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Knowing the amygdala: its contribution to psychiatric disorders

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Abstract

The present article provides a brief description of the anatomical and chemoarchitectonic organization of the primate amygdala reviewing the functional importance of this structure and analysing how its failure can result in brain disease with special reference to psychiatric disorders.

Key-words*: Amygdala; Anatomical and functional aspects; Psychiatric disorders.*

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ANATOMY

The amygdala owes its name to Burdach, and to its resemblance to an almond. The amygdaloid nuclear complex comprises a group of 13 nuclei (Amaral *et al.*, 1992) lying in the dorsomedial temporal pole, anterior to the hippocampus and near the tail of the caudate nucleus. There is no consistent nomenclature for the amygdaloid nuclei, and they display different spatial interrelationships in non-primate and primate species that appear to have been brought about by a ventromedial rotation of the complex as a result of the differentiation of the neocortex. The nomenclature herein adopted is that proposed by Amaral *et al.* (1992).

Most of the amygdaloid nuclei are divided into subnuclei called divisions. Information flow within the amygdala occurs through three distinct levels of connectivity: internuclear, interdivisional and intradivisional (Pikänen *et al.*, 1997). Major intrinsic connections in the macaque monkey have two main features: one is the tendency for information to flow in a lateral to medial direction, and the other is the tendency for in-

formation to flow in a ventral to dorsal direction (Aggleton and Saunders, 2000). The amygdala has cortical and subcortical connections making it capable of interacting with every sensory modality (Aggleton and Saunders, 2000). Through its subcortical connections, the amygdala can also affect autonomic, hormonal, and motor function (Aggleton and Saunders, 2000). Also, the amygdala has many connections with the cortex, and its central position is a reflection of the fact that the amygdala receives highly processed sensory information and is in a position to integrate information both across and within modalities.

Specifying, the amygdala projects to the brain stem mainly from the central nucleus. The brain stem also sends afferents to the amygdala: serotonergic afferents from the midbrain raphe (particularly to the magnocelular and parvicelular parts of the basal nucleus, medial edge of the central nucleus, medial nucleus and lateral nucleus), dopaminergic afferents from the ventral tegmental area and substantia nigra (terminating mainly in the medial division of the central nucleus, but also in the lateral and basal nuclei) and noradrenergic afferents from the locus coeruleus and subcoeruleus – densest concentration of fibers found in the medial part of the central nucleus of the amygdala (Fallon and Ciofi, 1992). The central nucleus of the amygdala is the major origin of projections to the hypothalamus whereas return projections are sparse. There is a substantial amygdaloid projection (predominantly from the basal and accessory basal nuclei) to the ventral parts of the striatum, especially the nucleus accumbens and olfactory tubercle, but also to the more dorsal and caudal parts of the striatum, and to the ventral pallidum. The nucleus accumbens has a substantial projection to the ventral pallidum and this, in turn, projects to the mediodorsal thalamic nucleus, which provides another pathway in addition to the direct projection from the amygdala to the mediodorsal nucleus of the thalamus and then with the prefrontal cortex (Amaral *et al.*, 1992). The amygdala also connects in a reciprocal and substantial way with the basal forebrain. Efferent fibres originate mainly in the basal, accessory basal and central nuclei and project to the magnocellular basal forebrain nuclei (which include the basal nucleus of Meynert). Afferent fibres to the amygdala reach mostly the basal nucleus (Amaral *et al.*, 1992). The projection from the basal nucleus of Meynert to the basal nucleus of the amygdala is the most important cholinergic projection of any forebrain region (Parent, 1996). Most amygdaloid nuclei project to the thalamus, particularly to its mediodorsal nucleus (mainly from the lateral, basal and accessory basal nuclei and the periamygdaloid cortex), but this does not project back to the amygdala (Aggleton and Mishkin, 1984; Russchen *et al.*, 1987). The part of the mediodorsal nucleus that receives afferents from the amygdala projects to identical medial and orbital prefrontal cortical areas that re-

