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Is there anybody out there? Neural circuits of threat detection in vertebrates

Ana G Pereira and Marta A Moita

Avoiding or escaping a predator is arguably one of the most important functions of a prey's brain, hence of most animals' brains. Studies on fear conditioning have greatly advanced our understanding of the circuits that regulate learned defensive behaviours. However, animals possess a multitude of threat detection mechanisms, from hardwired circuits that ensure innate responses to predator cues, to the use of social information. Surprisingly, only more recently have these circuits captured the attention of a wider range of researchers working on different species and behavioural paradigms. These have shed new light into the mechanisms of threat detection revealing conservation of the kinds of cues animals use and of its underlying detection circuits across vertebrates. As most of these studies focus on single cues, we argue for the need to study multisensory integration, a process that we believe is determinant for the prey's defence responses.

Address
Champalimaud Centre for the Unknown, Champalimaud Neuroscience Programme, Lisbon, Portugal

Corresponding author: Moita, Marta A (marta.moita@neuro.fchampalimaud.org)

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Introduction

Animals face a multitude of dangers many of which can be life threatening, such as an encounter with a predator. They have thus evolved a variety of mechanisms to detect impending danger using a multitude of cues that identify the threat or signal its approach. In addition, animals can detect threats indirectly using cues learned to be associated with the menace or cues provided by other alarmed prey. Studies on learned fear have greatly contributed to our understanding of how the brain learns to predict threat and have been the subject of several reviews [1,2]. However, in recent years there has been substantial progress in our understanding of innate mechanisms of direct predator detection in a variety of animal species. Interestingly, these studies revealed that similar kinds of stimuli, acting through partially conserved circuits, trigger defensive behaviours in a multitude of vertebrate species. These commonalities pave a way to understanding how neuronal circuits of defensive behaviours have evolved. We will focus on chemical, visual and auditory cues separately, and then discuss potential mechanisms for multisensory integration, which we believe is likely to play a crucial role in determining the animals' response to a threat.

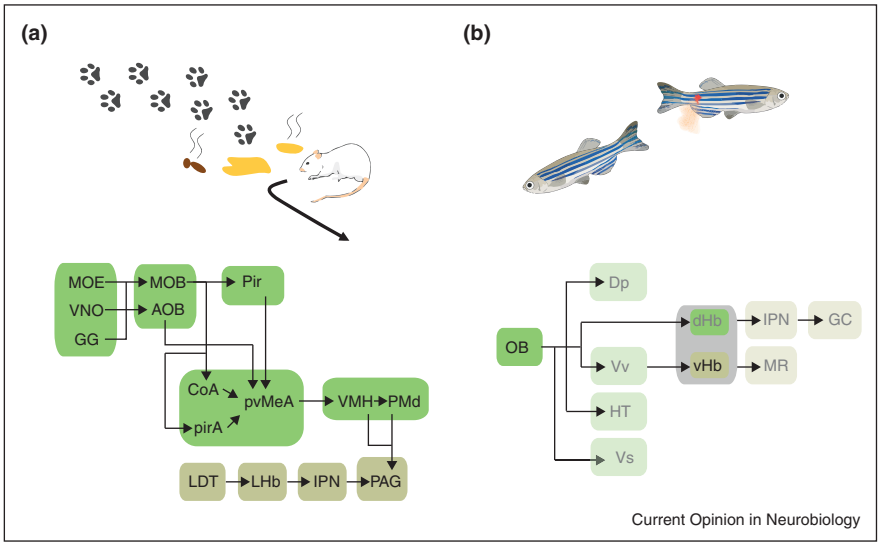
Chemical cues

Chemical cues from predators or injured/stressed conspecifics, are sufficient to trigger innate defensive behaviours in many vertebrates [3,4•,5•,6–9]. The olfactory system of most mammals, reptiles and amphibians has two entry points, the main olfactory epithileum (MOE) and the vomeronasal organ (VNO). However, some vertebrate lineages like teleost fish and higher primates have lost the VNO. Importantly, several mammal species have another chemosensing organ, the Grunenberg Ganglion (GG), implicated in interactions between conspecifics [4•].

