What is the amygdala?

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‘Amygdala’ and ‘amygdalar complex’ are terms that now refer to a highly differentiated region near the temporal pole of the mammalian cerebral hemisphere. Cell groups within it appear to be differentiated parts of the traditional cortex, the claustrum, or the striatum, and these parts belong to four obvious functional systems – accessory olfactory, main olfactory, autonomic and hippocampal association parts of the olfactory system, accessory and main olfactory, autonomic and hippocampal systems. The extent of its outer border, and number and classification of its subdivisions, remain controversial today. In this article, we present a model of amygdalar architecture based on recent embryological, neurotransmitter, synaptic, and functional data. When placed in the context of cerebral hemisphere architecture as a whole, the amygdala is neither a structural nor a functional unit.

the results suggest that, however defined today, 'amygdala' and 'amygdalar complex' refer to an arbitrarily defined set of cell groups.

Historical background

Meynert’s claim in 1867 that the amygdala of Burdach is a ventral, temporal lobe extension of the claustrum (according to Meynert the deepest layer of cortex) sparked a more than 50 year controversy about how to classify the amygdala in terms of basic parts of the cerebral hemisphere (telencephalon, endbrain). Equally distinguished neuroanatomists soon proposed, instead, that the amygdala is part of the lenticular nucleus (a gross anatomical term for the globus pallidus and putamen – two different cell groups in the basal nuclei or ganglia, rather than in the cortex), and observed that the amygdala is rimmed ventrally by olfactory cortex of the piriform lobe. In 1923, J.B. Johnston introduced the fundamental description of amygdalar structure in widest use today, based on detailed analysis of comparative vertebrate material. He proposed that the amygdala is divided into a primitive group of nuclei associated with the olfactory system (central, medial and cortical nuclei, and nucleus of the lateral olfactory tract), and a phylogenetically new group of nuclei (lateral and basal).

Interest in classifying the amygdala and its various parts in terms of cerebral hemisphere subdivisions and phylogeny waned in the last 50 years as attention shifted to determining input/output relationships of each neuronal group, and the neurotransmitter/receptor systems contained within these pathways. Currently available data are much more extensive and reliable than those available to Johnston, and when taken together suggest that the amygdala is a heterogeneous region, one part of which is a specialized ventromedial expanse of the striatum (central and medial nuclei, and anterior area), a second part of which is caudal olfactory cortex (nucleus of the lateral olfactory tract, cortical nucleus, and postpiriform and piriform–amygdalar areas), and a third part of which is a ventromedial extension of the claustrum (lateral, basal and posterior nuclei). Major evidence for this view will now be considered. The structural nomenclature is based on literature cited elsewhere.

Neurotransmitter evidence: the central and medial nuclei

Immunohistochemistry for GABA (Refs 7,8) and in situ hybridization for glutamic acid decarboxylase (GAD), the enzyme converting glutamate to GABA, reveals a characteristic, very dense band of labeled neurons that extends ventrally and uninterrupted through the caudoputamen, the central amygdalar nucleus (CEA), and then the medial amygdalar nucleus (MEA), where it ends along the ventromedial edge of the cerebral hemisphere (Fig. 2). In contrast, other
parts of the amygdala contain only scattered GABA neurons, most of which are probably involved exclusively in the formation of local circuits. This anatomical evidence, together with less complete electrophysiological data, suggests that the extrinsic projections of the CEA and MEA are predominantly GABAergic (like the dorsally adjacent caudoputamen), whereas the major extrinsic connections of the remaining amygdala are not, but instead are presumably glutamatergic. This supports the general conclusion that part of the amygdala is striatal (CEA and MEA) and the rest cortical.

