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Modulation of aversive value coding in the vertebrate and invertebrate brain

Emmanuel Perisse, Magdalena Miranda and Stéphanie Trouche



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.

Addresses

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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].

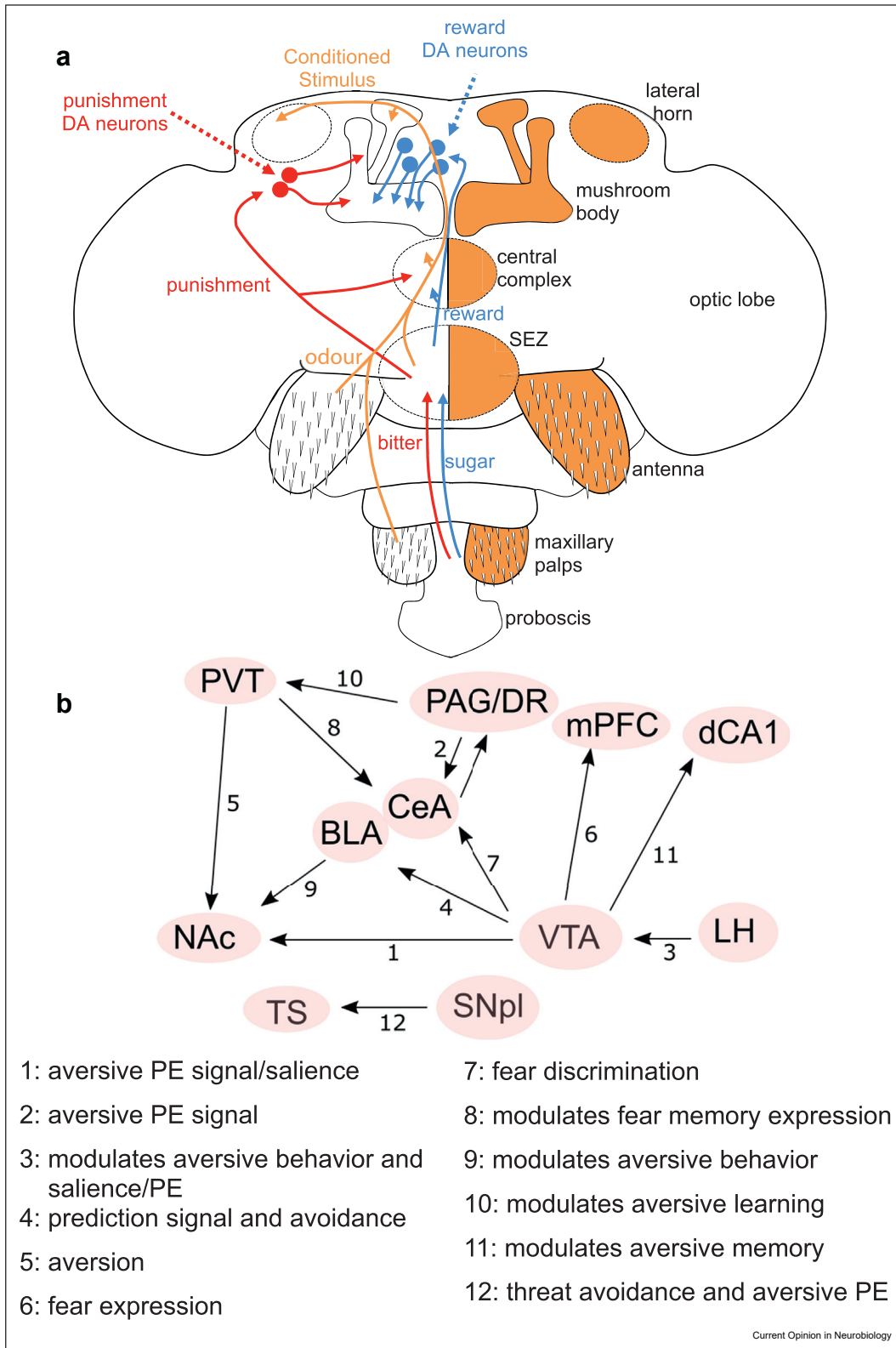
In insects, numerous lines of evidence point towards a similar aversive (and appetitive) distributed value signal computation during learning [36,52,54–56,74–76]. In *Drosophila*, this interconnected network includes different functional MB subdivisions, strongly innervated by reinforcing appetitive 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 adaptively 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.

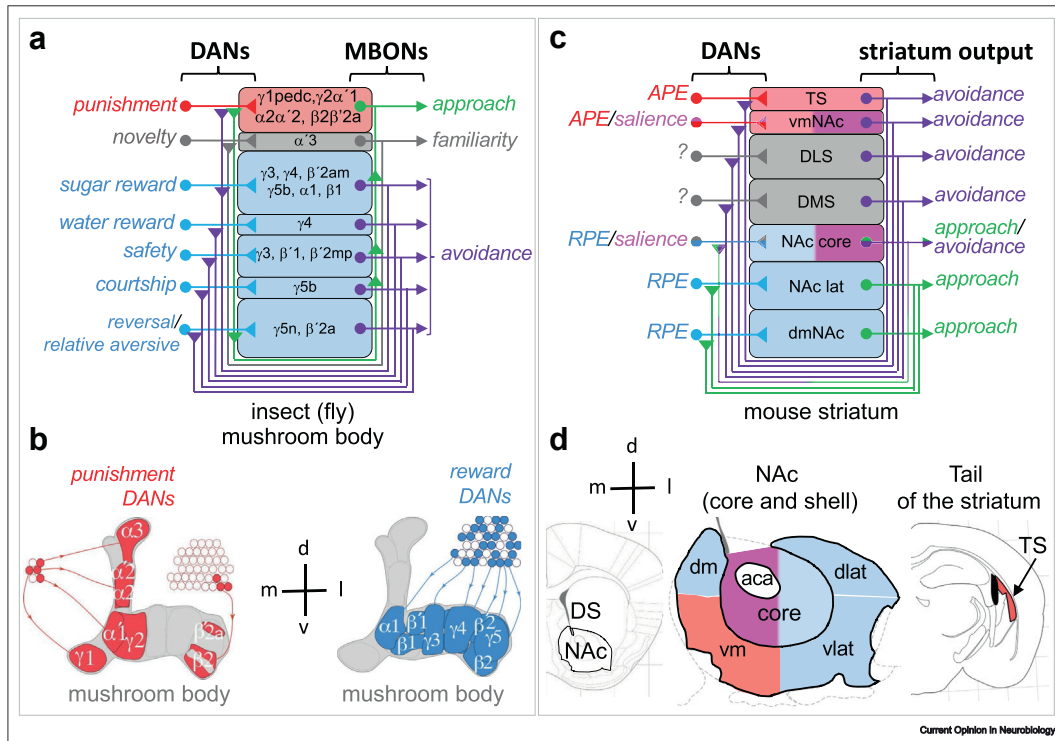
neurotensin-expressing neurons projecting to the BLA facilitate aversive (and appetitive) learning [107,108]. The PAG-aPVT-amygdalar interaction is therefore an essential component of aversive learning (Figure 1). Since the PVT is a key sensor of the animal’s internal state, the dorsolateral PAG-aPVT-amygdalar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

