

Limbic system – Emotional Experience

In preparation for the lecture I used four textbooks:

(1) Purves *Neuroscience* (4th Ed); (2) Kandel and Schwartz *Principles of Neural Science* (2nd Ed); (3) Squire, Bloom et al., *Fundamental Neuroscience*, Academic Press (2nd Ed); and (4) Duane E. Haines *Fundamental Neuroscience*, Churchill-Livingstone (2nd Ed). (5) Wikipedia (www.wikipedia.org). (6) YouTube (www.youtube.com).

(I) Anatomy

The word *limbus* means border or margin, and the term *limbic system* was loosely used to include a group of structures that lie in the border zone between the cerebral cortex and the hypothalamus.

Limbic structures include:

(1) The subcallosal gyrus, (2) cingulate gyrus, (3) parahippocampal gyrus, (4) the hippocampal formation; (5) the amygdaloid nucleus; (6) the hypothalamus; (7) anterior thalamic nucleus and (8) mediodorsal thalamic nucleus.

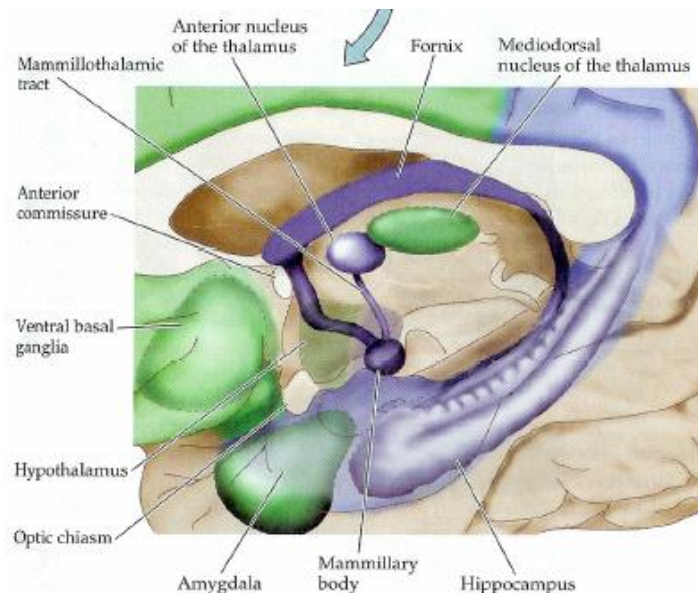
Extended Version (modern view) In addition, these structures are sometimes also considered to be part of the limbic system: (9) Mammillary body (Hypothalamus); (10) Pituitary gland; (11) Olfactory Bulb, (12) Entorhinal cortex and (13) Piriform cortex (structures 11 – 13 receive and process odors); (14) Nucleus accumbens; and (15) Orbitofrontal cortex.

Connecting Pathways

The alveus of the hippocampus, the fimbria, the fornix, the mamillothalamic tract, and the stria terminalis constitute the connecting pathways of the limbic system.

Fornix is a bundle of axons that connects hippocampus with the mammillary bodies of hypothalamus.

Stria Terminalis is a bundle of axons that connects amygdaloid body to septal nuclei in the medial basal forebrain and nuclei of the anterior hypothalamus. The FORNIX and STRIA TERMINALIS are two major afferent fiber bundles that reach the hypothalamus.



Amygdala

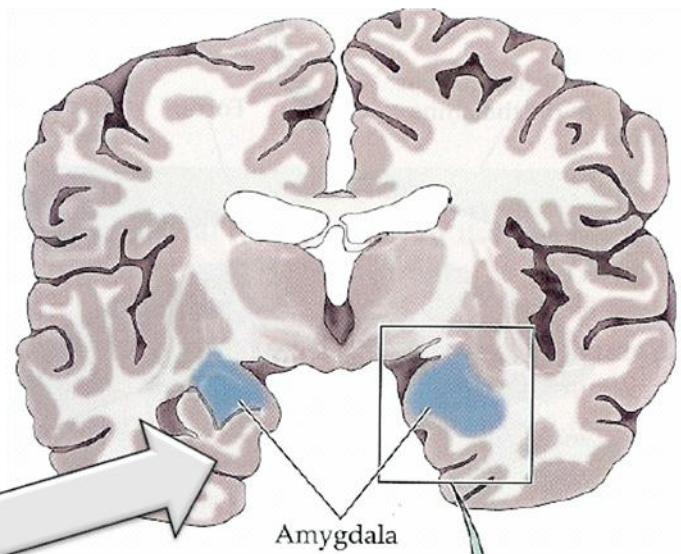
Amygdala is positioned in the frontal pole of the temporal lobe, beneath the portion of temporal cortex called “uncus”. Urbach-Wiethe disease is a hereditary disorder which affects amygdaloid function. NMDA-dependent long-term potentiation is a cellular mechanism responsible for fear conditioning in animals. It is thought that identical cellular mechanisms are involved in memorizing important, emotionally charged, events, and also for the formation of phobias in humans.

