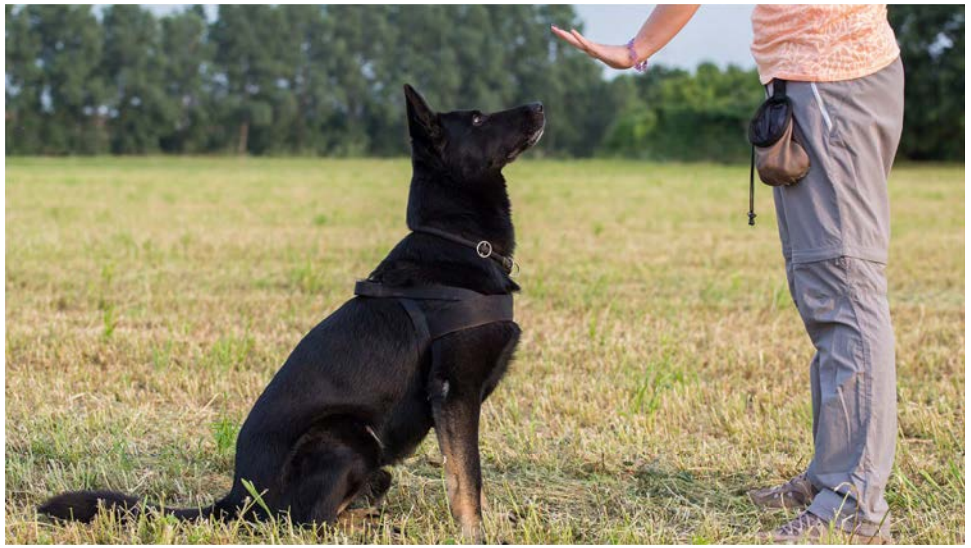
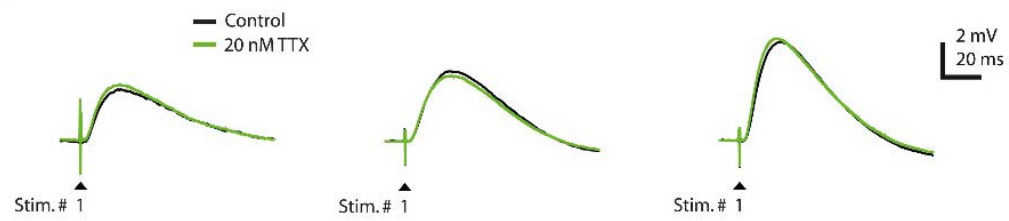
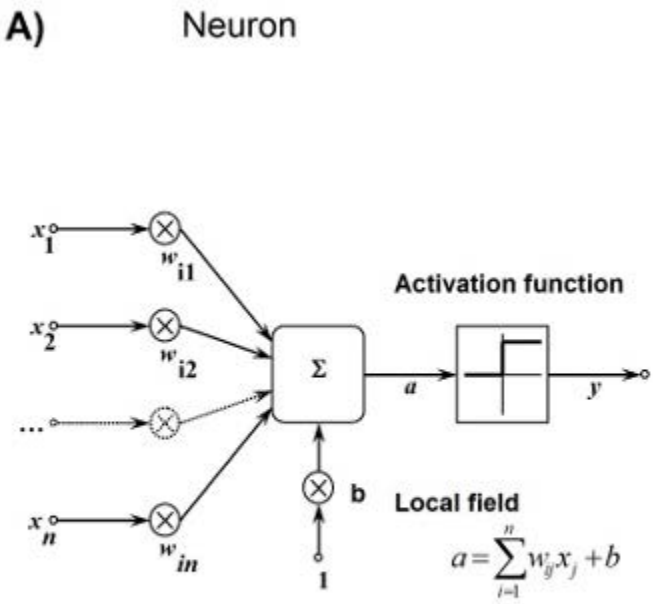
1. Neurobiology of Learning and Memory
2. Alzheimer Disease