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
 - of outstanding interest
1. Brosch T, Sander D: *Handbook of value: perspectives from economics, neuroscience, philosophy, psychology and sociology*. Oxford University Press; 2015.
 2. Montague PR, Berns GS: **Neural economics and the biological substrates of valuation**. *Neuron* 2002, **36**:265–284.
 3. Rangel A, Camerer C, Montague PR: **A framework for studying the neurobiology of value-based decision making**. *Nat Rev Neurosci* 2008, **9**:545–556.
 4. Glimcher PW, Fehr E: **Neuroeconomics**. In *Decision making and the brain*. 2nd ed. Elsevier; 2014.
 5. Daw ND, O’Doherty JP: *Multiple systems for value learning*. 2nd ed. Neuroeconomics Decis Mak Brain; 2014 [Chapter 21].
 6. Vlaev I, Chater N, Stewart N, Brown GDA: **Does the brain calculate value?** *Trends Cognit Sci* 2011, **15**:546–554.
 7. Louie K, Glimcher PW: **Efficient coding and the neural representation of value**. *Ann N Y Acad Sci* 2012, **1251**:13–32.
 8. Stott JJ, Redish AD: **Representations of value in the brain: an embarrassment of riches?** *PLoS Biol* 2015, **13**:1–7.
 9. Hayden BY, Niv Y: **The case against economic values in the orbitofrontal cortex (or anywhere else in the brain)**. *Behav Neurosci* 2021, **135**:192–201.
 10. O’Doherty JP: **The problem with value**. *Neurosci Biobehav Rev* 2014, **43**:259–268.
 11. Dabney W, Kurth-Nelson Z, Uchida N, Starkweather CK, Hassabis D, Munos R, Botvinick M: **A distributional code for value in dopamine-based reinforcement learning**. *Nature* 2020, **577**:671–675.
- Propose that reward prediction is represented as probability distribution of multiple future outcomes in parallel within different population of VTA DA neurons.
12. Shin EJ, Jang Y, Kim S, Kim H, Cai X, Lee H, Sul JH, Lee SH, Chung Y, Lee D, et al.: **Robust and distributed neural representation of action values**. *Elife* 2021, **10**:1–17.
 13. Hunt LT: **Hayden BY: a distributed, hierarchical and recurrent framework for reward-based choice**. *Nat Rev Neurosci* 2017, **18**:172–182.

