

## THE NEUROBIOLOGY OF EMOTION

### Neural systems, the amygdala, and fear

*Is emotion a magic product, or is it a physiologic process which depends on an anatomic mechanism?*  
-J.W. Papez, 1937

Throughout the day, we experience a variety of *emotions*. For the most part, these emotions are transient in nature. However, when these emotions become intense or are unremitting they can have very dramatic effects on our behavior. The depressive syndrome is an example of a state that is characterized by unrelenting sadness accompanied by a deficit in one's ability to derive pleasure from positive situations. William James proposed one of the first theories of emotion that attempted to relate experience of emotion to physiological functions. He tried to describe the human experience of emotion:

“Conceive of yourself, if possible, suddenly stripped of all the emotion with which your world now inspires you, and try to imagine as it exists, purely by itself, without your favorable or unfavorable, hopeful or apprehensive comment. It will be almost impossible for you to realize such a condition of negativity and deadness. No one portion of the universe would then have importance beyond another; and the whole collection of its things and series of its events would be without significance, character, expression, perspective. Whatever of value, interest, or meaning our respective worlds may appear imbued with are thus pure gifts of the spectator's mind.”

The primary emotions are **anger, fear, pleasure, sadness, and disgust**. Emotions can be conceptualized in terms of their *functional or adaptive (help us survive) significance*. Negative emotions such as anger and fear may promote avoidance or defensive behavior whereas the positive emotion of pleasure may facilitate ingestive, exploratory, sexual, or novel-seeking behavior. Thus, emotions and feelings may serve to achieve homeostasis or to facilitate adaptive behavior and equilibrium.

Emotions can be elicited by external stimuli. However, the stimuli must have relevance or motivational significance in order to guide appropriate, adaptive behavior. Is the stimulus good, bad, or neutral? Does it evoke anger, fear, or pleasure? What are its previous associations, what does it predict, what is an appropriate reaction? This general concept of **stimulus relevance** is important in guiding behavior in many spheres: consummatory, sexual, reproductive, defensive, approach/avoidance and fight/flight.

We typically view emotions as primitive and instinctive responses that are not associated with complex intellectual or cognitive functions. Certainly, key stimulus elements in the environment can trigger instinctive emotional responses (imagine confronting a large, threatening animal). However, cognitive-emotional interactions are extremely important in the elicitation of everyday emotions. In primates and humans, the brain has a striking capacity to learn and remember the emotional significance of diverse stimuli and events. Furthermore, our cognitive capacity allows us to assign **emotional valence** to stimuli, and to change the value that was previously assigned to a stimulus. For example, a child may be initially fearful of dogs, but through positive experiences the child may eventually enjoy and approach them. As another example,

imagine the emotions associated with a new relationship. Initially, seeing the person may evoke positive emotions of desire and happiness. However, after a nasty breakup, the same person could easily elicit emotions of anxiety, tension, and anger. This second example illustrates two important points. First, the sensory or perceptual analysis of the person is the same (i.e., this is Bob). The physical expression of emotion may also be the same (i.e., racing heart, flushed sensations, increased breathing rate). Second, the emotional reaction to the stimuli depends on cognitive processing. In other words, the evaluation of the stimulus (the person) in conjunction with past experiences determines the feelings or the conscious experience of joy or anger. Studies of brain functions reveal that neural pathways exist for these important cognitive-emotional interactions.

### Brain systems in emotion

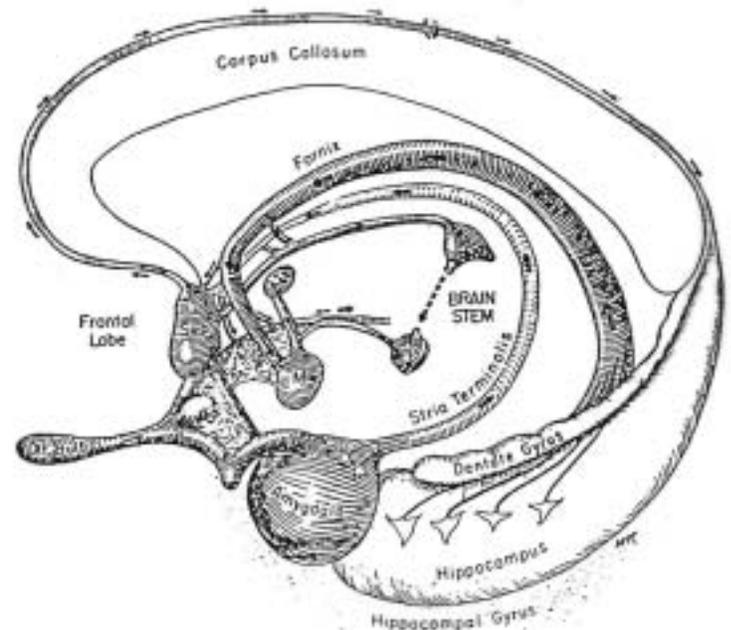
The neural basis of emotion has been studied for over a century. Early explorations suggested that specific brain regions are involved in the expression of emotional behavior. Studies in the '30s and '40s showed that electrodes placed in the hypothalamus elicited widespread activation of the sympathetic nervous system as well as coordinated expression of defensive reactions or presumed feelings of pleasure.

In our examination of emotions, emphasis will be placed on the role played by the limbic system and the monoamine systems.

### Limbic system

As you know from your earlier lectures, the limbic system (Fig. 1) was originally proposed to consist of interconnected subcortical structures with pathways to the hypothalamus. The limbic system was proposed to modulate the emotional quality of stimuli and support autonomic effector mechanisms associated with emotional states. A key limbic structure that has a critical role in **emotional** expression is the **amygdala**. The amygdala has an important role in evaluating the emotional valence of stimuli. Support for this view arises from extensive work done with lesions of the amygdala. For example, animals with amygdala lesions have difficulty learning associations between environmental stimuli and emotional states. They may fail to learn that a stimulus predicts reward or danger, they may fall in social rank, or show decreased affiliative behavior. Damage to other limbic structures can also produce changes in emotional behavior.

Fig. 1. Schematic drawing of limbic structures and their connections.



It is important to note that an interaction exists between cortical brain regions and the limbic system. There are massive connections between cortical regions, particularly from the frontal and temporal lobes, to subcortical limbic structures (Fig. 2). The implication of these connections is that complex sensory information processing occurring in the cortex can directly influence the limbic system. Conversely, limbic processing can strongly influence higher-level cognitive integration occurring in the cortex. Disconnection in the transmission of information between the cortical and subcortical limbic structures can have dire consequences. For example, patients with frontal lobe lesions show inappropriate emotional and social behavior in the absence of intellectual deficits. These patients might cry or laugh inappropriately, urinate in public, or use profanity.

