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# The Human Amygdaloid Complex: Cellular Architecture and Dopaminergic Innervation

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## Abstract

The human amygdaloid complex (AC) is associated with the perception of fear and consequent anxiety-related behaviors, apart from other functions ranging from attention to memory and emotion. The AC is composed of several regions with specific cytoarchitectures, chemistry, and connections that encode different aspects of fear. Detailed understanding of AC cell composition is basic to determining whether cell number alterations coincide with neurological and psychiatric pathologies associated to anxiety imbalances, as well as with changes in brain functionality during aging. Here, we describe quantitative data gathered applying stereological methods to human AC tissue; the amounts of neurons, glial and endothelial cells, as well as of various interneuron subsets that populate the AC regions were noted and compared with those collected in the AC of non-human primates and rodents. This chapter also addresses the dopaminergic innervation of the AC, which exerts a modulatory effect over the intrinsic AC network and is critical for reward-related learning and fear conditioning. This innervation is twice as abundant in the main output nuclei as in the principal entry nuclei of the human AC, and this irregularity may indicate functional variations between these entry and output amygdaloid territories.

**Keywords:** amygdala, human, dopamine, stereology, dopamine transporter, neurons, glia, endothelial cells

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## 1. Introduction

The amygdaloid complex (AC) is a heterogeneous structure described for the first time by Burdach as an “almond-shaped” mass of grey substance located in the anterior part of the temporal lobe [1]. Since then, the various AC nuclei, which have diverse developmental features and functions, have been considered either as part of a single structural unit [2] or a collection of randomly aggregated structures [3]. There have also been many attempts to consistently

demarcate the various AC nuclear components and their subdivisions in the human and other non-human primates, but there is no consensus as yet [3].

The AC receives highly integrated sensory information of all modalities and is needed for the association between each sensory stimulus and its emotional and motivational significance [4, 5]. The AC also contributes to the visceral and somatic expression of endocrine response to these stimuli. Direct stimulation of the AC produces a subjective perception of fear and anxiety, as well as increased heart rate and blood pressure with pupil dilation [6]. A huge number of studies have related the AC with fear perception and the generation of appropriate affective responses to these types of stimuli [7–14]. Other investigations have, nevertheless, demonstrated that the activity of the AC also increases in response to positive emotional stimuli in humans [15–17] and non-human primates [5]. The AC is crucial to the acquisition, consolidation and extinction of fear memories, as well as to their retrieval after extinction. Therapies known as “exposition therapies” try to produce the extinction of those fear memories that trigger anxiety behaviors [12].

Bilateral lesion of the medial temporal lobes containing the AC produces a visual-limbic disconnection [18] or a sensory-affective dissociation [19]. Both alterations seem to be present in Rhesus monkeys affected by the Klüver-Bucy syndrome [20]. A variety of symptoms including aphasia, amnesia, or dementia have been observed in human patients with a bilateral temporal lobe lesion, and lesions specifically affecting the AC seem to be related to the difficulty in identifying the emotional significance of facial expressions [21].

The dopaminergic innervation received by the AC is intense in rats [22–26], non-human primates [27–29], and humans [30]. This particular neurochemical input is required to acquire, consolidate or extinguish fear-related memories, as well as to generate appropriate affective responses toward aversive stimuli [31–36]. A dysfunction of the dopaminergic system is related to psychiatric diseases such as schizophrenia [37, 38] and/or other stress-related disorders [39, 40]. In addition, the hyperdopaminergic phenotype of transgenic mice lacking the dopamine transporter (DAT) can show the positive symptoms observed in schizophrenic patients [41]. As discussed below, the dopamine in the AC affects projection neurons either directly or through various types of interneurons.

The present chapter will review data collected in recent years in the human AC related to the amount of neurons, glial and endothelial cells, as well as more specific quantitative data on two main AC interneuron populations, which modulate the activity of the projection neurons. The amount, distribution and specific neuronal targets, of the dopaminergic innervation of the human AC will also be addressed.

## 2. Anatomical delineation and nomenclature of the human amygdaloid complex

Numerous studies have addressed the anatomical nuclear division in the primate AC [2, 42–50], but the lack of well-defined anatomical limits between the various AC nuclei has complicated any consensus on the delineation of the AC nuclei and their subdivisions. **Table 1** shows the most relevant divisions and nomenclature used in the last years to define the AC nuclei in human and

