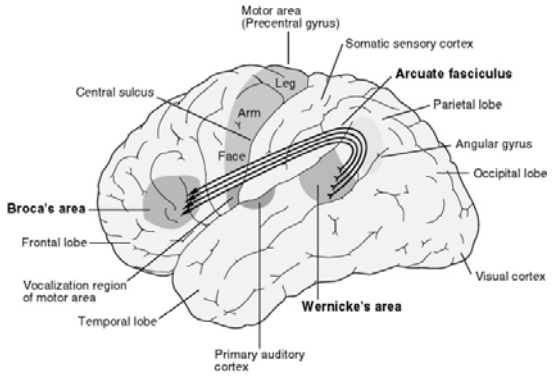
Cellular Mechanisms of Learning and the Biological Basis of Individuality

The Study of Memory Has Two Parts:

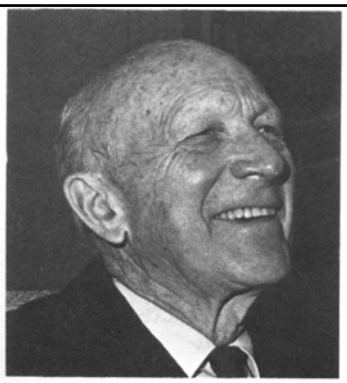
(1) The *Systems* Problem of Memory:
Where in the brain is memory stored?

(2) The *Molecular* Problem of Memory:
How is memory stored at each site?

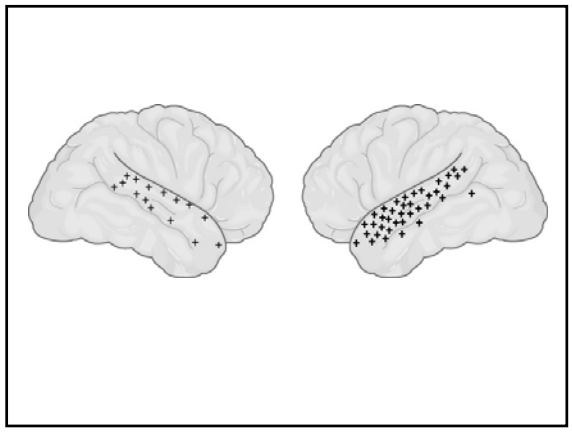


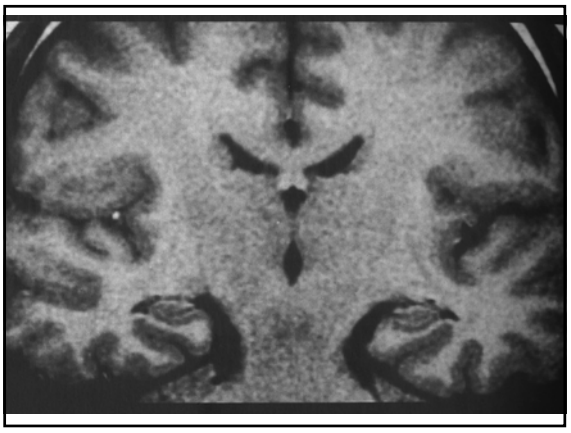
Karl Lashley (1890-1950)

Marie-Jean-Pierre Flourens (1794–1867).

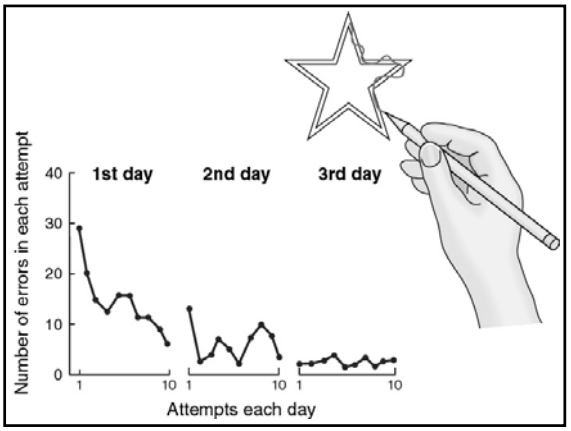


Wilder Penfield (1891-1976)