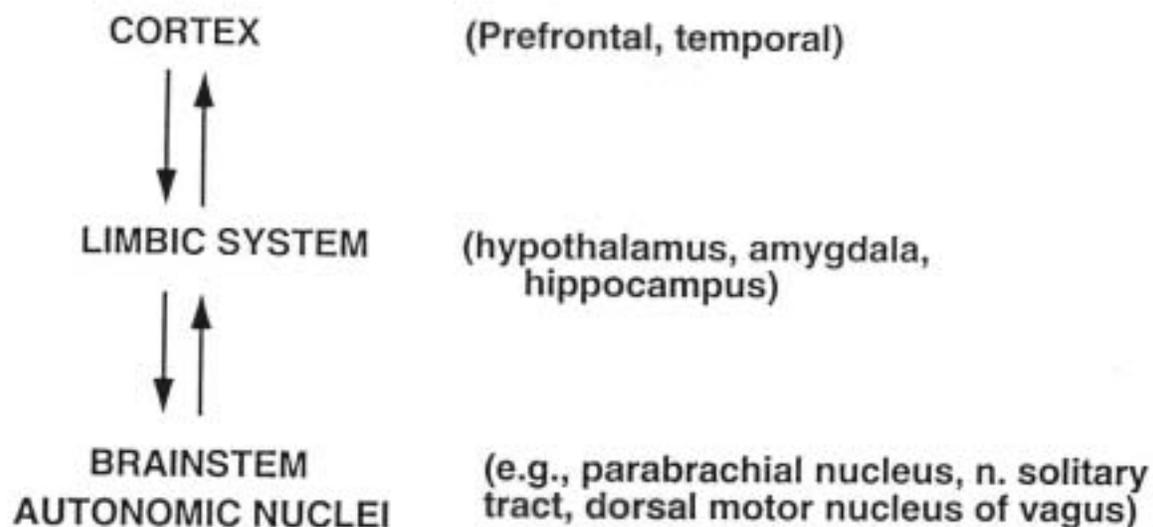


Fig. 2. Schematic diagram emphasizing the interactions between structures in the limbic system and cortical regions of the brain. Reciprocal connections exist between the prefrontal and temporal cortical areas, and both regions project extensively to different limbic structures. Therefore, the cortex has a strong influence on mechanisms governing emotional and autonomic responses. Limbic and brain stem regions may also influence the cortex via pathways through the thalamus (not shown), and via direct connections from the amygdala and hippocampus.

### **Monoaminergic systems (serotonin, norepinephrine, dopamine)**

The neural circuits and brain structures involved in emotions are modulated by a myriad of chemical neurotransmitters. The ascending monoamine systems have received considerable attention over the past several decades. These include the **serotonin, norepinephrine, and dopamine** systems. Prior to the discovery of neurotransmitters, researchers believed that a major ascending neural system was responsible for arousal of forebrain (epithalamus, thalamus, subthalamus) and telencephalon (cerebral cortex, basal ganglia and associated structures like the nucleus basalis of Meynert and the nucleus accumbens). This neural system used to be called the **ascending reticular activating system**, before the monoamines were characterized. It is believed that a balance among these systems (as well as other neurotransmitters) is necessary for normal emotional states and arousal. Over the last three decades, the neurochemical basis of this ascending system was described and receptors identified.

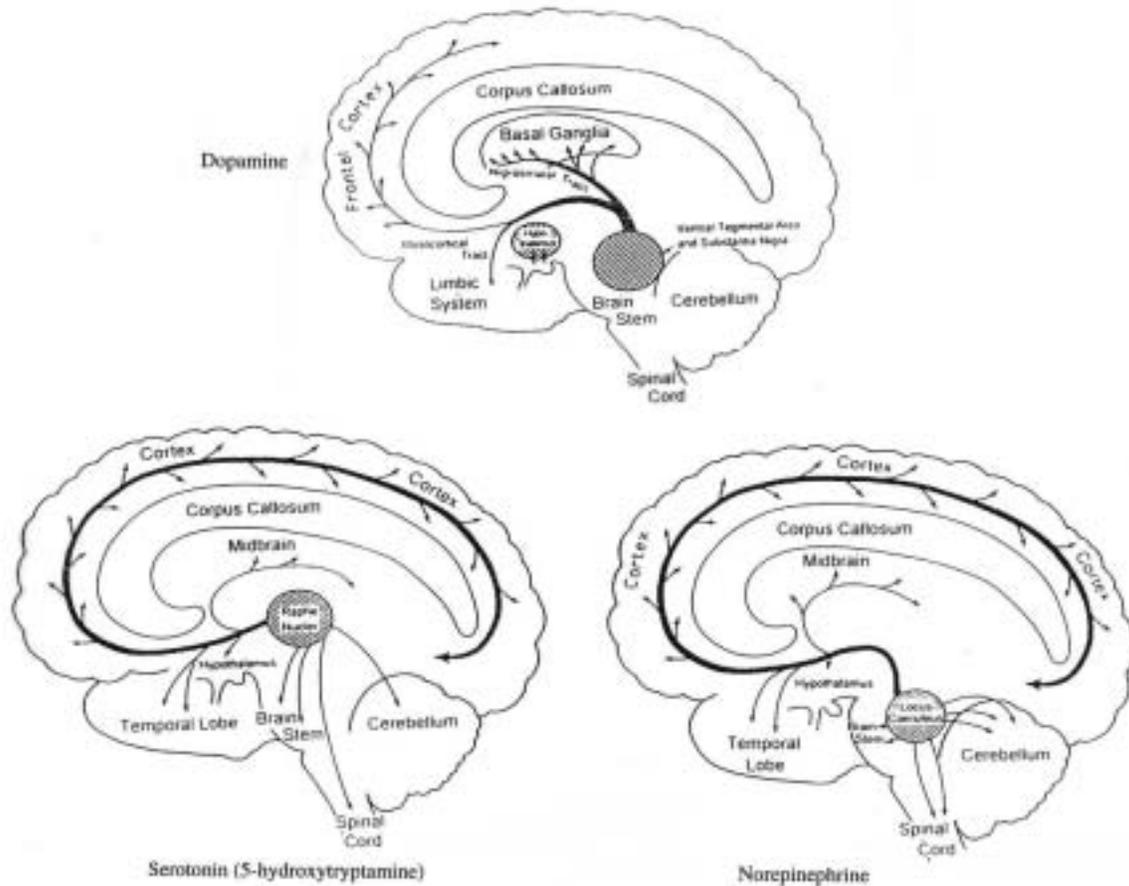


Fig. 3. The brain stem dopamine (DA) system (top), serotonin system (bottom left) and norepinephrine system (bottom right). Cell bodies of the **dopamine** system are located in the ventral tegmental area and substantia nigra and project to regions such as the basal ganglia, limbic system, and **frontal and temporal cortex**. The **raphe nucleus** contains **serotonin** cell bodies that project to **all** areas of the cerebral cortex, temporal lobe structures, (amygdala, hippocampus, hypothalamus), the midbrain as well as the cerebellum and sites in brain stem and spinal cord. **Locus coeruleus** cell bodies contain **norepinephrine** and innervate **all** areas of cortex, cerebellum and spinal cord.

### The Neural Substrates of Fear and Anxiety

This class of emotion is elicited by threatening situations and it functions as an internal signal to alert the organism to potential danger. In response to fear, individuals engage in defensive or protective acts that serve to promote survival. These behaviors include **fleeing** or **withdrawing** from a situation, freezing to remain inconspicuous, or fighting.

