# BASAL FOREBRAIN ORGANIZATION

Basal ganglia. Structures usually included in the basal ganglia are: caudate nucleus, putamen, globus pallidus, substantia nigra and subthalamic nucleus. The lentiform nucleus is used as a general term for the putamen and globus pallidus. These two structures, however, are characterized by great differences in histologic structures and anatomic relationships, and a functionally more appropriate alignment is established between the caudate nucleus and putamane, which are referred to as striatum.

Striatum: Although the caudate nucleus and putamen are separated by the projection fibers forming the internal capsule, bridges of cells connect the two nuclei in many places, especially at more rostral levels. The large rounded part of the caudate that forms the lateral wall in the anterior horn of the lateral ventricle is known as the head of the caudate. There is a broad region of continuity between the two structures underneath the rostroventral part of the internal capsule. This area is often referred to as the the fundus striati or nucleus accumbens. The body of the caudate tapers and sweeps downward in a semicircular fashion behind the internal capsule and then forward into the temporal lobe towards the region of the amygdaloid body, following closely the course of the inferior or temporal horn of the lateral ventricle.

Globus pallidus and ventral pallidum. The globus pallidus is subdiveded into and outer (lateral) and an inner (medial) segment by a medullary lamina. Whereas the medial and dorsal boundaries of the globus pallidus are well demarcated against the internal capsule, its ventral border is more difficult to define. Traditionally, only a small part of the globus pallidus was defined underneath the anterior commissure. However, recent studies with modern tracing techniques and immunohistochemical methods for the identification of pallidal markers, e.g. GAD, Substance P, or enkephalin, have shown convincingly that the ventral striatum is accompanied by a ventral extension of the globus pallidus, ie. ventral pallidum.

Septum, diagonal band, basal nucleus of Meynert, and substantia innominata.

The septum pellucidum is a thin lamina of glia and fibers that stretches between the anterior part of the corpus callosum and the fornix, thereby separating the anterior parts of the two lateral ventricles. This part of the septum is generally devoid of nerve cells. However, the ventral parts of the septum, the true septum contains important cell groups which merge rostroventrally with the nucleus of the diagonal band. The diagonal bad nucleus, and its accompaning fiber tract, the diagonal band, sweeps downward in front of the anterior commissure on the medial side of the hemisphere and then proceeds caudally and laterally into an ill-defined but extensive basal forebrain region traditionally referred to as the substantia innominata. This region contains a heterogeneous population of neurons and is traversed by a variety of fiber tracts. It extends laterally and caudally deep to the optic tract, between the basal surface of the brain and the lateral extension of the anterior commissure.

Substantia innominata has received considerable attention in the last few years, and the region is of considerable importance for those interested in behavioral disorders. One of its main components is the basal nucleus of Meynert, which can be easily identified in Nissl stained sections of the human brain because of its dense accumulation of large hyperchromeatic neurons. Many of the cells of the basal nucleus of Meynert and in the nucleus of the diagonal band are cholinergic and the two nuclei together with cells in the medial septum project in topographioc fashion to all of the cerebral cortex and the basolateral amygdala. The basal nucleus of Meynert which is the most conspicuous part of the corticopetal system is only one of several important basal forebrain systems in the region of the substantia innominata. The ventral striatopallidal system and the extended amygdala are the other two important systems which are intermingled with the corticopetal system.

Amygdaloid body and Bed nucleus of the Stria Terminalis

The amygdala is a major telencephalic structure that dominates the ventromedial part of the temporal lobe largely in front of the anterior tip of the temporal horn of the lateral ventricle, and immediately underneath the uncus of the parahippocampal gyrus. Traditionally, the amygdaloid complex has been regarded as a key structure in the limbic system, and characterized primarily by its close realtionships to the hypothalamus. In fact, the amygdaloid complex contains many different nuclei, each with its own specific input-output relations: the basolateral group, a centromedial group which in human is located as a dorsal cap on the large basolateral complex - and a smaller cortical group which fuses with the olfactory cortex on the

medial aspect of the parahippocampal gyrus. The basolateral amygdala, although undoubtedly subcortical by definition, is in many aspects reminiscent of cortical structures.

