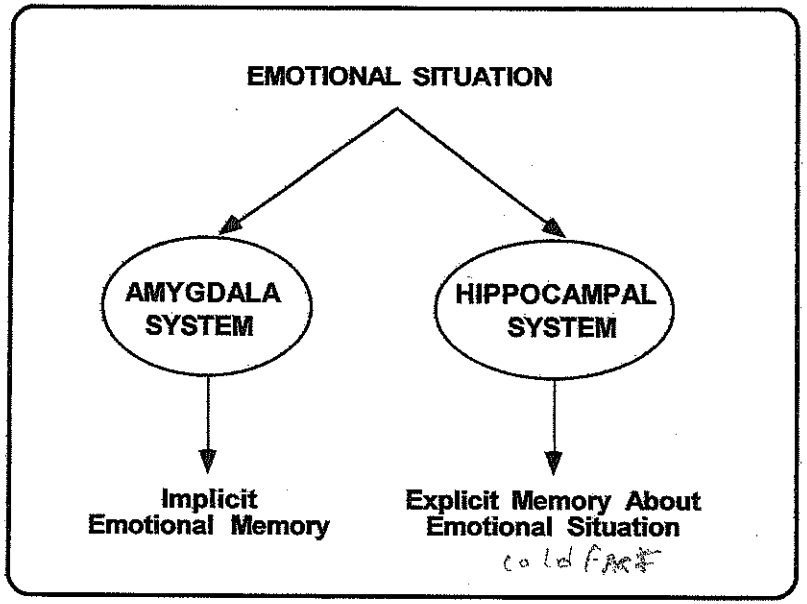

FIGURE 7-5
Brain Systems of Emotional Memory and Memory of Emotion.

It is now common to think of the brain as containing a variety of different memory systems. Conscious, declarative or explicit memory is mediated by the hippocampus and related cortical areas, whereas various unconscious or implicit forms of memory are mediated by different systems. One implicit memory system is an emotional (fear) memory system involving the amygdala and related areas. In traumatic situations, implicit and explicit systems function in parallel. Later, if you are exposed to stimuli that were present during the trauma, both systems will most likely be reactivated. Through the hippocampal system you will remember who you were with and what you were doing during the trauma, and will also remember, as a cold fact, that the situation was awful. Through the amygdala system the stimuli will cause your muscles to tense up, your blood pressure and heart rate to change, and hormones to be released, among other bodily and brain responses. Because these systems are activated by the same stimuli and are functioning at the same time, the two kinds of memories seem to be part of one unified memory function. Only by taking these systems apart, especially through studies of experimental animals but also through important studies of rare human cases, are we able to understand how memory systems are operating in parallel to give rise to independent memory functions.

importantly, they are the tiny spaces formed by the adjoinment of two neurons at the points where those neurons exchange information.

Synapses, you'll recall, involve the contact of an axon terminal of one neuron with the dendrite of another. Electrical impulses flow from the cell body of the sending neuron through its axon to the terminal. The terminal then releases a chemical, called a neurotransmitter, that flows into the synaptic space and binds to receptor molecules (made for the purpose of receiving that particular transmitter substance) located on the dendrite of the receiving neuron. If enough transmitter binds to the receptors on the receiving neuron, it will "fire" electrical impulses down its axon, which will contribute to the firing of the next neuron, and so on.

In 1949, Donald Hebb, the great Canadian psychologist, proposed a way that learning might take place at the level of synapses.[76] Imagine two neurons, X and Y, that are anatomically interconnected but have a weak synaptic relation. That is, when X fires, Y could potentially fire but does not. However, if on some occasion Y is firing when the impulses from X reach Y, something happens between those two cells—a functional bond is created. As a result, the next time X fires, the likelihood that Y will also fire is increased. A connection between two cells that is strengthened in this way is now referred to a Hebbian synapse.[77] Perhaps nothing captures the essence of the Hebbian idea better than the oft-used slogan "cells that fire together wire together." Hebbian plasticity is shown in Figure 7-9.

