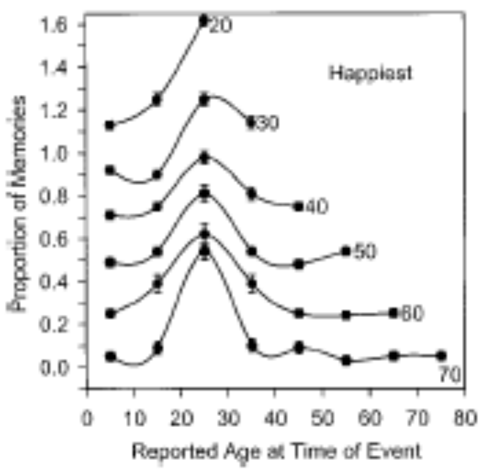


Figure 3. The distribution of happiest autobiographical memories. Each decade age group is labeled by the youngest age included and is offset by 0.20 from the next oldest age group to make all plots visible. Standard errors are shown for all plots.

Figure 11. The distribution of best and worst autobiographical memories of the participants interviewed in Siegler and George (1983).

(Berntsen & Rubin 2002)

The capacity of LTM is also not unlimited

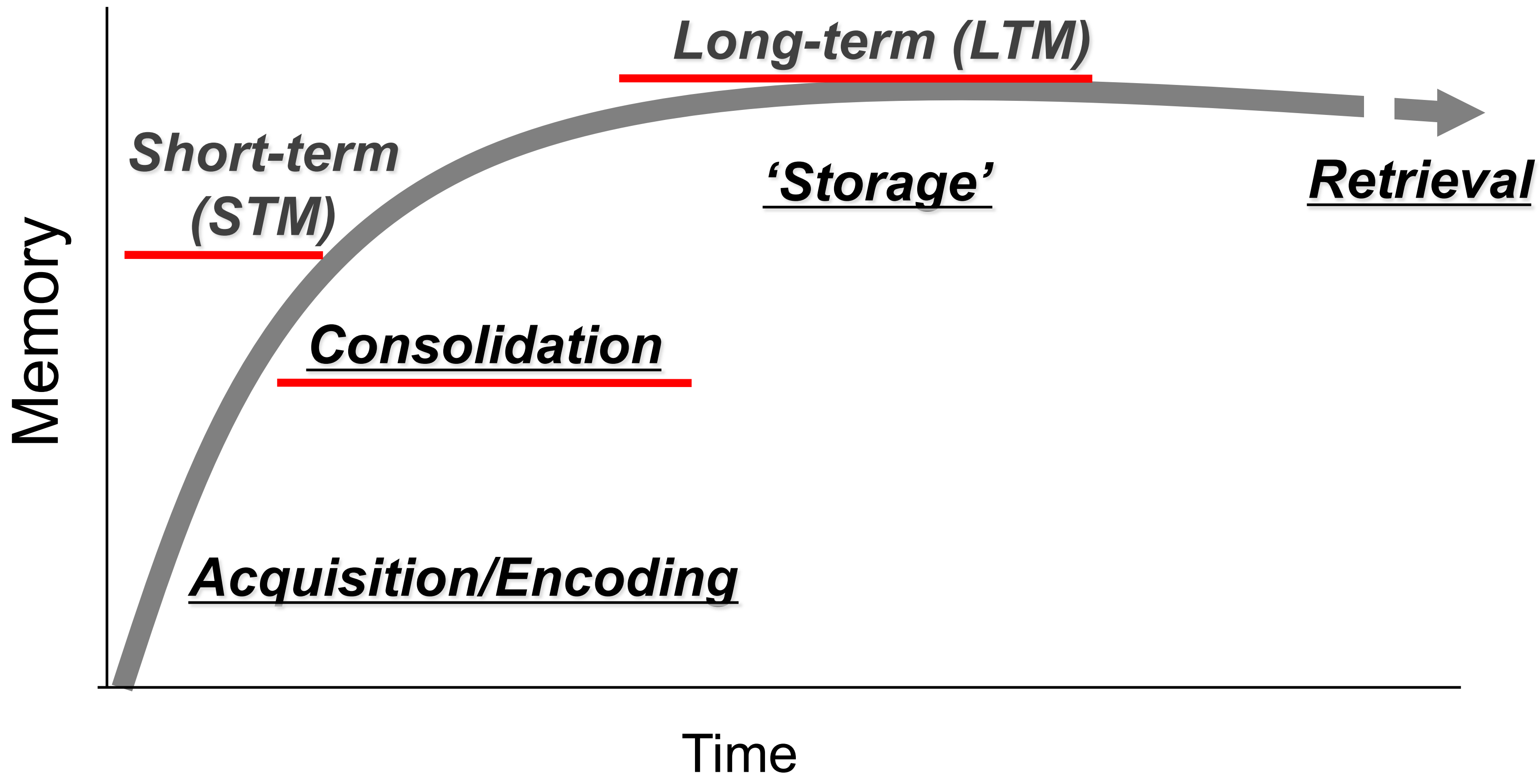
Store	Size	Reference
Words in language (mother tongue)	25,000-50,000	Nagy and Anderson (1984)
Pictures recognized	>10,000	Standing (1973)
Game patterns by a chess master	10,000 – 100,000	Chase and Simon (1973)
Facts by mnemonists	100,000	Yates (1966)
Core personal episodes	Thousands	Dudai (1997)
Items in expert databases in orally-reliant societies	500-2,000	Levi-Strauss (1966); Berlin (1992)

(Dudai 1998)

(Note the issue of retrieval vs. reconstruction)

To understand better the properties and mechanisms of key human memory systems, we should address the ontogeny of an item in long-term memory, first in general, then in declarative memory

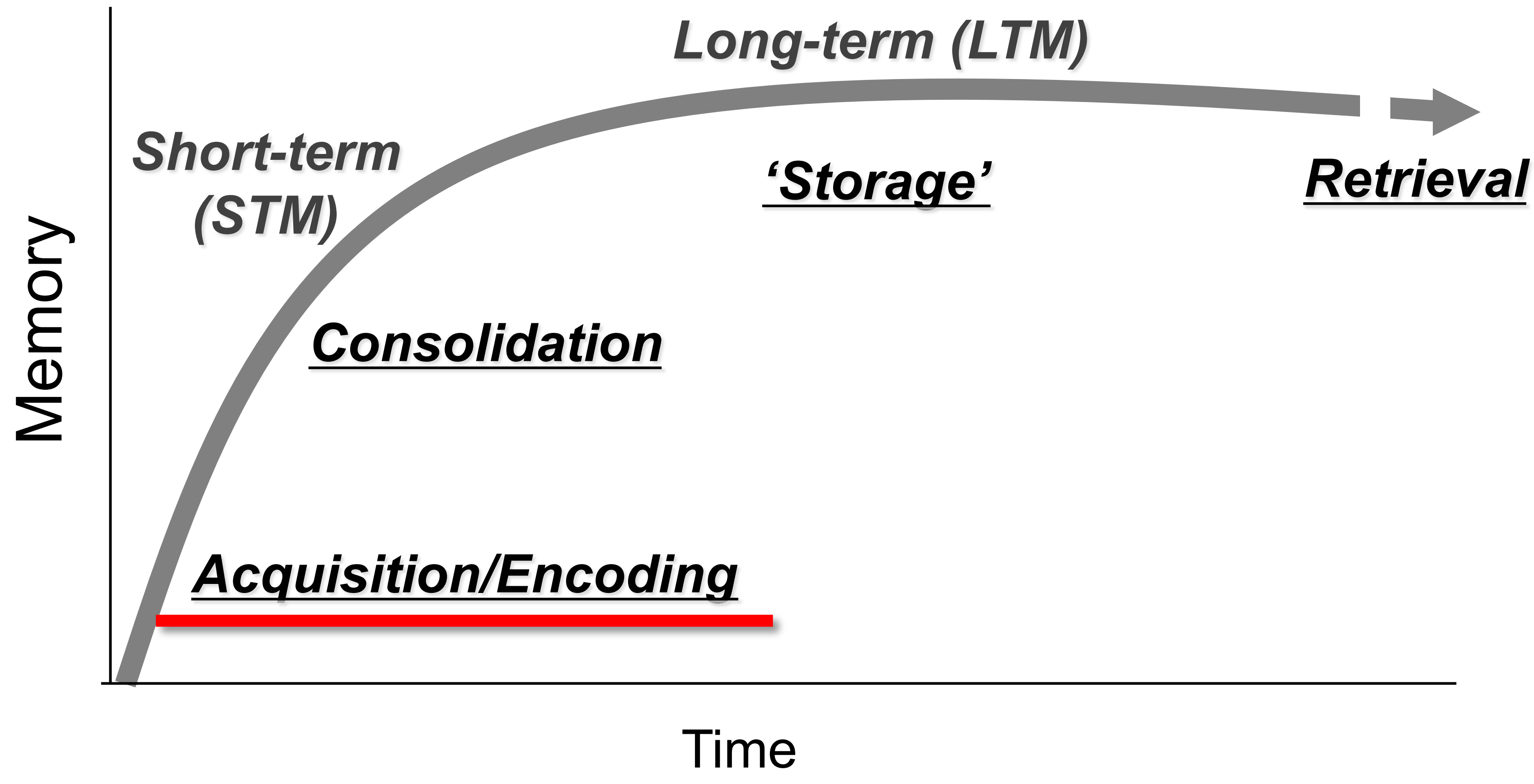
The biography of an item in memory



- ***The dual-trace hypothesis***
- ***The consolidation hypothesis***

LTM = f(Growth)

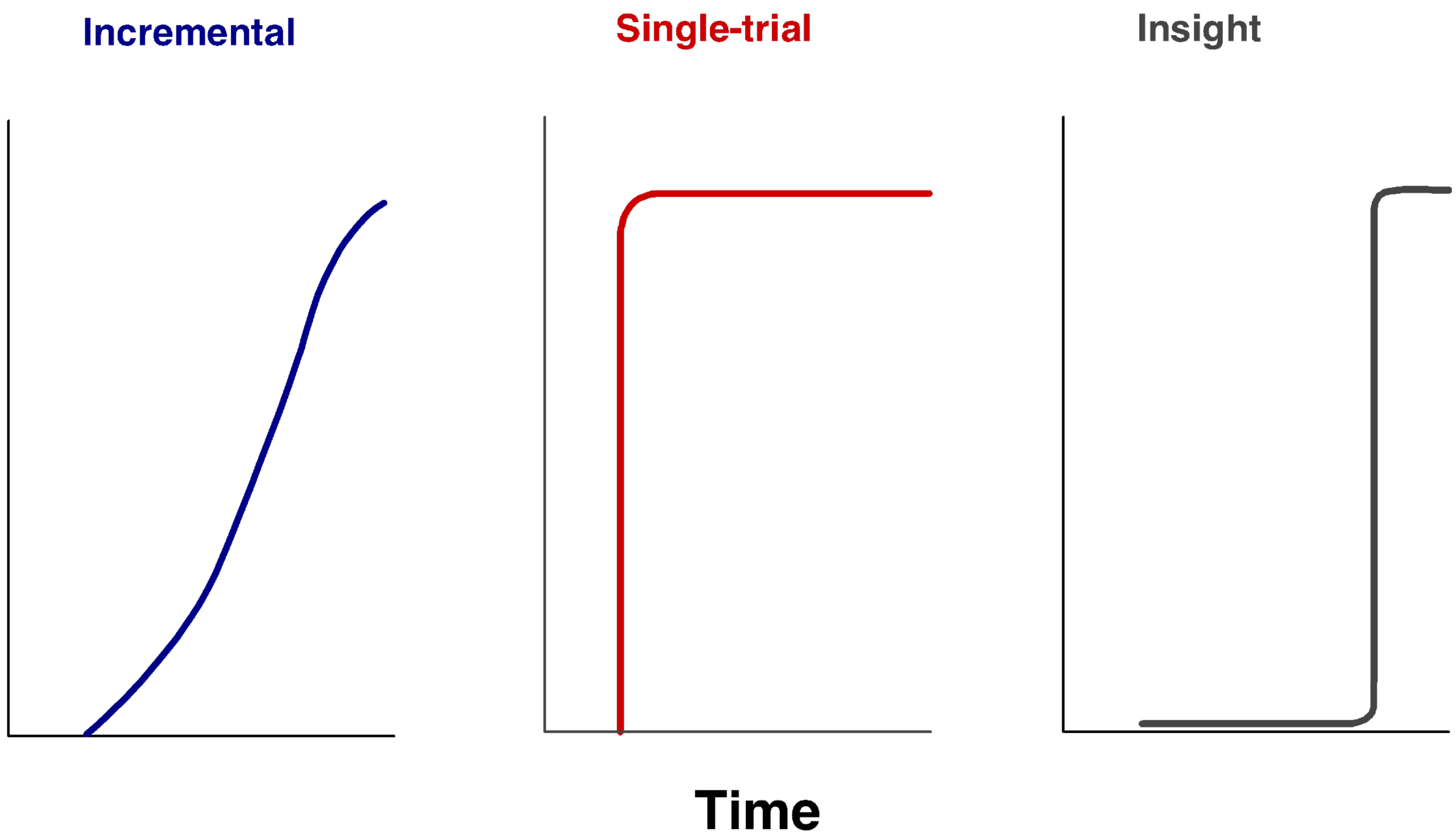
The biography of an item in memory



Acquisition (Encoding):

- The initial phase in the formation of a memory trace
- The process by which new information is converted into a memory trace
- The change in performance during training which is taken to represent the progression of learning

Three types of acquisition modes



Acquisition: The goal(s) of the system

- *Register input*
- *Register associations*

- *Register input:* detect change in intensity or probability
- *Register associations:* detect coincidence detection or contingency

Candidate algorithms:

- **Prime** with a salient *Xi* so that subsequent *Xj* is read out differently (non-associative/ associative)
- **Summate/anticipate** read *Xi, Xj, … Xn,* to detect mismatch of the input, in time or magnitude, with criterion (non-associative /associative)
- Detect **coincidence** (associative)

Summation/Anticipation: The Rescorla-Wagner Model

$$\Delta V_X^{n+1} = \alpha_X \beta(\lambda - V_{tot})$$

and

$$V_X^{n+1} = V_X^n + \Delta V_X^{n+1}$$

where

- ΔV_X is the change in the strength of association of X
- α is the salience of the CS (bounded by 0 and 1)
- β is the rate parameter for the US (bounded by 0 and 1), sometimes called its association value
- λ is the maximum conditioning possible for the US
- V_X is the current associative strength
- V_{tot} is the total associative strength of all CS

