Modulation of aversive value coding in the vertebrate and invertebrate brain

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Abstract

Avoiding potentially dangerous situations is key for the survival of any organism. Throughout life, animals learn to avoid environments, stimuli or actions that can lead to bodily harm. While the neural bases for appetitive learning, evaluation and value-based decision-making have received much attention, recent studies have revealed more complex computations for aversive signals during learning and decision-making than previously thought. Furthermore, previous experience, internal state and systems level appetitive-aversive interactions seem crucial for learning specific aversive value signals and making appropriate choices. The emergence of novel methodologies (computation analysis coupled with large-scale neuronal recordings, neuronal manipulations at unprecedented resolution offered by genetics, viral strategies and connectomics) has helped to provide novel circuit-based models for aversive (and appetitive) valuation. In this review, we focus on recent vertebrate and invertebrate studies yielding strong evidence that aversive value information can be computed by a multitude of interacting brain regions, and that past experience can modulate future aversive learning and therefore influence value-based decisions.

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Introduction

'Value' is a complex and multi-faceted notion whose definition changes depending on the theoretical framework of reference [1]. In neuroscience and neuroeconomics, the term of 'value' is approached from a computational perspective. According to this view, subjective value (or "utility" in economics) must be learned through experience and computed in distributed brain regions during learning and decision-making processes. From invertebrates to vertebrates, this value information is then used to facilitate behavioural choices that maximise expected rewards and minimise expected punishments [2–5]. Does the brain only calculate subjective value or different types of value signals (e.g. teaching value, action value, outcome value etc.) [5–10]? These pending questions arise from evidence for the existence of multiple systems for value learning [5], coupled with the fact that value representations may be computed across distributed neural circuits within and between brain structures [8,11–13]. Value signals also seem to be encoded and used relatively to a reference [7,14–16] but the brain also encodes and uses absolute value information in decision-making processes [17–20]. In addition, it remains hotly debated whether appetitive and aversive values are represented on the same value scale, or on different scales that interact and/or are compared at decision time [15,21–25]. Finally, value computation is also modulated by past experience, by the surrounding environment under which learning and decision took place, and/or by the animal's internal state (e.g. hunger) [6,7,9,10,14,26–29].

At the system level, associations between nociceptive/painful and/or fear-related signals and environmental stimuli involve the amygdala, ventral tegmental area (VTA), substantia nigra (SN), periaqueductal grey (PAG), prefrontal cortex (PFC), thalamus, striatum, hippocampus and hypothalamus [30–34] (Figure 1), brain areas also recruited in appetitive contexts. In insects, the mushroom body (MB) is a critical integrative central brain structure for appetitive and aversive associative memories which require reinforcement through distinct populations of dopaminergic (DA) neurons [35–39]. Following much debate, vertebrate DA circuits have been shown to be involved not only in appetitive [40], but also in aversive learning [31,41]. In flies and mammals, this conserved function of DA circuits can be modulated by internal state and prior experience to signal an appropriate value during learning and enable adequate behaviour [20,42–45]. These recent

discoveries, matching proposed models [46–49], also highlight the importance of interactions between the appetitive and aversive systems for learning different aversive (or appetitive) value information and making appropriate decisions [50]. Such interactions could be crucial for the computation of a prediction error (PE) (i.e. the comparison between expected versus actual outcome) and to signal an instructive value, a central concept for reinforcement learning in both vertebrates and invertebrates [11,51–58]. Neuroeconomics mainly focuses on the computation of reward PE while learning from aversive PE is just as essential for survival, yet, much less investigated [59–62]. This review refers to recent work to develop a foundation for deepening our understanding of distributed and interactive aversive circuits. We will also discuss on how internal state and prior experience modulate aversive value computation in both vertebrates and invertebrates.