14. Seymour B, McClure SM: **anchors, scales and the relative coding of value in the brain.** *Curr Opin Neurobiol* 2008, **18**: 173–178.
15. Palminteri S, Khamassi M, Joffily M, Coricelli G: **Contextual modulation of value signals in reward and punishment learning.** *Nat Commun* 2015, **6**:8096.
16. Bavard S, Lebreton M, Khamassi M, Coricelli G, Palminteri S:
 • **Reference-point centering and range-adaptation enhance human reinforcement learning at the cost of irrational preferences.** *Nat Commun* 2018, **9**.
- Demonstrate and propose models showing that state-dependent valuation in humans comes at the cost of supposed irrational choices (when options are extrapolated out from their original contexts).
17. Padoa-Schioppa C, Assad JA: **The representation of economic value in the orbitofrontal cortex is invariant for changes of menu.** *Nat Neurosci* 2008, **11**:95–102.
18. Zhang B, Kan JYY, Yang M, Wang X, Tu J, Dorris MC: **Transforming absolute value to categorical choice in primate superior colliculus during value-based decision making.** *Nat Commun* 2021, **12**:1–14.
19. Klein TA, Ullsperger M, Jocham G: **Learning relative values in the striatum induces violations of normative decision making.** *Nat Commun* 2017, **8**:1–12.
- Reveal that humans learn value relative to current options with neural activity in the striatum displaying the neural signature of a relative value PE used to update relative values.
20. Villar ME, Pavão-Delgado M, Amigo M, Jacob PF, Merabet N,
 •• Pinot A, Perry SA, Waddell S, Perisse E: **Differential coding of absolute and relative aversive value in the *Drosophila* brain.** *Curr Biol* 2022, **32**:1–17.
- Explore the circuits that allow flies to assign and compare olfactory aversive memories of different intensities, and characterize key differences in the circuits recruited to assign absolute aversive value and relative aversive value. They notably show that specific reward DA circuits compare and assign relative aversive value necessary for ensuing appropriate choices.
21. Bromberg-Martin ES, Matsumoto M, Hikosaka O: **Dopamine in motivational control: rewarding, aversive, and alerting.** *Neuron* 2010, **68**:815–834.
22. Pessiglione M, Delgado MR: **The good, the bad and the brain: neural correlates of appetitive and aversive values underlying decision making.** *Curr Opin Behav Sci* 2015, **5**:78–84.
23. Kahnt T, Park SQ, Haynes JD, Tobler PN: **Disentangling neural representations of value and salience in the human brain.** *Proc Natl Acad Sci U S A* 2014, **111**:5000–5005.
24. Hayashi K, Nakao K, Nakamura K: **Appetitive and aversive information coding in the primate dorsal raphe nucleus.** *J Neurosci* 2015, **35**:6195–6208.
25. Lammel S, Lim BK, Malenka RC: **Reward and aversion in a heterogeneous midbrain dopamine system.** *Neuropharmacology* 2014, **76**:351–359.
26. Tremblay L, Schultz W: **Relative reward preference in primate orbitofrontal cortex.** *Nature* 1999, **398**:704–708.
27. Tymula A, Plassmann H: **Context-dependency in valuation.** *Curr Opin Neurobiol* 2016, **40**:59–65.
28. Gershman SJ: **Context-dependent learning and causal structure.** *Psychon Bull Rev* 2017, **24**:557–565.
29. Hunter LE, Daw ND: **Context-sensitive valuation and learning.** *Curr Opin Behav Sci* 2021, **41**:122–127.
30. Herry C, Johansen JP: **Encoding of fear learning and memory in distributed neuronal circuits.** *Nat Neurosci* 2014, **17**: 1644–1654.
31. Ozawa T, Johansen JP: **Learning rules for aversive associative memory formation.** *Curr Opin Neurobiol* 2018, **49**: 148–157.
32. Hughes RN, Bakhurin KI, Petter EA, Watson GDR, Kim N, Friedman AD, Yin HH: **Ventral tegmental dopamine neurons control the impulse vector during motivated behavior.** *Curr Biol* 2020, **30**:2681–2694.e5.
33. Gross CT, Canteras NS: **The many paths to fear.** *Nat Rev Neurosci* 2012, **13**:651–658.
34. Morales M, Margolis EB: **Ventral tegmental area: cellular heterogeneity, connectivity and behaviour.** *Nat Rev Neurosci* 2017, **18**:73–85.
35. Heisenberg M: **Mushroom body memoir: from maps to models.** *Nat Rev Neurosci* 2003, **4**:266–275.
36. Waddell S: **Reinforcement signalling in *Drosophila*; dopamine does it all after all.** *Curr Opin Neurobiol* 2013, **23**:324–329.
37. Vergoz V, Roussel E, Sandoz J, Giurfa M: **Aversive learning in honeybees revealed by the olfactory conditioning of the sting extension reflex.** *PLoS One* 2007, **2**:e288.
38. Wissink M, Nehring V: **Appetitive olfactory learning suffers in ants when octopamine or dopamine receptors are blocked.** *J Exp Biol* 2021:224.
39. Mizunami M, Matsumoto Y: **Roles of octopamine and dopamine neurons for mediating appetitive and aversive signals in Pavlovian conditioning in crickets.** *Front Physiol* 2017, **8**: 1–8.
40. Schultz W: **Neuronal reward and decision signals: from theories to data.** *Physiol Rev* 2015, **95**:853–951.
41. Verharen JP, Zhu Y, Lammel S: **Aversion hot spots in the dopamine system.** *Curr Opin Neurobiol* 2020, **64**:46–52.
42. Krashes MJ, DasGupta S, Vreede A, White B, Armstrong JD, Waddell S: **A neural circuit mechanism integrating motivational state with memory expression in *Drosophila*.** *Cell* 2009, **139**:416–427.
43. Matsumoto H, Tian J, Uchida N, Watabe-Uchida M: **Midbrain dopamine neurons signal aversion in a reward-context-dependent manner.** *Elife* 2016, **5**:1–24.
44. Sharpe MJ, Batchelor HM, Mueller LE, Gardner MPH,
 •• Schoenbaum G: **Past experience shapes the neural circuits recruited for future learning.** *Nat Neurosci* 2021, **24**:391–400.
- Describe how a prior rewarding experience can modify the neural circuits for future aversive learning, making them reliant on LH GABAergic neurons.
45. Lutas A, Kucukdereli H, Alturkistani O, Carty C, Sugden AU,
 • Fernando K, Diaz V, Flores-Maldonado V, Andermann ML: **State-specific gating of salient cues by midbrain dopaminergic input to basal amygdala.** *Nat Neurosci* 2019, **22**: 1820–1833.
- Show that the responses to cues predicting food rewards of VTA DA neurons innervating BLA neurons are attenuated in sated mice (compared to that of hungry mice) while responses to cues predicting unescapable punishments persist or increase in sated mice.
46. Konorski J: *Integrative activity of the brain: an interdisciplinary approach.* Chicago University Press; 1967.
47. Dickinson A, Dearing MF: **Appetitive-aversive interactions and inhibitory processes.** In *Mechanisms of learning and motivation: a memorial. Jerzy Konorski (to)*. Edited by Dickinson AA, Boakes A, Totawa, NJ: Erlbaum; 1979:203–231.
48. Nasser HM, McNally GP: **Neural correlates of appetitive-aversive interactions in Pavlovian fear conditioning.** *Learn Mem* 2013, **20**:220–228.
49. Abraham AD, Neve KA, Lattal KM: **Dopamine and extinction: a convergence of theory with fear and reward circuitry.** *Neurobiol Learn Mem* 2014, **108**:65–77.
50. Barberini CL, Morrison SE, Saez A, Lau B, Salzman CD: **Complexity and competition in appetitive and aversive neural circuits.** *Front Neurosci* 2012, **6**:1–13.
51. Rescorla RA, Wagner AR: **A theory of Pavlovian conditioning: variations in the effectiveness of reinforcement and nonreinforcement.** In *Classical conditioning II: current research and theory*. Edited by Black AH, Prokask WF, New York: Appleton-Century-Crofts; 1972:64–69.
52. Terao K, Matsumoto Y, Mizunami M: **Critical evidence for the prediction error theory in associative learning.** *Sci Rep* 2015, **5**:8929.