For many years, Hebb's hypothesis was considered an interesting but ungrounded idea about how learning might take place. It was a hypothesis in need of a factual basis. In the early 1970s it got just the factual boost it needed to become everyone's favorite idea about how learning surely takes place. The boost came from a series of studies of hippocampal synaptic function carried out by Tim Bliss and Terje Lømo.[78]

It was known at the time that electrical stimulation of the pathway that connects the transition areas with the hippocampus elicits neural activity in the hippocampus. The activity can be measured as a neural response called a field potential, which reflects the overall synaptic response of the various hippocampal cells that are fired by the stimulus. Bliss and Lømo showed that the size of the field potential, and thus the magnitude of the synaptic response, could be in-

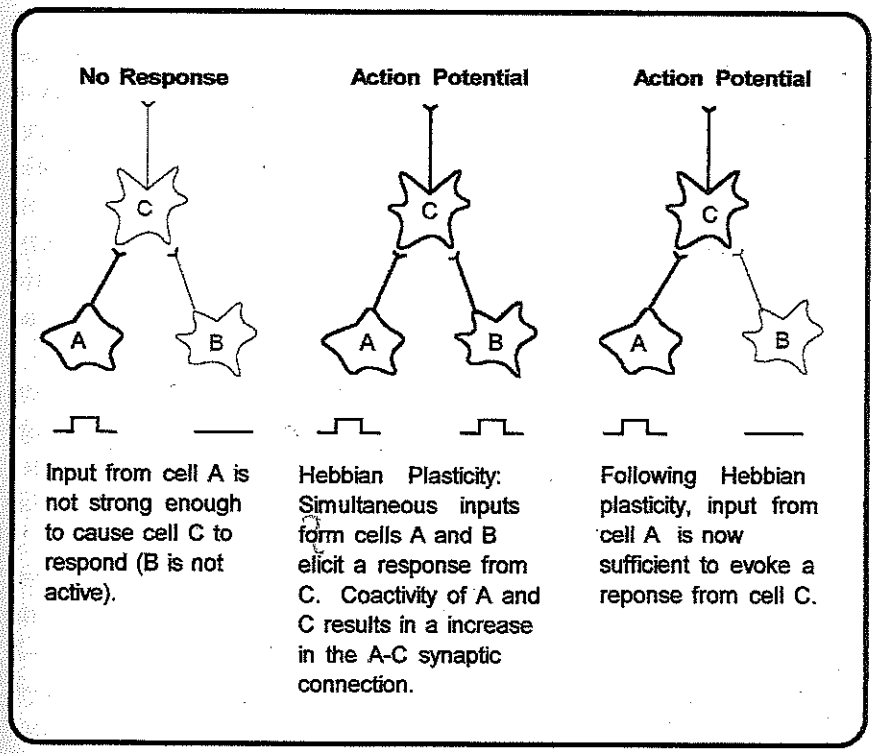

FIGURE 7-9
Hebbian Plasticity.

In 1949, Donald Hebb proposed that learning might involve changes in neural function brought about when two cells are active at the same time. Today, so-called Hebbian plasticity is everyone's favorite idea about how learning and memory work at the level of individual cells in the brain. As the figure shows, Hebbian plasticity occurs between two cells (A and C) if they fire at the same time. In the illustration, A does not normally fire C but B does. So if B causes C to fire and A happens to fire at the same time, something occurs in the link between A and C such that A acquires the ability to fire C on its own. The exact nature of what occurs between A and C has been a mystery. However, recent work in neuroscience has identified a mechanism that makes Hebbian-like plasticity possible. This mechanism is called long-term potentiation (LTP) and involves glutamate and its receptors. LTP and glutamate receptor function are illustrated in figures 7-10 and 7-11, respectively.

creased by a simple manipulation. They zapped the pathway with a brief period of stimulation at a very high rate (one hundred stimulus pulses in a second). The size of the synaptic response elicited by a single pulse test stimulus was bigger after than before the intervening zap. The zap, in other words, increased the strength of the synaptic connection between the transition region and the hippocampus. And most importantly, the changes that were produced appeared to be enduring rather than fleeting. The production of changes in synaptic strength as a result of brief stimulations is usually referred to as "long-term potentiation" (LTP) (see Figure 7-10).

The fact that a brief episode in the life of a neuron can produce long-lasting changes in the behavior of that neuron immediately suggested that LTP might just be the stuff of which memories are made. This notion, considered somewhat fanciful at first, gained credence as later discoveries identified additional properties of LTP.

One of these is the specificity of LTP.[79] A given neuron receives inputs from many others. Neuron Z, for example, receives inputs from X, Y, and others. If induction of LTP by stimulating the X–Z pathway facilitated not only the X–Z synapses but also the Y–Z synapses, then there would not be much specificity to the phenomenon and its usefulness as a model of how memories are created through very specific learning experiences would be limited. But zapping the X–Z pathway changes the synaptic strength of this connection and leaves unaltered the strength of the Y–Z connection. LTP does not change the whole post-synaptic neuron, making it more sensitive to any input; it only changes the particular synapses on the post-synaptic neuron that were involved in the experience. Like learning, LTP is experience-specific.

