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Review

# Sexual pheromones and the evolution of the reward system of the brain: The chemosensory function of the amygdala

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**Abstract**

The amygdala of all tetrapod vertebrates receives direct projections from the main and accessory olfactory bulbs, and the strong similarities in the organization of these projections suggest that they have undergone a very conservative evolution. However, current ideas about the function of the amygdala do not pay sufficient attention to its chemosensory role, but only view it as the core of the emotional brain. In this study, we propose that both roles of the amygdala are intimately linked since the amygdala is actually involved in mediating emotional responses to chemical signals. The amygdala is the only structure in the brain receiving pheromonal information directly from the accessory olfactory bulbs and we have shown in mice that males emit sexual pheromones that are innately attractive for females. In fact, sexual pheromones can be used as unconditioned stimuli to induce a conditioned attraction to previously neutral odorants as well as a conditioned place preference. Therefore, sexual pheromones should be regarded as natural reinforcers. Behavioural and pharmacological studies (reviewed here) have shown that the females' innate preference for sexual pheromones is not affected by lesions of the dopaminergic cells of the ventral tegmental area, and that the systemic administration of dopamine antagonists do not alter neither the attraction nor the reinforcing effects of these pheromones. Anatomical studies have shown that the vomeronasal amygdala gives rise to important projections to the olfactory tubercle and the islands of Calleja, suggesting that these amygdalo-striatal pathways might be involved in the reinforcing value of sexual pheromones.


*Keywords:* Vomeronasal; Olfactory; Dopamine; Ventral tegmental area; Olfactory tubercle; Islands of Calleja

## Contents



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## 1. Introduction

At the beginning of the 20th century, comparative neuroanatomists such as Herrick [14] and Johnston [16] already pointed out that the amygdaloid formation of different vertebrate species was closely related to the olfactory system. These observations were confirmed in mammals in the 1960s and 1970s using earlier tracing techniques [37,40]. In fact, the direct chemosensory (olfactory and vomeronasal) inputs constitute a defining feature of the amygdala [38], which has been widely used in comparative studies to identify the amygdala of reptiles [19,24] and amphibians [41]. Even in birds, which lack a vomeronasal system, the projections from the main olfactory bulbs [39] are a useful landmark to identify portions of the amygdala [25,26].

The highly conservative evolution of the projections from the main and accessory olfactory bulbs to the amygdala in tetrapods [26] suggests that the chemosensory inputs to the amygdala play a key functional role for survival and reproduction. However, current ideas about the function of the amygdala consider it as the core of the emotional brain [21,17], a view that is supported by a large amount of data obtained in behavioural paradigms of aversive learning (such as fear conditioning). In contrast, and in spite of its important chemosensory inputs, the role of the amygdala in chemosensory processing is frequently neglected [1]. In this study, we propose a hypothesis that explains the relation between the chemosensory role of the amygdala and its position as a key component in the network mediating emotional responses. In this respect, it has been suggested that the amygdala is a heterogeneous group of structures that have neither structural nor functional relationship among them [5,45] and, therefore, one possible explanation of the emotional versus chemosensory dichotomy would be that these two divisions of the amygdala are simply unrelated. However, the strong interconnections among the amygdaloid nuclei [36], which are well conserved in tetrapods [26], suggest that the amygdala constitutes a true structural and functional unit [20] and, therefore, the chemosensory input to the amygdala would be intimately involved in a more general amygdaloid function, such as mediating innate emotional responses to chemical signals.

## 2. The amygdala and the response to sexual pheromones

Since the amygdala contains all the nuclei of the brain that are targeted by direct projections of the accessory olfactory bulb [32,40], it is undoubtedly involved in the processing of vomeronasal information. The vomeronasal system is specialized in detecting pheromones [9] (although there are also olfactory-detected pheromones [42] and some non-pheromonal odorants have been shown to activate vomeronasal neurons [46]). Some animals, such as silk moths, are known to produce pheromones involved in intersexual attraction, the so-called sexual pheromones. However, the existence of sexual pheromones in mammals is controversial [6,8,15, see discussion in 29]. If they exist, mammalian sexual pheromones should be stimuli with intrinsic positive emotional value, and therefore it may be possible to use these pheromones as unconditioned reinforcers. To test