Sims and Williams [49]	<sup>1</sup> Brady [52]	<sup>2</sup> Price et al. [48], Sorvari et al. [58]	Mai et al. [119]	García-Amado and Prensa [55]
DEEP NUCLEI			BASOLATERAL GROUP (BL)	
<u>LATERAL</u>	<u>LATERAL</u>	<u>LATERAL</u>	<u>LATERAL</u>	<u>LATERAL (L)</u>
• External		• Lateral	• Dorsolateral	• External (Lex)
• Dorsal		• Medial	• Dorsomedial	• Dorsal (Ld)
• Lateral			• Dorsal anterior	• Lateral (Li)
• Medial			• Intermediate	• Medial (Lm)
			• Ventral	
<u>BASAL</u>	<u>BASAL</u>	<u>BASAL</u>	<u>BASOLATERAL</u>	<u>BASAL (B)</u>
• Lateral	• Magnocellular	• Magnocellular	• Dorsal	• Magnocellular (Bmc)
• Central	• Intermediate	• Intermediate	• Intermediate	• Intermediate (Bint)
• Medial	• Parvocellular	• Parvicellular	• Ventromedial	• Parvocellular (Bpc)
			• Ventrolateral	
			• Paralaminar	
<u>ACCESSORY BASAL</u>	<u>ACCESSORY BASAL</u>	<u>ACCESSORY BASAL</u>	<u>BASOMEDIAL</u>	<u>ACCESSORY BASAL (AB)</u>
• Dorsal	• Magnocellular	• Magnocellular	• Dorsomedial	• Dorsal (ABd)
• Ventral	• Parvocellular	• Parvicellular	• Centromedial	• Ventral (ABv)
		• Ventromedial	• Ventromedial	
			• Dorsolateral	
		<u>PARALAMINAR</u>		
		• Medial*		
		• Lateral*		
<u>CORTICO-MEDIAL (CM) GROUP</u>		<u>SUPERFICIAL NUCLEI AND/OR AREAS</u>		<u>CORTICO-MEDIAL (CM) GROUP</u>
<u>CORTICAL</u>	<u>CORTICAL</u>	<u>CORTICAL</u>	<u>CORTICAL</u>	<u>CORTICAL (Co)</u>
• Medial	• Ventral	• Anterior	• Anterior	• Medial (Com)
• Lateral	• Dorsal	• Posterior	-- Dorsal portion	• Lateral (Col)
			-- Ventral portion	
			• Posterior	
<u>MEDIAL</u>	<u>MEDIAL</u>	<u>MEDIAL</u>	<u>MEDIAL</u>	<u>MEDIAL (Me)</u>
		PERIAMIGDALOID CORTEX	• Anterior	
		LATERAL OLFACTORY TRACT NUCLEUS		

Sims and Williams [49]	<sup>1</sup> Brady [52]	<sup>2</sup> Price et al. [48], Sorvari et al. [58]	Mai et al. [119]	García-Amado and Prensa [55]
DEEP NUCLEI			BASOLATERAL GROUP (BL)	
REMAINING NUCLEI AND/OR AREAS			CENTRAL GROUP (Ce)	
<u>CENTRAL</u>	<u>CENTRAL</u>	<u>CENTRAL</u>	<u>CENTRAL</u>	<u>CENTRAL</u> (Ce)
•Medial	•Medial	•Medial	•Medial	•Medial (Cem)
•Lateral	•Lateral	•Lateral	•Lateral	•Lateral (Cel)
•Dorsolateral				
•Ventrolateral				
•Interstitial				
CORTICO-AMIGDALOID TRANSITION AREA	CORTICAL TRANSITION AREA		PARAHIPOCAMPAL-AMIGDALOID TRANSITION AREA	CORTICO-AMIGDALOID TRANSITION AREA (CTA)
ANTERIOR AMIGDALOID AREA	ANTERIOR AMIGDALOID AREA	ANTERIOR AMIGDALOID AREA	ANTERIOR AMIGDALOID AREA	PERIAMIGDALOID AREA (PA)
			PREAMIGDALOID CLAUSTRUM	
			PERIAMIGDALOID AREA	
INTERCALATED CELLULAR GROUPS	INTERCALATED NEURONS	INTERCALATED NUCLEI		
		AMYGDALO-HIPOCAMPAL AREA	AMYGDALO-HIPOCAMPAL AREA	

\* Subdivisions added to the classification proposed by Price et al. [48]. The abbreviations used in this chapter are indicated in bracket.

<sup>1</sup> Classification developed in *Saimiri sciureus* and in humans.

<sup>2</sup> Classification developed in *Macaca fascicularis*. The other studies are referred to humans.

**Table 1.** Anatomical delineation of the human amygdaloid complex.

non-human primates. The correct and detailed division of the AC is important because its various nuclei have distinct developmental origins, specific connections, and codify different aspects of fear [7]. The proper delineation of the AC is also necessary to perform accurate quantitative studies such as stereological estimations of cell numbers or nuclear volumes, and the comparisons of such data collected in different studies. For instance, the basolateral group, especially the lateral nucleus, processes the emotional significance of every stimulus, allowing other structures access to this information, and it is involved in the suppression of fear responses and their

retrieval after extinction [7, 8, 11]. The central nucleus is activated by the basolateral group and can initiate key defense mechanisms against species-specific predators representing a danger to an individual given species [7, 8, 13, 51]. The corticomedial group and the lateral nucleus become activated after the presentation of faces expressing fear [52].

One of the first descriptions of the architectonic organization of the AC was made by Völsch [2, 42–50] in primates. Later, Brockhaus published a detailed report of the human AC architecture employing Nissl and myelin staining [47]. However, these classifications were rather complex and Crosby and Humphrey proposed a simpler nomenclature, which is still widely used and based on the one suggested by Johnston [53, 54]. Johnston grouped the amygdaloid nuclei into two groups based on developmental origin and age: the first group included the primitive or little-modified central, medial, cortical, and nucleus of the lateral olfactory tract; the second group included the more recently evolved basal and lateral nuclei formed by infolding or cell immigration. The basal and lateral nuclei together with the accessory basal nucleus conform the basolateral group of the AC, which has undergone a huge increase of volume in humans [2, 49].

