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Abstract

Evolution selects those adaptive features that increase reproductive probabilities and facilitate survival. Analysing the brain circuits mediating risk-avoidance (e.g. defense) and those allowing reward-seeking (motivated) behaviours in different vertebrates leads to several main conclusions. First, circuits mediating risk-avoidance are similar in all studied vertebrates, where they include amygdala homologues located in the posterior half of the cerebral hemispheres, in close relationship with the chemosensory systems. Second, in all vertebrates, reward-seeking behaviours involve the activity of tegmento-striatal dopaminergic pathways, plus other inputs to the ventral striatum, including amygdalo-striatal glutamatergic projections. Third, output structures in these forebrain circuits for both risk-avoidance and reward-seeking behaviours occupy the caudal and rostral poles of the ventral striato-pallidum, namely the central amygdala and nucleus accumbens-olfactory tubercle respectively. This brain configuration was already present in at least the ancestral amniote, likely also in anamniotes. Finally, social behaviours (sexual, agonistic-territorial, parental) are fundamental for reproduction and survival. Consequently, the so-called socio-sexual brain network that governs these conducts is closely related with brain centres mediating motivation (maybe also risk-avoidance). Central nonapeptidergic circuits are apparently required for endowing social stimuli with rewarding (attractive) properties. More studies in non-mammals are required to further test and expand these ideas.

Keywords	comparative neurobiology; reproduction; reward; motivation; avoidance; defense; neural circuitry; amygdala; ventral striatum

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Highlights

- Similar neural circuits mediate appetitive and aversive responses in vertebrates
- Circuits mediating risk-avoidance include amygdala homologues
- Reward-seeking behaviours involve tegmentostriatal and amygdalostriatal projections
- Accumbens and central amygdala are rostral and caudal poles of the ventral striatum
- Appetitive/aversive responses involve the accumbens/central amygdala, respectively

TITLE: **Evolution of vertebrate survival circuits**

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Abstract

Evolution selects those adaptive features that increase reproductive probabilities and facilitate survival. Analysing the brain circuits mediating risk-avoidance (e.g. defense) and those allowing reward-seeking (motivated) behaviours in different vertebrates leads to several main conclusions. First, circuits mediating risk-avoidance are similar in all studied vertebrates, where they include amygdala homologues located in the posterior half of the cerebral hemispheres, in close relationship with the chemosensory systems. Second, in all vertebrates, reward-seeking behaviours involve the activity of tegmento-striatal dopaminergic pathways, plus other inputs to the ventral striatum, including amygdalo-striatal glutamatergic projections. Third, output structures in these forebrain circuits for both risk-avoidance and reward-seeking behaviours occupy the caudal and rostral poles of the ventral striato-pallidum, namely the central amygdala and nucleus accumbens-olfactory tubercle respectively. This brain configuration was already present in at least the ancestral amniote, likely also in anamniotes.

Finally, social behaviours (sexual, agonistic-territorial, parental) are fundamental for reproduction and survival. Consequently, the so-called socio-sexual brain network that governs these conducts is closely related with brain centres mediating motivation (maybe also risk-avoidance). Central nonapeptidergic circuits are apparently required for endowing social stimuli with rewarding (attractive) properties. More studies in non-mammals are required to further test and expand these ideas.

Introduction

In all vertebrates, survival behaviours include anti-predatory and reproductive, plus other homeostatic behaviours. All of them are associated to two opposite states: appetitive (responses to attractive or rewarding stimuli) or aversive (responses to life-threatening situations). As discussed in the following sections, the neural circuits mediating these behaviours are evolutionarily conserved (at least in tetrapod vertebrates), and give rise to behavioural responses similar to those described in mammals. Thus, in amphibians, reptiles and birds, the responses observed either in the presence of threats or in the presence or rewarding stimuli share many of the motor, vegetative and endocrine components observed in mammals. Not surprisingly, then, the neural circuits involved the appetitive and aversive responses named above can be recognized in the cerebral hemispheres of vertebrates.

In humans, survival behaviours are often associated with the subjective states that we call emotions and feelings. Even if, as we will discuss, the neural circuits involved in the expression of these behaviours are, to some extent, similar in different vertebrate species, we cannot infer that survival behaviours include also emotions in animals. Therefore, following the conceptual framework proposed by LeDoux [1], we avoid focusing this review on the neural substrate of specific emotions (fear, happiness or anger) that we introspectively associate with concrete survival behaviours (e.g. risk-avoidance, reproduction or aggression). We will discuss, instead, the neural basis of those behaviours in mammals and non-mammalian species, to try to understand the evolutionary history of the survival circuits in the brain of vertebrates..

1. Circuits for reward/attraction

Animals struggle for survival requires different kinds of appetitive responses related to: a) temperature maintenance, food intake balanced with energy expenditure and hydro-saline homeostasis (thirst and liquid intake balanced with diuresis and salt intake); b) mating and reproduction. In most animals both kinds of appetitive behaviours, "homeostatic" and reproductive, are somewhat inter-related. For instance, in territorial animals, competition with conspecifics for good territories having food and water resources and privileged access to mates ultimately facilitates both kinds of appetitive behaviours. That's why reward and appetitive behaviours are closely related to social behaviours, including agonistic confrontations for territory (which, if successful, grant all kind of resources ensuring homeostasis) and for mates, as well as sexual and reproductive behaviours, which are appetitive and rewarding themselves.

