Outline 12/5/03 - Learning

- Tests of associative learning
- Brain structures involved in memory:
  - Amnesic patients
- Cellular model of memory formation:
  - LTP in the mammalian hippocampus
  - Gene expression & synapse formation
- Gene Overexpression and Knock-out Experiments

Questions for today’s Lecture:
- What behavioral paradigms & animal models have been used to study memory formation?
- How do perceptions get turned into memories? Where in the brain does this happen?
- What happens to neuronal activity during the process of memory formation?
- What are the cellular mechanisms mediating long term changes in neuronal activity?

What behavioral paradigms & animal models have been used to study memory formation?

Classical (Pavlovian) Conditioning
New conditioned stimulus (CS; in this case the bell) paired with unconditioned stimulus (US; hamburger) that normally elicits desired response (salivation). With training, the dog learns to associate the bell with the food and will salivate in response to the bell alone.

Classical Conditioning at the Neuronal Level (hypothetical)
Unconditioned Synapse is STRONG, elicits Response in motorneuron controlling salivation.
Conditioned Synapse is initially WEAK, elicits NO Response in motorneuron controlling salivation.
With training, Conditioned Stimulus elicits Response in the motorneuron controlling salivation.

How do perceptions get turned into memories? Where in the brain does this happen?

Brain structures involved in learning and memory
Originally identified by postmortem examination of injuries and surgical treatment of epilepsy
Example: H.M. – hit by a bicycle when he was 9. Injuries resulted in untreatable bilateral temporal lobe seizures. Couldn’t lead normal life. At 29, agreed to surgical removal of brain structures where seizures activity originated. This was in 1953. After surgery, seizures gone, but ability to convert short term memories into long term memories also lost.
Slide compares the brain of H.M to that of a normal individual.
Structures removed to treat H.M.’s seizures:
A, amygdala; H, hippocampus; MMN, medial mammillary nucleus; EC, entorhinal cortex; PR, perirhinal cortex; cs, calcarine sulcus

Memory Formation:
Perception takes places in sensory cortex. Perception consolidated by neurons in the hippocampus and other mid- and lower-temporal lobe brain regions. Long term memories stored in cortical association areas (cortical regions neighboring primary sensory cortex).

Hebb’s Postulate: Learning occurs when two connected neurons are active simultaneously in a way that strengthens the synaptic connection. (Donald Hebb, 1940’s) OR “Cells that fire together, wire together.”

What happens to neuronal activity during the process of memory formation?

LTP as a Model for Memory
-- Bliss & Lomo found that synaptic connections in the Hippocampus could be strengthened by high frequency electrical pulses (called tetanic stimulation, e.g. 100 Hz or 100 APs/sec). Stengthening of synapses dubbed Long Term Potentiation (LTP). LTP most often studied in neurons of the hippocampus.
LTP increases the size of EPSPs at stimulated synapse. Short-term increase in EPSP size due to activation of NMDA receptors. Activation of NMDA receptors allows Ca2+ influx which, by activating a number of intracellular messenger pathways, results in long-term changes in synapse function.
Glutamate Receptor Subtypes in Postsynaptic Neuron:
- AMPA channel - requires Glutamate to open
- NMDA channel - requires Glutamate & Depolarization of postsynaptic neuron to open
  (NMDA = N-Methyl D-Aspartate, an agonist)
- NMDA receptor channels are Coincidence Detectors
- Ca²⁺ only enters postsynaptic neuron through channel if the neuron has been recently depolarized…….kicks extracellular Mg²⁺ OUT of the way so Ca²⁺ can flow in.
- Ca²⁺ influx into postsynaptic site causes more prolonged changes

What are the cellular mechanisms mediating long term changes in neuronal activity?

How To Strengthen Synaptic Connections
1. Increase the amount of Neurotransmitter released
   - nitric oxide synthase
2. Increase the numbers of Postsynaptic Receptors
   - AMPA Receptors are transported to membrane after tetanic stimulation
   - Receptors move from inside nerve cells to the surfaces of dendritic spines
   - Blocked by NMDA receptor inhibitors
3. Increase Receptor (=Ligand-gated Channel) Open Time
   - phosphorylation of AMPA receptor
4. Increase the number of Synaptic Contacts
   - Ca²⁺ activation of adenylate cyclase activates protein kinase A and turns on gene transcription causing formation of more synapses, specifically between pre- and post-synaptic neurons
   - LTP produces new Dendritic Spines

Learning: gene overexpression and knock-out experiments (transgenic mice)

Effect of removing NMDA receptors –
- No LTP observed in experiments on hippocampal neurons
- Spatial learning affected. Spatial learning assayed using Morris Water Maze.
  - Morris Water Maze: invisible underwater platform. Mouse has to swim around pool and find platform to get out of the water. Objects positioned along the edge of pool to serve as visual cues to platform location. To access learning:
    a) measure how long it takes the mouse to find the platform (=escape latency) in repeated trials;
    b) measure how much time mouse spends in each quadrant of the pool if platform removed (= transfer test).

>>> Without the NMDA receptor, mice take a much longer time to learn the location of the platform and never attain normal escape latencies.

Effect of adding more NMDA receptors –
- Mice smarter if they have more NMDA receptors.
  True for spatial learning (morris water maze), object recognition, and fear conditioning.