Review

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Aversive stimuli and loss in the mesocorticolimbic dopamine system

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There is mounting evidence that the mesolimbic dopamine system carries valuation signals not only for appetitive or gain-related stimuli, with which it is traditionally associated, but also for aversive and loss-related stimuli. Cellular-level studies demonstrate that the neuronal architecture to support aversive stimuli encoding in this system does exist. Both cellular-level and human neuroimaging research suggest the co-existence of appetitive and aversive prediction-error signals within the mesocorticolimbic system. These findings shift the view of the mesocorticolimbic system as a singular pathway for reward to a system with multiple signals across a wide range of domains that drive value-based decision making.

Neural underpinnings of value-based decision making

Revealing the biological basis of human decision making has been the goal of much neuroscience research in the past few decades. Specifically, value-based decision making research has grown exponentially from the early 2000s to present, due, in part, to the growth of the field of neuroeconomics (see Glossary). In value-based decision making, in order to make a choice between several different actions or objects, the individual assigns a value to each alternative and subsequently chooses the option with the highest value. This process can be described through economic models of decision making, such as expected utility theory [1], whereas tools from neuroscience and psychology have helped pinpoint where variables in these models are represented in the human brain [2,3].

One conclusion that has been drawn from value-based decision research is that brain regions within the mesocorticolimbic dopamine system play a crucial role in representing value, changes in value, and other variables related to the decision process. The primary neuroanatomical structures in the mesocorticolimbic system are the ventral tegmental area (VTA), the ventral striatum (VS), and regions of the prefrontal cortex, including the ventromedial prefrontal cortex (vmPFC). These regions were first identified as being important for reward-related learning on the basis of brain stimulation experiments in the 1950s [4], electrophysiological studies [5], and more recently human neuroimaging [6–8]. The majority of these studies have used either appetitive stimuli or monetary gains for human decision making tasks. In comparison, much less is known about whether the mesocorticolimbic system also processes decision variables across gains and losses in humans, and appetitive and aversive stimuli in other animals. Human neuroimaging studies find support both for [9–11] and against [6,12,13] the idea of a single neuroanatomical system that represents value across these domains (also known as a 'common neural currency' [14]), with most of the disparity arising from decisions over financial losses. In studies that do find both appetitive and aversive representation of value in mesocorticolimbic structures, it is unclear whether this value is represented by an appetitive signal, an aversive signal, or both.

Animal studies show that the neural architecture to support aversive coding in the mesocorticolimbic system does exist. Separate populations of neurons that are stimulated and inhibited by aversive stimuli exist within the VTA [15]. These populations could underlie the separate appetitive and aversive prediction-error signals found in both the ventral striatum and orbitofrontal cortex by neuroimaging studies [16]. A close underlying neuroanatomical relationship between pleasure and pain has been

Glossary

Appetitive/aversive stimuli: such stimuli are differentiated based on the hedonic state that they create. Appetitive stimuli satisfy basic needs (e.g., food, sex, etc.) and thus create a pleasurable hedonic state. They generally reinforce behavior that leads to these hedonic states and are often associated with approach behavior. Aversive stimuli generate unpleasant hedonic states and tend to extinguish behavior or result in avoidance of the stimuli [74]. Whether a stimulus is appetitive or aversive can depend on the physiological state that the person or animal is in. For example, healthy rats consider hypertonic sodium solutions to be aversive, but in a state of sodium depletion, the solution becomes appetitive [75,76].

Common neural currency hypothesis: the hypothesis states that the brain converts all types of reward into a common scale, allowing for comparisons of value across disparate stimuli [14].

Gain/loss: an increase/decrease in a stimulus from a reference amount. For humans, gains and losses are typically referenced in the context of monetary decision making. What is considered a gain or loss depends on the reference point, which could range from a person's total wealth to the amount of money with which they are endowed at the beginning of an experiment. Thus, the framing of potential choices may have a large effect on choice behavior.

Neuroeconomics: the interdisciplinary science of decision making that combines economics, neuroscience, and psychology. The majority of neuroeconomic studies use fMRI to measure the brain's activity while people make decisions. These decisions are often over monetary outcomes, as money is easily manipulated and measurable and thus ideal for testing economic models of decision making.