Therefore, motivation circuits must be viewed as part of the "survival circuitry" of the brain. In the early 1950's, Olds and Milner discovered that electrodes positioned in different locations of the brain induced electric auto-stimulation (EAS) [2], thus revealing the existence of specific circuits involved in reward and motivation. Maximum rates of EAS are observed when electrodes were placed in regions of the lateral hypothalamus that are crossed by catecholaminergic fibres. Moreover, anti- and pro-dopaminergic drugs influence EAS and other, naturalistic reward-seeking behaviours and dopamine agonists are among the most addictive drugs. These lines of evidence lead to the dopamine hypothesis of reward [3], according to which dopaminergic pathways, specifically tegmento-striatal (ventral tegmental area to ventral striatum) and meso-limbic (tegmental pathways to limbic prefrontal cortical areas) projections are activated by natural reinforcers, drugs and EAS, as well as by cues predicting them. Two-stage phasic release of dopamine to these target centres in response to salient stimuli (including reinforcers)

constitute an utility prediction error signal [4] that would have a causal role in goal-seeking, motivated behaviours.

The evolutionary origins of these motivation circuits are very old. Midbrain dopaminergic cell groups are present in all vertebrate classes (including key groups such as agnathans or lungfishes [5][6]) and project to subpallial portions of the cerebral hemispheres equivalent to the striatum. In fact, in all the studied vertebrates this striatum homologue shows medium-sized GABAergic projection neurons with spiny dendrites and cholinergic interneurons providing a dense acetylcholinesterase-positive neuropile, plus other populations of interneurons [7,8].

In some non-mammals there is evidence indicating that these dopaminergic pathways are involved in reward-seeking, motivated behaviours. In anamniotes amphetamine (a blocker of dopamine reuptake) can induce conditioned place preference [9][10]. Even if the dopamine transporter is not expressed in reptiles and birds [11], D1 antagonists block conditioned place preference induced by cocaine in birds [12], suggesting a similar role of dopamine in reward in *Sauropsida* and mammals. Therefore, the ancestral vertebrate would likely had had ascending dopaminergic systems involved in reward induction by natural reinforcers ensuring survival and reproduction.

Experiments in mammals indicate that the amygdala is also a locus for EAS, independently of other (classical) centres supporting EAS [13]. Recently, the use of *in vivo* optogenetics has shown that mice nose-poke to self-stimulate glutamatergic cells in the basolateral amygdala, provided that D1 dopamine receptors in the nucleus accumbens are not blocked. In addition, optogenetically hyperpolarising basolateral amygdala neurons during a reward-seeking task (licking to a 20% sucrose-delivering port), reduces reward acquisition in response to a cue [14]. This demonstrates that activation of glutamatergic amygdaloid projections resulting in dopamine release in the nucleus accumbens is a key event to actively seeking and acquiring rewards in response to reward-predicting cues. It is interesting to note that similar optogenetic self-stimulation does not occur when light activates other inputs to the nucleus accumbens, namely the prefrontal cortex.

Amygdalar pathways targeting the ventral striatum are therefore critical for reward-seeking behaviours. In fact, amygdalo-striatal pathways are massive in mammals [15] and similar pathways have been described in non-mammals [7][16,17][18]. The region of the amygdala giving rise to the most massive pathways to the striatum (dorsal and ventral) is the basolateral nucleus in mammals, and equivalent regions in the brain of reptiles, birds and amphibians [19]. Among other defining features, this basolateral amygdala-equivalent region of the brain of non-mammals displays a prominent dopaminergic innervation, which was the basis for the proposal of it representing a prefrontal cortex in the brain of birds [20]. An alternative view, consistent with the pattern of expression of morphogenetic genes in different vertebrates, neurochemical and hodological data and easy to fit with similar data in other vertebrates (reptiles), would be that birds and *Sauropsida* in general, would have underwent an expansion of the basolateral amygdala [19]. In the absence of a neocortex in birds, this portion of the amygdala would have assumed the functions that the prefrontal cortex plays in mammals allowing birds to have cognition without a true isocortex [21] (but see [22]).

As a conclusion, dopaminergic ascending pathways plus amygdalo-striatal projections represent the basic circuitry for reward processing and reward-seeking motivated behaviours that is present in at least all tetrapods, where it may subserve acquisition of homeostatic reinforcers. However, these circuits must also include the specific neural

machinery for the search and acquisition of social stimuli, thus ensuring social interactions and, ultimately, reproduction.

2. Reward circuitry and the socio-sexual brain network

It is quite established that in all vertebrates social behaviours are controlled by the so-called socio-sexual brain network (SBN) [23], a set of neural centres that are profusely interconnected, express receptors for steroid hormones (which, in this way, regulate all kind of social conducts) and are distributed in the basal telencephalon (including the extended amygdala), hypothalamus and midbrain periaqueductal grey. The nodes of the SBN control sexual interactions, agonistic encounters for territory and mates, and parental behaviours. In spite of the large variety of social behaviours displayed by different vertebrates, the structure of the SBN has been conserved during evolution [24] and encompasses centres belonging to the mesolimbic reward system [25] such as the medial (extended) amygdala, the lateral septum and portions of the ventral striato-pallidum [26].

In rodents, where chemosignals play a key role in social interactions, male pheromones detected by the vomeronasal organ of females seem to owe their rewarding properties [27,28] to direct amygdalo-ventral striatal pathways [15] [29] rather than to ascending tegmento-striatal dopaminergic projections [30][31]. Indeed, lesion or inactivation of the ventral striatal neural structures being targeted by projections from the vomeronasal amygdala in mice (the medial olfactory tubercle, islands of Calleja and adjoining ventral striatal bridges) [32] [33] suppresses preference of female mice for male chemosignals, whereas preference of other reinforcers (sucrose) remains intact. Non-chemosensory social stimuli, such as courtship vocalisations in songbirds, might be rewarding under appropriate physiological conditions [34] and this requires the confluence of hormonal inputs (occurring in the reproductive season) and conspecific vocalisations (courtship song, newborn chicks' chirps). Both kinds of stimuli seem to converge into the nidopallium caudale, which, according to current view on the comparative neuroanatomy of the avian brain [19], is interpreted as part of the enlarged basolateral division of the avian amygdala and, as such, gives rise to abundant projections to the ventral (and dorsal) striatum [17,18].