In a more recent study, García-Amado and Prensa suggested a detailed nuclear division and nomenclature for the human AC based on the proposal by Sims and Williams [49] and Ledo-Varela et al. [56], and that also resembled those used by Schumann and Amaral [57] and Sorvari et al. [58] (**Table 1**; see [55] for further details). The García-Amado and Prensa study [55] was focused on providing accurate and objective limits of the entire AC and its various nuclear groups, nuclei, and nuclear subdivisions. The establishment of consistent anatomical limits is essential for making comparisons among quantitative data collected in different studies. To this end, the 2012 García-Amado and Prensa study did not outline as a single whole the structures with rather fuzzy boundaries like the anterior amygdaloid area described by Sims and Williams [49]. Instead, they only outlined the most lateral part of this region, the periamygdalar area, since this area can be objectively identified by its high content in acetylcholinesterase. Other relevant aspects of the study of García-Amado and Prensa are the consideration of the dorsal subdivision on the lateral nucleus, whose cells are much smaller and more packed than the ones that populate its three other subdivisions, and the inclusion of the paralaminar region within the parvocellular subdivision of the basal nucleus because the former has unclear limits.

### 3. Volume of the human AC

The volumes of the AC as a whole and some of its nuclei have been estimated in many studies dealing with psychiatric disorders as well as in others on Alzheimer's disease [59–64]. The range of AC volume for individuals without any neurological or psychiatric disease varied from 630 to 1380 mm<sup>3</sup> depending on the study [59–65]. The variability in the delineation of the AC nuclei and/or the different protocols used to process the human tissue could be responsible for the large range of AC volume reported in normal individuals in the different studies. Similar investigations performed in tissue obtained from schizophrenic and bipolar disorder patients report a decrease in the volume of several AC nuclei, such as the basal and lateral ones [63, 64].

The stereological study by García-Amado and Prensa [55] of the human AC from individuals without any neurological or psychiatric disease showed that the entire complex reached a volume of approximately 950 mm<sup>3</sup> with more than 80% of that volume corresponding to the basolateral group, 10% to the corticomedial group, and 6% to the central group (**Table 2**; [55]). Overall, these volumes fall within the ranges reported by other authors [59–64]. The volume of the total AC as estimated by García-Amado and Prensa [55] was smaller than the one reported earlier by Schumann and Amaral [62] due to the unclear limits of particular structures such as the nucleus of the lateral olfactory tract, the anterior amygdaloid area, the periamygdaloid cortex and the amygdalohippocampal area, some of which were not included in the AC by the former study. Nevertheless, the volume estimations for individual AC nuclei reported in these two studies were more alike except for certain minor differences in the lateral and basal nuclei. Chance et al. [61] and Berretta et al. [63] reported smaller volume estimations than García-Amado and Prensa [55], the disparities being most probably due to the difference in the methods used during tissue processing or to the variations in delineation of the nuclei (see [55] for details).

Region	Schumann and Amaral [62]			Berretta et al. [63]			Kreczmanski et al. [64]			García-Amado and Prensa [55]		
	N	V	Nv	N	V	Nv	N	V	Nv	N	V	Nv
L	4	452	8980	2.07	243	8598	4.5	400	11,000	5.48	376	14,608
B	3.24	343	9380	1.23	151	8173	–	220	–	5.02	259	19,510
AB	1.28	152	8600	0.59	69	8519	–	60	–	1.73	123	13,770
Co	–	–	–	0.41	44	9118	–	–	–	1.14	69	16,210
Ce	0.36	34	10,610	–	–	–	–	–	–	0.82	60	14,720
Total AC	12.21	1380	8870	–	–	–	–	–	–	15.39	956	16,088

N: number of neurons (× 10<sup>6</sup> ); V: regional volumen (mm<sup>3</sup>); Nv: neuronal density (neurons/mm<sup>3</sup>); –: no estimation reported. For abbreviations see **Table 1**.

**Table 2.** Estimations of the regional volume, and the neuronal number and density of the human AC.

#### 4. Cellular architecture of the human AC

The AC contains three types of cell populations: neurons, glial, and endothelial cells. The morphology, number and density of the first two and the possible changes that they might present in pathologies such as schizophrenia or autism have been discussed in the last years [57, 60, 62–64, 66–68]. There are several morphological neuronal subtypes in the human AC [69]. Some 70% of neurons in the basolateral group show a pyramidal morphology and are thought to be projection neurons; the remaining 30% are interneurons. Cell morphology in the central and medial nuclei is quite variable, but pyramidal cells are not as common as in the basolateral group [70].

Data about the glial cells in the AC are scarce and mostly centered on astrocytes [70, 71]. Certain glial cell populations, such as oligodendrocytes, undergo quantitative changes in major depressive disorder [66, 67]. Further investigations are needed to determine whether other glial cell types (i.e. astrocytes and/or microglia) are involved in this and other psychiatric disorders [72]. The available data on endothelial cells are also very limited and mostly centered on determining the effects on microvasculature that are produced by the antipsychotic treatments or the schizophrenia [73, 74].