The suggestion that the CEA and MEA form caudoventral differentiations of the striatum is supported by histochemical evidence (1) that most amygdalar neuropeptide expression is found in them10,11,12,13, and (2) that many of the same peptides are also expressed in other striatal regions including the caudoputamen (dorsal striatum), nucleus accumbens and olfactory tubercle (ventral striatum), and the caudoputamen (dorsal striatum), nucleus accum- bens and olfactory tubercle (ventral striatum), and the caudoputamen (dorsal striatum), nucleus accum-bens and olfactory tubercle (ventral striatum), and (3) that limited peptide expression in the basolateral complex is restricted mostly to interneurons10 rather than to projection neurons. Topographically, the MEA lies just caudal to the olfactory tubercle, which is now regarded as a part of the ventral striatum with GABAergic projection neurons15. As we shall see below, the olfac-tory tubercle receives a direct input from the main olfactory bulb, whereas the MEA receives a direct input from the accessory olfactory bulb12. Based on a similar group of arguments, we would also include the anterior amygdalar area (AAA) within the striatal group, along with the bed nucleus of the accessory olfactory tract, which could easily be a tiny ectopic part of the MEA.

Considerable evidence now indicates that most, if not all, cortical projection neurons (pyramidal cells) use glutamate as a neurotransmitter (with peptide expression concentrated in interneurons), whereas descending projections of the striatum (and of the globus pallidus) use GABA as a neurotransmitter (with peptide expression concentrated in interneurons), whereas descending projections of the striatum (and of the globus pallidus) use GABA as a neurotransmitter (with peptide expression concentrated in interneurons).

If this is true, it implies that non-GABA-projecting regions of the amygdala are part of the cortex.

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**Box 1. Abbreviations**

AAA, anterior amygdalar area; ACC, nucleus accumbens; Alp, agranular insular area; anterior part; Alv, alveus; ans, amygdalar capsule; ANS, brainstem autonomic centers; AOB, accessory olfactory bulb; AUDV, ventral ventral auditory areas; AV, anteroventral nucleus thalamus; BLApc, basolateral nucleus amygdala, anterior, posterior parts; BN, basal nuclei (ganglia); BSTpr, bed nuclei stria terminalis, posterior division, principal nucleus; CA1, field CA1, Ammon’s horn; cc, corpus callosum; CEA, central nucleus amygdala; CL/vm, claustrum, ventromedial part; COA, globus pallidus, cortical nucleus amygdala; anterior part, posterior part, lateral zone, posterior zone, ventral zone; CPA, central nucleus amygdala, anterior, posterior parts; CEA, central amygdala, anterior; CP, caudoputamen; SPD, cerebral peduncle; CTX, cerebral cortex; CTXolf, olfactory cortex, amygdalar component; d, medial hypothalamic defensive behavior system; DA, dopamine; EC, external capsule; ECT, ectorhinal area; en, extreme capsule; ENL, lateral hypothalamic area, lateral part; ENS, endopiriform nucleus; eE, exten-soral parts; f, fimbria; FS, fundus of the striatum; f, claustrum, frontal component; FT, frontotemporal com-ponents of amygdala; fx, columns of the fornix; GABA, gamma-aminobutyric acid; GLU, glutamate; GPlm, globus pal-lidus, lateral, medial segments; HIP, hippocampal region; i, medial hypothalamic ingestive behavior system; IA, intercalated nuclei amygdala; ILA, infralimbic area; INS, insular region; int, internal capsule; LA, lateral nucleus amygdala; MDm, lateral hypothalamic area, caudal part; MT, lateral olfactory tract; m, mantle layer (neural tube); MEm, medial entorhinal nucleus thalamus, medial part; MEA, medial nucleus amygdala; MEH, lateral hypothalamic area, caudal part; P, lateral olfactory tract; c, claustrum, olfactory component; OFL, olfactory components of amygdala, optic tract; PA, posterior nucleus amygdala; PAA, piriform–amygdalar area; PAC, paraolfactory area; PAG, periaqueductal gray; PAR, perirhinal area; PB, piriform area; PBN, pontine reticular nucleus; PVT, periventricular nucleus thalamus; r, medial hypothalamic reproductive behavior system; r, rhinal fissure; RSP, retrosplenial area; RT, reticular nucleus thalamus; S, substantia innominata; SNc, substantia nigra, compact part; ST, somatosensory area; S1, supplemen-tal somatosen-sory area; st, striatum terminals; STN, subthalamic nucleus; STK, striatum, THy, ventral temporal association area; THyg, thalamus; perigeniculate region (includes medial geniculate complex, posterior limiting nucleus, and parvicellular sub-ventricular nucleus); TR, postpiriform transition area, v, ventricular layer (neural tube); V3, third ventricle; VAB, ventral anterior-lateral complex thalamus; VISC, viscerotopic area; Vl, lateral ventricle; VM, ventral medial nucleus thalamus; VPL, ventral posterior lateral nucleus thalamus; VPM, ventral posteromedial nucleus thalamus; ZI, zona incerta.
Olfactory cortex of the caudal piriform lobe