Although it is assumed that social stimuli such as vocalisations in anuran amphibians [35] or birds [36] are also rewarding to conspecifics, the neural basis of this effect is poorly understood. Similarly, visual displays or simple conspecific visual stimuli in primates (including humans) might constitute rewarding social stimuli (that we, humans, judge as beautiful) and it has been shown that they activate, among other structures, portions of the amygdala and ventral striatum [37]. Activation of amygdalo-striatal pathways is also likely to have a causal role in reward induced by other social stimuli in humans [38].

Anatomo-functional data on that point are very scarce and incomplete in non-mammalian vertebrates. In snakes (squamate reptiles) the vomeronasal cortex-like amygdaloid structure called *nucleus sphericus* projects to a part of the ventral striatum named as "olfactostriatum" [39]. Although the role of this pathway in reptiles is far from being understood, since vomeronasal stimuli were shown to be rewarding in snakes [40] it is likely that this noteworthy projection represents an "enlarged" amygdalo-striatal pathway [39] for chemosensory reward in a highly macrosmatic animal.

One of the defining features of the SBN is that it includes the main central nonapeptidergic circuits, including oxitocinergic/isotocinergic and vasopressinergic/vasotocinergic cells and pathways [41]. Besides the magnocellular neurosecretory cell groups,

nonapeptidergic cells are located in the preoptic region/medial extended amygdala, whereas nonapeptidergic fibres innervate the whole SBN [26,42]. This reflects the important role that these nonapeptides play in social interactions (pair bonding, social grouping behaviour and parental behaviours) in all vertebrates. This has been investigated using a comparative approach in closely related species of mammals (monogamous vs polygamous voles; [43][44]), birds (flocking vs territorial finches; [45][46]) and fish (grouping and non-grouping cichlids; [47]), differing in specific aspects of their social biology. In most cases, differences in social behaviours are correlated with different density in the expression of nonapeptides or their receptors in the ventral striatum (oxytocin) and/or septum (vasopressin/vasotocin).

At the level of the ventral striatum, oxytocin has been shown to play a key role in the rewarding properties of social stimuli (revealed by means of conditioned place preference induced by the presence of conspecifics). This function is due to oxytocinergic projections originating in the paraventricular nucleus of the hypothalamus to the nucleus accumbens, where oxytocin acts onto presynaptic receptors on serotonergic fibres from the dorsal raphe nucleus [48]. Other inputs might also be under the influence of nonapeptides as several afferents to the accumbens express oxytocin receptors, including different amygdaloid nuclei, as well as dopaminergic and glutamatergic cells in the ventral tegmental area [49]. In addition, recent work has shown a similar, social reward-promoting effect of oxytocin mediated by the pathway from the paraventricular hypothalamic nucleus onto dopaminergic cells in the ventral tegmental area [50]. These observations might explain the devastating effects of knocking out the genes for oxytocin or its receptor on most social behaviours (see [51]).

Functional data on the role of nonapeptides in social behaviours in nonmammals are scarce. Nonetheless, it has been shown that mesotocin (oxytocin homologue) and vasotocin (vasopressin homologue) promote sociability (proximity to large groups of same sex conspecifics) in finches [45], although the specific mechanisms and brain locations where this effect takes place are currently unknown. In lizards, indirect data show a correlation between activation of mesotocine-expressing cells in the paraventricular hypothalamus and accessory hypothalamic nuclei with the expression of courtship behaviour [52]. Again, though, whether this function of nonapeptides occurs in the ventral striatum or other centres of the mesolimbic reward system is currently unknown. Future research on the involvement of nonapeptides in reward induced by mates, pups or adult conspecifics in different vertebrates, will shed light on the evolutionary history of the interaction of the SBN with the reward brain circuitry.

3. The neural basis of risk avoidance in vertebrates

Escaping from predators and avoiding predator signals are essential behaviours for survival [52]. Thus, it is not surprising that the neural circuits controlling anti-predatory responses are evolutionary conserved. These responses include (but are not limited to) immobility to avoid being located (freezing), escaping to secure locations (flight), fighting against predators, and finally simulating death (tonic immobility). These behavioural responses are executed as a function of the proximity of the predator [54] or other factors such as the availability of a safe place [55][56]. The neural circuits underlying these responses have been well characterised in rodents [56], and a key structure in these circuits is the amygdaloid complex. The amygdala includes a sensory interface (the lateral nucleus [57]; together with the basolateral and basomedial nuclei), receiving multimodal sensory information from associative cortical areas and subcortical centres such as the thalamus, and a major output structure (the central nucleus) projecting to the

hypothalamus, periaqueductal gray and brainstem centres. This output centre controls endocrine and autonomic responses [59]. Olfactory (and vomeronasal) stimuli have a privileged access to the amygdala, thanks to direct projections from the olfactory bulbs to several cortical amygdaloid nuclei, and to the medial amygdala, which constitutes another output structure projecting mainly to the hypothalamus [60].

