them a remarkable illustration of the power of the evolutionary process to create varied biological types from a single ancestral form. Moreover, their close phylogenetic proximity to humans makes them invaluable subjects for comparative study. Presently, the power of this comparative framework is being realized in the study of primate genomics and cognition. Because the toothcombed primates are the sister clade to the Anthropoidea, comparisons between the two have the unique ability to reveal primate-specific traits that almost certainly originated with the ancestral primate species. The current project to sequence the genome of the gray mouse lemur, *Microcebus murinus* (http://www.genome.gov/10002154), is a preliminary but crucial step towards understanding the changes to the mammalian genome that characterize the primate genome. This comparison offers the singular opportunity for genomicists to recognize those traits that are diagnostic of primates, separate from all other mammals. It is an essential first step towards identifying those genomic traits that are unique to humans. In the same way, ground breaking studies of lemur cognition are showing that lemurs have abilities for list memorization and numerosity discrimination that are similar to those of monkeys. This latter finding, in particular, is revolutionary as it demonstrates that the higher cognitive functions thought to uniquely characterize anthropoid primates were almost certainly present in the earliest primates — mammals that first evolved some 80 million years ago. Without doubt, comparative studies of lemurs and humans will continue to refine and revolutionize our understanding of primate evolution and biology, from genotype to phenotype.

What does the future hold for lemurs? At first glance, the future does not look very good for lemurs in Madagascar, or for the habitats in which they reside. Forests are being destroyed at an alarming rate, and to be a lemur — any lemur — is to be an endangered species. There may

be light at the end of the tunnel, however. Madagascar's current president, Marc Ravalomanana, is as committed to biodiversity preservation as any president in Madagascar's history. In September 2003, he announced to the world his commitment to triple the amount of Madagascar's protected areas within the following five years. Labeled as 'the Durban Vision', the plan is approaching its targeted year for realization. Big strides have been made towards achieving the stated goals. Moreover, in June 2007, the World Heritage Committee has named a significant proportion of Madagascar's eastern rainforests as one of three new UNESCO World Heritage List sites. Thus, we can hope that the global coordination of captive lemur breeding programs, and the protection of Madagascar's remaining natural habitats, will together provide a stable future for these fascinating primates.

Where can I find out more about lemurs and Madagascar?

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The amygdala

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The amygdala is a complex structure involved in a wide range of normal behavioral functions and psychiatric conditions. Not so long ago it was an obscure region of the brain that attracted relatively little scientific interest. Today it is one of the most heavily studied brain areas, and practically a household word. Art critics are explaining the impact of a painting by its direct impact on the amygdala; essential oils are said to alter mood by affecting the amygdala; and there is a website where you can unleash your creativity by clicking your amygdala, and thereby popping your frontal cortex. In this Primer, I will focus on the scientific implications of the research, discussing the anatomical structure, connectivity, cellular properties and behavioral functions of the amygdala.

Anatomical organization
The amygdala was first recognized as a distinct brain region in the early 19th century. The name, derived from the Greek, was meant to denote an almond-like shape structure in the medial temporal lobe. Like most brain regions, the amygdala is not a single mass but is composed of distinct subareas or nuclei (Figure 1). The almond shaped area that gives the amygdala its name was really only one of these nuclei, the basal nucleus, rather than the whole structure.