#### **Nature vs. Nurture**

**Fear behavior is essential for survival and much of its development appears to be innate.** In humans, behavioral responses associated with fear are evident within the first months of life. However, it is not until sometime later that infants display fear reactions that are selectively elicited by unfamiliar situations. For example, most infants go through a period known as stranger anxiety around one year of age. At this time, infants that once smiled indiscriminately now begin to act extremely wary in the presence of strangers.

Developmental studies further indicate that some infants differ in their tendency to exhibit fear. For example, some infants become extremely agitated when confronted with unfamiliar stimuli such as a stranger. These infants display high levels of crying and motor activity, e.g., flexing and extending the arms and legs. In childhood, they often appear behaviorally inhibited. In an unfamiliar context, these children are characterized as very shy, timid, and cautious. In addition, inhibited children have larger increases in heart rate, pupillary dilation, skeletal muscle tension, and a greater HPA response to cognitive stress in comparison to uninhibited children. In adolescence and young adulthood, inhibited individuals may begin to develop problems dealing with anxiety. They may have nightmares and develop phobias. Studies conducted on identical twins and nonhuman primates suggest that a significant part of the tendency to develop extreme behavioral inhibition is inherited. Thus, some individuals appear to have a **genetic predisposition** to express intense fear and stress responses in unfamiliar or changing situations.

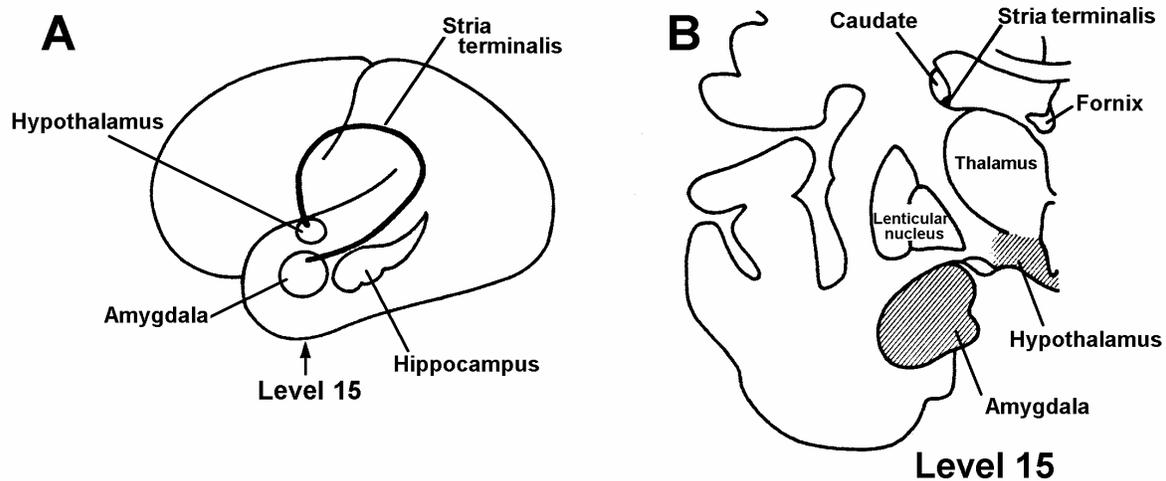
As indicated earlier, certain stimuli are more likely to elicit a fear response than others. However in many cases, a stimulus may acquire properties through learning to elicit a fear response. In addition, we may be "**biologically prepared**" to associate certain stimuli with emotional responses more readily than with other stimuli. Research on the fear of snakes in rhesus monkeys illustrates these important points. For years it was assumed that rhesus monkeys were innately fearful of snakes. Early studies at the Harlow Primate Laboratory demonstrated that when monkeys were exposed to snakes they became upset, grimaced their faces, attempted to run away, and emitted high pitched shrieks. However, it was later noted that these monkeys all shared a common background: they were born and reared in the wild. Subsequent studies conducted using laboratory bred monkeys suggested that the fear of snakes appeared to be learned. When lab-bred monkeys were first presented with a snake they showed little signs of any disturbance. However, if these infants were given the opportunity to observe their mothers interacting fearfully with a snake, they became distressed and acquired a long-lasting phobia of snakes. It appears that fear of snakes is not an innate reaction but a response transmitted from mother to infant by observational learning.

Studies further demonstrate that rhesus monkeys appear **biologically prepared** to learn to fear snakes. Infant monkeys were shown videotapes of their mothers displaying fear grimaces in the presence of snakes. As expected, these infants rapidly acquired a fear of snakes. The same monkeys were shown a videotape that was altered by editing a picture of brightly colored flowers in place of the snake. These infant monkeys now saw their mother acting fearful in the presence of flowers. However, the infants failed to acquire a phobia to flowers. Thus, young monkeys were biologically prepared to learn to be fearful of snakes but not flowers. Therefore, it is perhaps not by chance that we tend to be fearful of certain objects. Our brains are genetically programmed to associate certain stimuli with emotions such as fear.

### **The amygdala: A key structure mediating fear**

Given the complexity of the mammalian brain, is it possible to localize emotional states of fear and anxiety to specific regions of the brain? It turns out that a complex of related cells exists in the limbic system and appears to be involved in fear reactions and the learning of fear. In the 1930's, Kluver and Bucy noted that large lesions of the temporal lobe made monkeys tame in the presence of previously fearful stimuli, such as humans and snakes (you hopefully

remember the **Klüver-Bucy syndrome** from an earlier lecture on the limbic system). The absence of an appropriate behavioral response to fear-eliciting stimuli was termed "**psychic blindness**" because it was presumed that the **cognitive** processing of emotional stimuli was altered. This taming effect could be produced by lesions restricted to the amygdala (Klüver Bucy monkeys had much larger lesions of the temporal lobe). In contrast to the taming effects of amygdala lesions, electrical stimulation of the amygdala elicits defensive and flight reactions in cats and feelings of fear and anxiety in humans. Increased autonomic activity, i.e., heart rate, blood pressure also occurs after electrical stimulation of the amygdala.



**Schematic diagram showing the course of the stria terminalis that connects the amygdala to the hypothalamus (A), and the positions of the amygdala, hypothalamus, and stria terminalis (B) in level 15 of the coronal section series. Don't expect to see the stria terminalis on the lab slides (it is lightly myelinated and very difficult to discern).**

The amygdala contains four important nuclei: the central nucleus, the lateral nucleus, the basal nucleus and the accessory basal nucleus. All sensory inputs terminate in the lateral nucleus, which then projects to each of the other three nuclei; the basal and accessory basal both feed into the central nucleus. The **central nucleus (CeA)** contains the output cells of the amygdala and connects to many other areas of the brain concerned with emotional responses (fig 5).

Stimuli associated with a highly charged emotional context acquire the emotional qualities of that situation and subsequently have a dramatic effect on the mental life and behavior of the individual. This association can be demonstrated in the laboratory using classical (Pavlovian) conditioning procedures. In classical conditioning (also Pavlovian conditioning), an initially neutral stimulus comes to predict an event. For instance, Pavlov found that a dog would salivate when presented with an auditory or visual stimulus **if** the stimulus came to predict an event that normally caused salivation. Thus, if the experimenter rang a bell just before putting meat powder in the dog's mouth, repeating this sequence a few times would cause the dog to respond to the bell itself by salivation. In this case the sound is called the **conditioned stimulus (CS)** and the meat powder in the mouth the **unconditioned stimulus (US)**. The meat powder in the mouth already evokes an **unconditioned response (UR)** and the acquired response to the conditioned response is called the **conditioned response (CR)**.