Intricate interconnections between the amygdaloid centres receiving multimodal non-chemosensory (visual, auditory and somatosensory) and chemosensory (vomeronasal and olfactory) inputs, ensure an integrated processing of the emotional responses to the different types of sensory information [60].

This scheme of olfactory-vomeronasal and multisensory circuits organized in parallel, with two main outputs through the central and medial amygdala, is very similar in all mammalian species studied. In fact these circuits are already present in the brain of reptiles and birds, and can be recognized in amphibians [19,61]. In all of these vertebrate groups, the chemosensory and multimodal amygdaloid centres share a pallial origin, whereas the output structures are mainly of subpallial origin (the medial amygdala has a mixed pallio-subpallial origin) [61].

An important addition to these circuits is the extended amygdala, which is composed of the bed nucleus of the stria terminalis plus portions of the substantia innominata and the interstitial nucleus of the posterior limb of the anterior commissure. The extended amygdala has two major components, the central and medial extended amygdala, associated (and connected) with the two output nuclei mentioned above, the central and medial amygdaloid nuclei [63], respectively. These two components of the extended amygdala are also present in the brain of amphibians, reptiles and birds. In the brain of non-mammals, these structures are anatomically adjacent to the central and medial amygdaloid nuclei[64]. In contrast, in mammals the stria terminalis has been displaced by the enormous development of the internal capsule, and thus the bed nucleus of the stria terminalis cannot be adjacent to the medial and central amygdaloid nuclei.

In amphibians we find only three amygdaloid structures: the lateral amygdala, which includes the olfactory and multimodal sensory interfaces, the central amygdala, probably homologous to its mammalian homonymous, and the medial amygdala, also likely homologous to the mammalian medial amygdala [65] (Fig. 1). Therefore, the scheme found in amphibians is a simplified version with only one multimodal structure with pallial origin, and two major output structures, the medial and central amygdala, of mainly subpallial origin.

In reptiles, the circuit is further elaborated with the differentiation within the sensory interface of a chemosensory cortical amygdala (located superficially and composed of several nuclei) and a multimodal complex of structures deeply located, all of them of pallial origin[19]. Within the chemosensory cortical amygdala, olfactory and vomeronasal nuclei can be recognised, and within the nonchemosensory amygdala, at least two structures can be distinguished: the posterior dorsal ventricular ridge and adjacent structures are likely homologous to the lateral amygdala of mammals, and the dorsolateral amygdaloid nucleus is probably homologous to the basolateral nucleus. The medial amygdala of reptiles is likely homologous to its amphibian and mammalian homonymous structures, and the central amygdala has been named here striato-amygdaloid transition area [64] (Fig. 1).

In birds, the reptilian pattern of organization is conserved, but the chemosensory amygdala is reduced because of the loss of the vomeronasal system and a relative reduction of the olfactory system (at least in a majority of species). In contrast, the multimodal amygdala is greatly enlarged [18], and includes part of the caudal nidopallium and the arcopallium (see Table 1). Medial and central amygdaloid structures are also recognized [66,67](Fig. 1).

In amphibians, reptiles and birds, functional evidence of the role of the amygdaloid complex in defensive or antipredatory behaviours is scarce. In lizards, lesions of the presumptive central amygdala leads to a decrease in tonic immobility response [68]. In birds, lesions of the anterior arcopallium caused a decrease in several defensive behaviours (including tonic immobility [69]), and lesions encompassing most of the arcopallium decreased anxiety in an open field test [70] and prevented the acquisition of passive avoidance learning [71]. Although, to our knowledge, there are no works investigating the role of the arcopallium and adjacent structures in Pavlovian aversive conditioning, recently, classical tone-shock conditioning has been shown to increase the mature form of BDNF in the amygdala of pigeons [72], and blocking NMDA transmission in the caudal nidopallium or parts of the arcopallium (multimodal amygdala, see Table 1) affects extinction in appetitive conditioning [73,74]. Therefore, further research is needed to confirm with functional data in non-mammalian vertebrates the anatomical, neurochemical and developmental evidence of the amygdaloid circuits reviewed above.

4. Two poles in the ventral striato-pallidum: reward vs risk avoidance

The data reviewed above indicate that, in all tetrapod vertebrates, reward-seeking responses require appropriate signalling from the multimodal amygdala to the rostral ventral striatum (nucleus accumbens and olfactory tubercle), whereas responses to threats require signalling from the multimodal amygdala to the central amygdaloid nucleus. The central amygdala can be seen as the caudal ventral striatum[19,61] (Box 1), and from this point of view both the amygdalo-striatal circuitry involved in attraction/reward and the multimodal-to-central intraamygdaloid circuitry involved in aversion/threat-responding can be considered as cortico-striatal circuits, originated in the cortical (pallial) amygdala and innervating respectively rostroventral and caudal striatal regions (Box 1). In this evolutionarily conserved organizational scheme, the medial amygdala is an output structure specialised in responses to conspecifics, which can be either appetitive, such as those related to sexual behaviour, or aggressive/defensive, such as those found in agonistic encounters with competitors. In rodents, given the key role of chemical signals in sociosexual behaviour, the medial amygdala is directly innervated by the main and accessory olfactory bulbs [75]. Our hypothesis predicts that in species in which other sensory cues are critical in social and sexual responses, information about these particular types of cues should be relayed to the medial amygdala (e.g., auditory cues in songbirds, or visual cues in primates and birds with sexually dimorphic colourful feathers). This explains why the medial amygdala has not disappeared in microsmatic species, such as humans [76], or even in anosmic animals, such as dolphins [77].