Nuclei within brain areas like the amygdala are typically distinguished on the basis of histological criteria such as the density, configuration, shape and size of stained cells, the trajectory of fibers, and/or chemical signatures (Figure 1). Recently, more subtle measures, such as microscopic features of processes (axons and dendrites) have also been used. There has been much debate about how the amygdala should be partitioned on the basis of the various criteria, and how the
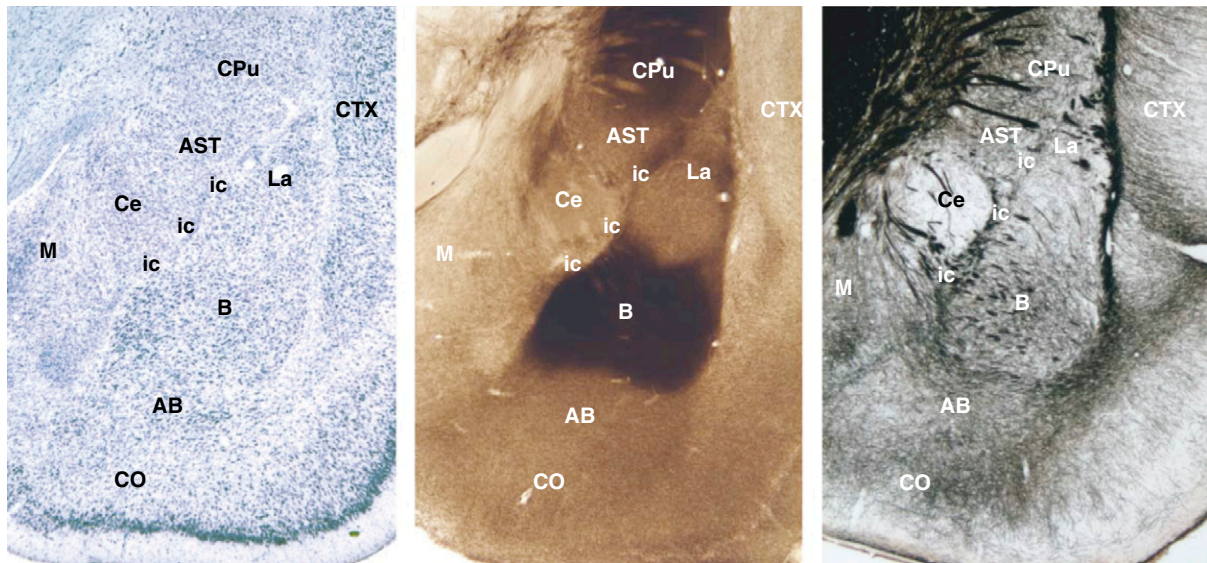
Figure 1. Key areas of the amygdala, as shown in the rat brain.
The same nuclei are present in primates, including humans. Different staining methods show amygdala nuclei from different perspectives. Left panel: Nissl cell body stain. Middle panel: acetylcholinesterase stain. Right panel, silver fiber stain. Abbreviations of amygdala areas: AB, accessory basal; B, basal nucleus; Ce, central nucleus; itc, intercalated cells; La, lateral nucleus; M, medial nucleus; CO, cortical nucleus. Non-amygdala areas: AST, amygdalo-striatal transition area; CPu, caudate putamen; CTX, cortex.

subdivisions relate to other brain regions.

One long-standing idea is the amygdala consists of an evolutionarily primitive division associated with the olfactory system (the cortico-medial region) and an evolutionarily newer division associated with the neocortex (the basolateral region). The cortico-medial region includes the cortical, medial, and central nuclei, while the basolateral region consists of the lateral, basal and accessory basal nuclei. More recently, however, it has been argued that the amygdala is neither a structural nor a functional unit, and instead consists of regions that belong to other regions or systems of the brain.

In this scheme, for example, the lateral and basal amygdala are viewed as nuclear extensions of the cortex — rather than amygdala regions related to the cortex — while the central and medial amygdala are said to be ventral extensions of the striatum. This scheme has merit, but in this Primer I shall focus on the organization and function of the nuclei and subnuclei that are traditionally said to be part of the amygdala since most of the functions of the amygdala are understood in these terms. For

example, the lateral nucleus of what is now called the amygdala will continue to be an important region in fear learning even if the overall concept of the amygdala were eliminated.

It is easy to be confused by the terminology used to describe the amygdala nuclei, as different sets of terms are used. This problem is especially acute with regard to the basolateral region of the amygdala. One popular scheme refers to the basolateral region as consisting of the lateral, basal and accessory basal nuclei. Another scheme uses the terms basolateral and basomedial nuclei to refer to the regions that are named as the basal and accessory basal nuclei in the first scheme. Particularly confusing is the use of the term basolateral to refer to both a specific nucleus (the basal or basolateral nucleus) and to the larger region that includes the lateral, basal and accessory basal nuclei (the basolateral complex).

Each of the nuclei can be further partitioned into subnuclei. For example, the lateral nucleus has three major divisions: dorsal, ventrolateral and medial. Further division is also possible: the dorsal subdivision has a superior and an inferior region. That such fine distinctions are relevant is

illustrated by the fact that, as described below, cells in the superior and inferior parts of the dorsal subarea of the lateral nucleus have been shown to be involved in different aspects of fear memory (the superior part in learning and the inferior part in long-term storage).