Now, regarding the amygdala. Consider a rat that is exposed to a tone (CS) at the same time as an aversive footshock stimulus (US). Subsequent presentations of the tone CS will elicit fear reactions even in the absence of foot shock. The amygdala plays a key role in conditioned or learned fear. Rats with amygdala lesions show a dramatic reduction in freezing that normally occurs in response to conditioned fear stimuli. Moreover, if the lesions are made prior to learning, the animals will not learn the association. It appears, therefore, that the amygdala is involved not only in the cognitive evaluation of emotional stimuli (remember the Kluver Bucy monkeys) but also in the associational learning of stimuli that predict aversive events (classical conditioning experiments).

The amygdala may also be involved in what is termed “**emotional memory.**” We seem to be able to better recall events surrounding a strong, negative emotional experience than events not linked to any particular experience. Many people in the U.S. of a certain generation can remember exactly where they were and what they were doing when informed that President Kennedy was shot. Younger people may clearly remember the day the space shuttle Challenger blew up. The amygdala may be involved in this phenomenon, although the precise mechanisms are not known.

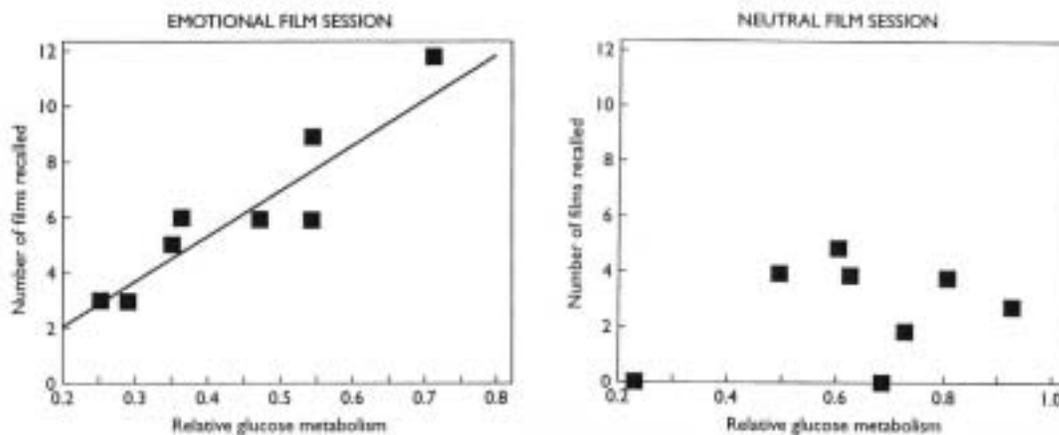


Fig. 4. Eight volunteers viewed emotionally distressing or neutral film clips while their brains were being imaged by positron emission tomography (PET), which measures general metabolic activity. Three weeks later, and without forewarning, a memory test was given to determine how well subjects recalled the film clips. Not surprisingly, recall was better for the arousing film clips. Interestingly, amygdala activity, as demonstrated by relative glucose metabolism (shown on axis), increased with the number of emotionally distressing film clips recalled; thus, the more active the amygdala at the time of learning, the more it has enhanced storage of those memories. (From Cahill et al, 1996).

A human case study illustrates the importance of the amygdala in the recognition of emotional **stimuli**. A patient suffered from **Urbach-Wiethe disease**, a rare genetic disorder, that resulted in bilateral calcification and atrophy of her amygdala. When asked to rate the intensity of various facial expressions, the patient judged faces showing fear expressions to be considerably less intense than ratings made by normal control subjects. Other facial expressions (smiling for instance) were also judged by the patient to be less intense than those reported by controls, but not to the degree made when viewing **fear** expressions. **Bilateral** amygdala damage appears to produce a profound insensitivity to the intensity of fear shown by faces. The patient, however, had no difficulty recognizing people by their faces and could rapidly learn the identity of new faces. These results demonstrate that the human amygdala is involved in the processing of facial

emotions/expressions, especially those related to fear. Damage to the amygdala appears to result in an inability to link visual representations of facial expressions with the emotion of fear.

In summary, the patient, S. M., could learn new facts, had no problems with language or movements and had normal basic intelligence. However, it was as though she were devoid of negative emotions such as fear and anger. She was unable to attribute correctly the emotion of fear in the face of others, or to mimic an expression of fear. If all faces appear trustworthy and approachable, it is hard to appreciate social risks, and this leads to increased vulnerability to environmental dangers.

Below find an interesting article regarding S.M. and the amygdala

*The woman who knows no fear*

17 Dec 94

*A patient who cannot read fear on other people's faces has given researchers a valuable clue to how the human brain processes emotions. Her confusion shows for the first time that the brain processes fear and mixed emotions through a different pathway from those used to process other feelings. The woman, known as S. M., has a rare disease, which has damaged the amygdala region of her brain. She also has problems perceiving other "negative" emotions, such as anger. The amygdala is an almond-shaped structure at a crossroads in the brain's circuitry: it links the cortex, which is responsible for conscious thought, with regions of the brain that control the body's emotional responses. Scientists knew that the amygdala helps regulate reactions associated with strong emotion - such as quickened heart rate and sweating. But what exactly does it do?*

*Brain researchers determine the function of a part of the brain by studying people whose brains are damaged in that region. But patients with damage to the amygdala alone are very unusual, according to Antonio Damasio of the University of Iowa, who led the team that made the new discovery. S. M. first turned up at a hospital suffering from epilepsy. Later, when her doctors looked for the root of the problem using magnetic resonance imaging, they found that her amygdala was destroyed. This was the result of Urbach-Wiethe disease, which deposits calcium in the amygdala. With S. M.'s consent, the Iowa researchers subjected her to a battery of psychological tests devised by Damasio's colleague Ralph Adolphs, asking her to say what emotions were being expressed by the people pictured in a series of photographs.*

*S. M. failed what Damasio calls "the Doris Day test". "When we showed her a film clip of Doris Day screaming, she asked, 'What is she doing?'," he says. In fact, S. M. was baffled by any picture showing a fearful expression. She also had problems deciphering mixtures of negative emotions, such as anger and surprise. By contrast, she had no difficulty with "positive" emotions such as happiness. She was also perfectly able to recognise familiar faces (Nature, vol 376, p 669).*