The centromedial complex, unlike the basolateral group, does have significant relations with the hypothalamus as well as other parts of the autonomic nervous system. It is continuous with the bed nucleus of the stria terminalis (BST), which straddles the anterior commissure close to the midline. Centromedial amygdala and the bed nucleus of the stria terminalis are interconnected via cell columns in the sublenticular substantia innominata and to a lesser extent via cells alongside the stria terminalis. The centromedial amygdala and the BST together with these interconnecting cells form an "extended amygdala", which is particularly relevant to emotional behavior.

# AMYGDALOID BODY

The amygdaloid body is a large subcortical structure located in the rostromedial part of the temporal lobe in front of the hippocampus. The amygdaloid body is involved in a large number of functions ranging from motor activities, basic drives like eating and sexual behavior, cardiovascular and endocrine mechanisms, to memory and other higher cognitive processes. Some of the most prominent pathways to the amygdaloid body come from cortical areas in the temporal and frontal lobes. These pathways transmit highly processed sensory information to the amygdaloid body, where the information is being evaluated in terms of its biological significance.

## 1. Subdivisions

The amygdaloid body is located just in front of the hippocampus and the temporal horn of the lateral ventricle and immediately underneath the uncus of the parahippocampal gyrus. A distinction can be made between a basolateral, cortical and centromedial nuclear groups.

Basolateral amvgdala. A large part of the amygdaloid complex is occupied by the basolateral nuclear group, which is closely related to the cerebral cortex. In fact, its histology, histochemistry and connections are in many ways reminiscent of a cortical structure.

Cortical Amvgdala. It is located on the surface of the amygdaloid body adjacent to the temporal cortex and the medial amygdaloid nucleus. Since the primary input to the cortical nuclear group comes from the olfactory bulb and the olfactory cortex, the cortical nuclear group is referred as the olfactory amygdala.

Centromedial Amygdala. The centromedial part (CM) of the amygdaloid body is directly continuous with another large nucleus close to the midline, i.e. the bed nucleus of the stria terminalis (BST). The CM, BST and the cell columns between them form the so called "extended amygdala".

## 2. Connections

Basolateral Amygdala.

Cortical conenctions. The BL receives highly processed sensory information from prefrontal, temporal and insular regions. The cortico-amygdaloid pathways, which uses glutamate and/or aspartate as their transmitters, are reciprocated by similar amygdalocortical pathways to limbic, associational cortices and even to the primary visual cortex. The amygdaloid complex does not receive an input from primary sensory or early associational areas of the cerebral cortex but those areas which do send fibers to the lateral and/or basolateral nuclei have been shown to receive convergent multisensory pathways. Interestingly, some axons from the amygdala are non-reciprocal in the sense that they project to early association cortices and even some primary sensory (visual, somatosensory) areas (Amaral and Price). This nonreciprocal projection suggest that amygdaloid structures can alter initial sensory processing in the cortex and/or can reactivate or select percepts unique to, or stored in, early association cortical areas (Damasio).

Subcortical connections. Like the rest of the cerebral cortex, the basolateral amygdala projects to the striatum, especially its ventral part, and it also send fibers to the mediodorsal nucleus of the thalamus, which in turn projects to the prefrontal cortex. This provides another route, whereby the amygdaloid body can influence the activity in the medial and orbital prefrontal cortex. Thalamo-amygdaloid projections are also prominent, for example, the BL receive projections from the pulvinar, the intralaminar and the mediodorsal nucleus of the thalamus. The BL apparently receive modality-specific (viscerosensory, auditory/spinothalamic) information from the thalamus. Another similarity between BL and the rest of the cerebral cortex is that both structures receives cholinergic input from the basal nucleus of Meynert.

Olfactory Amygdala. Olfactory input reaches superficial parts of the amygdala, i.e. the cortical nuclear group, both directly from the olfactory bulb and indirectly from the olfactory cortex. The olfactory amygdala, in turn, projects to the centromedial amygdala and to the hypothalamus.