Connectivity
In the brain, connections define functions, and each nucleus of the amygdala has unique inputs and outputs. A thorough discussion of all the connections is beyond the scope of this article, so just a few key examples will be given.

The lateral amygdala is generally viewed as the gatekeeper of the amygdala. It is the major site receiving inputs from sensory systems — the visual, auditory, somatosensory (including pain), olfactory, and taste systems all have inputs to this region (olfactory and taste information is also transmitted to other nuclei as well). Other amygdala regions receive inputs from other brain areas, allowing diverse kinds of information to be processed by the amygdala (Figure 2).

The auditory input connections of the lateral amygdala have been studied most thoroughly. Auditory inputs reach the lateral
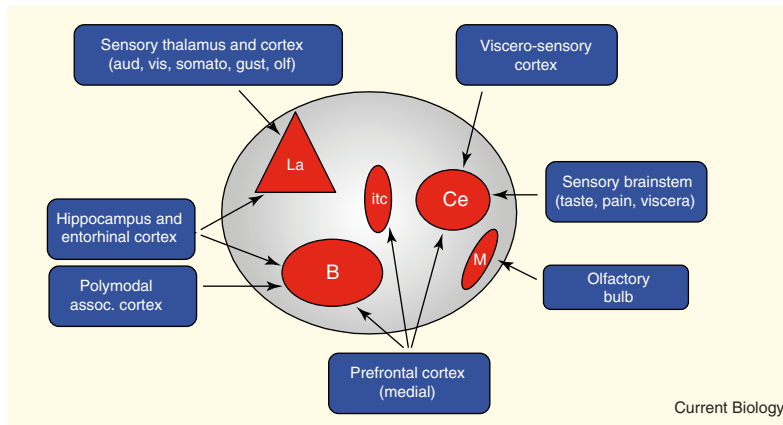
Figure 2. Inputs to some specific amygdala nuclei.

Abbreviations of amygdala areas: B, basal nucleus; Ce, central nucleus; itc, intercalated cells; La, lateral nucleus; M, medial nucleus. Sensory abbreviations: aud, auditory; vis, visual; somato, somatosensory; gust, gustatory (taste).

amygdala from the auditory thalamus and auditory cortex. The thalamic inputs are from extralemniscal areas that weakly encode frequency properties of the auditory stimulus. These provide a rapid but imprecise auditory signal to the amygdala. Cortical inputs from the auditory and other sensory systems arise from the association areas, rather than from the primary cortical regions. These provide the amygdala with a more elaborate representation than could come from the thalamic inputs. However, because additional synaptic connections are involved, transmission is slower.

The sensory inputs to the lateral amygdala terminate most extensively in the dorsal subnucleus. The dorsal subregion then communicates with the ventrolateral and medial areas, which then connect with other amygdala areas.

Just as the lateral nucleus is the sensory gateway into the amygdala, the central nucleus is believed to be an important output region, at least for the expression of innate emotional responses and associated physiological responses (Figure 3). The expression of these responses involves connections from the medial subdivision of the central nucleus to brainstem areas that control specific behaviors and physiological responses.

In order for sensory information received by the lateral amygdala to influence behavior the information must be routed through intramygdala connections
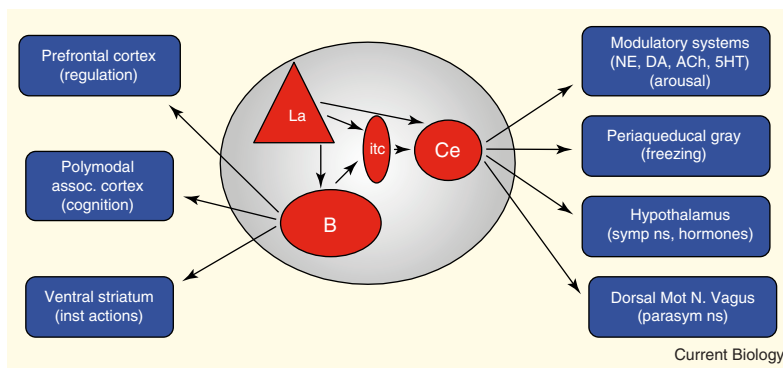
(Figures 3 and 4). There are some direct connections from the lateral nucleus to the central nucleus but these are relatively sparse. The main channels of communication between the lateral and the central nucleus are thus thought to involve connections from the medial part of the lateral nucleus to other amygdala nuclei that then connect with the central nucleus. For example, the lateral nucleus projects to the basal nucleus which projects to the central nucleus. In addition, both the lateral and basal nuclei project to the intercalated cells which then connect with the central nucleus.

