Remembering, forgetting and the neurobiological bases of identity

Rapaport-Klein Study Group

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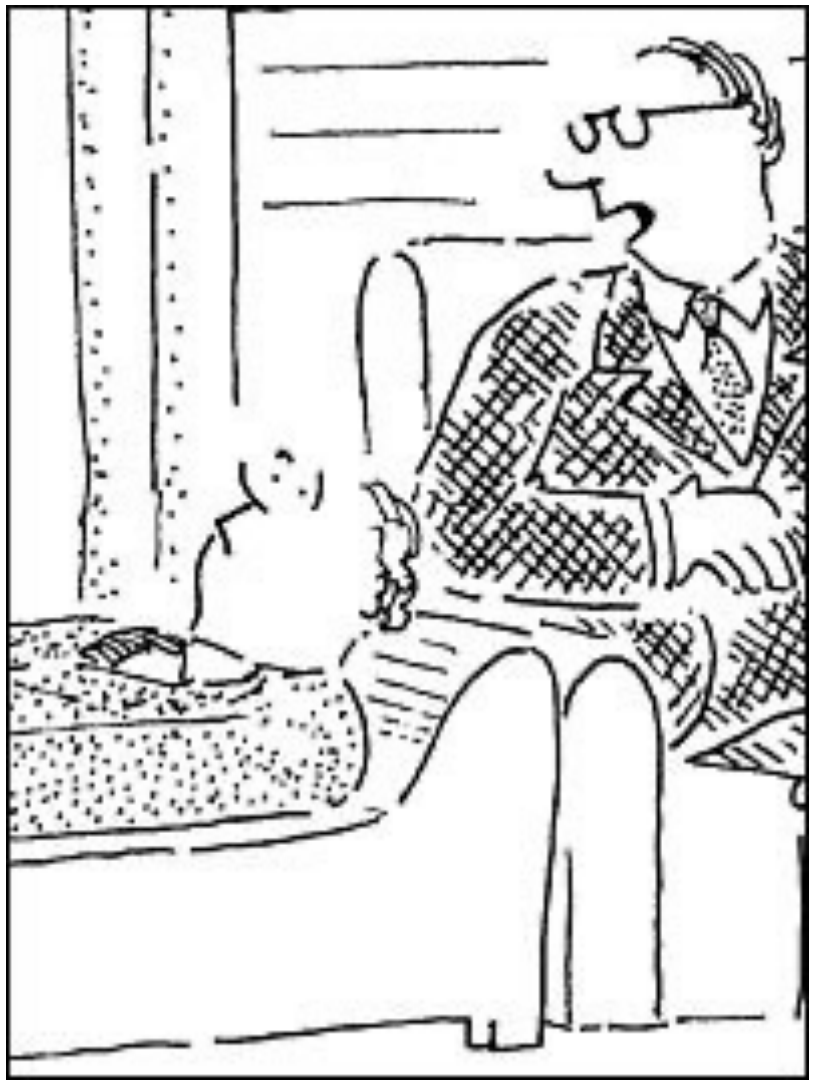
Cristina M. Alberini

Center for Neural Science, New York University



Psychotherapy mechanisms: A major question in the field,
Is it all about memories?

Psychotherapy, Psychoanalysis, and Memories

So much should be discussed, but here are a few points

- Memories are the essence of who we are, therefore, how we think, feel, and act
- Understanding the mechanisms of memories will provide the understanding of information processing, mindset, personality traits, but also body representations, and where/how changes can occur
- Therapeutic approaches, whether via “the talking cure” or body language and bodily communications, are rooted into the processes of memory reactivation and new memory formation

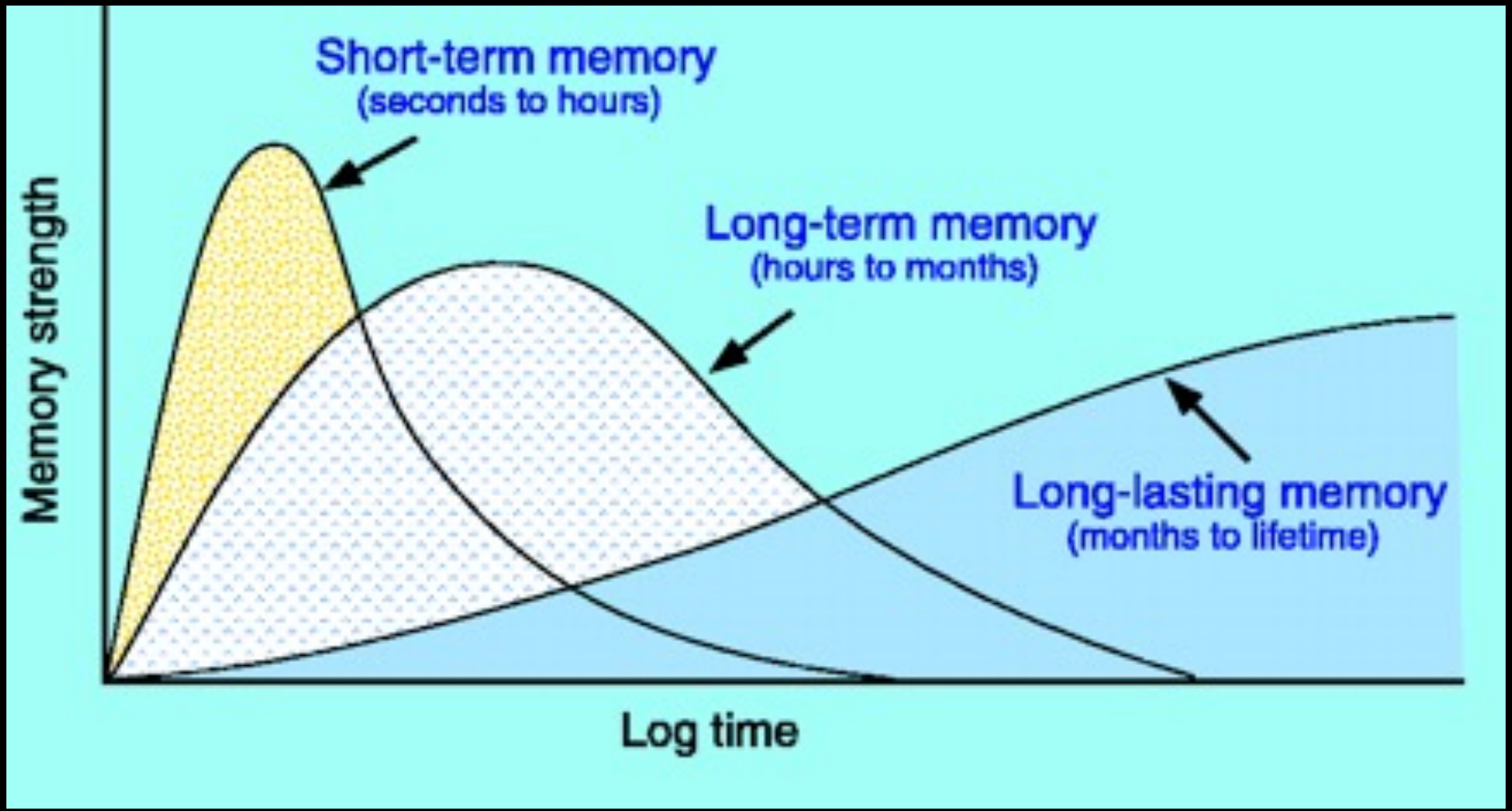
Today's focus

- **the dynamic nature of memories of the "explicit" system (the medial temporal lobe –mediated)**
- **its ontogeny, i.e., episodic memories formed in infancy**

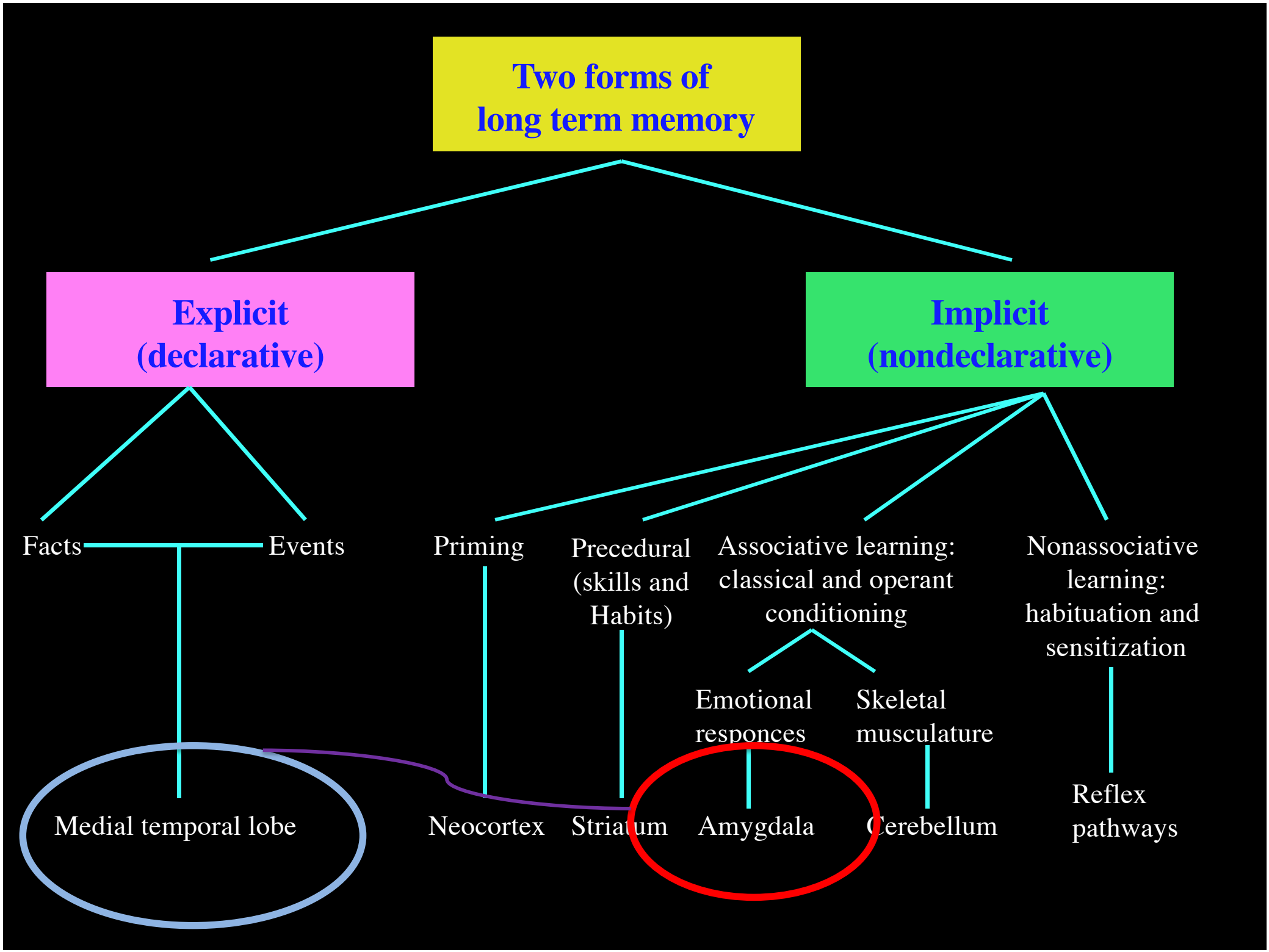
- Definitions
- Formation of new memories: memory consolidation
- Remembering: memory retrieval, reactivation and reconsolidation
- Memories formed in a new system: infantile memories

Memories: the retention of information acquired through learning

Memories exist in many forms

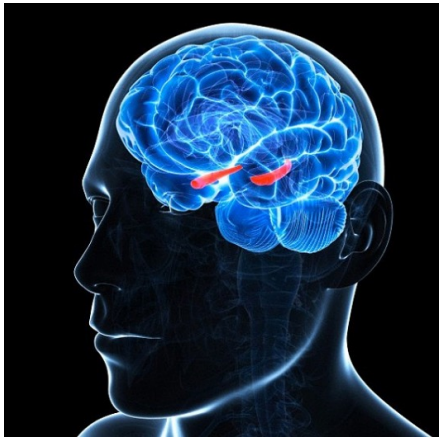


From: McGaugh. Memory-a century of consolidation. Science, 2000

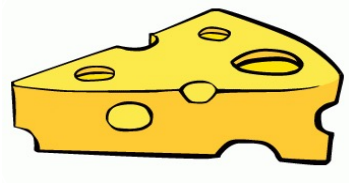

Two forms of long term memory
Explicit (declarative)
Implicit (nondeclarative)
Facts
Events
Priming
Precedural (skills and Habits)
Associative learning: classical and operant conditioning
Nonassociative learning: habituation and sensitization
Emotional responces
Skeletal musculature
Medial temporal lobe
Neocortex
Striatum
Amygdala
Cerebellum
Reflex pathways

The goal of my laboratory: to unravel the biological mechanisms of memory

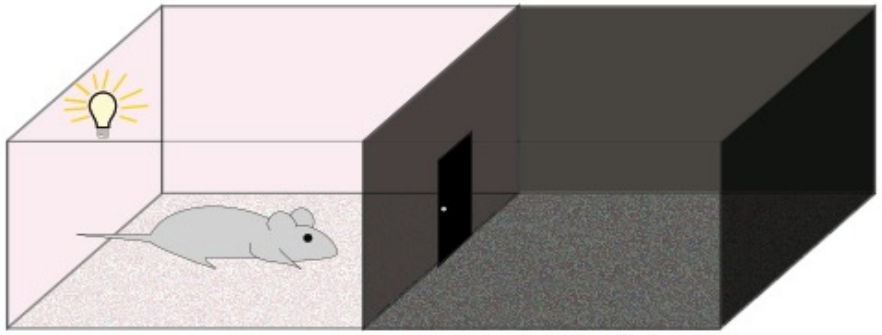
Episodic memories- evolutionarily conserved



Who? What? Where? When?