53. Watabe-Uchida M, Eshel N, Uchida N: **Neural circuitry of reward prediction error.** *Annu Rev Neurosci* 2017, **40**:373–394.
54. Mizunami M, Terao K, Alvarez B: **Application of a prediction error theory to Pavlovian conditioning in an insect.** *Front Psychol* 2018, **9**:1–8.
55. Zhao C, Widmer YF, Diegelmann S, Petrovici MA, Sprecher SG, Senn W: **Predictive olfactory learning in *Drosophila*.** *Sci Rep* 2021, **11**:1–17.
56. Bennett JEMM, Philippides A, Nowotny T: **Learning with reinforcement prediction errors in a model of the *Drosophila* mushroom body.** *Nat Commun* 2021, **12**:1–31.
57. Jiang L, Litwin-Kumar A: **Models of heterogeneous dopamine signaling in an insect learning and memory center.** *PLoS Comput Biol* 2021, **17**:1–29.
58. Glimcher PW: **Understanding dopamine and reinforcement learning: the dopamine reward prediction error hypothesis.** *Proc Natl Acad Sci USA* 2011, **108**:17647–17654.
59. Fanselow MS: **Pavlovian conditioning, negative feedback, and blocking: mechanisms that regulate association formation.** *Neuron* 1998, **20**:625–627.
60. McNally GP, Johansen JP, Blair HT: **Placing prediction into the fear circuit.** *Trends Neurosci* 2011, **34**:283–292.
61. Iordanova MD, Yau JOY, McDannald MA, Corbit LH: **Neural substrates of appetitive and aversive prediction error.** *Neurosci Biobehav Rev* 2021, **123**:337–351.
62. McHugh SB, Barkus C, Huber a, Capitaio L, Lima J, Lowry JP, Bannerman DM: **Aversive prediction error signals in the amygdala.** *J Neurosci* 2014, **34**:9024–9033.
63. Pavlov IP: *Conditioned Reflexes: an investigation of the physiological activity of the cerebral cortex.* New York: Dover Publications, Inc.; 1927.
64. LeDoux JE, Moscarello J, Sears R, Campese V: **The birth, death and resurrection of avoidance: a reconceptualization of a troubled paradigm.** *Mol Psychiatr* 2017, **22**:24–36.
65. Cognigni P, Felsenberg J, Waddell S: **Do the right thing: neural network mechanisms of memory formation, expression and update in *Drosophila*.** *Curr Opin Neurobiol* 2018, **49**:51–58.
66. Gibson WT, Gonzalez CR, Fernandez C, Ramasamy L, Tabachnik T, Du RR, Felsen PD, Maire MR, Perona P, Anderson DJ: **Behavioral responses to a repetitive visual threat stimulus express a persistent state of defensive arousal in *Drosophila*.** *Curr Biol* 2015, **25**:1401–1415.
67. Fanselow MS: *Conditioned and unconditional components of post-shock freezing*, vol. 15; 1980:177–182.
68. Belova MA, Paton JJ, Morrison SE, Salzman CD: **Expectation modulates neural responses to pleasant and aversive stimuli in primate amygdala.** *Neuron* 2007, **55**:970–984.
69. Delgado MR, Li J, Schiller D, Phelps EA: **The role of the striatum in aversive learning and aversive prediction errors.** *Philos Trans R Soc B Biol Sci* 2008, **363**:3787–3800.
70. Johansen JP, Tarpley JW, LeDoux JE, Blair HT: **Neural substrates for expectation-modulated fear learning in the amygdala and periaqueductal gray.** *Nat Neurosci* 2010, **13**:979–986.
71. Fadok JP, Darvas M, Dickerson TMK, Palmiter RD: **Long-term memory for pavlovian fear conditioning requires dopamine in the nucleus accumbens and basolateral amygdala.** *PLoS One* 2010, **5**:1–6.
72. Yeh LF, Ozawa T, Johansen JP: **Functional organization of the midbrain periaqueductal gray for regulating aversive memory formation.** *Mol Brain* 2021, **14**:1–9.
- Describe a population of dorsolateral PAG glutamatergic neurons that project to the aPVT as crucial for aversive learning (but not fear expression).
73. Walker RA, Wright KM, Jhou TC, McDannald MA: **The ventrolateral periaqueductal grey updates fear via positive prediction error.** *Eur J Neurosci* 2019, **51**:866–880.
- Demonstrate that ventrolateral PAG activity at the time of aversive PE is necessary to strengthen and update a cue–shock association.
74. Riemensperger T, Völler T, Stock P, Buchner E, Fiala A: **Punishment prediction by dopaminergic neurons in *Drosophila*.** *Curr Biol* 2005, **15**:1953–1960.
75. Adel M, Griffith LC: **The role of dopamine in associative learning in *Drosophila*: an updated unified model.** *Neurosci Bull* 2021, **37**:831–852.
76. Eichler K, Li F, Litwin-Kumar A, Park Y, Andrade I, Schneider-Mizell CM, Saumweber T, Huser A, Eschbach C, Gerber B, et al.: **The complete connectome of a learning and memory centre in an insect brain.** *Nature* 2017, **548**:175–182.
77. Dolan MJ, Belliart-Guérin G, Bates AS, Frechter S, Lampin-Saint-Amaux A, Aso Y, Roberts RJV, Schlegel P, Wong A, Hammad A, et al.: **Communication from learned to innate olfactory processing centers is required for memory retrieval in *Drosophila*.** *Neuron* 2018, **100**:651–668.e8.
- Identify specific *Drosophila* lateral horn (LH) neurons receiving inputs from MB output neurons whose activity are modulated by aversive learning and required for aversive memory retrieval. They propose a circuit mechanism integrating learned (from the MB) and innate (from the LH) olfactory information to drive appropriate behaviour.
78. Wu CL, Xia S, Fu TF, Wang H, Chen YH, Leong D, Chiang AS, Tully T: **Specific requirement of NMDA receptors for long-term memory consolidation in *Drosophila* ellipsoid body.** *Nat Neurosci* 2007, **10**:1578–1586.
79. Zhao B, Sun J, Zhang X, Mo H, Niu Y, Li Q, Wang L, Zhong Y: **Long-term memory is formed immediately without the need for protein synthesis-dependent consolidation in *Drosophila*.** *Nat Commun* 2019, **10**.
80. Hu W, Peng Y, Hu W, Peng Y, Sun J, Zhang F, Zhang X, Wang L, Li Q, Zhong Y: **Fan-shaped body neurons in the *Drosophila* brain regulate both innate and conditioned nociceptive article fan-shaped body neurons in the *Drosophila* brain regulate both innate and conditioned nociceptive avoidance.** *Cell Rep* 2018, **24**:1573–1584.
- Identify specific *Drosophila* fan-shaped body neurons in the central complex brain area that regulate both innate and conditioned avoidance of noxious stimuli.
81. Aso Y, Sitaraman D, Ichinose T, Kaun KR, Vogt K, Belliart-Guérin G, Plaçais P-Y, Robie Aa, Yamagata N, Schnaitmann C, et al.: **Mushroom body output neurons encode valence and guide memory-based action selection in *Drosophila*.** *Elife* 2014, **3**, e04580.
82. Oswald D, Waddell S: **Olfactory learning skews mushroom body output pathways to steer behavioral choice in *Drosophila*.** *Curr Opin Neurobiol* 2015, **35**:178–184.
83. Dylla KV, Raiser G, Galizia CG, Szyszka P: **Trace conditioning in *Drosophila* induces associative plasticity in mushroom body kenyon cells and dopaminergic neurons.** *Front Neural Circ* 2017, **11**:1–14.
84. McCurdy LY, Sareen P, Davoudian PA, Nitabach MN: **Dopaminergic mechanism underlying reward-encoding of punishment omission during reversal learning in *Drosophila*.** *Nat Commun* 2021:12.
85. Springer M, Nawrot MP: **A mechanistic model for reward prediction and extinction learning in the fruit fly.** *eNeuro* 2021 Jun 16;8(3):ENEURO.0549-20.2021..
86. Felsenberg J, Barnstedt O, Cognigni P, Lin S, Waddell S: **Re-evaluation of learned information in *Drosophila*.** *Nature* 2017, **544**:240–244.
87. Gkaniyas E, McCurdy LY, Nitabach MN, Webb B: **An incentive circuit for memory dynamics in the mushroom body of *Drosophila melanogaster*.** *Elife* 2022, **11**:1–39.
88. Eschbach C, Fushiki A, Winding M, Schneider-Mizell CM, Shao M, Arruda R, Eichler K, Valdes-Aleman J, Ohyama T, Thum AS, et al.: **Recurrent architecture for adaptive regulation of learning in the insect brain.** *Nat Neurosci* 2020, **23**:544–555.
89. Grabe V, Sachse S: **Fundamental principles of the olfactory code.** *Biosystems* 2018, **164**:94–101.