Brenda Milner 1918–

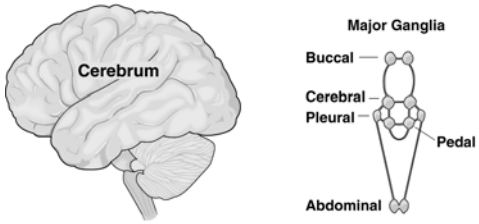


There are Two Major Forms of Long Term Memory

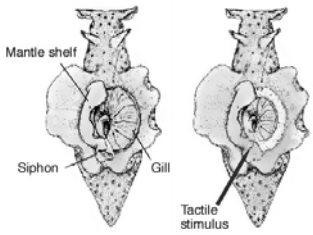
Explicit (Declarative)	Implicit (Procedural)
Facts and Events; People, Objects and Places	Skills and Habits; Nonassociative And Associative Learning
Medial Temporal Lobe Hippocampus	Amygdala, Cerebellum, Reflex Pathways
Requires Conscious Attention	Does Not Require Conscious Attention But Often Requires Salience Signals

The Human Brain is complex: 10^{12} Neurons

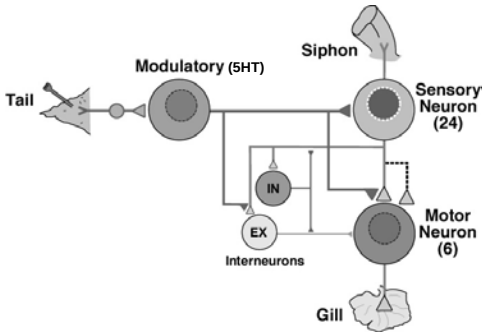
The *Aplysia* Brain is simple: 2×10^{4} Neurons



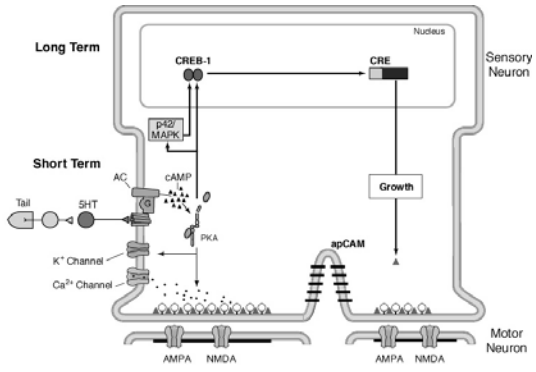
Gill Withdrawal Reflex



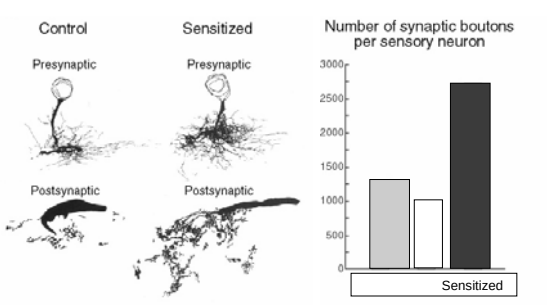
The Gill Withdrawal Reflex has a Simple Stereotypical Internal Representation. Long Term Sensitization Leads to Altered Gene Expression and the Growth of New Synaptic Connections.

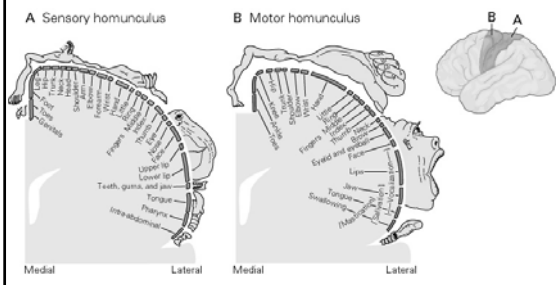


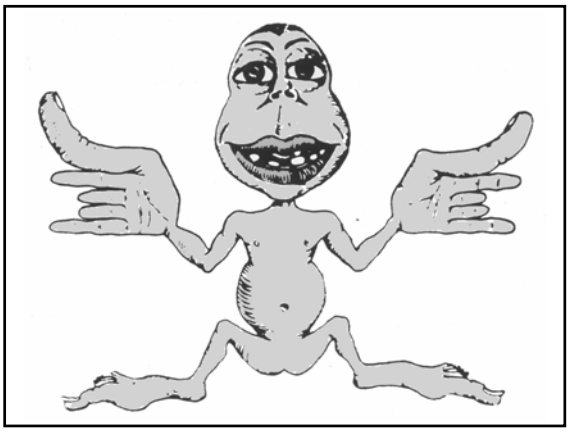
Long-Term Memory Requires a CREB1-Mediated Transcriptional Cascade