#### **4.1. Number and density of neurons, glial, and endothelial cells**

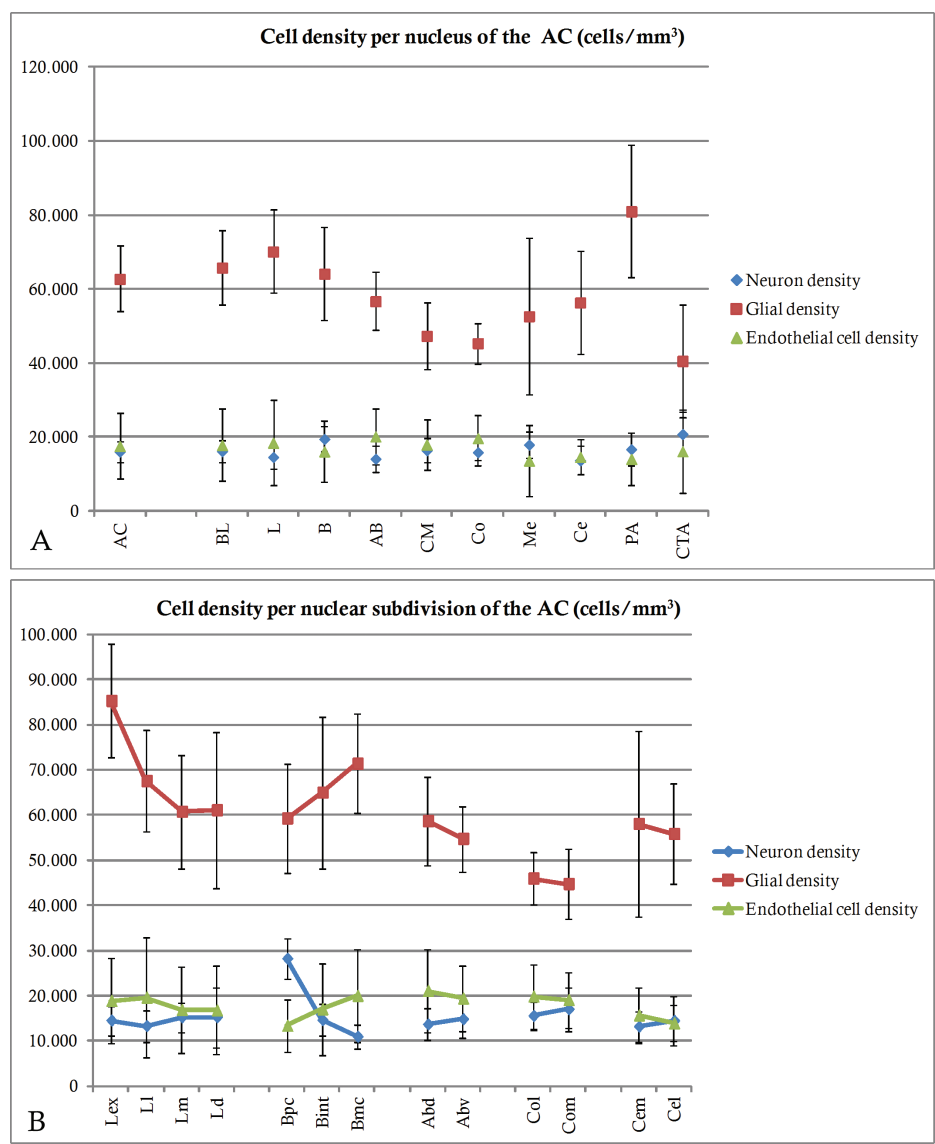
The human AC contains approximately 15 million neurons of which 80% are located inside the basolateral group, 10% in the corticomедial group and 5% in the central group [55]. The number of endothelial cells is quite similar to that of neurons, whereas the glial cell number is almost four times higher, and this proportion is maintained in most of the nuclear subdivisions of the AC. This glial/neuron ratio differs from that found in the cerebral cortex, where it ranges from 1.55 to 2.19 depending on the cortical area examined [75], or the one in subcortical structures, which varies from 14 in the mediodorsal thalamic nucleus and ventral pallidum to 3 in the nucleus accumbens [60]. The glial/neuron ratio in the AC increases across species, from rat to human [76], suggesting that the AC is more complex in primates than in rodents.

In terms of neuron number and density in the AC, the estimations of García-Amado and Prensa [55] (**Figure 1**) are comparable with, although slightly higher than, those reported in other studies performed in the lateral, basal, accessory basal, and central nuclei [62–64, 66]. Differences in neuron number between studies are due to variations in the delineation of the nuclei whereas differences in neuron density between studies might be the result of different nuclear volume estimations. Particular attention should be given to the work of Dall'Oglio et al. [70], which reported a neuronal and glial cell density in the medial nucleus that was almost 10 times higher than the one reported by García-Amado and Prensa [55]; this huge difference is probably explained by technical differences in the method used during tissue processing [77] and/or to a different delimitation of the nucleus.

Regarding neuronal density, the differences among the AC nuclei described in the various studies are consistent [55, 62–64, 66]. The neuronal density in the basal nucleus is considerably higher than that in the rest of the AC nuclei, and this is probably due to the extremely high neuronal density of its parvocellular subdivision [78–80]. The number of neurons in the different AC nuclei and nuclear subdivisions in several non-human primate species was analyzed by Carlo et al. [81]. Despite the fact that the values reported by these authors are markedly lower than those reported in the human brain by García-Amado and Prensa [55], the percentages of neurons between nuclei and their subdivisions are roughly similar. Consequently, what Carlo and his colleagues found indicates an increase in the number of neurons in every nucleus of the AC during the evolution of primate species. The percentage of increase in the central nucleus was markedly less than in the rest of AC nuclei.

The reported number and density of glial cells in the AC are consistent in the various studies [65, 66]. The high density of glial cells in the lateral nucleus may be related to the numerous projections from sensory associative cortical structures [82].





**Figure 1.** Density of neurons, glial and endothelial cells (cells/mm<sup>3</sup>) in the human AC. (A) Mean and standard deviation of the density of neurons (rhombus), glia (squares) and endothelial cells (triangles) in the whole AC and their nuclear groups and nuclei. (B) Mean and standard deviation of the density of neurons (rhombus), glia (squares) and endothelial cells (triangles) in the nuclear subdivisions of the AC. For abbreviations see **Table 1**.