It now seems clear that the cortical amygdalar 'nucleus' (COA) and the 'nucleus' of the lateral olfactory tract (NLOT) are in fact distinct areas of the olfactory cortex (forming the caudal end of the piriform lobe), partly because they lie on the surface of the hemispheres ventral to the rhinal sulcus and display a laminated organization with radially oriented pyramidal cells, and partly because they lie caudally adjacent to the piriform area and receive differential inputs from the main and accessory olfactory bulbs. Like the piriform area, the NLOT, anterior cortical nucleus (COAa), and postero-lateral cortical nucleus (COAp) receive input from the olfactory bulb, whereas the posteromedial cortical nucleus (COApdm) receives an input from the accessory olfactory bulb. Thus, traditional names for these parts of the amygdala are misnomers if they are cortical areas rather than nuclei.

Based on topographic considerations, two adjacent cortical areas should probably also be included within the amygdalar olfactory cortical group. One is the postpituitary transition area (TR), which has often been included in the entorhinal area. It lies adjacent to the COA and also receives a massive input from the main olfactory bulb, and recent Phaseolus vulgaris-leucoagglutinin (PHA-L) analyses indicate that it does not project to the dentate gyrus, but instead generates a massive input to the CEA (G.D. Petrovich, PhD thesis, University of Southern California, 1997; S. Shammah-Lagnado, pers. commun.). The other is the piriform–amygdalar area (PAA), which also lies adjacent to the COA, receives a dense main olfactory bulb input, and projects to several parts of the amygdala (Ref. 19; L.W. Swanson and G.D. Petrovich, unpublished observations). Thus extended, the cortical division of the amygdala contains the COApdm (accessory olfactory bulb input), as well as the rest of the COA, the NLOT, and areas TR and PAA (main olfactory bulb input).

The basolateral complex and the claustrum

This leaves us with the basolateral complex, which is the most problematic in terms of classification. It corresponds to the region originally called amygdala by Burdach, and identified as a temporal extension of the claustrum by Meynert and others in the last century. Based on embryological considerations and adult topographic relations, we suggest that Meynert was correct in his assignment of what are now referred to as the lateral and basal nuclei to the deepest layer of cortex, along with the dorsally adjacent claustrum proper (and endopiriform 'nucleus').

Early morphological features and homeobox gene expression patterns in the developing telencephalic ventricle clearly distinguish a dorsal presumptive cortical region from a ventral (or basal) presumptive nuclear region (Fig. 3). The claustrum proper is the deepest pan of the insular cortex. During embryogenesis, its neurons are separated by an incipient fiber layer known in the adult as the extreme capsule. Thus, the claustrum proper may form at least part of the subplate or deepest layer of the insular cortex, between the external and extreme capsules.

The endopiriform nucleus, which is commonly described as a ventrolateral, olfactory, extension of the claustrum, almost certainly forms the deepest layer of the piriform area, and it too is separated from more superficial layers by a very broad fiber system that has not been named but appears to be a ventrolateral extension of the extreme capsule system. We suggest that the basolateral complex forms at least part of the subplate layer for regions of the temporal, piriform and perhaps frontal lobes. This deepest layer is separated from more superficial layers of cortex by a fiber lamina often mis-identified as the external capsule when it is really a component of the extreme capsule system that we have recently called the amygdalar capsule (Fig. 4).