Centromedial Amygdala. Although the centromedial amygdala and the rest of the extended amygdala also receive input directly from the cerebral cortex, it is largely restricted to fibers from the insula and orbitofrontal cortex, and is not reciprocated. It also receive viscerosensory/auditory/spinothalamic information from the thalamus. A massive system of intra-amygdaloid association fibers reach the centromedial amygdala from the basolateral amygdala, which in turn receives a wealth of modality specific and multimodal sensory input from the cerebral cortex. The centromedial amygdala does not project to the striatum, instead it projects, together with the rest of the extended amygdala, to many regions in the hypothalamus and brain stem. It is through these pathways, which proceed both in the stria terminalis and the ventral amygdalofugal pathway, that the amygdaloid body can directly influence areas that generates various autonomic, endocrine and somatomotor aspects of emotional behavior and motivational states or drives, e.g. eating, drinking and sexual behavior.

## 3. Four amygdaloid sensory-motor systems

Based upon connectional data primary in rodents, Turner and Herkenham (1991) hypothesized the existence of several amygdaloid subsystems subserving different sensory-motor transformations.

A)The corticomedial amygdaloid system: unimodal (pheromonal) relays to the medial basal forebrain and medial hypothalamus. All of the amygdaloid and hypothalamic nuclei in this system have receptors for circulating androgens and estrogens. The output of this system is to the PAG and the ventromedial field of the brainstem tegmentum. Destruction of the medial amygdaloid nucleus eliminates male sexual behavior, supporting the notion that the function of this nucleus is to relay 'relevant chemosensory cues during both appetitive and consummatory phases of mating behavior. Destruction of its hypothalamic targets

–the medial preoptic area and the ventromedial hypothalamic nucleus -eliminates male and female sexual behaviors.

B)<u>The lateral-basomedial amygdaloid system</u>: multimodal (auditory and viscerosensory) relays to the medial basal forebrain and ventromedial hypothalamus. This system is organized around the lateral nucleus. Within the amygdala further convergence of all four modalities occurs. This combined information is relayed to the core of the ventromedial hypothalamus, where it is further mixed with pheromonal information from the corticomedial system and with endocrine information. Because both corticomedial na dlateral-basomedial systems are convergent in the medial basal forebrain and medial hypothalamus, their outputs to the medial brainstem are identical. This system appears to be identical with the fear conditioning system of LeDoux.

C)<u>The system of the central complex</u>: multimodal (viscerosensory and auditory) relays to the lateral basal forebrain, lateral hypothalamus and brainstem. There is evidence that the viscerosensory and auditory connections of the central complex are engaged in the conditioning of cardiovascular responses to auditory stimulus which signal the imminent onset of aversive or stressful conditions. Drewett and Zbrozyna (1985) found that increases in the systolic and diastolic blood pressures that normally occur in response to electrical shock can be conditioned such that the buzzer alone will come to elicit these rises in blood pressure. That such behavioral stimulus –response conenctions may occur in the central nucleus is suggested by conditioned changes in the firing patterns of these cells after tone-shock conditioning (Kapp, 1985). Finally, lesions of the outflow pathways of the central nucleus abolish cardiovascular and escape responses conditioned to sensory stimuli (LeDoux et al., 19880.)

D)<u>The basolateral system:</u> a unimodal (viscerosensory) relay to the lateral basal forebrain and lateral brainstem

According to this hypothesis afferent sensory information is restructured in the amygdala and distributed to two output channels in the basal forebrain, hypothalamus and brainstem in order to achieve particular functional outcomes.

 <u>The medial divison channels</u> sensory information processed by the corticomedial and lateral-basomedial amygdaloid systems to the ventromedial substantia innominata, medial bed n. of the stria terminalis (BST), medial preoptic, anterior andventromedial hypothalamic nuclei. From here the information is channeled to the periagueductal gray (PAG) and ventromedial tegmental field, raphe magnus and pallidus. These neurons in turn project, respectively, to the dorsal and ventral horns of the entire spinal cord. This system uses endocrine, pheromonal, visual, orosensory, viscerosensory, auditory/spinothalamic information in their organization of male and female sexual behaviors, affective attack, defense or feeding. Their diffuse spinal terminations suggests that this system functions as a lever setter and pain thresholds.

