Synaptic plasticity and hippocampal memory

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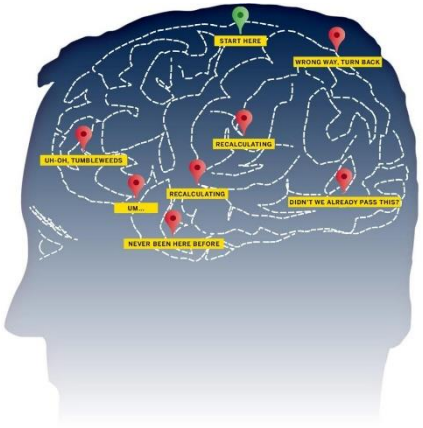

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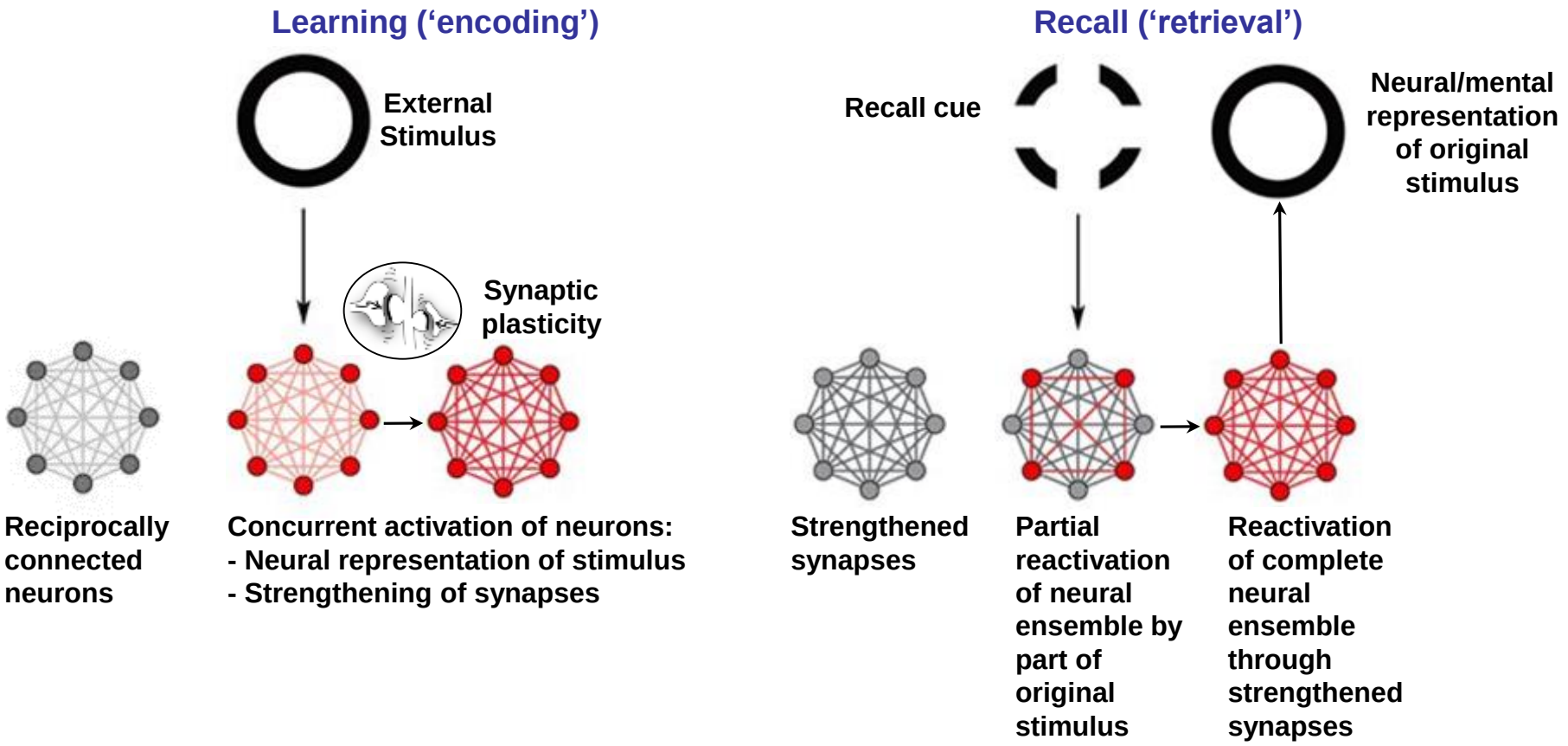
Synaptic plasticity as the neurophysiological substrate of learning