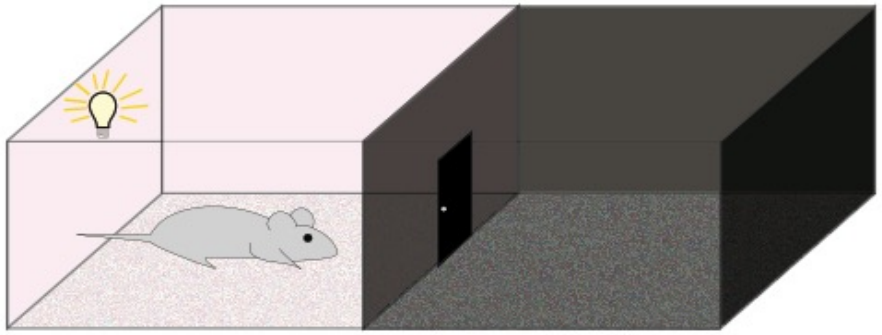
Inhibitory Avoidance

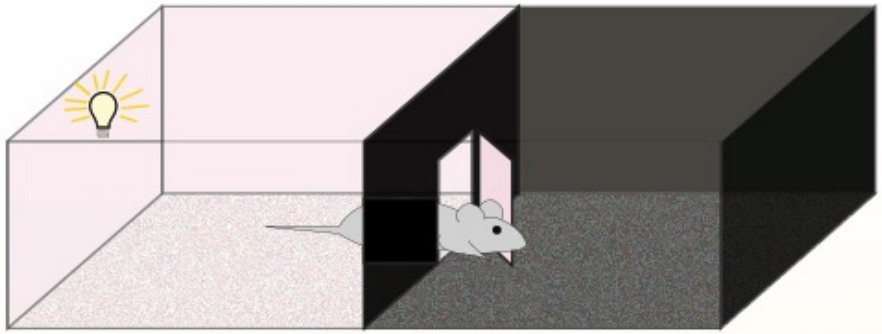


Training

Testing

Inhibitory Avoidance

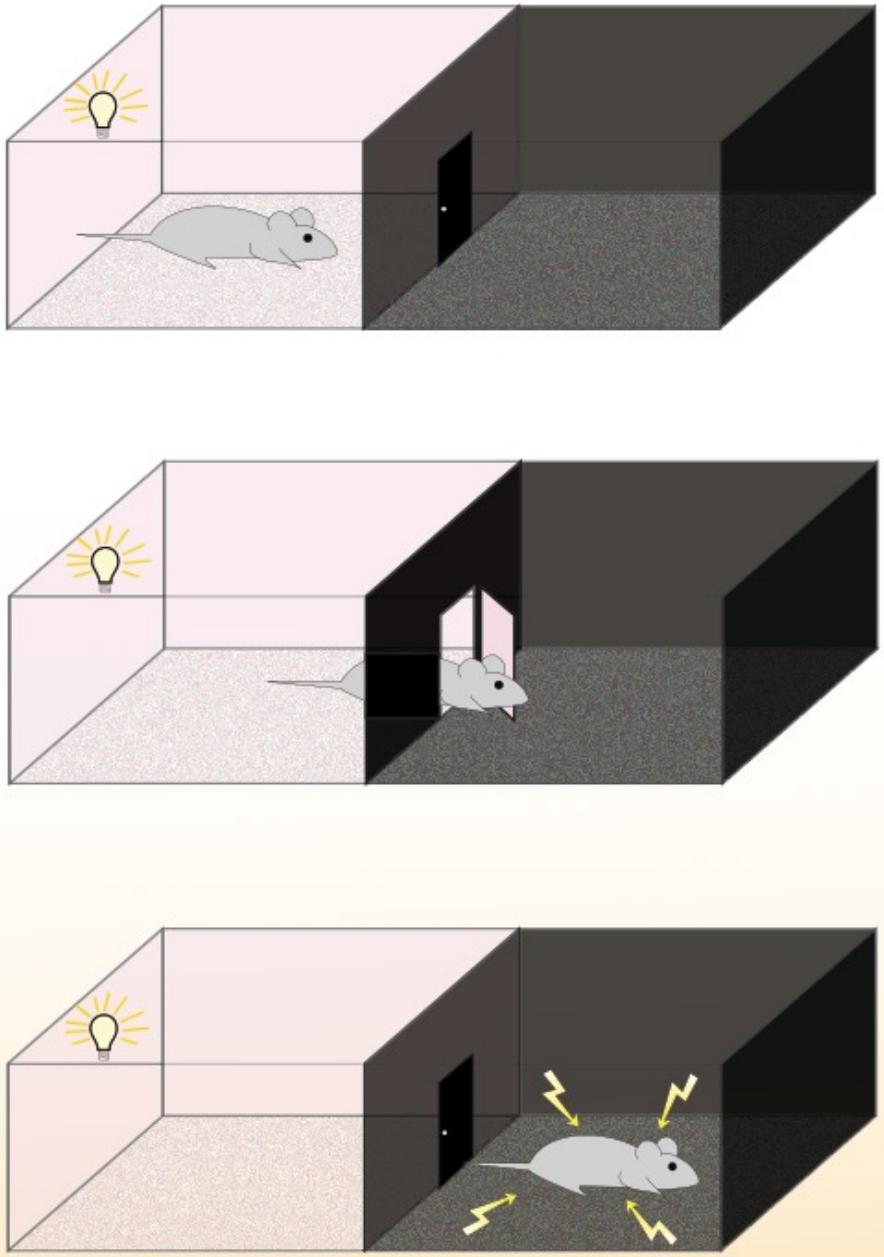




Training

Testing

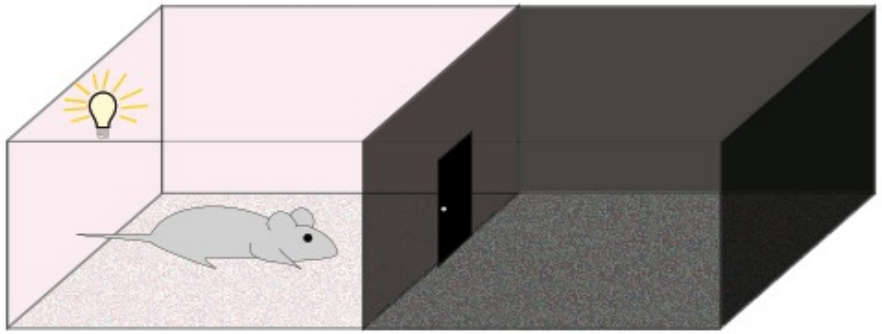
Inhibitory Avoidance

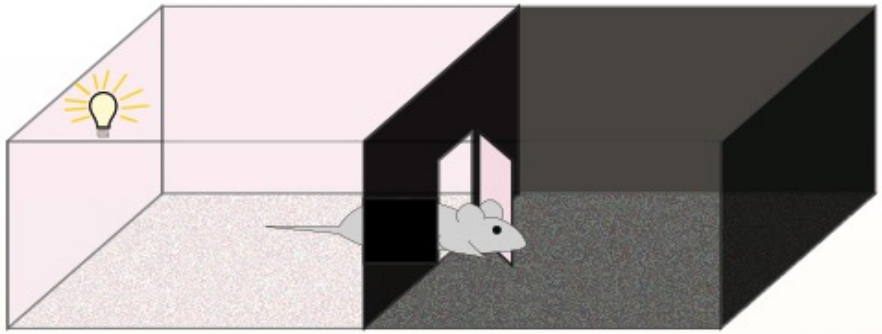


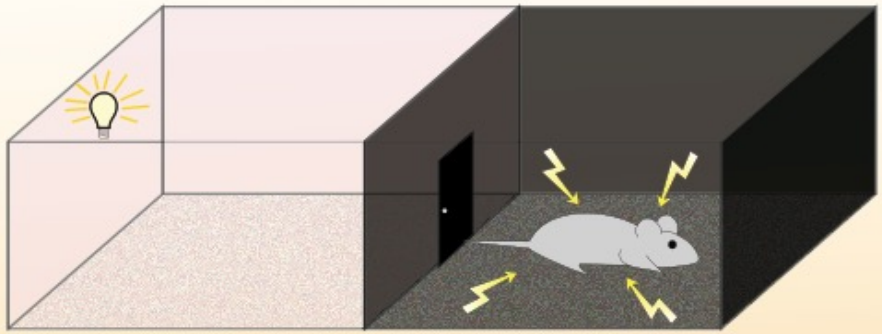
Training

Testing

Inhibitory Avoidance







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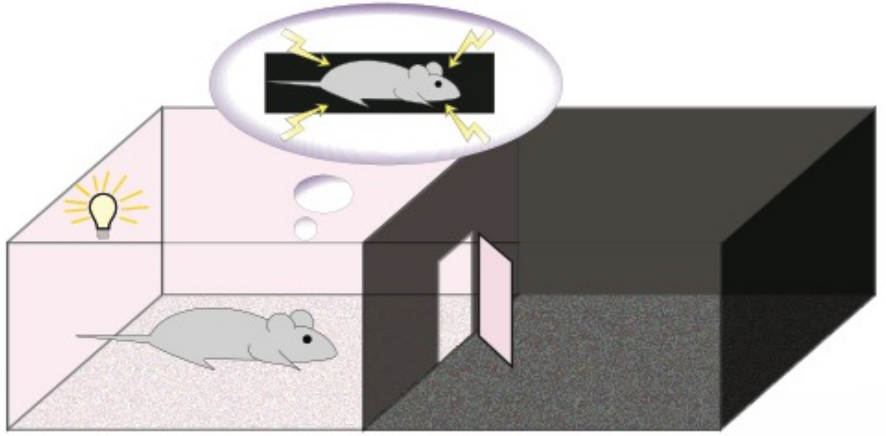
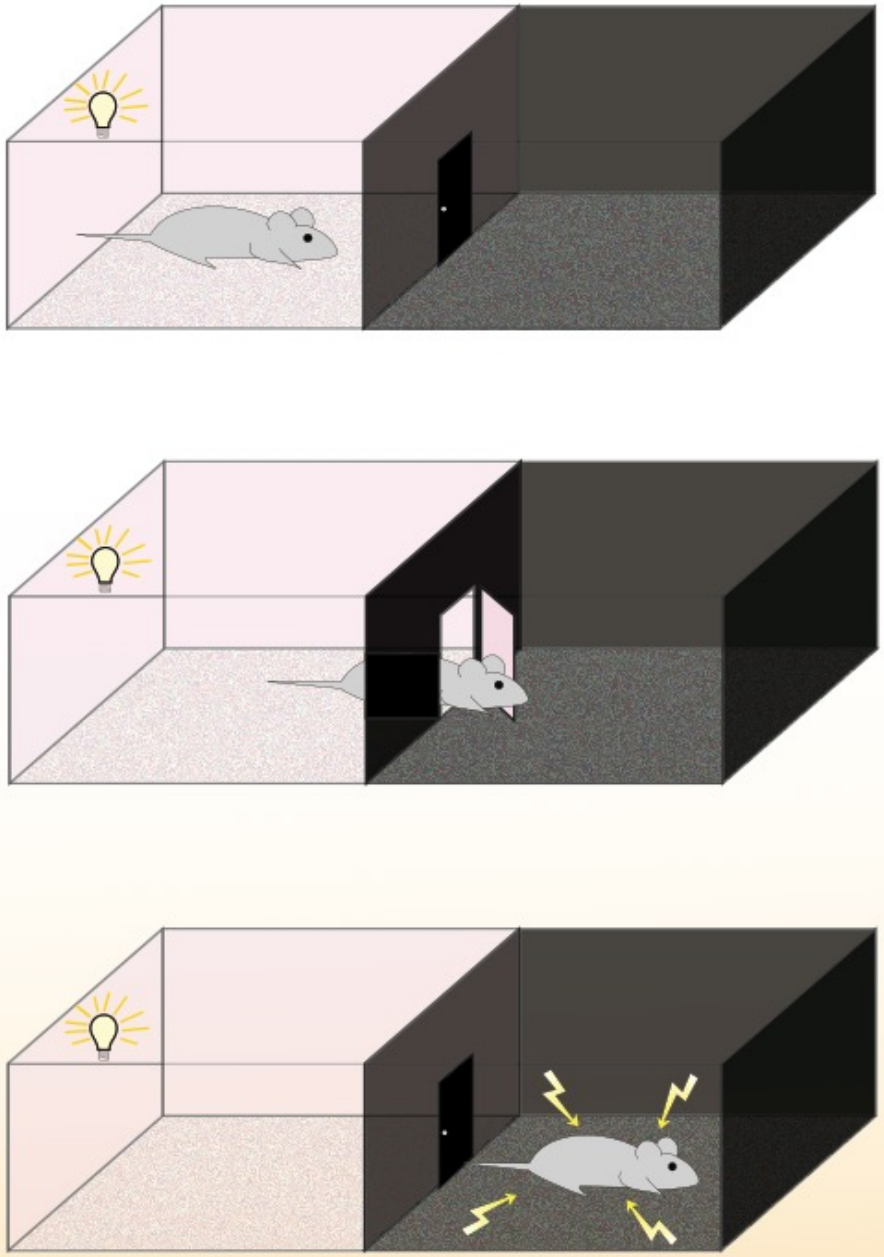
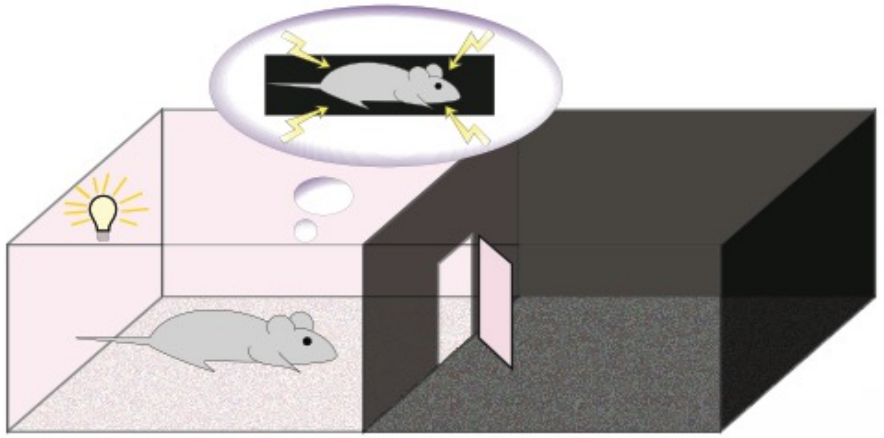