The density of neurons and endothelial cells in the AC tends to respectively decrease or increase with age, especially in the basolateral group [55]. In contrast, the number and density of glial cells in the grey matter of AC nuclei tend to increase moderately with age, an observation that could be interpreted as either a compensatory mechanism or a response by the glial cell

population to the neuronal loss occurring during aging. Both gliosis and fiber loss have been described as stages of age-dependent degeneration [83]. The parvocellular subdivision of the basal nucleus is the only AC region that did not show a decrease in the number of neurons over time [55]. The presence of a large number of immature neurons in the paralaminar territory of the basal nucleus in the adult brain might counteract the decrease in neuron number with aging [79, 80]. The increase in the number and density of the AC endothelial cells during aging is considered an adaptation of the brain to maintain the rate of oxygen delivery to this region when the blood flow decreases [84, 85].

#### 4.2. Interneurons in the human AC

Various histochemically and electrophysiologically well-characterized subsets of interneurons exist in the AC (for review see Ref. [86]). Each of these subsets of AC interneurons is characterized by specific firing patterns, by their targets in discrete subcellular domains of projection neurons, and by their specific modulation by external sensory stimuli [87, 88]. From the functional view point, the AC interneurons exert an important inhibitory effect over the projection neurons of the basolateral nucleus and contribute to generating synchronous theta activity between the amygdala and the hippocampus during the acquisition of emotional memories [87]. The interneurons of the basolateral amygdala are activated by the hippocampal input with theta frequencies that reach the amygdala; this activation causes a transient feedforward inhibition of projection neurons that is followed by the increase of active excitatory synapses and the induction of long-term potentiation of these synapses during fear memory retrieval [89]. Alterations in the expression of calcium-binding proteins in some interneuron subsets of the AC [90] or of the cerebral cortex [91–95] have been described in disorders like anxiety in which the extinction of fear memories can be impaired.

As in rodents, four different subsets of interneurons have been determined in primates: (1) parvalbumin (PV) positive (+) interneurons (25% of these also contain calbindin (CB) [86, 96]; (2) CB+ interneurons (30–35% also contain PV) [86, 97, 98]; (3) somatostatin + interneurons [86, 99, 100]; and (4) calretinin (CR) + interneurons [86, 101]. Most of these data were obtained in non-human primates and the studies performed in humans did not precisely define either the number of AC interneuron subsets or the quantities and percentages of each interneuron population in the various AC nuclei. Nevertheless, PV+ and CR+ interneurons are the most abundant non-overlapping populations among all the calcium-binding protein-containing interneuron populations in the primate AC [86]. Furthermore, these two neurochemically well-defined interneuron populations are also distinguished by their electrophysiological properties; the PV+ interneurons are associated with “fast” and “burst” firing patterns, whereas the CR+ interneurons show a “regular” firing pattern [102]. PV+ interneurons can innervate the soma, proximal dendrites or the initial axon segment of pyramidal neurons [87, 88], and they receive excitatory inputs from axon collaterals of local pyramidal cells, which form a powerful inhibitory feedback [103].

In terms of their topographic distribution within the AC, the PV+ interneurons are restricted to the basolateral group, whereas CR+, as well as CB+, interneurons are homogeneously distributed through the AC. This means that PV+, CR+ and the CB+ subsets of interneurons exist in the basolateral group, but only CR+ and CB+ subsets of interneurons are present in the corticomедial and the central nuclear groups. CR+ interneurons are especially abundant

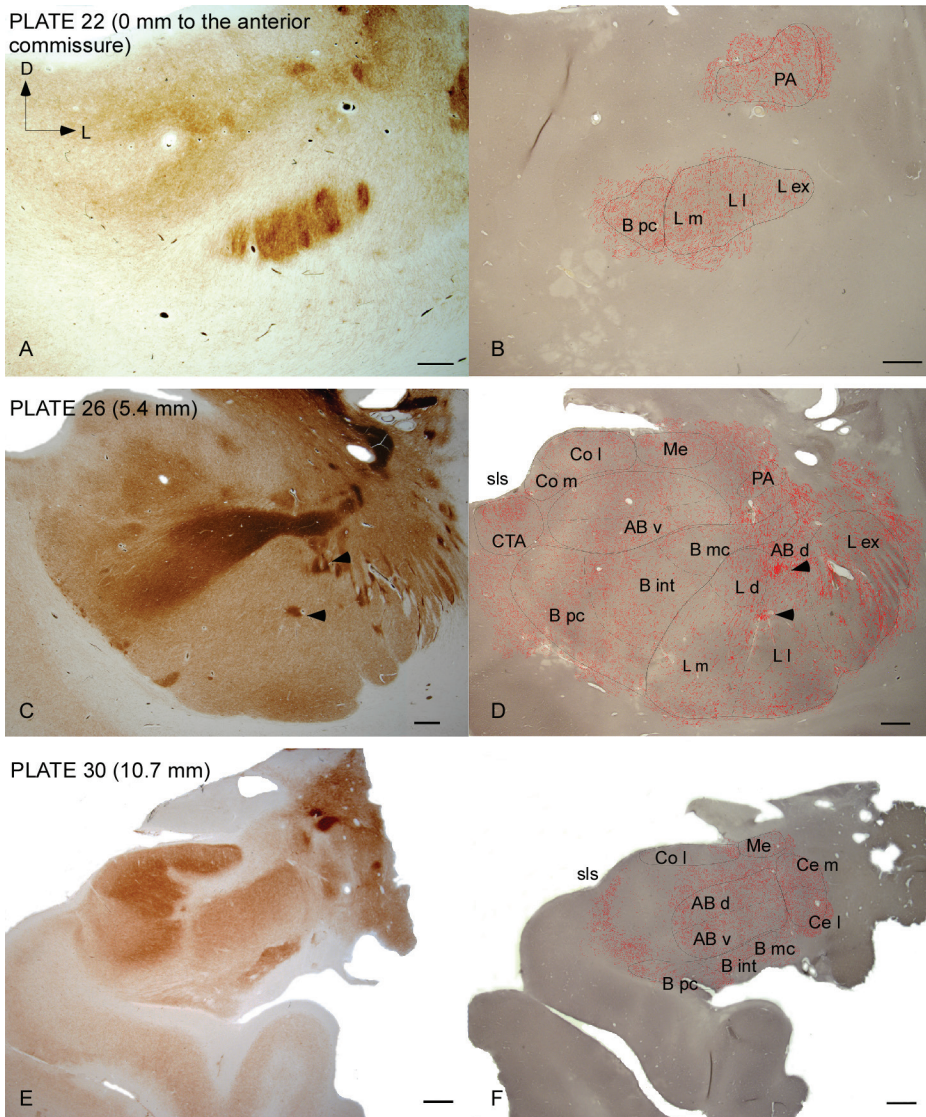
in the accessory basal nucleus, whereas the PV+ cells abound in the lateral nucleus and gradually diminish toward the more medial regions of the basolateral group [58, 96, 101, 104, 105].