Hebb's Hypothesis (1949)

- **Long-lasting change in the strength of the connections ('synapses') between neurons is the physiological basis of lasting memory.**
- **Synapses between neurons are strengthened when the neurons are active together: 'neurons that fire together, wire together'.**

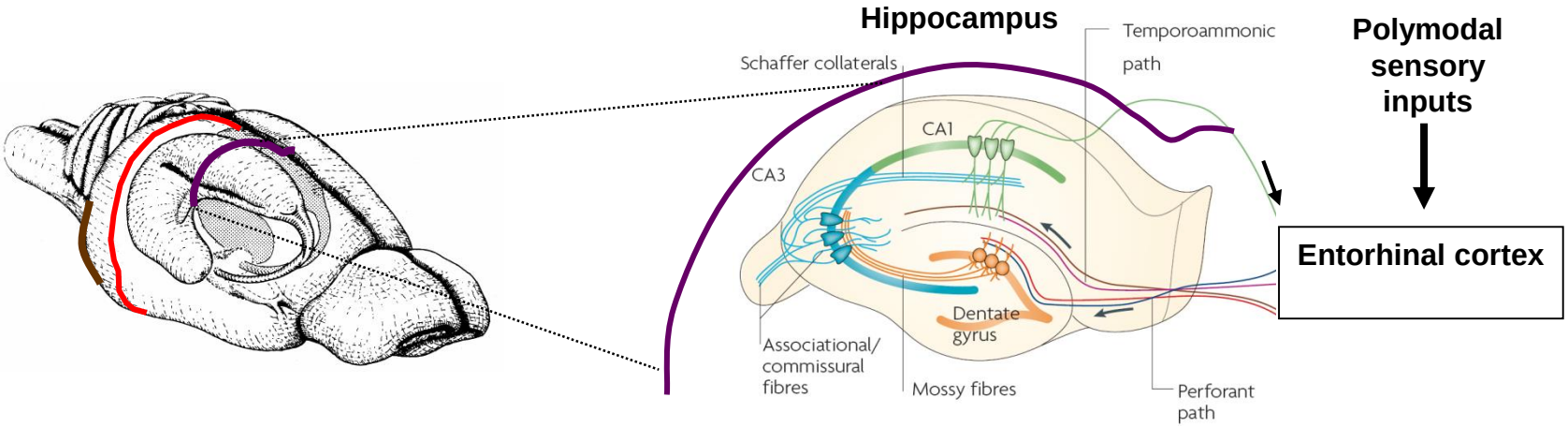


Adapted from Fig. 24.4. in Bear, Connors, Paradiso (2014, 4th Ed) *Neuroscience: exploring the brain.*

Also compare Bast (2007, Rev Neurosci), Fig. 2, specifically focusing on hippocampal synaptic plasticity and its role in place learning.