Another important property of LTP is cooperativity.[80] In order for LTP to occur, a certain number of inputs to a cell have to be stimulated so that enough synapses are activated. If too few are stimulated, LTP does not result. Inputs, in other words, have to cooperate for LTP to occur.

A special version of cooperativity that is particularly important for drawing the connection between LTP and learning is associativity.[81] Again consider neuron Z that receives inputs from X and Y. If the X–Z and the Y–Z pathways are zapped at the same time, test stimuli applied to either pathway give a bigger synaptic response than if either

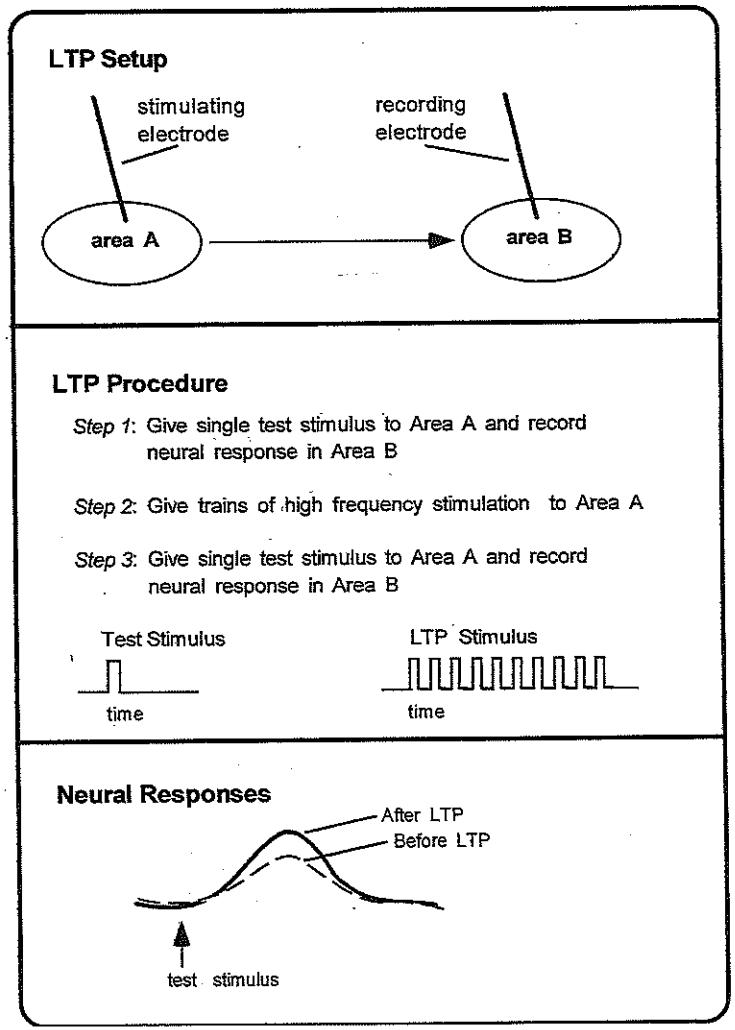

FIGURE 7-10
Long-Term Potentiation (LTP).

LTP involves a strengthening of the functional connection between two brain areas (areas A and B). Because connections between brain areas involve synapses, LTP is believed to involve an enhancement in transmission across synapses. LTP is induced in the laboratory by giving a burst of electrical stimuli to area A. As a result of this treatment, the neural response to a single test stimulus is amplified. Since the same stimulus gives a bigger response after the pathway has been treated with the burst, the burst enhances transmission in the pathway.

pathway had been zapped alone. This is cooperativity between two pathways. The two pathways are now linked or associated.

The associative property of LTP provides a key link to the Hebbian learning principle and suggests a potential means by which associations between events are formed in natural learning experiences. However, the Hebbian basis of learning gained even more weight as discoveries about the molecular basis of LTP and learning in the hippocampus began to roll in.

Mnemonic Glue

An enormous amount of work on the molecular basis of hippocampal LTP suggests that the neurotransmitter glutamate plays a crucial role. In particular, it has been shown that hippocampal LTP requires a special class of glutamate receptor molecules. The finding that hippocampal-dependent memory requires these same receptors is an important link between memory and LTP.