ceive amygdaloid afferents directly (Porrino *et al.*, 1981). The central and medial nuclei of the amygdala project to midline nuclei of the thalamus and these project back to the amygdala – primarily to central and basal nuclei (Price and Amaral, 1981; Aggleton and Mishkin, 1984). The parvicelular ventral posterior medial and the medial geniculate nuclei also project to the amygdala (Amaral *et al.*, 1992). The lateral, accessory basal and basal nuclei contribute with the largest proportion of projections to the hippocampal formation, mainly to the rostral entorhinal cortex but also to the hippocampus and subiculum. The hippocampal projections to the amygdala are less extensive with the border zone of the CA1 field and adjacent subiculum and perhaps also the entorhinal cortex, sending efferents mainly to the basal nucleus of the amygdala (Amaral *et al.*, 1992). Cortical inputs to the amygdala arise in unimodal and polymodal regions of the frontal, cingulated, insular, and temporal neocortex. Amygdala projections to the cortex arise mainly in the basal nucleus, and efferents from the lateral and cortical nuclei can also be demonstrated.

Besides the referred monoaminergic and cholinergic innervations of the amygdala, the monkey amygdala contains high concentrations of GABA, glutamate and aspartate (Amaral *et al.*, 1992). Interest has focused on the GABAergic system of the amygdala because of the high concentration of benzodiazepine binding sites, especially $GABA_A$ binding sites in the lateral and accessory basal nuclei (Niehoff and Kuhar, 1983; Niehoff and Whitehouse, 1983), which is known to mediate changes in anxiety (File, 2000). Glutamatergic afferents from frontal, cingulate, insular and temporal cortex, hippocampus, entorhinal cortex, claustrum, and midbrain peripeduncular nuclei end in the basolateral nuclear group (Parent, 1996). There are many neuropeptide-containing neurons in the amygdaloid complex: somatostatin, vasoactive intestinal peptide (Hayashi and Oshima, 1986), neuropeptide Y (Beal *et al.*, 1987), vasopressin, oxytocin (Caffé *et al.*, 1989), corticotrophin releasing hormone (Basset and Foot, 1990), cholecystokinin (Kritzer *et al.*, 1988) and opioid peptides (e.g., Inagaki and Parent, 1985). Parts of the amygdaloid complex have quite high numbers of steroid hormone concentrating neurons and binding sites (e.g., Clark *et al.*, 1988).

FUNCTIONS

The first informations regarding amygdala functions came from Klüver and Bucy (1937) reports of monkeys with bilateral temporal lobe damage having visual agnosia, hyperorality, hypermetamorphosis, blunting of fear or rage and hypersexuality. Later studies confirmed this syndrome to be due to bilateral amygdala damage (Weiskrantz, 1956).

The amygdala is related to emotional and social behaviour, to learn-

ing and memory (e.g., Aggleton, 1993). Studies of amygdala function in animals use conditioning (e.g., Hatfield *et al.*, 1996), amygdala lesion techniques (eg., Roozendaal *et al.*, 1991), models of anxiety and depression (e.g., Duncan *et al.*, 1986), electric or chemical (ex.: cocaine), kindling (e.g., Kalynchuk *et al.*, 1997), and social interactions (e.g., Emery *et al.*, 1998).

Converging evidence from these studies indicates that the amygdala, and its many efferent projections, represents a central fear system involved in both the expression and the acquisition of conditioned and unconditioned fear (Davis, 2000). The amygdala receives highly processed sensory information primarily through its lateral and basolateral nuclei, which project to the central nucleus and in-turn this nucleus projects to hypothalamic and brainstem target areas that directly mediate specific signs of fear and anxiety (Davis, 2000). Most studies of fear conditioning have used auditory stimuli as conditional stimuli (CSs), which act through different pathways in fear conditioning depending on the nature of the stimuli and the learning task. In this context, it is known that, for conditioning to a tone, projections from lateral to central amygdala nuclei are involved, whereas for contextual conditioning, projections from the hippocampus to the basal and/ /or accessory basal nuclei of the amygdala are needed. On the other hand, to learn an instrumental fear response controlled by a tone CS, projections from lateral to the basal nuclei are used. In this case, it has been demonstrated that the response is controlled by projections from the basal nucleus to the striatum (LeDoux, 2000). During fear conditioning, the firing properties of cells in the lateral nucleus of the amygdala are modified, but this does not mean that the amygdala is a site of memory storage (Cahill and McGaugh, 1998); instead, it modulates memories that are formed elsewhere. There are multiple memory systems in the brain and the amygdala modulates declarative or explicit memories formed through hippocampal circuits or habit memories formed through striatal circuits (Packard *et al.*, 1994).