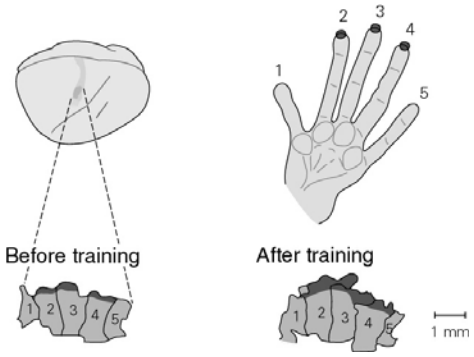
Sensitization Produces Both Pre- and Postsynaptic Structural Changes in the Intact Animal (HRP)

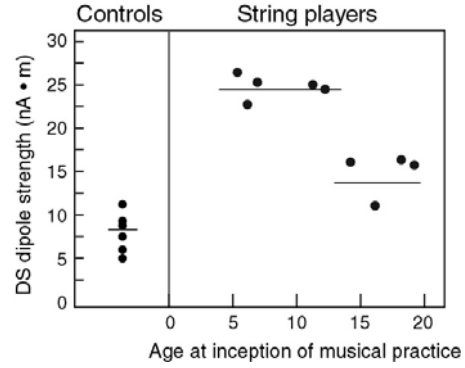






Cortical Representation of Fingers



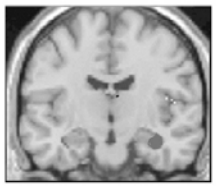


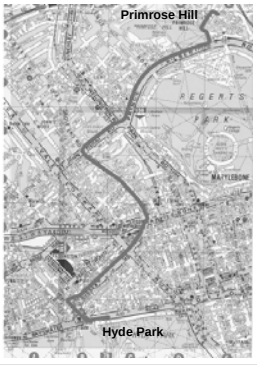
There are Two Major Forms of Long Term Memory

Explicit (Declarative)	Implicit (Procedural)
Facts and Events; People, Objects and Places	Skills and Habits; Nonassociative and Associative Learning
Medial Temporal Lobe Hippocampus	Amygdala, Cerebellum, Reflex Pathways
Requires Conscious Attention	Does Not Require Conscious Attention

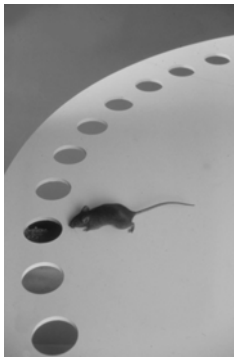
Hippocampus of Humans Encodes Space

Route from Hyde Park to Primrose Hill

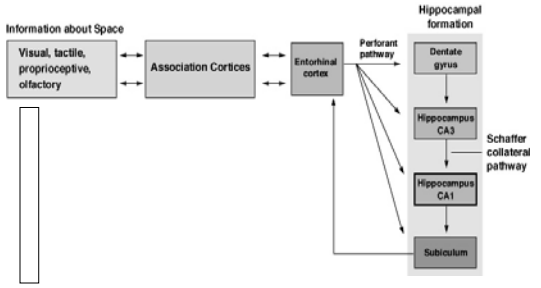




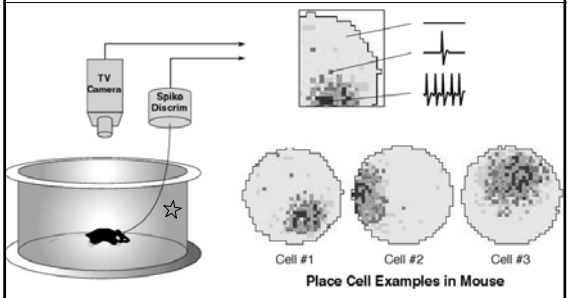
Hippocampus of Mice Also Encodes Space



Multi Sensory Information About Spatial Memory is Only Brought Together in the CA1 Region of the Hippocampus