Long-term potentiation (LTP) of hippocampal synapses

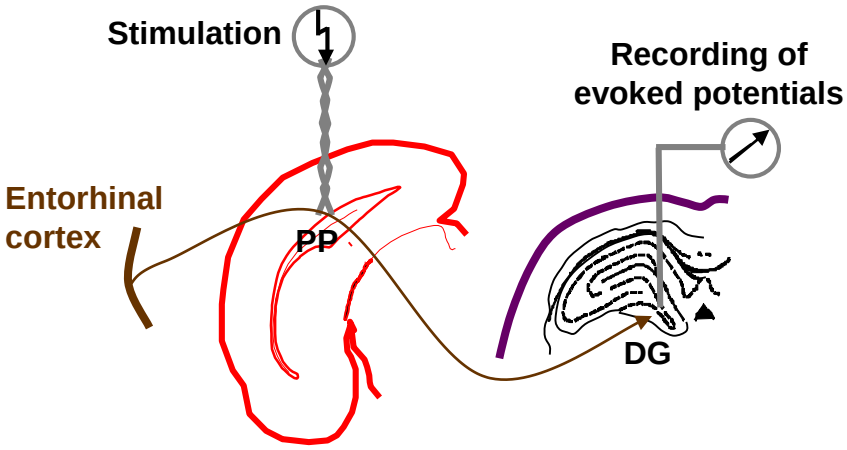
Entorhinal-hippocampal circuitry

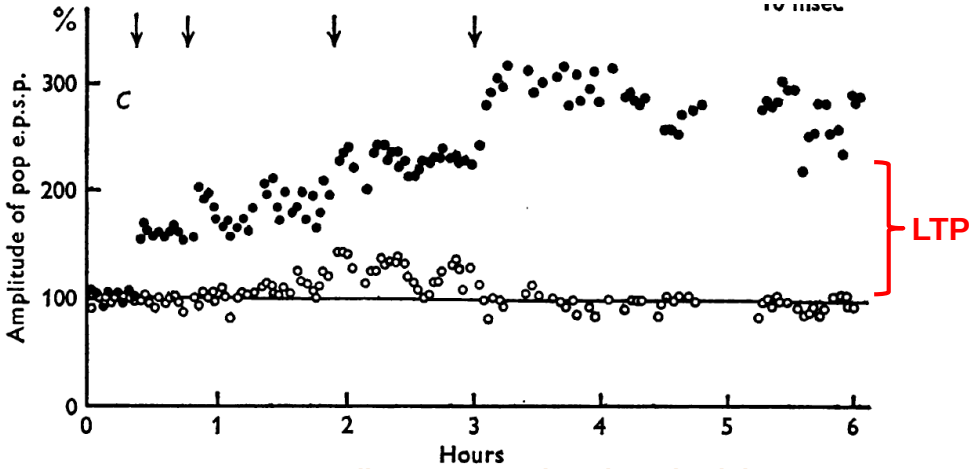


Adapted from G Neves, FS Cook, TVP Bliss (2008) *Nature Rev. Neurosci.* 9, 65-75

LTP of perforant path-dentate gyrus synapses *in vivo*

LTP = sustained increase in the synaptic efficiency of a monosynaptic excitatory pathway caused by tetanic stimulation of the pathway, i.e. strong concurrent stimulation of a large proportion of the synaptic connections that make up the pathway (Bliss & Collingridge, 1993, *Nature*).