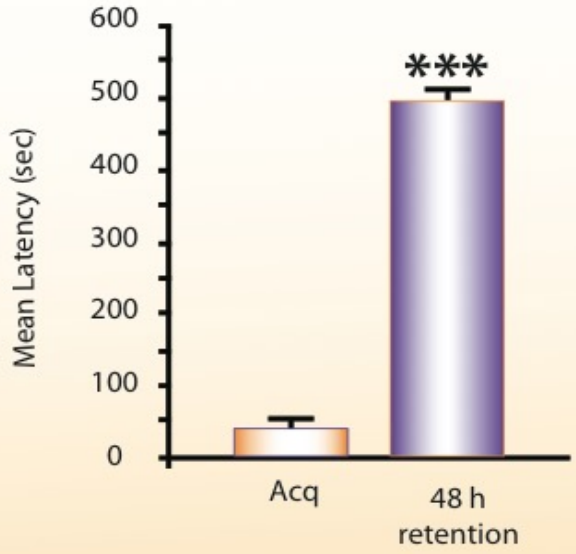
Testing

Inhibitory Avoidance



Training





Testing

Memories undergo a process of CONSOLIDATION

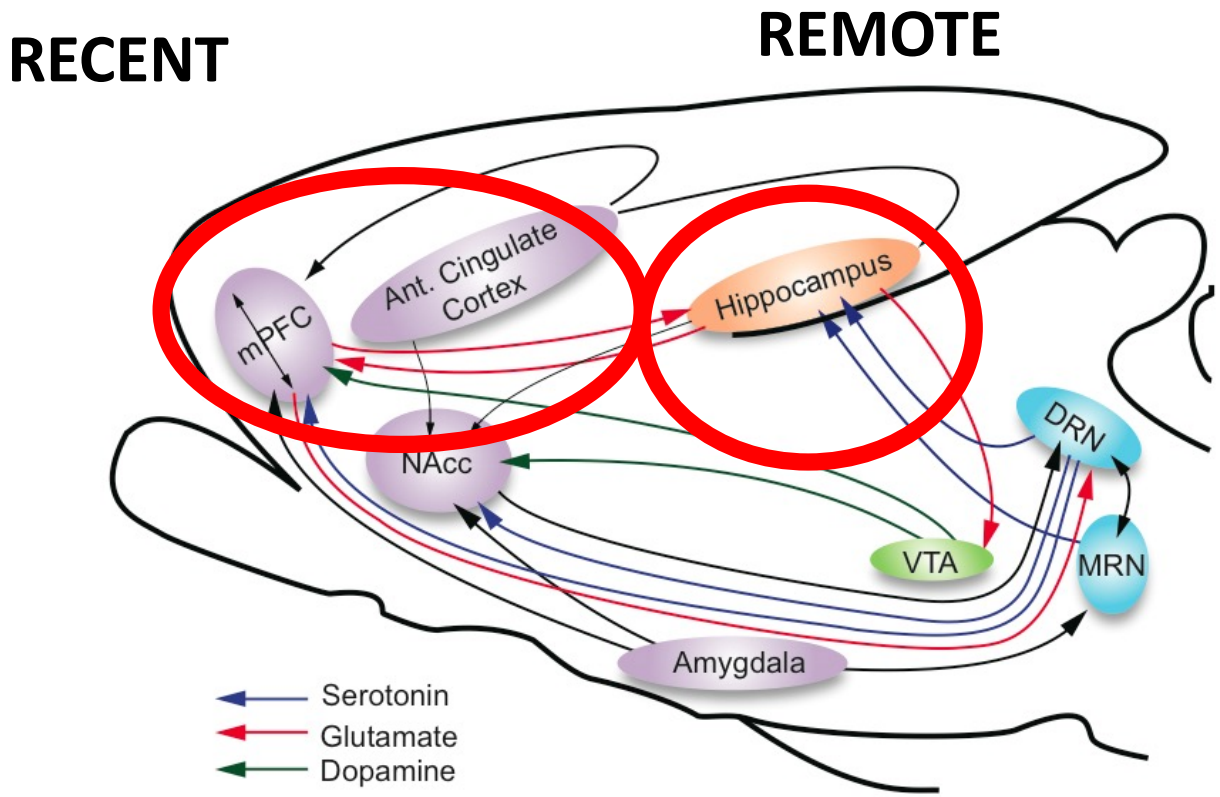
Classical consolidation hypothesis

Long-term memories are initially fragile and become stable through a process known as *consolidation*.

After being consolidated, the memory is stable and resistant to disruption

Consolidation requires that a number of biological changes take place in the memory system (molecular consolidation)

Explicit memories undergo also system-CONSOLIDATION: over time the memory representation re-distributes



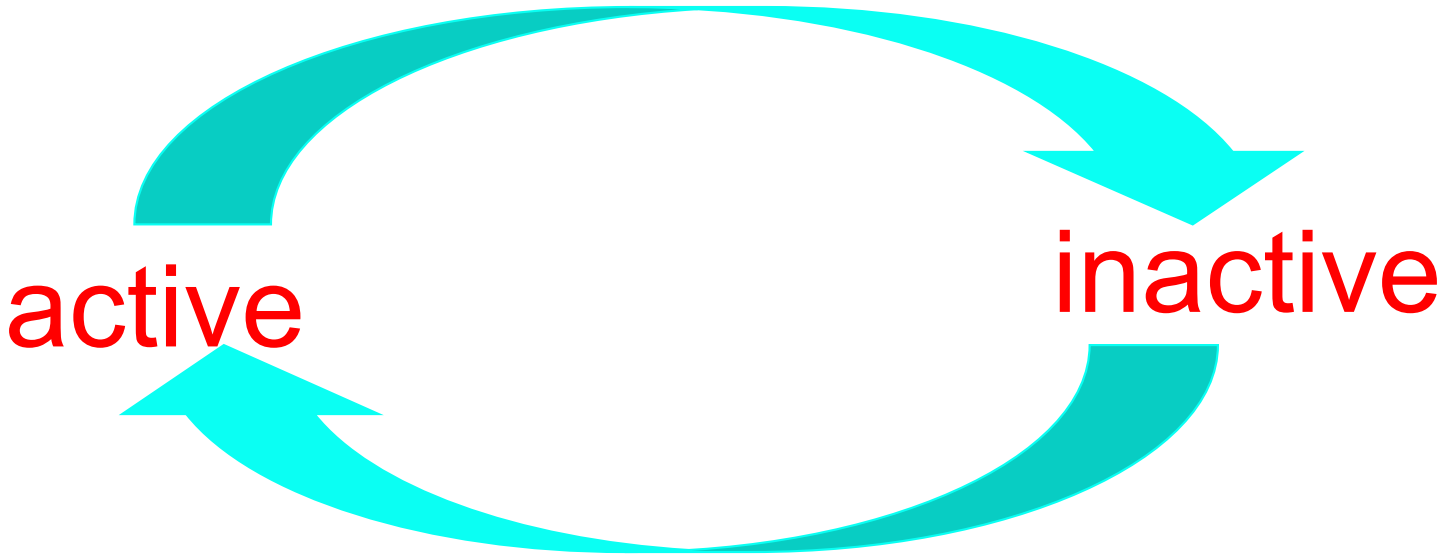
For many decades it was believed that via consolidation the memories become sort of "fixated" and then can be retrieved when needed

This concept is NOT correct

Many data support the conclusion that the storage of memories is highly dynamic

First dynamic dimension: reconsolidation

An established memory becomes labile if recalled, and, like during consolidation, it again undergoes a stabilization process, known as *reconsolidation*



Reconsolidation has several boundaries and cannot not -alone- explain the therapeutic process

- **Reconsolidation does not occur with all retrievals.**
- **Retrievals lead to several processes, including reconsolidation, new learning, counterconditioning, and in some cases extinction**

-Reconsolidation does not occur every time a memory is recalled

-One major variable is the age of the memory: reconsolidation is temporally limited. Older episodic memories do not show fragility after recall, i.e., they do not reconsolidate

-A second major variable is memory strength: Very strong memories, such as memories of traumatic events, do not become labile after recall

-Reconsolidation of different types of memories (e.g. implicit memories), including procedural memories have distinctive features. It is NOT a one size fits all

-Memory updating with distinct information occurs via new memory consolidation

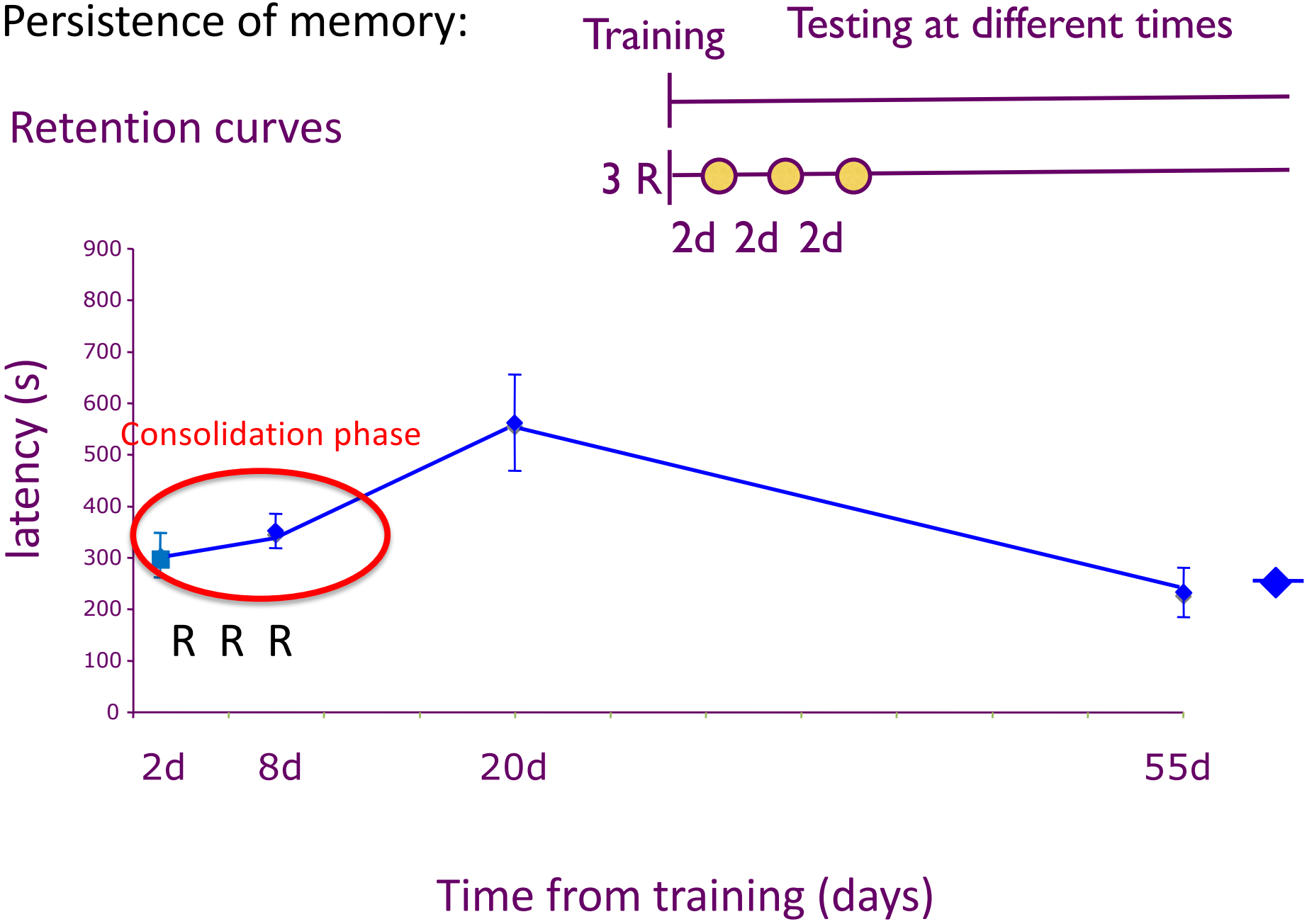
Milekic and Alberini, Neuron 2002; Alberini TINS 2005; Tronel et al. Plos Biol. 2005; Inda et al. J. Neurosci 2011; Alberini Frontiers 2011; Alberini JAPA, 2015; Book on memory reconsolidation