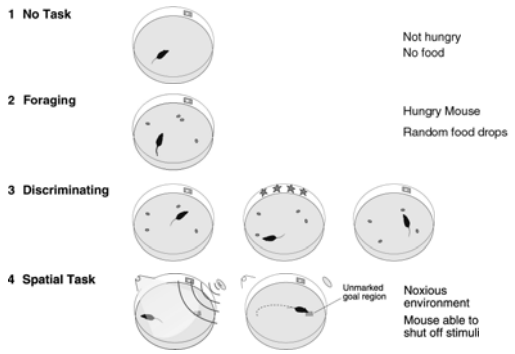


The Hippocampal Pyramidal Cells Encode a Cognitive Map of Space :Is Attention Importand for Formation of the Map or for its Perpetuation

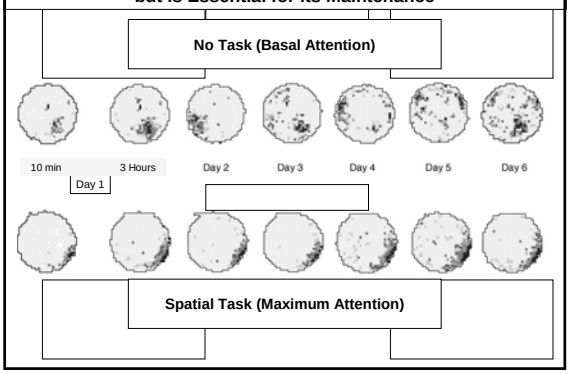


Is Attention Important to Form the Spatial Map or to Stabilize and Perpetuate it?

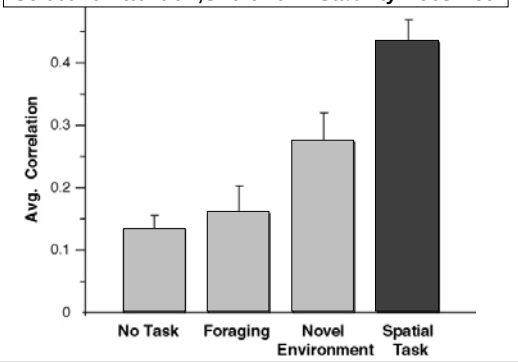
Four Degrees of Attention



Selective Attention is not Required for the Formation of the Map but is Essential for its Maintenance

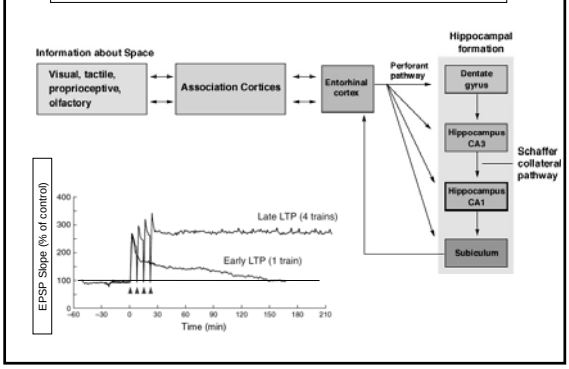


Long Term Place Cell Stability Requires Selective Attention;Short Term Stability Does Not.