Other studies suggest that the amygdala plays a crucial role in many aspects of social cognition which encompass the regulation of emotional responses, the establishment and maintenance of social bonds, the decoding of sensory social signals from other individuals and the development of appropriate sexual behaviours and proper maternal responses to infants (Bachevalier, 2000). Given the relationship of the amygdala with emotional and behavioural responses, it is not surprising that it affects almost all aspects of social cognition (Kling and Brothers, 1992). Studies of social interaction demonstrate a significant contribution of the amygdala to affiliative behaviours (Emery *et al.*, 1998; Kling *et al.*, 1979). Several studies indicate that the amygdala appears to code and process facial movements, body postures, and gestures

that are important signals for the production and modulation of appropriate social and emotional responses towards other individuals (e.g., Perret *et al.*, 1984; Rolls, 1994). As described by Klüver and Bucy (1937) amygdalectomy is associated with hypersexuality and Kling (1972) found that amygdala damage has profound effects on maternal behaviours.

Kindling is an experimental paradigm used to model temporal lobe epilepsy (Weiss *et al.*, 2000), in which repeated electrical stimulation of central nervous system structures leads to the progressive development of motor seizures (Goddard, 1967).

The amygdala has shown extreme vulnerability to kindling (Fudge *et al.*, 1998). It is suggested that delineation of the cellular mechanisms underlying kindling may reveal substrates of plasticity operative in non-epileptic situations ranging from normal memory formation to evolving, pathological neuropsychiatric conditions (Weiss *et al.*, 2000).

FUNCTION STUDIES IN HUMANS

Studies regarding amygdala function in humans were first conducted in humans with amygdala lesions either in result of disease (Markowitsch *et al.*, 1994; Adolphs *et al.*, 1994) or after surgical resection, to treat patients with temporal lobe epilepsy (Phelps *et al.*, 1998; LaBar *et al.*, 1995). Now, with the advent of functional neuroimaging techniques, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), study of the human amygdala function *in vivo* has been improved (Irvin *et al.*, 1996; Morris *et al.*, 1996; Schneider *et al.*, 1997).

Animal studies have revealed a critical role for medial temporal lobe structures, particularly the amygdala, in the simple and complex associative emotional responding. Coping with these experimental studies, in humans with unilateral anteromedial temporal lobectomy, both simple and conditional discrimination tasks showed impaired conditioned response acquisition, relative to control subjects, which was reported to be likely due primarily to amygdala damage. This suggests that the role of the structures governing simple and complex conditioned fear associations, as postulated in animal models of fear conditioning, extends to the human brain (LaBar *et al.*, 1995). In a study of bilateral amygdala damage, Bechara *et al.* (1995) found blocked ability to acquire conditioned skin conductance response to the conditioned stimuli (monochrome slides and computer generated tones) but did not preclude the acquisition of facts about which stimuli were followed by the unconditioned stimuli. The authors suggest that the amygdala is indispensable for emotional conditioning and for the coupling of exteroceptive sensory information with interoceptive information concerning somatic states (emotion and affect).

Adolphs *et al.* (1994) studied a pa-

tient suffering from Urbach-Wiethe disease that caused nearly complete bilateral destruction of the amygdala and found a severe recognition impairment specific to fear and inability to perceive similarity between expressions of different emotions, but preserved recognition of the unique identity of faces. From this situation they advanced that the amygdala appears to be an important component of the neural systems subserving social cognition, in part because of its involvement in recognizing face signaling as being essential for successful behavior in a complex social environment. Another study of two patients with the same disease and similar lesions of the amygdala (Markowitsch *et al.*, 1994) found certain memory tasks disturbed, especially those likely to have affected the patients emotionally. The authors concluded that the amygdala (and septal nuclei) are structures which influence memory performance by structuring, selecting and filtering out information of different relevance to the individual (Markowitsch *et al.*, 1994).