Another important set of output connections of the amygdala arise from the basal nucleus (Figure 3). In addition to connecting with the central nucleus, it also connects with striatal areas involved in the control of instrumental behaviors. Thus, while the output connections of central amydgala to the brainstem are involved in controlling emotional reactions, like freezing in the presence of a predator, connections from the basal amygdala to the striatum are involved in controlling actions, like running to safety.

Cellular mechanisms

The amygdala is a relatively 'silent' area of the brain. It contains a strong inhibitory network that keeps spontaneous cellular activity low and that prevents cells from firing action potentials to irrelevant stimuli. Novel stimuli elicit responses, but these rapidly habituate if the stimulus is repeated. As I shall discuss later, this inhibition can be overcome when a novel stimulus is presented in association with a significant event. In this case, rather than dissipating, the responses are potentiated.

Most of the inputs to the amygdala involve excitatory pathways that use glutamate as a transmitter. These inputs form synaptic connections on the dendrites of excitatory principal neurons that transmit signals to other regions or subregions of the amygdala or to extrinsic regions. Principal neurons are thus also called projection neurons because they project out. However, axons

Figure 3. Outputs of some specific amygdala nuclei.

Abbreviations of amygdala areas: B, basal nucleus; Ce, central nucleus; itc, intercalated cells; La, lateral nucleus. Modulatory arousal system abbreviations: NE, norepinephrine; DA, dopamine; ACh, acetylcholine; 5HT, serotonin). Other abbreviations: parasym ns, parasympathetic nervous system; symp ns, sympathetic nervous system.

of principal neurons also give rise to local connections to inhibitory interneurons, which then provide feedback inhibition to the principal neurons. In addition to terminating on projection neurons, some of the excitatory inputs to the amygdala terminate on local inhibitory interneurons which, in turn, connect with principal neurons, giving rise to feedforward inhibition. These connections allow stimulus-driven inhibition to build up and account for the decrease in responses when stimuli are repeated.

The scheme of inputs and connections just described applies to the neurons of the basolateral region (the lateral and basal nuclei) more than to neurons within the corticomedial group. For example, the projection neurons in the central nucleus tend to be inhibitory in nature. Thus, excitation of these leads to inhibition of output activity, while their inhibition gives rise to increased output activity. How, then, might these inhibitory outputs lead to the expression of emotional responses? One possibility is that activation of the inhibitory intercalated cells by the lateral and basal amygdala may inhibit the central amygdala output cells, thus disinhibiting their targets and leading to the expression of responses.

The flow of information through amygdala circuits is modulated by a variety of neurotransmitter systems. Thus, norepinephrine, dopamine, serotonin and acetylcholine released in the amygdala influence how excitatory and inhibitory neurons interact. Importantly, output connections of the central nucleus terminate on these cells as well as in response-control regions. Thus, activation of the amygdala leads to the release of these neurotransmitters throughout the forebrain, including within the amygdala.