The topographic relationship of the claustrum proper and endopiriform nucleus to the insular cortex and piriform area is still unclear. While some authors regard scattered neurons along the rostral border of the claustrum proper and endopiriform nucleus to be part of the basolateral complex, others regard the relationship of basolateral complex cell groups to other regions of the claustrum to be established. Thus, it appears that the basolateral complex forms at least part of the extreme capsule system. We suggest that because the amygdala innervates the bed nucleus of the stria terminalis (BST) and intervening regions of the substantia innominata (ventral pallidum), and because the latter two regions share with the amygdala similar patterns of descending projections, the BST and caudal-dorsal regions of the substantia innominata belong to the (extended) amygdala as well (but see Ref. 24). Somewhat indirect embryological evidence suggests that these regions are derived from the pallidal ridge along with the adjacent substantia innominata, so that this division would be pallidal. Moreover, they regard scattered neurons along the length of the stria terminalis to a point just before it enters the BST as a dorsally extended part of the amygdala. On embryological grounds, these cells appear to form a dorsal extension of the MEA along the sulcus terminalis, and would thus be striatal according to the present model.

Organization of major amygdalar connections

The evidence reviewed thus far, together with the connections we shall now review, suggest the arrangement of amygdalar cell groups illustrated in Figs 4 and 5. Structurally, these cell groups are differentiated parts of the stria terminalis and claustral complex, whereas functionally they belong to the olfactory, autonomic and frontotemporal cortical systems. The literature on amygdalar connections is vast, complex, contradictory and incomplete, and cannot be reviewed thoroughly here. Instead, we shall focus on major pathways established with reliable methods.
in the rat that clarify amygdalar circuitry at the systems level – especially in view of the subdivisions proposed in Fig. 5. It is especially important to consider whether putative cortical, claustral and striatal regions of the amygdala display basic connectional features of accepted cortical, claustral and striatal regions, as well as how they may be specialized or differentiated. All of the amygdalar projections cited here have been confirmed in a collection of about 125 PHAL experiments with injections centered in all of the amygdalar cell groups, except the NLOT and intercalated nuclei (Refs 24–27; G.D. Petrovich, PhD thesis, University of Southern California, 1997; unpublished observations).

The accessory olfactory system component

The most obvious place to start is with the MEA and COApm (Fig. 6A), which are the only major projection fields of the accessory olfactory bulb17. If the accessory olfactory bulb is the primary sensory cortical area for pheromonal information (as Brodmann28 held, in principle), then the present interpretation indicates that it projects in turn to the striatum (MEA) and to another cortical area (COApm), which might be involved in the perception of pheromonal stimuli. This is similar to projections from the main olfactory bulb to the rostroventral striatum (olfactory tubercle) and the rest of the cortical amygdalar division17. It is also similar to connections of the primary visual area, except that here optic nerve information is transmitted through the lateral geniculate nucleus rather than directly to the primary sensory cortical area – which, in the case of area 17, projects to the dorsal striatum and to other visual cortical areas. This component is completed with the PA, which shares massive bidirectional connections with, and lies just deep to, the COApm, and also has bidirectional connections with the MEA (Refs 24,25). Thus, local connections include bidirectional pheromonal pathways between cortical, claustral and striatal parts.

Other major inputs to the accessory olfactory component arise in the main olfactory system16, in the
medial prefrontal and agranular insular cortical regions (which process visceral, olfactory and gustatory information), in the ventral subcuculum of the hippocampal formation, and in the medial hypothalamus. Obviously, the accessory olfactory component of the amygdala does not deal exclusively with unimodal sensory information. Instead, it is dominated by pheromonal information (from the vomeronasal organ and nerve), and its cortical parts are probably more accurately referred to as ‘pheromonal association’.

The accessory olfactory component of the amygdala has four major known outputs. One is to the cerebral cortex (back to essentially the same olfactory, prefrontal, insular and hippocampal areas that project to it), the second is to differentiated regions of the striatum (the nucleus accumbens and CEA), the third is to the medial hypothalamus, and the last is to the medial part of the mediodorsal thalamic nucleus. The innervated region of the mediodorsal nucleus projects back to medial prefrontal and agranular insular cortical areas, whereas accessory olfactory amygdalar projections to the medial hypothalamus are especially prominent and selectively innervate parts of three systems that control the expression of parity innate reproductive, defensive and ingestive behavior. This projection is modulated by a ‘relay’ through the principal nucleus of the BST (Ref. 13).