Reinforcement learning: a type of learning that requires interaction with the environment (as opposed to supervised learning). An agent using reinforcement learning algorithms will try to optimize behavior based on reward- or punishment-related feedback from the environment.

Value: a metric used to compare potential outcomes for which an individual makes decisions. Value can be objective (e.g., calculated mathematically as expected value) or subjective ('utility').

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1364-6613/$ – see front matter
 http://dx.doi.org/10.1016/j.tics.2013.04.001

Box 1. Differential behavior over gains and losses

People behave differently when making choices between financial gains versus choices between financial losses. When faced with decisions over gains, people tend to behave in a risk-averse manner. When faced with decisions over losses, people tend to behave in a risk-seeking manner. This is known as the 'reflection effect' and is described in prospect theory by Kahneman and Tversky [51]. People also behave as if losses were twice as bad as gains are good – this behavior is known as 'loss aversion' [77]. This difference in behavior over gains and losses suggests that they are treated as separate domains, potentially with separate underlying neural pathways.

Prospect theory demonstrates this non-uniform treatment of gains and losses behaviorally and thus begs the question of where this is reflected in the brain. It has already been demonstrated that financial gains elicit increases in activation in mesocorticolimbic structures, but what about financial losses? Tom *et al.* [33] demonstrated an increase in BOLD response to potential financial gains and a decrease in response to potential financial losses, a result that is consistent with an appetitive PE. Furthermore, the heavier weighting of losses was reflected by a steeper response to losses in the ventral striatum than gains. Although other studies of loss aversion have implicated alternative brain regions, namely the amygdala [78,79], recent animal and human studies suggest that even disparate domains of decision making recruit the ventral striatum, OFC, and other mesocorticolimbic structures [16,34,46,64,65].

suggested before [17,18]. Behavior over these separate domains differs substantially, and this suggests the existence of separate, perhaps parallel, neuroanatomical substrates (Box 1). Here, we review evidence for the role of the mesocorticolimbic system in representing value across all domains, with an eye toward its respective role in decision making over losses and aversive outcomes. Ultimately, we aim to shift the view of the mesocorticolimbic system as a singular reward-related hub to a system that contains multiple signals across disparate domains that drive value-based decision making.

The mesolimbic dopamine system and prediction error

The mesocorticolimbic system has long been known to be involved in reward [4,19,20], but the application of reinforcement learning theories helped shed light on what dopamine might be signaling. Current evidence points to dopaminergic neurons as signaling prediction errors (PEs). In its simplest form, a reward PE is a learning signal that represents the difference between the reward that is expected and the reward that is actually received [21,22]. Reward PE is positive when rewards are greater than expected, zero when expectations are met, and negative when they are worse than expected. Phasic fluctuations in dopamine correlate with reward PE signaling as it pertains to learning and reinforcement [23,24]. Unpredicted rewards increase phasic firing rates of dopaminergic neurons in the VTA, whereas fully-predicted rewards do not [25,26]. In naïve monkeys, before they have learned a reward association, midbrain dopamine neurons increase their firing rate to a reward that follows an unconditioned cue. Once the monkeys are trained, the same midbrain dopamine neurons respond to the conditioned cue, but not the reward [5]. This is consistent with reward PEs not just signaling differences between expectation and received reward, but differences between expectation and conditioned reward cues. Also consistent with reward PEs, human neuroimaging studies find increases in blood flow to the ventral striatum for both unpredicted rewards and unpredicted information that predicts future rewards, but not for rewards that are fully predicted [27–30]. The magnitude of these reward PE-like responses in mesolimbic regions have been observed to scale with the size of the PE [31].

Theoretically, a single PE signal could be positive for appetitive outcomes and negative for aversive outcomes. However, even within this framework, there are two possible interpretations of PE signals. For example, a positive PE could result from a stimulus that is more appetitive than expected or a stimulus that is less aversive than expected. The context of the decision dictates the representation. To disambiguate these possibilities, the brain would need to maintain separate appetitive and aversive PE signals even within the mesocorticolimbic system (Box 2). This would serve to motivate separate sets of behavior, such as approach and avoidance [32]. Evidence for both a unitary [33] and separate PE [16,34] signals for appetitive and aversive stimuli exist in the literature. We discuss this literature below.