Second dynamic dimension: new experiences building on past memories

Consolidation of new memories and reconsolidation can occur in parallel following retrieval. They contribute to different types of memory updating

In the adult brain: trace reassociation and the role of the past (individual experiences)

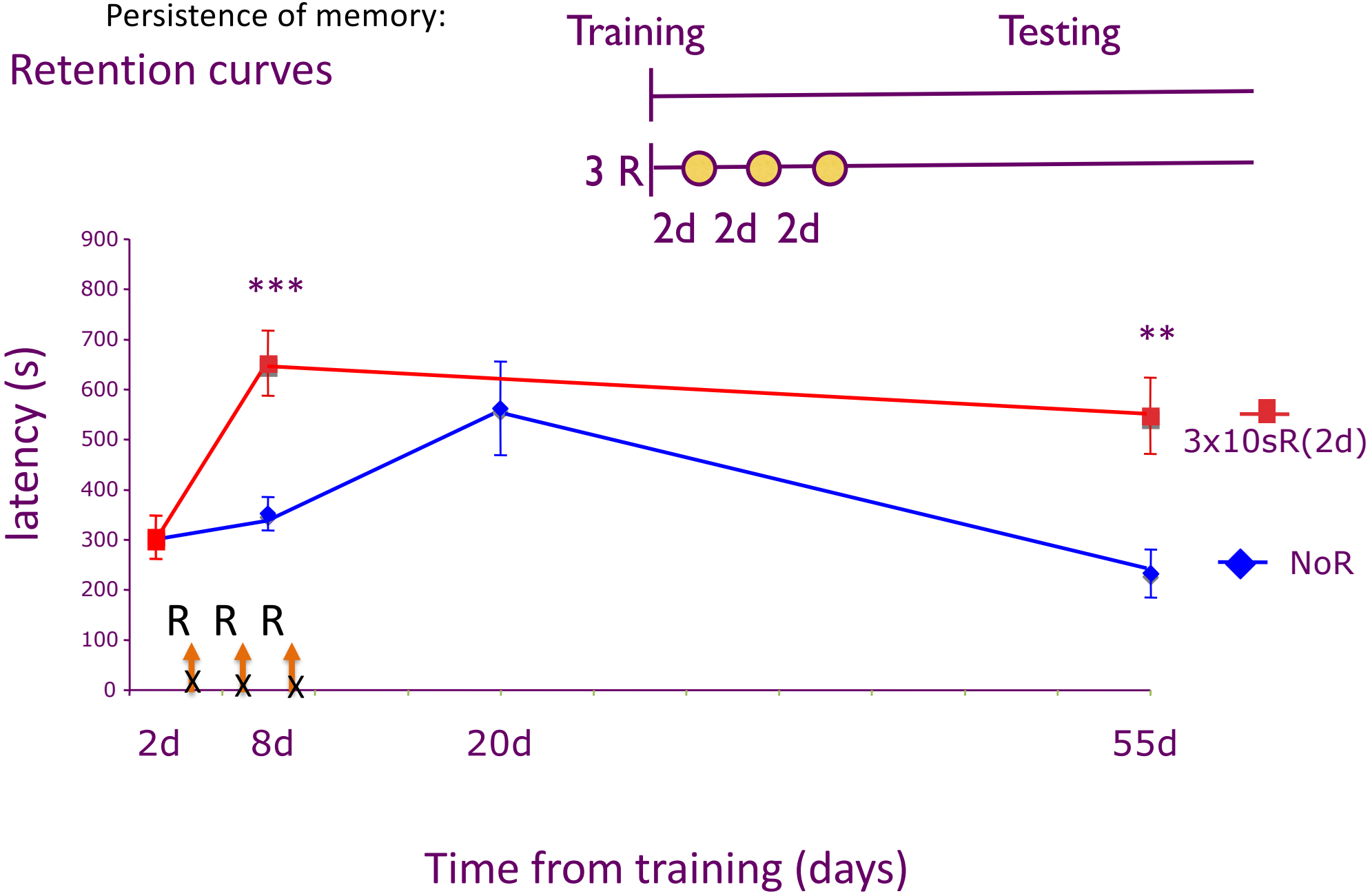
Persistence of memory:



Inda et al. J Neuroscience 2011

Persistence of memory:

Retention curves



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Persistence of memory:

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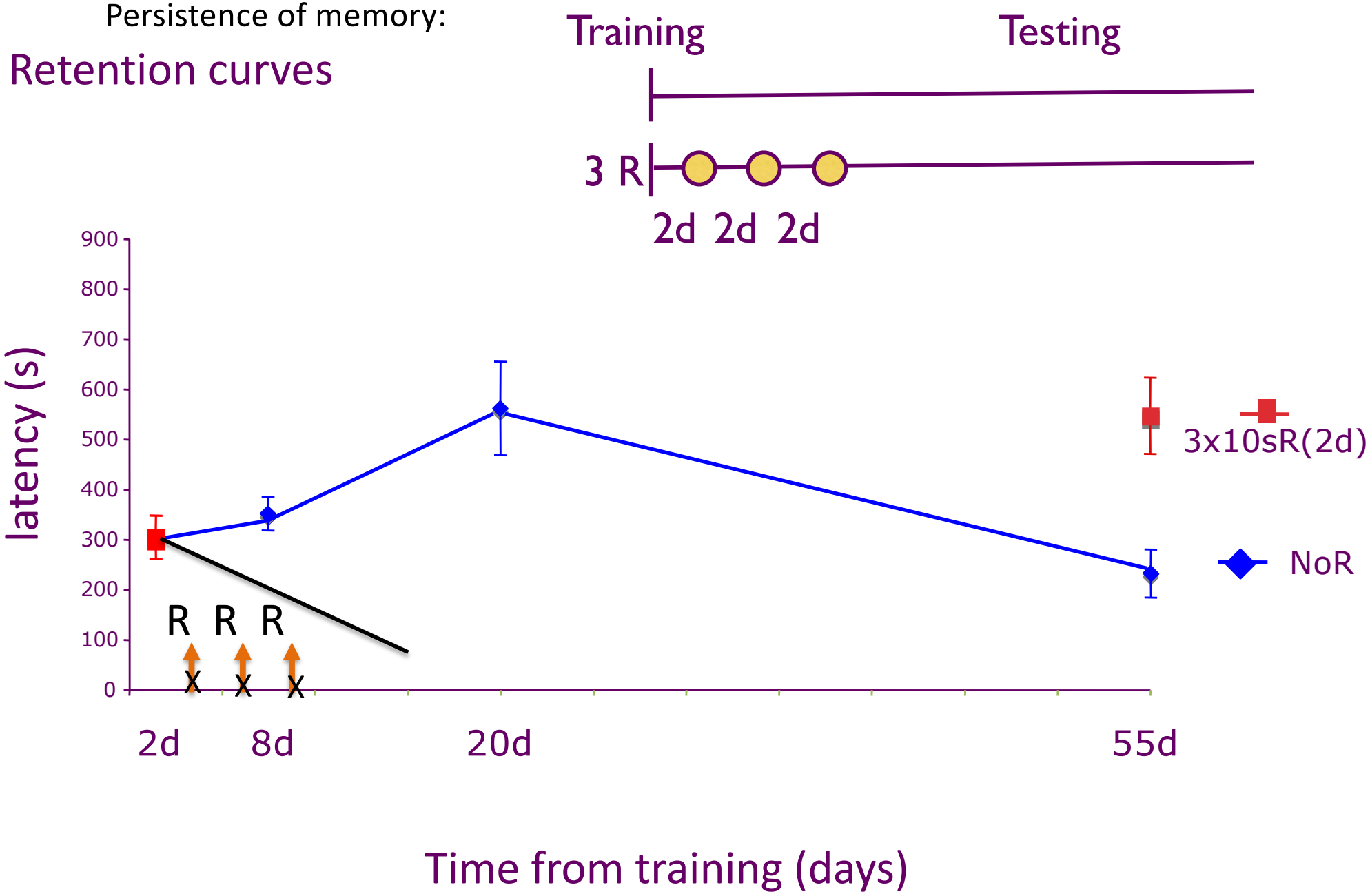
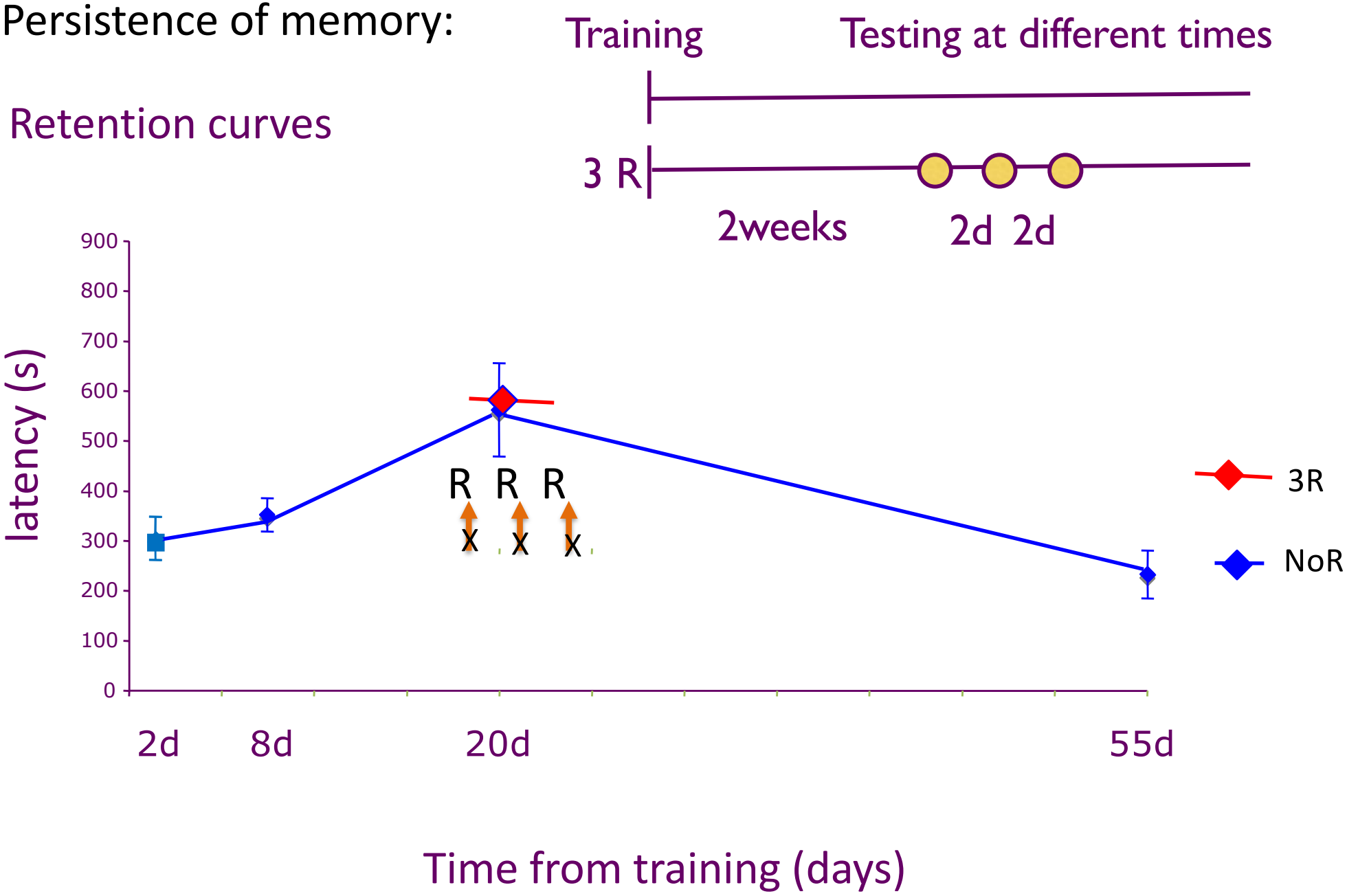