Receptors for the various neuromodulators are differentially distributed in the various amygdala nuclei. Also differentially distributed are receptors for various hormones, including glucocorticoid and estrogen hormones. Numerous peptide receptors are also present in the
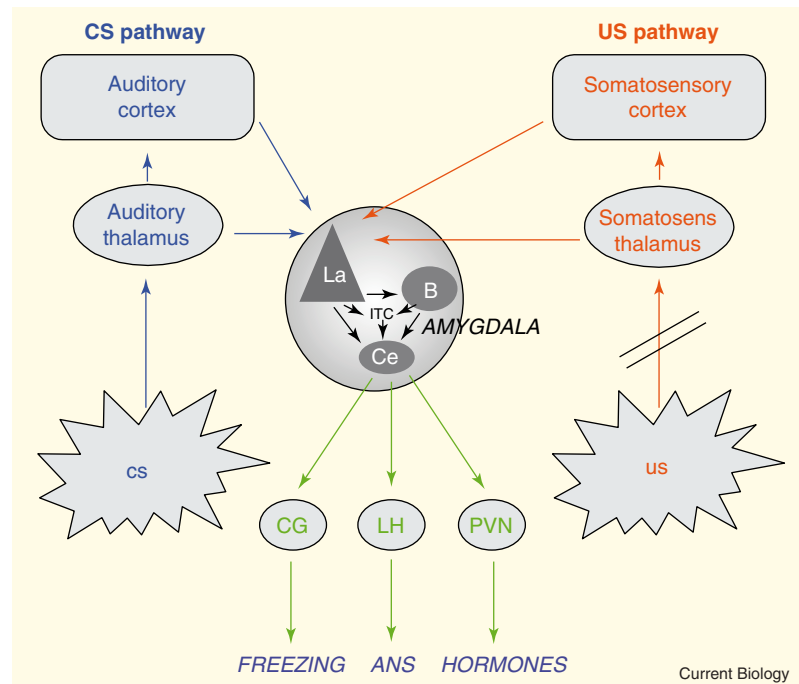

Figure 4. Auditory fear conditioning pathways.

The auditory conditioned stimulus (CS) and somatosensory (pain) unconditioned stimulus (US) converge in the lateral amygdala (La). The La receives inputs from each system via both thalamic and cortical inputs. CS–US convergence induces synaptic plasticity in La such that after conditioning the CS flows through the La to activate the central amygdala (CE) via intraamygdala connections. Outputs of the Ce control the expression of emotional reactions involving behavioral (freezing) and autonomic and endocrine responses that are components of the fear reaction. Other abbreviations: B, basal amygdala; CG, central gray; LH, lateral hypothalamus; ITC, intercalated cells of the amygdala; PVN, paraventricular nucleus of the hypothalamus.

amygdala, including receptors for opioid peptides, oxytocin, vasopressin, corticotropin releasing factor and neuropeptide Y, to name a few.

An important challenge for the future is to understand how these various chemical systems interact to set the overall tone of the amydgala. For example, it is known that release of serotonin inhibits cellular activity in the lateral nucleus. However, this is achieved by serotonin exciting GABAergic cells that inhibit projection neurons. Furthermore, the glucocorticoid hormone corticosterone is necessary for these effects of serotonin. Many possible interactions are likely to exist amongst the various chemical systems in the amygdala.

Behavioral functions
In the late 1930s, researchers observed that damage to the temporal lobe resulted in profound changes in fear reactivity, feeding

and sexual behavior. Around mid-century, it was determined that damage to the amygdala accounted for these changes in emotional processing. Numerous studies subsequently attempted to understand the role of the amygdala in emotional functions. The result was a large and confusing body of knowledge about the functions of the amygdala, because much of the research ignored the nuclear and subnuclear organization of the amygdala, which was not fully appreciated, and partly because the functions measured by behavioral tasks were not well understood.

Fear
Fear has been the function most associated with the amygdala. Early studies following up on the Kluver-Bucy syndrome used fear-motivated avoidance conditioning tasks. These measure fear in terms of how well an animal
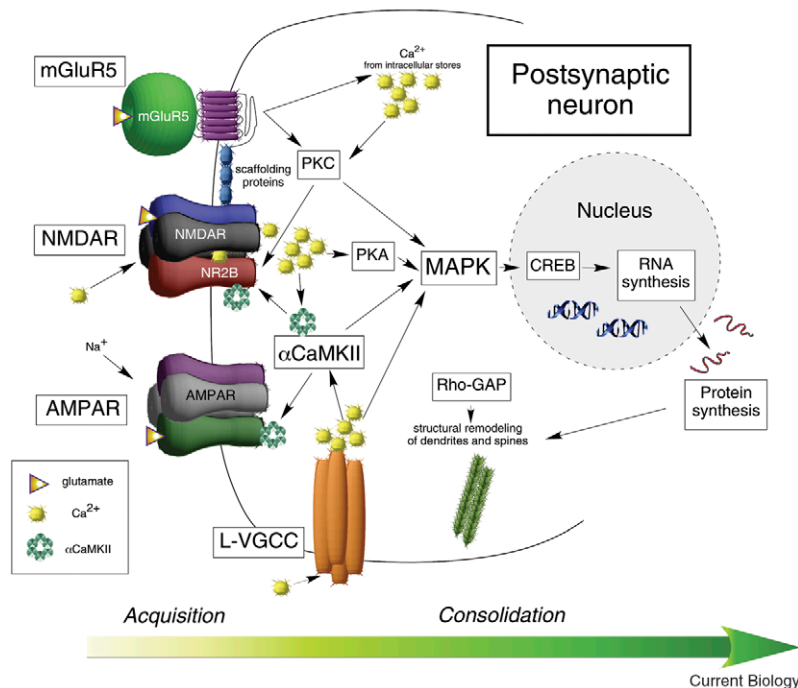
Figure 5. Signal transduction pathways in the lateral amygdala involved in fear learning and memory.