Neuronal architecture for aversive coding

At the cellular level, it is clear that both appetitive- and aversive-responsive neuronal populations exist within the VTA, one of the primary regions of dopamine synthesis in the human brain. Mirenowicz and Schultz [25] electrophysiologically sampled dopamine neurons in the ventral tegmental area and substantia nigra in monkeys, and found that 76%–78% of the neurons responded to appetitive stimuli, whereas between 3% and 14% responded to aversive stimuli. More recent rodent research found a range of appetitive-responding neurons in the VTA, ranging from 0% to 67% of the sampled neurons [35–37]. A portion of the appetitive-responding neurons are also inhibited by aversive stimuli [15,38]. Some evidence suggests that these neurons are arranged in a dorsal-ventral gradient in the VTA, where more ventral VTA neurons are excited by aversive stimuli, and more dorsal neurons by appetitive stimuli [39]. Emerging literature suggests that not all appetitive- or aversive-responding neurons in the VTA are dopaminergic. GABAergic neurons in the VTA have been shown to represent expectation [40] and might constitute a portion of aversive-responding neurons [41]. Several laboratories have identified putative inputs into the VTA that drive these aversive- and appetitive-signaling neuronal populations, which include the lateral habenula and the rostromedial tegmental nucleus [42–45]. Ultimately, electrophysiological research suggests that there are at least two separate PE signals at the level of the VTA.

The nucleus accumbens (NAcc) is the main target of efferent VTA neurons. Dopamine release within the NAcc mirrors what has been found electrophysiologically – that there are at least two distinct appetitive and aversive signals. Similar to the findings of electrophysiological studies, cyclic voltammetry has been used to demonstrate a differential dopaminergic response to aversive stimuli. Cyclic voltammetry is an electrochemical method that

Box 2. Appetitive and aversive prediction error

There is evidence at both the cellular- and systems-level that at least two separate learning signals are carried in the mesocorticolimbic system. The most commonly referred to signal, the appetitive PE signal, is also referred to as reward prediction error (RPE). The appetitive PE signal is larger when outcomes or information about future outcomes is better than expected. It does not differentiate between the receipt of a reward or a less aversive stimulus. An aversive PE is a mirror image of an appetitive PE: it is larger when outcomes or information about future outcomes is worse than expected. This is illustrated well by Seymour *et al.* [16], where the researchers manipulated the level of pain a participant was experiencing by either increasing or decreasing the temperature of a patch of skin that had capsaicin topically applied. The participants were presented with cues which predicted the temperature change (either relief or pain). The researchers modeled both appetitive and aversive PEs, looking for regions whose BOLD response fit the time course of these signals (Figure I). They found that these signals were co-expressed in the ventral striatum, insula, and rostral anterior cingulate cortex.