Inda et al. J Neuroscience 2011

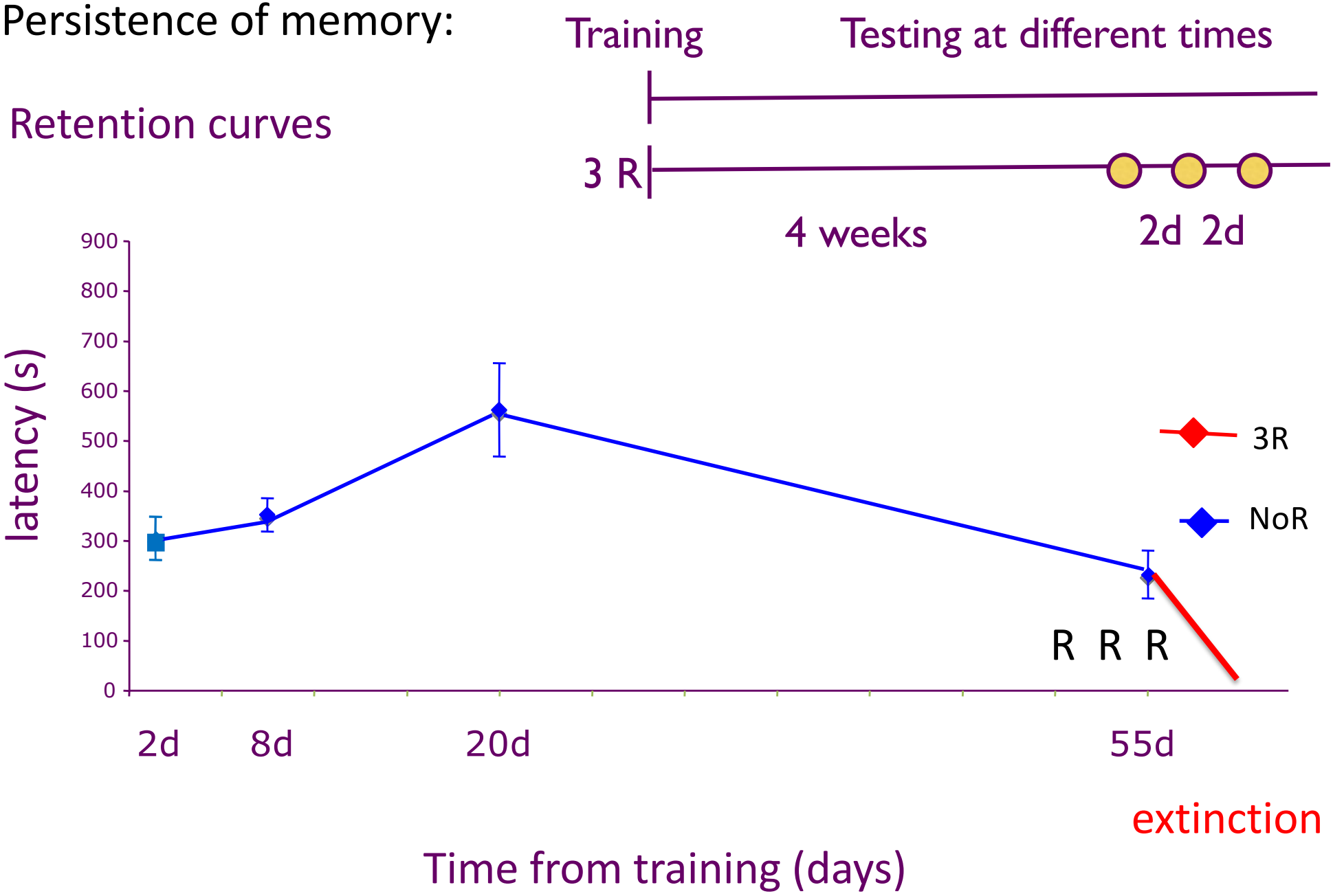
Persistence of memory:



Inda et al. J Neuroscience 2011

Persistence of memory:

Retention curves



Inda et al. J Neuroscience 2011

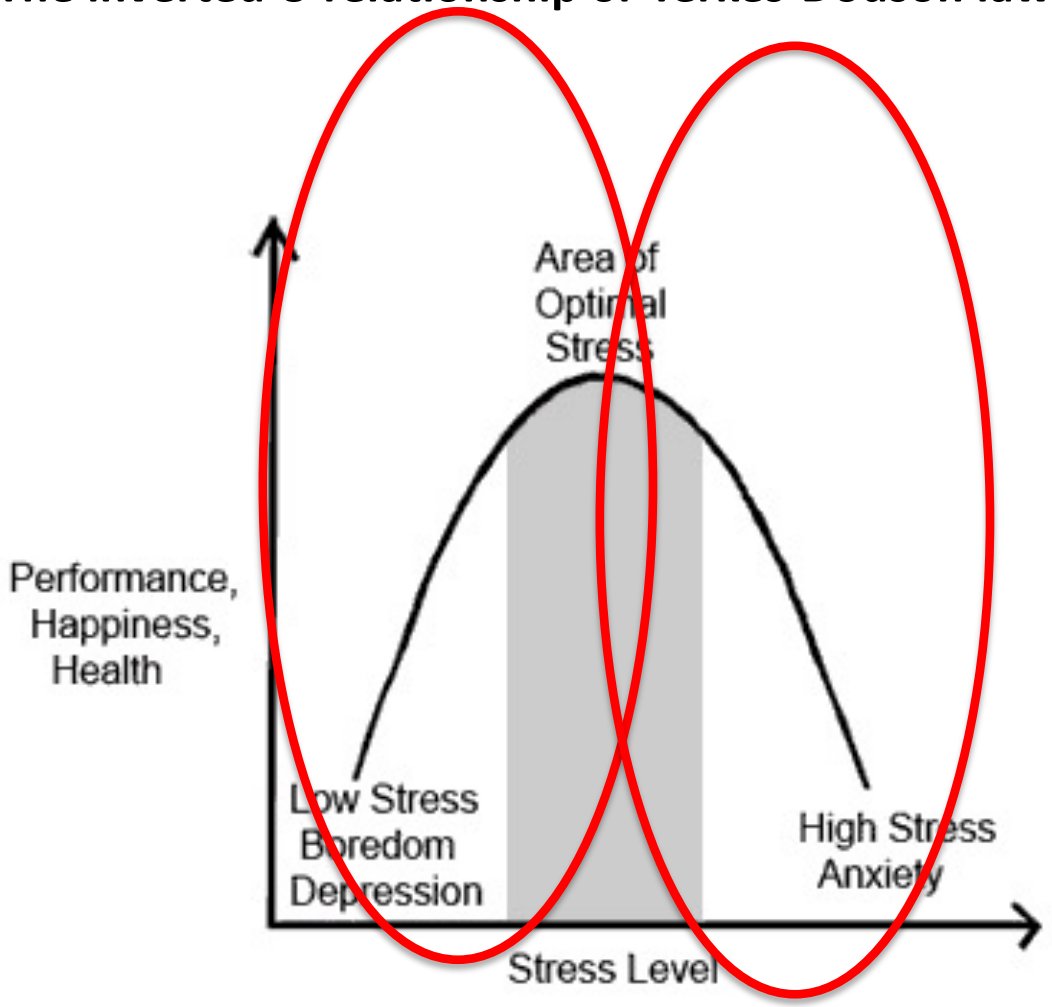
A major contributor of the dynamic nature of memory is TIME, hence the AGE of the memory

- Consolidation takes time
- Reconsolidation is temporally limited
- Forgetting

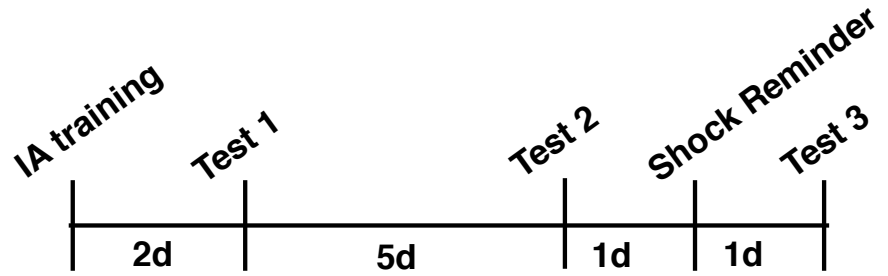
Third dynamic dimension: the strength of the memory and modulation (stress) levels (from adaptive to traumatic memories)

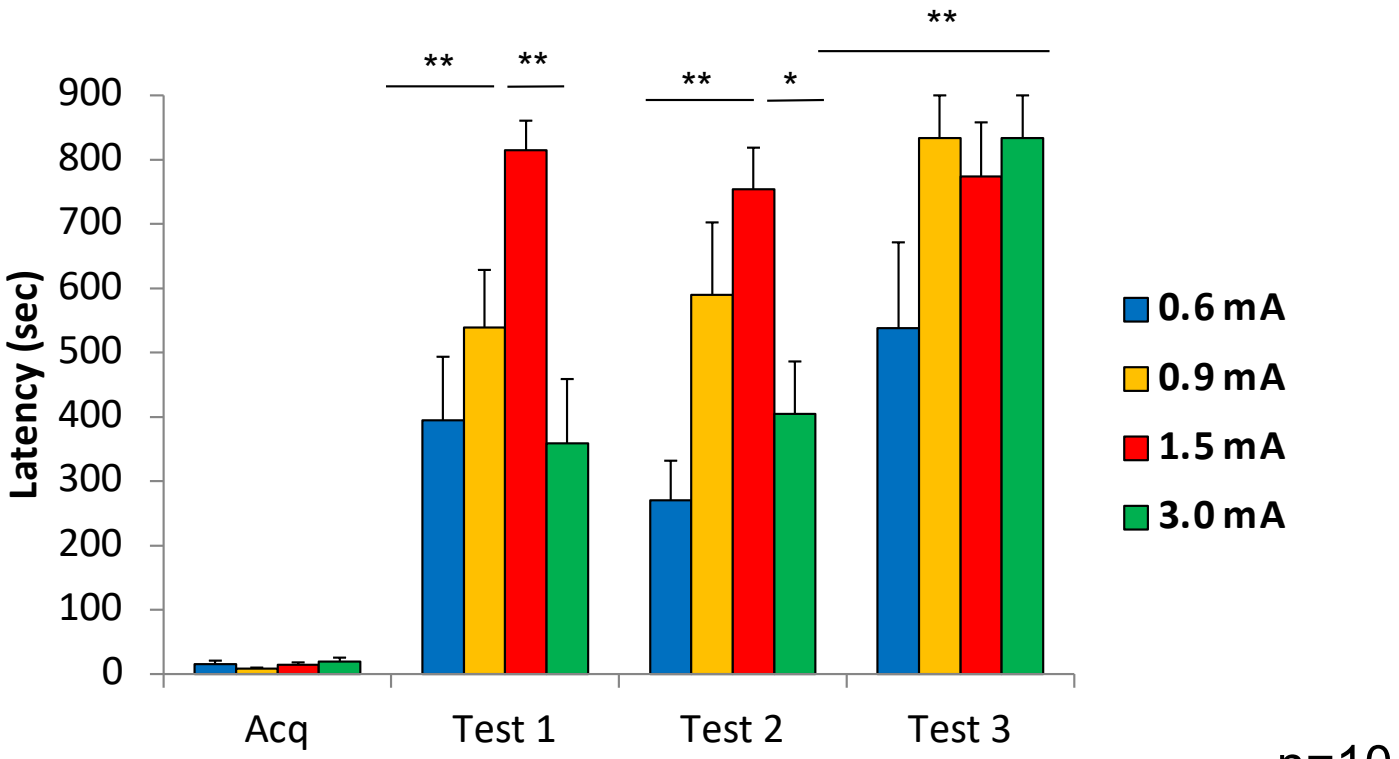
The emotion and stress level during learning modulates memory expression and storage

The inverted U relationship or Yerkes-Dodson law



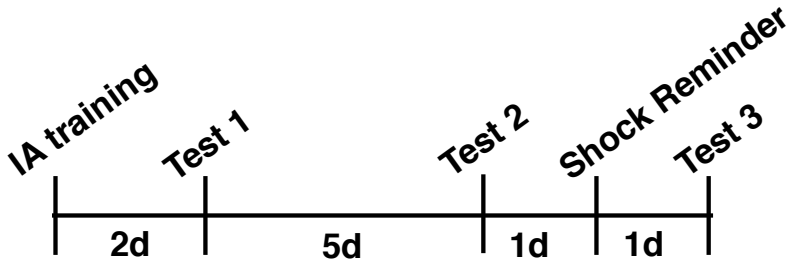
Stress and memory: and 'inverted-U' affaire

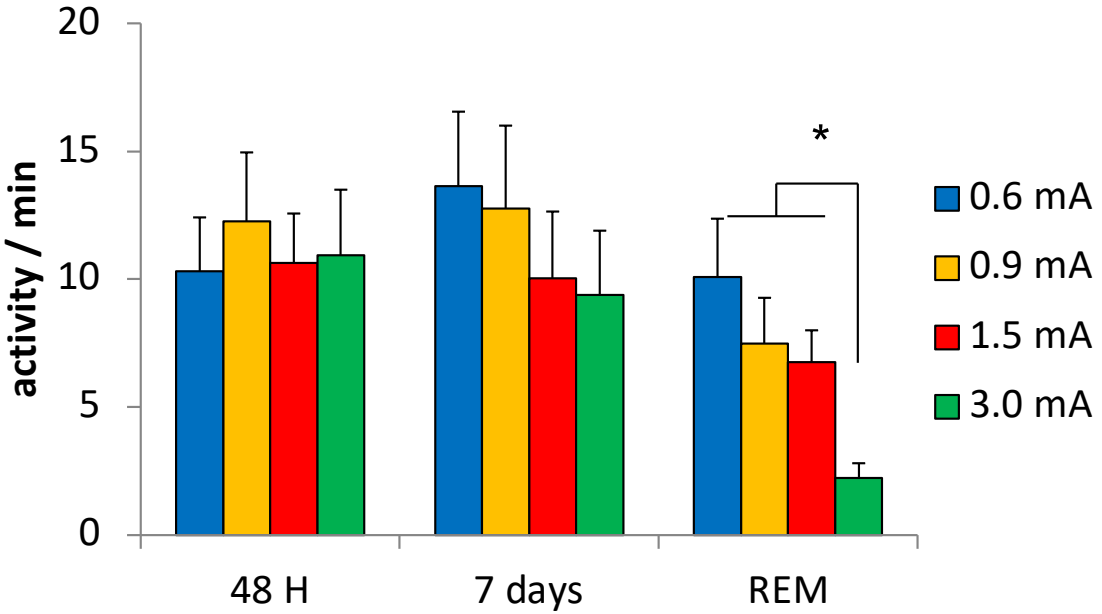




n=10

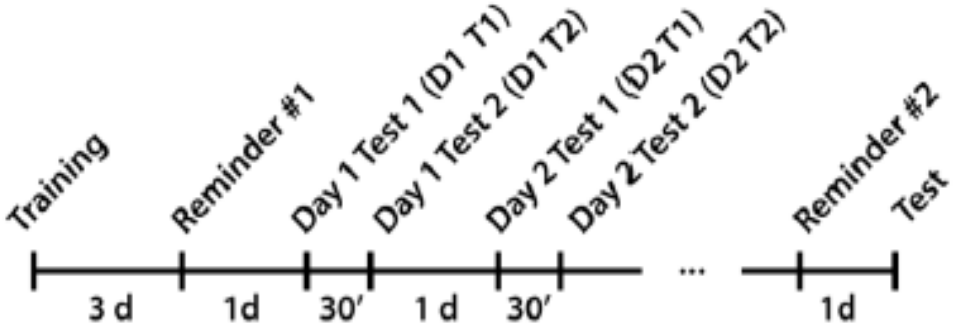
Activity during memory testing, an index of anxiety