Box 1. Two poles in the survival brain

Survival and reproduction are related to avoidance of risks and reward seeking through goal-directed behaviours. The neural basis of this dichotomic response (avoidance vs approach) can be found in the two-pole organisation of ventral striato-pallidum. The

rostral pole of the ventral striato-pallidum, the nucleus accumbens-olfactory tubercle complex (Acb-Tu), is involved in goal-directed behaviours. The caudal edge of the ventral striato-pallidum constitutes the central extended amygdala, related to avoidance of threatening stimuli. Unconditioned avoidance responses are elicited by stimuli that reach directly the central extended amygdala from the brainstem-thalamus (unexpected strong stimuli, bitter taste, pain…) [78][79]. Part of this ascending pathway is rich in CGRP [80,81] and can be identified in non-mammalian vertebrates [82,83], where its termination defines the central extended amygdala. A part of the extended amygdala is also involved in aversive responses to chemosignals, such as predator kairomones [84] or, maybe, alarm pheromones (even in humans, [85]). Other risk-associated stimuli (e.g. alarm vocalisations; fear facial expressions) might have access to the extended amygdala through direct or indirect connections.

In contraposition, stimuli eliciting innately appetitive responses (sweet and salty food, comfort temperature) target the Acb-Tu through the ascending projection from the tegmental area that is rich in dopamine. This innervation is also a defining feature of the Acb-Tu of non-mammals (see text). Chemosensory inputs related to conspecifics can also be innately rewarding, sexual pheromones being a paradigmatic case [27,86,87]. Direct amygdalo-striatal pathways, found in every studied vertebrate, might be the neural substrate for such attractive responses to chemosensory cues. Other amygdalo-striatal pathways might convey rewarding, complex social stimuli such as visual displays or vocalisations.

The basolateral division of the amygdala (BLA) also receives relatively minor (nonetheless important) afferents conveying these kinds of stimuli, which are revealed by CGRP and dopamine innervation of the BLA found in the studied tetrapods. Additional afferents to the amygdala from sensory and associative pallial areas allow convergence of innately aversive or attractive stimuli with neutral cues within the BLA. Synaptic plasticity at this level mediates pavlovian association leading to learned responses of attraction or aversion to sensory cues that predict innately attractive or aversive stimuli [88], and projections to the Acb and the central extended amygdala have been demonstrated to mediate positive or negative reinforcement, respectively [89]. This adaptive function of the BLA (anticipative responses ensuring survival and/or reproduction) has likely been a driving force in the evolution of the cerebral hemispheres in higher vertebrates.

This explains the explosive increase in the size of sensory and associative pallial areas in mammals and birds. Both vertebrate classes share a huge development of the telencephalic pallium. Even if the areas enlarged in the brain of mammals and birds are different (isocortex in mammals, nidopallium and mesopallium in birds) they project directly and indirectly to the BLA (or its homologue; caudal nidopallium, dorsal arcopallium in birds), thus allowing sensory and cognitive processing of stimuli for their discrimination and subsequent associative tagging as potentially harmful/aversive or rewarding/attractive. This fine-tuned tagging constitutes an adaptive function as it mediates anticipative attraction/aversion responses to all kind of cues, what increases the probabilities of survival and reproduction.

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ABBREVIATIONS

Acb, nucleus accumbens; BLA, basolateral division of the amygdala; CGRP, calcitonin gene-related peptide; EAS, electric autostimulation; SBN, socio-sexual brain network; Tu, olfactory tubercle.

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FIGURE LEGEND

Figure 1. The amygdaloid complex in tetrapod vertebrates

Schematic representations of frontal sections of the brain of amphibians, reptiles, birds and mammals (rodents) through the caudal telencephalon, with indication of the components of their amygdalae. The different structures are color-coded as in Table 1. In amphibians (a male frog croaking), only a multimodal amygdala (LA) is recognized, which projects to the main subpallial output structures, the medial (MA) and central amygdala (CeA), as well as to the hypothalamus and the ventral striatum. This basic pattern of connectivity is also found in reptiles (a lizard in tonic immobility), birds (a rooster executing a courtship display) and mammals (a female mouse caring for pups). Major differences among groups are relative to the degree of development and differentiation of the different structures within the multimodal amygdala, as well as the relative enlargement or reduction of the chemosensory structures. The figure also summarises the main inputs and outputs of the amygdala, which allow basic physiological and behavioural reactivity for ensuring survival and reproduction. Artwork by Hugo Salais. For abbreviations, see Table 1.

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14. •• Stuber GD, Sparta DR, Stamatakis AM, Van Leeuwen WA, Hardjoprajitno JE, Cho S, Tye KM, Kempadoo KA, Zhang F, Deisseroth K, et al.: Excitatory transmission from the amygdala to nucleus accumbens facilitates reward seeking. Nature 2011, 475:377–382.

The authors use optogenetics to demonstrate massive projections from the basolateral amygdala (BLA) to the accumbens (Acb) that are the subject for intense optic self-stimulation. This seems specific for the amygdala, as optical activation of other inputs to the Acb (e.g. afferents from the prefrontal cortex) do not to induce self-stimulation. Optical activation of the BLA-Acb pathway depolarises Acb cells in a glutamate dependent manner. Dopamine is also involved in amygdalo-striatal reward, as intra-Acb application of D1R (but not D2R) antagonists block optical self-stimulation. Moreover, optically hyperpolarising amygdalo-accumbens neurons (using a Cl^--specific channelrhodopsin) reduces consumption of a natural reinforcer (licking to a sucrose solution). These findings demonstrate that afferent- specific glutamatergic neurotransmission from the BLA to the NAc is both necessary and sufficient to promote the expression of motivated behaviours.