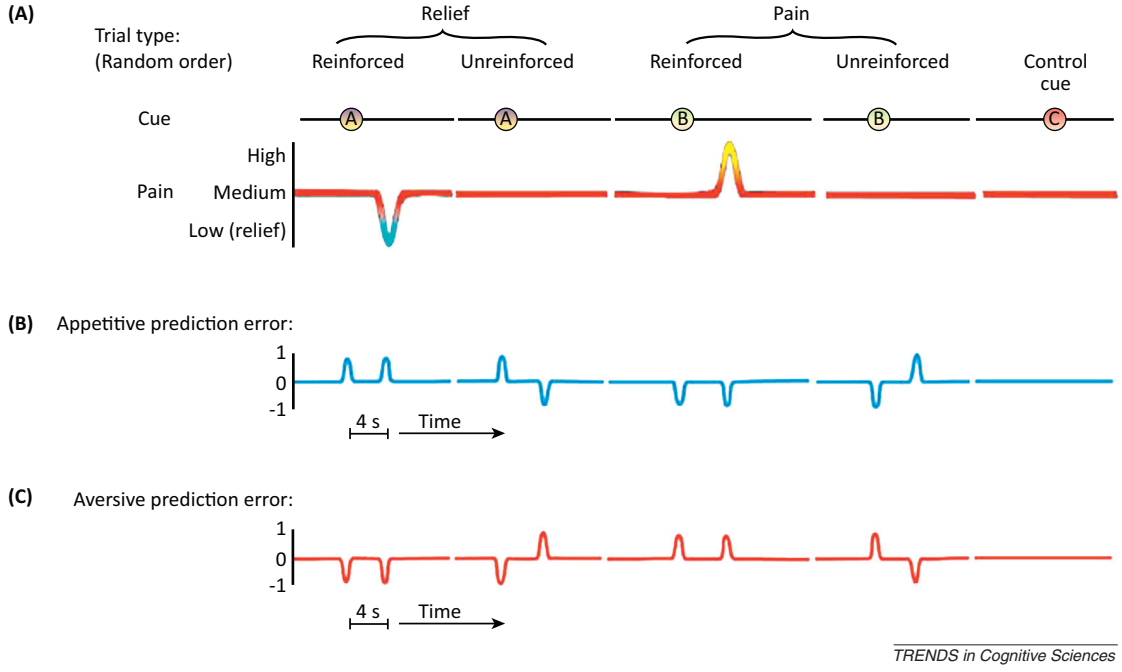

Figure I. Appetitive and aversive PEs. Adapted, with permission, from Seymour *et al.* [16].

allows *in vivo* detection of neurotransmitter release with sub-second resolution. Both increases [46] and decreases [47,48] in dopamine transmission have been demonstrated in the NAcc to aversive stimuli. Data from Budygin *et al.* [46] suggest that these phasic changes in dopamine release have a specific time course of onset and offset. Onset of an aversive stimulus elicits an increase in dopamine release in the NAcc core, whereas the offset of an aversive stimulus results in an increase in dopamine in the NAcc shell. There is also evidence for a spatial separation between appetitive and aversive stimuli in the NAcc, similar to the dorsal–ventral separation suggested for the VTA. In rats, Badrinarayan *et al.* [49] used fast scan cyclic voltammetry to measure dopamine fluctuations in the NAcc core and shell. The rats were trained using Pavlovian fear conditioning to associate an auditory cue with an aversive stimulus (a foot shock). After conditioning, the cue elicited a decrease in dopamine transmission in the NAcc core, but an increase in the NAcc shell. These results suggest that both an appetitive PE (core) and aversive PE (shell) coexist in the NAcc. Combined with electrophysiological evidence, it is clear there is an architecture for both types of stimuli to be processed within the mesocorticolimbic system, but as separate signals.

Human mesolimbic dopamine system and monetary losses

In humans, it is less clear whether monetary losses are represented in the mesolimbic dopamine system. Some neuroimaging studies show either no response to monetary loss in the NAcc or find activations in other regions, such as the amygdala and insula [6,12,13]. However, there are also studies that show responses in the NAcc and other mesolimbic structures to monetary losses [9–11]. A meta-analysis of 142 neuroimaging studies revealed that the NAcc was commonly activated for both gains and losses, with the anterior insula, ACC, and lateral PFC preferentially activated for losses [50]. Using a classic economic decision task, Tom *et al.* [33] asked participants to accept or reject a 50/50 gamble of a financial gain/loss. By varying the amounts of the gains/losses, the researchers were able to identify brain regions that correlated with the gains and losses separately during the decision process. The blood-oxygen-level-dependent (BOLD) response in the NAcc correlated positively with the size of the potential gains and negatively with the size of the potential losses. The slope of the correlation also reflected the behavioral finding that participants weighed losses twice as much as gains [51].

These results fit with a single appetitive PE signal, which increases for potential gains, but decreases for

potential losses. However, this finding is not consistent across the neuroimaging literature. This lack of consensus may be related to the difficulty in studying loss in an experimental setting. Inducing a true financial loss is prohibited by most rules of human experimentation, and studies that have used truly aversive stimuli (such as electric shocks) are relatively few. Other factors related to participant incentives could also affect human neuroimaging results [52]. For example, a simple endowment of money from which participants win or lose might not be sufficient to elicit true feelings of loss. Activity in the NAcc has been demonstrated to be reference-dependent [31,53,54], whereas the dorsal striatum and orbitofrontal cortex have been shown in some studies to track reference-independent value [55,56]. Thus, incentives and potential outcomes must be carefully structured so that participants' reference points allow the stimuli to be judged as losses.