90. Eschbach C, Fushiki A, Winding M, Afonso B, Andrade IV, Cocanougher BT, Eichler K, Gepner R, Si G, Valdes-Aleman J, *et al.*: **Circuits for integrating learned and innate valences in the insect brain.** *Elife* 2021, **10**:1–36.
91. Strauss R: **The central complex and the genetic dissection of locomotor behaviour.** *Curr Opin Neurobiol* 2002, **12**:633–638.
92. Donlea JM, Alam MN, Szymusiak R: **Neuronal substrates of sleep homeostasis; lessons from flies, rats and mice.** *Curr Opin Neurobiol* 2017, **44**:228–235.
93. Fisher YE: **Flexible navigational computations in the *Drosophila* central complex.** *Curr Opin Neurobiol* 2022, **73**, 102514.
94. Silva C, McNaughton N: **Are periaqueductal gray and dorsal raphe the foundation of appetitive and aversive control? A comprehensive review.** *Prog Neurobiol* 2019, **177**:33–72.
95. Yau JOY, McNally GP: **Brain mechanisms controlling pavlovian fear conditioning.** *J Exp Psychol Anim Learn Cogn* 2018, **44**:341–357.
96. Janak PH, Tye KM: **From circuits to behaviour in the amygdala.** *Nature* 2015, **517**:284–292.
97. Josselyn SA, Frankland PW: **Memory allocation: mechanisms and function.** *Annu Rev Neurosci* 2018, **41**:389–413.
98. Bowen AJ, Chen JY, Huang YW, Baertsch NA, Park S, Palmiter RD: **Dissociable control of unconditioned responses and associative fear learning by parabrachial cgrp neurons.** *Elife* 2020, **9**:1–50.
99. Uematsu A, Tan BZ, Ycu EA, Cuevas JS, Koivumaa J, Junyent F, Kremer EJ, Witten IB, Deisseroth K, Johansen JP: **Modular organization of the brainstem noradrenaline system coordinates opposing learning states.** *Nat Neurosci* 2017, **20**:1602–1611.
100. Barsy B, Kocsis K, Magyar A, Babiczky Á, Szabó M, Veres JM, Hillier D, Ulbert I, Yizhar O, Máttyás F: **Associative and plastic thalamic signaling to the lateral amygdala controls fear behavior.** *Nat Neurosci* 2020, **23**:625–637.
101. Bordi F, LeDoux JE: **Response properties of single units in areas of rat auditory thalamus that project to the amygdala - II. Cells receiving convergent auditory and somatosensory inputs and cells antidromically activated by amygdala stimulation.** *Exp Brain Res* 1994, **98**:275–286.
102. Ozawa T, Ycu EA, Kumar A, Yeh L-FF, Ahmed T, Koivumaa J, Johansen JP: **A feedback neural circuit for calibrating aversive memory strength.** *Nat Neurosci* 2016, **20**:1–11.
103. Groessl F, Munsch T, Meis S, Griessner J, Kaczanowska J, Pliota P, Kargl D, Badurek S, Kraitsy K, Rassoulpour A, *et al.*: **Dorsal tegmental dopamine neurons gate associative learning of fear.** *Nat Neurosci* 2018, **21**:952–962.
104. Poulin JF, Caronia G, Hofer C, Cui Q, Helm B, Ramakrishnan C, Chan CS, Dombeck DA, Deisseroth K, Awatramani R: **Mapping projections of molecularly defined dopamine neuron subtypes using intersectional genetic approaches.** *Nat Neurosci* 2018, **21**:1260–1271.
105. Kim EJ, Horowitz O, Pellman BA, Tan LM, Li Q, Richter-Levin G, Kim JJ: **Dorsal periaqueductal gray-amygdala pathway conveys both innate and learned fear responses in rats.** *Proc Natl Acad Sci U S A* 2013, **110**:14795–14800.
106. Penzo MA, Robert V, Tucciarone J, De Bundel D, Wang M, Van Aelst L, Darvas M, Parada LF, Palmiter RD, He M, *et al.*: **The paraventricular thalamus controls a central amygdala fear circuit.** *Nature* 2015, **519**:455–459.
107. Li H, Namburi P, Olson JM, Borio M, Lemieux ME, Beyeler A, Calhoun GG, Hitora-Imamura N, Coley AA, Libster A, *et al.*: **Neurotensin orchestrates valence assignment in the amygdala.** *Nature* 2022, **608**:586–592.
- Demonstrate that neurotensin (NT)-expressing neurons in the PVT projecting to the BLA guide valence assignment in the BLA. They reveal that NT action across different timescales (sub-seconds, minutes, weeks) leads to distinct behavioural outcomes.