<u>The lateral divison funnels</u> the sensory information processed by the central and basolateral amygdaloid system via the lateral BST, dorsolateral SI, LH to the brainstem (PAG, parabrachial nuclei, NTS, dorsal motor nucleus of the vagus, etc). The brainstem termination of these fibers include premotor neurons which are involved in respiration, vomiting, swallowing, chewing, licking and control of vascular bed. This lateral system corresponds to the 'third motor system' of Holstege (1990) and is hypothesized to be important for the expression of functions organized by the amygdala and hypothalamus. Hypothalamically elicited biting is blocked by medial and ventral lesions of the midbrain tegmentum, whereas affective attack or defense and vocalization are blocked by central gray/ventroalteral tegmental lesions. The behavioral component (freezing) of conditioned fear, an amygdala function is blocked by destruction of the caudal ventral PAG. The lordosis reflex of estrogen-primed or hypothalamically stimulated female rats is eliminated by lesions of the dorsal PAG (Pfaff).

## 4. Functional Aspects

1)The Circuit of Papez and the Limbic System Concept
2)The Kluver-Bucy Syndrome
3)The amygdala in olfactory processing
4)Emotional recognition and the human amygdala
6) Influence of emotional processing on other aspects of cognition
7)Fear Conditioning

8)Anxiety/Mood Disorders
9)Temporal Lobe Epilepsy
10) Schizophrenia

## Theories of Emotion. The Circuit of Papez and the Limbic System Concept

According to the James-Lange theory emotional feelings (conscious experience of emotion) are responses to information from the periphery (increase or decrease of blood pressure, heart rate, muscular tension, etc)."We feel sorry because we cry.., afraid because we tremble and not that we cry, because we are sorry, angry or fearful" (James) In the Cannon-Bard hypothesis, the emphasis is on the fight-or-flight responses following emotional feelings. Cannon suggested that the flight-or-fight response was mediated by the sympathetic component of the autonomic nervous system and the hypothalamus and cerebral cortex played a key integrative role in emotional processes (Bard, 1929, Cannon, 1931). In 1937, Papez proposed a circuit of emotion involving the hypothalamus, anterior thalamus, cingulate cortex, and hippocampus. The amygdala was not included. MacLean's (1949, 1952) limbic system hypothesis expanded the emotional system to include much of the subcortical forebrain (including the orbitofrontal cortex and the amygdala) and several additional cortical structures as well.

Even though the connectional scheme of Papez is basically correct, it has been modified on several important points. A unified functional role of the circuit in the expression of emotions has not been corroborated by later research. For example, the afferent fibers of the mammillary nuclei (passing in the fornix) do not come from the hippocampus itself but from adjacent regions in the parahippocampal gyrus. Also, the hippocampus, mammillary bodies and the anterior thalamic nuclei which were central to Papez' circuitry about emotion, were found not to be involved in emotion but rather important for cognitive forms of memory storage. Today, the hippocampus is generally viewed as more involved in excplicit memory than emotional processes, with the amygdala standing out as the brain region most often implicated in emotional processes. It is thought that the amygdala via the hypothalamus and brainstem integrate autonomic, neuroendocrine and musculoskeleteal responses associated with emotions.

## The Kluver-Bucy Syndrome

Kluver and Bucy (1937) described that temporal lobe lesions, including the amygdala produces tameness, hypoemotionality, psychic blindness (visual agnosia) and changes in dietary and sexual behavior. Geschwind (1965), studying the Kluver-Bucy syndrome, helped to identify specific pathways involved in emotional information processing by the amygdala. His work suggested that unless visual information processed in cortical areas reaches the amygdala, its affective (motivational) significance will not be registered.

Anatomical studies have shown that each primary sensory receiving area of the cortex is linked with the amygdala trough a series of corticocortical connections. In the visual system, these involve transmission through striate cortex, peristriate cortex, and temporal netcortex, which then projects to the amygdala.

Studies of the Kluver-Bucy syndrome have contributed significantly to the view that the amygdala is a focal structure in the processing of emotion. Specifically, this work has led to the view that sensory stimuli are endowed with emotional and motivational significance by transmission of sensory input to the amygdala. It is proposed that the K-B syndrome may result in part from an inability to associate stimuli across different modalities (Mishkin).