19. •• Martinez-Garcia F, Novejarque A, Lanuza E: Evolution of the amygdala in vertebrates. In Edited by Kaas, J.H. Elsevier Academic Press; 2007:255–334.

The amygdala is a structure located in the caudolateral cerebral hemispheres, closely associated to the olfactory tract. An in-depth comparative analysis of this region (considering topology, the expression of morphogenetic genes during development, connections and neurochemistry) allows identifying the amygdala and its major divisions in the brain of tetrapods. Like mammals, amphibians, reptiles and birds posses a chemosensory amygdala (cortical amygdaloid nuclei plus medial amygdala) which is relatively reduced in microsmatic animals (e.g. birds, most primates). In addition, the pallial amygdala includes a basolateral division characterised by important projections to the striatum and to the hypothalamus (pallial component of the stria terminalis), which arise from distinct cell populations. In all studied vertebrates, a subpallial (extended amygdala) has been observed to include a central-amygdala component (projecting to hypothalamus and brainstem and receiving thalamic and brainstem inputs rich in CGRP) plus a medial-amygdala component (related to the olfactory system and giving rise to the subpallial component of the stria terminalis). This view challenges old (but successful) ideas, such as McLean's triune brain hypothesis: reptiles and amphibians already possess a "limbic" system brain subserving emotional expression.

32. • Agustín-Pavón C, Martínez-García F, Lanuza E: Focal lesions within the ventral striato-pallidum abolish attraction for male chemosignals in female mice. Behav Brain Res 2014, 259:292–296.

33. • DiBenedictis BT, Olugbemi AO, Baum MJ, Cherry JA: DREADD-Induced Silencing of the Medial Olfactory Tubercle Disrupts the Preference of Female Mice for Opposite-Sex Chemosignals. eNeuro 2015, 2:1–16.

These two papers demonstrate, separately, that there is a specific region of the ventral striato-pallidum that is fundamental for the attraction of female mice for male chemosignals (putative sexual pheromones).

34. •Maney DL: The incentive salience of courtship vocalizations: Hormone-mediated "wanting" in the auditory system. Hear Res 2013, 305:19–30.

Songbirds use complex vocalisations for social communication, in the context of sexual and agonistic behaviours. This paper reviews evidence indicating that exposure to male conspecifics' songs elicits monoamine release (from midbrain monoaminergic cell groups) not just in the ventral striatum, but also in forebrain regions corresponding to the enlarged "basolateral amygdala" of birds, namely the caudomedial nidopallium (NCM). In some sparrows with seasonal reproduction, females are more sensitive to males's song during reproductive season. This is accompained by enhanced monoaminergic activity in many brain centres (including the NCM). This is the best published evidence linking socially relevant rewarding stimuli to the activity of monoaminergic afferents to the amygdala and striatum in sauropids.

38. • Abrams DA, Chen T, Odriozola P, Cheng KM, Baker AE, Padmanabhan A, Ryali S, Kochalka J, Feinstein C, Menon V: Neural circuits underlying mother's voice perception predict social communication abilities in children. Proc Natl Acad Sci 2016, 113:6295–6300.

Using fMRI in 7-12 years old children, the authors analyse the brain response to mother's voice (as compared to non-familiar adult women's voice) pronouncing a four-syllable nonsense word. Children accurately identified their mother's voice, which elicited strong activity in their auditory system (inferior colliculus, primary and associative auditory cortical areas, voice-selective temporal cortex). It also activated portions of the visual cortex and face processing circuitry. More importantly, the reward brain system was strongly activated by mother's voice: amygdala, nucleus accumbens and adjoining ventral putamen, as well as orbitofrontal and ventromedial prefrontal cortex. This demonstrates that salient social stimuli use the same reward circuits that other, non-social natural reinforcers.

48. •• Dölen G, Darvishzadeh A, Huang KW, Malenka RC: Social reward requires coordinated activity of nucleus accumbens oxytocin and serotonin. Nature 2013, 501:179–84.

In mice, conditioned place preference induced by interaction with conspecifics is blocked by oxytocin (OT) antagonists applied systemically or into the Acb, where OTergic fibres from the paraventricular hypothalamus terminate. However, OT is not acting directly onto Acb cells, but influences presynaptically afferent fibres expressing OT receptors. Specifically, the authors demonstrate that social reward involves OT action onto serotonergic fibres in the Acb arising in the dorsal raphe nucleus, thus requiring a combined action of OT and serotonin ultimately resuling in LTD in both D1- and D2-receptor-expressing medial spiny stellate cells of the nucleus accumbens. This is a clear example of the key role of reward pathways and centres in social behaviour, and demonstrates the interaction of nonapeptidergic and dopaminergic inputs (among others) to the ventral striatum in such a fundamental function for survival and reproduction.