According to the common neural currency hypothesis, monetary losses are represented in the same brain regions as aversive stimuli. Direct comparisons of decisions over aversive stimuli and monetary loss reveal similar responses in mesocorticolimbic structures. Brooks *et al.* [57] replaced monetary outcomes with electric shocks in the same paradigm used by Tom *et al.* [33] and found that the expected value of entirely aversive gambles was encoded in the ventral striatum. Increased striatal activity was associated with 'less bad' gambles, consistent with a reward PE signal. Similarly, Delgado *et al.* [52] had participants complete a classical conditioning task, where unconditioned stimuli (either electric shocks or monetary losses) were paired with cues while undergoing functional MRI (fMRI) and skin conductance response (SCR) measurements. A conjunction analysis revealed that ventral striatum activity increased for both cues that predicted electric shocks and cues that predicted monetary losses. Furthermore, the SCRs to both shock- and monetary loss-conditioned cues were not distinguishable from each other. The results of Brooks *et al.* [57] were consistent with a reward PE signaling better than expected outcomes, similar to that found by Tom *et al.* [33] with monetary losses. Delgado *et al.* [52] found an aversive PE in the ventral striatum, similar to that found in other studies for noxious stimuli [58–61]. At the spatial scale measured with fMRI, information about monetary losses appears to be carried by the same underlying substrates as aversive stimuli.

Both cellular-level and neuroimaging research suggest the co-existence of appetitive and aversive PE signals within the mesocorticolimbic system. O'Doherty *et al.* [62] demonstrated a medial–lateral gradient for processing the value of monetary gains and losses in the orbitofrontal cotex (OFC), respectively. A similar gradient was found with appetitive and aversive smells by Gottfried *et al.* [63]. Other studies also show that the OFC encodes the value of both appetitive and aversive options [64,65]. In one study, Seymour *et al.* [16] applied capsaicin (a compound found in various capsicums that gives hot peppers their hotness) topically on the left leg of participants as they underwent fMRI. Cues were presented that were 50% predictive of either a painful or relieving outcome.

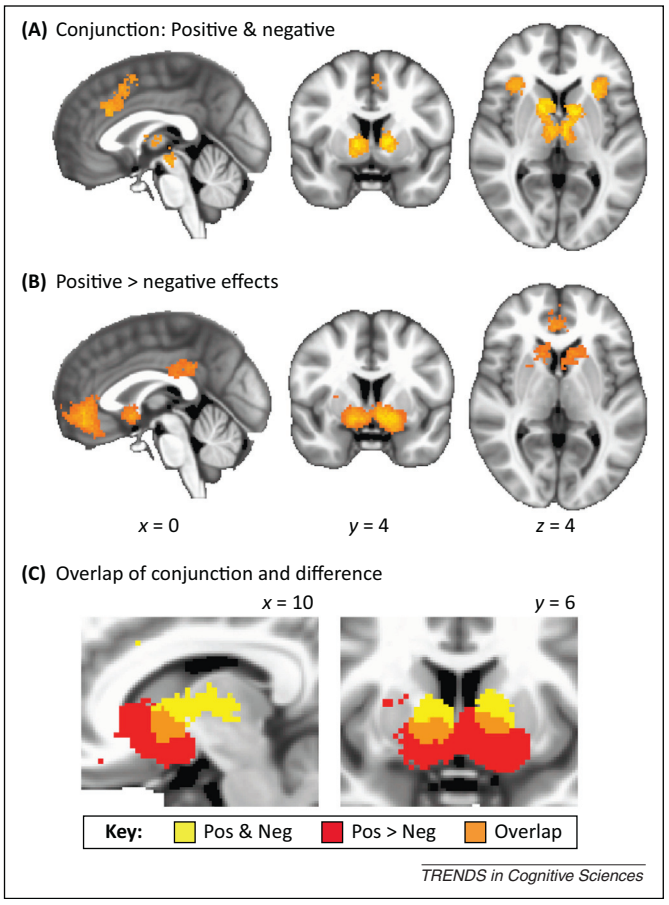

Figure 1. Meta-analysis of appetitive and aversive signals in the human brain. A meta-analysis of 206 neuroimaging publications revealed both independent and overlapping regions that encode an appetitive and aversive signals (termed 'positive' and 'negative' responses, respectively). **(A)** Regions showing both appetitive and aversive signals. **(B)** Regions with larger clustering for appetitive signals than aversive signals. **(C)** Map illustrating the overlap between panel (A) and (B). Adapted, with permission, from Bartra *et al.* [66].