Electrophysiological recording in the amygdala during exposure to emotional stimuli confirmed that amygdala neurons are more sensitive to complex sensory events with biological significance than to simple meaningless stimuli. It appears, however, that amygdala units are not capable of modifying their responsivity to changing stimulus-reward relations, in other words, emotional memories established through the amygdala are indelible. Apparently, the orbito-frontal cortex play a role in rapid modifications in stimulus-reward relations (Rolls, 1990).

## The amygdala in olfactory processing

It has long been recognized that the only sensory modality to gain direct access to the amygdala is smell, as all other modalities reach the amygdala in stepwise manner via sensory association cortices. The amygdala receives direct input from both the main and the accessory OB. There is considerable evidence demonstrating the importance of the vomeronasal organ in pheromone detection, although the olfactory receptors have also some role in pheromone detection.

A striking feature of some of the structures linked to the accessory olfactory systems is that they exhibit sexual dimorphism. Thus, within the rat amygdala, the medial nucleus and the closely related BST both show gender difference in terms of volume, neurochemistry, synaptology. Many of the medial and cortical amygdala neurons are androgen and oestrogen sensitive and are well positioned to integrate chemosensory and hormonal signals to control social and sexual behavior. Many of these effects are via the amygdala's efferents to the medial hypothalamus. It should be noted that while the vomeronasal organ is present in foetal humans, it has proved difficult to show that it has a role adult humans and apes.

Some of the first evidence came from studies of male hamsters showing that lesions of the medial nucleus but not the basolateral one, eliminated mating behavior. Similarly, exposure to pheromonal cues or copulatory stimuli leads to increased Fos immunoreactivity throughout the olfactory circuits, including the medial amygdala, BST and medial preoptic area. The same medial nuclei in which olfactory and vomeronasal system transmission is modulated by populations of oestrogen- and androgen-sensitive neurons form part of a larger integrative system that controls both male and female sexual and parental behavior, as well as some form of aggression. The medial amygdala is one of a series of structures that coordinate the olfactory recognition of ofsprings. The stimulus involves airborne odours rather than pheromones, and learning initially is triggered by the release of oxytocin as a result of vagioncervical stimulations at birth. In contrast to its clear involvement in social/sexual behavior signaleld by chemosensory inputs, the amygdala appears less important for other forms olfactory-related behavior. For example, Eichenbaum et al reported that bilateral amygdala lesions did not affect the learning of multiple odor discriminations. The reason for the lack of clear deficits would appear to stem, in part, from the existence of parallel olfactory inputs to other regions (piriform cortex, orbitofrontal, entorhinal cortex, thalamic MD nucleus) that can compensate for the loss of amygdala routes. In a study a total of 229 neurons were recorded in the basolateral amygdala during olfactory discrimination learning. Of these neurons, 60 were found to show selective responses depending on whether a particular olfactory cue was paired with a pleasant or an unpleasant outcome. The contribution of the primate amygdala in olfactory processing remains poorly understood.

## Emotional recognition and the human amygdala

In humans, (Adolphs et al.,1994; Young et al., 1995), bilateral amygdala damage results in deficit in identification of fear in facial expressions. (see Appendix for a case report). A further insight came form studies which used stimuli that could not be perceived consciously. Whalen et al (1998) reported amygdala activation when subjects viewed facial expressions of fear that were presented so briefly that they could not be recognized consciously, showing that the amygdala plays a role in non-consious processing of emotional stimuli. Data from SM (see Appendix) and other patients with amygdala lesions suggests that the human amygdala is a component of a neural system specialized for rapidly triggering physiological states related to stimuli that signal threat or danger. It is not that amygdala damage impairs all knowledge regarding fear, rather it impairs the knowledge that fear is highly arousing, which may be an important correlate of the ability to predict potential harm or danger. The human amygdala appears to play a general role in guiding preferences for visual stimuli that normally are judged to be aversive, or to predict aversive consequences.

This function may be especially critical with regard to judgement of social stimuli such as faces. The findings argue that the amygdala helps link percepts of external sensory stimuli with the retrieval of pertinent knowledge, the formation of advantageous decisions and the choice of adaptive behavioral responses that are appropriate to the emotional or social relevance of the stimulus. The role of the amygdala in human social behavior may be most important not in innate feature detection, but in the evaluation of complex stimuli that have acquired relevance through prior experience with similar exemplars.