Neurotransmitters released from axon terminals either result in excitation or inhibition when they bind to their receptors on the other side of synapses. Excitatory transmitters make the cell on the other side of the synapse (the postsynaptic cell) more likely to fire, and inhibitory transmitters make it less likely to fire. Glutamate is the major excitatory transmitter in the brain. The primary way that glutamate transmission works is that packets of glutamate released from the axon terminal cross the synapse and bind to the AMPA class of glutamate receptors.[82] When this happens, the postsynaptic cell fires impulses down its axon. Normally, another class of glutamate receptors, NMDA receptors, are cooped up and glutamate reaching them has no effect.[83] But when the postsynaptic cell fires, the NMDA receptors become available to bind glutamate (see Figure 7-11).

The fact that NMDA receptors are only open to the public when the cell that possesses them has just fired allows the NMDA receptor to serve as a means for forming associations between stimuli. The NMDA receptor, in fact, seems to be the way the Hebbian rule (neurons that fire together wire together) is actually realized in the brain.

Imagine that impulses from one input pathway cause the release of glutamate, which binds to the postsynaptic neuron and causes the

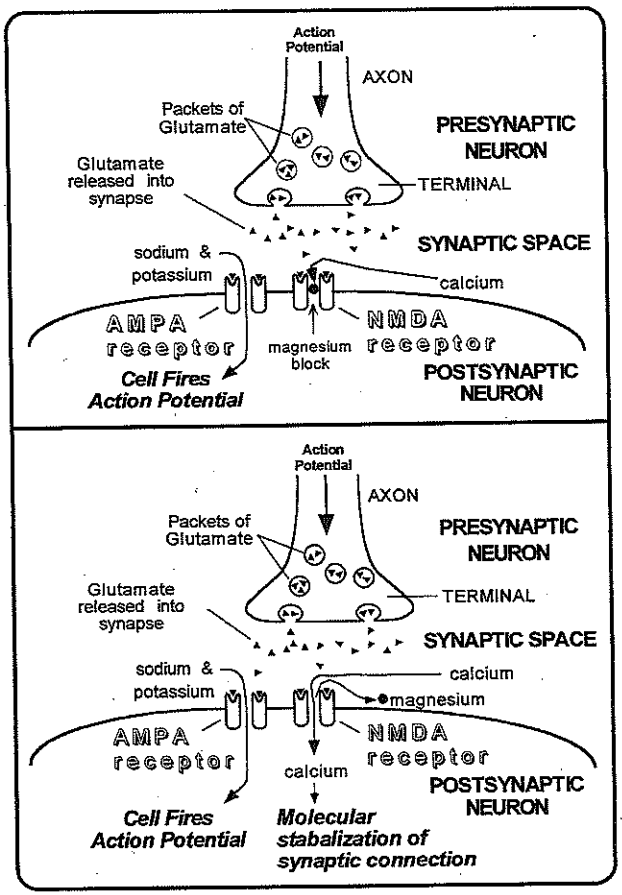

FIGURE 7-11
Glutamate Receptors.

When an action potential comes down the axon to the terminal area, it causes packets of glutamate to be released from the terminal of the presynaptic neuron. The released glutamate diffuses into the synaptic space and binds to AMPA and NMDA receptors on the dendrites of postsynaptic neurons. When glutamate binds to AMPA receptors, sodium and potassium flow into the postsynaptic neuron and help generate an action potential (above). Although NMDA receptors are normally blocked by magnesium, the magnesium block is removed by the action of glutamate at AMPA receptors. Calcium then flows into the cell below, resulting in a host of molecular changes that then strengthen and stabilize the connection between the pre- and postsynaptic neuron. (Illustration based on figure 1 in F.A. Edwards (1992), Potentially right on both sides. *Current Opinion in Neurobiology* 2: 299–401.)

postsynaptic cell to fire. If impulses from a different input pathway cause glutamate to be released at synapses on the same cell, and these impulses arrive when the cell is firing, then the glutamate binds to the briefly open NMDA receptors on this cell (as well as to AMPA receptors). The net result is that an association or connection is formed between the two inputs.

NMDA receptors thus provide a way in which the associative property of LTP, the Hebbian learning principle, might be achieved, and, more generally, a way in which simultaneously occurring events might come to be associated as part of the memory of an experience.[84] It is thus significant that administration of drugs that block the binding of glutamate to NMDA receptors prevents LTP from occurring in hippocampal circuits and also interferes with hippocampal-dependent learning (for example, spatial learning in the water maze).[85] The exact manner in which NMDA receptors contribute to LTP and memory is currently one of the most heavily studied topics in neuroscience. Involved is the influx of calcium into the postsynaptic cell, which sets into motion a whole cascade of additional molecular steps that stabilize the synaptic connections and thus the enhanced synaptic response (see discussion of molecular blindness below).