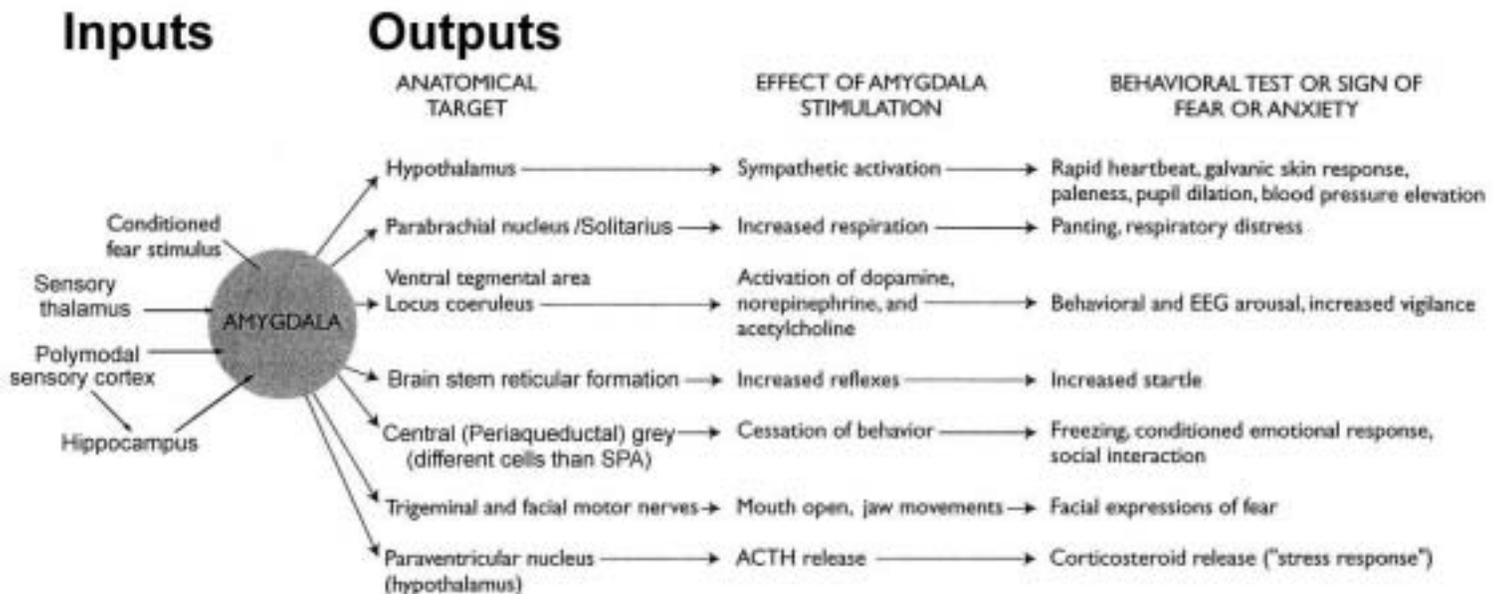
*These results, says Damasio, indicate that the amygdala has a pivotal role in linking frightening signals from the environment with the body's fear responses. Fear is universally important for survival in animals, Damasio notes, so it is reasonable that a special brain system has evolved to deal with it. The amygdala also seems to help us respond correctly to complex mixtures of negative emotions expressed by other people. Because she often fails to recognise criticism or*

aggression, S.M. has difficulty interacting socially. Positive emotions seem to be processed in another region of the brain. Just where is a mystery. "We've never seen a patient who can't recognise a happy face," says Adolphs.

JENNIFER ALTMAN From *New Scientist* magazine, vol 144 issue 1956, 17/12/1994,

The amygdala is well positioned anatomically to play a role in emotional learning. Its lateral sector receives afferent input from sensory nuclei of the thalamus, all sensory cortical regions (visual, auditory, somatosensory) and the hippocampus. Thus, sensory information from all modalities converges on the lateral nucleus of the amygdala. In turn, the amygdala has connections to hypothalamic and brain stem areas via the central nucleus that appear to be involved in many of the features associated with the fear response (Fig 5). The central nucleus projects to the hypothalamus for activation of the sympathetic autonomic nervous system (remember those darn descending fibers from the hypothalamus to the T1-L2 outflow in the spinal cord???) that accompanies fear and anxiety states. Projections also reach the dorsal motor nucleus X, which controls varied autonomic functions (when you are scared you want to inhibit dorsal motor X).

The parabrachial nucleus (part of the solitary complex that you learned in Brain Stem) is involved in respiration (remember, there are descending brain stem pathways to phrenic and intercostal neurons in the spinal cord). The central nucleus projection to the parabrachial nucleus may be involved in the increased respiration during fear. Electrical stimulation of the central nucleus enhances respiration, a major symptom of fear and panic disorder (see the accompanying Panic disorder section).



The central nucleus of the amygdala makes direct connections with a variety of target areas in the brain that express the various symptoms of fear.

Fig. 5. The amygdala mediates many of the behavioral and autonomic aspects of the reaction to **both** unconditioned (e.g. shock) and conditioned (e.g. light that has been paired with shock) stimuli. It is believed that an associative process takes place in the amygdala, which then projects to hypothalamic and brain stem targets in order to mediate the various symptoms of fear.

The amygdala receives direct, multimodal sensory input from cortex, sensory thalamic areas and the hippocampus; it is via these pathways that conditioned and unconditioned stimuli could reach the amygdala. (Adapted from Davis, 1999)

The central nucleus of the amygdala has direct projections to other brain stem target sites. These include the **ventral tegmental area** (VTA), which contains **dopamine** (DA) cell bodies and the locus coeruleus (LC), whose cell bodies contain norepinephrine (NE). Thus, the central nucleus has the potential to influence a wide array of neurotransmitter systems.

Behavioral fear reactions such as the startle reaction, freezing, facial expressions and reduction of social interactions are also influenced by amygdala projections to brain regions such as the central or periaqueductal grey (to a different part than that concerned with stimulation produced analgesia, SPA) and the trigeminal (motor V) and facial motor (motor VII) nuclei.

The stress-induced endocrine response is modulated in part by central nucleus projections to the paraventricular nucleus of the hypothalamus. Stimulation of the CeA increases plasma concentration of corticosteroids.

### **Role of corticotropin-releasing hormone (CRH) systems in fear and anxiety**

There is increasing evidence to suggest that extrahypothalamic corticotropin-releasing hormone (CRH) systems play an important role in the onset of fear and anxiety. Remember, cells in the central nucleus contain CRH. Axons of central nucleus cells target locus coeruleus neurons (which have CRH receptors and contain NE). In animals, administration of CRH into the cerebral ventricles (so as to eventually reach receptors on amygdala and LC cells) effectively induces anxiety responses, including hypervigilance, enhancement of the freezing posture, and decreased exploration in unfamiliar situations. Furthermore, in anxiety-provoking situations that typically elicit these behavioral responses, administration of a CRH antagonist produces a reduction in the occurrence of these reactions. In rats, infusion of a CRH antagonist into the central nucleus reduces expression of fear behavior ("freezing" in an environment where the animal had been previously shocked) suggesting that blockade of CRH receptors in the central nucleus has an antianxiety effect. In addition, stimulation of the central nucleus with microinfusions of CRH increases the release of norepinephrine and epinephrine from the adrenal medulla (via the sympathetic outflow). It is hypothesized that dysregulation of CRH systems may underlie or contribute to a state of chronic fear or anxiety by affecting behavioral and autonomic activity.