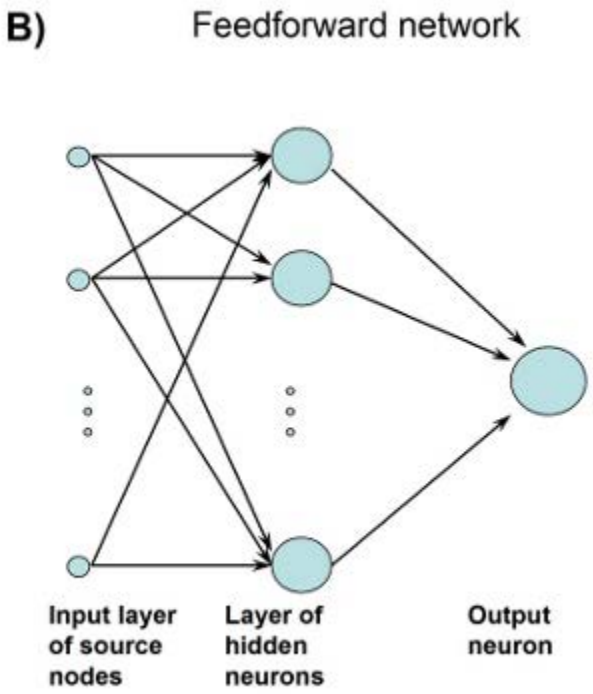
Basar Cenik, MD, PhD

Learning-Memory-Neuronal Plasticity

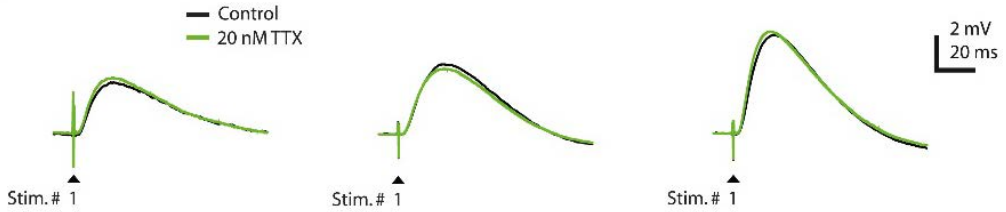


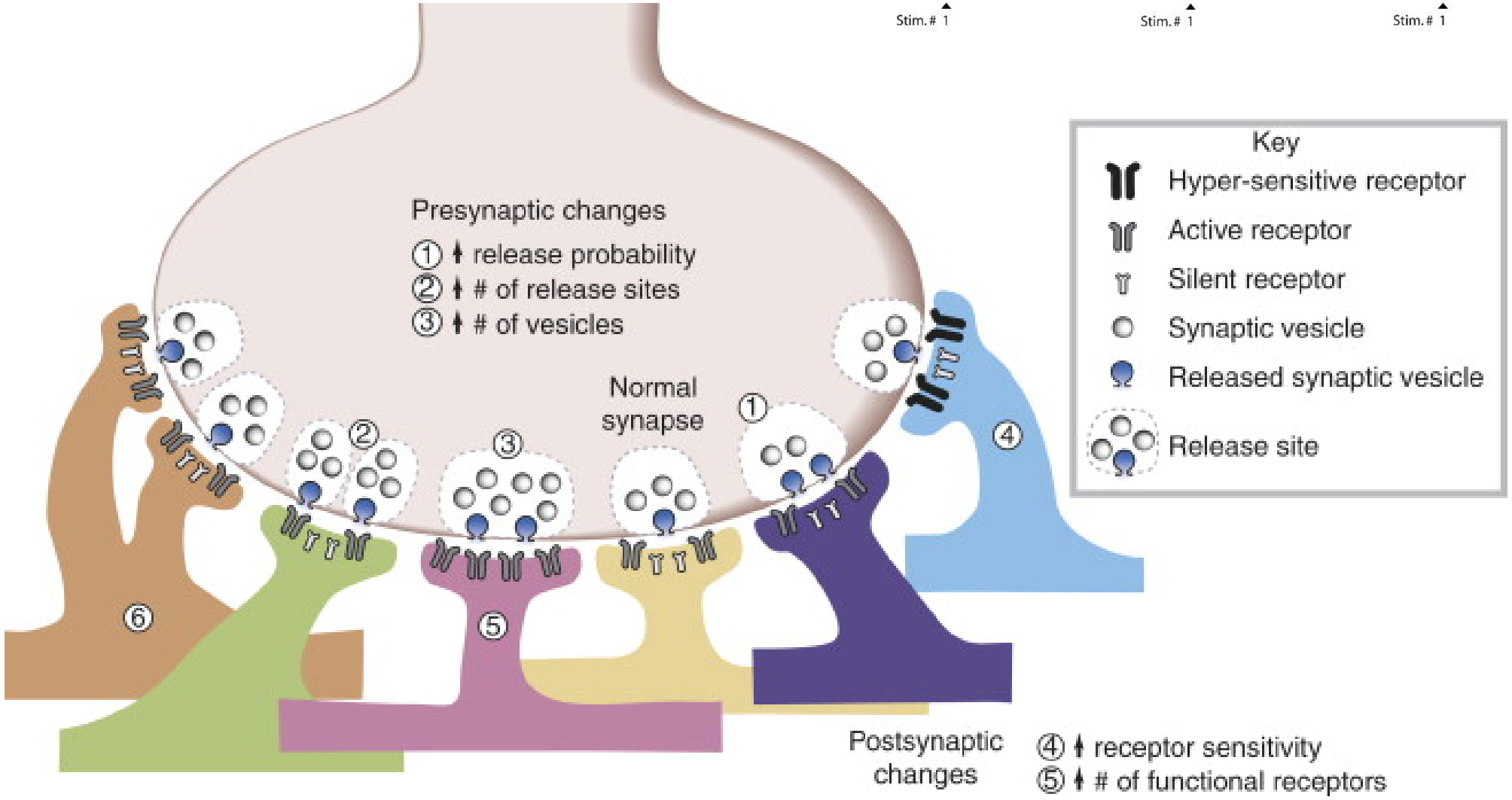






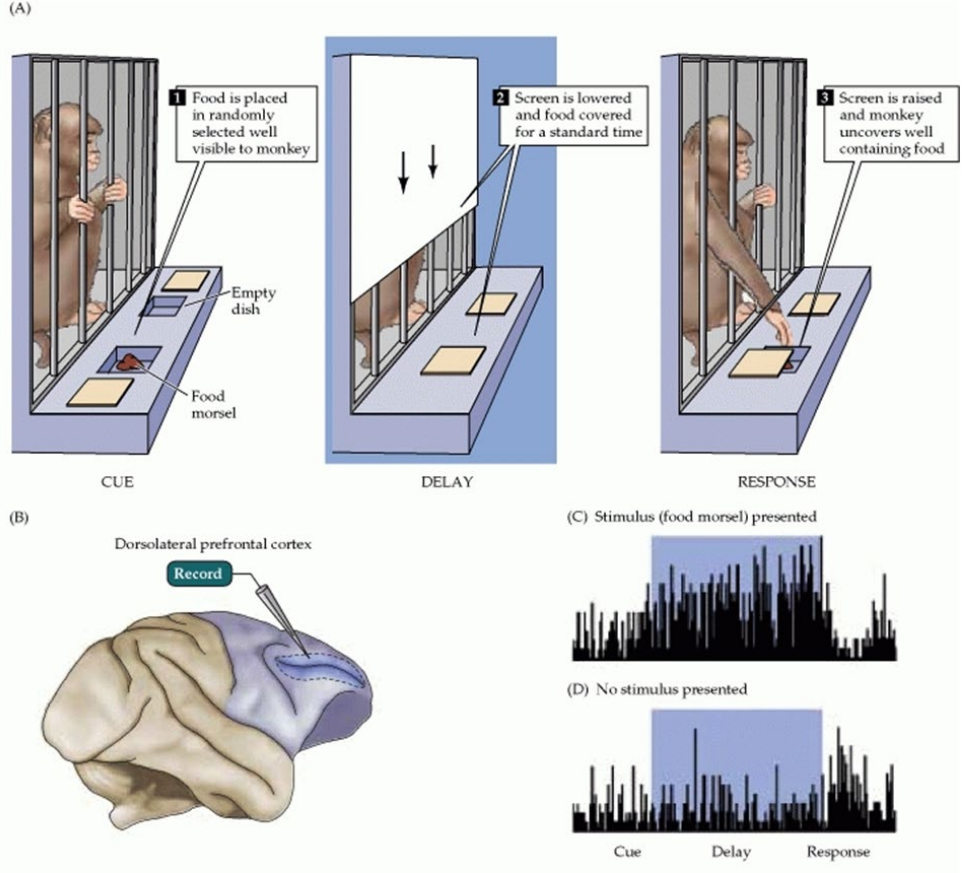
Synaptic Plasticity

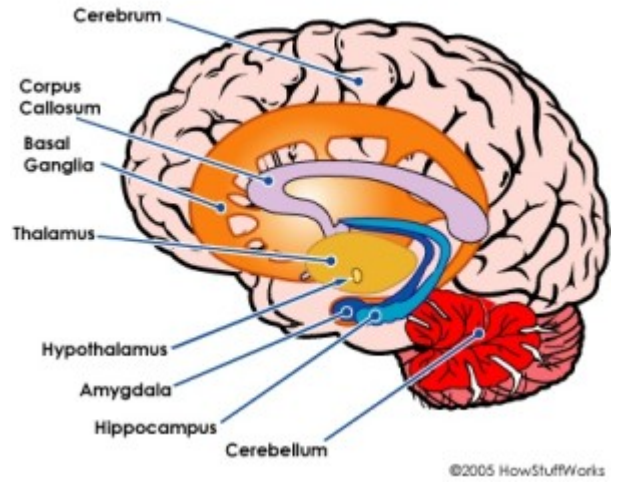


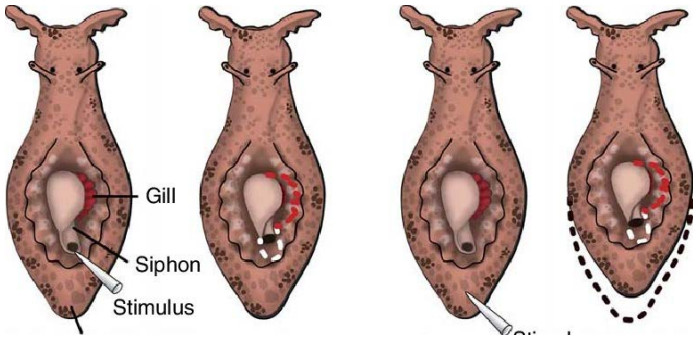


Memory Classification

- Short-Term
  - **Working memory** (seconds to minutes)
    - Phonological (*posterior parietal lobe*, *Broca's area [frontal]*)
    - Visuospatial (*neocortex, mostly frontal lobes*)
      - Object knowledge
      - Spatial knowledge
  - **Intermediate** (minutes to hours)
- Long-Term (hours to days)
  - **Explicit (Declarative)** (*medial temporal lobe, neocortex*)
    - Episodic
    - Semantic
  - **Implicit (Procedural)**
    - Associative (Conditioning) (*amygdala, cerebellum*)
      - Classical (two stimuli)
      - Operant (behavior and stimuli)
    - Non-associative
      - Priming (*neocortex*)
      - Skill learning (*basal ganglia, cerebellum*)
      - Habit memory (*basal ganglia*)
      - Habituation
      - Sensitization







Laboratory Mouse

Education

Caltech, Oxford, Stanford, Harvard, MIT, Princeton, Cambridge, Imperial, Berkely, Chicago, Yale, ETH Zurich, Columbia, UPenn, John Hopkins, UCL, Cornell, Northwestern, UMichigan, Toronto, Carniege Mellon, Duke, UWashington, UTexas at Austin, GA Tech, Tokyo, Melbourne, Singapore, UBC, Wisconsin-Madison, Edinburgh, McGill, Hong Kong, Santa Barbara, Karolinska Institute, UMinnesota, Manchester ... and just about every other major university, medical school & research institution in the world.

Nobel Prizes

1905 - Transmission and treatment of TB
1906 - Structure of Nervous System
1907 - Role of protozoa in disease
1908 - Immunity to infectious diseases
1928 - Investigations on typhus
1929 - Importance of dietary vitamins
1939 - Discovery of antibacterial agent, Prontosil
1945 - Discovery of penicillin
1951 - Yellow fever vaccine
1952 - Discovery of streptomycin
1954 - Culture of the polio virus
1960 - Understanding of immunity
1970 - Understanding of neurotransmitters
1974 - Structural & functional organisation of cells
1975 - Tumour-viruses and genetics of cells
1977 - Hypothalamic hormones
1984 - Techniques of monoclonal antibody formation
1986 - Nerve growth factor and epidermal growth factor
1990 - Organ transplantation techniques
1992 - Regulatory mechanisms in cells
1996 - Immune-system detection of virus-infected cells
1997 - Discovery and characterisations of prions
1999 - Discovery of signal peptides
2000 - Signal transduction in the nervous system
2004 – Odour receptors and organisation of olfactory systems
2008 - Role of HPV and HIV in causing disease
2010 - Development of in vitro fertilization
2011 - Discoveries around innate and adaptive immunity
2012 - Reprogramming mature cells to pluripotent ones

CV of a Lifesaver

Overview

- Involved in around 75% of research
- Short life-span and fast reproductive rate means mice are suitable for studying disease across whole life cycle
- 98% of genes have comparable genes in humans
- Similar reproductive and nervous systems and suffer many of the same diseases as humans including cancer diabetes and anxiety
- Can be genetically modified to include human genes in enhance biological relevance
- Can act as an avatar for a human cancer to allow drug therapies to be trialled safely

Research Areas

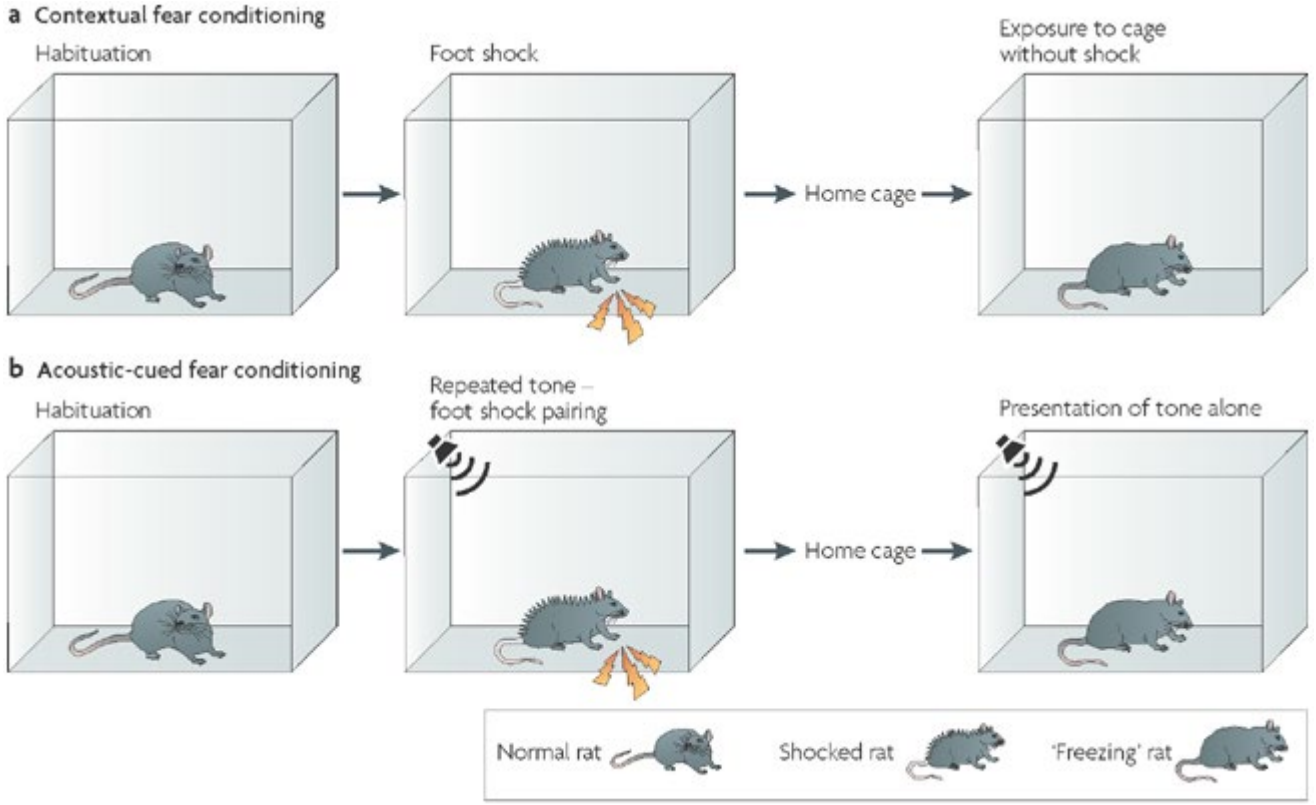
Alzheimer's disease, anaesthetics, AIDS & HIV, anticoagulants, antidepressants, asthma, blindness, bone and joint disease, brain injury, breast cancer, cardiac arrest, cystic fibrosis, deafness/hearing loss, Down's sndrome, drugs for high blood pressure, transplant rejection, Hepatitis B, C & E, Huntington's disease, influenza, leukaemia, malaria, motor neurone disease, multiple sclerosis, muscular dystrophy, Parkinson's disease, prostate cancer, schistomiasis, spinal cord injury, stroke, testicular cancer, tuberculosis,

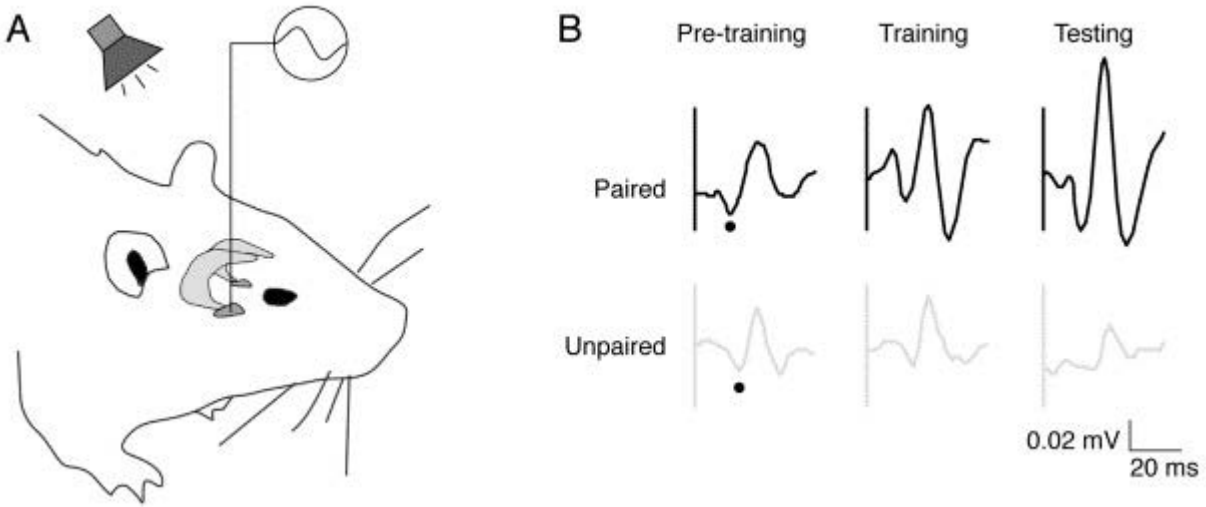
Contact

www.understandinganimalresearch.org.uk
www.animalresearch.info
www.amprogress.org
www.speakingofresearch.com