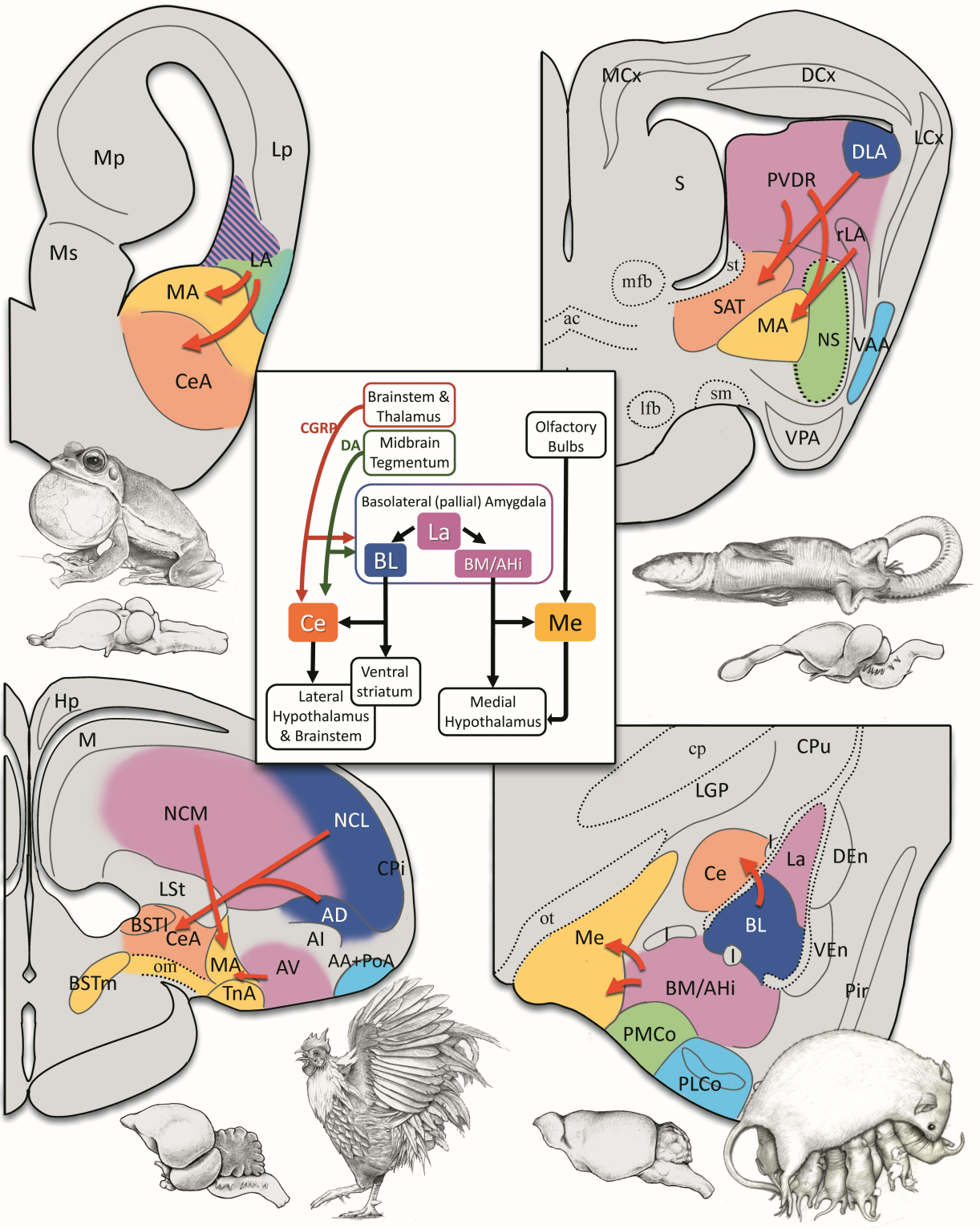
61. •• Medina L, Abellán A, Vicario A, Castro-Robles B, Desfilis E: The Amygdala. In Evolution of Nervous Systems, vol.1. Edited by Kaas J. Elsevier Inc.; 2017:427–478.

Recent comprehensive review of the developmental and genetic evidences that reveal the homologies among the different components of the amygdaloid complex in tetrapod vertebrates, including a detailed analysis of the embryonic origin and molecular profile (pattern of expression of morphogenetic genes during development) of the diferent amygdaloid structures.

69. • Saint-Dizier H, Constantin P, Davies DC, Leterrier C, Lévy F, Richard S: Subdivisions of the arcopallium/posterior pallial amygdala complex are differentially involved in the control of fear behaviour in the Japanese quail. Brain Res Bull 2009, 79:288–295.

70. • Lowndes M, Davies DC: The effect of archistriatal lesions on “open field” and fear/avoidance behaviour in the domestic chick. Behav Brain Res 1995, 72:25–32.