Olfactory cues, mostly present in predators' secretions, trigger defensive behaviours in rodents. A number of volatile molecules, such as TMT, 2-PEA and 2-PT that result from meat digestion are detected by neurons in the main olfactory system (MOS) and GG (responses to 2-PEA in GG were not tested), thereby triggering defensive responses [3,4•,5•,7]. Furthermore, trace amine-associated receptors (TAARs) in the MOE are sensitive to these at very low concentrations. These findings suggest that prey uses molecules that result from meat metabolism as long-range cues of a predator's presence [10]. On the other hand, non-volatile chemicals such as major urinary proteins (Mups) act as short-range cues and are sensed by the Acessory Olfactory System [6].

Recent studies have also identified alarm pheromones produced by stressed rodents constituting an indirect mechanism of predator detection. SBT, isolated from stressed mice, is structurally similar to cues from carnivores such as TMT or 2-PT, and also activates the main olfactory bulb (MOB) and GG neurons [4•,11]. In addition to SBT, a mixture of hexanal and 4-methyl pentanal has been identified as an alarm pheromone in rats, which activates the vomeronasal system [12].

Figure 1



Circuit for detection of chemical cues of threat. **(a) Rodents.** Top drawing illustrates avoidance by rodents of cues present in predators' secretions. Bottom scheme summarizes the known elements of olfactory circuit for threat detection described in rodents. Regions coloured in green have known inputs conveying olfactory information, regions in khacki have been implicated in olfactory driven defensive behaviours but the olfactory input to them is less clear. **(b) Zebrafish.** Top drawing illustrates response to the alarm substance produced by damaged skin of conspecifics. Scheme follows same colour code as in (a), however, regions in paler colour and grey letters indicate regions of the fish homologous to regions in mammals that have been implicated in defensive behaviours, but whose role in zebrafish remains to be tested or is under debate.
Abbreviations: AOB — accessory olfactory bulb; pirA — amygdalo-piriform transition area; CoA — cortical amygdala; IPN — interpeduncular nucleus; LDT — laterodorsal tegmentum; LHb — lateral habennula; pvMEA — posterioventral region of the Medial Amygdala; MOB — main olfactory bulb; MOE — main olfactory epithelium; GG — grunenberg ganglion; Pir — piriform cortex; PMd — dorsal premammillary nucleus; VMH — ventromedial hypothalamus; VNO — vomeronasal organ.

Downstream of the olfactory system, neurons in the posteroventral part of the medial nucleus of the amygdala (pvMeA) respond to the presentation of predator odours detected by the MOE, VNO and GG [3,4•,5•,6,13]. Therefore, the MeA may be a point of convergence and integration of threat related olfactory information provided by different subsystems. The MeA projects to the ventromedial hypothalamus (VMHdm), where the responses to predator odours are recapitulated [5•]. Activity in the VMHdm can drive defensive behaviours through multiple routes including its projections to the peri-acqueductal gray (PAG) [14–16,17••] (Figure 1a).

Briefly, in rodents both the direct and indirect (through conspecifics) detection of predators using chemical cues relies on multiple and overlapping input channels to downstream targets such as the MeA. Whether these correspond to redundant mechanisms or fulfil complementary functions remains largely unexplored. Recent evidence points to the later [4•,5•]. Moreover, the detection of alarm pheromones seems to have evolved through co-option mechanisms, since these cues share structural similarities with predator odours activating similar input channels.

Reptiles and amphibians also display an array of defensive behaviours triggered by both intra and interspecies chemical cues [9,18]. Although homologies in the amygdaloid complex across vertebrates are still a matter of debate, comparative studies provided evidence for extensive homologies between reptiles/amphibians and the mammalian olfactory amygdala. As in rodents, information from the MOE and VNO project to different subnuclei of the amygdaloid complex. The nucleus homologous to the MeA receives input from the VNO and constitutes a major source of chemosensory information to the hypothalamus [19,20]. Homologous structures to an olfactory amygdala have however been more difficult to assert for the avian brain due to its reduced reliance on chemosensation and for fish due to distinct brain development processes [19,20].

In fish, olfactory driven defensive behaviours can be triggered by an alarm substance (AS) present in damaged skin of conspecifics [8,21]. Recently, glycosaminoglycan chondroitin was identified as an active component of AS. This compound triggers neuronal activity in the dorsomedial posterior region of the OB that sends asymmetric projections to the right dorsal habenula (dHb), (the homolog of the mammalian medial habenula (mHb)), which responds to olfactory stimuli [8,22,23]. However, exposure to AS failed to trigger neuronal activity in this region of the dHB [24]. Hence, it remains unclear which pathway underlies the defensive responses triggered by AS. Interestingly, there are dense projections from the