Fear Conditioning

- Requires **amygdala**
- **Contextual** fear conditioning also requires **hippocampus**
- The mechanism is believed to be **long-term potentiation (LTP)**
- Requires the **transcription factor CREB** for consolidation

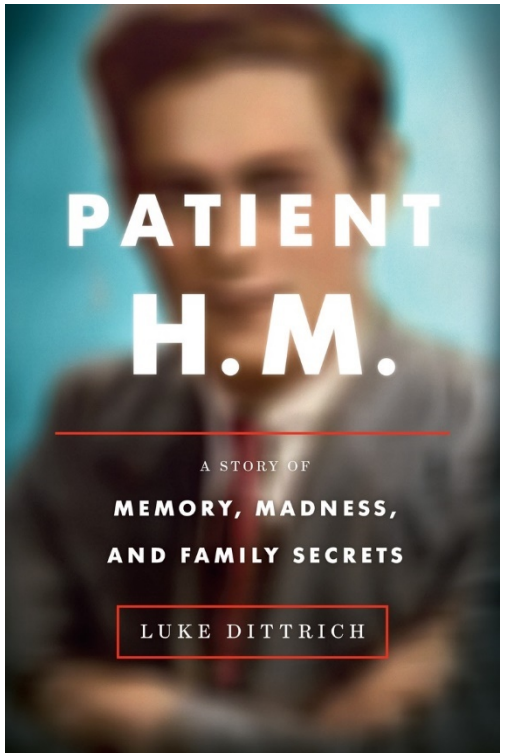


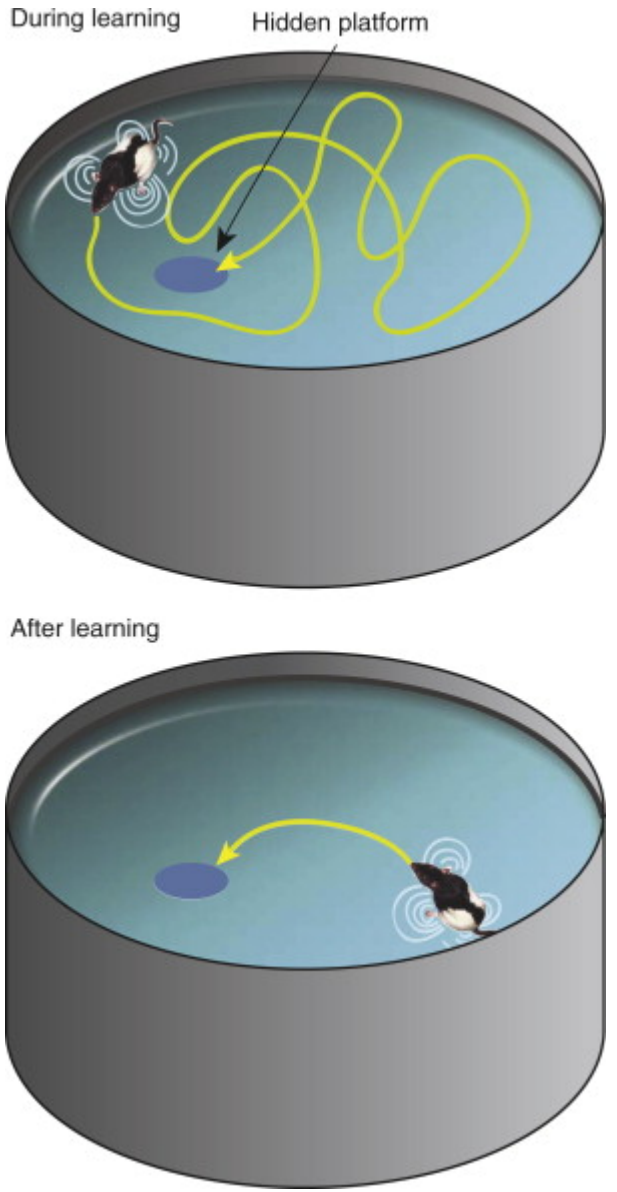


TINS Vol. 22, No. 12, 1999

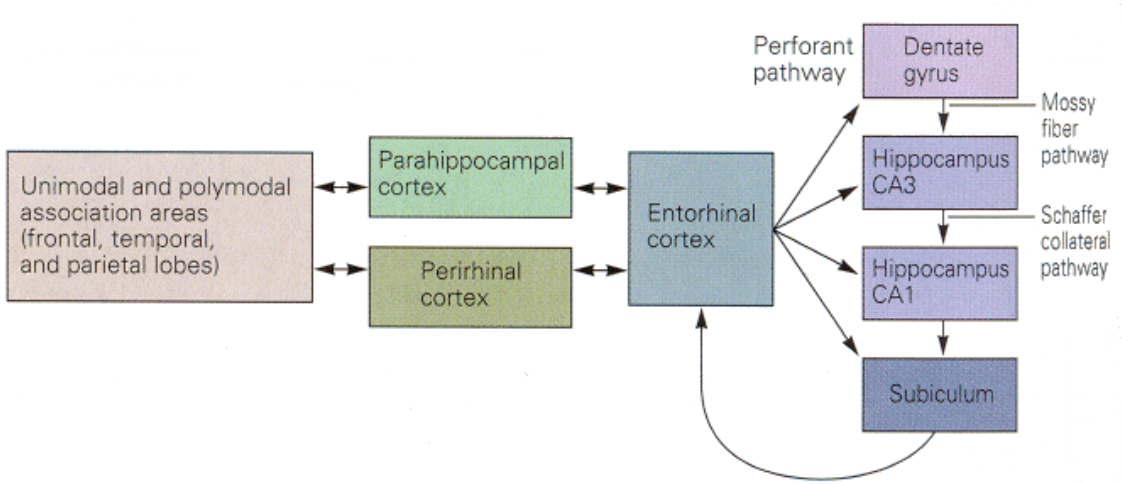
Explicit Memory

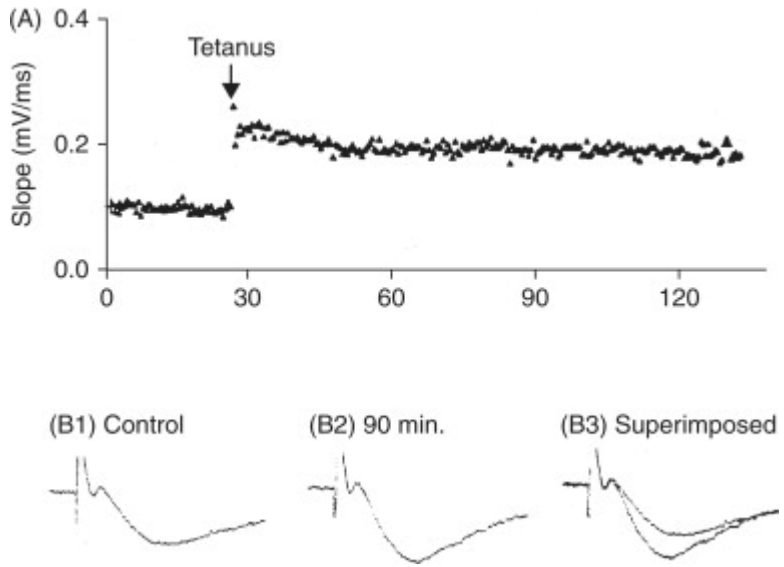
- Requires **hippocampus** as revealed by famous clinical cases
- **Spatial memory** in rodents is a close approximation
- Overwhelming evidence suggests that **long-term potentiation (LTP) and long-term depression (LTD)** are the molecular underpinnings