The main olfactory system component consists of five distinct cortical areas, each with an apparently associated part of the claustral complex with which it shares connections (Fig. 6B). The cortical fields are heavily interconnected (association projections), whereas the claustral parts are not (G.D. Petrovich, PhD thesis, University of Southern California, 1997).

The major input to the cortical areas is the main olfactory bulb. However, the cortical areas also receive inputs from other parts of the main olfactory system and the accessory olfactory system, and from medial prefrontal, agranular insular, perirhinal and hippocampal cortical areas. In addition, the COA/BAlex receive ascending inputs from the parabrachial nucleus (visceral and possibly gustatory information) and caudal thalamic regions in and near the medial geniculate nucleus (possibly auditory and somatosensory information). Analogous to the accessory olfactory component, this component of the amygdala should probably be regarded as ‘main olfactory association cortical areas’ (including their claustral components).
The outputs of the main olfactory component are similar to those from the accessory component. They include projections: (1) back to regions of cortex from which it receives inputs25,26,29,45–47; (2) to the striatum19,25,26,32,36,47–49; (3) to the pallidum (BST and substantia innominata)25,26,36; (4) to the medial mediodorsal nucleus25,26,37,45; and (5) to the hypothalamus25,26,36. Specifically, in the striatum, all parts of this component project to both the MEA and CEA; the BMAa, BMAp and BLAp also project to the striatal fundus; and the BLAp and BMAp also project to the nucleus accumbens. In the hypothalamus, the COApl and PA, BMAp and BLAp innervate selectively the three medial hypothalamic drive controllers mentioned above, whereas the COAa and BMAa project directly to a caudolateral region of the lateral hypothalamic area.

The autonomic system component

We suggest that the CEA is that region of striatum specialized for modulating autonomic motor outflow because it has characteristic brainstem projections to autonomic-related centers, including the dorsal motor nucleus of the vagus nerve, nucleus of the solitary tract and parabrachial nucleus50 (Fig. 6C), as well as to regions of the lateral hypothalamic area (Ref. 50; G.D. Petrovich, PhD thesis, University of Southern California, 1997) and periaqueductal gray50,51 thought to modulate autonomic responses, and a region of the pontine reticular nucleus thought to modulate acoustic startle52, nictitating membrane53 and perhaps other reflexes. Obviously, the dorsal striatum (caudoputamen) is specialized for modulating somatic motor outflow.

The CEA receives a wide range of sensory information from descending cortical inputs and ascending thalamic and brainstem inputs (including a dopaminergic input from the ventral midbrain54). More specifically, the CEA receives inputs from main and accessory olfactory systems (including all those in the amygdala55,24,30,32,49, from medial prefrontal56, agranular insular57,58 and ventral subicular57 cortical
regions, from the nucleus of the solitary tract and parabrachial nucleus (probably involving visceralceptive, nociceptive and gustatory information), and from the perigeniculate thalamic (probably transmitting somatosensory and auditory information). In addition, the CEA receives inputs from the thalamic paraventricular nucleus (which receives massive inputs from the hypothalamus, including the suprachiasmatic nucleus) and from the LA and BLA, to be considered next.

The extrapontine orbital component

This leaves us with the LA and BLA, which we suggest together form a ventromedial extension of the claustrum, related closely with the temporal and frontal lobes (Fig. 6D). Both cell groups also share bidirectional connections with the olfactory system and with parts of the frontal and insular regions, whereas the LA is distinguished by such connections with temporo- and hippocampal regions (Rofs et al., 1957; G.D. Petrovich, PhD thesis, University of Southern California 1997; unpublished observations) and the BLA is distinguished by such connections with somatosensory-motor areas in the frontal and parietal lobes.

The striatal projections of this component are unusual in that both parts innervate the caudoputamen as well as the nucleus accumbens (Rofs et al., 1957). The LA also innervates the CEA directly (as well as indirectly via the BMA and BLA) (Petrovich et al., 1997), whereas the BLA is atypical in the sense that it is the only part of the amygdala that does not receive any direct projection to the CEA (G.D. Petrovich, PhD thesis, University of Southern California, 1997).