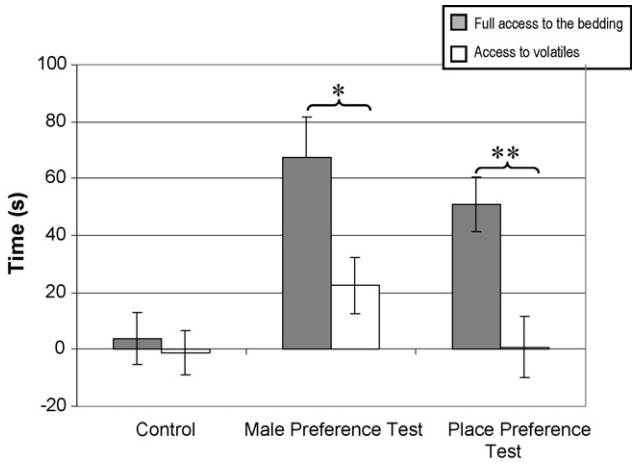


Fig. 1. Rewarding properties of male sexual pheromones to female mice. Bar histogram (mean ± S.E.M.) showing the preference displayed by two groups of female mice for one of two dishes (time exploring dish 1 minus time exploring dish 2) during two-choice tests under two different conditions, namely direct access to the bedding ($n = 7$) or access only to volatiles ($n = 9$). During the pre-training control test and the place preference test, both dishes contained bedding soiled by castrated males, whereas in the male preference test dish 1 contained intact male-soiled bedding and dish 2 bedding soiled by castrated males. An ANOVA followed by appropriate post-hoc analysis indicates that the two groups differ in the male preference test and in the place preference test of the group that can contact the bedding. The place preference test follows to four 10-min training sessions in which dish 1 contains male-soiled bedding that acts as a reinforcer. Because of this training, females having full access to the bedding (but not those having access only to the volatiles) acquire preference for the place where the rewarded dish was located. (*) Indicates a $p$-value < 0.05; (**) indicate $p$-value < 0.01, in the post-hoc analysis.

this hypothesis, we first examined the attractiveness of chemical stimuli present in bedding soiled by male mice to females with no previous experience with chemical signals derived from adult males. Using these "chemically naïve females", we performed different kinds of two-choice tests in which response to male-soiled bedding was compared to response to either female-soiled bedding, bedding soiled by castrated males or clean bedding. In all these instances, the chemically naïve females consistently preferred intact male-soiled bedding provided that direct contact with the bedding was possible, but not when they could only detect volatiles emanating from the bedding because a perforated platform or cover separated the animals from the bedding during the test (Fig. 1).

This finding led to three main conclusions. First, since females prefer intact male- to castrated male-soiled bedding, males produce, in a testosterone dependent manner, sexual pheromones that are innately attractive to females. Second, these male sexual pheromones are nonvolatile or contain critical nonvolatile compounds. Third, male-derived volatiles alone are not innately attractive to females and, therefore, cannot be considered pheromones on their own [28–30]. This evidence strongly suggests that sexual pheromones mediating innate intersexual attraction in mice are vomeronasal stimuli, since the vomeronasal organ is able to detect nonvolatile chemicals [22,50]. In fact, in chemically naïve female mice, the exploration of the nonvolatile male sexual pheromone activates all the secondary vomeronasal centres in the amygdala as well as the

accessory olfactory bulbs, whereas chemoinvestigation of male-derived volatiles does not activate the vomeronasal system, but only main olfactory-recipient structures [31].

Noteworthy, after a few exposures to the male-soiled bedding in which females have access to both its volatile and nonvolatile components, the volatile stimuli acquired attractive properties [29,31]. We hypothesized that, during repeated exposure to male-soiled bedding, a Pavlovian associative learning had taken place, in which the nonvolatile, innately attractive, vomeronasal-dependent pheromone acted as an unconditioned stimulus, whereas male-derived volatiles detected by the olfactory epithelium became conditioned stimuli. The analysis of c-fos expression induced in female mice by chemoinvestigation of male-derived volatiles, before and after experience with male bedding, suggests that this olfactory–vomeronasal association may occur in the basolateral amygdala [31].

Therefore, the amygdala seems to be involved in the innate response to sexual vomeronasal-mediated pheromones as well as in the learning process leading to a conditioned response to male-derived (volatile) odorants.