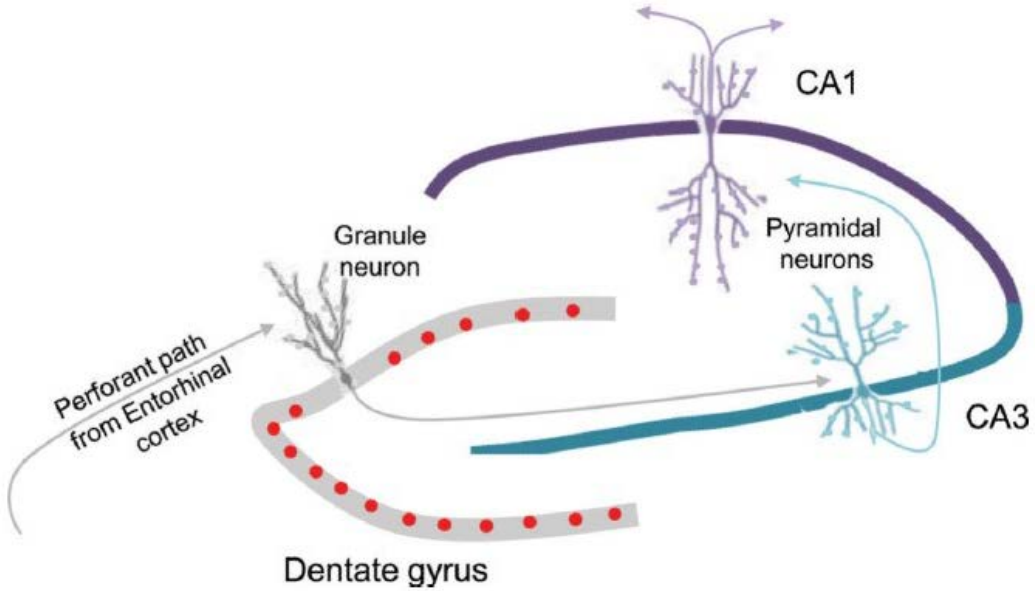


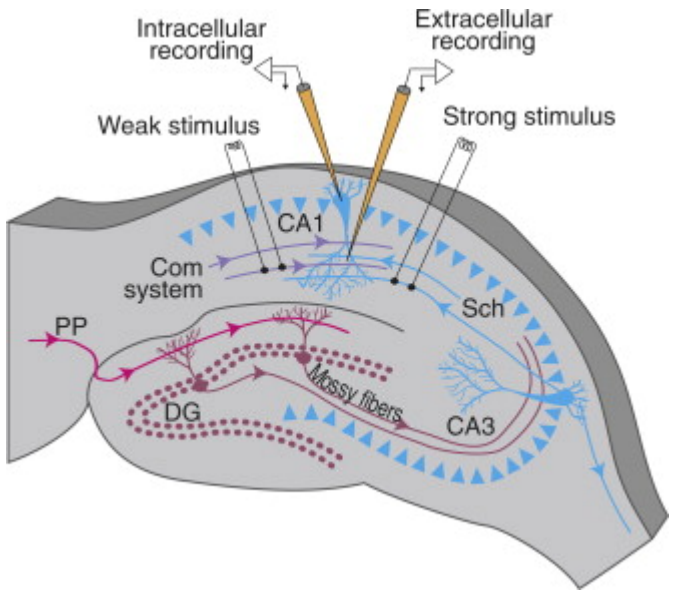


Hippocampal LTP





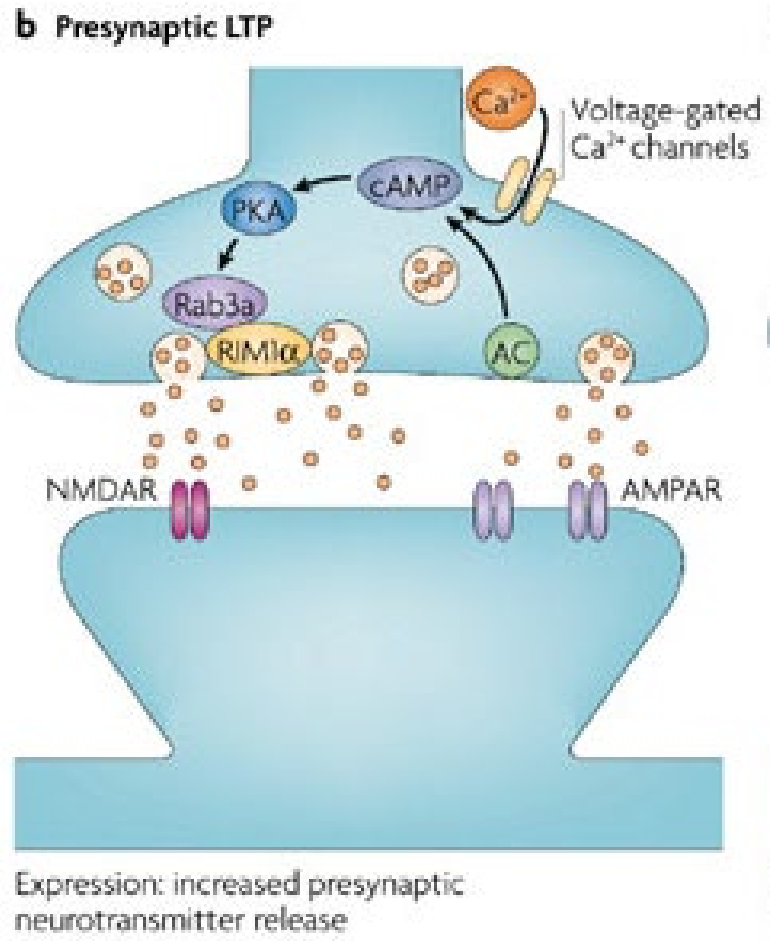




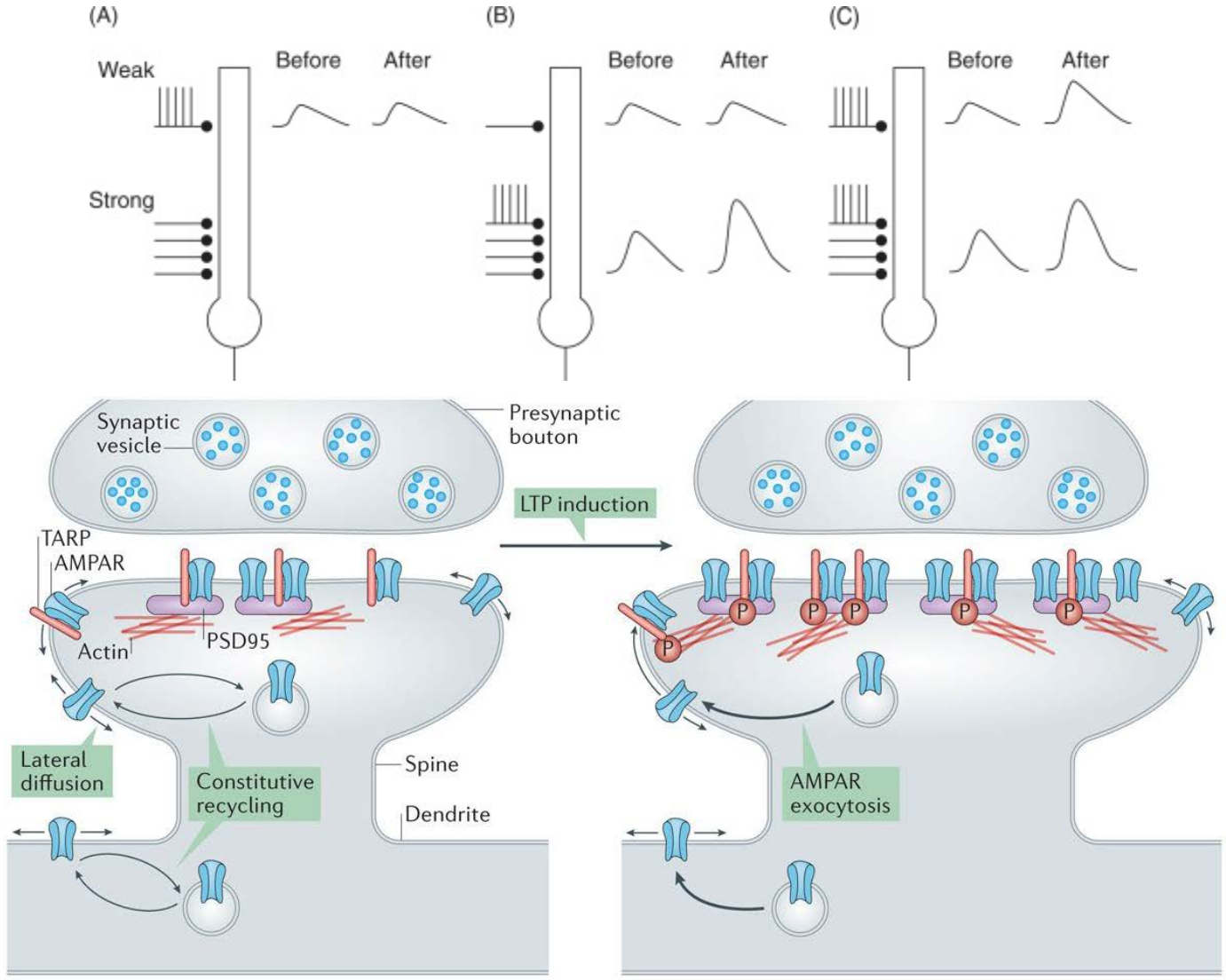
LTP

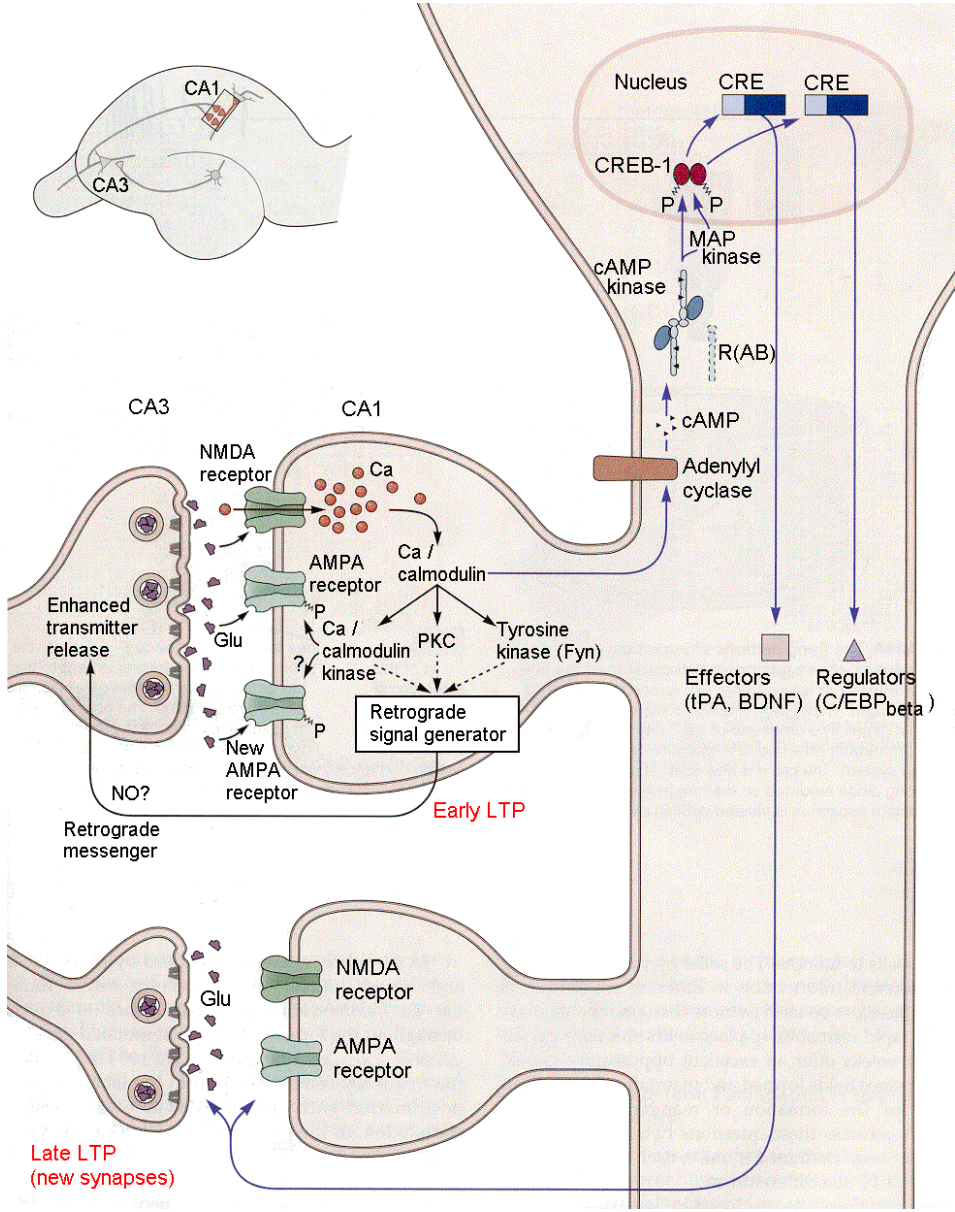
Pre-synaptic

Post-synaptic



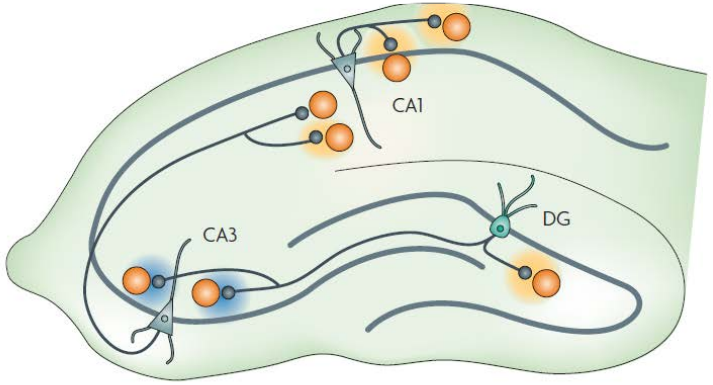
Associative (Hebbian) postsynaptic LTP

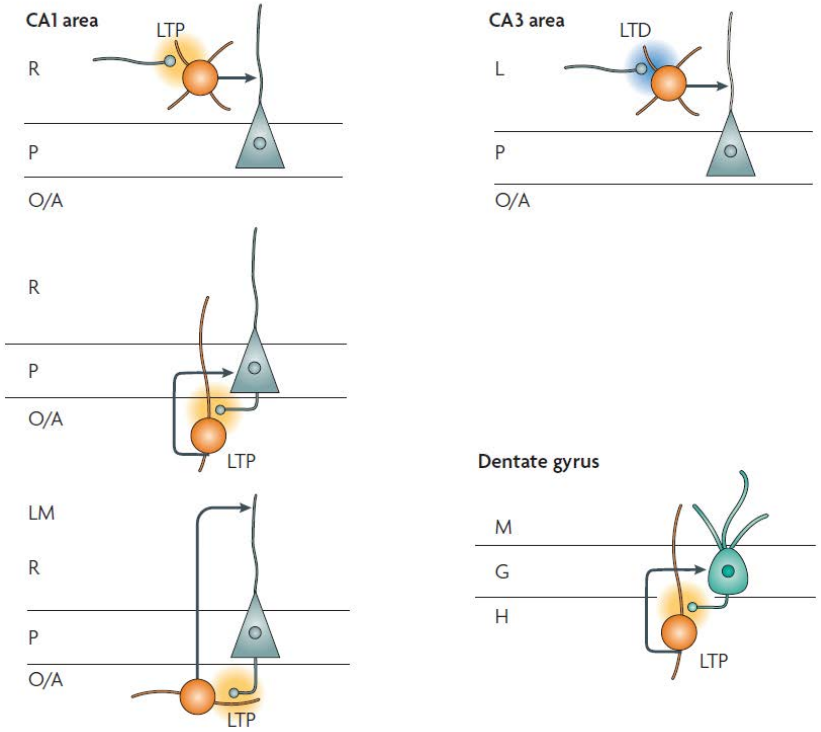


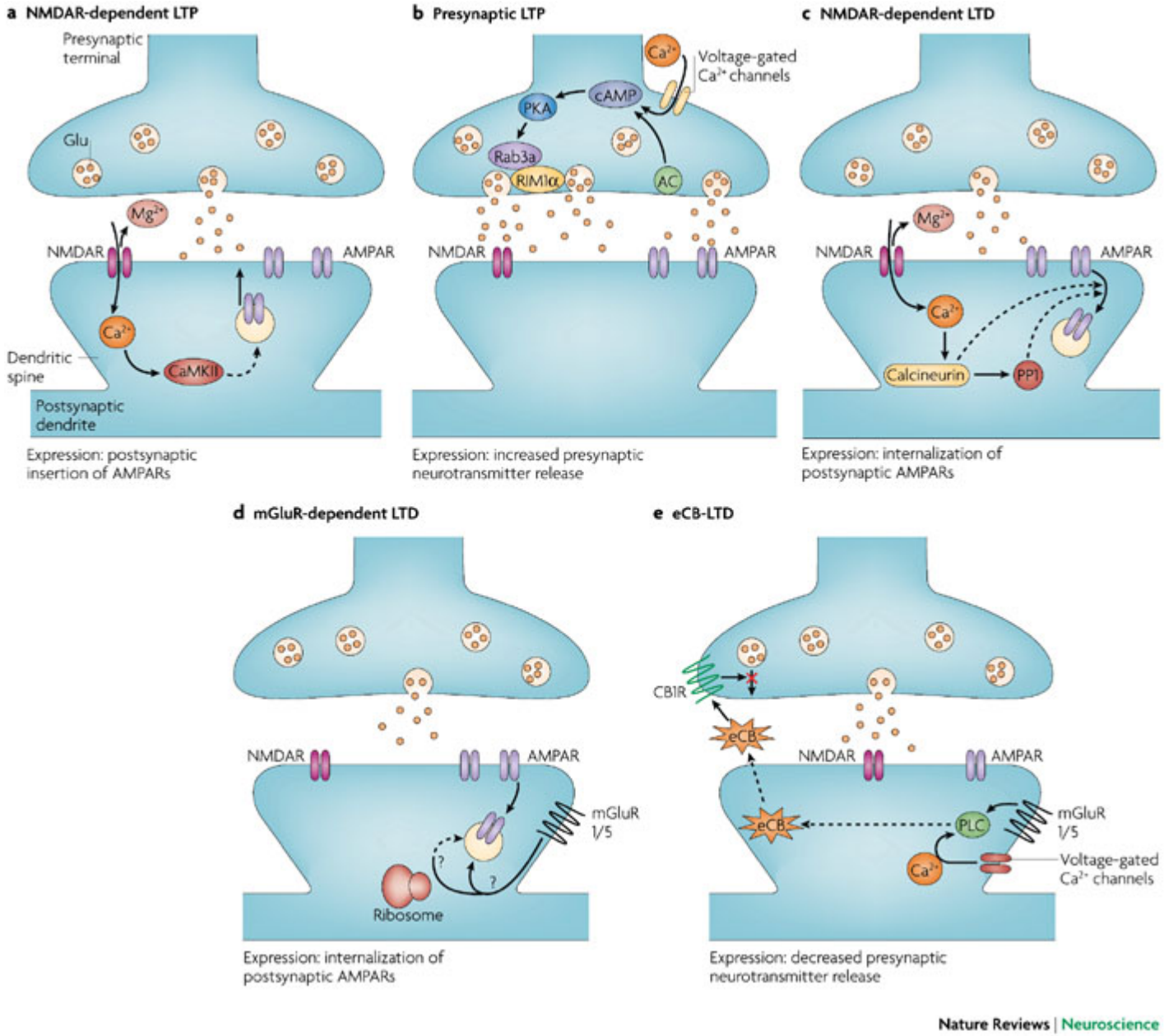


Nature Reviews Neuroscience **17**, 337–350 (2016)

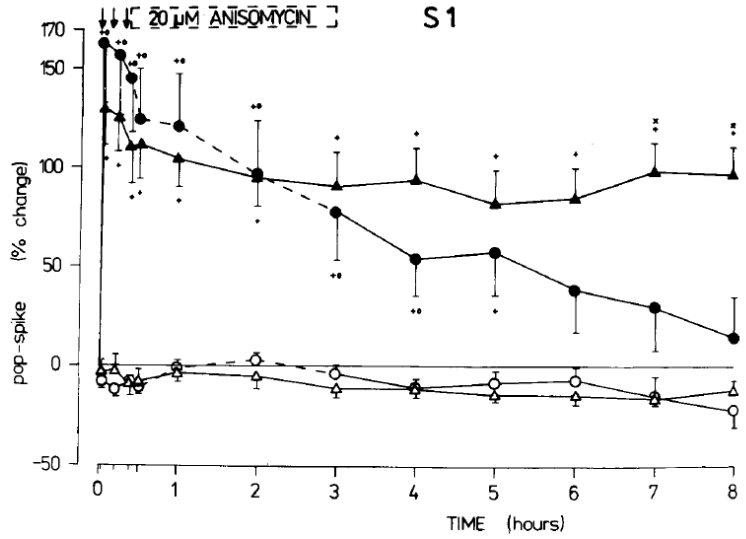
LTD


CA1
CA3
DG

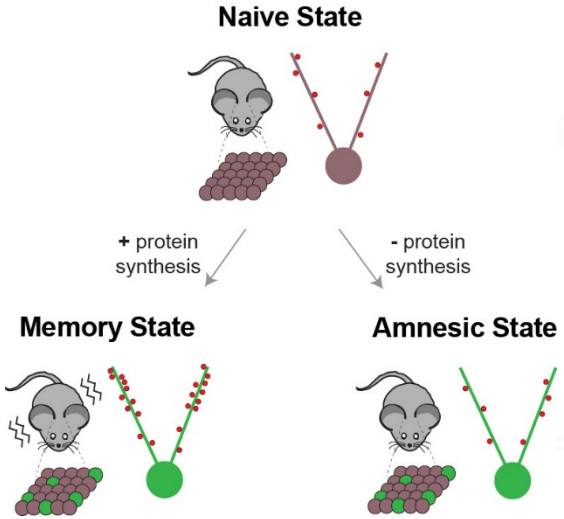

CA1 area
LTP
R
P
O/A
CA3 area
LTD
L
P
O/A
R
P
O/A
LTP
LM
R
P
O/A
LTP
Dentate gyrus
M
G
H
LTP

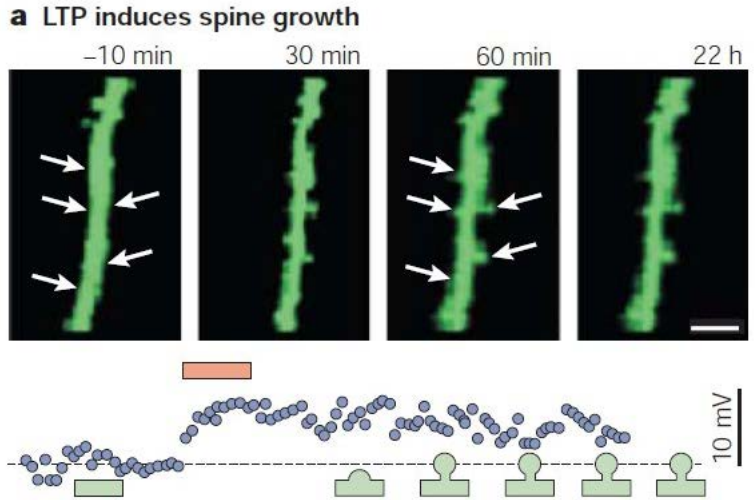

a NMDAR-dependent LTP
Presynaptic terminal