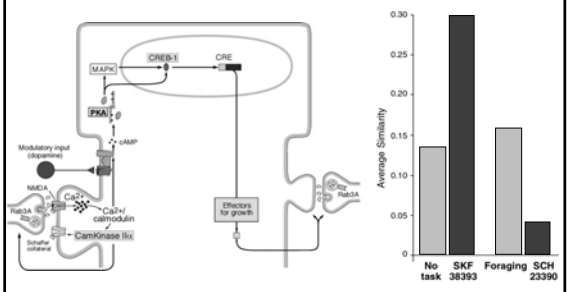


LTP is a Candidate Synaptic Mechanism for Spatial Memory

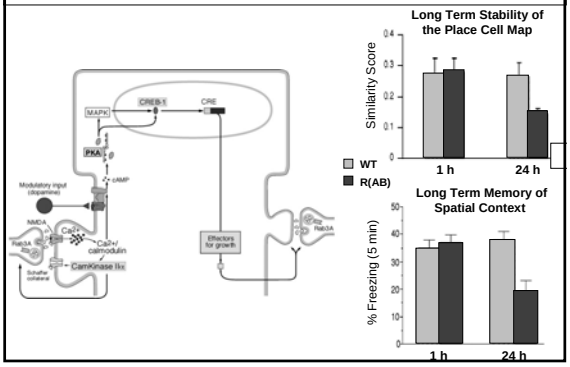
LTP has both an Early and a Late Phase



Dopamine as a Candidate Mediator of Attention



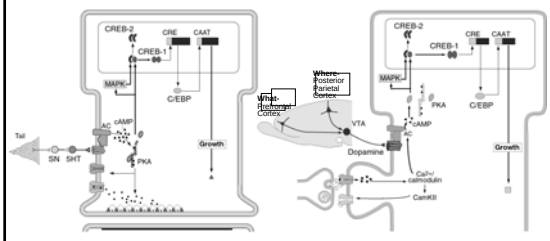
Both the Long-Term Memory for Spatial Context and the Long-Term Stability of the Place Cell Map Require PKA



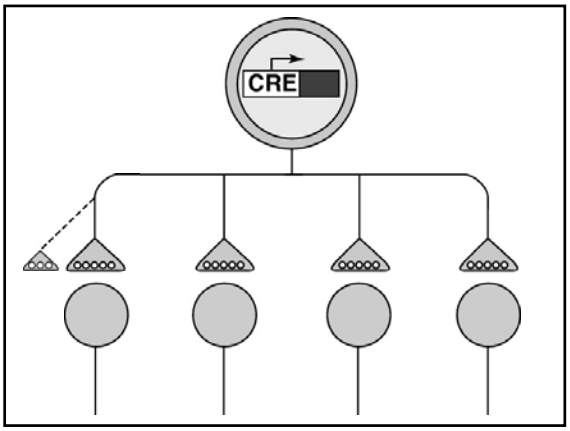
Both Explicit and Implicit Memory Storage Use Modulatory Transmitters as a Salience Signal and a CREB-Mediated Transcriptional Switch for Converting Short-Term to Long- Term Memory

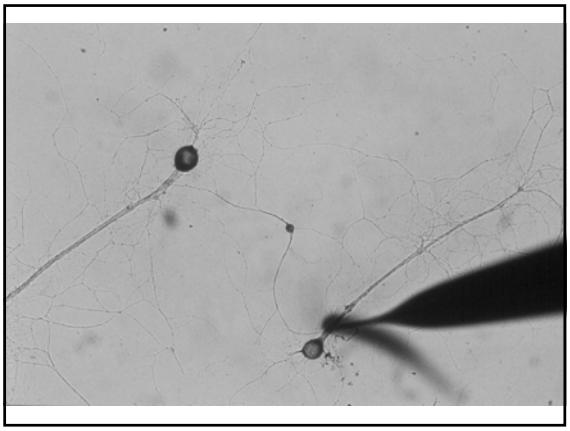
Aplysia
(bottom up modulation)

Hippocampus
(top down modulation)

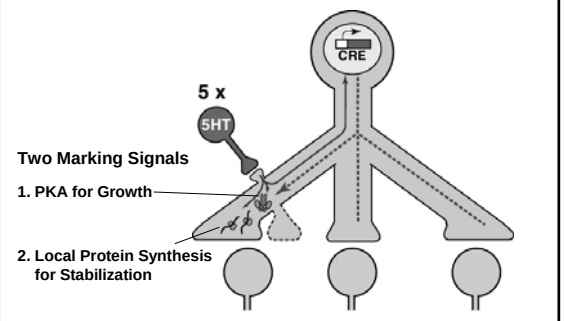


How is synapse specificity achieved? How is it maintained for the long term?