**Influence of emotional processing on other aspects of cognition**

Several recent functional imaging studies have reported that encoding and consolidation of declarative knowledge into long-term memory activated the amygdala, when the material that is being encoded is emotionally arousing. Emotionally arousing stimuli activate the amygdala during encoding, and are remembered better. In contrast, encoding of material that is emotionally neutral correlates with activation of the hippocampus, but not the amygdala (Alkire et al., 1998). Furthermore, the amygdala activation observed correlated with activation of the hippocampus (Hammann et al., 1999), consistent with findings from animal studies that emotional arousal engages amygdala-dependent modulation of hippocampal memory system. The mechanisms for the emotional facilitation of declarative memory consolidation in humans are not well understood.

It is known that emotional processing contributes importantly to decision making under conditions of uncertainty, a function that has been studies with regard to the ventromedial prefrontal cortex (Damasio). Recent studies suggest that the amygdala does contribute importantly to making decisions on the basis of prior emotional associations with similar situations. Thus, like the subjects with ventromedial prefrontal damage, SM (see Appendix) is also impaired in a gambling task on which choices must be made on the basis of hunches under conditions of uncertainty (Bechara et al., 2000). Amygdala and ventromedial prefrontal cortices may play complementary roles in guiding choices by feelings.

**Learned Emotional Responses. Fear Conditioning**

It is well established that emotionally neutral stimuli can acquire the capacity to evoke striking emotional reaction following temporal pairing with an aversive event. Conditioning does not create a new emotional responses but instead simply allow new stimuli to serve as triggers capable of activating existing, often hard-wired, species-specific emotional reactions. In the rat, a pure tone previously paired with footschock evokes a conditioned fear reaction consisting of freezing behavior accompanied by a host of autonomic adjustments, including increases in arterial pressure and heart rate. Recent studies have identified neural circuits which are essential for the conditioning of the autonomic and behavioral fear responses (see Fig. of LeDoux). The pathway involves the relay of the auditory stimulus through the primary acoustic structures of the brain stem to the inferior colliculus and then to the medial geniculate body. From there, the auditory signal is transmitted directly to the lateral amygdaloid nucleus. From here through the output from the central amygdaloid nucleus (ACE) the pathway separates into two components: projections from the ACE to the lateral hypothalamic area, which in turn, is connected with brain stem and spinal premotor neurons of the autonomic nervous system, are critically involved in the control of autonomic changes, whereas, behavioral fear responses depend upon projections to the midbrain central gray region.

The pathways mediating fear conditioning involve a direct thalamo-amygdala projection and thus bypass the neocortical auditory system. This observation indicates that fear conditioning does not require

the auditory cortex when a simple acoustic event serves as conditioned stimulus. Presumably, however, if the conditioned stimulus information is increased in complexity, such that cortical analysis is required, the pathway would indeed involve the auditory cortex and cortico-amygdaloid projections. The lateral amygdala is thus a site of convergence of acoustic pathways originating in the thalamus and neocortex. While the thalamic pathway provides the amygdala with a rapid but crude representation, the auditory cortex transmits slower but refined message. Interaction between the thalamic and cortical sensory information in the amygdala may play an important role in emotional processing.

Subjects presented repeatedly with a neutral visual stimulus (CS) together with an offensively loud noise (US) soon show an emotional response –sweating hands, dry mouth, and facial perspiration –to the neutral image alone. In contrasts, patients with damage to the amygdala do not learn to fear the neutral images even though most were consciously aware that the neutral image and the offensive noise were paired together. In contrast, patients with hippocampal lesions showed the opposite pattern: they are unable to report the pairing of a neutral stimulus with CS but learned the conditioned fear response. Patients with lesions in both the amygdale and hippocampus showed neither autonomic conditioning nor knowledge of the testing situation. This double dissociation between patients who have amygdala lesions and patients with hippocampal lesions highlight the fact that the amygdale is necessary for the implicit expression of emotional learning and the hippocampus is necessary to acquire explicit or declarative knowledge of the emotional properties of a stimulus.