Amygdala is involved in regulating:

- Fear
- Emotions related to fear
- **Memory related to fear**
- Panic
- Anxiety

The bilateral damage to Amygdala results in inability to recognize the emotion of fear in the facial expressions of other people.

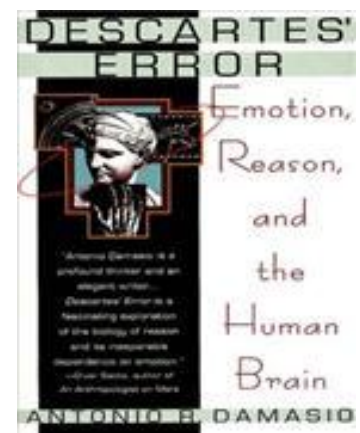
Urbach-Wiethe disease, bilateral calcification and atrophy of the anterior-medial temporal lobes.



Fear conditioning – LTP - NMDA

For a long time it was thought that Urbach-Wiethe patients have only one symptom; inability to recognize emotion of fear in the facial expressions of other people. This changed in December 2010, when Antonio Damasio and his colleagues from Iowa University tested their patient S.M. S.M is a 44 year-old women with bilateral lesions of amygdala. S.M. is the most studied patient with Urbach-Wiethe disease. After a battery of tests, which included spiders and snakes, Iowa team concluded that S.M. has a greatly diminished fear response. She did not experience fear, in situations in which other people normally showed a fear response.

Amygdala is involved in the formation and storage of memories associated with emotional events, including fear,



as well as an appetitive (positive) conditioning.
Individuals with larger amygdalae had larger and more complex social networks.

Amygdala, Traumatic experiences and PTSD

When we lose a battle, a match, or a job, the hippocampus is stimulated making sure we would remember the loss forever. The center of our emotions, the amygdala, fuses this sense of memory into a profound notion of misery. This all creates a powerful reminder of failure to put us off making the same mistake again.



Hippocampus and amygdala are two parts of the Limbic System that are central in memory storage. These two related parts of the brain, and closely located parts of the brain, are essentially involved in response to traumatic events, and in the memory of traumatic events. The amygdala stores highly charged emotional memories, such as terror and horror and it has been shown that the amygdala becomes very active when there is a traumatic threat. Amygdala is a relatively primitive part of the brain (evolutionary old) that gets activated by fearful stimuli faster and more reliably than the cerebral cortex (before full awareness sets in). We become scared before we are fully aware about what scared us. Amygdala is thus a part of an emotional reflex that couples fearful stimuli with autonomic response (fight or flight). This is analogous to a knee jerk reflex. Knee jerk reflex is an ancient mechanism that couples sudden extension of the muscle with the contraction of the same muscle in order to counterpart the unwanted extension (and fight gravity).

In Posttraumatic Stress Disorder (PTSD) patients are re-experiencing the TRAUMATIC event in varying sensory forms, such as flashbacks; and they are in the state of chronic hyperarousal in the Autonomic Nervous System.

Increased arousal of the autonomic nervous system is at the core of PTSD: accelerated heartbeat, cold sweating, rapid breathing, heart palpitations, hypervigilance, and hyper startle response (jumpiness). Over time these symptoms lead to sleep disturbances, loss of appetite, sexual dysfunction and difficulties in concentrating, which again are the hallmarks of PTSD. Because amygdala is part of the brain involved in coupling fearful stimuli with rapid and unconditional autonomic response, it is believed that PTSD is in part mediated by alterations in the amygdala circuitry.



(II) Function

Evolution

Some of the structures that comprise "limbic system" developed with the emergence of the inferior (primitive) mammals. The limbic system thus commands certain behaviors that are necessary for the survival of all mammals. It gives rise and modulates specific functions that allow the animal to distinguish between the agreeable and the disagreeable. The limbic system generates specific affective functions, such as the one that induces the females to nurse and protect their offspring, or the one which induces these animals to develop ludic behaviors (playful moods). Emotions and feelings, like wrath, fright, passion, love, hate, joy and sadness, **are mammalian inventions**, originated in the limbic system.