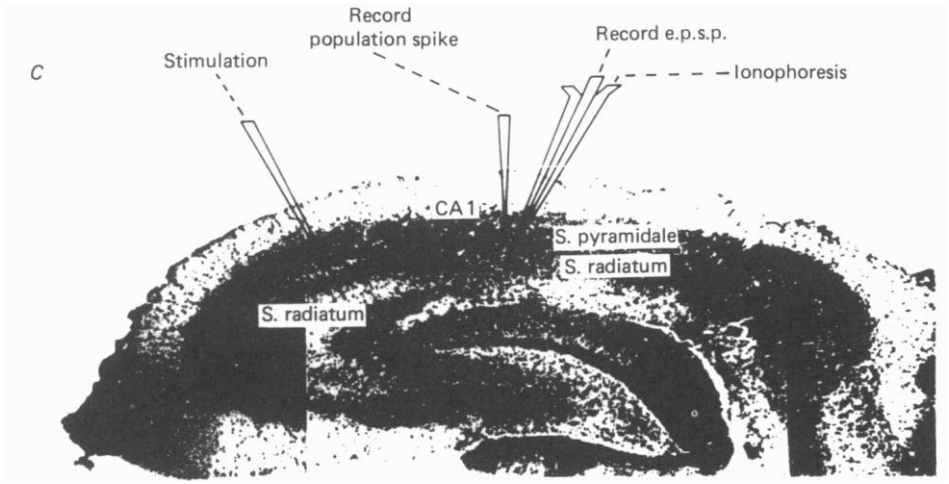


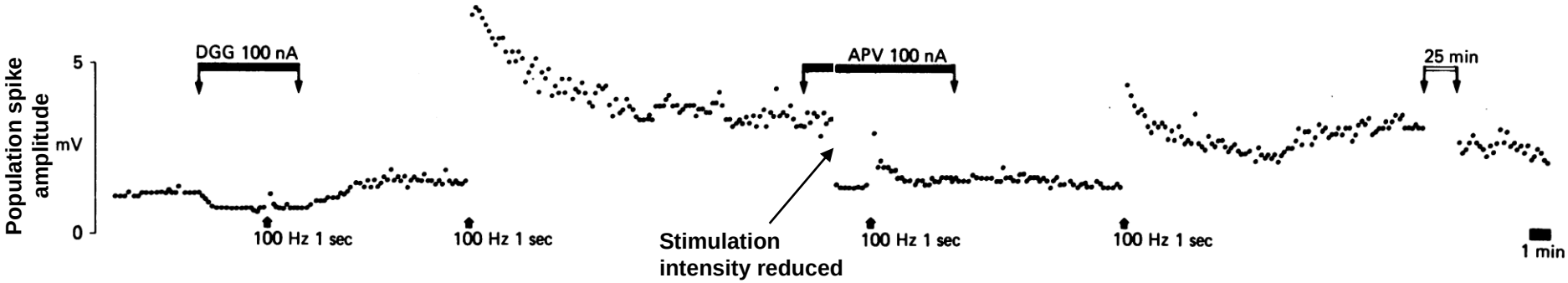
TVP Bliss & T Lomo (1973) *J. Physiol.* 232, 331-356

All excitatory pathways in the hippocampus show LTP (TVP Bliss & GL Collingridge,1993, *Nature* 361:31),