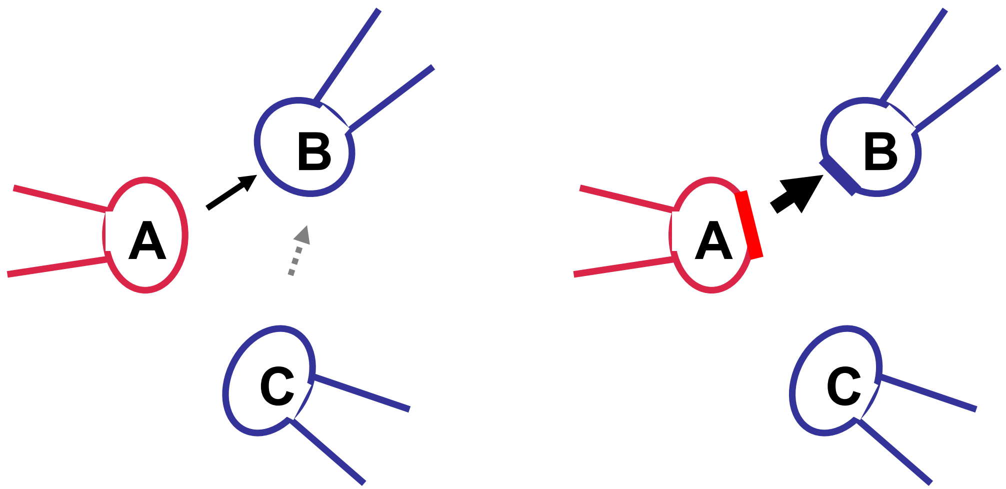
Qualitatively: The more the event is far from the expected, the stronger it is encoded

Coincidence detector:

- A device that responds only on receiving two stimuli simultaneously
- A device that responds only on receiving a complete set of two or more stimuli

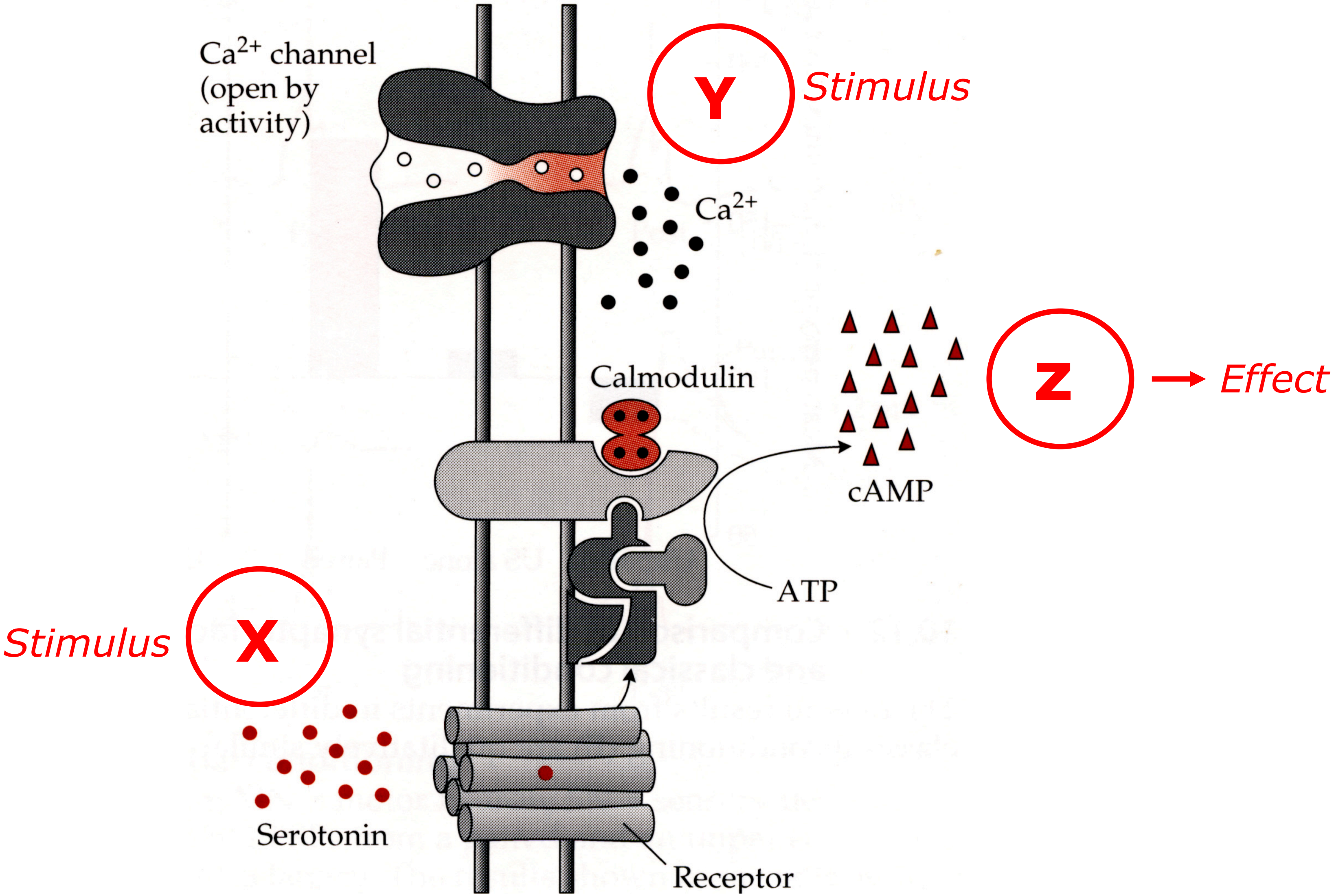
- What is *simultaneously*?

<u>Hebb's postulate:</u>
<u>A cellular/circuit algorithm</u>

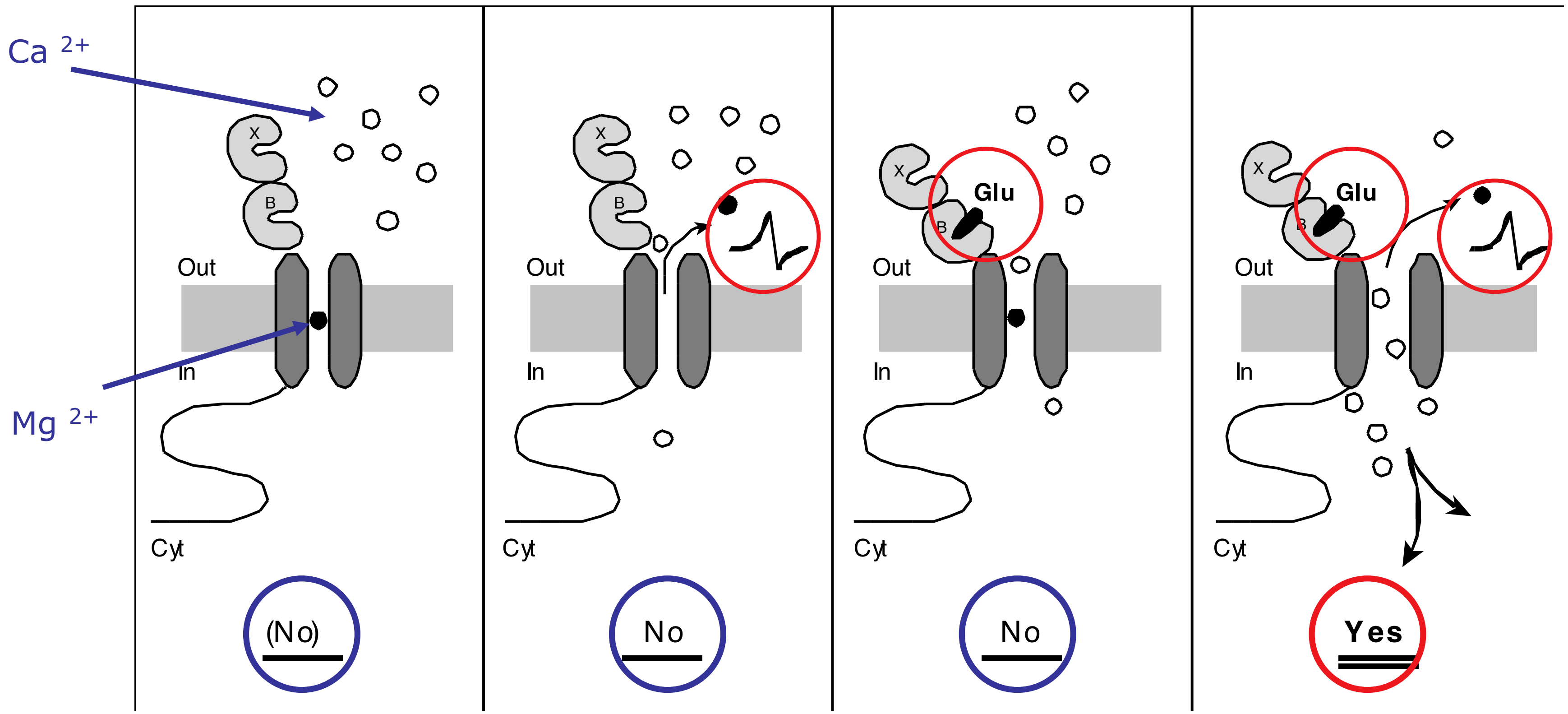


When an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth processes or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased ("Darwinian")

A candidate for hardware implementation of coincidence detection: Calcium/calmodulain-dependent adenylyl cyclase

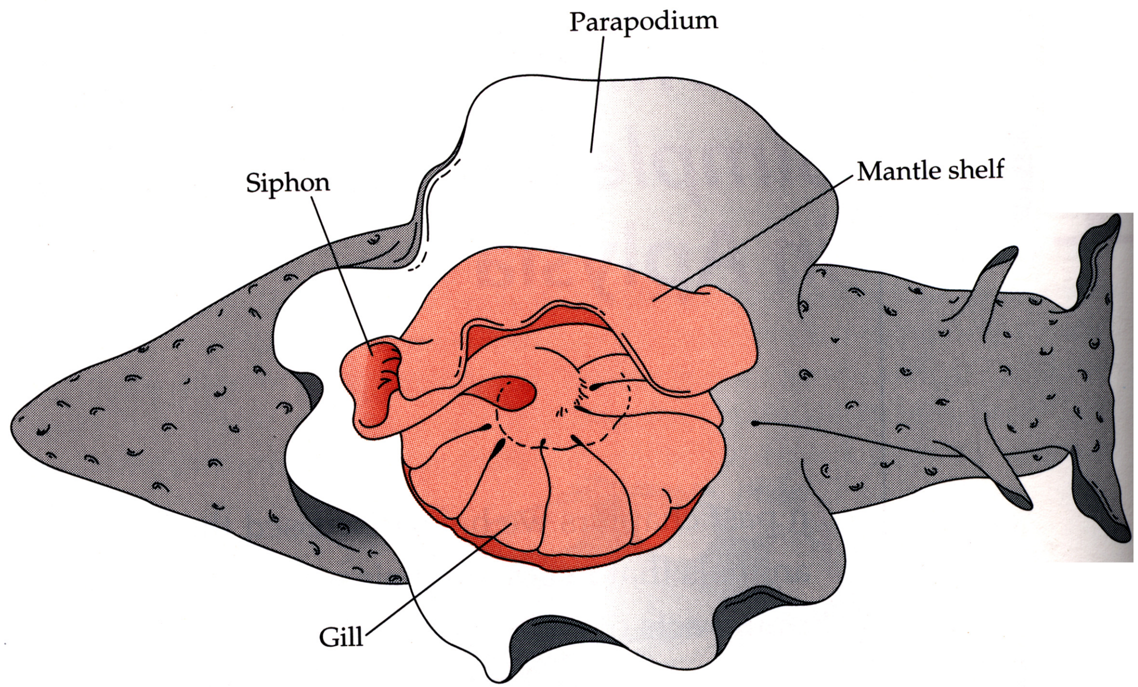


Another candidate for hardware implementation of coincidence detection: The NMDA receptor

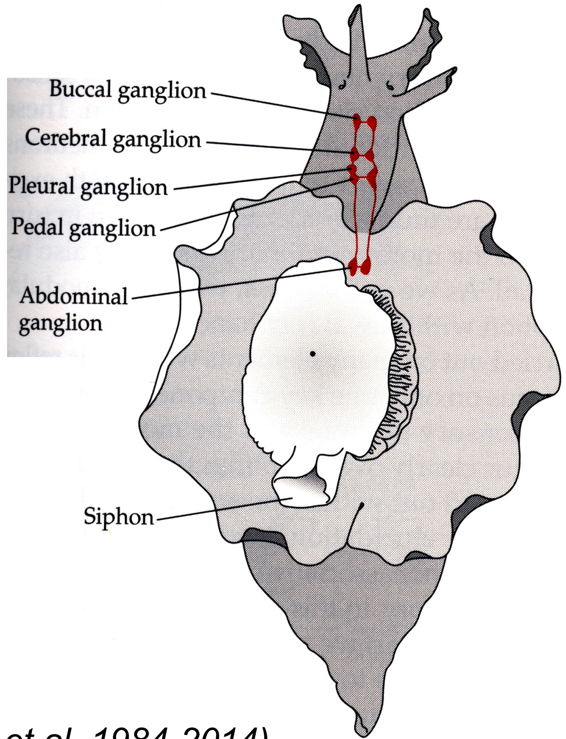


Many receptors, enzymes and transcription factors can serve as coincidence detectors, depending on the time window of required coincidence; their involvement in plasticity *in vivo* must be demonstrated