Distributed aversive signals

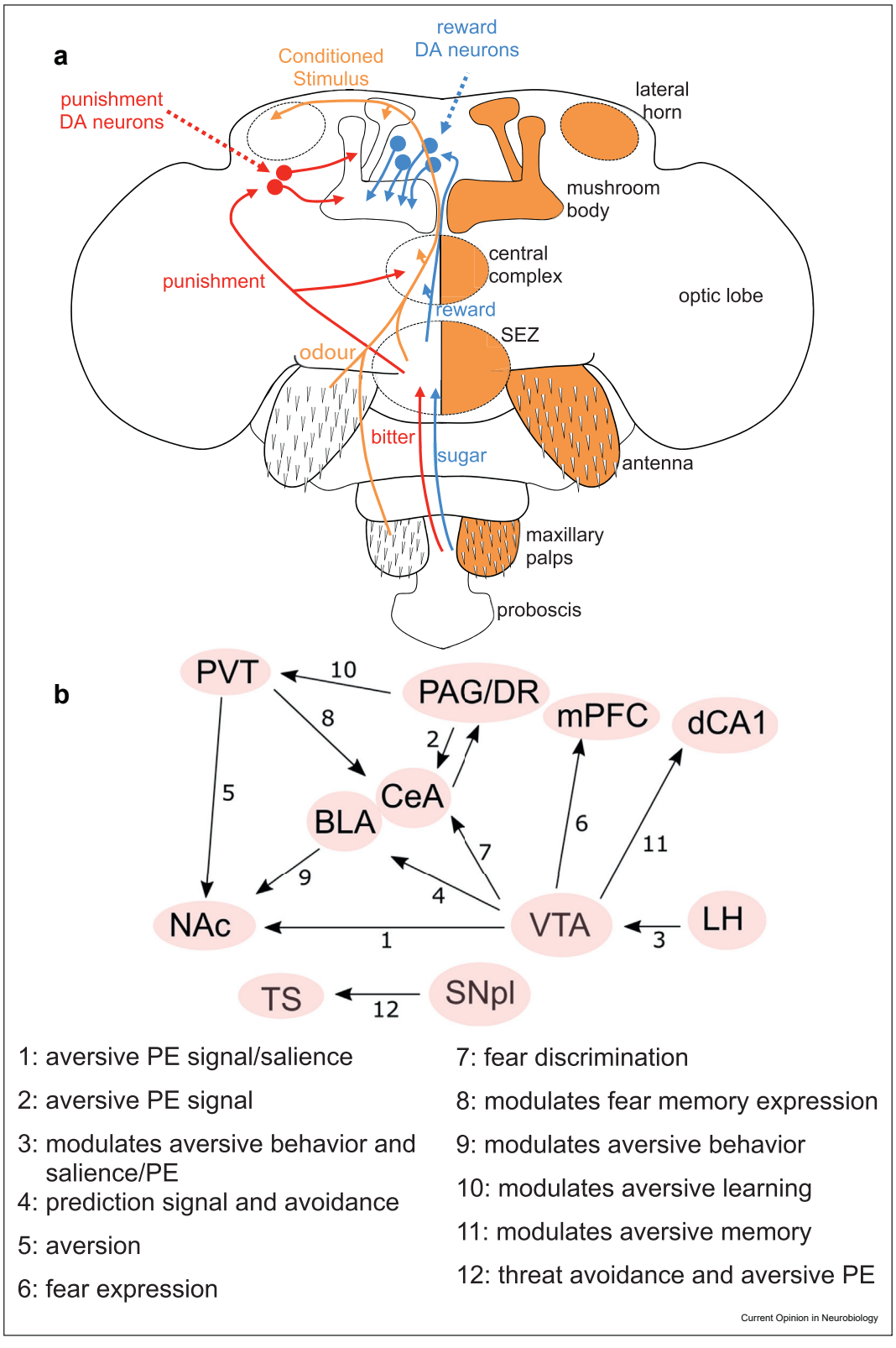
During associative aversive learning, animals learn to predict a punishment via its previous association with surrounding cues and/or contexts [63]. Such associative learning shapes adaptive behavioural strategies to escape punishment, including freezing and avoidance behaviour [64–67]. As both the conditioned stimulus (CS) (e.g. a tone or an odour) and unconditioned stimulus (US) (e.g. an electric foot shock) are represented within diverse circuits, the CS-US aversive memory formed using a PE mechanism is likely to be distributed across specific and interactive brain regions as proposed for appetitive behaviour [11,13]. In rodents, instructive and predictive aversive PE signals have been found in the amygdala, the PAG and the ventral striatum [61,62,68–73] with a key role for specific DA circuits [31].