Glu
Mg2+
NMDAR
AMPAR
Ca2+
CaMKII
Dendritic spine
Postsynaptic dendrite
Expression: postsynaptic insertion of AMPARs
b Presynaptic LTP
Ca2+
Voltage-gated Ca2+ channels
cAMP
PKA
Rab3a
RIM1α
AC
NMDAR
AMPAR
Expression: increased presynaptic neurotransmitter release
c NMDAR-dependent LTD
Mg2+
NMDAR
AMPAR
Ca2+
Calcineurin
PP1
Expression: internalization of postsynaptic AMPARs
d mGluR-dependent LTD
NMDAR
AMPAR
mGluR 1/5
Ribosome
Expression: internalization of postsynaptic AMPARs
e eCB-LTD
CB1R
eCB
NMDAR
AMPAR
eCB
PLC
mGluR 1/5
Ca2+
Voltage-gated Ca2+ channels
Expression: decreased presynaptic neurotransmitter release
Nature Reviews | Neuroscience

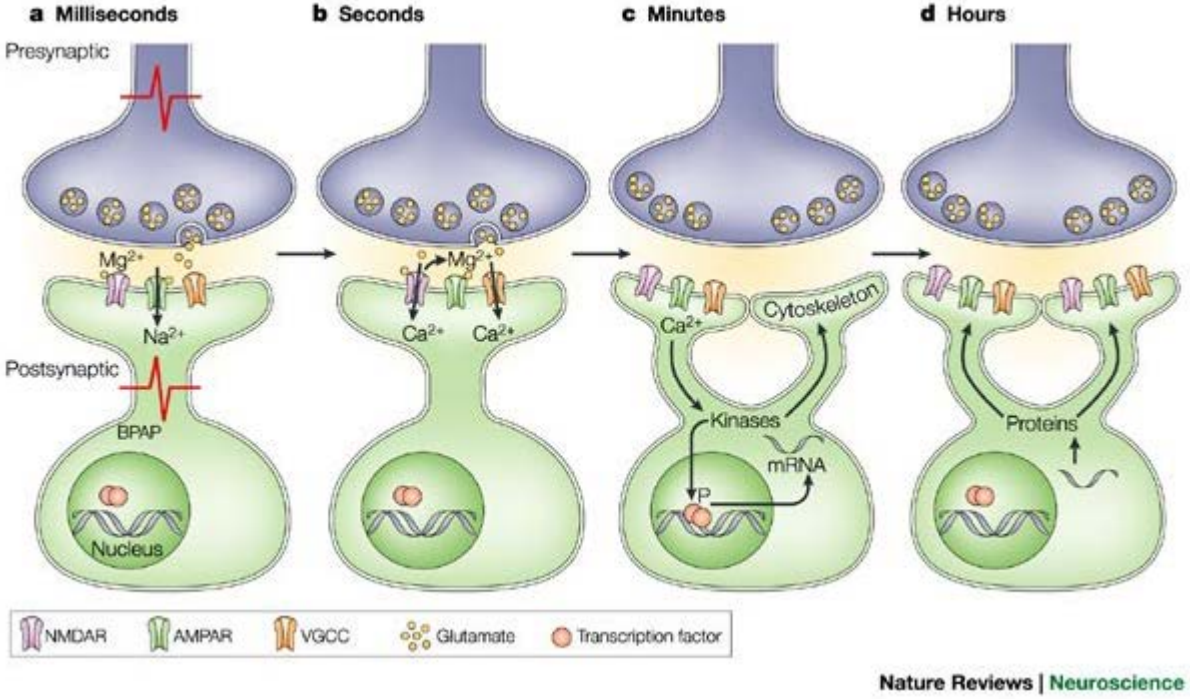
Long term plasticity requires **protein synthesis** and **structural changes**