An example of a model system for dissecting mechanisms of acquisition: *Aplysia*



A dorsal view with its gill exposed



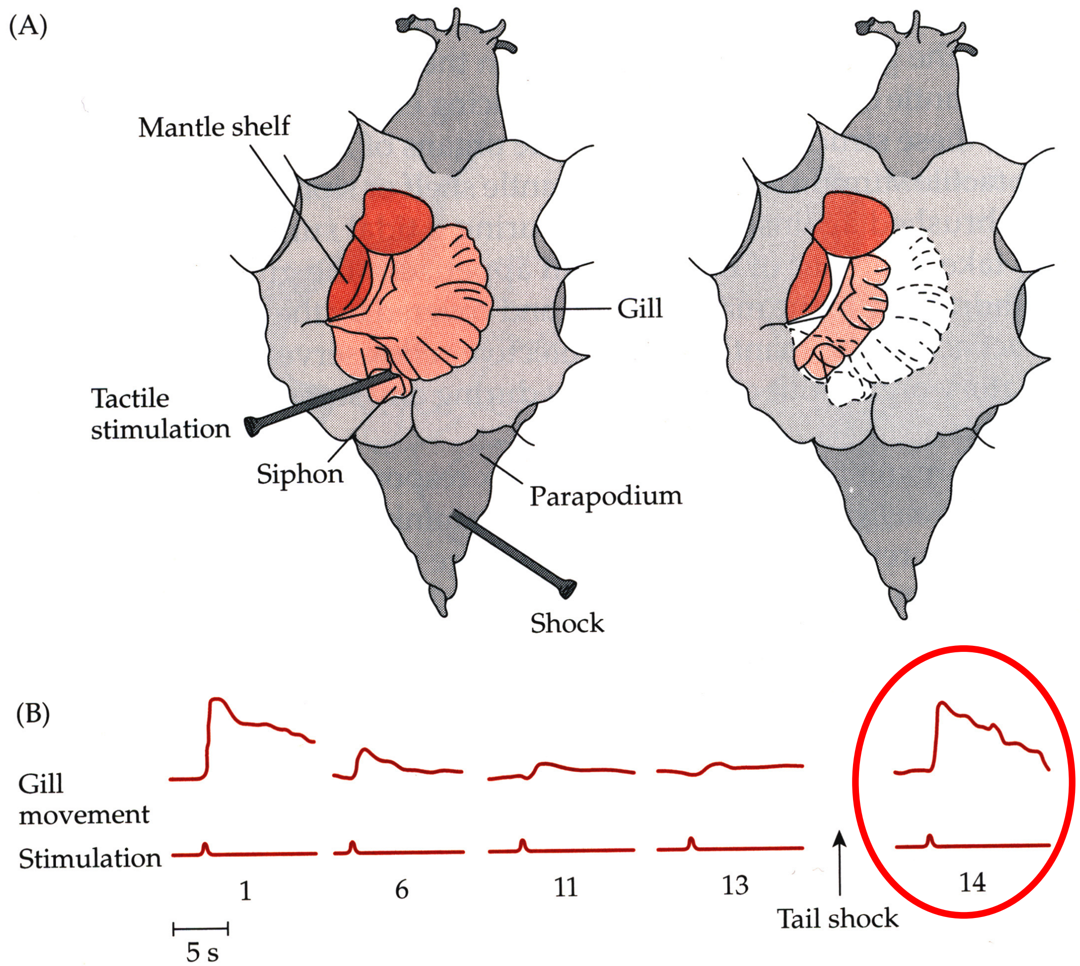
The central nervous system (transparent view)

(Kandel et al. 1984-2014)

Why Aplysia?

- Reasonable number of neurons (~ 20,000)
- Accessible ganglia
- Large nerve cells
- Identifiable nerve cells
- Simple behvioural repertoire
- Easy to handle

The defensive, gill-and-siphon withdrawal reflex undergoes habituation and sensitization



Sensitization

(After Kandel & Schwartz)

Methods used in the *Aplysia* projects

- Lesions: Inference of function from dysfunction
- Correlations: Concomitant activity in identified neurons and effector organs
- Simulation (mimicry): Activation of effector organ by stimulating neurons

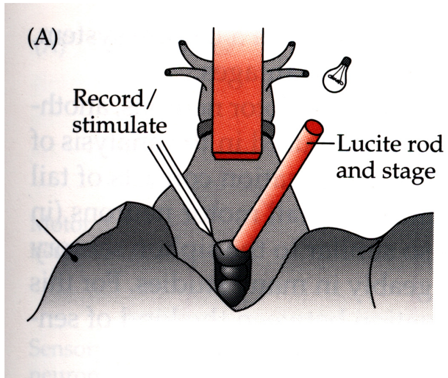
Conceptual and pragmatic steps:

- Reductive step: A shift from one level of analysis to the other (e.g., behavioural to circuit)
- Simplifying step: A down shift in the complexity of the preparation without abandoning levels of analysis

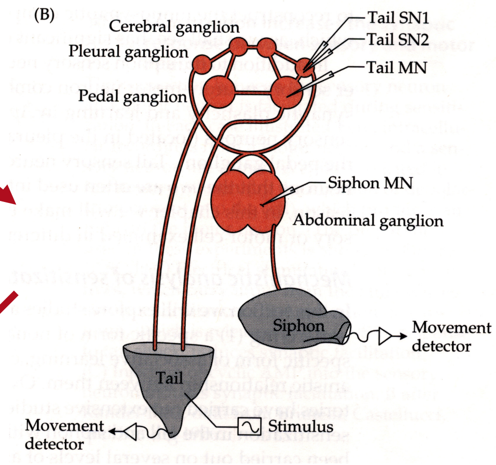
(What is a simple system?)

Reductive and simplifying steps in the analysis of *Aplysia*

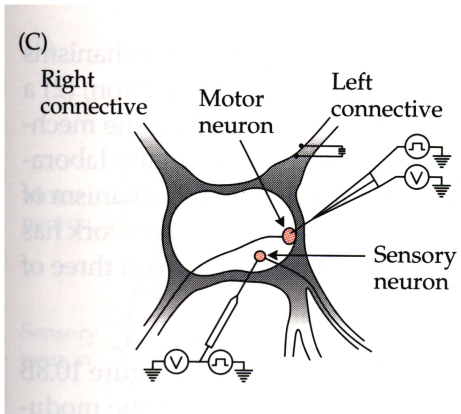
The behaving organism



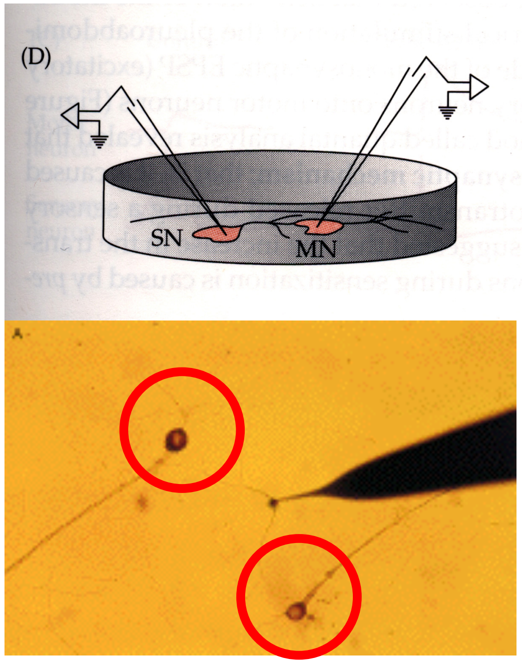
Cellular analysis in the intact organism (reductive step)



Cellular analysis in a Nerve-muscle preparation (simplifying step)



Cellular analysis in the isolated ganglion (simplifying step)

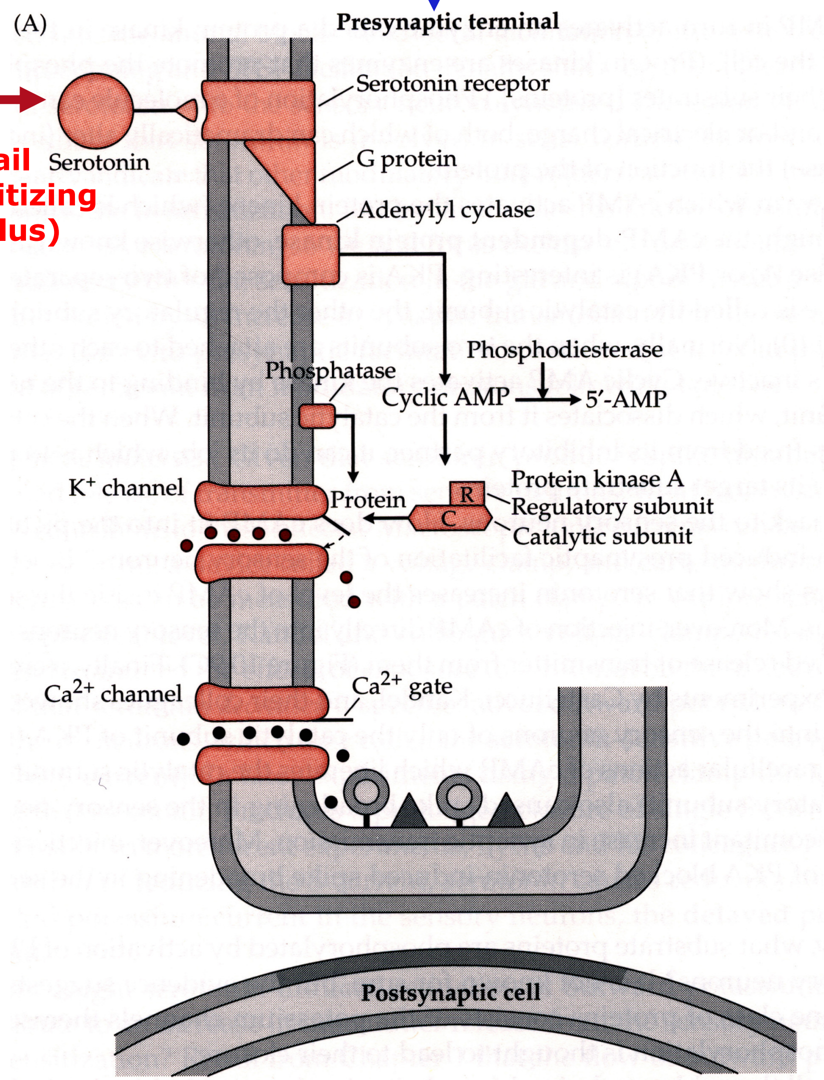


Cellular and molecular analysis of sensory-motor cultures (reductive step)

Acquisition of sensitization in *Aplysia*: The simplest cellular model

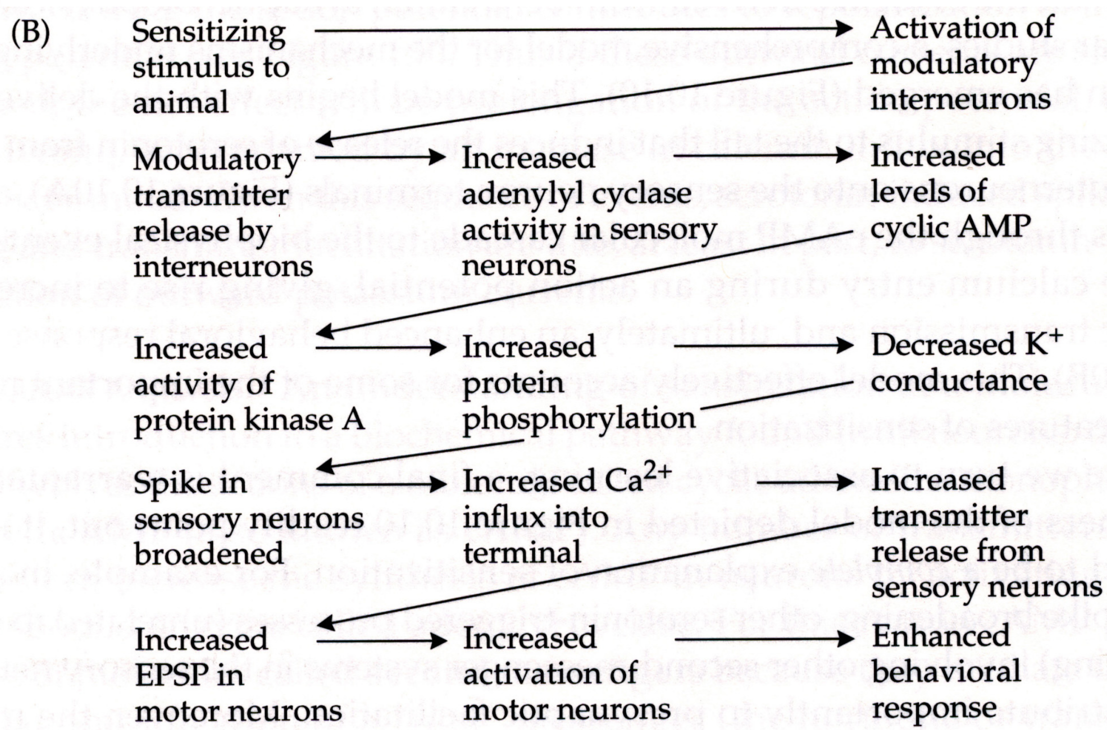
From the skin (test stimulus)

From the tail (sensitizing stimulus)



To the muscle (response)

The flowchart



Note: the actual mechanism includes additional components (e.g., PKC) and is context- and history- dependent