## 3. The attraction for sexual pheromones: a case of emotional behaviour

As we discuss above, nonvolatile, innately attractive chemicals (sexual pheromones) can be used to induce a conditioned attraction to male-derived volatiles [29,31]. This suggests that sexual pheromones are not just 'attractive' but are intrinsically rewarding. Therefore, we decided to test whether sexual pheromones are capable of acting as unconditioned reinforcers, by using them to condition a spatial preference for a given location in a test cage where the pheromone was systematically located [28]. We used an unbiased protocol of place conditioning, in which the females initially showed no preference for any particular location in the test cage. The females were subsequently given four 10-min training sessions (one per day on 4 consecutive days) in which bedding soiled by intact males was located on one side of the test cage, whereas bedding soiled by castrated males was present on the opposite side of the cage. After this training, females show a clear preference for the side of the test cage that had contained intact male chemosignals (Fig. 1). Again, for the induction of a conditioned place preference to occur, the females required direct contact with the male-soiled bedding (Fig. 1). Consequently, a nonvolatile, likely vomeronasal-mediated male sexual pheromone was rewarding (thus 'attractive') to the female mice.

Therefore, in female mice the amygdala (at least its vomeronasal portion) is involved in the expression of a preprogrammed emotional response consisting in the 'search' for attractant male sexual pheromones that also function as unconditioned reinforcers. The association between these pheromones and neutral male-derived odorants would result in a learned attraction to the odorants that would allow the females to detect and track males at a distance. This association between olfactory and vomeronasal stimuli is likely to take place in the basolateral amygdala [31].

## 4. The dopaminergic tegmento-striatal pathway is not involved in pheromone reward

The previous experiments demonstrate that sexual pheromones present in male-soiled bedding are natural reinforcers. The neural circuitry involved in processing the reinforcing value of these chemical signals is unknown, but it is reasonable to hypothesize that it should include pathways linking the vomeronasal amygdala with the dopaminergic tegmento-striatal projection, classically considered the key pathway in reward signalling [49]. To test the implication of the tegmento-striatal pathway in pheromone reward, we placed neurotoxic lesions in the ventral tegmental area (VTA), by means of injections of 6-hydroxydopamine (destroying dopaminergic cells), in chemically naïve female mice and analysed the effects of these lesions on the preference they showed for male pheromones. As a control of the effectiveness of the lesions, we also analysed if they had affected the preferential consumption of a sweet sucrose solution (vs. water), another natural reinforcer that has been reported to be dependent on the dopaminergic tegmento-striatal pathway [44].

To our surprise, the lesions of the VTA impaired the preference for sucrose but not for male sexual pheromones [23]. The integrity of the dopaminergic tegmento-striatal pathway was needed for the expression of long-term (48 h) sucrose overconsumption but not for the preference for male sexual pheromones in our 5-min tests. This result was further supported by the fact that the number of dopaminergic cells surviving the injection of the neurotoxic agent (indicative of the size of the VTA lesion), was correlated with the behavioural preference for sucrose (i.e., the larger the lesion the smaller the sucrose preference) but showed no correlation with the preference for sexual pheromones (Fig. 2). Consistent with this finding, the VTA was not activated (no c-fos expression) by the exploration of male-soiled bedding, even when it was preferred by the animals [31].

Since the dopaminergic tegmento-striatal projection is not necessary for the expression of the behavioural preference for pheromones, the next question we examined was whether dopamine is involved in pheromone reward signalling at all. To answer this question we tested the effects of systemic administration of dopamine antagonists on the attractive value of male pheromones [2]. The results showed that neither antagonist of the dopamine D1 receptors nor of the D2 receptors had any effect on the innate attraction that females show towards male pheromones (Fig. 3). In contrast, amphetamine (a dopamine indirect agonist) abolished the preference for male-soiled bedding even at low doses that did not affect the locomotor behaviour or the exploratory behaviour normally displayed on female-soiled bedding [2]. These effects of amphetamines are mimicked by the specific D1 agonist SKF38393 [31]. Therefore, dopamine is not necessary for the innate preference for pheromones to be expressed, but it seems to play a modulatory (inhibitory) role on the processing of pheromone information, probably acting through D1 receptors.