The limbic system is responsible for some aspects of personal identity and for important functions related to memory. And, when the superior mammals arrived on the Earth, the cerebral unit (neopallium – the rational brain – mostly in the prefrontal cortex) was finally developed, a highly complex net of neural cells capable of producing a symbolic language, thus enabling man to exercise skillful intellectual tasks such as speech, reading, writing and performing calculations, making inventions and generating abstract thoughts.

Humans display the largest web of connections between the prefrontal area and the traditional limbic structures. Perhaps, that is why they present, among all species, the greatest variety of feelings and emotions.

Clinical significance: The subjective feelings and associated physiological states known as emotions are regulated by the limbic system. EMOTIONS are essential features of normal human experience.

- Regulation of homeostasis is under the influence of EMOTIONS.
- Autonomic nervous system (sympathicus and parasympathicus) are under the influence of EMOTIONS.
- Sensory processing is under the influence of EMOTIONS.
- Cognitive processing, learning, memory, planning and decision making, are all under the influence of EMOTIONS.

The limbic system provides a custodial function for the maintenance of a healthy and conscious state of mind. Some of the most devastating psychiatric disorders involve EMOTIONAL (affective) disorders. Affective disorders: (1) Major depression; (2) Manic depressive disorder (bipolar disorder); (3) General anxiety disorder (GAD); (4) Autism; (5) Social phobia; (6) Attention deficit hyperactivity disorder (ADHD); (7) Bulimia nervosa, etc.

(III) Three Stages

Emotional regulation occurs at three different “phylogenetically determined” levels of the brain—the brainstem, subcortex, and neocortex. The type of emotion experienced, and the linking/delinking of emotion to action and thought, and the level of emotion experienced depend on which level of the brain the structure is in.

a. **Brain Stem** — controls wide, nonspecific swaths of brain activation which in turn leads to the undulate experience of emotion—diffuse and nonspecific aggression, fearfulness, irritability, etc.

b. **Subcortical regions** — these regions connect with brain stem regions and lead to the experience of specific emotions in some context or reflexively (example 1: **Anxiety** when you see a spider. Example 2: **Rage** when someone purposely cuts you off on the highway, etc).

c. **Cortical regions** — links emotion with specific cognitions (Example 3: Medical students who are expecting their first child become anxious when they wonder (**worry**) how they will handle the cost of raising the child, pulling long hours during residency training. Example 4: A soldier away from home, evoking pleasant memories and indulging in **nostalgia**, etc.).

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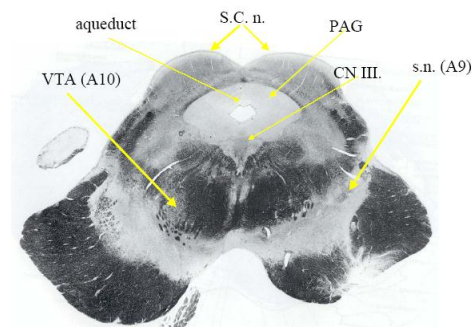
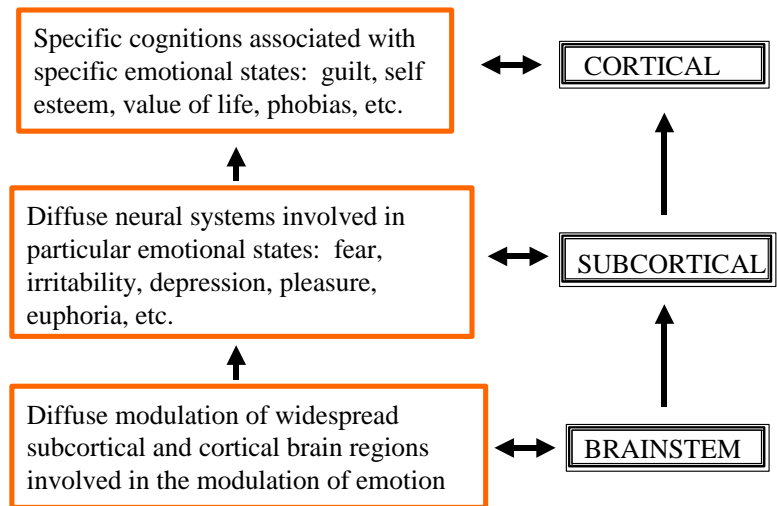
Brain stem (The source of Dopamine, Serotonin and Norepinephrine)

Brain stem is “officially” not a part of the limbic system. However, its function is most intimately related to the control of both **emotions** and **higher cognitive functions**.