A Popular Mammalian Paradigm: [Contextual] Fear Conditioning

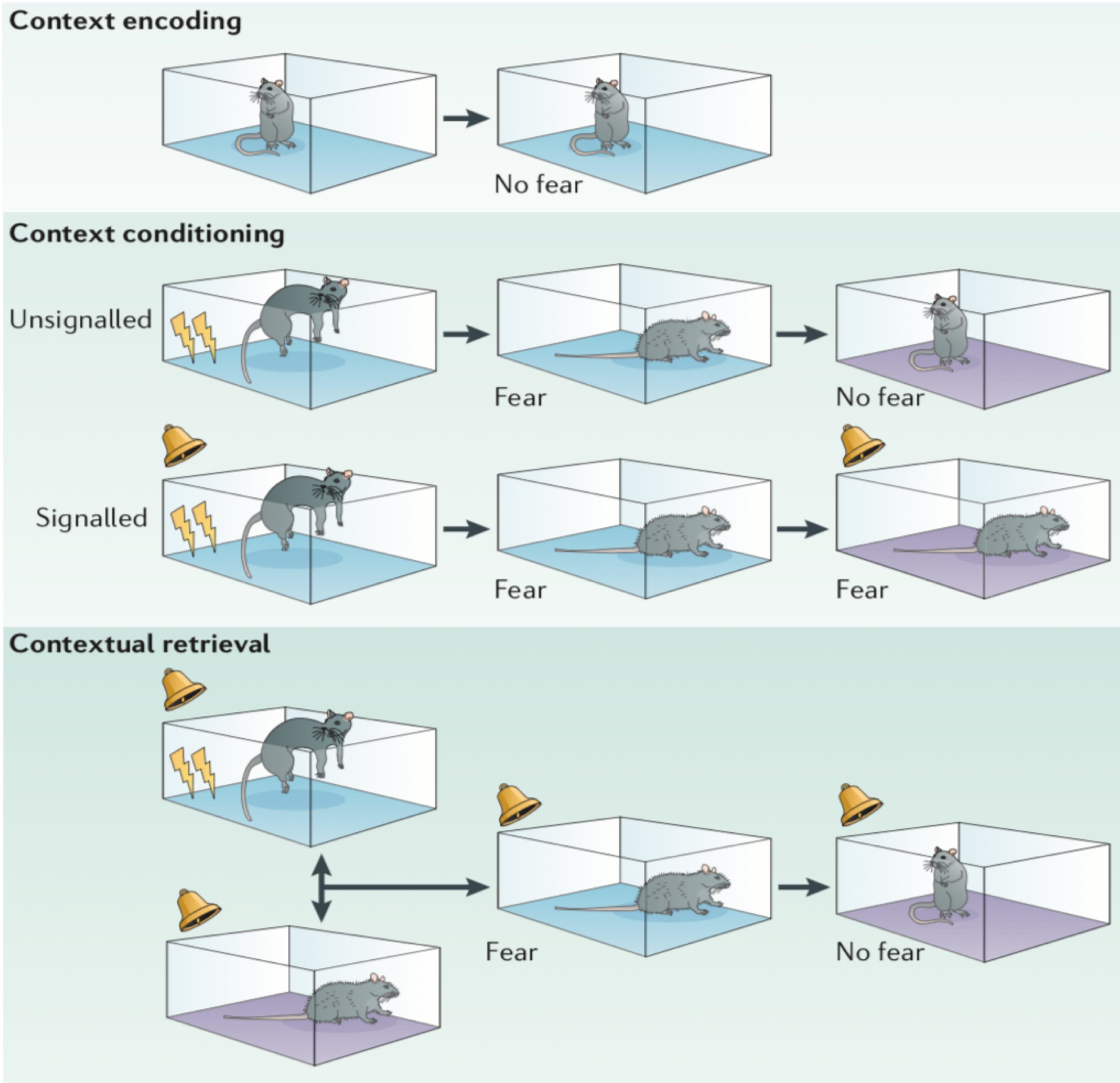


Figure 2 | **Context encoding, conditioning and retrieval tasks in rodents.**

Context Only

Context & Elemental Auditory

Differential UCS: Contextual Conditioning Test

(Maren et al. 2013)

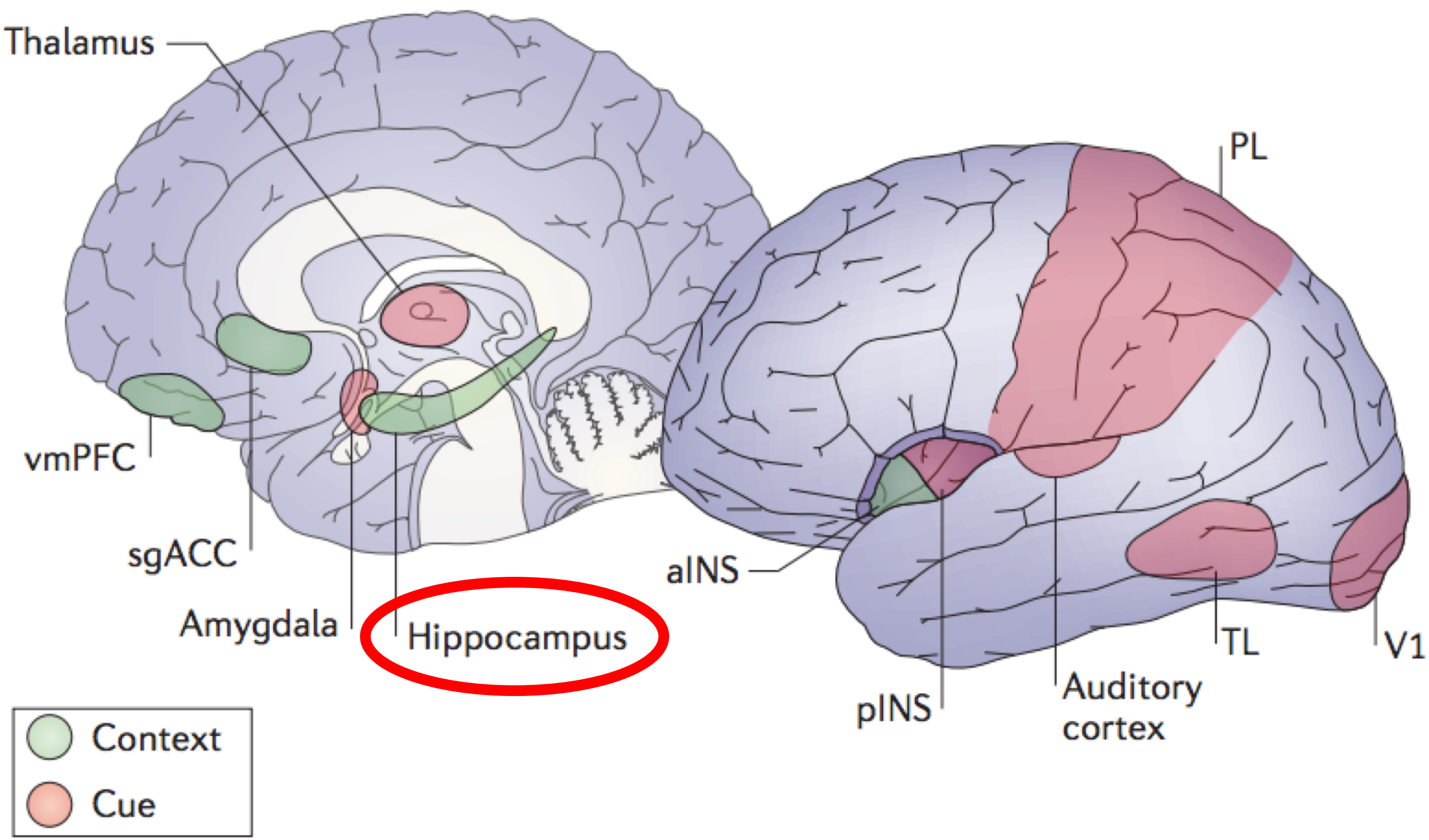


Figure 3 | **Brain circuits involved in cue and context processing in the human brain.**

(Maren et al. 2013)

Optogenetic stimulation of a hippocampal engram activates fear memory recall

Xu Liu[1]*, Steve Ramirez[1]*, Petti T. Pang[1], Corey B. Puryear[1], Arvind Govindarajan[1], Karl Deisseroth[2] & Susumu Tonegawa[1]

A specific memory is thought to be encoded by a sparse population of neurons[1,2]. These neurons can be tagged during learning for subsequent identification[3] and manipulation[4–6]. Moreover, their ablation or inactivation results in reduced memory expression, suggesting their necessity in mnemonic processes. However, the question of sufficiency remains: it is unclear whether it is possible to elicit the behavioural output of a specific memory by directly activating a population of neurons that was active during learning. Here we show in mice that optogenetic reactivation of hippocampal neurons activated during fear conditioning is sufficient to induce freezing behaviour. We labelled a population of hippocampal dentate gyrus neurons activated during fear learning with channelrhodopsin-2 (ChR2)[7,8] and later optically reactivated these neurons in a different context. The mice showed increased freezing only upon light stimulation, indicating light-induced fear memory recall. This freezing was not detected in non-fear-conditioned mice expressing ChR2 in a similar proportion of cells, nor in fear-conditioned mice with cells labelled by enhanced yellow fluorescent protein instead of ChR2. Finally, activation of cells labelled in a context not associated with fear did not evoke freezing in mice that were previously fear-conditioned in a different context, suggesting that light-induced fear memory recall is context-specific. Together, our findings indicate that activating a sparse but specific ensemble of hippocampal neurons that contribute to a memory engram is sufficient for the recall of that memory. Moreover, our experimental approach offers a general method of mapping cellular populations bearing memory engrams.

Optogenetic activation of hippocampal fear engram

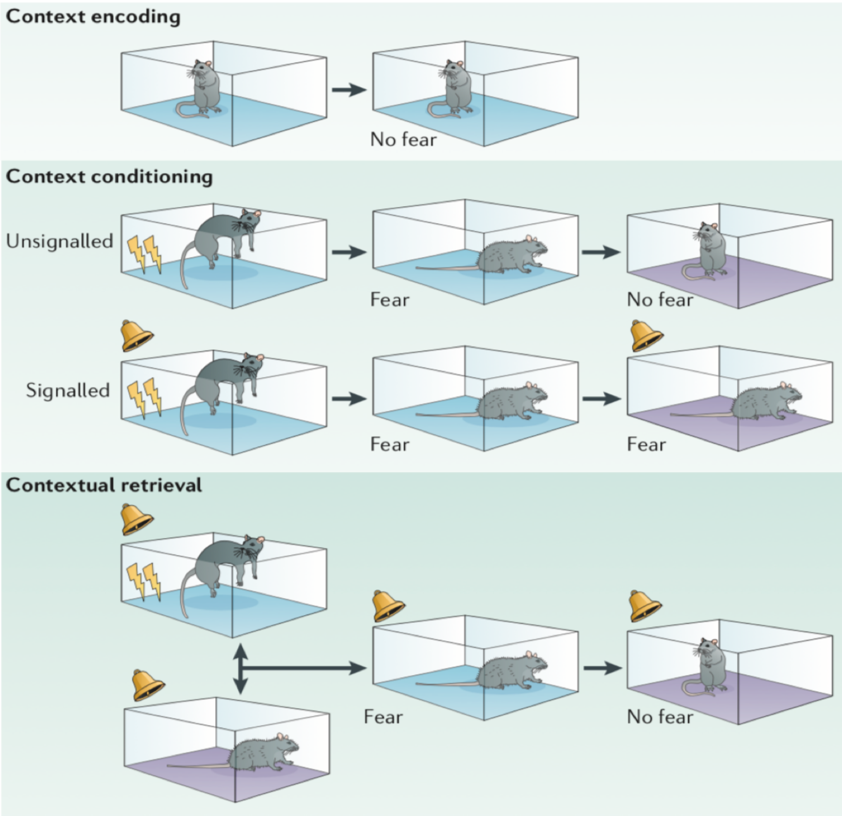


Figure 2 | **Context encoding, conditioning and retrieval tasks in rodents.**

(Maren et al. 2013)

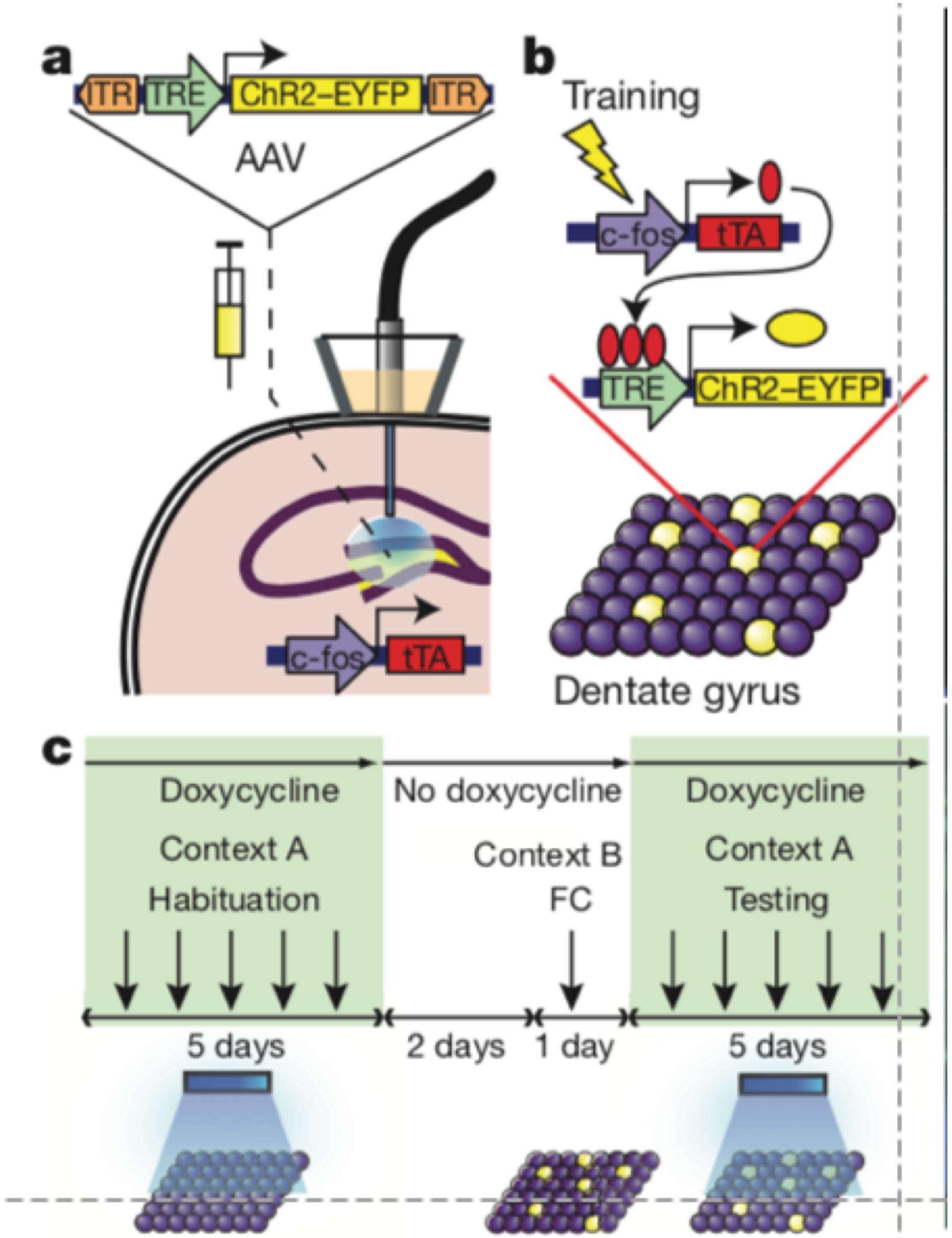


Figure 1 | Basic experimental protocols and selective labelling of DG cells by ChR2–EYFP. a, The c-fos-tTA mouse was injected with AAV_9-TRE-ChR2-EYFP and implanted with an optical fibre targeting the DG. **b**, When off Dox, training induces the expression of tTA, which binds to TRE and drives the expression of ChR2–EYFP, labelling a subpopulation of activated cells (yellow) in the DG. **c**, Basic experimental scheme. Mice were habituated in context A with light stimulation while on Dox for 5 days, then taken off Dox for 2 days and fear-conditioned (FC) in context B. Mice were put back on Dox and tested for 5 days in context A with light stimulation. (