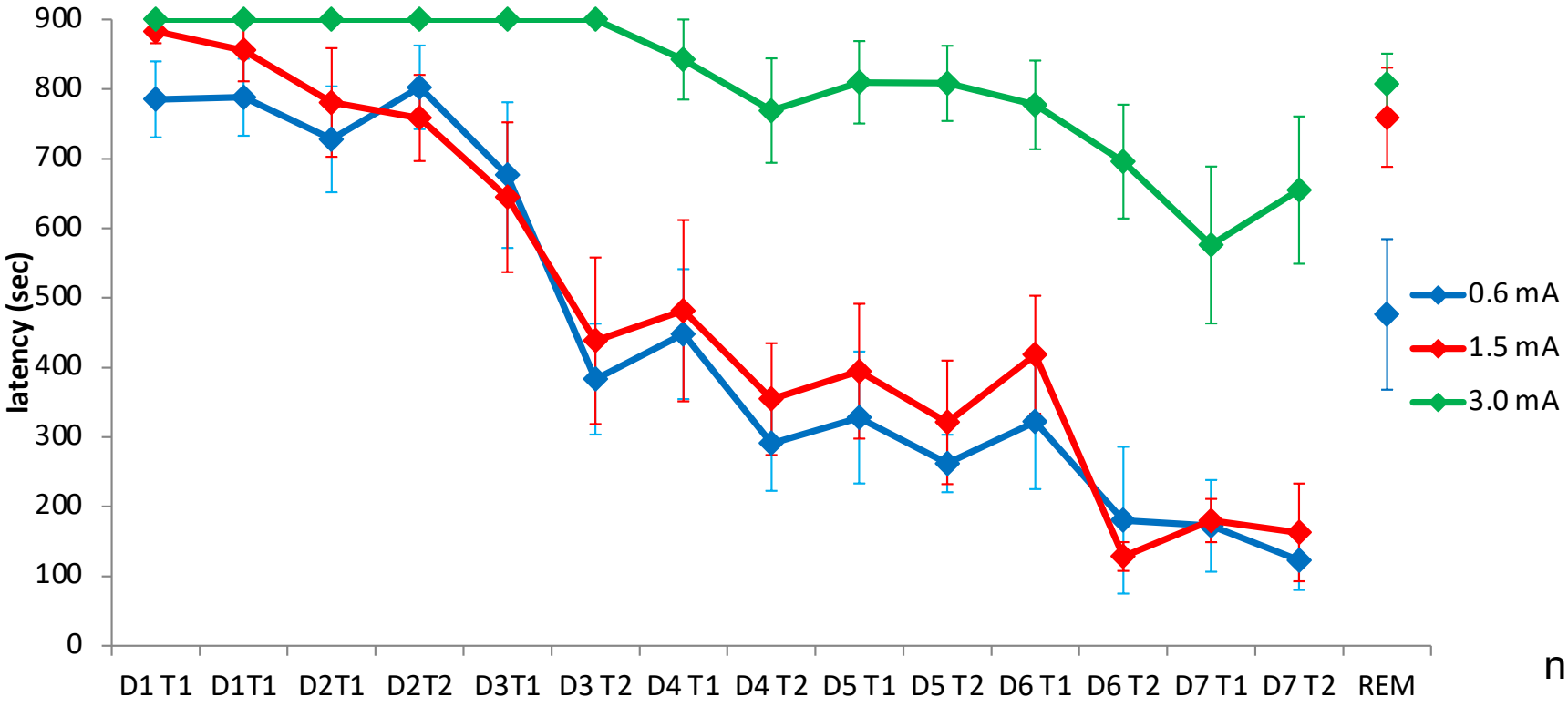




n=8

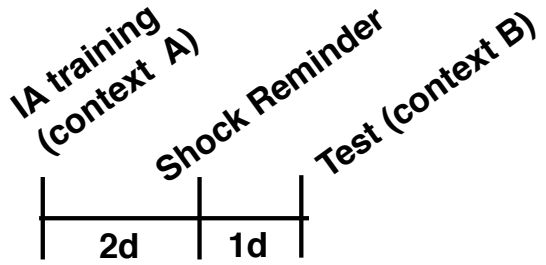
Memory extinction after different footshocks intensities

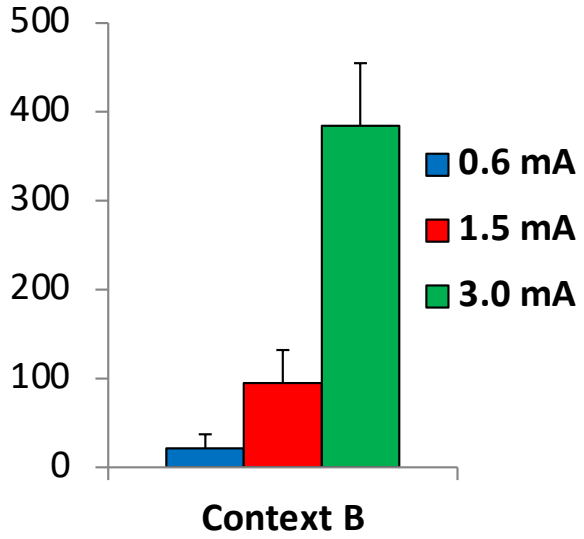




n = 8

Generalization following exposure to different footshock intensities





The biological bases of traumatic memories: we found

- **Unpredictability and uncontrollability is the root of pathology**

A second unpredictable, but not predictable, traumatic experience leads to PTSD-like responses (extinction resistance and generalization)

- **The biological mechanisms and circuitry used in traumatic memories are different**

Forth dynamic dimension:

- Age: memories formed at early ages are very different

The behavior is different

The biology is different

Learning and memory in early development

Childhood memories, Dania Piotti

"No one calls in question the fact that the experiences of the earliest years of our childhood leave ineradicable traces in the depths of our mind"

(Freud, 1899, Screen memories, SE3, p.301)

Infantile amnesia

Paradox: **Are early memories lost? If so, how can they influence behavior throughout life?**

Several hypotheses had been proposed to explain infantile amnesia:

1- Freud was the first one to offer an explanation: repression of infantile memories due to their disturbing content of sexual nature

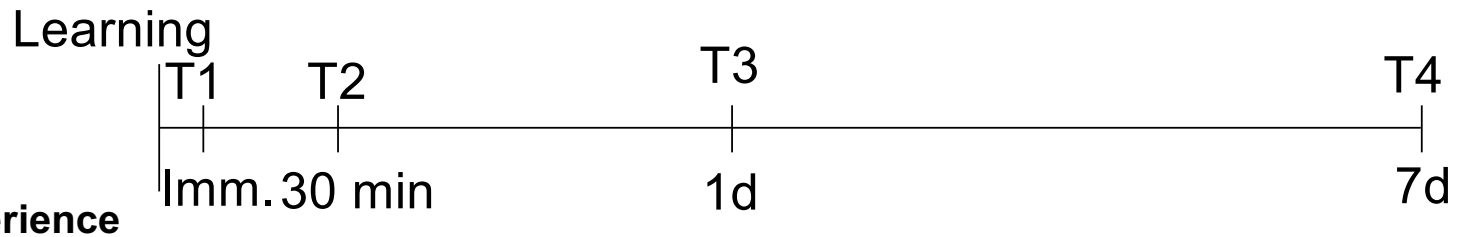
2- Lack of language skills and of sense of self

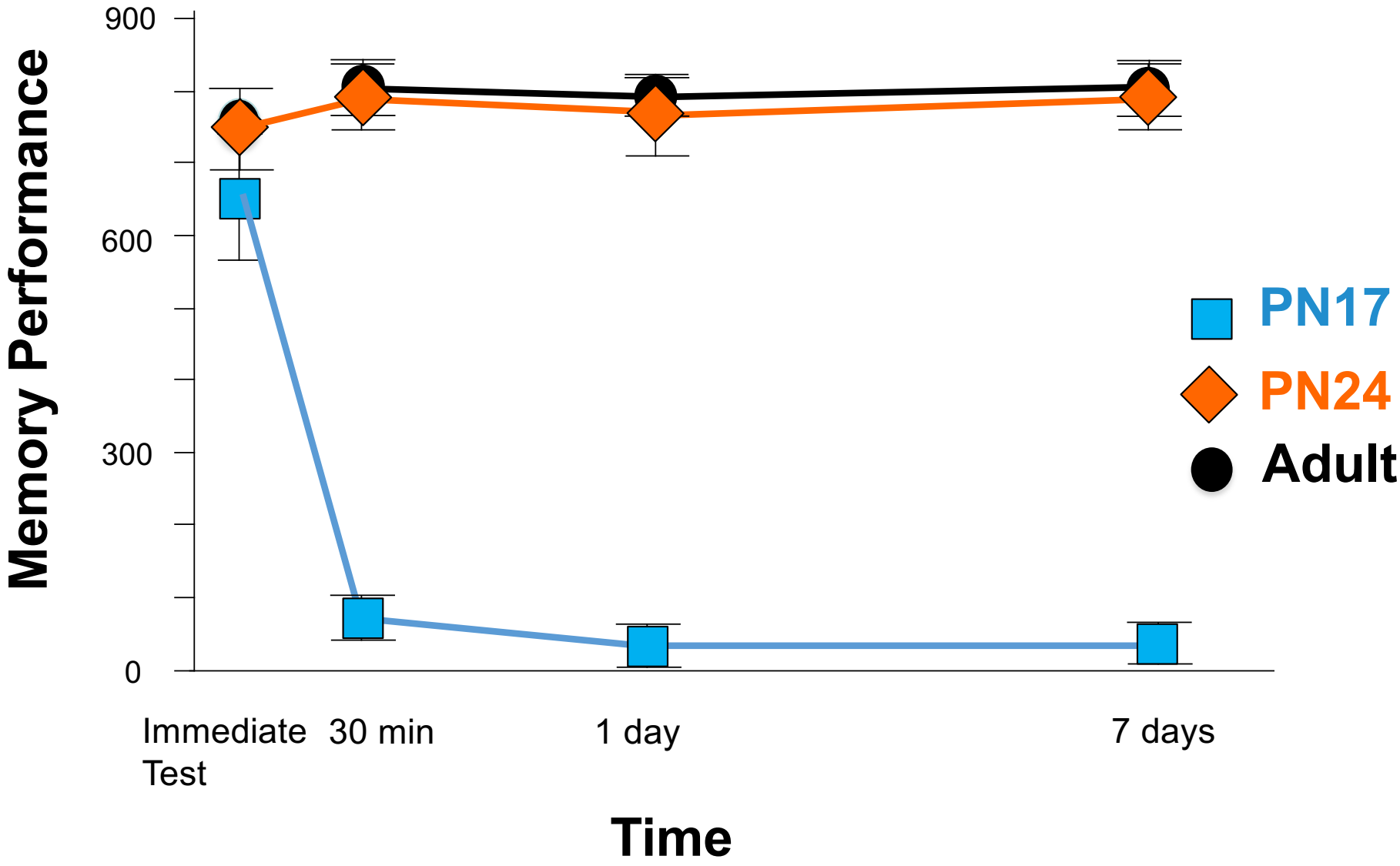
But rapid forgetting exists in non-human animals:

3- The hippocampus is immature and not capable to process episodic information, therefore not "online" (developmental hypothesis)