Quantitative data regarding the relative proportion of the PV+ and the CR+ interneuron subtypes with respect to both the total interneuron population and the total neurons in the AC in rodents, primates and humans are already available in the literature. In the basolateral group, the PV+ interneurons represent 19–43% and the CR+ interneurons 17–20% of the total of all interneurons in rodents [106]. In the non-human primate basolateral group, the PV+ interneurons represent 28–37% of the GABAergic interneurons, while CR+ interneurons represent 23–27% [86]. In rats, PV+ interneurons make up 6% of the total AC neuron population whereas CR+ interneurons are 4% [26]. In the human AC, however, the proportion of PV+ interneurons is lower than that of CR+ interneurons with respect to total AC neurons; PV+ interneurons do not reach 1% in any AC territory whereas CR+ interneurons range from 4 to 23% depending on the AC area studied [105]. Taken together, these data show that the amount of PV+ and CR+ interneurons in the AC decreases and increases, respectively, over the phylogenetic scale, a finding that is in agreement with previous reports made in the striatum, in comparisons of humans with the squirrel monkey and the rat [107].

## 5. The dopaminergic innervation of the human AC

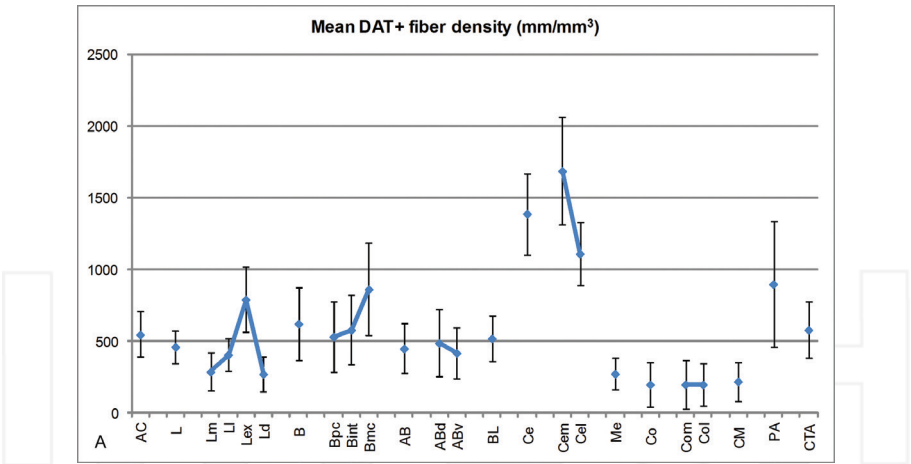
The AC receives a substantial dopaminergic innervation originating mainly from the A8, A9 and A10 ventral mesencephalic groups [29] and dopamine is a key neurotransmitter in the AC that modulates the entry of information through the basolateral group. Furthermore, this dopaminergic innervation is required for the acquisition, consolidation and extinction of fear memories as well as for generating appropriate affective responses [31–36] and, as mentioned earlier, dysfunctions of this dopaminergic system have been proposed as pathogenic mechanisms in psychiatric diseases such as schizophrenia [37, 38] and stress-related disorders [39, 40]. Accurate quantitative data regarding the amount of dopaminergic axons and their distribution in the AC from human donors who had not been diagnosed with neurological or psychiatric diseases before their death was collected by García-Amado and Prensa [108] using DAT immunoreactivity as a marker for the dopaminergic fibers and stereological approaches. Since intrinsic dopamine instability prevents its immunodetection in brain tissue that has not been rapidly fixed by perfusion after the donor's death, previous studies that were focused on analyzing the dopaminergic innervation of the human AC had used the TH protein to detect dopaminergic profiles. However, TH protein also labels noradrenergic and adrenergic fibers in the AC [109, 110]. Since the AC consists of several nuclear groups with a vast array of interconnections with the cerebral cortex, hippocampal formation, basal ganglia, thalamus, hypothalamus, and brainstem (for review see Refs. [48, 50]), information on the content of dopaminergic axons in each of the nuclear groups is needed to better understand the internal functional organization of this complex.

