

Summary of Neuroscience Information in

**In Search of Memory:
The Emergence of a New Science of Mind**

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Habituation, sensitization, conditioning, and short-term memory:

Using as his subject the giant sea snail *Aplysia*, whose relatively simple nervous system and large neurons provide convenient neuronal models of these phenomena, Kandel found that habituation (produced by repeated application of a stimulus) to the axon of the neuron that mediates transmission of the sensory impulse results in a progressive weakening of the activity of the presynaptic terminal and reduction of the amount of the neurotransmitter glutamate that is released into the synapse.

Sensitization (produced by repeated application of, say, shocks), and the behavioral changes associated with certain classical conditioning effects, persist for minutes following the stimulus applications and involve increased release of glutamate¹ into the synapse during those minutes. The amount of glutamate released into a synapse by the sensory mediating neuron is modulated by other neurons, called modulatory interneurons. A modulatory interneuron connects to the mediating neuron near the synaptic terminal, where it exerts its modulatory effect by releasing serotonin, which binds to mating receptor sites on the mediating neuron's membrane. The modulatory interneuron's serotonin release fine-tunes the strength of synaptic transmission by regulating the amount of glutamate released into the synapse by the mediating neuron.

The release of serotonin by the modulatory interneuron may be momentary but its effect on the mediating neuron's glutamate releasing activity lasts minutes. The serotonin does this by triggering the release, inside the mediating neuron, of the enzyme adenylyl cyclase, which mediates the production, over that same period of minutes, of thousands of molecules of cyclic AMP. These, in turn, set in motion a chain of chemical reactions within the neuron, starting with the activation of protein kinase A, which acts as a catalyst in the production of the additional glutamate

¹ An amino acid which functions as the major excitatory neurotransmitter in vertebrate and invertebrate nervous systems.

(still over that same period of minutes). Another way the serotonin released by the modulatory interneuron contributes to the production of glutamate is by increasing the availability of the critical ingredient calcium. It does so by slowing the descending stroke of the mediating neuron's action potential, thereby allowing more time for calcium ions to flow into the neuron at the terminal. That, in brief, is the physiological mechanism of short-term memory.

Long-term memory: The conversion of a short-term memory into a long-term memory, including any kind of learning, requires the growth of new presynaptic terminals at the same synapses that participated in the formation of the short-term memory. The increase in the mediating neuron's presynaptic terminals is matched by dendritic outgrowths from the receiving (postsynaptic) neurons. The number of repetitions of the conditioning procedure or of impulses from modulatory interneurons (and the frequency or intensity of the stimuli) determines the amount of new growth and consequently the length of time that the memory will last. If and as the number of presynaptic terminals is permitted to drop again with the passage of time, it doesn't drop all the way back to its former level and neither does the memory, corresponding to the behavioral observation first discovered by Ebbinghaus that an animal can learn a task more readily a second time.

The new growth required for the formation of long-term memory involves protein synthesis (as all growth does), which in turn requires the creation of RNA templates. Therefore, the DNA in the mediating neuron's nucleus needs to become involved. *How this happens:* As the modulatory interneurons release serotonin that binds to the mediating neuron's serotonin receptors at the terminals, more cyclic AMP is produced inside the neuron, with the resulting activation of more protein kinase A where it activates the genes (DNA segments) that get copied to messenger RNA, which in turn provide the templates for the manufacture (in the ribosomes) of the proteins from which the new terminals are built. The protein kinase A activates those genes by phosphorylating a regulatory protein called CREB-1, which is present in the nucleus. This CREB-1 then switches on the genes for new synaptic growth.