Transmission of an auditory conditioned stimulus to presynaptic terminals in the lateral amygdala leads to release of glutamate. Glutamate binds to postsynaptic receptors (AMPAR, NMDAR, mGluR5). If a strong unconditioned stimulus activates the cell at the same time (not shown), calcium enters the postsynaptic cell through NMDARs and L-type voltage gated calcium channels (L-VGCC). The combined calcium signal leads to the phosphorylation of MAP kinase (MAPK). Other kinases are also activated, including PKC, PKA and CaMKII. MAPK translocates to the cell nucleus, where transcription factors such as CREB are activated, leading to the synthesis of RNA and protein. The new proteins have a variety of roles. For example, new receptors become available for insertion into the cell membrane to bind glutamate. In addition, new proteins may contribute to structural changes in synaptic connectivity by altering actin and other cytoskeletal functions mediated in part by Rho-GAP. These and other postsynaptic effects contribute to the stabilization or consolidation of long-term memory. Nitric oxide released into the extracellular space contributes to presynaptic aspects of plasticity (not shown). Similar (though not identical) molecular changes engaged during retrieval contribute to the reconsolidation of fear memory.

learns to avoid shock. However, avoidance is a two stage process in which Pavlovian conditioning establishes fear responses to stimuli that predict the occurrence of the shock, and then new behaviors that allow escape from or avoidance of the shock, and thus that reduce the fear elicited by the stimuli, are learned. In the 1980s, researchers began to use tasks that isolated the Pavlovian from the instrumental components of the task to study the brain mechanisms of fear.

In Pavlovian fear conditioning, a neutral conditioned stimulus (CS) that is paired with a painful shock unconditioned stimulus (US) comes to elicit fear responses such as freezing behavior and related changes in body physiology. Studies in rodents have mapped the inputs to and outputs of amygdala nuclei and subnuclei that mediate fear conditioning. In particular, it is widely accepted that convergence of the CS and US leads to synaptic plasticity in the lateral amygdala. When the CS then occurs alone later, it flows through these potentiated synapses to the other amygdala targets and ultimately to the medial part of the central nucleus, outputs of which control conditioned fear responses (Figure 4).

Single unit recording studies have shown that cells in the dorsal subnucleus of the lateral amygdala have the kinds of properties needed to be involved in fear conditioning. These cells receive convergent CS inputs from the auditory thalamus and cortex. The same cells also receive inputs about the footshock US. After the CS and US are paired, the cellular response to the CS is greatly enhanced (more action potentials are elicited). Initially, cells in the superior part of the dorsal lateral amygdala rapidly undergo plasticity. Over several trials, they reset their responses back to the start point. By this time, however, cells in the inferior dorsal lateral nucleus have slowly changed and these then maintain the plasticity over time. Even when the animal has fully extinguished the fear and is no longer responding behaviorally, these inferior cells retain the memory. Such cells may be responsible for the well known phenomenon that fear in people and animals can be successfully eliminated by treatment but then brought back by stress.