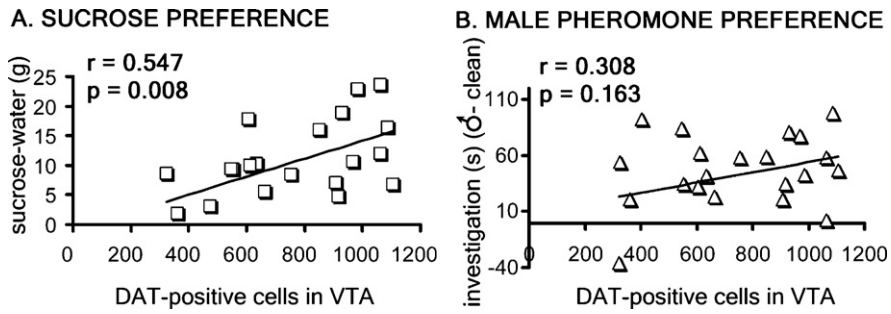


Fig. 2. Effect of lesions of dopaminergic cells in the ventral tegmental area of female mice on the reward of pheromones and sucrose. The preference for sucrose (A), but not preferential investigation of male-soiled bedding (B), depends on the integrity of the tegmento-striatal dopaminergic pathway. (A) Correlation analysis reveals a moderate, significant correlation of sucrose preference (sucrose minus water intake) with the number of dopamine transporter (DAT) immunoreactive cells in the ventral tegmental area (VTA) of control and 6-OHDA injected animals. (B) In contrast, preference for male pheromones (time exploring male-soiled bedding minus time exploring clean bedding in a two-choice test) is not correlated with the number of DAT positive cells in the VTA (see [23]).

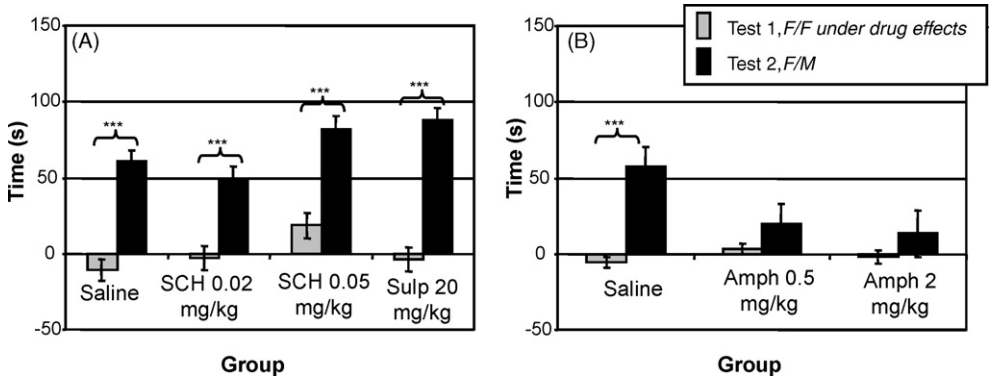


Fig. 3. Effects of dopaminergic drugs onto female mice's preference for male sexual pheromones. (A) Bar histograms showing the preference (time exploring dish 1 minus time exploring dish 2) displayed during two-choice control (female vs. female-soiled bedding, F vs. F) and male preference tests (female vs. male, F vs. M) by chemically naive females that received intraperitoneal injections of different doses of a D1 receptor antagonist (SCH-23390), a D2 receptor antagonist (sulpiride, Sulp) or vehicle injections (Saline). Statistical analysis using an ANOVA indicates that neither dopamine antagonist had significant effect on females' preference for male-soiled bedding. (B) Histogram showing the effects of two doses of amphetamine (Amph), a non-specific dopamine agonist, on the preference of chemically naive female mice for male-soiled bedding. Even low doses of amphetamine that cause no detectable effects on other behaviours (such as locomotion) abolish preference for male vs. female soiled bedding. This effect is mimicked by the specific D1 agonist SKF (see [2]).