Dopamine-releasing neurons live in the midbrain (mesencephalon – see figure on the right). More specifically, the cell bodies of dopaminergic neurons reside in the substantia nigra (s.n.) and the ventral tegmental area (VTA), while their axons project diffusely throughout the entire CNS. In this way a relatively small number of dopaminergic cells (several hundred thousands) exert their influence on billions of neurons located in the prefrontal cortex, striatum, cerebellum and hippocampus. Two out of 5 dopaminergic projections (1. mesocortical and 2. mesolimbic) exert strong influence on emotional states and cognitive processing. Drugs that modulate dopaminergic function (e.g. dopamine receptor antagonists, uptake of dopamine) are used to treat major psychiatric disorders (e.g. schizophrenia).

Serotonin and **norepinephrine (noradrenaline)**-releasing neurons, just like dopamine-

NEURANATOMICAL CONTROL OF EMOTION



releasing neurons send distant projects to very widespread regions of the brain and tonically regulate emotional states. Cell bodies of **serotonergic** neurons reside in nucleus raphe of the pons. Cell bodies of **noradrenergic** neurons reside in locus ceruleus (a nucleus of the pons). A suboptimal tone of serotonin or NE in the limbic system and prefrontal cortex causes anxiety and depression. Excellent drugs have been developed in the past 20 years to elevate the concentration of serotonin and norepinephrine in the brain and alleviate symptoms of anxiety and depression. Some of these new drugs predominantly influence serotonin levels (selective serotonin reuptake inhibitors – **SSRI**). The most common SSRI include (1) Fluoxetine (Prozac); (2) Sertraline (Zoloft) and (3) Paroxetine (Paxil).

Some patients do not get sufficient improvement from SSRI therapy. They simply do not respond to this therapy and continue to suffer. In addition, SSRIs may come with adverse side effects (sexual dysfunction, significant weight gain). To address these two extremely serious issues psychiatrists often use antidepressants which have effect on both serotonin and norepinephrine transmission (Serotonin Norepinephrine Reuptake Inhibitors – **SNRI**).

SNRIs were developed more recently than SSRIs, and there are relatively few of them. Their efficacy as well as their tolerability appears to be somewhat better than the SSRIs, owing to their compound effect. The most common SNRI are: (1) Venlafaxine (Effexor XR); (2) Nefazodone (Serzone) and (3) Duloxetine (Cymbalta).

(IV) The Prefrontal Cortex (PFC)

Definition: Cortical areas anterior to the pre-central gyrus (primary motor cortex) and associated motor areas, such as the premotor cortex and the frontal eye fields.

PREFRONTAL CORTEX HAS THREE MAJOR DIVISIONS TO IT: TWO ARE INVOLVED WITH THE CONTROL OF EMOTION:

(THE STORY OF PHINNEAS GAGE)

KEY CONCEPT

PREFRONTAL CORTEX

Orbital PFC

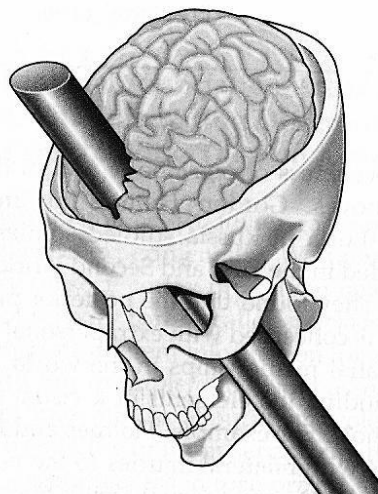
links emotion with societal expectations, appropriate behaviors

Medial PFC

generation of drive, emotional responding

Dorsal-lateral PFC

cognition



PURVES, CHPT 28, PG 687

Modern definition: PFC includes those cortical areas (in the frontal lobe) which receive direct projections from the mediodorsal thalamic nucleus.

Damage to medial PFC causes serious emotional and cognitive problems.

The prefrontal cortex is comprised of three regions of the frontal cortex anterior to Brodmann's area 6 (the frontal eye fields).

- Medial Prefrontal Cortex (includes Anterior Cingulate)
- Orbital Prefrontal Cortex (Orbital gyrus and Gyrus Rectus)
- Dorsal-lateral prefrontal cortex (Brodmann's area 9, 46, 47)

Phineas Gage ushered in the modern era of cognitive neuroscience when his orbital and medial prefrontal cortices were destroyed in a freak railroad accident.