This component of the amygdala is also unusual in that it sends little if any projection through the striato-nigral terminalus. Thus, it generates little if any direct projection to the KNI and hypothalamus.

The role of connections between the LA and CEA in at least some aspects of fear conditioning to auditory conditioning stimuli has been reviewed recently. In this context, it is interesting that Penfield’s human patients reported the experience of fear only when in the inferior regions of their temporal lobes were stimulated electrically.

What is the amygdala?

However one chooses to define the precise borders of the amygdala, it is a structurally and functionally heterogeneous region of the cerebral hemispheres. We have attempted to classify the various parts of the amygdala (as currently understood) in terms of larger cerebral hemisphere divisions, to provide a reasonable list of parts in each division, and to review the major neural inputs and outputs of the various parts. Overall, the evidence suggests that it is necessary to ask whether the concept of a structurally and functionally defined amygdala is indeed valid, or whether the concept is hindering attempts to understand general principles of telencephalic architecture by imposing an arbitrary classification on heterogeneous structures that belong to different functional systems.

We suggest that the latter is the case. First, a major part of the amygdala is an integral component of the olfactory system. Along with the accessory olfactory bulb, the MEA, COApn and PA form the core of the vomeronasal sensory-motor system, which is sexually dimorphic, whereas the rest of the COA, the NLOT, areas FAA and TR, and the BMA and BLAp are integral components of the main olfactory system. Second, the CEA is a specialized region of the striatum that projects to visceral centers in the brainstem. It receives inputs from prefrontal, insular, temporal and olfactory cortical areas, as well as from almost all other parts of the amygdala, from brainstem viscero-sensory and nociceptive centers, and from parts of the caudal thalamic transmitting auditory and somatosensory information. Third, the LA and BLAs appear to form a ventromedial extension of the claustrum for large regions of the frontal and temporal lobes. It also projects to widespread, differentiated regions of the striatum, including the caudoputamen, nucleus accumbens and CEA.

This interpretation is broadly consistent with Johnston’s original parcellation, except that his primitive group is now divided into an olfactory group or part, and an autonomic part (the CEA). The dynamics of information flow through the circuits outlined here by and large remain to be characterized. Furthermore, insufficient connectional data are available to specify with any certainty what homologies there may be among components of the basolateral complex (claustral division) in rats and primates.

References

28 Brodmann, K. (1909) Vergleichende Lokalisationslehre der Grosshirnrinde, Barth [for English translation, see Garey, L.J.].
Some years ago, when investigating the presence of vasopresin (VP) precursor products that theoretically could not exist\(^8\), we discovered a novel type of transcript variability in homologous Beattiboro rats\(^9\). These rats suffer from hypothyroid diabetes insipidus as a result of a single-base-gene–line mutation in the VP gene that encodes an aberrant VP precursor. Surprisingly, we found that an additional mutation (GA\(\rightarrow\)GA) in the VP transcripts results in restoration of the wild-type reading frame and the synthesis of a functional VP protein that can enter the secretory pathway and undergo axonal transport\(^10,11\). Two sites of the dinucleotide deletion (GA\(\rightarrow\)GA) were found that occurred preferentially in GAGAG motifs of the VP mRNA. Moreover, the mutation rate

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**Mutations in RNA: a first example of molecular misreading in Alzheimer’s disease**

Fred W. van Leeuwen, J. Peter H. Burbach and Elly M. Hol

In the past decade, considerable progress has been made in the understanding of the neurodegenerative changes that occur in Alzheimer’s disease (AD). Knowledge about this disease is based mainly on studies of inherited forms of AD, although most cases of AD are of the non-familial type. Recently, a novel type of mutation in ‘vulnerable’ dinucleotide repeats in messenger RNA was discovered in AD patients: in this type of mutation a mutated transcript is produced from a correct DNA sequence, a process that we call ‘molecular misreading’. The resulting mutated +\(\text{T}\) proteins are prominent neuropathological hallmarks of AD and they are present in most elderly non-demented people also. This suggests that the dinucleotide deletions in transcripts could be one of the earliest events in the neuropathogenesis of AD and an important factor in normal aging.

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**Perspectives on Disease**

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