A number of researchers have attempted to link LTP and memory more directly.[86] Some have shown that induction of LTP in a pathway affects learning processes that depend on that pathway. Others have found that natural learning influences the ease with which LTP occurs. And still others have found that during learning, changes similar to those occurring in LTP take place in pathways that mediate the learning.

While the correspondence between LTP and natural learning is becoming more and more compelling, the case for LTP being the basis of learning remains unproven. No study has actually shown that the changes induced by LTP actually account for learning. Many laboratories are working fast and furiously to convert the correlations between LTP and learning into a causal linkage. Many workers in the field believe that the causal connection is there and that it is just a matter of time until the appropriate way to demonstrate the relation is discovered.

The Molecular Blindness of Memory

Initially, LTP was believed to be mainly a hippocampal phenomenon. This certainly added fuel to the fiery attempts to develop animal models for studying the contribution of the hippocampus to memory. Now, it is known that LTP occurs in many brain regions and in many learning systems. Of special relevance to our concern here is the fact that LTP has been demonstrated in pathways that are involved in fear conditioning,[87] and that blockade of NMDA receptors in the amygdala prevents fear conditioning.[88]

NMDA-dependent synaptic plasticity may be a fairly universal way that the brain learns and stores information at the molecular level. While there are other forms of plasticity that do not depend on NMDA receptors (even in the hippocampus),[89] it nevertheless seems that NMDA-dependent plasticity is one of the major learning devices, and that the brain may in fact have a limited number of learning mechanisms that it uses in a variety of different situations.

If we look more closely at how memories are stabilized, the idea that fairly universal mechanisms are used to form different kinds of memories becomes even more compelling. Studies of species as different as snails, mice, and fruit flies have converged in their conclusions about the kinds of molecular events that convert learning experiences into long-term memories. Protein synthesis, which is controlled by genetic machinery located in the cell nucleus, seems to play a crucial role. If protein synthesis is blocked, long-term memories are not formed.[90] The long-term memory of an experience, in other words, may be maintained by proteins made in cells after learning has taken place. Proteins appear to be important because they make up genes, which control the manufacture of certain chemicals that are required for memory stabilization. Disruption of protein synthesis appears to interfere with the formation of most kinds of long-term memories in most kinds of animals. It also interferes with the long-term maintenance of LTP.[91]

One chemical that appears to be particularly important is cyclic AMP (cAMP). This substance takes over where neurotransmitters leave off. Neurotransmitters allow cells X and Y to communicate with Z; cAMP then helps Z remember that the firing of X and Y at Z oc-

curred at the same time—that X and Y were associated. cAMP is involved in communication between different parts within a cell rather than between cells. The contribution of cAMP to memory was first shown in studies of snails by Eric Kandel, one of the leading researchers of the neurobiology of memory.[92] Kandel also showed that drugs that block the expression of cAMP disrupt hippocampal memory and LTP.[93] New genetic tools have been used to create animals that are incapable of making cAMP. Tim Tully has shown that fruit flies lacking this gene have amnesia for certain long-term memory tasks,[94] and Kandel and Alcino Silva[95] have each shown that genetically engineered mice that are unable to make cAMP have deficient hippocampal LTP and are unable to form new long-term memories in tasks that are dependent on the hippocampus. The mechanisms of memory stabilization appear to be remarkably similar across diverse species and diverse learning procedures. Although there may be more than one such mechanism, the number of them may be relatively small.

The idea that nature might use one or a few molecular mechanisms in many different learning networks in many different kinds of animals has a very important implication. Different forms of learning are not necessarily distinguishable at the level of molecular events, but instead obtain their unique properties by way of the circuits of which they are part. There may well be a universality, or a least a generality, of memory at the molecular level, but there is a multiplicity of memory at the systems level.