The human AC is targeted by widespread DAT-positive fibers, which are dense and unevenly distributed in every subdivision of this nuclear complex [108] (**Figures 2 and 3**). Furthermore, their study has yielded accurate information regarding the quantity of DAT-ir fibers per neuron in each amygdaloid territory. As shown by these authors, the amount of DAT-ir axons in



**Figure 2.** Distribution of DAT-positive fibers in the human AC. Series of two adjacent coronal sections stained for acetylcholinesterase (AChE) (A, C, E) and DAT (B, D, F) at three anteroposterior levels of the AC, with the corresponding plates from Ref. [119]. The stippling in B, D and F represents the DAT-positive axons drawn with camera lucida at 20× and superimposed over the same micrographs stained for DAT. Arrowheads in C and D indicate patches with either AChE or DAT enriched staining, respectively. For abbreviations see **Table 1**. Scale bar: 1 mm.

the human AC varies among the several nuclei of the AC and also varies considerably in the various subdivisions of a given AC nucleus (**Figure 2**), indicating functional variations among these territories.



**Figure 3.** Length density of DAT-positive fibers in the human AC. Mean DAT-positive fiber length density for every nuclear group, nucleus and nuclear subdivision of the AC. The error bars represent standard deviation. For abbreviations see **Table 1**. Modified from García-Amado and Prensa [108].

One of the most striking gradients in the amount of the DAT-ir fibers occurred along the mediolateral axis of the lateral nucleus: the total length of DAT-ir axons range from nearly 300 mm/mm<sup>3</sup> in its medial subdivision to nearly 800 mm/mm<sup>3</sup> at its external (most lateral) subdivision (**Figures 2 and 3**). This large variation in the amount of DAT-ir fibers between the medial and lateral sectors of the lateral nucleus might be related to their differentiated extrinsic and intrinsic connections. Thus, the lateral nucleus would be the main target of sensory information from the external world, and it sends heavy projections to the other amygdaloid nuclei [111]. The external subdivision of the lateral nucleus receives most of these sensory projections (**Figures 2 and 3**), and the information flows toward the medial side of the nucleus [111, 112]; in addition, this AC region has the shortest latency of conditioned responses elicited by sensory stimuli associated with adverse events in emotional learning tasks [113]. On the other hand, the medial subdivision of the lateral nucleus receives information from higher-order cortical processing areas [114–117]. In the hippocampus, DAT-positive axons were present only in the outer two-thirds of the molecular layer of the dentate gyrus, where the perforant pathway ends [118], indicating that dopamine may potently and selectively regulate the input from the entorhinal cortex and thus the early stages of hippocampus processing, as might be the case for the sensory information entering the AC lateral nucleus.

The central nucleus receives information from the rest of the AC nuclei and is one of the main output nuclei of the AC [111]. Descending projections from the central nucleus terminate in a wide mediolateral region of mesencephalic dopamine cells [120]. In turn, this nucleus receives the heaviest DAT-positive dopaminergic innervation of all the AC nuclei, however its innervation is not uniformly distributed and markedly decreases along a mediolateral gradient, a finding that agrees with the distribution pattern of TH-ir fibers [27]. In the basal and accessory basal nuclei of the AC, the content in DAT-ir fibers decreases from dorsal to ventral



sectors, though this gradient is much less marked in the latter than in the former nucleus (see **Figure 2A and B**) [27–29, 49, 58, 121].

The regulation of extracellular dopamine levels is controlled by distinct mechanisms in different brain areas and is probably related to DAT content. Thus, whereas the dorsal striatum and the nucleus accumbens show an “uptake-dominated” regulation (i.e. one in which dopamine is quickly recaptured from the extracellular space to end its action), the medial prefrontal cortex and the AC show a “release-dominated” regulation (i.e. dopamine is maintained in the extracellular space more time) [122]; these findings agree with the observation that there is more DAT in the striatum than in the other two structures [27–29, 49, 58, 121].

The AC is a main target for mesencephalon projections made up of cells from the substantia nigra pars compacta (A9 dopaminergic group), the ventral tegmental area (A10 dopaminergic group) and the retrorubral field (A8 dopaminergic group) [4, 123–125]. In the human mesencephalon, DAT abounds in neurons located in the lateral ventral tegmental area and in the substantia nigra pars compacta and is largely absent from the medial ventral tegmental area [30]. DAT mRNA is more abundant in the A9 ventral tier than in the dorsal tier [125]. The human AC nuclei that contain the most DAT-ir fibers correspond to those that receive strong projections from the ventral mesencephalon, as also observed in primates [29]. There are, nevertheless, other AC regions showing a high density of DAT-positive fibers, such as the lateral subdivision of the central nucleus, that do not seem to receive innervation from any part of the ventral midbrain [29]. There are other possible sources of AC dopamine that lie outside the ventral midbrain, but whether they contribute to the DAT-ir fibers encountered in the AC or not, is not yet clear. The parabrachial nucleus projects to the central and medial nuclei of the AC [29, 123, 124] and it contains putatively dopaminergic neurons that do not carry DAT [126]. Moreover, the neurons of the parabrachial nucleus that project to the AC also lack tyrosine hydroxylase (TH) [29, 123, 124]. The periaqueductal gray substance is another source of input to the AC and it contains dopaminergic neurons (i.e. A11 group) that contain DAT [126] and project to the central and medial AC nuclei [4, 123, 124, 127–129]. This dopaminergic connection is relevant as it specifically targets the lateral subdivision of the central nucleus, a region that sends efferent projections to the medial subdivision of the central nucleus, which in turn projects back to the periaqueductal gray substance handling “freezing” behavior in animals exposed to a potentially dangerous stimulus [12]. There are also TH+ cells in the dorsal raphe nucleus that project to the central AC nucleus [129], but the DAT content of these cells has not been yet determined.