(Liu et al. 2012)

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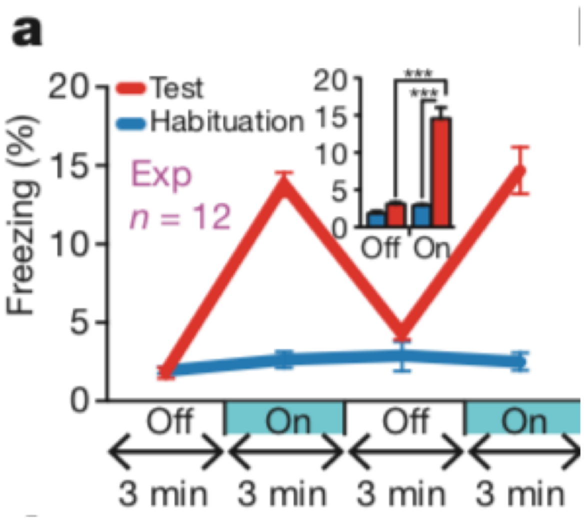

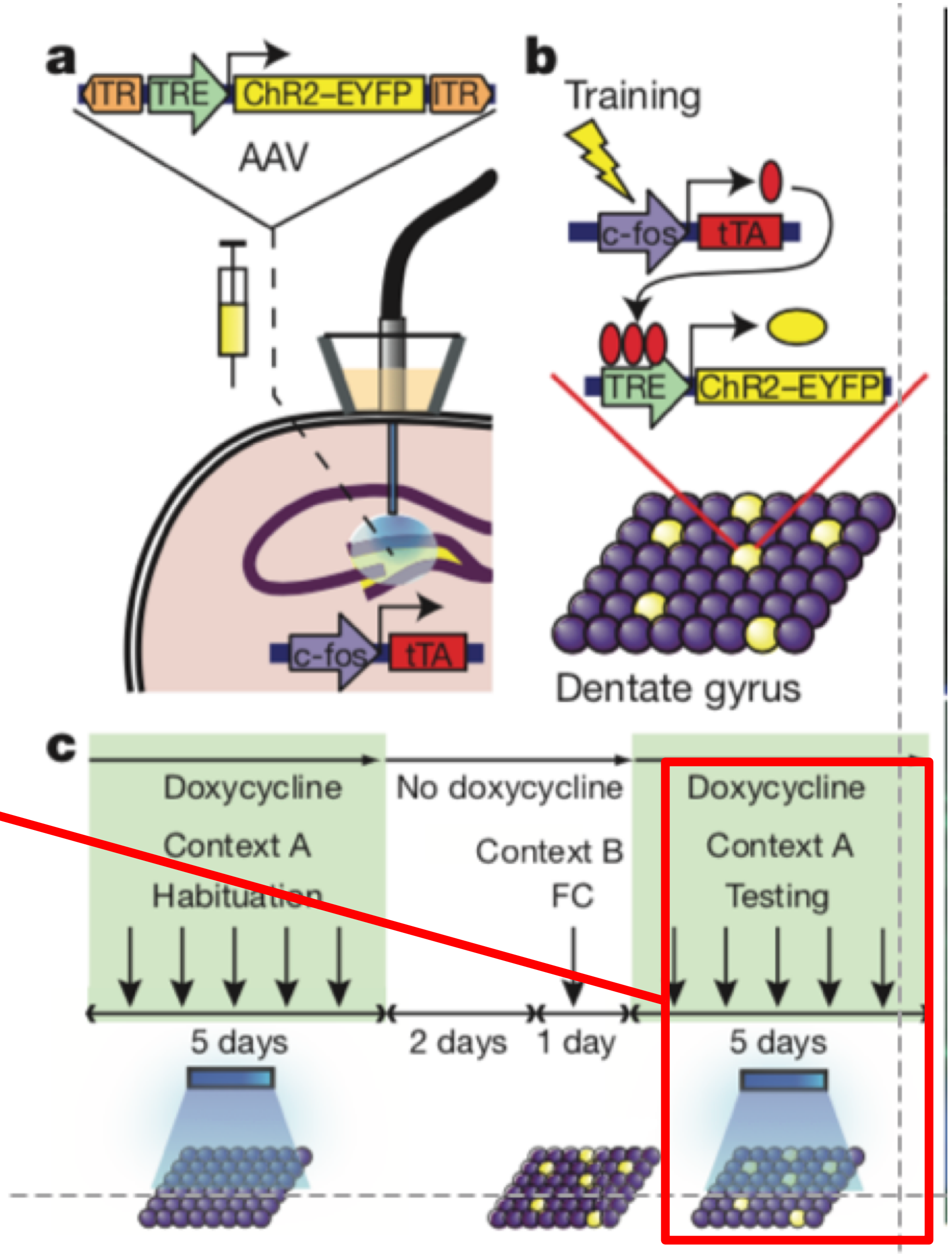

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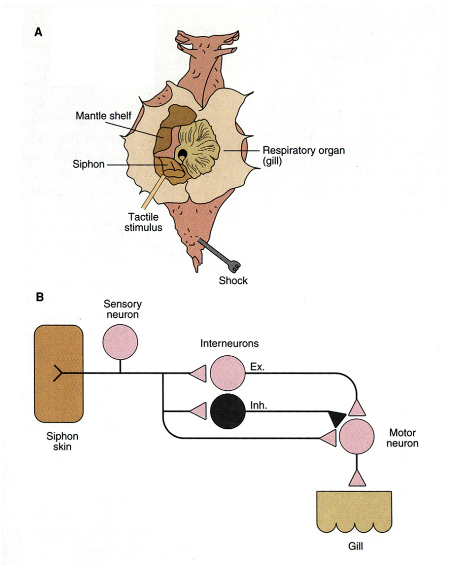
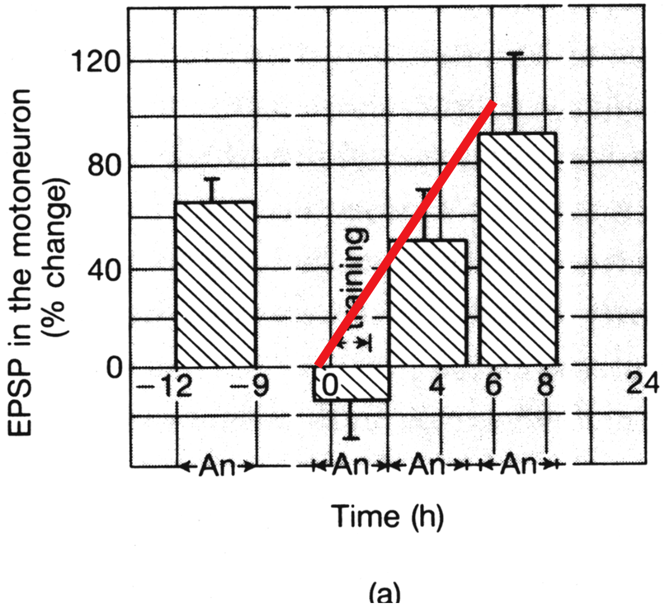
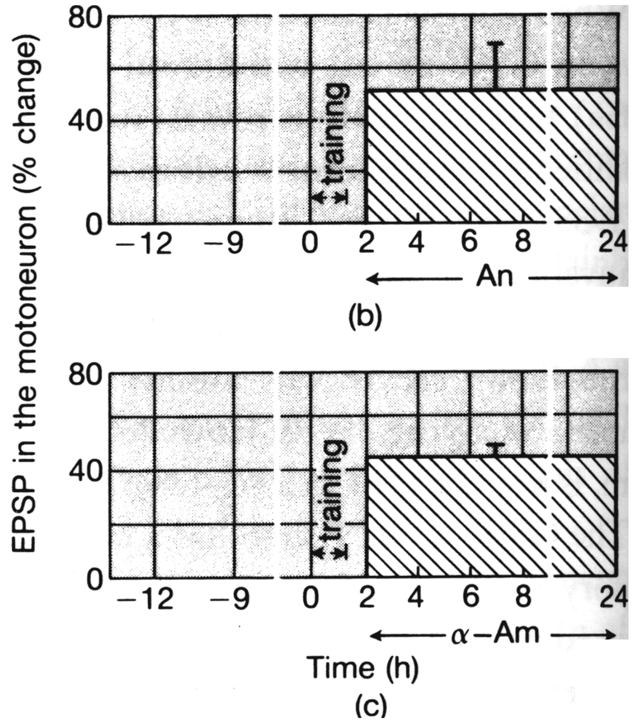
(Liu et al. 2012)

But is the memory stable?

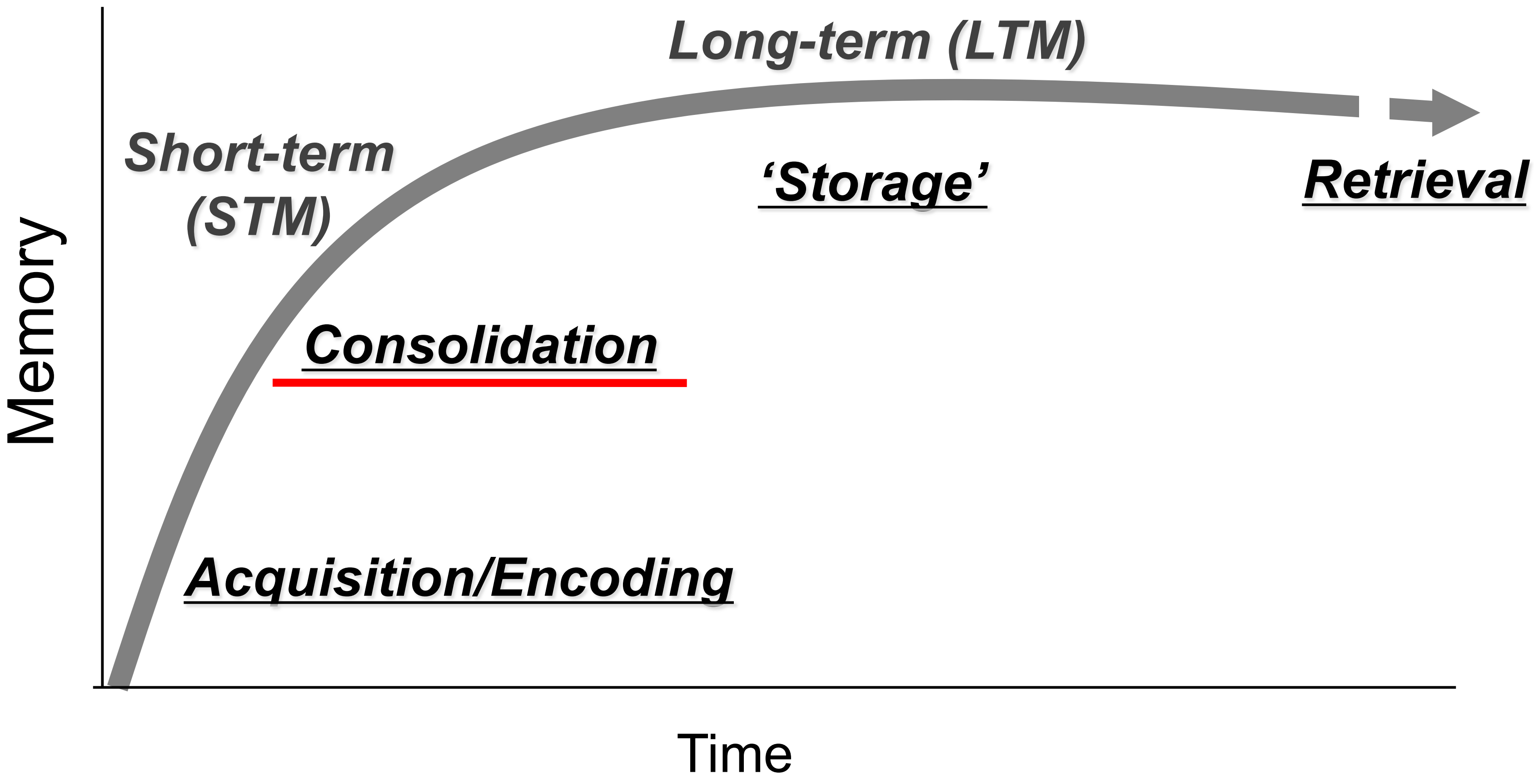






(Montarolo et al. 1986)

This leads us to memory consolidation



Consolidation is:

Process

- The progressive post-acquisition stabilization of the engram*.
- The memory phase(s) during which this stabilization takes place.

Phase

** Engram = physical memory trace*

(Dudai 2004, 2012)

How is consolidation unveiled?