### **Clinical correlates: panic attacks and panic disorder**

Panic attacks are an example of pathophysiology in the neural systems underlying fear and anxiety. These systems are integral to the original "fight/flight" concepts and appear to be evolutionarily important in protecting the organism from a wide variety of threats, particularly predators. Panic disorder is a prevalent and well-studied psychiatric disorder that consists of multiple disabling panic attacks. Between 2-3 % of people experience an episode of panic disorder in their lifetime and twice as many women as men suffer from the disorder. These panic attacks are characterized by extreme fear and an urge to flee as well as intense autonomic arousal involving a wide variety of symptoms. The symptoms originally occur spontaneously and

unpredictably, and vary in length from several minutes to upwards of 60 min. If they continue for prolonged periods of time, they can be very disabling. Evidence suggests that panic attacks may be due to a hypersensitive autonomic nervous system involving an overly reactive **LC-NE** system.

**Agoraphobia** is the most common complication of panic disorder. It is defined as a fear of being in places or situations from which escape might be difficult or embarrassing, or in which help might not be available in the event of a panic attack

There are a number of naturalistic observations and research investigations that support the view that panic attacks occur as a result of hypersensitive alarm systems. For example, studies demonstrate that acute panic attacks are generated by abnormal neural activity in the brain stem. Clinical observations indicate that attacks are largely experienced by patients as "storms" of autonomic nervous activity. Patients frequently are fearful of the multiple physical symptoms associated with an attack, including light-headedness, a racing heart, difficulty breathing, chest discomfort, generalized sweating, or weakness.

Research investigations indicate that administration of various doses of pharmacological agents can produce panic attacks in panic-prone, but not in normal individuals. In these studies, the physical symptoms of panic attacks can be reproduced, albeit in varying degrees, by carbon dioxide, yohimbine, and caffeine and epinephrine administration.

Yohimbine (a mild hallucinogen/stimulant extracted from South African tree bark) is an **alpha<sub>2</sub>-noradrenergic receptor antagonist**. The majority of alpha<sub>2</sub> receptors act as **autoreceptors**. Normally, release of endogenous NE from the LC cell will modulate its own release by binding to its autoreceptor; this in turn prevents the release of NE. Thus, alpha<sub>2</sub>-noradrenergic receptor **agonists** act as a negative feedback signal to **reduce** the release of NE. Antagonists, like yohimbine, that bind to the alpha<sub>2</sub> receptor, block this negative feedback signal. Consequently, the LC cell continues to release NE.

In the laboratory, administration of yohimbine to panic-prone patients reproduces many of the symptoms of a panic attack including dizziness, sweating, respiratory distress, lightheadedness, palpitations, and fear. Results of these clinical studies suggest that the NE system may be overly sensitive or hyperactive in individuals predisposed to develop panic disorder. Further evidence to support the involvement of the LC-NE system in panic disorder is obtained from studies showing that administration of clonidine has transient antipanic effects. Clonidine is an alpha<sub>2</sub> noradrenergic receptor agonist that effectively reduces the firing of LC neurons. Thus, pharmacological agents that increase LC-NE activity produce panic attack symptoms, whereas agents that reduce LC-NE firing rates appear to reduce panic attacks.

### **Role of carbon dioxide**

Carbon dioxide inhalation is capable of inducing panic symptoms in patients with panic disorder but not in normal subjects. In the clinical laboratory, inhalation of 5% carbon dioxide was found to potentiate a rapid increase in ventilation before the panic (ventilation is mediated by receptors that sense carbon dioxide in the lungs, heart, and brain stem medulla). These results have

suggested that patients with panic disorder may have very sensitive brain stem carbon dioxide receptors, i.e., “suffocation alarm mechanisms.”

Of potential relevance to the NE system, animal studies demonstrate that carbon dioxide produces a dose-dependent increase in LC firing rates. This effect of carbon dioxide on LC discharge rates is probably influenced by medullary (nucleus solitarius-remember, it receives visceral afferent information) projections to the LC.

There continues to be debate on the etiology of panic attacks. However, it appears that some factors are involved in acting centrally upon vulnerable brain stem regions to provoke panic attacks. For example, physiological functions and metabolic demands occurring in the periphery are closely regulated by cells in the brain stem. Information from the cardiovascular and respiratory system reaches the solitary complex and are relayed to, and activate, the LC-NE system. Fearful perceptions and thoughts emanating from the cerebral cortex may also contribute by further lowering the threshold in brain stem systems, and thereby potentiate the production of panic symptoms (one pathway underlying this would be from cortex to amygdala to LC). Some individuals are more likely to experience panic attacks after exposure to stress associated with losses (i.e., death of loved ones, divorce) or certain situations (i.e., exams, near fatal accidents, trapped in a highly confined place). Recently it has been observed that the neuropeptide **cholecystokinin (CCK)** is involved in panic disorders. Some investigators have hypothesized that panic attacks start with an excitation of the CCK neurons in the brain stem (in what is called the reticular formation; those areas that were kind of “left over” in our travels through the brain stem). Such CCK neurons stimulate the noradrenergic neurons of locus coeruleus and the panic attack begins.

### **Sadness and negative affect**

Negative emotions and sadness are commonly elicited by situations associated with the loss of an important social relationship (death of a spouse) or object (loss of a home due to fire). Sadness is an internal state that signals the need for affiliation and functions to motivate individuals to seek supportive social relationships. As with fear and anxiety, this emotion is present from birth and when expressed early in life alerts the caregiver to meet the infant's needs.

Many years ago, Harry Harlow at the University of Wisconsin observed that when infant monkeys were separated from their mothers, they emitted a high-pitched vocalization (coo call) which alerted the mothers to retrieve the infant. Infant monkeys subjected to prolonged maternal separation frequently succumbed to a state characterized by loss of interest in the environment, a reduction in food intake and huddling in the corner. Harlow drew parallels between this emotional state and that reported in institutionalized human infants undergoing prolonged maternal separation.

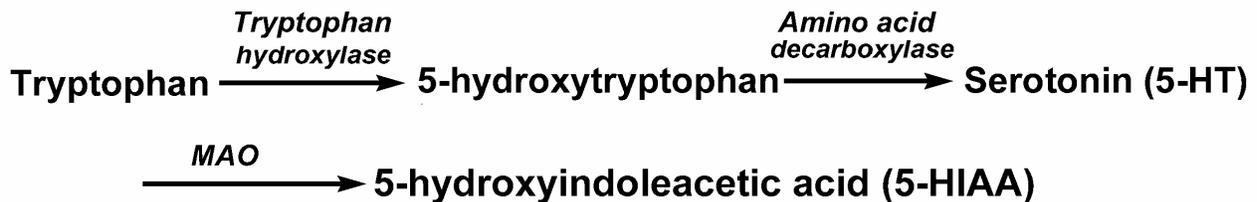
Prolonged disruption of the maternal-infant bond can also have a profound impact on subsequent behavior. Newborn monkeys socially isolated from an early age would not interact with other monkeys. They would not play, fight, or show any sexual interest. Older monkeys subjected to comparable periods of social isolation failed to develop these behavioral alterations. It appears that developmental, environmental, and biological interactions are important factors in determining the individual's emotional patterns of behavior.