Claparede Redux

It should now be clear how it was possible for Claparede's patient to have formed an implicit memory of the pinprick without having an explicit conscious memory of the experience that led to the formation of the implicit memory. Most likely, her temporal lobe memory system was damaged. And, given that the implicit memory she formed involved fear conditioning, it also seems likely that her amygdala was alive and well. Admittedly, these are retrospective guesses since we have no idea where the lesion was in her brain. However, these guesses are based on forty years of research into the neural basis of memory, and even if for some unknown reason they are wrong in her

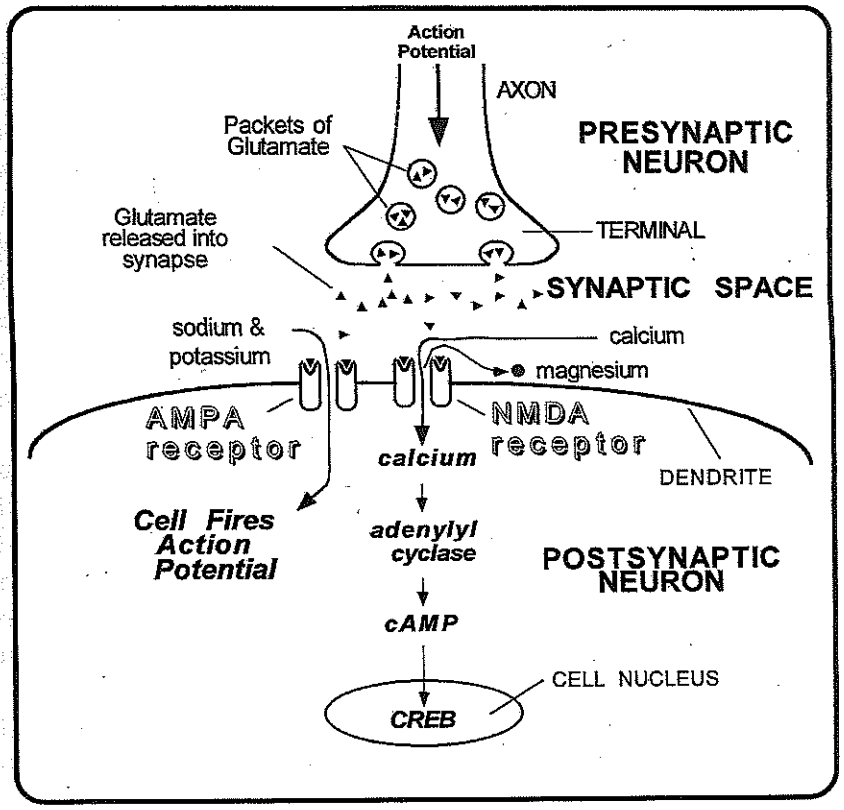

FIGURE 7-12
Molecular Stabilization of Synaptic Plasticity and Memory.

When glutamate binds to the NMDA receptors of a cell that has just fired an action potential, the magnesium block of the NMDA receptor is removed and calcium flows in. Calcium influx, in turn, activates adenylyl cyclase, which leads to an increase in cyclic AMP (cAMP); cAMP elevation then activates cAMP-inducible genes in the cell nucleus by way of the gene transcription factor, CREB. CREB induces proteins, such as synaptic effector proteins, that may contribute to the long-term maintenance of LTP, possibly by stabilizing changes in the structure of the postsynaptic dendrites. (Based on figure 7-12 above and figure 1 in M. Mayford, T. Abel, and E.R. Kandel [1995], Transgenic approaches to cognition. *Current Opinion in Neurobiology* 5:141–48.)

case (something we'll never know), they will surely turn out to often be correct predictions for future cases in which we can verify the locus of brain damage.

The multiplicity of memory at the systems level is what makes a

given kind of memory the kind of memory that it is. Hippocampal circuits, with their massive neocortical interconnections, are well suited for establishing complex memories in which lots of events are bound together in space and time. The purpose of these circuits, according to Eichenbaum, is to provide representational flexibility.[96] No particular response is associated with these kinds of memories—they can be used in many different ways in many different kinds of situations. In contrast, the amygdala is more suited as a triggering device for the execution of survival reactions. Stimulus situations are rigidly coupled to specific kinds of responses through the learning and memory functions of this brain region. It is wired so as to preempt the need for thinking about what to do.

These are clearly oversimplifications of the functions of the hippocampus and amygdala, and even oversimplifications of the contribution of these structures to declarative and emotional memory. However, the simplifications are consistent with the conclusions that have resulted from behavioral studies of these structures and capture at least part of how these structures participate in the forms of memory with which each has come to be associated.

If looked at microscopically, which is to say molecularly, implicit (unconscious) emotional memory and explicit (conscious) memory of emotion may be indistinguishable. But at the level of neural systems and their functions, these are clearly unique operations of the brain. Although we know much more at this point about the separate operation of these two systems, we are beginning to also see how they interact. And these interactions are at the core of what gives emotional qualities to memories of emotions past.