In insects, numerous lines of evidence point towards a similar aversive (and appetitive) distributed value signal computation during learning [36,52,54–56,74–76]. In *Drosophila*, this interconnected network includes different functional MB subdivisions, strongly innervated by reinforcing appetitive and aversive DA neurons [36], as well as the lateral horn and the central complex [65,77–80] (Figure 1), although much remain to be investigated about the function of these brain area interactions for aversive (and appetitive) associative learning. The MB is an integrative brain structure involved in learning and memory, as well as in goal directed behaviour [35,81,82]. While direct evidence for aversive PE remain unclear at single DA neurons level targeting the MB [74,83,84], recent models (that are likely currently tested) propose the existence of a PE at the overall MB input/output network level for computing appetitive or aversive value signals [20,55,56,75,81,82,85–88]. The lateral horn is mostly involved in innate olfactory behaviour [89], but crucial for context-dependent memory retrieval [77,79,90]. The central complex is composed of 6 different substructures involved in locomotion, orientation, action-selection, sleep and memory consolidation [78,91–93]. Importantly, in flies and mammals, representations of appetitive and aversive information are found in all of these brain structures (even the PAG [94]), which can directly or indirectly interact to promote specific approach or avoidance behaviour.

The PAG-amygdalar interactive aversive circuits: A key role for the paraventricular nucleus of the thalamus?

The brain uses PE as an instructive/teaching signal to update the value of sensory cues or actions during learning and adaptatively guide behaviour. In rodents, the PAG-amygdala interaction is key for generating and regulating aversive PE [30,31,61,95]. The PAG receives nociceptive inputs from the spinal/trigeminal dorsal horn and is functionally divided into subregions that contribute to innate and learned defensive/aversive behaviour [33] (also see the study by Silva et al. [94]). The amygdala (consisting of the lateral (LA), basolateral (BLA) and central amygdala (CeA)) is an emotional memory centre [96] sparsely representing sensory cues [97], and also receiving nociceptive inputs. The CeA receives nociceptive information through the parabrachial nucleus [98] and locus coeruleus [99], while the BLA receives them through the locus coeruleus [99] and posterior intralaminar nucleus [100,101]. In turn, the CeA projection to the ventrolateral (vl)-PAG calibrates aversive memory strength as a predictive inhibitory signal [102] (Figure 1). The vl-PAG is therefore well-located to compare predicted aversive value from the CeA and outcome value from the nociceptive unconditioned shock stimulus during learning to compute a positive PE of stimulus-predicting shock [30,70,95]. In line with this model, vl-PAG was recently involved in strengthening cue–shock association during learning [73], and this probably through vl-PAG/dorsal raphe DA neurons reshaping the amygdalar network [103,104] (Figure 1). In addition, PAG inactivation attenuates US shock-evoked responses in LA neurons, thought to serve as a teaching signal to strengthen CS input to amygdala neurons during fear learning, and impaired fear learning [70]. The PAG can also modulate BLA PE computation indirectly via the thalamus [31,95]. Yeh et al. [72] shed new light on the role of PAG subdivisions in regulating fear/nociceptive learning and aversive PE via the anterior paraventricular nucleus of the thalamus (aPVT). They show that the dorsolateral (dl)-PAG (conveying both innate and learned fear responses [105]) interaction with the aPVT is critical for aversive learning. These results suggest that this projection could be essential in the aversive instructive signal and PE computation by the CeA and/or BLA [60,106]. Along the same lines, a recent study also demonstrated that PVT