108. Zhu Y, Nachtrab G, Keyes PC, Allen WE, Luo L, Chen X: **Dynamic salience processing in paraventricular thalamus gates associative learning.** *Science* 2018, **362**:423–429.
- Demonstrate that the activation of PVT neurons is scaled with the intensity of behaviorally relevant stimuli and modulated by changes in the behavioral context or internal state.
109. Lammel S, Lim BK, Ran C, Huang KW, Betley MJ, Tye KM, Deisseroth K, Malenka RC: **Input-specific control of reward and aversion in the ventral tegmental area.** *Nature* 2012, **491**:212–217.
110. Watabe-Uchida M, Zhu L, Ogawa SK, Vamanrao A, Uchida N: **Whole-brain mapping of direct inputs to midbrain dopamine neurons.** *Neuron* 2012, **74**:858–873.
111. Beier KT, Steinberg EE, DeLoach KE, Xie S, Miyamichi K, Schwarz L, Gao XJ, Kremer EJ, Malenka RC, Luo L: **Circuit architecture of VTA dopamine neurons revealed by systematic input-output mapping.** *Cell* 2015, **162**:622–634.
112. Tian J, Huang R, Cohen JY, Osakada F, Kobak D, Machens CK, Callaway EM, Uchida N, Watabe-Uchida M: **Distributed and mixed information in monosynaptic inputs to dopamine neurons.** *Neuron* 2016, **91**:1374–1389.
113. Aso Y, Hattori D, Yu Y, Johnston RM, Iyer N a, Ngo T-T, Dionne H, Abbott L, Axel R, Tanimoto H, *et al.*: **The neuronal architecture of the mushroom body provides a logic for associative learning.** *Elife* 2014, **3**:1–47.
114. Yuan Lei, Dou Yan-Nong, Sun Yan-Gang: **Topography of reward and aversion encoding in the mesolimbic dopaminergic system.** *J Neurosci* 2019, **39**:6472–6481.
115. Mao Z, Davis RL: **Eight different types of dopaminergic neurons innervate the *Drosophila* mushroom body neuropil: anatomical and physiological heterogeneity.** *Front Neural Circ* 2009, **3**:5.
116. Pezze Ma, Feldon J: **Mesolimbic dopaminergic pathways in fear conditioning.** *Prog Neurobiol* 2004, **74**:301–320.
117. Aso Y, Rubin GM: **Dopaminergic neurons write and update memories with cell-type-specific rules.** *Elife* 2016, **5**:1–15.
118. Watabe-Uchida M, Uchida N: **Multiple dopamine systems: weal and woe of dopamine.** *Cold Spring Harbor Symp Quant Biol* 2018, **83**:83–95.
119. Fadok JP, Dickerson TMK, Palmiter RD: **Dopamine is necessary for cue-dependent fear conditioning.** *J Neurosci* 2009, **29**:11089–11097.
120. Wenzel JM, Rauscher NA, Cheer JF, Oleson EB: **A role for phasic dopamine release within the nucleus accumbens in encoding aversion: a review of the neurochemical literature.** *ACS Chem Neurosci* 2015, **6**:16–26.
121. Poulin JF, Gaertner Z, Moreno-Ramos OA, Awatramani R: **Classification of midbrain dopamine neurons using single-cell gene expression profiling approaches.** *Trends Neurosci* 2020, **43**:155–169.
122. Brischox F, Chakraborty S, Brierley DI, Ungless M a: **Phasic excitation of dopamine neurons in ventral VTA by noxious stimuli.** *Proc Natl Acad Sci U S A* 2009, **106**:4894–4899.
123. Morrens J: **Dopamine neurons coding prediction errors in reward space, but not in aversive space: a matter of location?** *J Neurophysiol* 2014, **112**:1021–1024.
124. de Jong JW, Afjei SA, Pollak Dorocic I, Peck JR, Liu C, Kim CK, Tian L, Deisseroth K, Lammel S: **A neural circuit mechanism for encoding aversive stimuli in the mesolimbic dopamine system.** *Neuron* 2019, **101**:133–151.e7.
- Demonstrate that glutamatergic neurons in the LH represent key afferent inputs to inform about aversive outcomes to ventromedial NAC-projecting DA neurons.
125. Nieh EH, Vander Weele CM, Matthews GA, Presbrey KN, Wichmann R, Leppla CA, Izadmehr EM, Tye KM: **Inhibitory input from the lateral hypothalamus to the ventral tegmental area disinhibits dopamine neurons and promotes behavioral activation.** *Neuron* 2016, **90**:1286–1298.