**Anxiety/Mood Disorders**

The lateral amygdaloid nucleus receive also inputs from the hippocampus. Thoughts and memories processed in the hippocampus might, therefore, receive emotional coloration by way of information transfer to the amygdala. By this account, the distinction between fear and anxiety is based on whether the emotional processing mechanisms of the amygdala are activated directly by sensory information originating in thalamic and cortical areas or by cognitive processes organized in the hippocampus. The hippocampus (and other areas of the limbic system with which it is connected), then, would contribute to anxiety as a cognitive rather than as an affectlye processsing structure.

The amygdala contains a very high level of GABA/benzodiazepine receptors and may be a strong candidate region for the mediailion of anxyolitic effects of benzodiazepine drugs. Since the highest level of these receptors is located in the lateral nucleus, which receives most of the sensory information directed to the amygdala, it is plausible that the benzodiazapine drugs might act upon the lateral nucleus to prevent the linkage of emotional significance to sensory stimuli.

Similarly, recent experiments using PET to monitior local synaptic activity (reflected as regional cerebral blood flow, rCBF) support the involvement of the amygdala in the psychopathology of affective disorders. Thus, in studies of patients with severe unipolar depression, significant increases in rCBF were found in the amygdala and in areas to which it is closely connected in the ventrolateral and medial prefrontal cortex (Drevets). A similar interaction of the amygdala and many of the regions to which it is connected may underlie the phenomenon of panic disorder. Patients experiencing severe anxiety as part of a panic attack show increased rCBF in the cortex of the temporal lobe, a region that is extensively interconnected with the amygdala (Raichle).

**Temporal Lobe Epilepsy**

It has been known for over 100 years that epileptic seizure activity of the temporal lobe can give rise to psychic or experimental states (Jackson, 1880). Later studies by Penfield and associates confirmed and extended these observations by delivering electrical impulses to the temporal lobe in the course of surgical procedures aimed at relieving the epileptic condition (Penfield and Jasper, 1954). Such stimulations were found to produce hallucinations, illusions, memory flashbacks, 'déjà vu' experiences, fear and other emotions. Penfield attributed these phenomena to activation of neocortical memory networks. However, more recent work has suggested that the effects are due mainly to activation of the amygdala and hippocampus (Gloor, 1982). Given the role of the amygdala in emotion and the hippocampus in declarative memory (conscious recollection of facts and experiences), it is possible that together these structures and their cortical connections are involved in the affective or motivational coloration of conscious experiences.

In any case, these data are compatible with the notion that complex sensory information might be transmitted to the amygdala in order that an appropriate motivational tag be marshalled and transmitted for linkage in the neocortex. The amygdalocortical projections thus would provide the neocortex with an indication of the significance of the percept. With the route of cortical sensory input to the amygdala well established, it is important to find out what is the source of reward or affect related signal? Electrical stimulation of certain posterior orbital areas alone appears to be rewarding (Mora et al., 1980). These orbital areas are part of an orbital network that receives and integrates convergent olfactory, gustatory, visceral as well as visual and somatosensory inputs from the face and hand (Carmichael and Price, 1996). Therefore, the connections and the behavioral and physiological response properties of the posterior orbital cortex indicate that a reward construct may be abstracted from the sensory and visceral stimuli that accompany food consumption. Lesion of the amygdala disrupt prior food preferences and lead to novel ingestive behaviors, such as meat eating or coprophagy (Baylis and Gaffan, 1991). Amygdaloid lesions also lead to a generally heightened orality (Weiskrantz, 1956). Neurophysiological studies have identified amygdaloid neurons whose activity is altered by rewarding or aversive gustatory stimuli coupled to otherwise neutral objects (Nishijo et al., 1988). These data are at least compatible with the notion that the reward-related signal may arise in the orbital and medial prefrontal cortex (OMPFC) and transmitetd from here to the amygdala. An additional reward-related signal may arise from interactions with the nucleus basalis Meynert, which has heavy reciprocal connections with both the basal amygdaloid nucleus and the orbital cortex.

**Schizophrenia**

Schizophrenia is characterized by a mixture of symptoms, including thought disorders, delusions (false beliefs or wrong judgements), hallucinations (false perceptions), blunted affect and social withdrawal. Although no single structure or lesion can be specifically related to schizophrenia, there is considerable evidence, especially from recent imaging studies and postmortem examination of brains from schizophrenic patients, that pathologic processes and developmental abnormalities in the medial temporal lobe, including the hippocampus formation and amygdaloid body, are of special importance in a significant number of patients.