Before the injury he was a skillful and disciplined worker.

After the injury, Gage retained excellent engineering skills but could no longer act appropriately, maintain responsibility, stay focused on the job, or control his language and behavior. He was depressed, irritable, impulsive and socially inept.

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People with brain tumors in the medial prefrontal area (meningioma) cannot maintain good healthy relationships with family members and their co-workers. If the tumor progresses undiscovered, they become rejected from all levels of the society. At later stages of disease, when it is apparent that patients go through a major personality change, they are eventually referred to a psychiatrist. Interestingly, when approached by a psychiatrist, during the interview, people with damaged mPFC do not express concern or self-pity, as if this significant social degradation (loss of job, divorce, poverty) was not affecting them emotionally.

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Functional MRI studies revealed a reduced blood flow to the PFC in patients with major **depression** and in **schizophrenia**.

MAJOR DEPRESSIVE DISORDER (MDD) – SEROTONIN [Hypothesis](#)

The emotional experience during a *major depressive episode* (MDE) may be dominated by anxiety, irritability, or anhedonia (inability to derive pleasure or reward from activities). Patients often report that terms such as "psychic pain" describe their mood accurately. MDD has been associated with abnormalities in serotonergic, dopaminergic and noradrenergic function. The serotonin system has received a particular interest because SSRIs exert antidepressant effect. Interestingly, all three groups of antidepressant drugs [Selective serotonin reuptake inhibitors (SSRI), Tricyclic antidepressants (TCA); and Monoamine oxidase inhibitors (MAOI)] increase serotonin transmission.

Schizophrenia – [DOPAMINE Hypothesis](#)

Catastrophic mental disease with onset in adolescence. Deterioration of mind at an early age ("DEMENTIA PRAECOX") was an early name for schizophrenia. Positive

symptoms: DELUSIONS, hallucinations, disorganized speech, and bizarre behavior. Negative symptoms: AVOLITION, FLAT AFFECT, anhedonia, and alogia.

Two lines of evidence support dopamine hypothesis of schizophrenia: (1) Drugs that block dopamine receptors can alleviate some symptoms of schizophrenia. (2) Drugs that increase synaptic outflow of dopamine (amphetamine) can trigger a psychotic episode in schizophrenic patients.

Hypofrontality (poorly developed prefrontal cortex, or weak function of the PFC) is commonly found in young children. It is considered the major reason for emotional immaturity in young humans, as well as for the majority of behavioral problems associated with childhood and adolescence (delinquency).

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Psychomotor Stimulants

Amphetamine and cocaine are psychomotor stimulants that, in humans, have behavioral effects such as suppressing hunger fatigue and inducing euphoria. In animals, these drugs increase motor activity, decrease food intake, stimulate operant behavior, enhance conditioned responding and produce place preferences.

Addiction to psychomotor stimulants

A general rule is that psychomotor stimulants with a high potential for triggering addiction (substance abuse) have effects that lead to increase in the availability of monoamine neurotransmitters at synapses. More specifically, amphetamine and cocaine block the uptake of dopamine, norepinephrine and serotonin. However, the acute reinforcing effect of these drugs depends critically on dopamine system. Low doses of dopamine receptor antagonists injected either systematically or centrally into the:

NUCLEUS ACCUMBENS
BED NUCLEUS OF STRIA TERMINALIS
AMYGDALA

regularly block cocaine and amphetamine self-administration in rats (Koob, 1992). Three structures mentioned above belong to the LIMBIC SYSTEM. They express dopamine receptors and thus are sensitive to dopamine release. Dopaminergic fibers heavily innervate (dense innervation) the nucleus accumbens, amygdala and bed nuc. of stria terminalis. Because nuc. accumbens, amygdala and bed nuc. of stria terminalis belong to the LIMBIC SYSTEM, this particular pathway from mesencephalon (VTA) to limbic system is called MESOLIMBIC pathway. In summary, mesolimbic dopamine system/pathway has a specific role for addiction to cocaine and/or amphetamine.

Mesolimbic DA System plays a key role in natural rewards such as FOOD and SEX (Shultz W (2002) Getting formal with dopamine and reward, *Neuron*).

Appendix

Patient S.M.