Irvin et al., (1996) were the first to demonstrate amygdala activation (using echo-planar fMRI) in a normal human sample in response to affectively negative visual stimuli as compared to neutral visual stimuli. Experimentally induced sadness increases left amygdala blood flow (Schneider *et al.*, 1995) and sadness and happiness increase left amygdala signal intensity measured by fMRI (Schneider *et al.*, 1997). Morris *et al.* (1996) studying neural activity in normal subjects by PET in response to pictures of facial expressions of fear and happiness, found left amygdala activation related to fear facies and to the intensity of emotion (the more fearful more activation and the opposite with happiness). These studies are consistent with the importance of the amygdala in social interactions.

STUDIES IN HUMANS WITH PSYCHOPATHOLOGY

Involvement of the amygdala has been found in anxiety, depression (Sheline *et al.*, 1998), various dementing disorders (Chow and Cummings, 2000) and schizophrenia (Pearlson *et al.*, 1997).

Patients with a history of recurrent major depression had significantly smaller amygdala core nuclei (basolateral group) volumes than case-matched controls, but no significant reduction in the areas of the amygdala surrounding the core nuclei, nor was the reduction in core amygdala volumes a result of overall brain atrophy (Sheline *et al.*, 1998). Tebartz van Elst *et al.* (1999) found a highly significant enlargement of left and right amygdala volumes (using quantitative MRI) in patients with temporal lobe epilepsy (TLE) and dysthymia compared to healthy volunteers. They also found a positive correlation between left amygdala volumes and depression (as measured with the Beck Depression Inventory) and significantly larger female amygdala volumes. They consider the possibility that increased processing of emotional

information might increase amygdala blood flow and result in amygdala enlargement. Another study by Tebartz van Elst *et al.* (2000) also found significantly larger amygdala volumes in depressed patients with TLE and larger female volumes.

Postmortem studies of schizophrenic patients have found significant amygdala volume reductions as well as of other medial limbic structures (Bogerts, 1984; Bogerts *et al.*, 1985). Fudge *et al.* (1998) present a case of chronic psychosis in which postmortem examination revealed two small hamartias within the basolateral nucleus of the left amygdala which stained with an antibody to bcl-2, a marker of immature developing neurons. Measures of amygdala volumes with MRI of 46 schizophrenics compared to 60 normal controls and 27 bipolar subjects found right amygdala volumes smaller in schizophrenia and left amygdala volumes smaller in bipolar disorder (Pearlson *et al.*, 1997). Hirayasu *et al.* (1998) using MRI, studied 18 patients with first-episode schizophrenia, 16 with first-episode affective disorder and 18 age matched comparison subjects, all right handed, and found left-less--than-right asymmetry of the posterior amygdala-hippocampal complex in the psychotic group of subjects.

The amygdala has also been implicated in the pathophysiology of social phobia, with activation shown by fMRI when patients were exposed to slides of neutral faces as compared to control subjects (Birbaumer *et al.*, 1998).

De Bellis *et al.* (2000) used MRI to measure amygdala volumes and comparison brain regions of 12 child and adolescent subjects with generalized anxiety disorder and 24 matched control subjects and found significant larger right and total amygdala volumes. The authors conclude that the data, although preliminary, is in agreement with the view that alterations in the structure and function of the amygdala may be associated with pediatric generalized anxiety disorder.

In post-traumatic stress disorder (PTSD) there appears to be elements of a kindling like progression. In PTSD, traumatic and horrific events can lead to permanent alterations in the form of neuronal hyperexcitability, intrusive reexperiencing phenomena and withdrawal behaviours (Post *et al.*, 1995). It is hypothesized that PTSD is a triggered or spontaneous replay of emotional memories similar to the elicited and spontaneous replay of motor events in the classical amygdala-kindled seizure paradigm (Post *et al.*, 1998), although imaging studies using MRI of patients with PTSD or history of early trauma have failed to show differences in comparison to healthy controls (De Bellis *et al.*, 2001; Bonne *et al.*, 2001; Driessen *et al.*, 2000).

Schneider *et al.* (2001) studied a group of 10 recently abstinent male alcoholic patients before and after 3 weeks of standardized behavioral therapy with psychopharmacological intervention and 10 matched nonpatients using fMRI in order to map ce-

rebral response to ethanol odor. They found right amygdala/hippocampal activation in response to cue induced craving in the alcoholic group only before treatment, suggesting the emotional aspects of craving. Similar results have been obtained for cocaine craving (Childress *et al.*, 1999) and smoking cues in smokers (Due *et al.*, 2000).