These two works provide the main functional evidences of the role of the avian amygdala in fear behaviour, based on the effects of electrolytic lesions of the arcopallium in the responses observed in open field, novel object and tonic immobility tests. Unfortunately, the effects of similar lesions in simple fear conditioning tests (similar to those used in rodents) have not been reported.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VPA
Brainstem &
Thalamus
CGRP
DA
Midbrain
Tegmentum
Olfactory
Bulbs
Basolateral (pallial) Amygdala
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BL
BM/AHi
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Ventral
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Hypothalamus
& Brainstem
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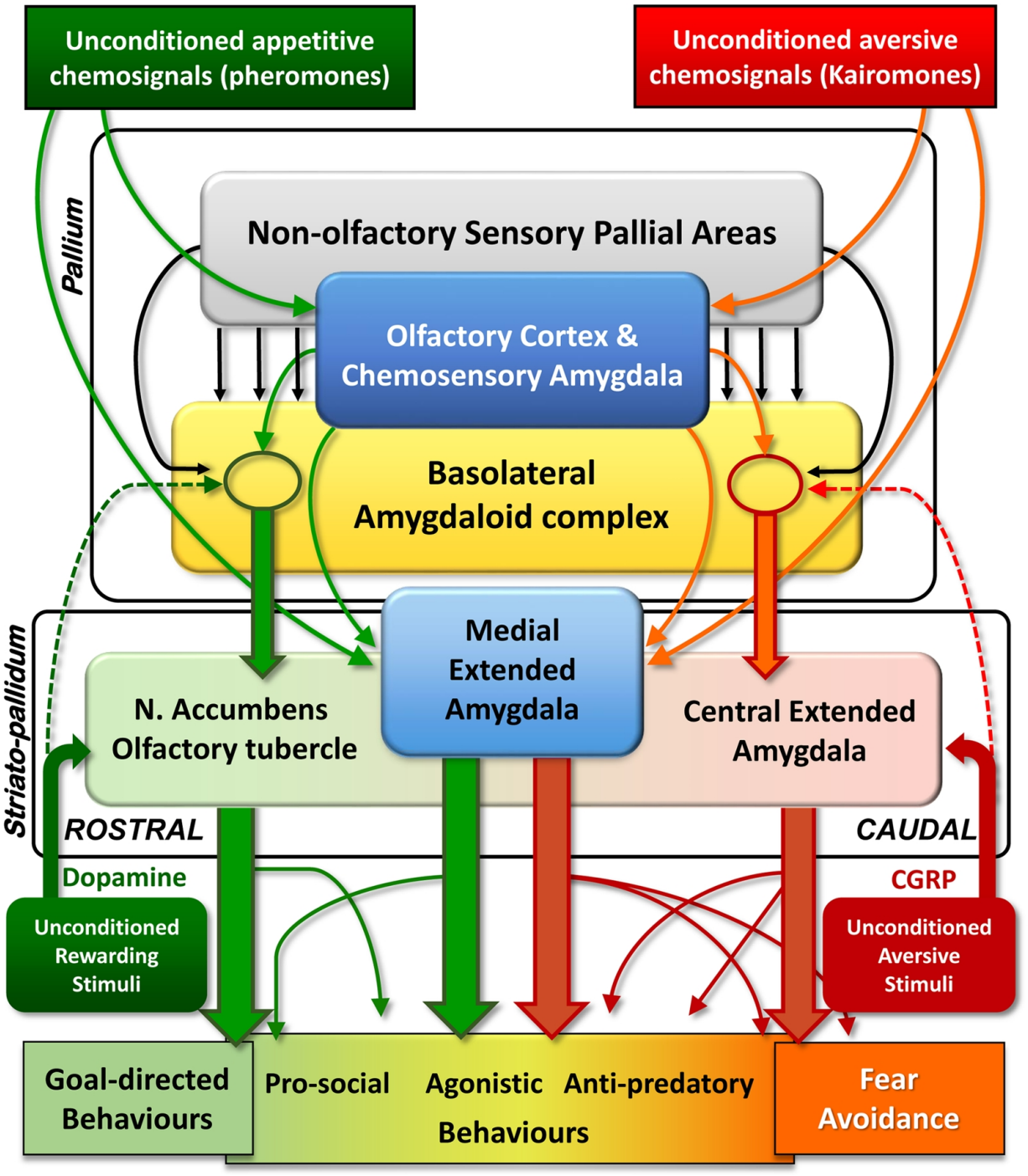
Unconditioned appetitive chemosignals (pheromones)
Unconditioned aversive chemosignals (Kairomones)
Pallium
Non-olfactory Sensory Pallial Areas
Olfactory Cortex & Chemosensory Amygdala
Basolateral Amygdaloid complex
Striato-pallidum
Medial Extended Amygdala
N. Accumbens Olfactory tubercle
Central Extended Amygdala
ROSTRAL
CAUDAL
Dopamine
CGRP
Unconditioned Rewarding Stimuli
Unconditioned Aversive Stimuli
Goal-directed Behaviours
Pro-social
Agonistic
Anti-predatory
Behaviours
Fear Avoidance

TABLE 1. Putative homologies of the amygdala and its divisions in tetrapod vertebrates

		AMPHIBIANS	REPTILES	BIRDS	MAMMALS
PALLIAL AMYGDALA	NON CHEMOSENSORY	LATERAL AMYGDALA	PDVR + rLA	NCM + AV	La +BM/AHi
			DLA	NCL +AD	BL
	OLFACTORY		VAA	Superficial AA	ACo + PLCo
	VOMERONASAL		NS	-	PMCo
SUBPALLIAL AMYGDALA	NON CHEMOSENSORY	CENTRAL AMYGDALA	SAT	CENTRAL AMYGDALA + pINP	CENTRAL AMYGDALA (Ce)
	CHEMOSENSORY	MEDIAL AMYGDALA	MEDIAL AMYGDALA	MEDIAL AMYGDALA	MEDIAL AMYGDALA (Me)

The color codes of the different structures are the same as in Fig. 1. For the amphibian amygdala, see mainly Moreno and Gonzalez, 2006 [64]; for the reptilian and avian amygdala, see mainly Martínez-García et al., 2007 [18], and Medina et al., 2017 [60].
Abbreviations:
Reptiles: DLA, dorsolateral amygdaloid nucleus; NS, nucleus sphericus; PDVR, posterior dorsal ventricular ridge; rLA, reptilian lateral amígdala; SAT, striatoamygdaloid transition área; VAA, ventral amygdaloid area
Birds: AA, anterior arcopallium; AD, arcopallium dorsale; AV, arcopallium ventrale; NCL, nidopallium caudolaterale; NCM, nidopallium caudomediale; pINP, peri-intrapeduncular nucleus
Mammals: ACo, anterior cortical amygdaloid nucleus; AHi, amygdalo-hippocampal área; BL, basolateral amygdaloid nucleus; BM, basomedial amygdaloid nucleus; La, lateral amygdaloid nucleus; PLCo, posterolateral amygdaloid nucleus; PMCo, posteromedial amygdaloid nucleus.