### Clinical correlates: alterations in brain monoamines are associated with depression

Although sadness is a transient emotional state, **depression** is a mood or syndrome characterized by thoughts of self-worthlessness, excessive guilt, death and/or suicide. Physiological systems are also dramatically altered during depression. Patients with depression may have difficulty concentrating on tasks and may suffer from insomnia, altered appetite, decreased interest in pleasurable activities, and fatigue. Depression is estimated to affect approximately 5% of the adult population at any one time. In addition, approximately 20% of all individuals are likely to experience an episode of depression during their lifetime.

An important clinical observation was made in the 1950's when the antihypertensive agent reserpine was prominently used. Clinicians noted that some individuals became markedly depressed after taking this drug, which produces a long-lasting depletion of monoamines (norepinephrine, serotonin and dopamine). Other work demonstrated that drugs that increased the level of monoamines were effective in the treatment of depression. Together, these observations led to the monoamine hypothesis of depression. According to this hypothesis, depression results from a deficit in brain norepinephrine or serotonin, or both.

#### Biosynthesis and Metabolism of Serotonin



The amino acid tryptophan is the substrate for the synthesis of serotonin. Tryptophan hydroxylase is the enzyme responsible for the hydroxylation of tryptophan to form 5-hydroxytryptophan. Once synthesized, 5-hydroxytryptophan is rapidly decarboxylated to form serotonin. After release from presynaptic terminals, the deamination of serotonin occurs following reuptake of serotonin and metabolism by monoamine oxidase (MAO) to yield 5-HIAA.

Additional support for the monoamine hypothesis of depression came from an examination of norepinephrine and serotonin metabolites in depressed patients. In some depressed patients, concentrations of a major metabolite of norepinephrine, 3-methoxy-4-hydroxyphenylglycol, **MHPG**, were found to be reduced in the cerebrospinal fluid. Similarly, some depressed patients have reduced concentrations of a major serotonin metabolite, 5-hydroxyindoleacetic acid (**5-HIAA**). Other work demonstrated that rapid dietary depletion of tryptophan, the precursor of serotonin synthesis, produces a rapid return to depression in patients with successful antidepressant treatment. Together, these results suggest that availability of brain monoamines is reduced in depressed patients. Remember, MHPG=norepi while 5-HIAA=serotonin.

### **Lowered brain serotonin is associated with suicide**

Monoamine oxidase inhibitors (MAOI), tricyclic antidepressants, and selective serotonin reuptake inhibitors (SSRIs) are effective antidepressants that share the pharmacological property of increasing the level of biogenic amines (DA, NE, epineph, serotonin, histamine) but in different ways. **MAOIs** are a class of drugs that block MAO, the major enzyme responsible for the oxidation of monoamines. The tricyclic drugs work by blocking the reuptake (keep it around longer) of NE and serotonin into the presynaptic terminal resulting in a net increase in neurotransmitter availability. Consequently, there is an increase in postsynaptic receptor activity. SSRIs work by selectively blocking the reuptake of serotonin. SSRIs are as effective as the tricyclic compounds but without some of the sedating and cardiovascular side effects of tricyclic antidepressants. As a result, SSRIs (e.g., Prozac, Zoloft) are now used widely and underscore the importance of serotonergic systems in regulating mood.

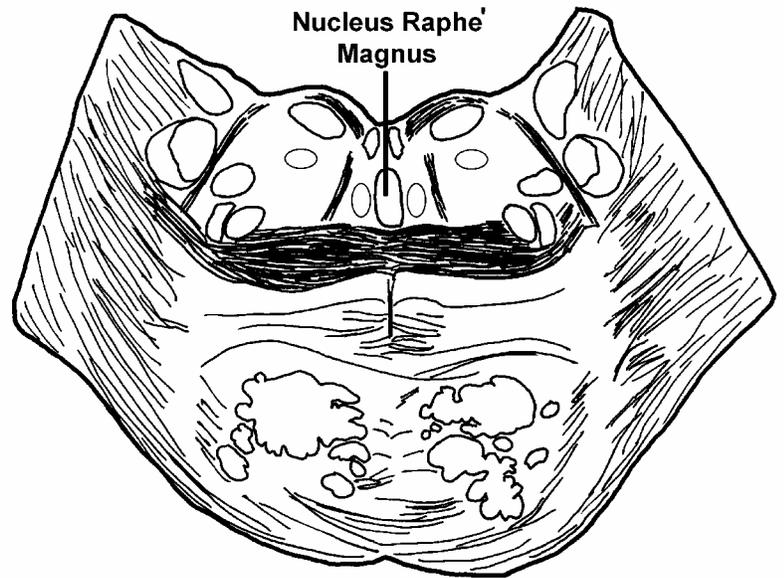
**Reboxetine** (mesylate), is the first of a novel class of drugs called selective norepinephrine reuptake inhibitors (SNRIs). As the name implies, they specifically boost levels of the neurotransmitter norepinephrine, which is thought to be associated with increased drive. With a unique mechanism of action and a relatively benign side-effect profile, reboxetine promises to give doctors new options for patients who are either treatment-refractory or unable to tolerate other antidepressants. And, although the concept is controversial, some researchers believe that reboxetine's specific effect on norepinephrine will make it particularly useful in the subset of depressed patients with decreased energy.

To summarize, **disruption of brain serotonin (5-HT) and NE concentrations appear to contribute to the depressive syndrome.** The hypothesis that depression is caused entirely by a reduction in monoamines is somewhat simplistic but provides a reasonable account of the pharmacological efficacy of antidepressants.

Suicide is a complex human behavior and remains a significant source of mortality with approximately 30,000 people taking their lives annually. Although suicide is generally thought to be the result of stress or depression, there is little information to distinguish who may successfully take their life by an act of suicide. For example, the majority of patients faced with painful life ending illnesses do not commit suicide. In addition, a number of individuals have taken their own life when it appears that stress was relatively minor, if not absent. Recent research efforts have broadened our understanding of the underlying neurochemistry of suicide.

Postmortem studies done a number of years ago revealed that brain stem levels (raphe nuclei; remember **nucleus raphe magnus** for SPA) of serotonin and its metabolite 5-HIAA are consistently reduced in suicide victims. More recent studies confirm a link between depression and low serotonin activity. These studies have shown that in depressed patients that have attempted or committed suicide, 5-HIAA levels in the CSF are considerably lower than in non-suicidal depressed patients. This association between CSF 5-HIAA levels and suicidal behavior is especially strong in those with violent suicidal attempts. It should be noted that although depression and suicide risk are both linked to disturbances in brain serotonin activity, evidence suggests that serotonin concentrations normalize after mood improvement in depressed patients.

It is presently unclear why reduced brain serotonin function predisposes individuals to commit suicide. One hypothesis is that low brain 5-HT values produce an increase in impulsive behavior. Impulsivity refers to a propensity to act without considering alternative options in a decision-making process. Although impulsivity is not synonymous with acting rapidly, impulsive individuals tend to act without time for reflection. In people with personality disorder characterized by chronic problems with impulsive behavior, the rate of completed suicide can be as high as 25%. The underlying cause of reduced brain serotonin remains unknown but could be related to heritable factors and/or neurological insults during development.