126. McNamara CG, Tejero-Cantero Á, Trouche S, Campo-Urriza N, Dupret D: **Dopaminergic neurons promote hippocampal reactivation and spatial memory persistence.** *Nat Neurosci* 2014, **17**:1658–1660.
127. Tsetsenis T, Badya JK, Wilson JA, Zhang X, Krizman EN, Subramaniyan M, Yang K, Thomas SA, Dani JA: **Midbrain dopaminergic innervation of the hippocampus is sufficient to modulate formation of aversive memories.** *Proc Natl Acad Sci U S A* 2021, **118**:1–10.
128. Broussard JI, Yang K, Levine AT, Tsetsenis T, Jenson D, Cao F, Garcia I, Arenkiel BR, Zhou FM, De Biasi M, *et al.*: **Dopamine regulates aversive contextual learning and associated in vivo synaptic plasticity in the Hippocampus.** *Cell Rep* 2016, **14**: 1930–1939.
129. Menegas W, Akita K, Amo R, Uchida N, Watabe-Uchida M:
 - **Dopamine neurons projecting to the posterior striatum reinforce avoidance of threatening stimuli.** *Nat Neurosci* 2018, **21**: 1421–1430.

Reveal that the activity of DA axons in the posterior tail of the striatum scales with the novelty and intensity of external stimuli, but not with the size of the reward, which involves the ventral striatum.

130. Steinberg EE, Gore F, Heifets BD, Taylor MD, Norville ZC, Beier KT, Földy C, Lerner TN, Luo L, Deisseroth K, *et al.*: **Amygdala-Midbrain connections modulate appetitive and aversive learning.** *Neuron* 2020, **106**:1026–1043.e9.

Reveal that CeA-projecting neurons in the SN pars lateralis respond to salient innate and appetitive/aversive conditioned stimuli. They also show this pathway as necessary for reward-seeking and defensive behaviours.

131. Valjent E, Gangarossa G: **Trends in the tail of the striatum : from anatomy to connectivity and function.** *Trends Neurosci* 2021 Mar;44(3):203-214..

132. Aso Y, Herb A, Ogueta M, Siwanowicz I, Templier T, Friedrich AB, Ito K, Scholz H, Tanimoto H: **Three dopamine pathways induce aversive odor memories with different stability.** *PLoS Genet* 2012, **8**, e1002768.

133. Hige T, Aso Y, Modi MN, Rubin GM, Turner GC: **Heterosynaptic plasticity underlies aversive olfactory learning in Drosophila.** *Neuron* 2015, **88**:985–998.

134. Al-Hasani R, McCall JG, Shin G, Gomez AM, Schmitz GP, Bernardi JM, Pyo C-O, Park S II, Marcinkiewicz CM, Crowley N a, *et al.*: **Distinct subpopulations of nucleus accumbens dynorphin neurons drive aversion and reward.** *Neuron* 2015, **87**:1063–1077.

135. Schwartzbaum JS, Leventhal TO: **Neural substrates of behavioral aversion in lateral hypothalamus of rabbits.** *Brain Res* 1990, **507**:85–91.

136. Hoebel B, Teitelbaum P: **Hypothalamic control of feeding and self-stimulation.** *Science* 1962, **135**:375–378.

137. Elmquist JK, Elias CF, Saper CB: **From lesions to leptin: hypothalamic control of food intake and body weight.** *Neuron* 1999, **22**:221–232.

138. Stuber GD, Wise RA: **Lateral hypothalamic circuits for feeding and reward.** *Nat Neurosci* 2016, **19**:198–205.

139. Sharpe MJ, Marchant NJ, Whitaker LR, Richie CT, Zhang YJ, Campbell EJ, Koivula PP, Necarsulmer JC, Mejias-Aponte C, Morales M, *et al.*: **Lateral hypothalamic GABAergic neurons encode reward predictions that are relayed to the ventral tegmental area to regulate learning.** *Curr Biol* 2017, **27**: 2089–2100.e5.

140. Eshel N, Bukwich M, Rao V, Hemmelder V, Tian J, Uchida N: **Arithmetic and local circuitry underlying dopamine prediction errors,** **525(7568)**; 2015 Sep10:243–246.

141. Tan KR, Yvon C, Turiault M, Mirzabekov JJ, Doehner J, Labouèbe G, Deisseroth K, Tye KM, Lüscher C: **GABA neurons of the VTA drive conditioned place aversion.** *Neuron* 2012, **73**: 1173–1183.

142. Pignatelli M, Umanah GKE, Ribeiro SP, Chen R, Karuppagounder SS, Yau HJ, Eacker S, Dawson VL, Dawson TM, Bonci A: **Synaptic plasticity onto dopamine neurons shapes fear learning.** *Neuron* 2017, **93**:425–440.

143. Tang W, Kochubey O, Kintscher M, Schneggenburger R: **A VTA • to basal amygdala dopamine projection contributes to signal salient somatosensory events during fear learning.** *J Neurosci* 2020, **40**. JN-RM-1796-19.

Show that VTA-projecting DA neurons to BLA, but not CeA, contribute to fear learning.

144. Perisse E, Oswald D, Barnstedt O, Talbot CB, Huetteroth W, Waddell S: **Aversive learning and appetitive motivation toggle feed-forward inhibition in the Drosophila mushroom body.** *Neuron* 2016, **90**:1086–1099.

145. Tsao C-H, Chen C-C, Lin C-H, Yang H-Y, Lin S: **Drosophila • mushroom bodies integrate hunger and satiety signals to control innate food-seeking behavior.** *Elife* 2018, **7**:1–35.

Elucidate the circuit architecture and function of reciprocal connectivity between the NAc and VTA DA and GABA subpopulations, focusing on the specific contribution of GABAARs and GABABRs in these pathways. They establish a critical role for NAc subregion-specific inputs to the VTA in regulating motivated behaviours.