Brain Research, 452 (1988) 57-65

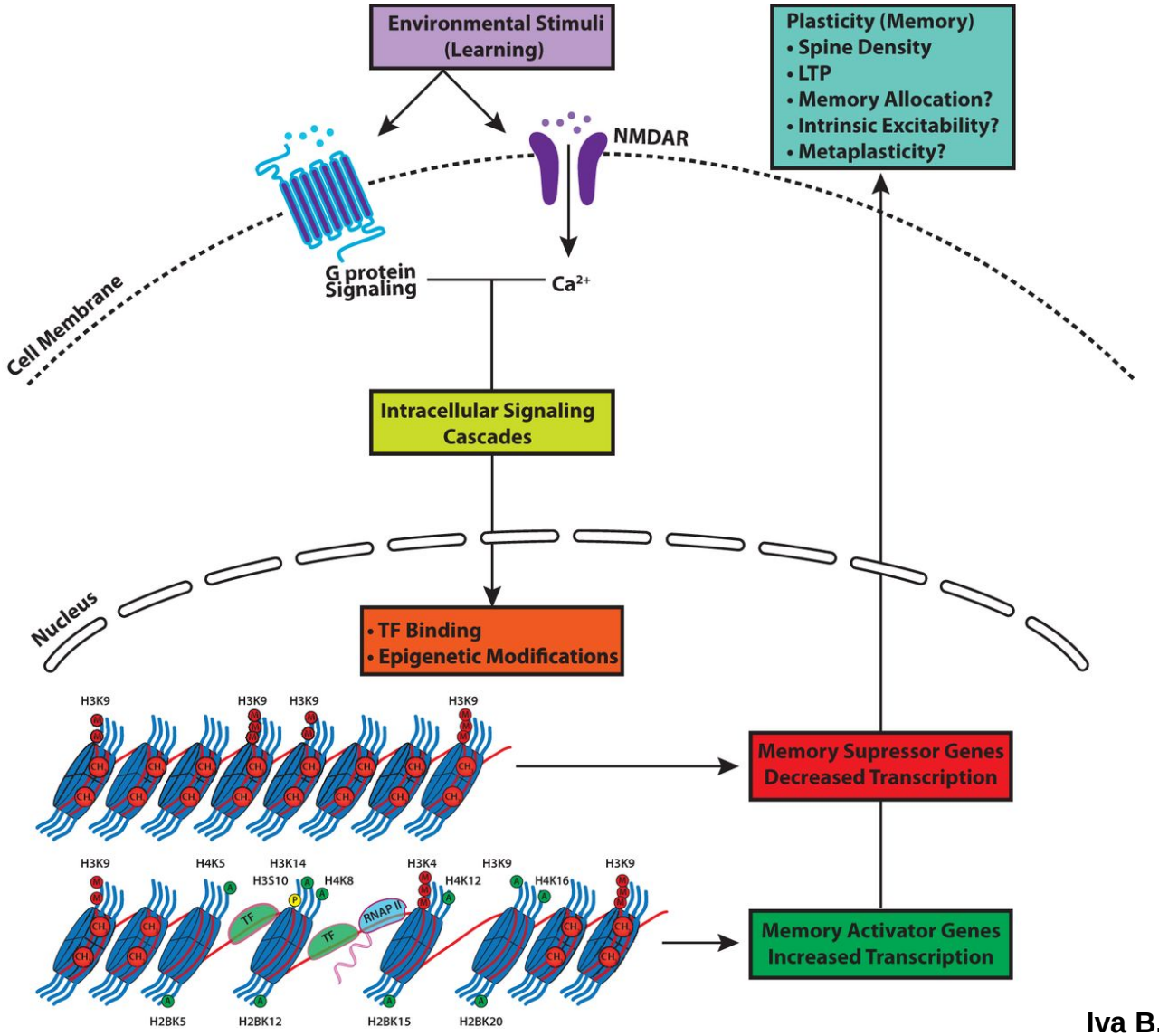






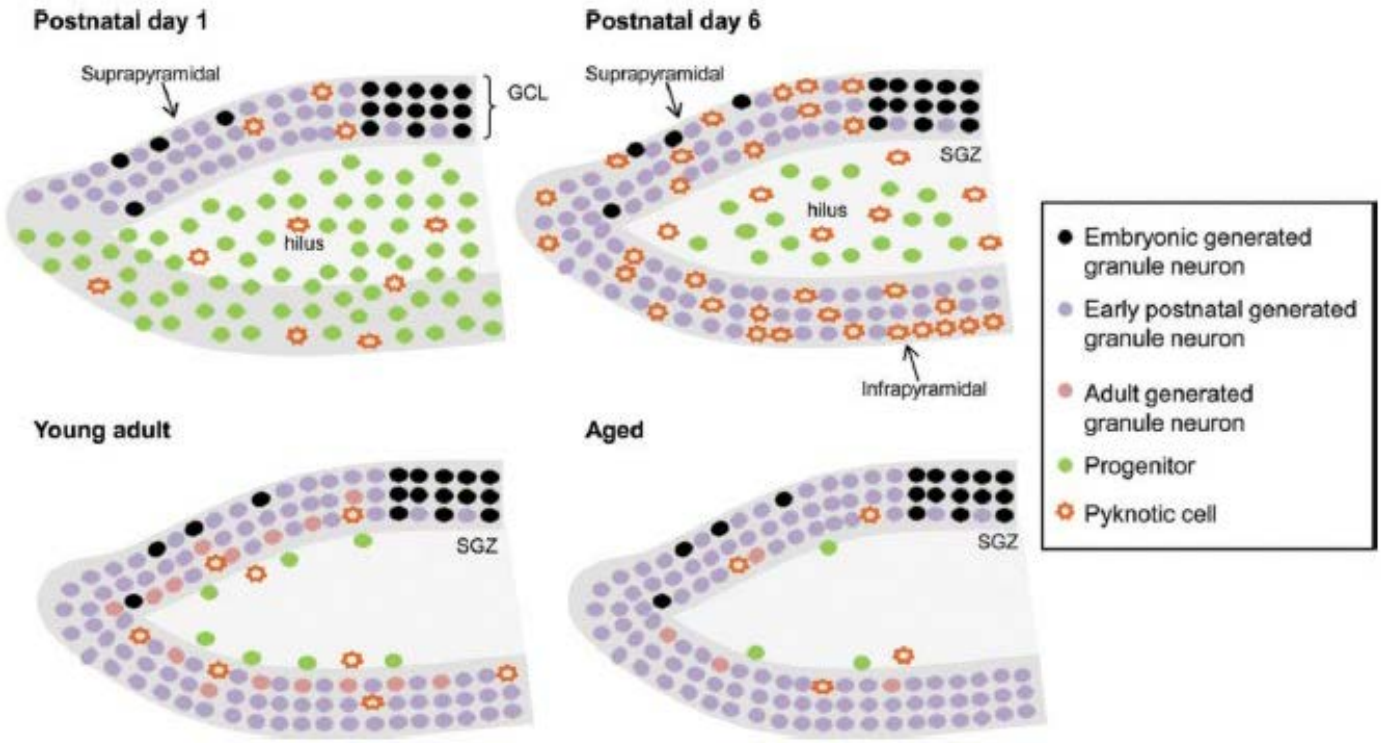
Nature Reviews Neuroscience **5**, 45-54 (January 2004)

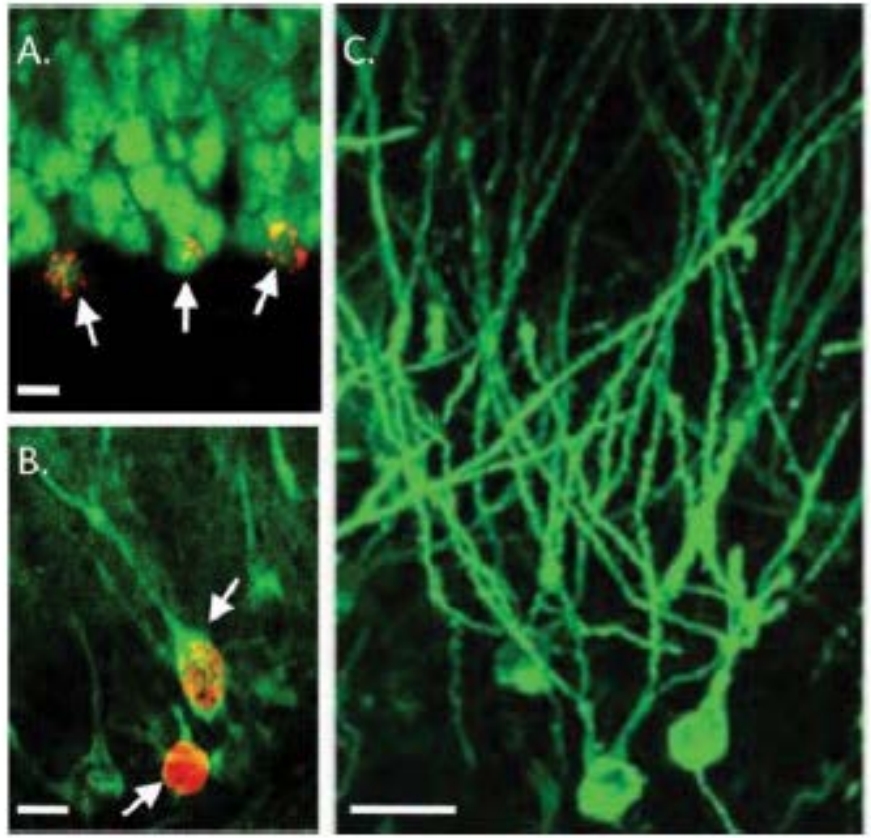
Epigenetic changes co-occur with synaptic plasticity