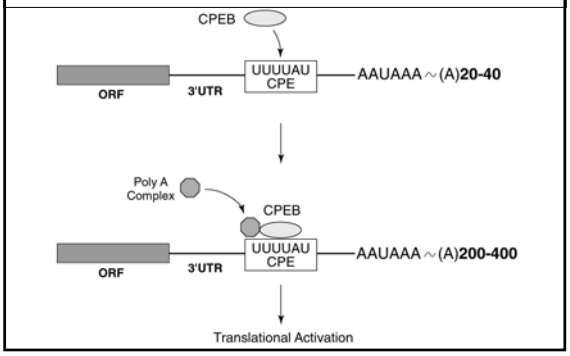




In Addition to Transcription the Growth of New Synapses Requires 2 Local Marking Signals



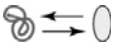
The Cytoplasmic Polyadenylation Element Binding Protein Is a Regulator of Local Protein Synthesis that Can Activate Dormant Transcripts



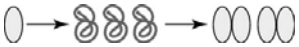
Properties of a "Prion" Protein (CPEB)

1) At least two distinct conformational states

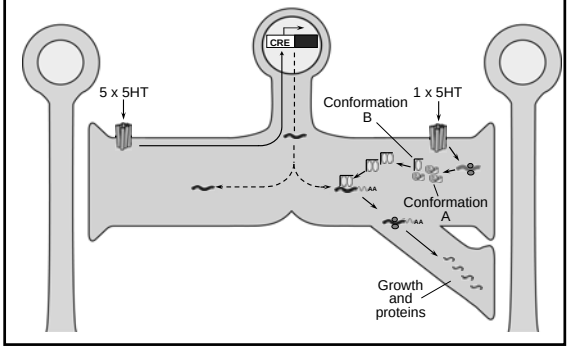
2) Conformational states are interconvertible



3) One of the conformational states is dominant and can self-perpetuate epigenetically



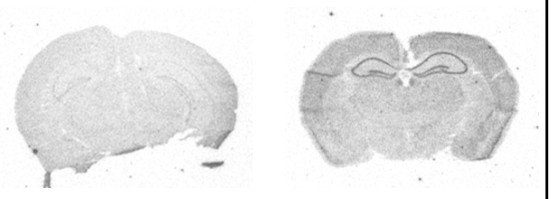
CPEB as a Candidate for the Self-Perpetuating Switch of Local Protein Synthesis



The "Prion-Like" Properties of *Aplysia* CPEB Are Different from Known Prions

- The conversion from one state to the other is regulated by a physiological signal.
- The dominant self-perpetuating state is the active state.
- *Aplysia* CPEB might be representative of a new class of proteins with prion like properties, which has normal physiological function.

Dopaminergic Stimulation Induces CPEB-3 Expression in the Hippocampus



CPEB-3
Naive animal

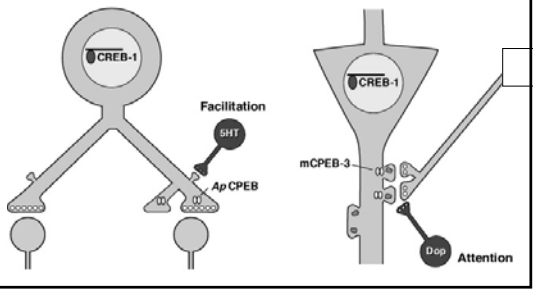
CPEB-3
D1/D5 receptor agonist
2 hr post injection

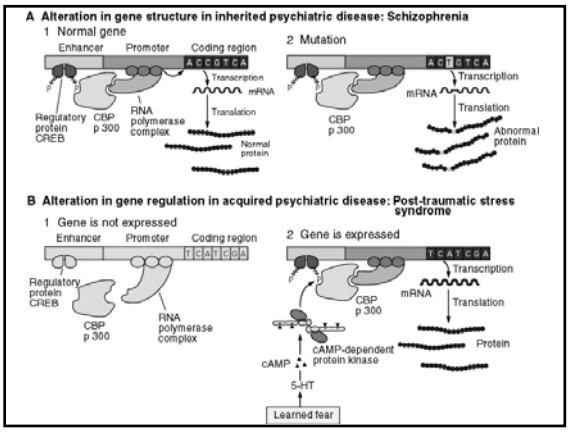
Modulatory Transmitters Serve as Salience Signals to Stabilize Synaptic Plasticity and Behavior for Both Implicit and Explicit Memory

Is the mechanism for maintenance also general?

Implicit Memory:
Sensitization in Aplysia

Explicit Memory:
Spatial Memory in the Mouse





Three Methods of Regulating Synaptic Strength

Period	Effect on Synapse	Mechanism
1. Development	Initial Synapse Formation	Molecular Cues
2. Critical Period	Synaptic Fine Tuning	Activity
3. Adult Learning	Synaptic Modulation	Learning