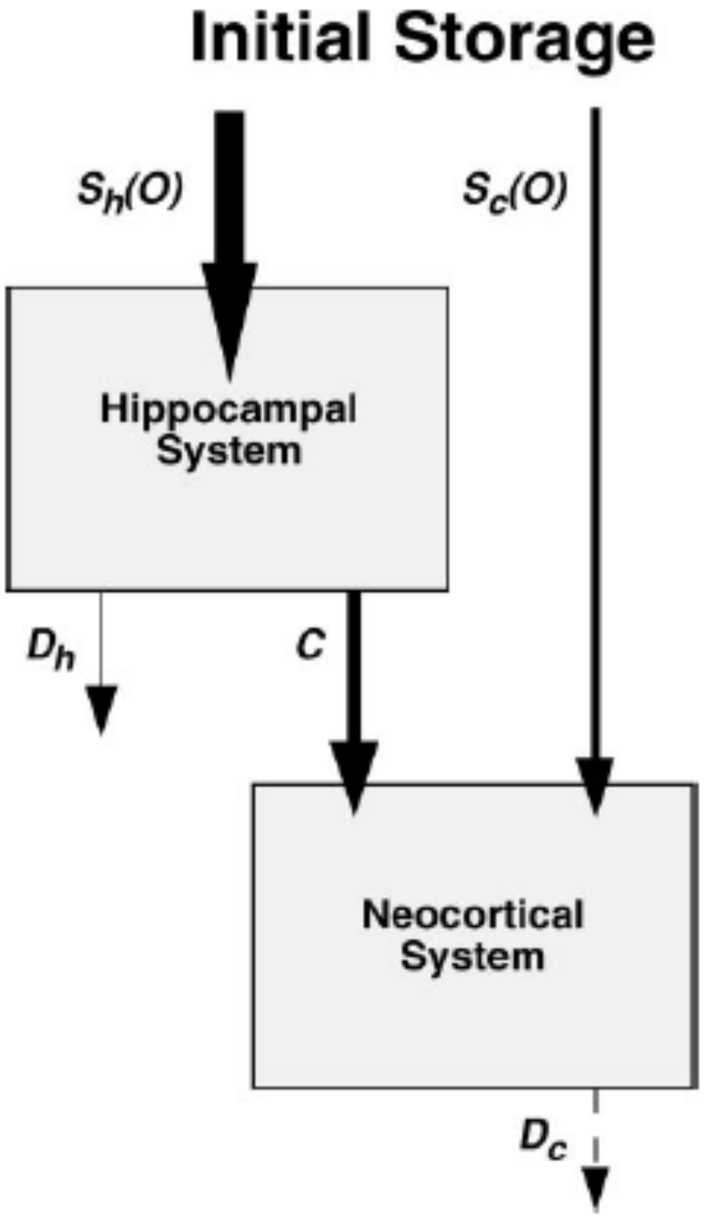
Commonly, by the use of amnesic agents:

- Distracting stimuli
- Electric shock
- Anesthesia
- Inhibitors of macromolecular synthesis
- [Lesions (e.g., organic amnesia)]

The criterion for consolidation:
Existence of a post-acquisition time window during which LTM can be prevented/abated.

How does systems consolidation work?

I. The Standard Consolidation Theory (SCT)



(McClelland et al. 1995, Dudai 2004)

How does systems consolidation work?

II. Multiple Trace Theory/Trace transformation Theory

Assumption: The hippocampal complex (HPC) subserves autobiographical/episodic memories as long as they are viable.

The HPC rapidly and obligatorily encodes all episodic information. This information is sparsely encoded in distributed ensembles of HPC neurons, acting as an index for neocortical circuits that attend the information and bind it into a coherent representation. Because reactivation of the representation commonly takes place in a different context, it results in new HPC traces that in turn bind new traces in the neocortex, resulting in multiple traces that share the information. Over time, having multiple traces facilitates extraction of the information into a semantic representation of the gist of the episode. Contextual information continues to be encoded by the HPC.
In the TTT variant, the original HPC (full) and the new (neocortical, transformed into semantic) representations co-exist, the latter are being transformed into such over time.

(Moscovitch, Nadel, Winocur, 1997-2011)

Hence the hypothesis is that episodic memory schematizes over time

Vivid

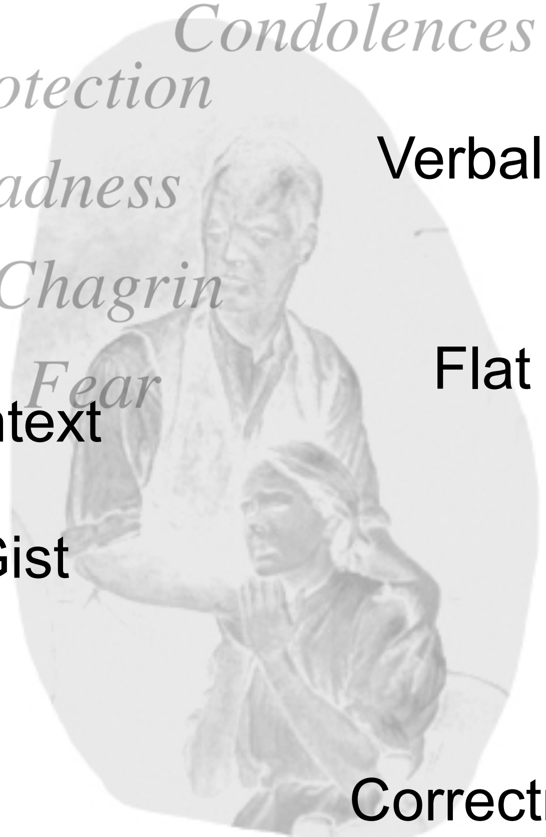
Details

Narrative

Contextual

Reenactment

Correctness



Verbal

Flat in detail

Poor context

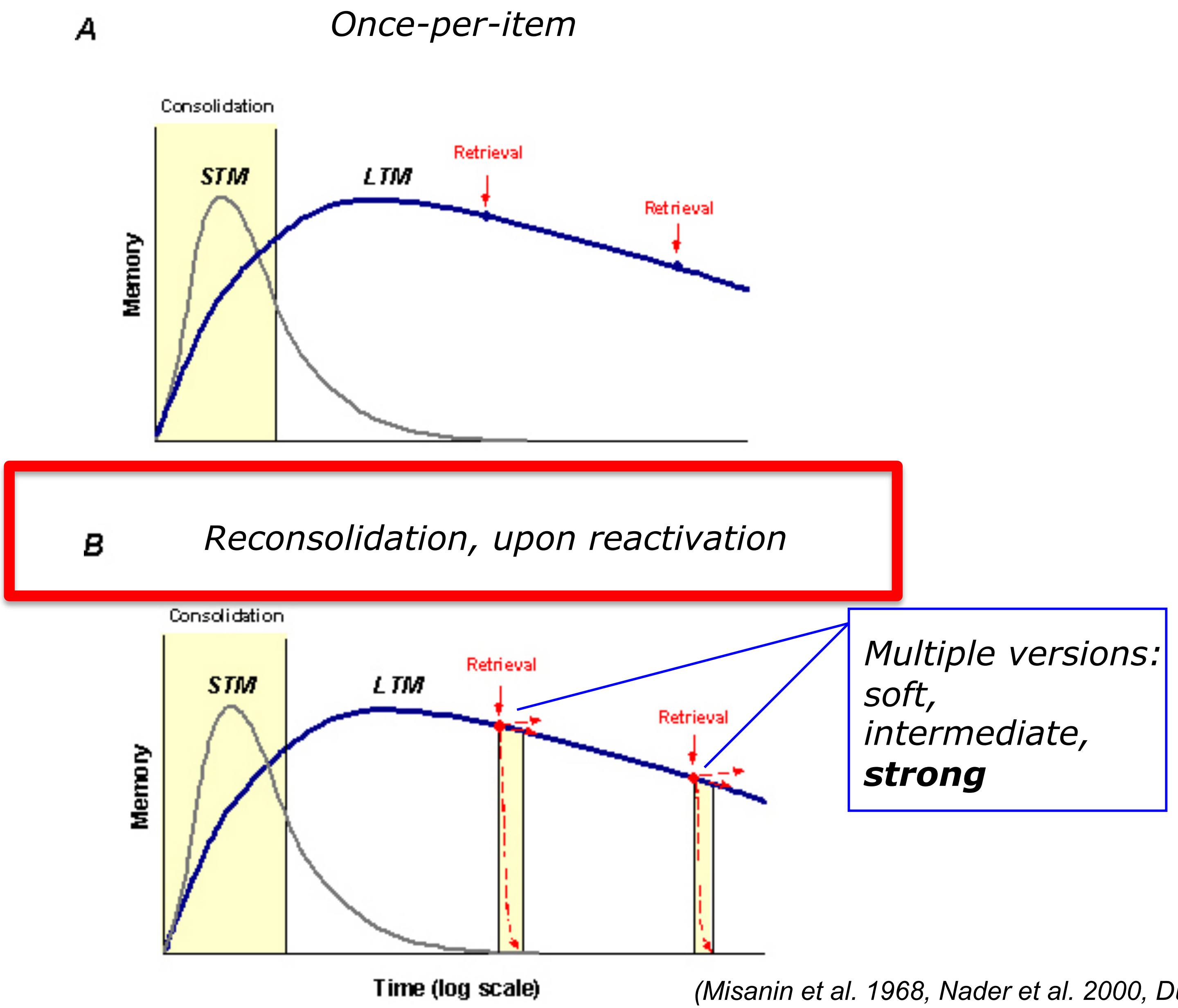
Gist

Correctness

Episodic

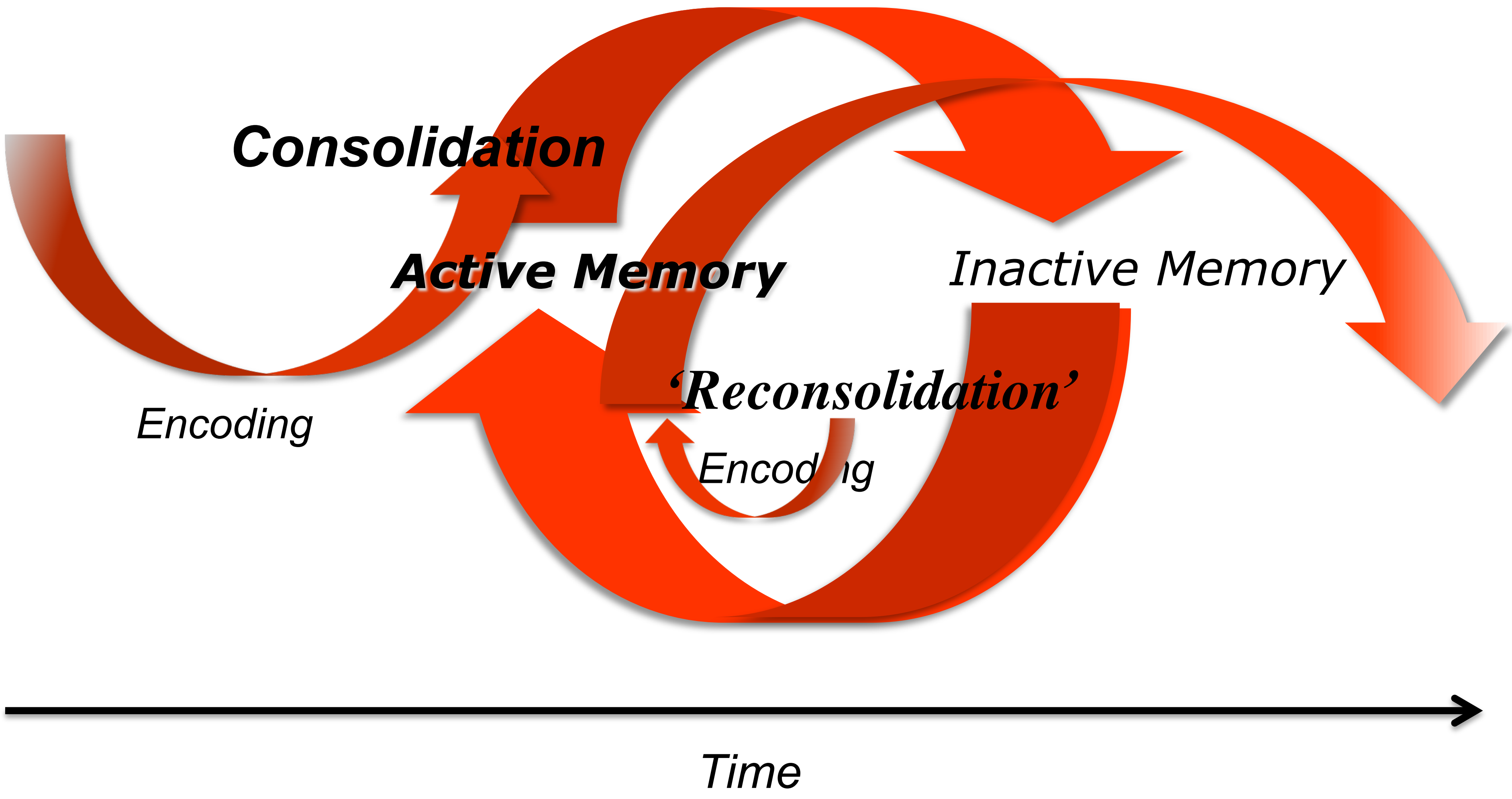
Semantic

Does consolidation occur just once per item?