Iva B. Zovkic et al. Learn. Mem. 2013;20:61-74

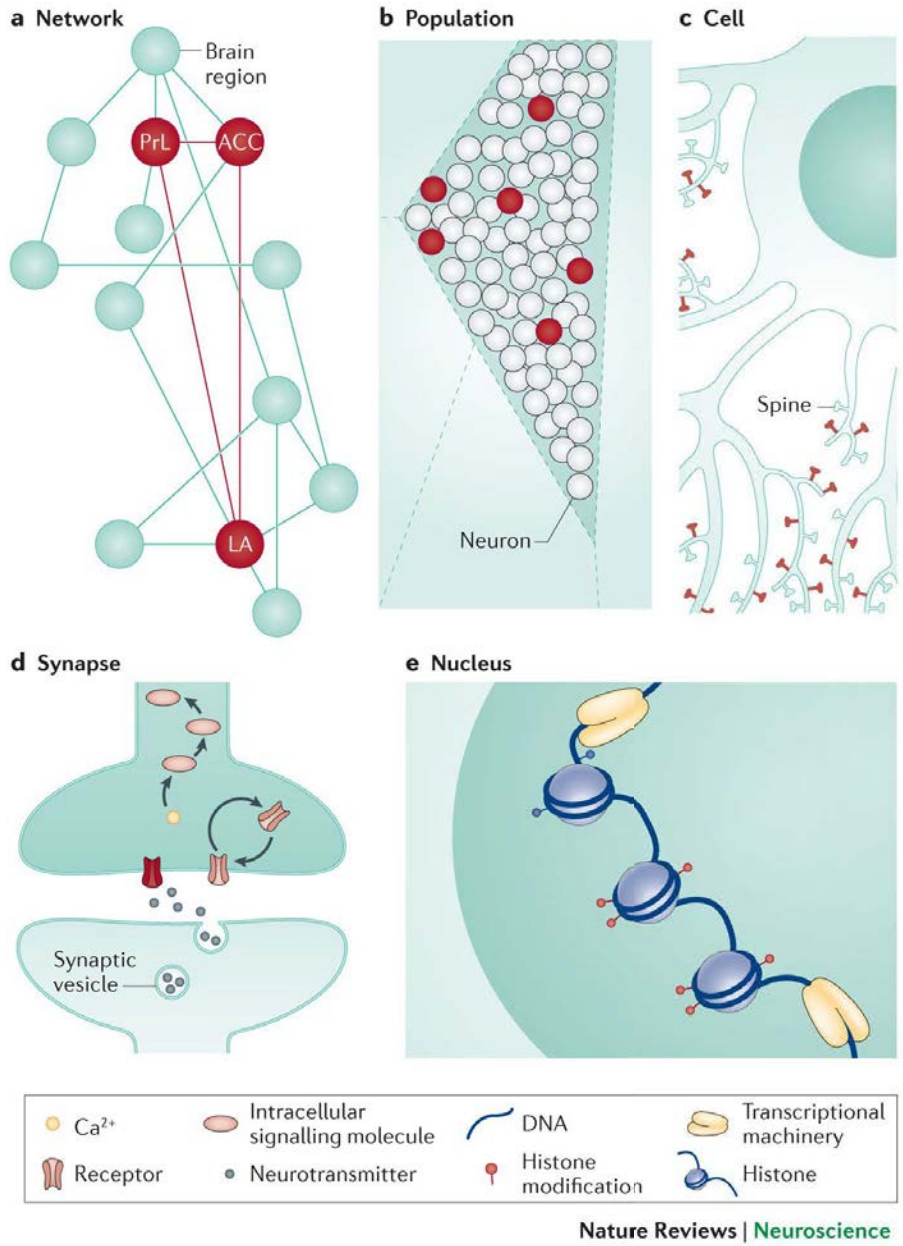
Neurogenesis (new neurons) happens in the dentate gyrus throughout the lifespan





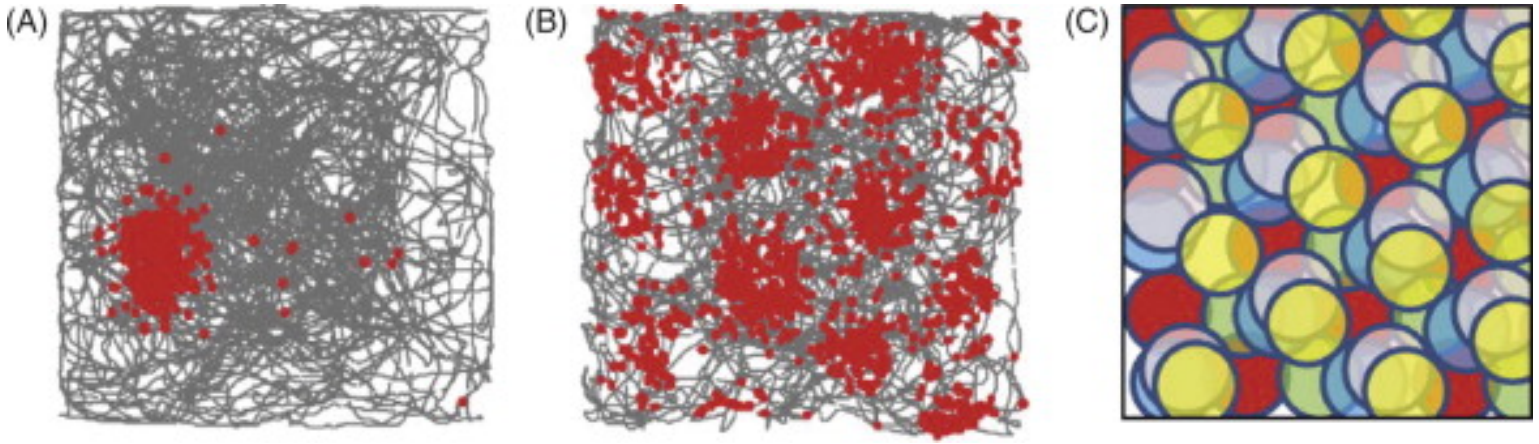
Annu Rev Psychol. 2010 ; 61: 111–C3.

Where are memories stored?



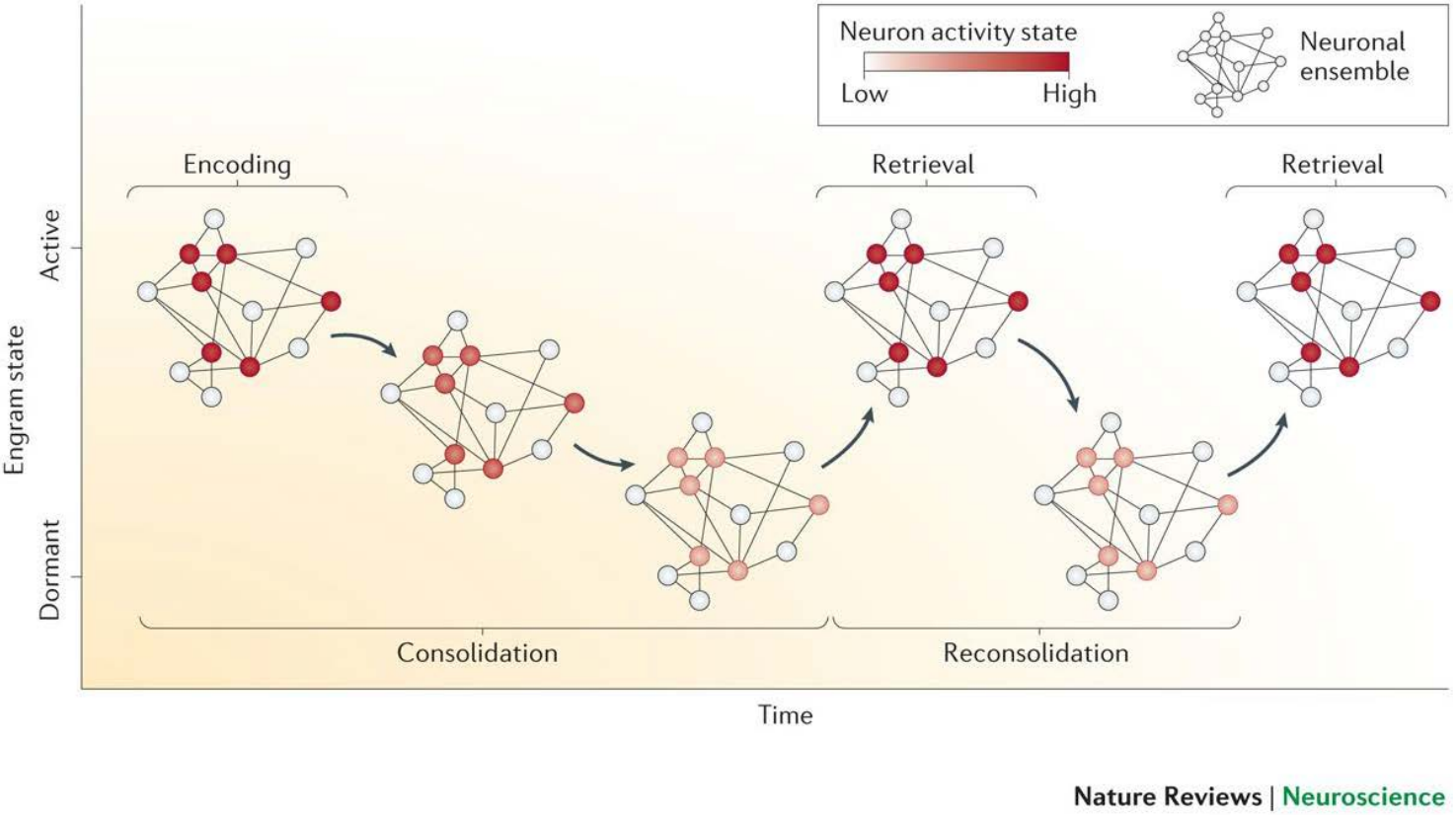
Nature Reviews Neuroscience 16, 521–534 (2015)