Figure 1



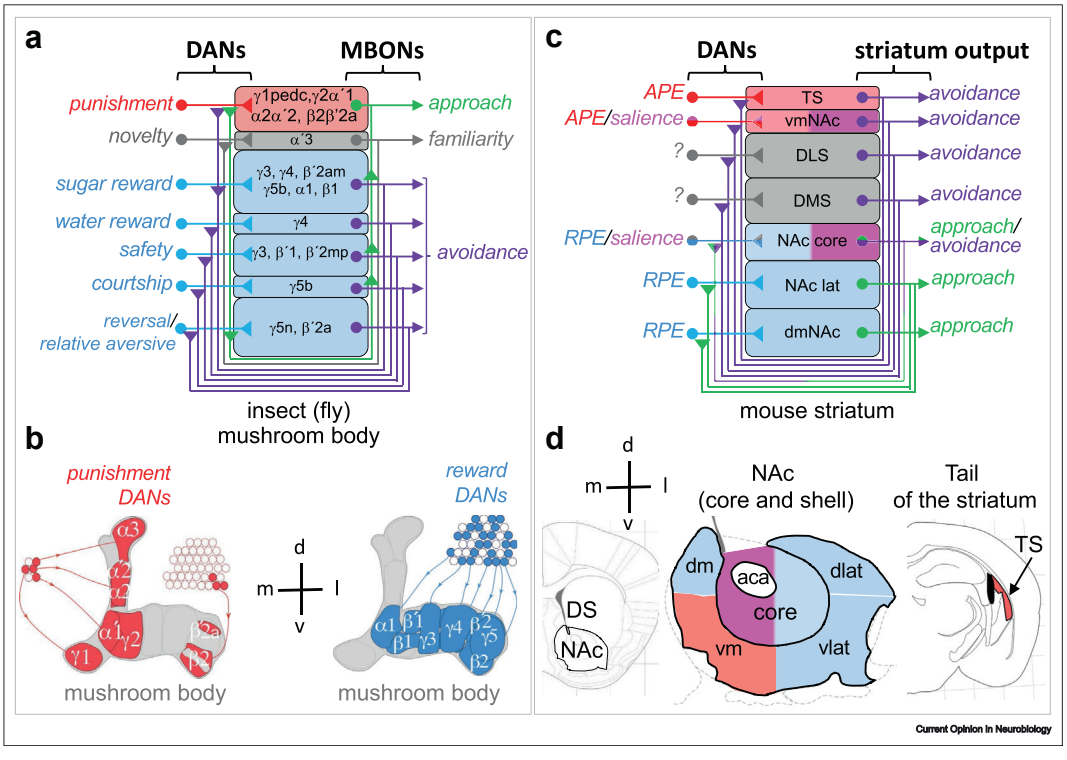
Schematic representation of a fly brain (**a**) and mouse brain areas (**b**) emphasizing the distributed aversive signals. SEZ: suboesophageal zone; PAG/DR: periaqueductal grey and dorsal raphe; VTA: ventral tegmental area; BLA: basolateral amygdala; CeA: central amygdala; NAc: nucleus accumbens; mPFC: medial prefrontal cortex; LH; lateral hypothalamus; PVT: paraventricular nucleus of the thalamus; dCA1: dorsal CA1 of the hippocampus; SNpl: substantia nigra pars lateralis; TS: tail of the striatum.

neurotensin-expressing neurons projecting to the BLA facilitate aversive (and appetitive) learning [107,108]. The PAG-aPVT-amygdalar interaction is therefore an essential component of aversive learning (Figure 1). Since the PVT is a key sensor of the animal's internal state, the dorsolateral PAG-aPVT-amygdalar interaction could modulate fear learning in different states.

Dopaminergic circuits and aversive learning

In vertebrates and invertebrates, DA circuits can be functionally segregated through diverse input–output connectivity [36,104,109–113]. This segregation dictates the responses of DA neurons to reward or punishing stimuli and their involvement in both appetitive and aversive learning, respectively, by targeting specific sub-compartments or neuronal subpopulations of the Nucleus Accumbens (NAc) and insect MB compartments (Figure 2; [21,36,40,114–120]). In the mouse VTA and the fly MB, DA neurons signalling aversion are less numerous compared with that of those signalling reward (Figure 2; [25,36,111,117,121]). This significant difference of representation and their location/innervation may have been part of the reason for the late recognition of DA function in aversive learning in vertebrates [21,122,123]. While for appetitive learning, reward PE is essentially found among specific, but broad populations of VTA DA neurons, aversive PE is mostly found in the amygdala-PAG interactive connectivity [62,68,70,102] (as discussed in the previous section). Recent work changed this view by showing that aversive PE can be found in a specific subpopulation of ventro-medial NAc (vmNAc)-targeting VTA DA neurons [124]. Aversive foot shocks, and cues that predicted them, evoke DA release in the vmNAc, while lateral NAc DA release is decreased by aversive foot shocks [124,125]. Furthermore, VTA DA neurons targeting the dorsal hippocampus [126] are involved in the modulation of spatial aversive memory [127,128]. In addition, DA neurons from the SN pars lateralis projecting to the tail of the striatum are crucial for threat-predicting and defensive behaviour [129–131] (Figure 2). In flies, punishment DA neurons targeting specific MB compartments in the vertical lobe (and few in the horizontal lobe [132]) respond differently to electric shock punishment intensities which drive intensity-dependent plasticity after olfactory aversive associative learning [20,133]. Combined with previous work [134], the dorsal reward – ventral aversion