The ultrastructural localization of DAT in the primate AC is unknown at present. In the cerebral cortex, most of the DAT-labeled profiles correspond to thin unmyelinated axons that rarely form synapses, whereas TH-labeled profiles vary more in their diameter and TH-ir varicosities contain abundant vesicles and frequently form synapses [118]. Consequently, Lewis et al. believe that DAT is likely to be restricted to the intervaricose segments [118]. The specific postsynaptic targets of the dopaminergic fibers that reach the human AC are not known. Several studies in rodents have demonstrated that these fibers make synapses with both projection neurons [23, 24, 130] and interneurons [25, 26, 130]. Although projection neurons receive the majority of dopaminergic synapses [130], the CR+ and PV+ interneuron

subsets are also innervated by these fibers, especially the ones containing PV [26]. The CR+ interneurons receive only 6% of the dopaminergic synapses, whereas the PV+ cells receive 40% [26]. In the central and basal nuclei, as well as in the paracapsular intercalated groups, the dopaminergic terminals form symmetric synapses more frequently than asymmetric ones [23, 24, 26, 130].

Dopaminergic fibers in the AC form perineuronal nets around the soma of the projection neurons and the PV+ interneurons, and 72% of the contacts that these nets establish with the PV+ interneurons are synaptic [25, 26, 130]. These nets are abundant in some 10–15% of all PV+ interneurons and they appear to avoid other interneuron subsets. These nets are functionally related with the strong inhibition observed in the activity of the projection neurons of the basolateral group after dopamine release [131, 132]. The dopaminergic innervation of the various interneuron populations of the AC could contribute to the induction of long-term potentiation mechanisms involved in conditioned fear acquisition, which requires suppression of GABAergic interneuron inhibition of projection neurons [35]. Dopamine inhibits the “fast firing” interneurons, which coincide with the PV+ interneurons [102], and reduces the inhibition of projection neurons in the lateral amygdaloid nucleus. More recently, Chu et al. have demonstrated that dopamine blocks GABA release from PV+ interneurons to projection neurons acting on type D2 presynaptic receptors but it does not affect the release of GABA to other interneuron types from this interneuron population [133]. The blockade of both D1 and D2 receptors in the basolateral group prevents fear conditioned acquisition [134–136].

## 6. Concluding remarks

The AC is a heterogeneous structure formed by numerous nuclei with diverse morphological and functional features. Numerous neurological or psychiatric diseases are linked to alterations in specific cell populations, as well as neurotransmission systems in the human AC. Understanding how AC dysfunction may be related to the pathogenesis of human disorders or accompany behavioral impairments requires a profound knowledge of the normal anatomy of the human AC. In this sense, several studies performed in the last 5 years have provided accurate quantitative data related to the cellular composition and dopaminergic innervation of the various nuclear complexes and their subdivisions that make up the human amygdala. Data from these studies have revealed, for instance, that the human AC contains approximately 15 million neurons with nearly 80% residing in the basolateral group, 10% in the corticomedial group and 5% in the central group. The number of endothelial cells is similar to the number of neurons whereas the number of glia is approximately four times that of neurons. Most amygdaloid neurons are glutamatergic or GABAergic neurons that project their axons outside the AC. The activity of the AC principal neurons is tightly modulated by local circuit interneurons and this modulation is required for the acquisition of fear memories. The AC interneurons are cataloged into different subsets based on their firing properties, their synaptic inputs and their expression in proteins such as calcium-binding proteins. Among all the interneurons containing calcium-binding proteins in the primate AC, the PV+ and the CR+ interneurons are the most abundant, representing 1% and 6–24% of the total neuron

population of the human AC, respectively. PV+ interneurons exert robust perisomatic inhibition of principal neurons, but their activity is likely to be mostly concentrated in the basolateral complex, since almost none of these neurons populate other AC territories. In contrast, the CR+ interneurons are, basically, homogeneously distributed through the entire AC. The human AC receives a heterogeneous dopaminergic innervation that mostly originates in the midbrain areas and regulates the activity of the various subsets of AC neurons. Dysfunctions of this dopaminergic system have been described in schizophrenia and stress-related disorders. Stressful events enhance dopamine release in the AC and this facilitates the formation of fear memories as well as appropriate affective responses. A recent study has demonstrated that the dopaminergic innervation of the human AC is heterogeneous and that the main output nucleus of the AC (i.e. the central nucleus) receives the highest density of dopaminergic axons containing the dopamine transporter, with almost double the density of these fibers compared to the density in the main entrance nucleus of the AC (the basolateral group). The postsynaptic targets of the dopaminergic fibers in the human AC remain unknown, but these fibers make synapses with both projection neurons and interneurons in rodents. The CR+ and the PV+ interneurons of the AC are important targets of the dopaminergic synapses in rodents, but further studies are needed to determine what the main neuronal targets of this neurotransmitter are in the human AC and the role that this innervation has in emotional learning.

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