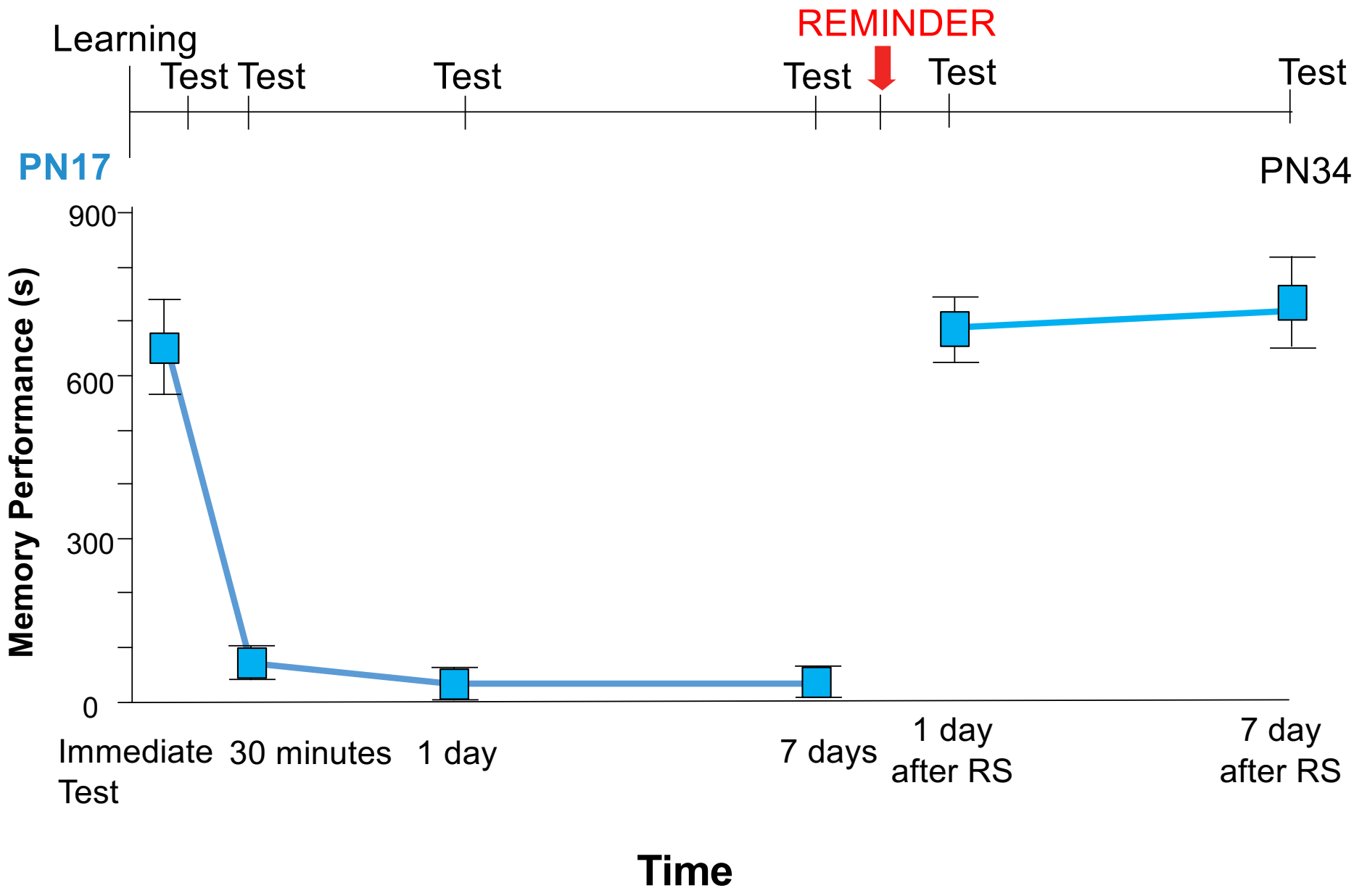
4- The infantile memories are stored but retrieval is impaired (retrieval hypothesis)

Episodic experience





A reminder of the experience, later in life, re-instates the memory



OUR STUDIES SHOWED THAT:

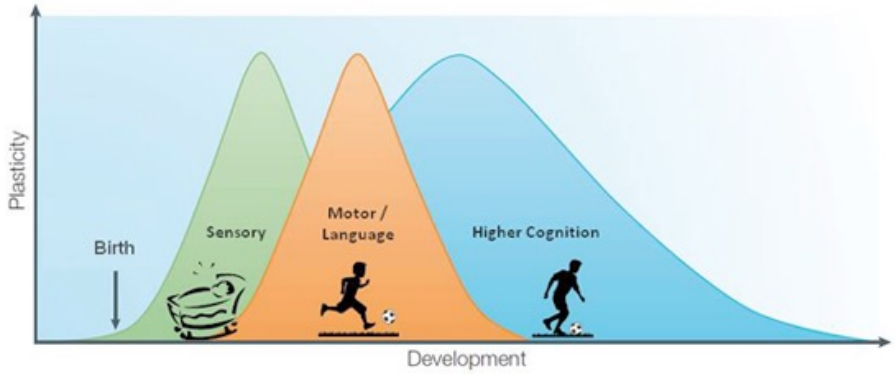
- **The hippocampus is required to store the infantile latent memories and**

- **Infantile memories recruit biological mechanisms typical of developmental critical periods**

(Travaglia et al. 2016 Nature Neuroscience; Alberini and Travaglia J. Neurosci. 2017. Travaglia et al. L&M 2018)

Molecular mechanisms of critical periods: they have been found to accompany critical period experience-dependent maturation of sensory systems (visual, somatosensory, auditory) (Carmignoto and Vicini, Bear, Maffei, Sun) and imprinting behavior in chicks (Nakamori)

Fig 1: Windows of plasticity in brain development



Adapted from Hensch, T. K. (2005). Critical period plasticity in local cortical circuits. *Nature Reviews Neuroscience, 6*(11), 877–888.

The also occur in the neonatal hippocampal slices over development (Barth and Malenka 2001) and upon LTP induction (Bellone and Nicoll 2007)

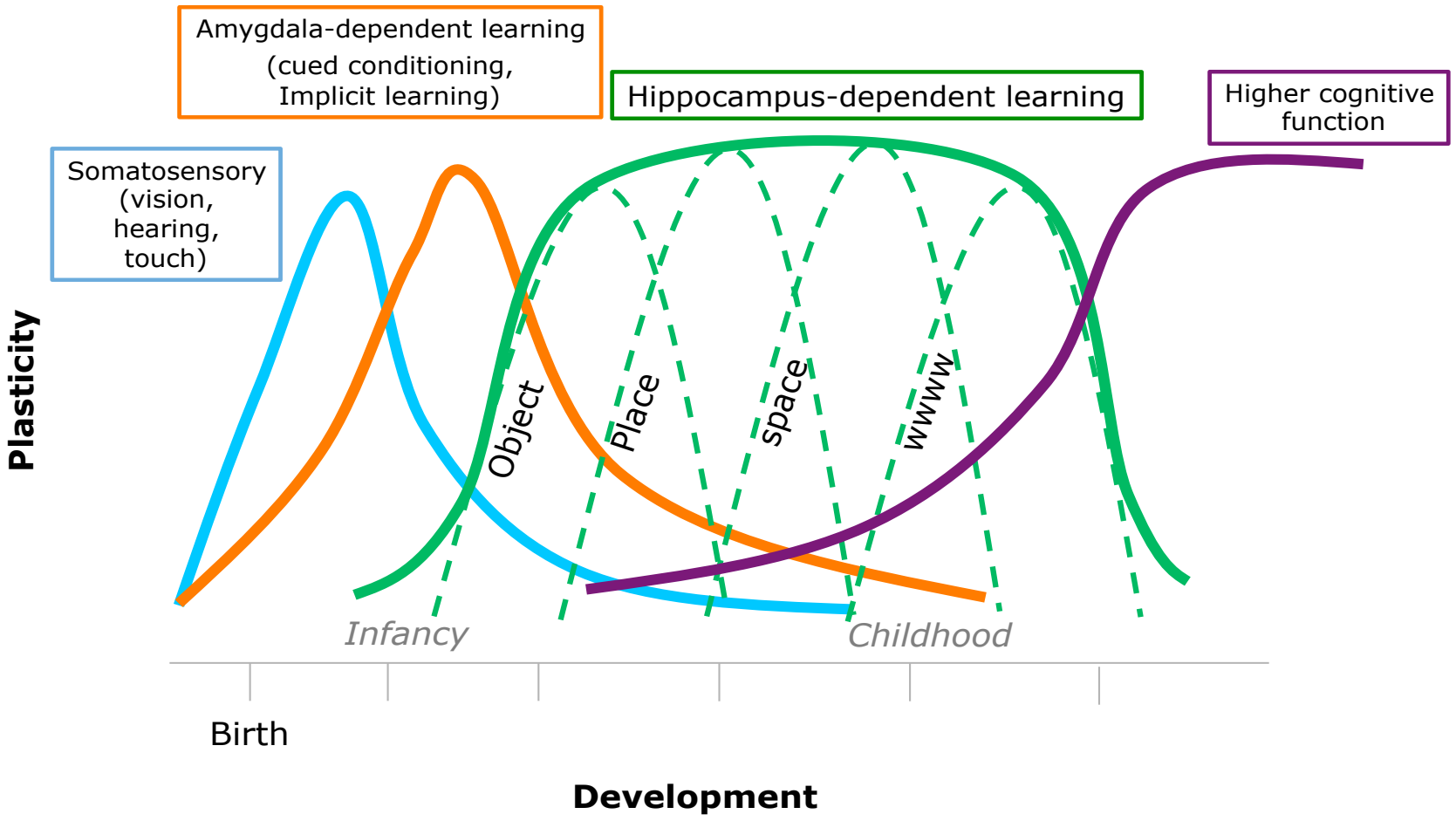
We propose that:
early in development the hippocampus undergoes a critical period during which it matures in response to experience. During this period the hippocampus-dependent memory system stores latent memory traces and through experience it matures the learning and memory function

Implication:

- **compromising the healthy development of this critical period leads to severe impairments in learning and related cognitive functions.**

- **Experiences during the critical period shape the brain and its functions and influence adult behaviors**

Our model: learning and memory systems, like sensory systems, develop and mature through critical periods



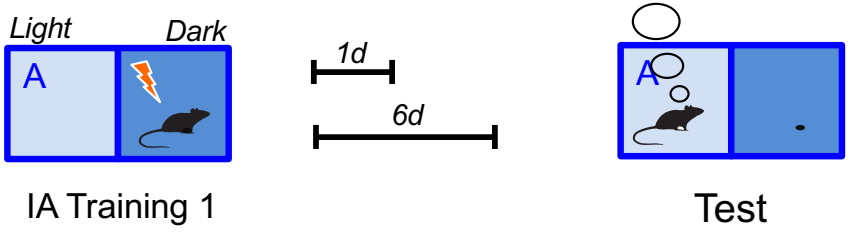
Alberini and Travaglia J. Neurosci. 2017.

A next very important question

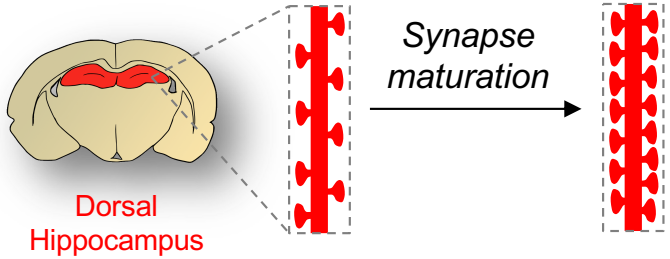
Does the experience-induced maturation of the hippocampus develop the system as a whole? Or is the maturation and development of the hippocampal memory system selectively shaped by the specific experience encountered?