Figure 2



Schematic representation of a fly mushroom body (MB) (**a-b**) and mouse striatum (**c-d**) targeted by specific dopaminergic neurons (DANs) relaying reward, punishment, novelty or saliency signals in specific MB/striatum compartments. MBONs: mushroom body output neurons; TS: tail of the striatum; NAc: nucleus accumbens; DLS: dorsolateral striatum; DMS; dorsomedial striatum; aca: anterior commissure. RPE: reward prediction error. APE: aversive prediction error.

processing gradient in the medial NAc resembles the horizontal appetitive − vertical aversive subdivision of the fly MB (Figure 2). Only more specific genetic tools in mice will help, as have been necessary in flies, to disentangle the specific function of subpopulations of DA (and other type of) neurons in aversive (and appetitive) value coding during learning [20,117,133].

Modulation of aversive learning by internal state and previous experience

Functional models of how the brain encodes and learns aversive value are complexified by numerous reports showing that aversive learning is modulated by internal state, related past experience and context. For instance, reward context can alter lateral VTA DA responses (at the cell body level) to aversive predictive stimuli [43]. In addition, two recent reports [44,124] demonstrate a pivotal role for the lateral hypothalamus (LH) in aversive learning [135], a region known to be critical for feeding behaviour and reward processing [136–139]. As mentioned above, among all NAc-projecting VTA DA neurons, only the ones projecting to the shell of the vmNAc exhibit increased response to aversive stimuli and aversive-predictive cues [124]. In addition, they showed that this latter response is regulated by glutamatergic LH circuits, confirming previous work [125]. A prior appetitive experience, relayed by GABAergic LH neurons, modifies neural circuits regulating aversive learning by reducing the associative strength acquired to the shock-predicting cue [44]. GABAergic LH neurons interacting directly with VTA GABAergic neurons [125] and indirectly with VTA DA neurons [140,141] could therefore modify internal VTA plasticity [142] and aversive PE (as for reward PE [140]) to regulate aversive learning [141] (Figure 1). As mentioned above, internal states, through PVT circuits, could modulate aversive learning. A recent study [45] showed that VTA DA neurons projecting to the BLA may provide an aversive [143] (and appetitive) reinforcement signal that is modulated by hunger state. In particular, cue-predictive aversive signals from VTA DA neurons projecting to the BLA persist and even increase in fed versus hungry mice. This important recent work clearly points toward an unappreciated and largely disregarded effect of previous experience and internal states (as for the PAG-aPVT-amygdalar connections) on aversive value coding.

In flies, internal state-related neuropeptide signals shape reinforcing DA circuits function in the MB to modulate naïve and learned behaviours [42,144–146]. The leucokinin neuropeptide bidirectionally alters different MB-innervating DA neurons to promote thirst or hunger-dependent water/sugar memory expression, respectively [147]. The *Drosophila* neuropeptide F (equivalent to NPY) acts on specific punishment MB-targeting DA neurons tonic activity [148], and gates learned appetitive behaviours [42,144] and aversive memory consolidation processes [149]. A lot remains to be investigated in *Drosophila* about how internal state and past experience alter the perception and the integration of sensory stimuli experienced during aversive learning.