NMDA-type glutamate receptors are required to induce hippocampal LTP

CA3-CA1 pathway



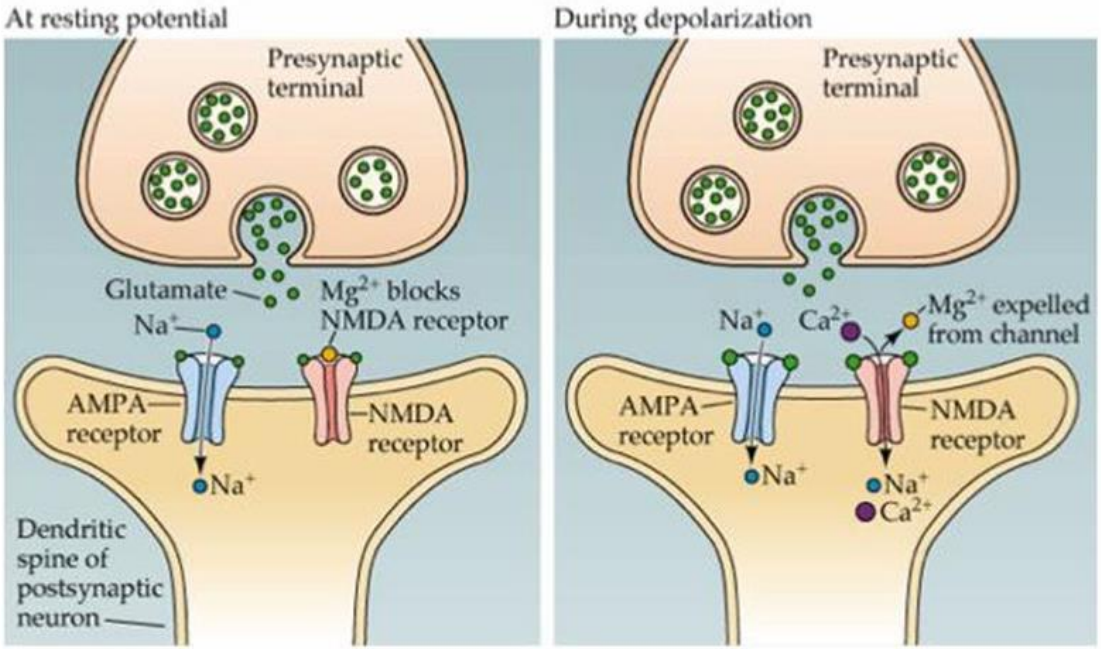


GL Collingridge, SJ Kehl, HT McLennan (1983) 334:33-46

For an *in vivo* demonstration of the selective contribution of NMDA receptors to LTP induction at perforant path dentate gyrus synapes see Bast et al. (2005, *J Neurosci*).

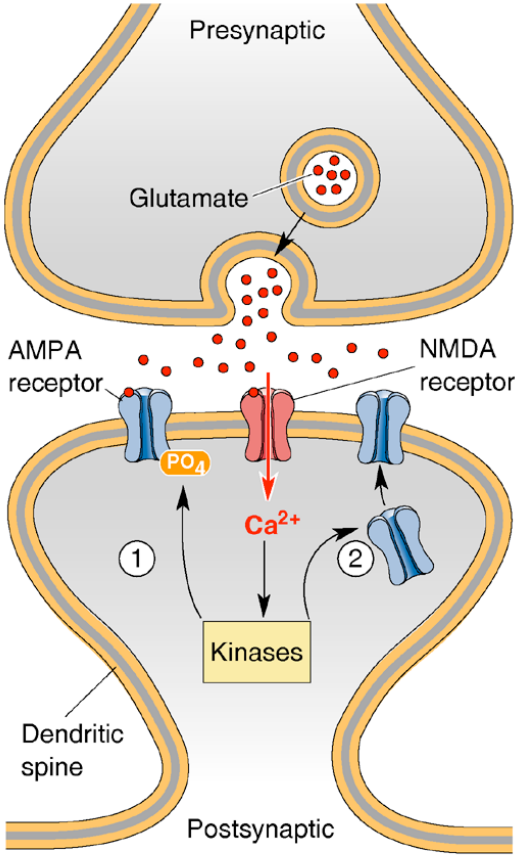
NMDA receptors and hippocampal LTP

NMDA receptor activation by concurrent pre- and postsynaptic activation



NMDA receptors act as 'coincidence' detectors

NMDA receptor activation triggers LTP induction

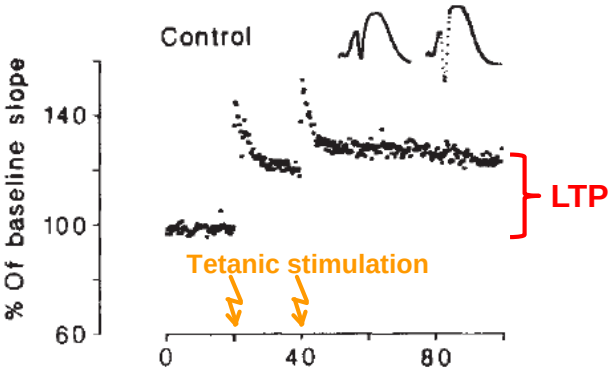


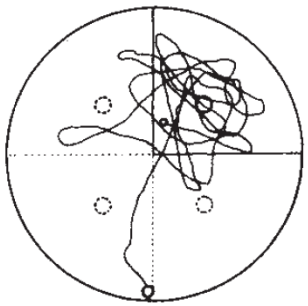
AMPA receptors are required for both induction and expression of hippocampal LTP.