Much has been learned about the cellular and molecular mechanisms within lateral amygdala cells that underlie the plastic changes in fear conditioning. This has been achieved in part by conducting studies of long-term potentiation (LTP), a cellular model of synaptic plasticity, in the lateral amygdala in parallel with studies of fear conditioning. Because the input synapses in the amygdala involved in fear conditioning are known, it is possible to induce LTP in pathways that play an established role in this form of learning. Because *in vitro* studies of LTP allow detailed analysis of cellular and molecular mechanisms, these make possible an understanding of the molecular basis of amygdala plasticity. The molecules involved can then be tested *in vivo* by infusion in the amygdala in conjunction with studies of fear conditioning. Such studies have found striking parallels between LTP and fear conditioning.

The overall molecular mechanisms involved in fear conditioning are summarized in Figure 5. In brief, during conditioning, glutamate released from sensory fibers in the lateral amygdala binds to

excitatory amino acid receptors (in particular, AMPA and NMDA receptors). AMPA binding leads to depolarizations that come to be inhibited with repetition. Binding to NMDA receptors is inconsequential because the level of depolarization produced by AMPA binding is insufficient to remove the magnesium block on NMDA receptors. If the cell is strongly depolarized by another input (such as an electric shock) around the same time, however, the magnesium block is removed and calcium is allowed to enter the cell.

This calcium is sufficient to maintain temporary plasticity, and thus short-term memory. The enduring plasticity that underlies long-term memory requires additional calcium which enters through voltage-gated calcium channels that are also opened by the shock stimulus. The combined level of calcium activates protein kinases (such as MAP kinase) which then translocate to the cell nucleus and trigger gene expression and protein synthesis. The synthesized proteins are then trafficked back to the plastic synapses and stabilize the connection with the presynaptic input. Particularly important may be AMPA receptor protein synthesis since AMPA trafficking has been implicated in the memory of fear conditioning.

The stabilization of memory via protein synthesis after learning is called consolidation. However, protein synthesis dependent memory stabilization also occurs in the lateral amygdala after fear memory is retrieved. During so-called reconsolidation molecular mechanisms similar to those engaged during consolidation come into play. Because memory can be disrupted after retrieval, efforts are underway to treat intrusive memories in posttraumatic stress disorder by blocking reconsolidation.

Other functions

Although fear is the emotion best understood in terms of brain mechanisms, the amygdala has also been implicated in a variety of other emotional functions. A relatively large body of research has focused on the role of the

Figure 6. Conditioned fear in the human brain.

Above: structural magnetic resonance image (MRI) of the human brain. The area containing the amygdala is within the box. (A) Fear conditioning. Functional MRI (fMRI) showing amygdala activation by a conditioned stimulus (CS) after pairing with an unconditioned stimulus (US). (B) Instructed fear. fMRI showing amygdala activation by a CS that was not directly paired with a US but instead the subjects were instructed US. (C) Observational fear learning. fMRI showing amygdala activation by a CS after the subjects observed someone else undergoing fear conditioning where the CS was paired with a US. (Images provided by Elizabeth Phelps.)
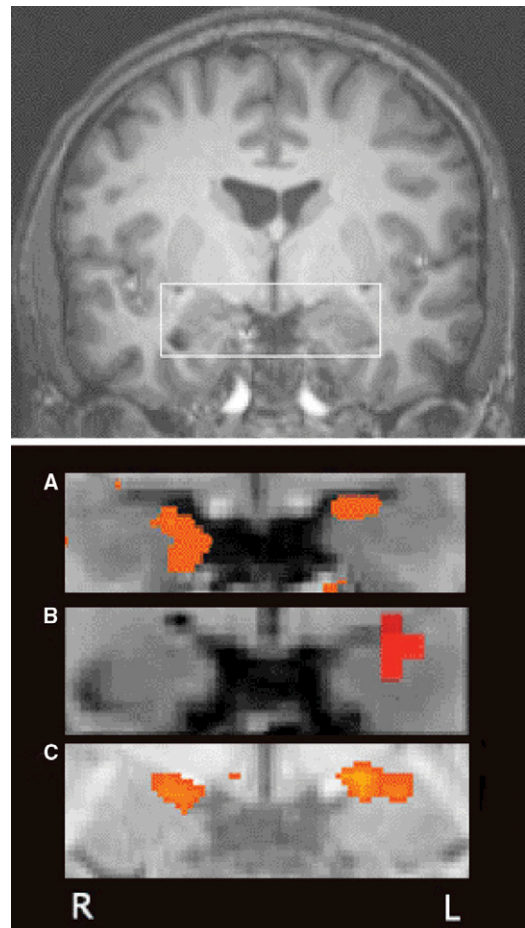
amygdala in processing of rewards and the use of rewards to motivate and reinforce behavior. As with aversive conditioning, the lateral, basal, and central amygdala have been implicated in different aspects of reward learning and motivation, as well as drug addiction. The amygdala has also been implicated in emotional states associated with aggressive, maternal, sexual, and ingestive (eating and drinking) behaviors. Less is known about the detailed circuitry involved in these emotional states than is known about fear.