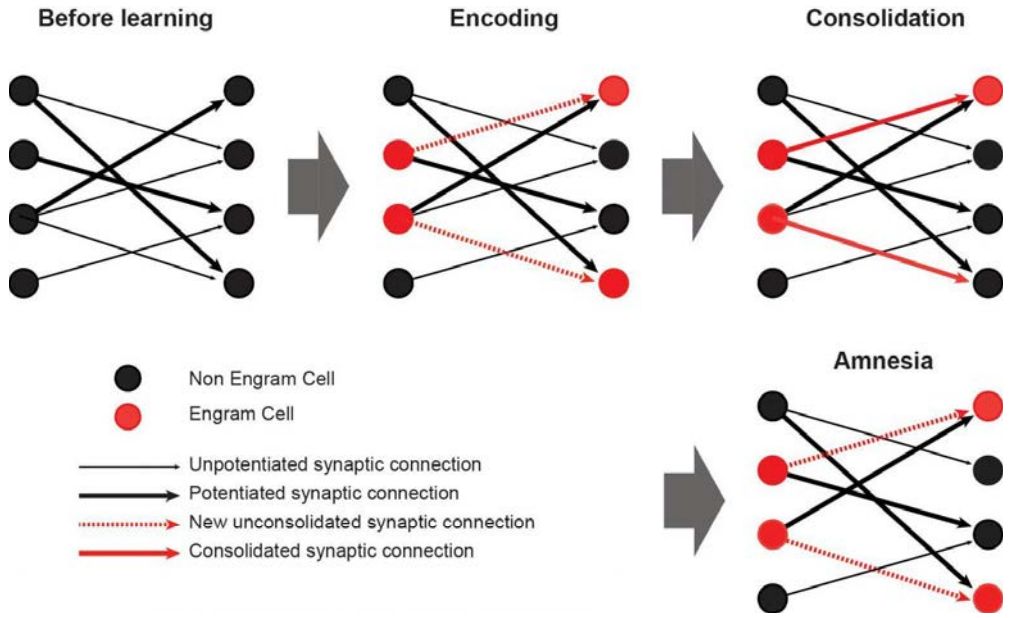
Place cells



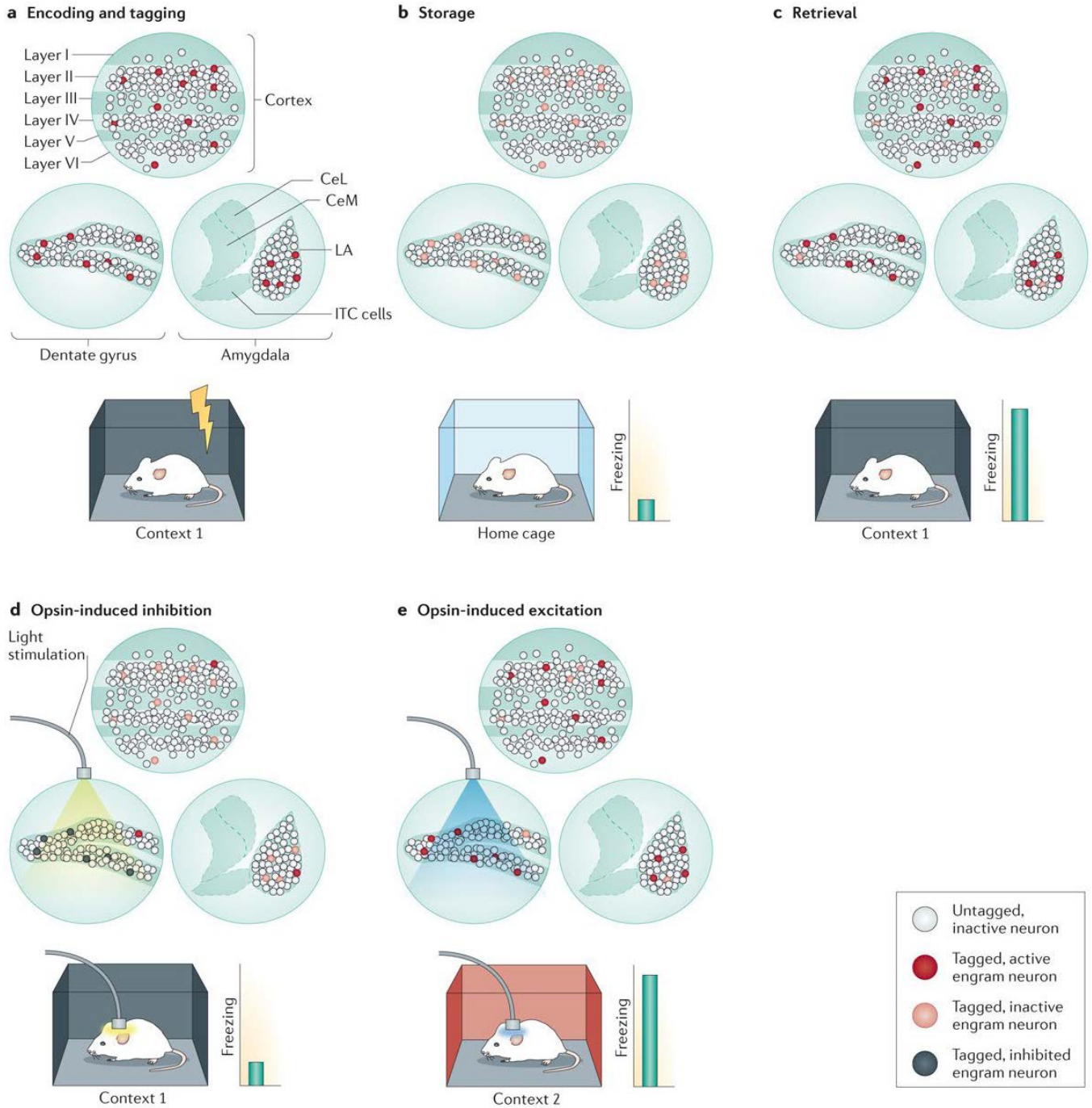
Conn's Translational Neuroscience 2017, Pages 693–708

The memory **engram**

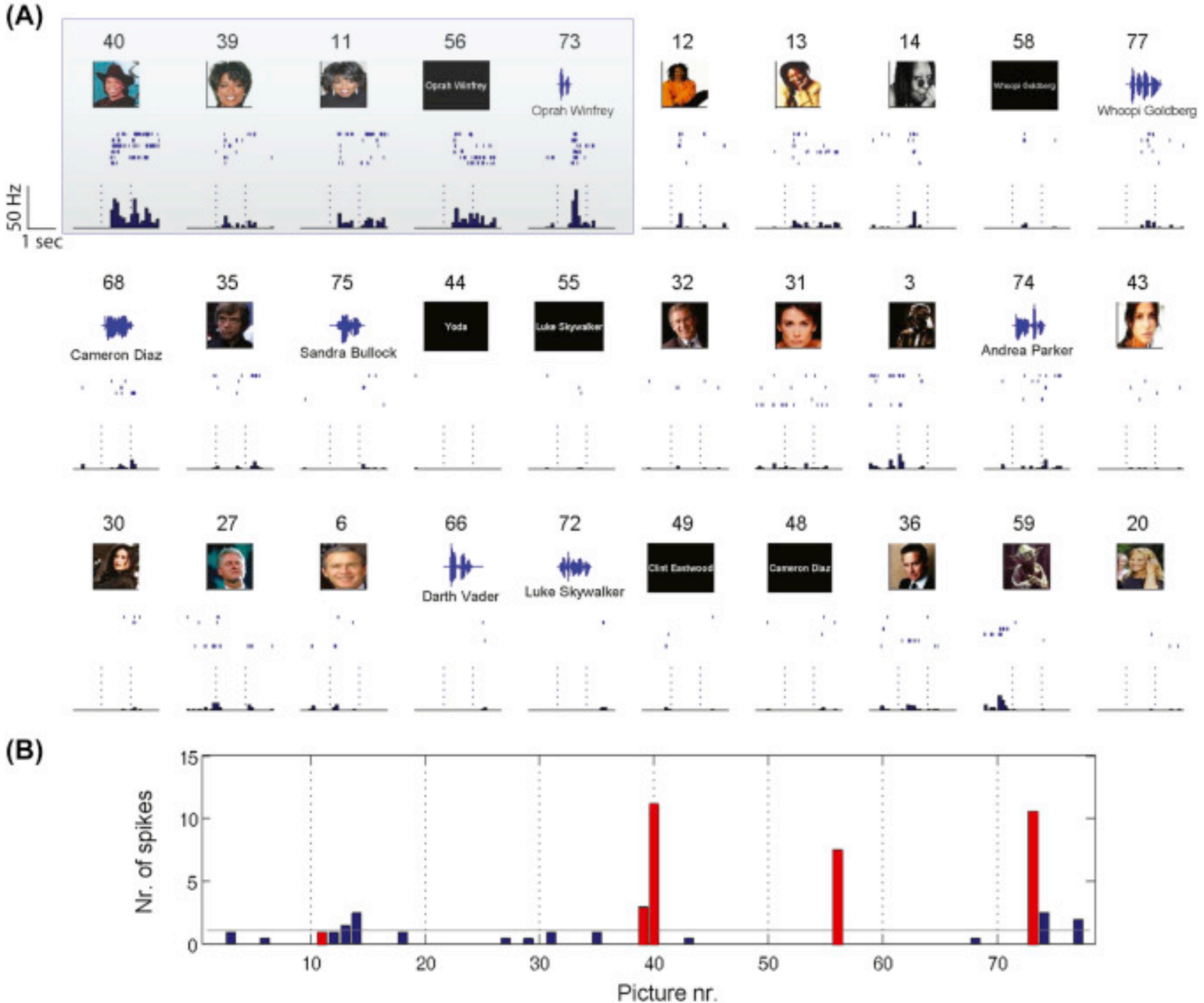




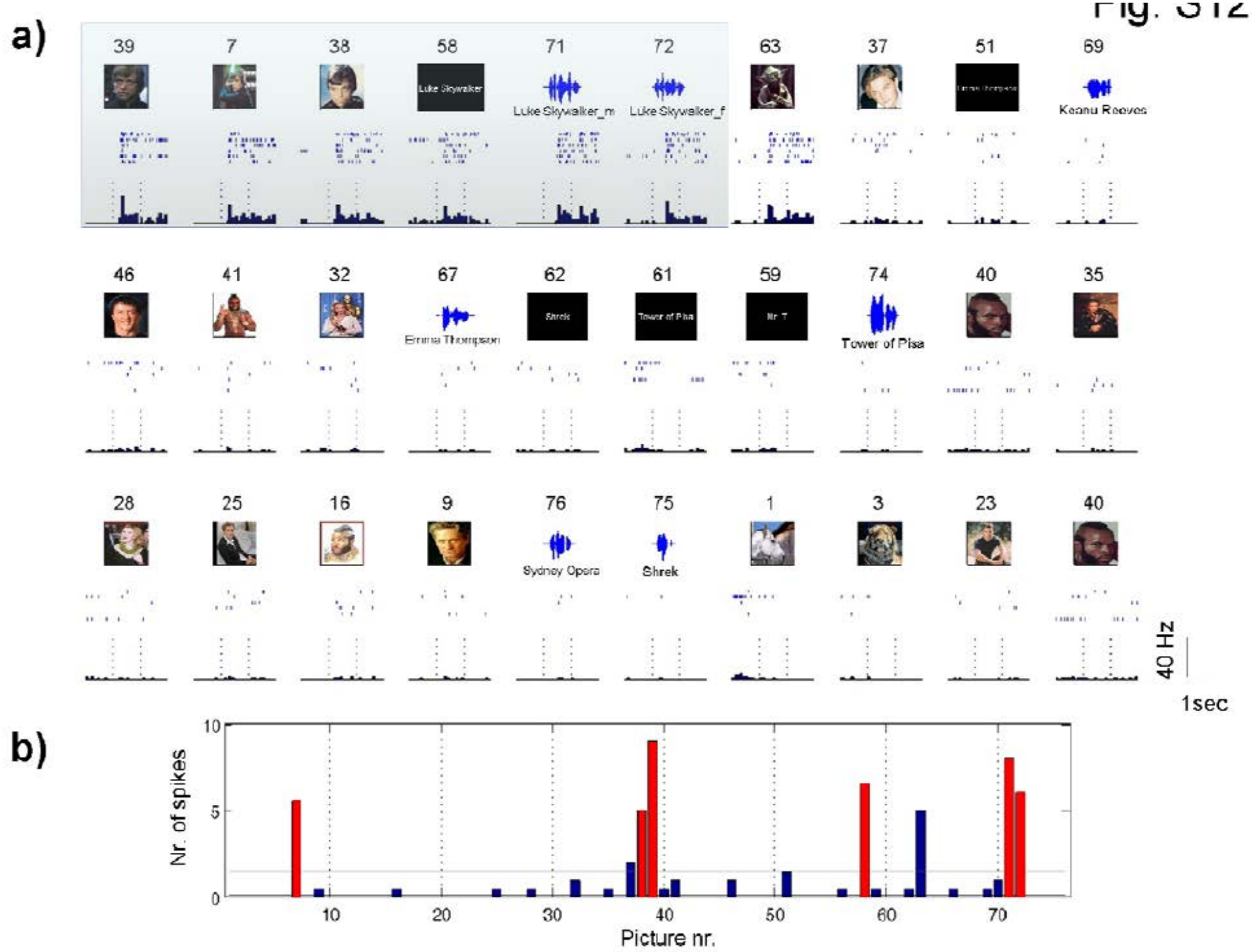
Nature Reviews Neuroscience 16, 521–534 (2015)


a Encoding and tagging
Layer I
Layer II
Layer III
Layer IV
Layer V
Layer VI
Cortex
CeL
CeM
LA
ITC cells
Dentate gyrus
Amygdala
Context 1
b Storage
Home cage
Freezing
c Retrieval
Context 1
Freezing
d Opsin-induced inhibition
Light stimulation
Context 1
Freezing
e Opsin-induced excitation
Context 2
Freezing
Untagged, inactive neuron
Tagged, active engram neuron
Tagged, inactive engram neuron
Tagged, inhibited engram neuron

Oprah


(A)
40
39
11
56
73
Oprah Winfrey
Oprah Winfrey
12
13
14
58
77
Whoopi Goldberg
50 Hz
1 sec
68
35
75
44
55
32
31
3
74
43
Cameron Diaz
Sandra Bullock
Yoda
Luke Skywalker
Andrea Parker
30
27
6
66
72
49
48
36
59
20
Darth Vader
Luke Skywalker
Clint Eastwood
Cameron Diaz
(B)
Nr. of spikes
15
10
5
0
10
20
30
40
50
60
70
Picture nr.

Luke


a)
39
7
38
58
71
72
63
37
51
69
Luke Skywalker
Luke Skywalker_m
Luke Skywalker_f
Keanu Reeves
46
41
32
67
62
61
59
74
40
35
Emma Thompson
Shrek
Tower of Pisa
Mr T
Tower of Pisa
28
25
16
9
76
75
1
3
23
40
Sydney Opera
Shrek
40 Hz
1sec
b)
Nr. of spikes
Picture nr.
0
5
10
10
20
30
40
50
60
70

Spiders and snakes