Using previous experience to code relative aversive value

Valuation in the brain was originally hypothesised to involve a dual-neural system for evaluation of positive and negative outcomes. However, many brain regions encode value signals relative to prior experience/reference such as the orbitofrontal cortex (OFC) [150], lateral intraparietal area [151,152], PFC ([153]), VTA DA neurons [154,155], ventral striatum [19,156] and amygdala [157,158]. In their pioneering experiments, Tremblay and Schultz [26] found that primate OFC neurons fire differently to one particular juice when presented in blocks with preferred or less preferred juice options. OFC neurons therefore seem to encode appetitive (and aversive) values in a relative manner [150,159]. Training in blocks in a specific spatial (same context) and temporal (in short inter-trial interval) window drastically changes the type of value signal associated with each option. Indeed, when presented in blocks with a negatively reinforced conditioned stimulus (CS+), a non-reinforced stimulus (CS-) can gain a positive/safety value [150,160]. This property can also be found in the *Drosophila* MB [161]. On the contrary, an 'absolute', rather than relative, value between options is encoded in the macaque OFC cortex when the options are not trained in blocks, but rather separated in time [17]. These experiments indicate that valuation is context-dependent and interaction between successive valuations is time-dependent. Moreover, such time and state/context-dependent valuations are essential in reinforcement learning theories and seem conserved from ants to humans [7,15,29,162–165]. Temporal contingency is important to relate and link events together in event boundaries [166,167]. Therefore, outside these spatial and temporal boundary conditions (i.e. outside of block conditions), a relative/memory link between events cannot be made. In *Drosophila*, a CS- presentation before the CS+, or repeated CS+/CS- presentation in massed, rather than spaced, aversive conditioning, seem to be boundary conditions enabling the CS- to gain a positive relative safety value signal [161].

The valuation of choice options relative to each other leads to decisions between approaching the best or avoiding the worst option. However, how a relative aversive value (better or worse) is encoded in the brain still remains elusive. The ventral striatum, usually described as an integrative centre for reward (but see above in the study by de Jong et al. [124]) and reward-related values such as pain relief [168], showed

increased BOLD response to better potential gambles where participants expected fewer electric shocks [156]. Notably, the 'hedonic flip' concept has been proposed in a human study [169] where a moderately painful stimulation representing the best possible outcome, shows higher BOLD responses in regions encoding the hedonic value of this stimulus, such as the ventro-medial PFC regions. Along with this physiological change, skin conductance response was attenuated when moderate pain represented what the authors refer to as relative relief [169]. Recent work [158] showed that in rats, the BLA is necessary to compare stimuli predicting different aversive outcomes (relatively), while leaving the revaluation of each aversive outcome (separately) unaffected. These studies echo recent findings in *Drosophila* demonstrating a role for reward-coding DA neurons in punishment omission [84,170] and relative judgement of aversive experiences [20]. In Villar et al. [20] they showed that a specific population of reward-encoding DA neurons increased their activity when flies experience a better aversive experience than the one learned just before. Importantly, these specific reward-coding DA neurons receive inputs from MB output neurons whose activity is modified by aversive learning. The authors therefore proposed a model in which specific reward-encoding DA neurons integrate and compare previous with current olfactory aversive experiences, in terms of learning-related plasticity, to signal a relative 'better than' aversive value during learning. Notably, relative 'better than' and 'worse than' aversive value signals seem to be encoded in overlapping and distinct circuits [20,156]. This cached ('pre-computed') relative aversive value is then used to optimise value-based decisions when animals are confronted with the two conditioned stimuli predicting different aversive outcomes [29].

Conclusion

As the field of neuroeconomics advances, understanding the complex relationship between the appetitive and aversive reinforcement systems is essential for developing comprehensive models of value-based learning and decision-making. This review notably highlights that, in both vertebrates and invertebrates, aversive signals are distributed across brain structures that also process appetitive information. This reinforces numerous models emphasising on appetitive-aversive systems-level interaction in value computation during learning and decision-making. Hence, while there is a need to define invariant aversive responses as 'absolute' aversive signals, the brain seems to compute value relative to previous experience/references to enhance its discrimination power. While a lot remain to be investigated to understand aversive value computation in different and interactive brain structures, it is crucial to consider its modulation by internal states and previous experience.

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Conflict of interest statement

Nothing declared.

Data availability

No data were used for the research described in the article.

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- •• of outstanding interest

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