The amygdala loses 2% of its volume during the course of normal ageing and this loss reaches 25.8% in patients with Alzheimer's disease (AD) (Herzog e Kemper, 1980). Jamada and Mehraein (1968) found higher densities of neurofibrillary tangles (NFTs) and plaques in the amygdala than in other neocortical areas of AD brains. Braak and Braak (1991) staged the longitudinal development of NFTs in AD cases and showed that the amygdala is the second region to develop isolated NFTs, preceded only by the entorhinal cortex. The cholinergic hypothesis of AD dictates that a deficiency of acetylcholine from the nucleus basalis of Meynert would deactivate the amygdala (Chow and Cummings, 2000). Noradrenaline modulation of cholinergic activation would also be defective as the locus coeruleus also suffers neuronal loss in AD (Forstl *et al.*, 1992). These anatomopathological findings have brought hope as to the role of the imaging studies in the early detection of AD, but MRI has not been useful even though it has shown amygdala volume reductions (e.g., Mori *et al.*, 1999). Instead, functional neuroimaging studies with PET might be useful to correlate cognitive or behaviour changes in AD with amygdala activity.

Autism has also been associated with amygdala dysfunction (e.g., deLong, 1992; Brothers, 1989). The social-emotional abnormalities usually start in the first years of life and persist into adulthood. Reports have shown that persons with autism are impaired in face recognition and identification of facial expression of emotions (Hobson *et al.*, 1988; MacDonald *et al.*, 1989). Similar findings have resulted from amygdala lesions in humans without autism (Adolphs *et al.*, 1994). Therefore, amygdala dysfunction as well as that of other components of the neural network supporting social cognition is an attractive proposal to guide the field of autism research (e.g., Baron-Cohen *et al.*, 1999).

CONCLUSION

The amygdala is composed of several nuclei with many intrinsic and extrinsic connections, and a rich neurochemical profile (Amaral *et al.*, 1992). It receives auditory, visual and somatosensory information which, after internal and external (through cortical connections) modulation, is capable of expression effected by efferents to hypothalamus and brain stem.

The absence of both amygdala has long ago been reported to cause sensory events, especially visual events, to lose their emotional implications (Klüver and Bucy, 1937). Since then,

multiple studies have tried to understand with greater detail the structure and function of this agglomerate of nuclei with a central localization in the brain. These were initially limited to animal studies or human observational studies of diseases affecting the amygdala. Lately, with the evolution of neuroimaging technology it is not only possible to measure with greater precision the amygdala *in vivo*, but it is also possible to study its function during specific task performance in humans.

The amygdala is related to emotional and social behaviour, to learning and memory (e.g., Aggleton, 1993). Animal studies have revealed a particular role for the amygdala in the simple and complex associative emotional responding, and studies in humans have suggested that it extends to the human brain (LaBar *et al.*, 1995). The amygdala is also an important component of the neural systems subserving social cognition, and influences memory performance by modulation of information of different relevance to the individual.

Amygdala involvement has been found in patients with depression, with either decreases (in patients with a history of recurrent major depression, but not presently depressed) or increases (presently depressed patients with TLE) in amygdala volume. Studies in patients with schizophrenia and bipolar disorder have also found decreased amygdala volumes. Studies in patients with anxiety disorders have found either activation (fMRI) or increased amygdala volumes. Although PTSD is hypothesised to be a triggered or spontaneous replay of emotional memories similar to the classical amygdala-kindled paradigm, imaging studies have not yet found amygdala involvement. Several studies have found amygdala activation in response to cue induced craving either to alcohol, cocaine or smoking. The amygdala is the second structure to be affected in the course of Alzheimer's disease and it is hoped that functional studies might help in the early detection of the disease so as to better delay its progression. Given the importance of the amygdala in social cognition and emotion its dysfunction has been associated with autism and is an interesting proposal to guide this field of research.

Even though studies have revealed at times conflicting results these probably reflect the fact that different disorders with different pathophysiologies have been studied. Further studies are needed to better understand the contribution of the amygdala to psychiatric disorders, which seems to be of major importance given the functions in which it is involved and these preliminary studies.

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