146. Siju KP, De Backer JF, Grunwald Kadow IC: **Dopamine modulation of sensory processing and adaptive behavior in flies.** *Cell Tissue Res* 2021, **383**:207–225.

147. Senapati B, Tsao CH, Juan YA, Chiu TH, Wu CL, Waddell S,
 - **Lin S: A neural mechanism for deprivation state-specific expression of relevant memories in Drosophila.** *Nat Neurosci* 2020, **22**:2029–2039.

Demonstrate that the neuropeptide leucokinin inhibits two types of MB-innervating DA neurons to promote thirst-specific water memory expression, whereas it activates other MB-innervating DA neurons to facilitate hunger-dependent sugar memory expression.

148. Placais P-Y, Preat T: **To favor survival under food shortage, the brain disables costly memory.** *Science* 2013, **339**: 440–442.

149. Plaçais PY, De Tredern É, Scheunemann L, Trannoy S, Goguel V, Han KA, Isabel G, Preat T: **Upregulated energy metabolism in the Drosophila mushroom body is the trigger for long-term memory.** *Nat Commun* 2017, **8**.

150. Hosokawa T, Kato K, Inoue M, Mikami A: **Neurons in the macaque orbitofrontal cortex code relative preference of both rewarding and aversive outcomes.** *Neurosci Res* 2007, **57**: 434–445.

151. Sugrue LP, Corrado GS, Newsome WT: **Matching behavior and the representation of value in the parietal cortex.** *Science* 2004, **304**:1782–1787.

152. Dorris MC, Glimcher PW: **Activity in posterior parietal cortex is correlated with the relative subjective desirability of action.** *Neuron* 2004, **44**:365–378.

153. Pischcheda D, Palminteri S, Coricelli G: **The effect of counterfactual information on outcome value coding in medial prefrontal and cingulate cortex: from an absolute to a relative neural code.** *J Neurosci* 2020, **40**:3268–3277.

154. Tobler PN, Fiorillo CD, Schultz W: **Adaptive coding of reward value by dopamine neurons.** *Science* 2005, **307**:1642–1645.

155. Lak A, Stauffer WR, Schultz W: **Dopamine neurons learn relative chosen value from probabilistic rewards.** *Elife* 2016, **5**:1–19.

156. Brooks AM, Pammi VSCC, Noussair C, Capra CM, Engelmann JB, Berns GS: **From bad to worse: striatal coding of the relative value of painful decisions.** *Front Neurosci* 2010, **4**:1–8.

157. Saez RA, Saez A, Paton JJ, Lau B, Salzman CD: **Distinct roles for the amygdala and orbitofrontal cortex in representing the relative amount of expected reward.** *Neuron* 2017, **95**: 70–77.e3.

158. Campese VD, Kim IT, Hou M, Gupta S, Draus C, Kurpas B,
 - **Burke K, LeDoux JE: Chemogenetic inhibition reveals that processing relative but not absolute threat requires basal amygdala.** *J Neurosci* 2019, **39**:8510–8516.

Analyse how updating the outcome value can affect conditioned behaviour in rats and describe the role of the basal amygdala in the revaluation of aversive outcome.

159. Elliott R, Agnew Z, Deakin JFWW: **Medial orbitofrontal cortex codes relative rather than absolute value of financial rewards in humans.** *Eur J Neurosci* 2008, **27**:2213–2218.

160. Harrison BJ, Fullana MA, Via E, Soriano-Mas C, Vervliet B, Martínez-Zalacáin I, Pujol J, Davey CG, Kircher T, Straube B, *et al.*: **Human ventromedial prefrontal cortex and the positive affective processing of safety signals.** *Neuroimage* 2017, **152**:12–18.
161. Jacob PF, Waddell S: **Spaced training forms complementary long-term memories of opposite valence in *Drosophila*.** *Neuron* 2020, **106**:977–991.e4.
 Demonstrate that within boundary conditions of order and CS+/CS-repetition, associative learning leads to a positive/safety value assigned to the CS- using specific population of reward DA neurons projecting to the MB.
162. Pompilio L, Kacelnik A, Behmer ST: **State-dependent learned valuation drives choice in an invertebrate.** *Science* 2006, **311**: 1613–1615.
163. Aw JM, Holbrook RI, Burt de Perera T, Kacelnik A: **State-dependent valuation learning in fish: banded tetras prefer stimuli associated with greater past deprivation.** *Behav Process* 2009, **81**:333–336.
164. Wendt S, Strunk KS, Heinze J, Roeder A, Czaczkes TJ: **Positive and negative incentive contrasts lead to relative value perception in ants.** *Elife* 2021, **8**:1–22.
 Demonstrate that ants value reward options relative to reference ones and that social information from the other ants affects perceived value.
165. Meindl JN: **Understanding preference shifts: a review and alternate explanation of within-trial contrast and state-dependent valuation.** *Behav Anal* 2012, **35**: 179–195.
166. Eichenbaum HB: **Memories linked within a window of time.** *Nature* 2016, **536**:405–406.
167. Clewett D, DuBrow S, Davachi L: **Transcending time in the brain: how event memories are constructed from experience.** *Hippocampus* 2019, **29**:162–183.
168. Gerber B, Yarali A, Diegelmann S, Wotjak CT, Pauli P, Fendt M: **Pain-relief learning in flies, rats, and man: basic research and applied perspectives.** *Learn Mem* 2014, **21**: 232–252.
169. Leknes S, Berna C, Lee MC, Snyder GD, Biele G, Tracey I: **The importance of context: when relative relief renders pain pleasant.** *Pain* 2013, **154**:402–410.
170. Felsenberg J, Jacob PF, Walker T, Barnstedt O, Edmondson-Stait AJ, Pleijzier MW, Otto N, Schlegel P, Sharifi N, Perisse E, *et al.*: **Integration of parallel opposing memories underlies memory extinction.** *Cell* 2018, **175**:709–722.