Learning at PN17 results in synapse maturation

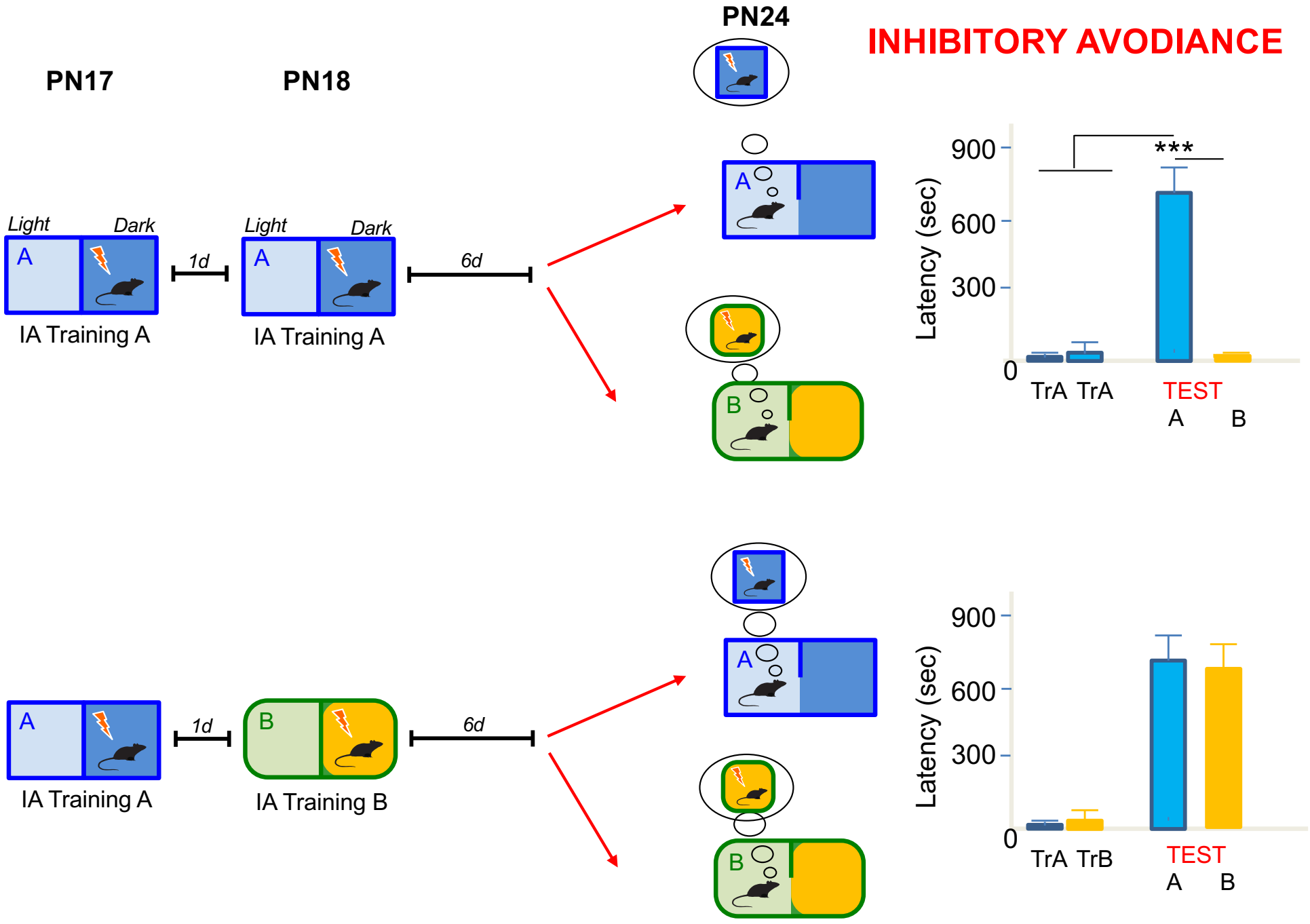
PN17

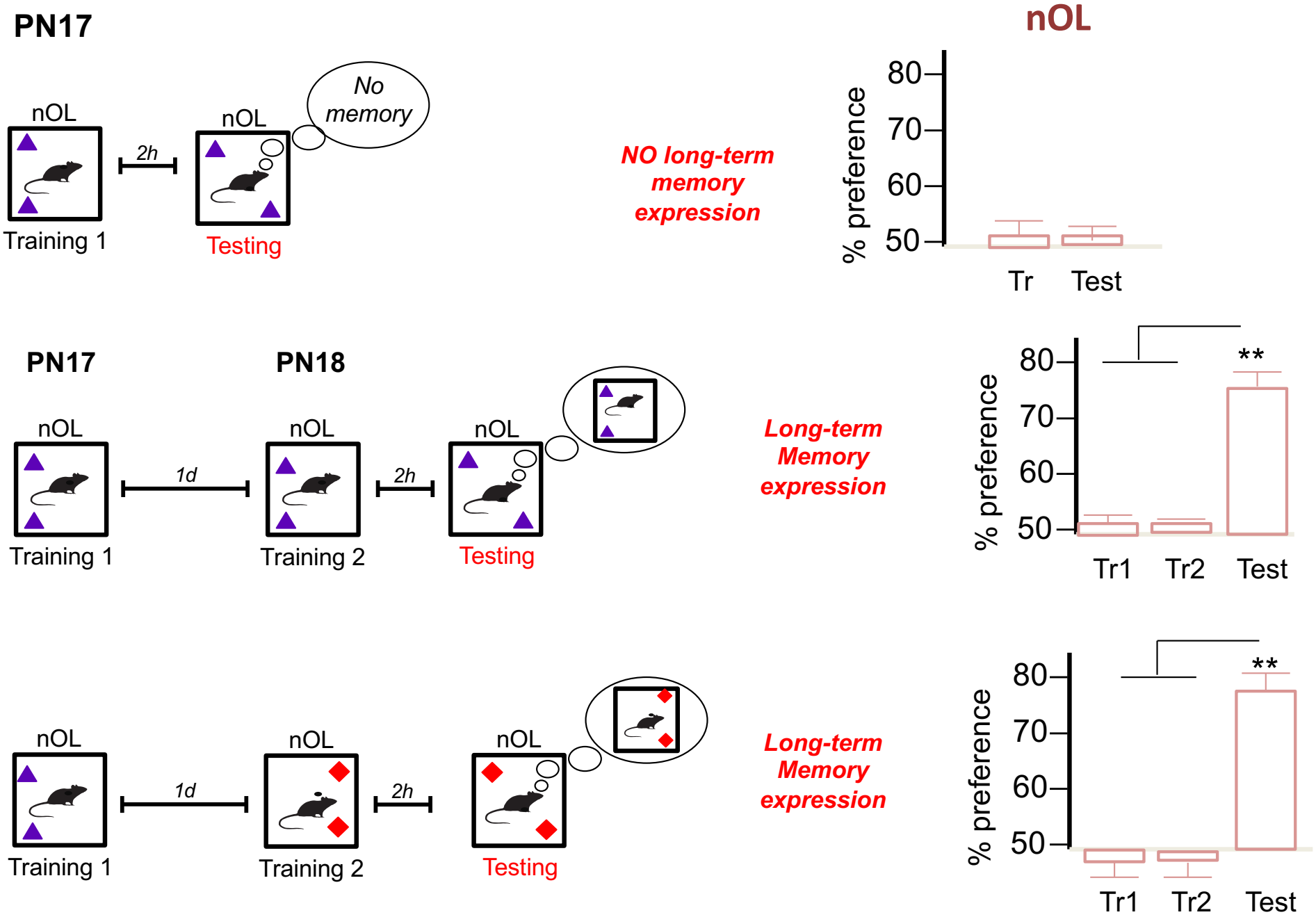


Significant at **24 hours** after training



A second, spaced learning results in memory competence within similar learning domains




PN17
nOL
2h
nOL
No memory
Training 1
Testing
NO long-term memory expression
nOL
% preference
80
70
60
50
Tr
Test
PN17
PN18
nOL
1d
nOL
2h
nOL
Training 1
Training 2
Testing
Long-term Memory expression
**
% preference
80
70
60
50
Tr1
Tr2
Test
nOL
1d
nOL
2h
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Training 2
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Long-term Memory expression
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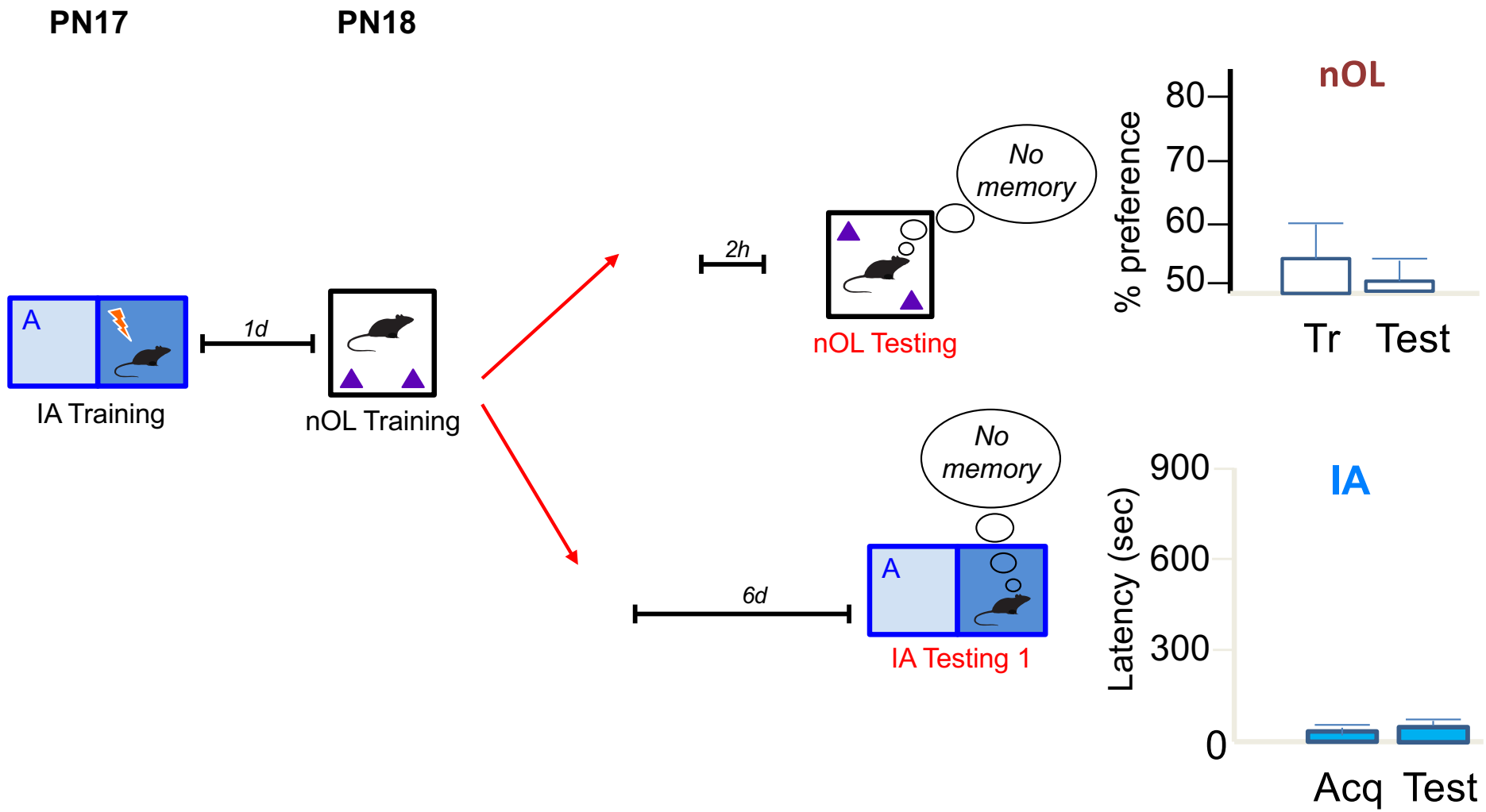
Tr2
Test

There is NO maturation of memory competence with distinct learning domains

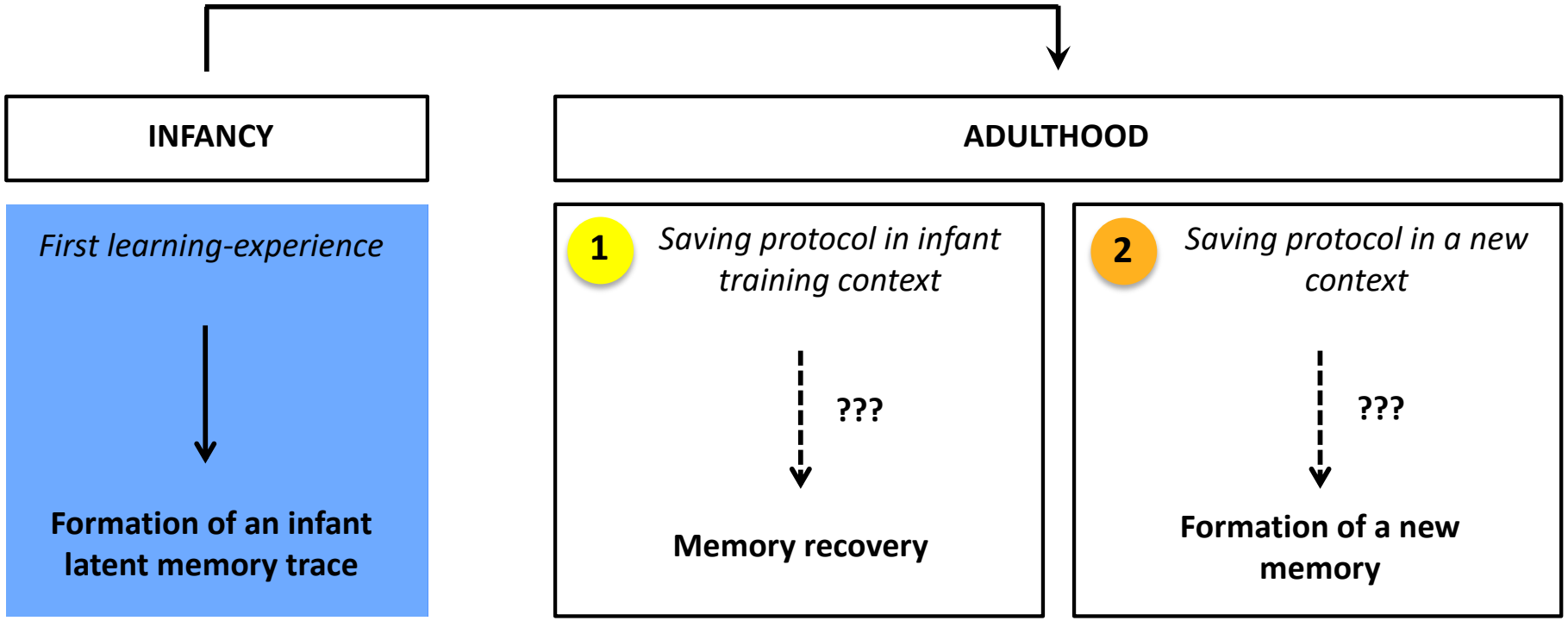


Or vice versa, when (a BDNF-enhanced) nOL is followed by IA

Do these infantile, latent memories influence adult behaviors? Can we visualize in some way the memory traces?

1. Can an infantile latent memory be recovered following a saving protocol in adulthood?

2. Can infantile memory influence a novel similar learning in adulthood?



Conclusions

1- The developmental maturation of the brain does not occur by default

2- Experiences encountered during early development (critical periods) mature the functional competence of the hippocampus-dependent memory system in an experience-selective manner

Hence experiences in early development selectively shape functional competences

In SUM

Episodic learning during early development shapes the maturation of the hippocampus (and connected system) in an experience–specific manner

Implications-Points of discussion

These findings may explain why early life experiences influence the development of personality traits and are in agreement with the idea of enduring individual effects of experiences consolidated during early childhood.

They offer an explanation for individual differences in abilities to process information and respond to experiences.

They indicate that there are temporal windows for experience-based shaping of identity. When possible, psychotherapeutic interventions during developmental ages may be fundamental.

Memories formed in infancy are very different than those formed adulthood: I propose that these representations are at the bases of unconscious behaviors.

THANK YOU