In addition to its role in emotion, the amygdala is also involved in the regulation or modulation of a variety of cognitive functions, such as attention, perception and explicit memory. It is generally thought that these cognitive functions are modulated by the amygdala's processing of the emotional significance of external stimuli. Outputs of the amygdala then lead to the release of hormones and/or

neuromodulators in the brain that then alter cognitive processing in cortical areas. For example, explicit memories about emotional situations are enhanced via amygdala outputs that ultimately affect the hippocampus: glucocorticoid hormone released into the blood stream via amygdala activity travels to the brain and then binds to neurons in the basal amygdala; the latter then connects to the hippocampus to enhance explicit memory.

The human amygdala

Over the past decade, interest in the human amygdala has grown considerably, spurred on by the progress in animal studies and by the development of functional imaging techniques. As in the animal brain, damage to the human amygdala interferes with fear conditioning and functional activity changes in the human amygdala in response to fear conditioning. Further, exposure to emotional faces potently activates the human

amygdala. Both conditioned stimuli and emotional faces produce strong amygdala activation when presented unconsciously, emphasizing the importance of the amygdala as an implicit information processor and its role in unconscious memory. Findings regarding the human amygdala are mainly at the level of the whole region rather than nuclei (Figure 6).

Structural and/or functional changes in the amygdala are associated with a wide variety of psychiatric conditions in humans. These include various anxiety disorders (PTSD, phobia and panic), depression, schizophrenia, and autism, to name a few. This does not mean that amygdala causes these disorders. It simply means that in people who have these disorders alterations occur in the amygdala. Because each of these disorders involves fear and anxiety to some extent, the involvement of the amygdala in some of these disorders may be related to the increased anxiety in these patients.

Conclusion

Not so long ago the amygdala was a neglected area of the brain, attracting much less scientific interest than other regions such as the neocortex, hippocampus, or cerebellum. In recent years, though, scientists have turned their attention to the amygdala, revealing its structural organization, physiological mechanisms, and functions, both in animals and humans. Recent studies have also implicated the amygdala in a variety of psychiatric disorders. In spite of this progress much remains unknown, especially about behavioral functions. However, the broad base of knowledge obtained in recent years provides a firm foundation upon which to build on in future work.

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The blastoporal organiser of a sea anemone

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In 1924 Hilde Mangold and Hans Spemann transplanted the dorsal blastopore lip of an amphibian embryo to a host embryo's ventral side. This experiment revealed that the dorsal blastopore lip can act as an 'organiser' to induce a secondary body axis [1]. The organiser experiment has fueled research in vertebrate developmental biology until today [2,3]. While an organiser might have been present in the chordate ancestor [4], it is not clear how widespread the principle of the blastoporal organiser is and what its evolutionary roots are. Here, we examined the organising activity of different parts of embryos of the sea anemone *Nematostella vectensis*, a representative of the basal animal phylum Cnidaria, which has retained many ancestral traits. We show by transplantation of small parts of the gastrula embryo that the blastopore lip — but not tissue from other parts of the embryo — is able to act as an organiser and to induce the formation of a secondary body axis with high efficiency.

We analysed the inductive capacity of different parts of the gastrula embryo of *Nematostella* by transplanting a vitally labeled small piece of the blastopore lip, the pre-endodermal plate or the aboral blastocoel roof blastoderm to the blastocoel roof of unlabeled host gastrula embryos. The size of the transplants corresponded to the equivalent of 10–20% of the circumference of the blastopore lip (about 20–30 μm diameter). We found that