## 5. Are amygdalo-striatal pathways involved in signalling the reward of sexual pheromones?

The results described above strongly suggest that sexual pheromones have their own neural mechanisms for reward signalling in which, in contrast to other natural reinforcers (e.g. sweet taste), the dopaminergic tegmento-striatal pathway is not involved. Vomeronasal information is processed in the medial and cortical posteromedial nuclei of the amygdala plus part of the bed nucleus of the stria terminals. Therefore, it is reasonable to suggest that projections from these centres of the vomeronasal amygdala to the ventral striatum may be the alternative pathways that may mediate the transfer of pheromonal information to the reward centres of the brain (Fig. 4). In fact, amygdalo-striatal pathways are known to be involved in the generation of goal-directed behaviours related to sex [10] and water in thirsty animals [4] and the amygdala is currently considered a key component of the reward circuits of the brain [3]. Indirect connections from the vomeronasal amygdala to the basolateral complex of the amygdala (Fig. 4) [36] and from this structure to the ventral striatum may also play a role in the expression of the female preference for male pheromones. In fact, both the basolateral nucleus of the amygdala and the medial shell of the accumbens are activated (as revealed by c-fos expression) by the exploration of male-soiled bedding [31]. We are currently investigating the organization of vomeronasal inputs to the ventral striatum [35], and the results indicate that the bulk of the projections from the vomeronasal amygdala to the ventral striatum terminates in the olfactory tubercle, some islands of Calleja and the adjoining cell bridges of the ventral striatum, but not as densely in the nucleus accumbens.

## 6. The amygdala as a device for emotional responses to chemosignals: a comparative approach

The results reported above describing the role of chemical signals presumably detected by the vomeronasal organ, in mediating intersexual attraction in mice indicate that, in rodents, the chemosensory amygdala plays a role in processing the rewarding value of sexual pheromones. Additional evidence suggests that the basolateral complex of the amygdala (part of the emotional amygdala) may participate in learning to associate these rewarding stimuli with other neutral stimuli that occur contingently [31], probably in association with the prefrontal cortex