The messenger RNA for manufacturing the proteins for new growth is sent to all of the neuron's synaptic terminals, of which there may be thousands. But the messenger RNA is activated to perform protein synthesis only at those terminals that are "marked for growth," namely those terminals that have activated protein kinase A caused by the increased serotonin stimulation from the modulatory interneuron. Although the protein kinase A at the marked terminal induces the manufacture of new proteins based on the template provided by the messenger RNA, this protein manufacturing process quickly fizzles if it is

not maintained. To maintain it (so as to create the long-term memory), a prion-like² version of the protein CPEB is required. The protein CPEB is present in all terminals, but increased serotonin stimulation is needed to convert the CPEB molecule into its prion version. Again, this conversion will occur only at the terminals that were marked for growth by virtue of having received an increased serotonin release from a modulatory interneuron.³

Mammalian long-term memory formation: Most of the above information was obtained in studies of the *Aplysia* preparation, in which the focus was on events relating to the presynaptic neuron. In mammalian brain physiology, the term “long-term potentiation” is applied to neural mechanisms that can serve as laboratory models of long-term memory. The mechanisms for long-term potentiation in the hippocampus, and presumably in other parts of the mammalian brain as well, are analogous to those described above for *Aplysia*, but differ in certain respects.

In the mammalian hippocampus the postsynaptic neuron has AMPA receptors and NMDA receptors. The AMPA receptors respond only to glutamate, which is released into the synapse by the presynaptic terminals. The NMDA receptors act as coincidence detectors when the pre- and postsynaptic cells are stimulated at the same time by sufficiently strong stimuli.

In the mammalian brain, modulatory neurons also often release dopamine, which is also associated with reinforcement and attention. Like serotonin in other neural circuits, dopamine stimulates the activation of cyclic AMP, but in the hippocampus this occurs in the postsynaptic rather than in the presynaptic neuron. Again, the activation of cyclic AMP initiates the sequence of events described earlier for *Aplysia*, culminating in the turning on of effector genes that produce new growth—dendritic in the case of postsynaptic neurons and of new terminals in the case of presynaptic neurons.

In short, long-term potentiation depends on activation of the NMDA receptors. Adequate stimulation results in the depolarization of the postsynaptic neuron and increases the pool of active NMDA receptors through which calcium enters the cell. The calcium activates a whole range of kinases including protein kinase A, which in turn recruit additional AMPA receptors and enhance the postsynaptic cell's

² Prions are proteins with unusual self-perpetuating properties. They come in dominant and recessive forms. It is the dominant form of the CPEB protein that behaves like a prion. The dominant form can turn recessives into dominants by coming into contact with them. The dominant form of CPEB induces the translation of messenger RNA into proteins. Incidentally, other known types of prions cause the Kreuzfeld-Jakob syndrome, mad cow disease, kuru, and are involved in yeast replication.

³ In humans, “High concentrations of serotonin are associated with feelings of well-being, whereas low concentrations are associated with symptoms of depression.”

subsequent responses to glutamate. If the stimulus is strong enough, protein kinase A and other kinases activate the transcription factor CREB leading to the synthesis of the new proteins required for the formation of new synapses, as described above for Aplysia.

Kandel also describes some of the functions of the cerebral cortex in an interesting way. Here is a summary:

The cerebral cortex has a mosaic of millions of terminals of neural columns whose origins are mostly at sensory cells. A column consists of the entire neural pathway from the sensory cells to the cortex, which includes the axons of several neurons and the ganglia that act as relay stations, terminating in the area of the cortex concerned with that particular sensory modality.

In the case of touch, there are separate sensory cells and separate columns for every skin area, and also separate cells for the different kinds of touch—pressure, pain, light brush, temperature, etc. In the case of the auditory system, the columns originate in the cochlea. In the case of the visual system, they originate in the retina, with different ones responding to each color and to contrast. At the visual cortex level, the impulses are further organized into edges, movement, flicker, contours, brightness, and patterns. It is at the cortical level that this data flow is combined with previously stored information to form meaningful features of the environment, like objects or faces. In some cases, single cells fire only when all of the relevant information reaches the visual cortex at the same time, enabling the behavioral phenomenon of recognition.

The hippocampus contains place cells that integrate sensory data for sight, sound, touch, and other inputs, thus providing a registry of information for space orientation—a virtual map. These cells respond only to the joint set of inputs that occurs only when the individual is in that particular location.