As indicated above, the amygdaloid body is part of a system that is crucially involved in attaching emotional and biological relevance to sensory stimuli. If this mechanism is destroyed or disturbed by a lesion in or around the amygdaloid body, the emotional response to external events and socially important stimuli may be diminished (blunted affect, emotional withdrawal) or distorted, e.g. in the form of excessive suspiciousness (paranoia), symptoms commonly seen in schizophrenia as well as temporal lobe epilepsy. A

recent fMRI study (Phillips et al., 1999) found evidence of abnormal amygadala activity to certain expressions in schizophrenics. Schizophrenics show increased level of DA in the left amygdala (Reynolds). A persistent problem for the dopamine theory is the fact that schizophrenia is associated with abnormalities in multiple sites. Notable among them is the prefrontal cortex. The challenge, therefore, is to bring together seemingly disparate pathologies in a manner consistent with the disorder. Recent developmental studies by showing that the maledevelopment of the medial temporal lobe results in abnormal prefrontal function and dopamine regulation, are now providing such a framework (Weinberger).

## APPENDIX

Neuroanatomy and Neuropsychological Background of SM. A case report.

SM is a 32 year old woman with a rare, heritable illness that affects primarily epithelial tissue, Urbach-Wiethe disease. The disease, also known as lipoid proteinosis, typically exhibits a variable phenotype of thickened skin, thickened vocal cords, beaded apperance of the eyelids, and diagnostic staining of epithelial tissue with lipophilic dyes. In roughly half the cases, patients develop avascular and atrophic mineralization of medial temporal neural tissue. This involves variable calcification of hippocampal, amygdaloid and adjacent parahippocampal, periamygdaloid, entorhinal and perirhinal cortices. In case of SM she sustained her amygdala demage in early childhood. MRI scans taken at various times show selective and complete bilateral damage of the amygdala as well as some minor damage to the anterior entorhinal cortices. There is no other damage in the brain. The hippocampus is not involved.

Behavior: Her interpersonal behavior show slight disinhibited style, she does not, however, exhibit any of the features of theclassic Kluver-Bucy syndrome.

Intellect: commensurate with her education

Memory: performance on all major components of the Wechsler Memory Scale-revised are within expectation

Speech and linguistic function: her speech is markedly hoarse. Naming, repetition, comprehension, reading and writing are all intact. She performs defectively on the Controlled Oral Word Association Test, which is interpreted as a mild weakness in 'executive function'.

Visuoperceptual, visuospatial, visuocontstarctional function: intact

Executive function: she had some difficulties on tasks of executive function, which tap abilities such as judgement, planning and cdecision making. Although she is normal on the Wisconsin Card Sort Test, she had difficulty with two 'tower' tasks (Tower of Hanoi, Tower of London).

Personality assessment: no evidence of any form of significant psychopathology. Some indication of antisocial behavior: comprising features such as rebelliosness, disregard of social convention and lack of respect for authority figures.

Recognition of emotion in facial expression: SM stands out as specifically impaired in her ability to assign normal ratings to faces of fear, but normal in her ability to recognize emotions other than fear. She also could not recognize some emotions as similar to one another. When she was with explicit questions about the degree of fear shown by the stimuli "Does this person look as though they might be feeling any fear at all, even the smallest amount? For 5/6 of the stimuli depicting prototypical fear, she responded that, while she was not sure what the emotion was, there was no trace of fear whatsoever. When she was asked the spontaneous naming of the emotions shown in faces, she virtually never used the label fear, typically

mislabeling such faces as surprised, angry or disgusted. Her ability was normal to recognize other information from faces. Interestingly, her recognizing emotions in prosody was intact.

    <u>Recognition of emotional arousal</u>: she was impaired in her ability to recognize the arousal signaled by stories and by words denoting negative emotions.

    It is hypothesized that amygdala damage early in life impaired her experience of emotional arousal in conjunction with certain classes of sensory stimuli and that she consequently failed to develop normal knowledge of which stimuli are emotionally arousing.