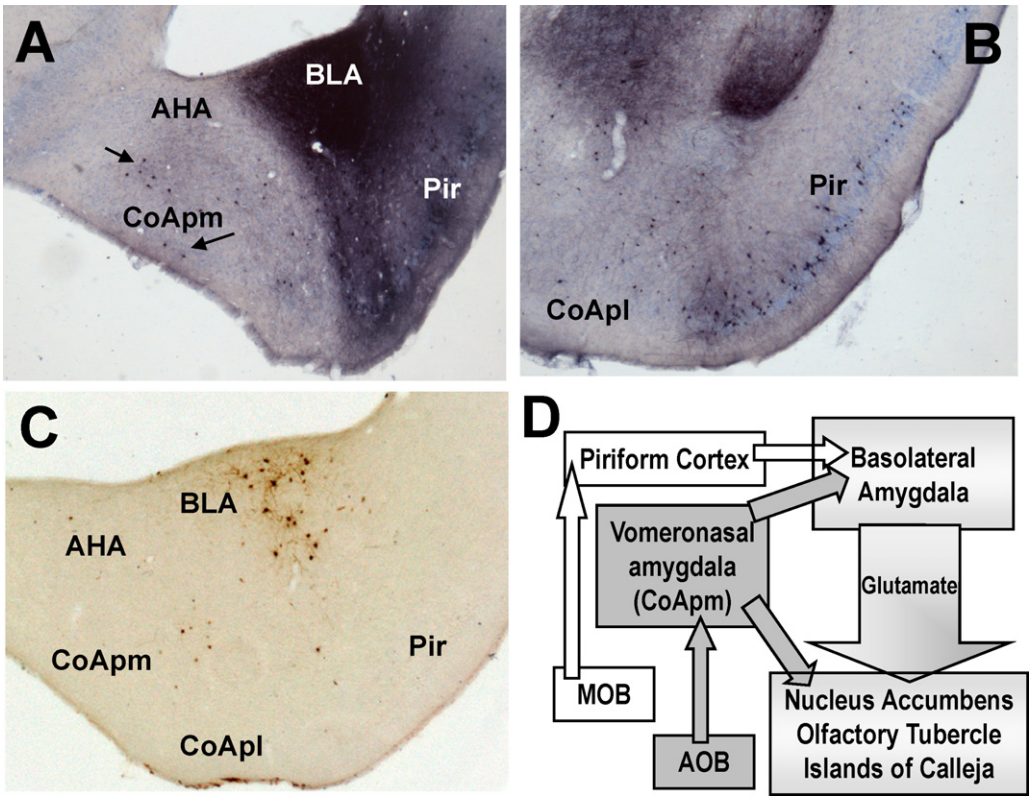


Fig. 4. Putative pathways for reward signalling of sexual pheromones and olfactory–vomeronasal associations. (A) Transverse section through the caudal amygdala of a mice showing an injection of neural tracer (biotinylated dextranamine) in the basolateral nucleus of the amygdala (BLA) and the resulting retrogradely labelled neurons in the posteromedial cortical nucleus of the amygdala (CoApm). (B) The same injection also gave rise to an important amount of retrograde labelling in the piriform cortex (Pir). (C) Retrograde labelling in the BLA following a tracer (rhodamine-labelled dextranamine) injection in the ventral striatum, affecting the shell of the nucleus accumbens. (D) Schematic map of the key neural pathways involved in processing male mice sexual pheromones. The vomeronasal and olfactory projections converge in the basolateral nucleus of the amygdala, which in turn give rise to important projections to the ventral striatum [35,47].

[43]. Therefore, the chemosensory amygdala seems involved in processing sexual chemosignals that induce unconditioned emotional responses, as well as in relaying this chemical information to the basolateral amygdala for emotional learning. Consequently, there is actually no clear-cut separation between the chemosensory and the emotional divisions of the amygdala, since they are interconnected and work together in the control of adaptive behaviours. Furthermore, sexual pheromones are probably not the only chemical signals inducing emotional responses that are detected by the vomeronasal organ and processed in the amygdala. Some odours derived from cats and foxes have been reported to be innately aversive for rats, and at least the cat-derived chemicals seem to be detected by the vomeronasal organ [7]. Therefore, the chemosensory portion of the amygdala, and especially the vomeronasal portion thereof, may be part of a neural device specialized in detecting chemicals with intrinsic biological significance, that are loaded with either positive (sexual pheromones) or negative (predator-derived signals) connotations.

This scenario in rodents raises the question of whether this constitutes a particular trait of some macrosomatic mammals or, in contrast, it is also present in other groups of mammals and non-mammalian vertebrates. Several lines of evidence indicate that a similar situation occurs in reptiles and amphibians. On the one hand, chemical signals that mediate intersexual attraction have been described in several species of amphibians and reptiles [12]. These sexually attractive chemicals are detected by the vomeronasal organ in salamanders [48] and snakes [13]. In addition, some species of snakes are able to detect in a specific way both predator-derived (therefore with negative emotional value) and prey-derived chemicals (endowed with positive emotional value) that constitute vomeronasal stimuli [12] and are reinforcing [11]. On the other hand, as in mammals [35,47], a direct projection from the vomeronasal amygdala to the ventral striatum (“olfactostriatum”) is present in amphibians [33], lizards [34] and snakes [27].

Therefore, the available data strongly suggest that in all the terrestrial vertebrates possessing a vomeronasal organ, the vomeronasal amygdala is involved in detecting chemical signals with an intrinsic emotional significance. This was, very likely, the main role of the vomeronasal system (including part of the amygdala) of ancestral tetrapods. In addition, in mammals (Fig. 4) and non-mammals [18] the vomeronasal amygdala relays information to the associative basolateral amygdala, allowing emotional tagging of neutral sensory cues that occur contingently with the unconditioned stimuli (be it a negative or a positive reinforcer). In the terrestrial environment, olfactory–vomeronasal associations are especially adaptive. Vomeronasal stimuli have intrinsic biological meaning and thus are very useful for mediating innate, unconditioned responses

(to pheromones and predator- or prey-related chemosignals). However, most (if not all) vomeronasal stimuli are nonvolatile or, at least, under normal conditions, require close contact of the nose, mouth or tongue of the animal with them [22,29]. Therefore, these unconditioned responses are only triggered when the animal is close to the source of the stimulus (conspecific, predator or prey) constituting a distinct disadvantage for the vomeronasal system. Tagging odorants with an emotional meaning (either attractive or aversive) by their association with biologically meaningful vomeronasal stimuli, allows anticipative responses to the presence of conspecifics, predators or preys, since these odorants are volatiles that can be detected from a distance and then avoided (predators, conspecific competitors) or tracked (mates, preys).

The adaptive value of the conditioning that takes place in the amygdala, in which vomeronasal stimuli act as unconditioned emotional triggers that allow emotional tagging of other chemical and non-chemical stimuli, explains the great success of the amygdala as neural machinery for survival and reproduction. Therefore, the chemosensory function of the amygdala is inseparable from its role as part of the emotional brain. In other words, from the beginning of its evolutionary history, the chemosensory and emotional parts of the amygdala probably constituted, together, a true functional system.

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