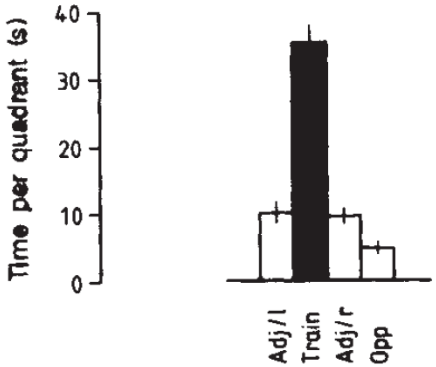
Compare Fig. 25.8 and 25.9. in Bear, Connors, Paradiso (2014, 4th Ed) *Neuroscience: exploring the brain*

Blockade of hippocampal NMDA receptors blocks hippocampal LTP and hippocampal learning

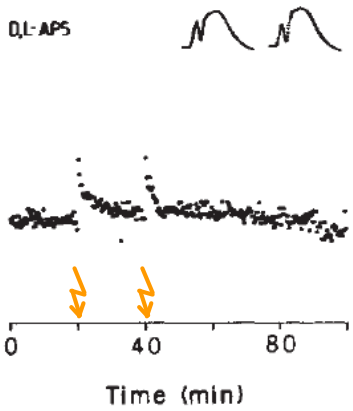
Control

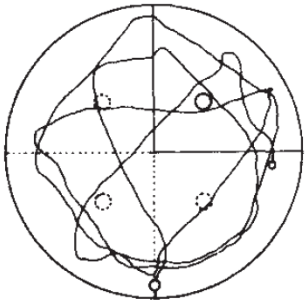






NMDA receptor blockade





RGM Morris et al (1986) *Nature* 319:774

Behavioral/Systems/Cognitive

Distinct Contributions of Hippocampal NMDA and AMPA Receptors to Encoding and Retrieval of One-Trial Place Memory

Tobias Bast, Bruno M. da Silva, and Richard G. M. Morris
Laboratory for Cognitive Neuroscience, Division of Neuroscience, University of Edinburgh, Edinburgh EH8 9JZ, United Kingdom

Allocentric place memory may serve to specify the context of events stored in human episodic memory. Recently, our laboratory demonstrated that, analogous to event–place associations in episodic memory, rats could associate, within one trial, a specific food flavor with an allocentrically defined place in an open arena. Encoding, but not retrieval, of such flavor–place associations required hippocampal NMDA receptors; retrieval depended on hippocampal AMPA receptors. This might have partly reflected the contributions of these receptors to encoding and retrieval of one-trial place, rather than flavor–place, memory. Therefore, the present study developed a food-reinforced arena paradigm to study encoding and retrieval of one-trial allocentric place memory in rats; memory relied on visuospatial information and declined with increasing retention delay, still being significant after 6 h, the longest delay tested (experiments 1 and 2). Hippocampal infusion of the NMDA receptor antagonist D-AP-5 blocked encoding without affecting retrieval; hippocampal infusion of the AMPA receptor antagonist CNQX impaired retrieval (experiment 3). Finally, we confirmed that the D-AP-5 infusions selectively blocked induction of long-term potentiation, a form of synaptic plasticity, whereas CNQX impaired fast excitatory transmission, at perforant-path dentate gyrus synapses in the dorsal hippocampus *in vivo* (experiment 4). Our results support that encoding, but not retrieval, of one-trial allocentric place memory requires the NMDA receptor-dependent induction of hippocampal synaptic plasticity, whereas retrieval depends on AMPA receptor-mediated fast excitatory hippocampal transmission. The contributions of hippocampal NMDA and AMPA receptors to one-trial allocentric place memory may be central to episodic memory and related episodic-like forms of memory in rats.