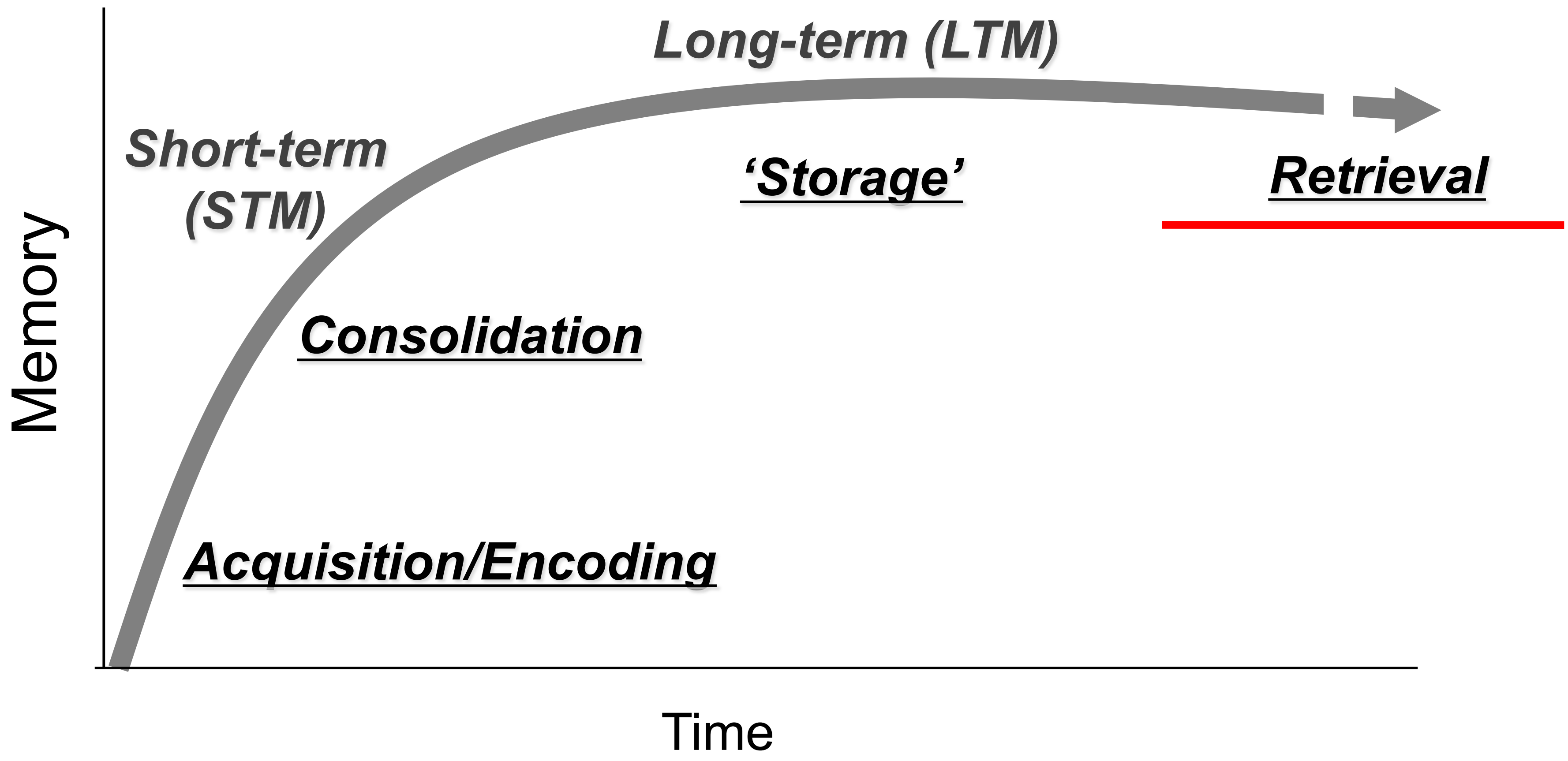
(Misanin et al. 1968, Nader et al. 2000, Dudai 2004)

Revision of a Paradigm: A dynamic model of memory



(After Lewis 1973, Dudai 2009)

This leads us to memory retrieval

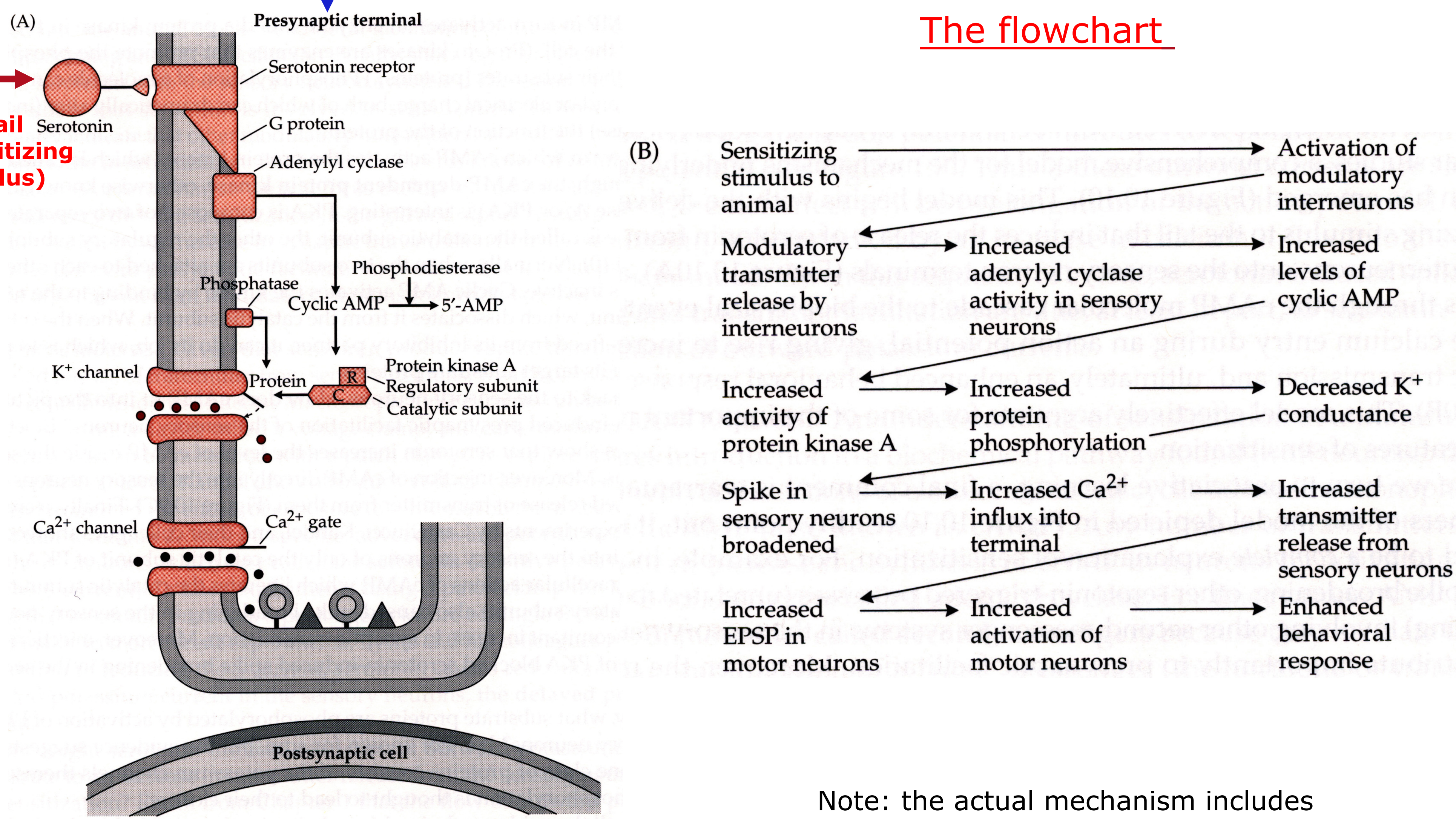


Recall that in simple learning in reflexes retrieval is Assumed to be straightforward read-out of the change

From the skin (test stimulus)

From the tail (sensitizing stimulus)

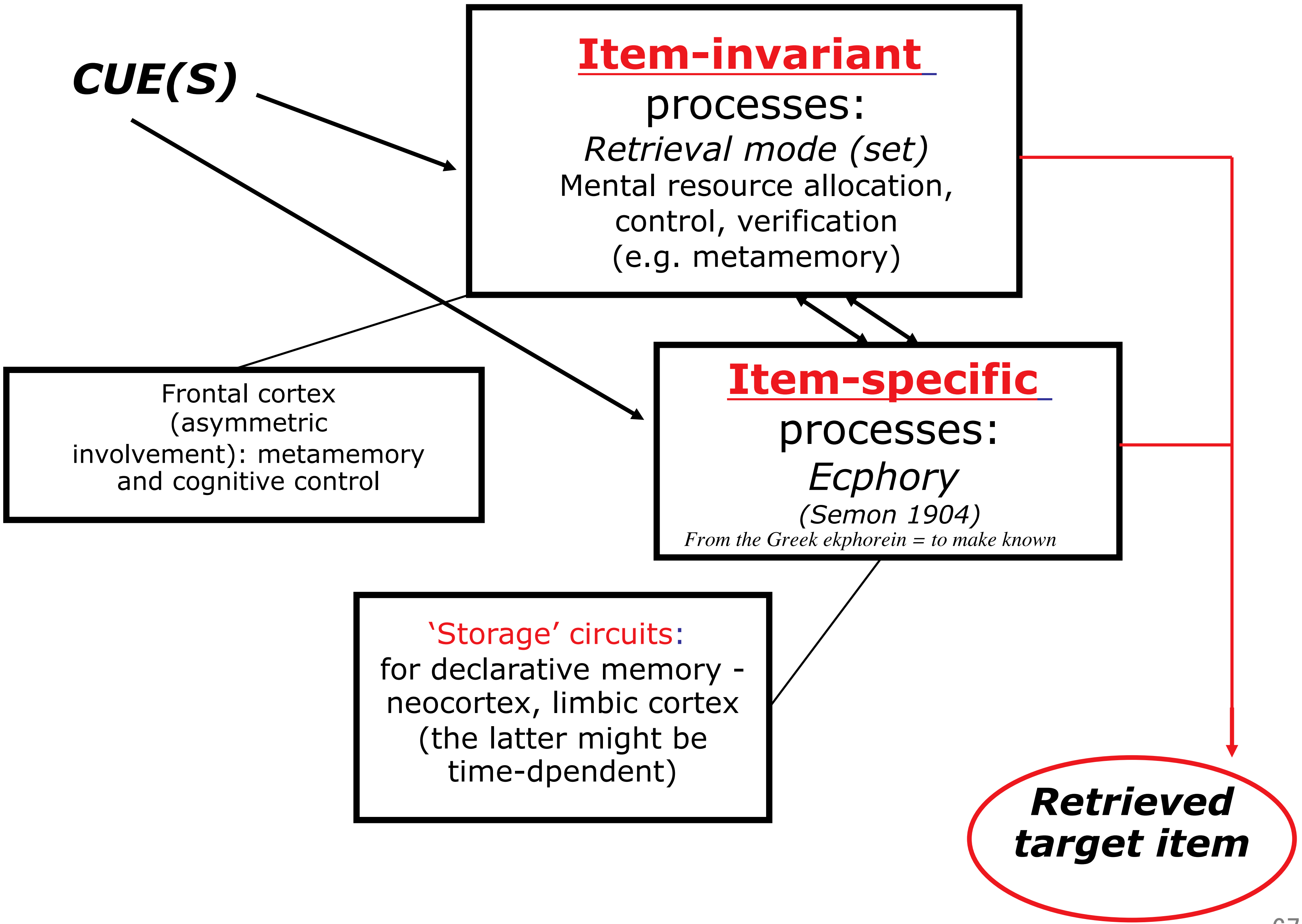
The flowchart



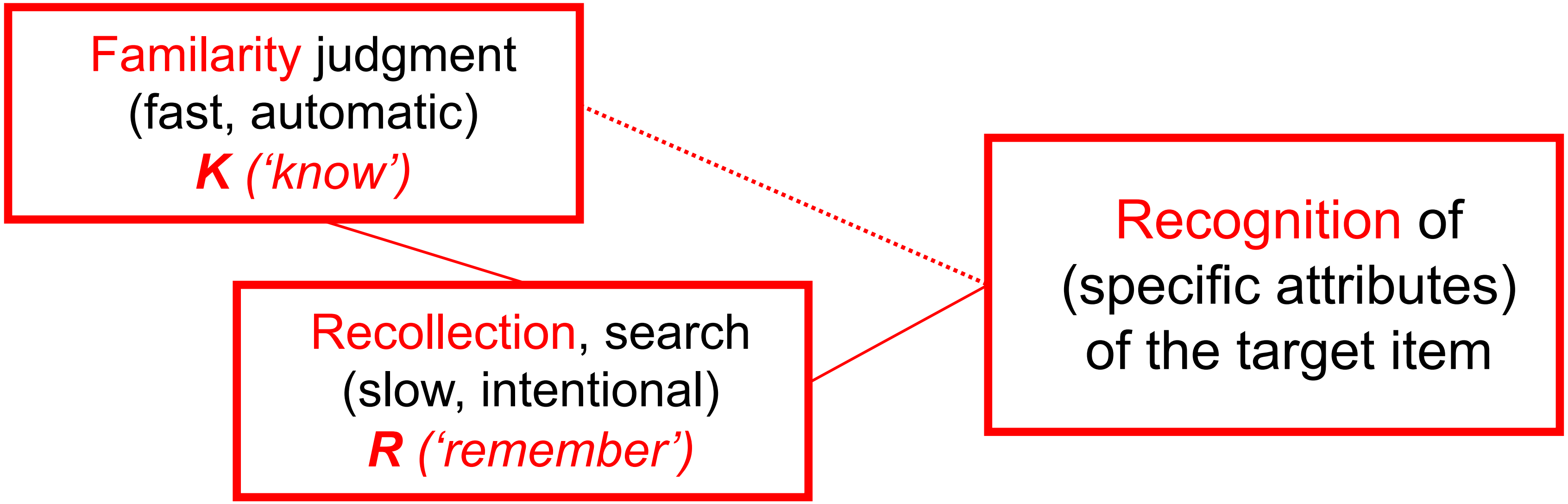
To the muscle (response)

Note: the actual mechanism includes additional components (e.g., PKC) and is context- and history- dependent

But in complex systems it is much more complex



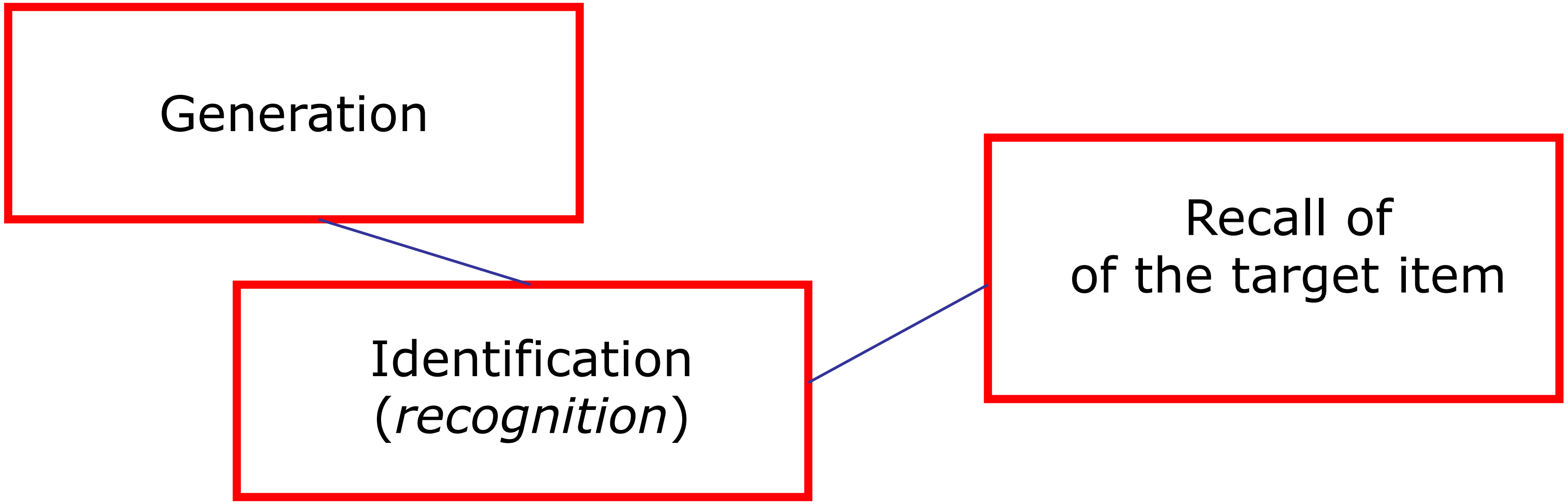
An influential block model of recognition:



The dual process model: Familiarity and Recollection

(Mandler 1980)

An influential block model of recall:

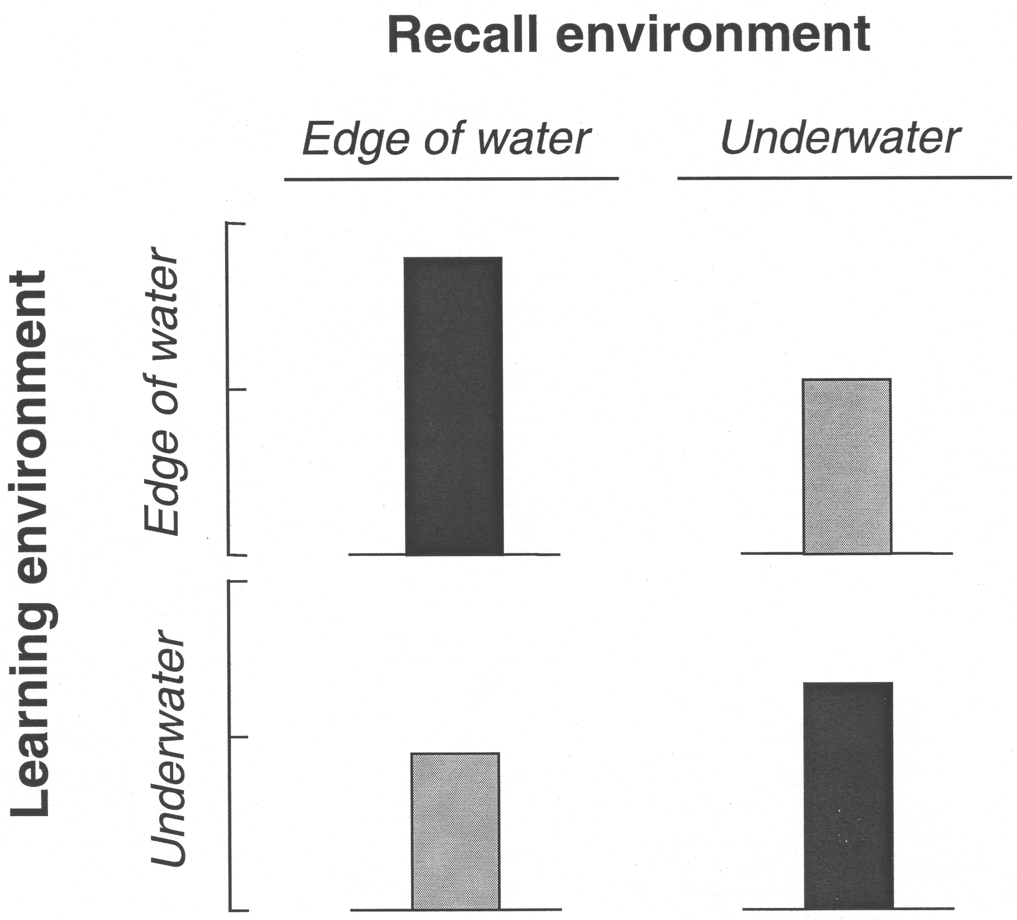


The two phase model: Generation & Identification

(Bahrick 1970)

The efficacy of retrieval depends is a function of matched cues and contexts in encoding and retrieval

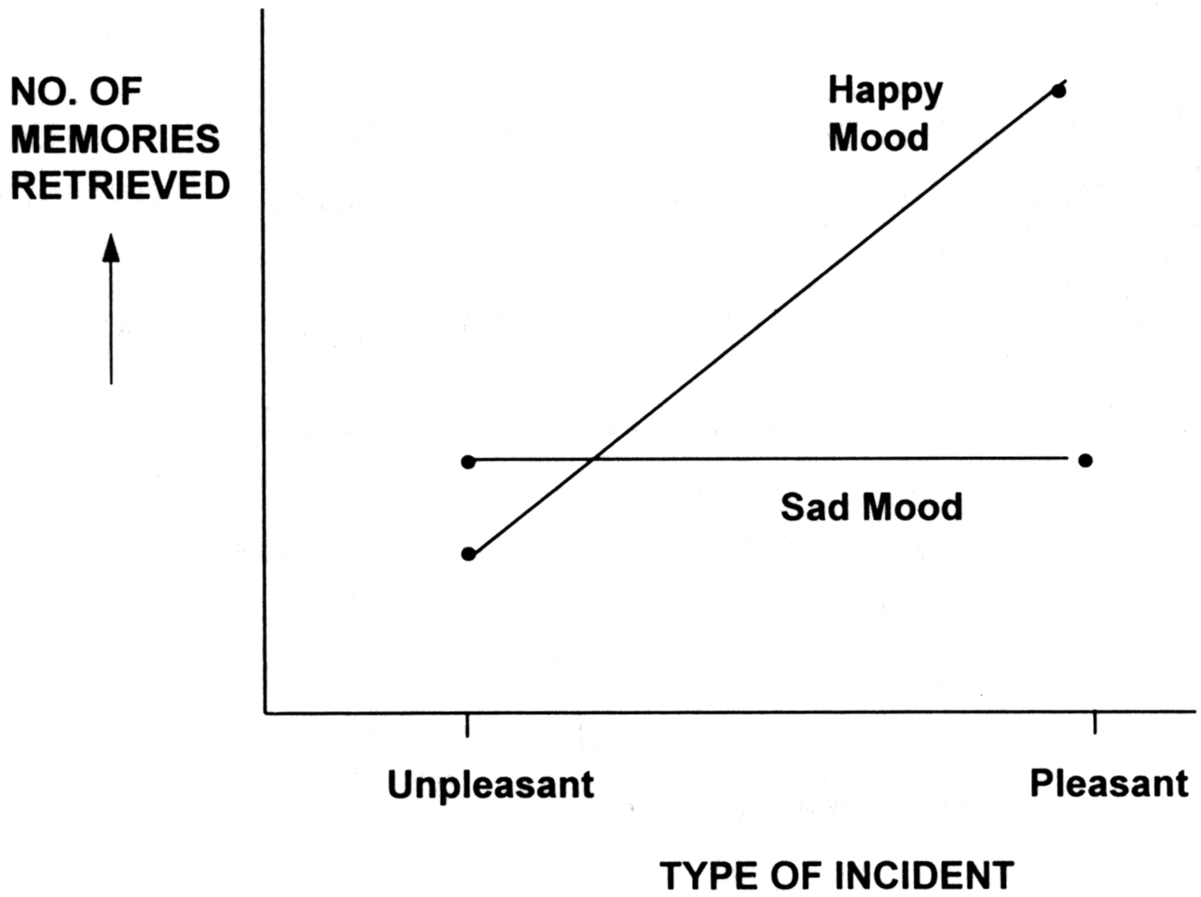
An example
of the effect of
manipulating the
external context:
what is learned underwater
is remembered better
underwater,
and vice versa



(Godden and Baddeley 1975)

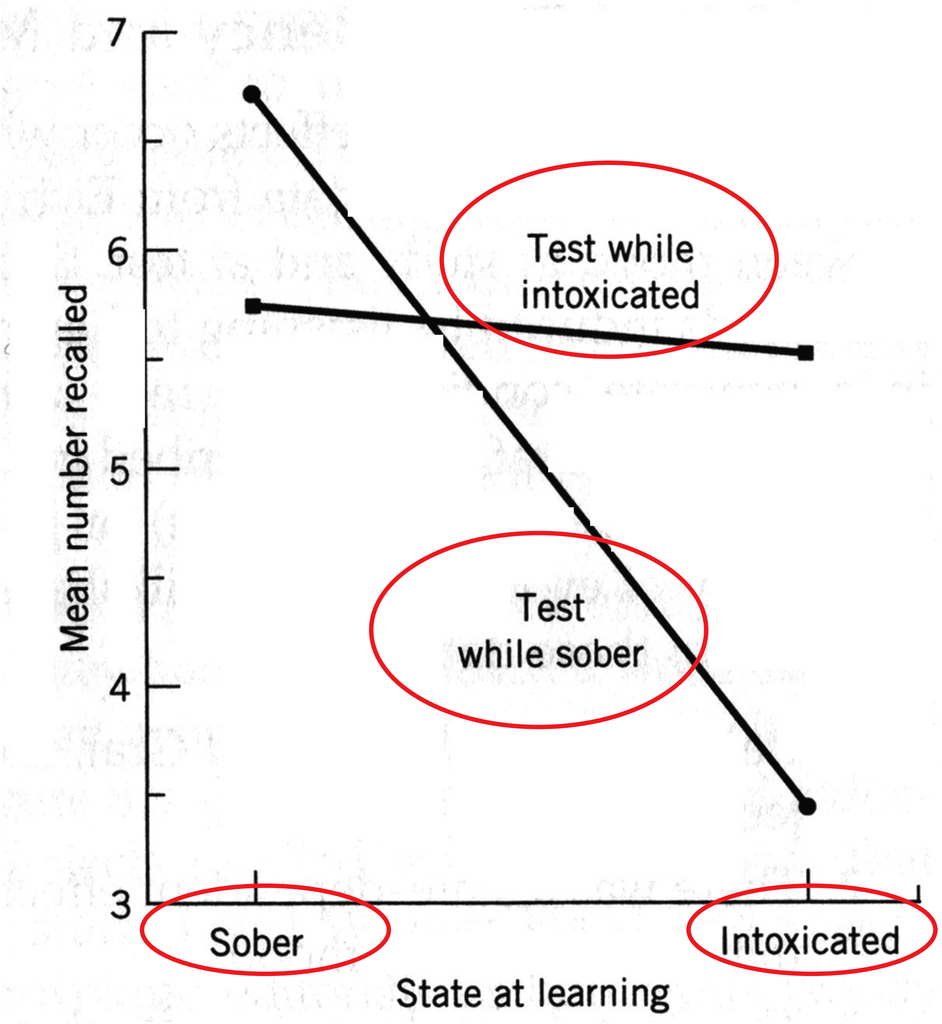
An example of the effect of internal context:

Effect of retrieval of pleasant and unpleasant childhood memories on mood at retrieval ('mood congruency')



(Bower 1981)

And yet another one

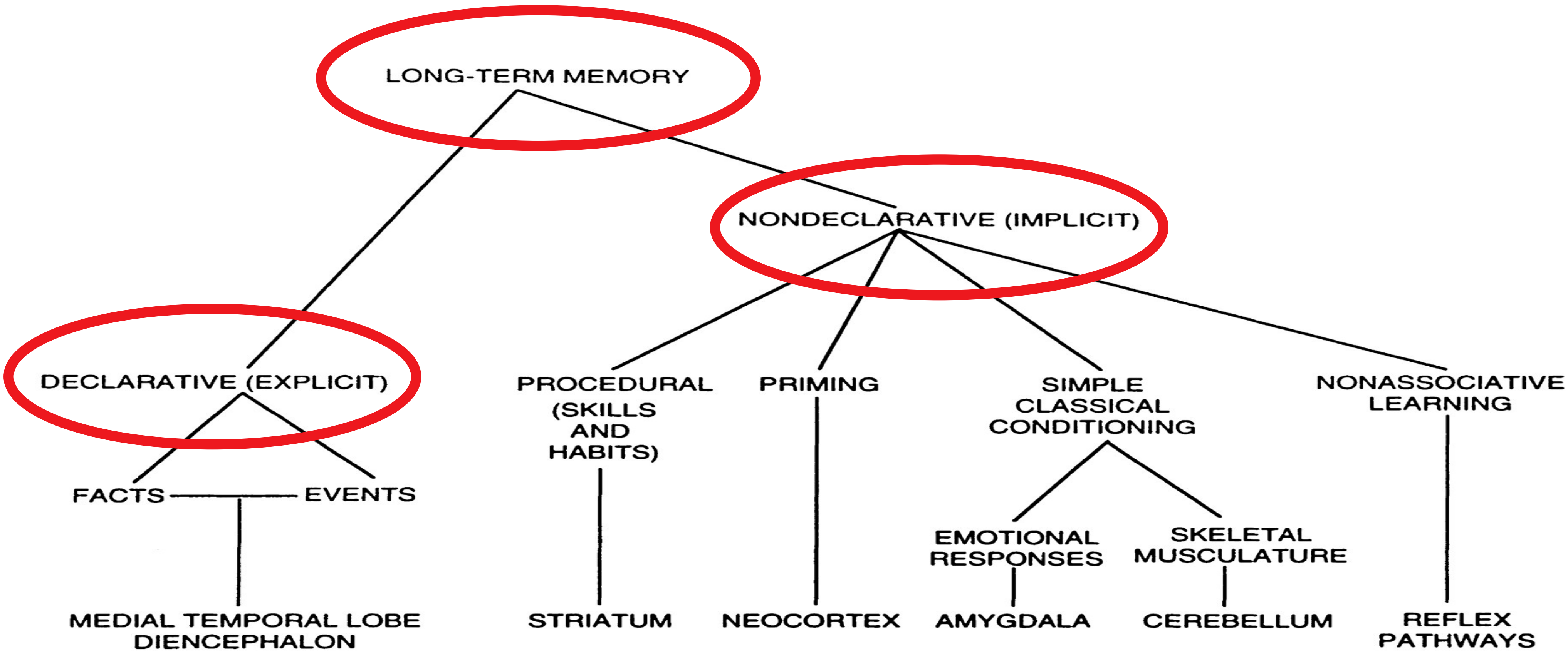


This is termed 'state dependent learning'

So what are memory systems?

- A set of units and their interrelationship
- A group of related elements organized for a purpose
- A portion of the universe selected for study

Reminder: The traditional view



More flexible views of memory systems: Ad-hoc computational systems

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Memory Systems, Processing Modes, and Components: Functional Neuroimaging Evidence

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<u>Which attributes/goals are the natural types of classifiers?</u>