On page 2 of this document Urbach-Wiethe patients were reported to lose the ability to recognize fear in other people's facial expressions. According to Purves textbook, other major fear-related dysfunctions have NOT been detected in Urbach-Wiethe patients. A new study questioned this statement (Curr Biol. 2010 Dec 16, see below).

Background: S.M. suffers from Urbach-Wiethe disease.

ABNORMAL FINDINGS in MRI taken from SM

Focal bilateral amygdala lesions caused by calcium deposits due to lipoid proteinosis (also known as Urbach-Wiethe disease), a rare congenital genetic disorder.

A circumscribed area of damage to white matter in the vicinity of the amygdala and to the anterior entorhinal cortex.

NORMAL FINDINGS in MRI taken from SM

The hippocampus proper as well as temporal neocortex appear entirely intact, as do other key neural structures related to emotion, namely, both insular cortices, both ventromedial prefrontal cortices, and the hypothalamus and brainstem, notably the periaqueductal gray.



S.M. performs within the normal range on standardized tests of IQ, memory, language, and perception yet is impaired in recognizing fear in facial expressions and in aspects of social behavior thought to be mediated by emotions related to fear. Importantly, none of the previous studies specifically assessed the induction and experience of fear in patient SM, and it is these two aspects of fear that form the basis for the NEW report.

Curr Biol. 2010 Dec 16. [Epub ahead of print]

The Human Amygdala and the Induction and Experience of Fear.

Feinstein JS, Adolphs R, Damasio A, Tranel D. University of Iowa, Iowa City, IA 52242, USA.

To provoke fear in S.M., the doctors exposed her to live snakes and spiders, took her on a tour of a haunted house, and showed her emotionally evocative films.

On no occasion did S.M. exhibit fear, and she never endorsed feeling more than minimal levels of fear.

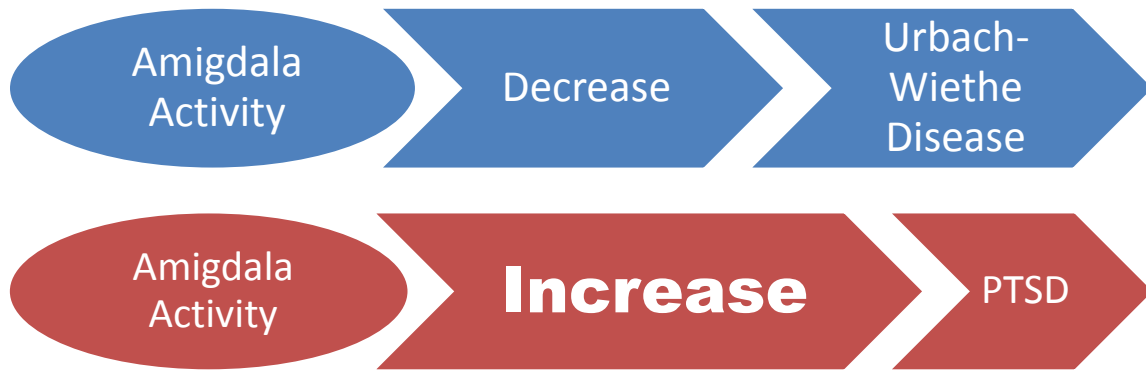
Despite her lack of fear, SM is able to exhibit other basic emotions and experience the respective feelings.

The findings support the conclusion that the human amygdala plays a pivotal role in triggering a state of fear and that the absence of such a state precludes the experience of fear itself.

The findings support the conclusion that each basic emotion is processed in a specific brain region. Amygdala is thus one of these brain regions specifically devoted to processing of fear.



Amygdala is implicated in some anxiety disorders and post-traumatic stress disorder (PTSD). The National Institute of Mental Health estimates that over 7.7 million individuals are affected with PTSD in the USA. It has been predicted that approximately 300,000 military personnel would return from combat in Iraq/Afghanistan with PTSD.



Based on the analogy with loss of fear response caused by a **decrease** in the activity of the amygdaloid complex (Urbach-Wiethe disease), it is reasonable to speculate that a pathological **increase** in the activity (irritability) of amygdala complex is causing PTSD.

Learning Objectives: Limbic System– Emotional Experience:

Students should know: The visceral and skeletomuscular activities associated with emotional reactions. The brain structures that constitute the new definition of the Limbic System, the pathways connecting component structures, and a particular function for each component. The importance of the amygdala and the anterior cingulate gyrus and the diseases associated with these areas. The neuromodulators produced in the brain stem and the most common psychiatric diseases associated with their dysfunction. >>end of document<<