Key words: allocentric spatial learning; hippocampus; synaptic plasticity; NMDA; microinfusions; episodic-like memory

THE BRAIN PRIZE WINNERS 2016

GRAHAM COLLINGRIDGE RICHARD MORRIS TIMOTHY BLISS

THE BRAIN PRIZE WINNERS 2016

The Brain Prize for 2016 is awarded to Timothy Bliss, Graham Collingridge and Richard Morris for *their ground-breaking research on the cellular and molecular basis of Long-Term Potentiation and the demonstration that this form of synaptic plasticity underpins spatial memory and learning.*

http://www.thebrainprize.org/flx/prize_winners/the_brain_prize_winners_2016/

Which conclusion can we draw from the finding that selective blockade of hippocampal NMDA receptors selectively blocks hippocampal LTP and hippocampus-dependent place learning?

a) Hippocampal LTP-like synaptic plasticity is necessary for such learning.

b) Hippocampal LTP-like synaptic plasticity is sufficient for such learning.

c) Both a) and b).

d) None of the above.

Synaptic plasticity = memory?

Synaptic plasticity and memory (SPM) hypothesis

Learning is mediated by synaptic plasticity, i.e. synaptic plasticity is both necessary and sufficient for memory

TABLE 1 Four formal criteria relevant to the assessment of the SPM hypothesis

DETECTABILITY: If an animal displays memory of some previous experience, a change in synaptic efficacy should be detectable somewhere in its nervous system.
MIMICRY: Conversely, if it were possible to induce the same spatial pattern of synaptic weight changes artificially, the animal should display 'apparent' memory for some past experience which did not in practice occur.
ANTEROGRADE ALTERATION: Interventions that prevent the induction of synaptic weight changes during a learning experience should impair the animal's memory of that experience.
RETROGRADE ALTERATION: Interventions that alter the spatial distribution of synaptic wieghts induced by a prior learning experience (see detectability) should alter the animal's memory of that experience.

SJ Martin, PG Grimwood, RGM Morris *Ann Rev Neurosci* 23:649

For a recent review of evidence supporting the SPM hypothesis, see Takeuchi, Duskiewicz, Morris (2014, *Phil. Trans. R. Soc. B*).

Synaptic plasticity and hippocampal memory – selected reading

Textbook chapters

Carlson N (2013,11th ed) Physiology of behavior. Pearson. Chpt. 13: Learning and memory.

or

Bear M, Connors BW, Paradiso MA (2016, 4th ed) Neuroscience: exploring the brain. Wolters Kluwer. Chpts 24 and 25 (Memory Systems and Molecular Mechanisms of Memory)

Whitlock JR, Moser EI (2009) Synaptic plasticity and spatial representations in the hippocampus. In: Gazzaniga MS, Cognitive Neuroscience (4th ed), p. 109-127.

Reviews

Bliss TV, & Collingridge GL (1993) A synaptic model of memory: long-term potentiation in the hippocampus. *Nature* 361(6407), 31.

Takeuchi T, Duszkiewicz AJ, Morris RG (2014) The synaptic plasticity and memory hypothesis: encoding, storage and persistence. *Phil Trans R Soc B* 369: 20130288.

Research papers

Morris, R. G. M., Anderson, E., Lynch, G. A., & Baudry, M. (1986). Selective impairment of learning and blockade of long-term potentiation by an N-methyl-D-aspartate receptor antagonist, AP 5. Nature, 319(6056), 774-776.

Bast, T., da Silva, B. M., & Morris, R. G. (2005). Distinct contributions of hippocampal NMDA and AMPA receptors to encoding and retrieval of one-trial place memory. Journal of Neuroscience, 25(25), 5845-5856.

Synaptic plasticity and hippocampal memory – Revision questions

- What was Donald Hebb's famous hypothesis on the physiological substrate of memories? How can it be used to explain memory?

- What is LTP and how is it demonstrated in vitro and in vivo?

- What are the roles of NMDA- and AMPA-type glutamate receptors in LTP?

- Which lines of evidence support that LTP-like synaptic plasticity mechanism mediate hippocampus-dependent learning and memory?

- Which criteria would need to be met to conclude that synaptic plasticity within a specific brain region, such as the hippocampus, is both necessary and sufficient for the memory representations supported by this brain region?