### Summary of the neurobiology of emotion

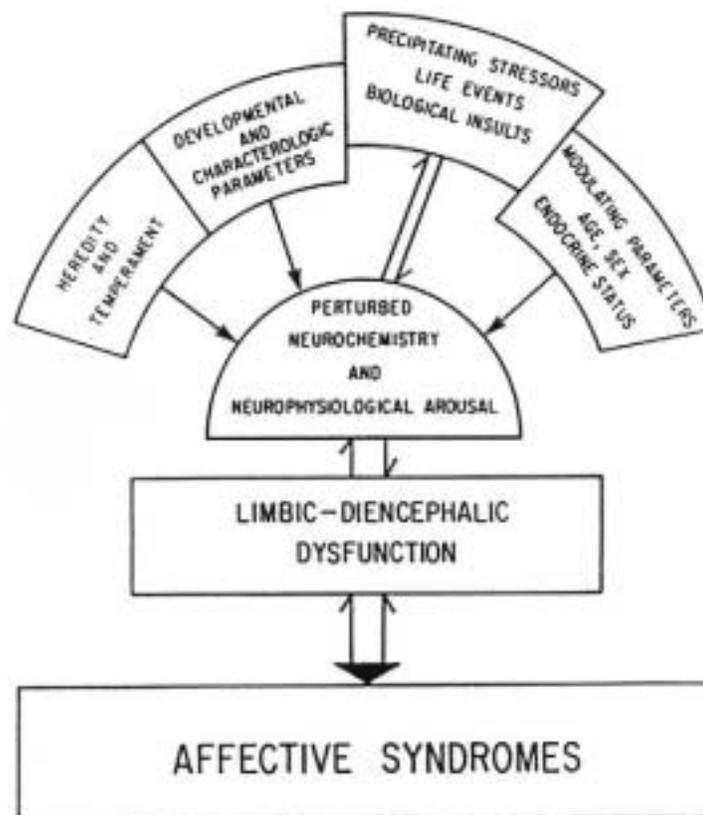


Fig. 6. This figure broadly summarizes how various factors and precipitating variables may interact to eventually induce behavioral disorders or affective illnesses. As we have seen, genetic, developmental, environmental and learning variables can influence neurochemical, limbic and cortical systems which ultimately affect behavior. Alterations in these neurochemical and/or neural structures associated with emotions may underlie or contribute to the emergence of psychiatric illness, particularly depression and anxiety.

### Problem Solving

1. Which of the following is **FALSE** regarding lesions of the amygdala?
  - A. affect emotional memories
  - B. result in taming effects
  - C. decrease in autonomic activity
  - D. decrease in secretion of epinephrine from the adrenal medulla
  - E. animals “freeze” in response to threats
  
2. Certain patients that have attempted or successfully committed suicide tend to have:
  - A. high CSF levels of 5-HIAA
  - B. high levels of brain NE receptors
  - C. low CSF levels of 5-HIAA
  - D. high levels of ACTH
  - E. high MHPG
  
3. Serotonin:
  - A. and NE concentrations are increased in suicide victims
  - B. reuptake inhibitors (SSRIs) are effective in reducing depression
  - C. depletion in the central nervous system has little effect on mood
  - D. cell bodies are located in the substantia nigra
  - E. cell bodies are located in the LC
  
4. Activity of LC neurons:
  - A. is reduced by CRH
  - B. is reduced by yohimbine, an alpha-2 noradrenergic antagonist
  - C. is increased by clonidine, an alpha 2 noradrenergic antagonist
  - D. is reduced by clonidine, an alpha 2 noradrenergic agonist
  - E. decreases during stress
  
5. If the amygdala is damaged:
  - A. a rat can learn a Pavlovian association between an aversive footshock and a neutral tone
  - B. a monkey’s responses to previously fearful stimuli will be intensified
  - C. a person will rate pictures of fearful facial expressions as less intense
  - D. extrahypothalamic CRH input to the LC will be increased
  - E. freezing responses will increase

6. Yohimbine:
- A. directly binds to and stimulates CRH receptors
  - B. acts as an agonist at presynaptic autoreceptors
  - C. elicits enhanced norepinephrine release by blocking alpha-2 noradrenergic receptors
  - D. is derived from the bark of American oak trees
  - E. is a drug that prevents panic attack-like symptoms
7. Which of the following statements about depression is **TRUE**?
- A. is correlated with normal levels of NE
  - B. decreased by reserpine
  - C. drugs which are helpful in depression include SSRIs, tricyclics, MAOIs, and alpha-2 noradrenergic antagonists
  - D. can result from an increase in NE
  - E. MHPG and 5-HIAA are increased
8. Which of the following statements about emotion is **TRUE**?
- A. negative emotions such as anger or fear promote defensive behaviors but not aggressive behaviors
  - B. the cognitive processing of an emotionally relevant stimulus does not contribute to emotional experience
  - C. emotion is primarily processed in limbic regions that are anatomically isolated from the neocortex
  - D. emotion is processed solely by the prefrontal cortex
  - E. none of the above are **TRUE**
9. Which of the following statements is **TRUE**?
- A. the amygdala receives input from the hippocampus and the sensory thalamus
  - B. the amygdala projects to the PVN, the dorsal motor X and the LC
  - C. patients with Urbach-Wiethe have difficulty judging the intensity of fear in a persons face
  - D. clonidine increases firing of LC neurons
  - E. three of the above are **TRUE**
10. Which of the following statements is **TRUE**?
- A. serotonergic (5-HT)projections arise from the raphe (zipper) nuclei and reach all cortical areas
  - B. norepinephrine (NE) projections arise from the locus coeruleus and reach all cortical areas
  - C. dopaminergic (DA) projections arise in the medulla
  - D. reboxetine is a selective serotonin reuptake inhibitor
  - E. two of the above are **TRUE**

11. Which of the following statements is **TRUE**?
- A. pathways from the nucleus solitarius to the LC play a role in panic attacks
  - B. carbon dioxide can increase the firing of LC neurons
  - C. stimulation of the LC results in an increase in the release of NE from the adrenal medulla
  - D. stimulation of the amygdala results in an increase in the release of NE from the adrenal medulla
  - E. all of the above statements are **TRUE**
12. Which of the following statements is **TRUE**?
- A. when lab-bred monkeys see a snake for the first time they exhibit fear
  - B. baby monkeys are biologically prepared to learn to be fearful of snakes
  - C. our brains are genetically programmed to associate certain stimuli with emotions such as fear
  - D. baby monkeys innately fear roses
  - E. two of the above are **TRUE**
13. Which of the following statements is **TRUE**?
- A. the neuropeptide CCK is thought to be involved in panic attacks
  - B. someone suffering from agoraphobia might avoid being in crowded places like malls and theaters
  - C. patients with Urbach-Wiethe disease have difficulty deciphering positive emotions such as happiness
  - D. patients with Urbach-Wiethe disease are all related to Doris Day
  - E. two of the above statements are **TRUE**

### **PROBLEM SOLVING ANSWERS**

- 1. E
- 2. C
- 3. B
- 4. D
- 5. C
- 6. C
- 7. C
- 8. E
- 9. E (A, B, C)
- 10. E (A, B)
- 11. E
- 12. E (B, C)
- 13. E (A, B)