The intensity and relief of the pain associated with the capsaicin was manipulated by either increasing or decreasing the temperature of an overlaid thermode. The authors found that both appetitive and aversive PEs were represented in separate brain regions, namely, the lateral

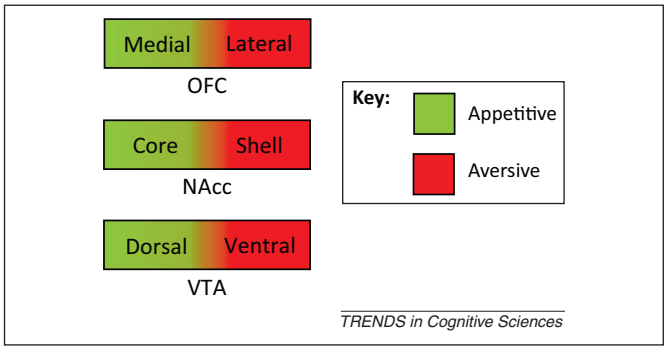

Figure 2. Proposed division of major mesocorticolimbic structures along appetitive–aversive lines. Neuroimaging studies have demonstrated a medial–lateral gradient for appetitive–aversive processing, respectively [62]. Cyclic voltammetry has also revealed a differential response in the NAcc core vs shell for appetitive–aversive stimuli [49]. Similarly, some electrophysiological studies have demonstrated a dorsal–ventral gradient for appetitive–aversive stimuli in the VTA [39]. Although the anatomical connectivity between these regions and their respective gradients are not entirely clear, the evidence suggests that there is a separate pathway within the mesocorticolimbic system for appetitive and aversive signals.

Box 3. Outstanding Questions

- What is the role of incentive structure in the conflicting neuroimaging results on financial loss?
- What is the relative contribution of appetitive and aversive signals to the BOLD response in mesolimbic structures?
- To what degree is a financial loss processed as an aversive signal?
- How do these appetitive–aversive signals interact to produce differential behavior in the face of reward or punishment?

OFC for aversive PE, and substantia nigra and amygdala for appetitive PE. However, a conjunction analysis revealed that these signals coexisted in the NAcc. Bartra *et al.* [66] analyzed 206 neuroimaging publications that involved fMRI and reward; they also found both independent and overlapping areas with appetitive and aversive signals in the striatum (Figure 1). The OFC is both structurally and functionally connected to the striatum; it is likely that the medial–lateral gradient evident in the OFC is related to dual appetitive–aversive signals found in the striatum and to the dorsal–ventral distinction in the VTA (Figure 2) [66–70]. Furthermore, these signals might arise from separate aversive- and appetitive-responding neuronal populations in the VTA. Information about aversive stimuli and financial losses are thus propagated through the mesolimbic dopamine system, just as an abundance of literature has demonstrated for appetitive signals.

Concluding remarks

There is strong evidence that the mesocorticolimbic dopamine system is a hub of valuation across appetitive and aversive stimuli, and monetary gains and losses. This neuroanatomical network, with dopamine as its primary neurotransmitter, is not limited to a single appetitive valuation signal that increases to better-than-expected outcomes and decreases to worse-than-expected outcomes. Neuroimaging studies have found that both appetitive and aversive signals exist within the OFC and NAcc. Electrophysiological research confirms that the VTA contains separate populations of neurons that respond to appetitive vs aversive stimuli. Cyclic voltammetry demonstrates a differential response in the NAcc core and shell to aversive stimuli. In this review, we have focused solely on the mesolimbic dopamine system, but there is evidence that valuation signals exist in other regions, such as the insula, amygdala, and areas of the parietal cortex [71–73]. Future research might help elucidate how these separate appetitive and aversive valuation signals interact to produce approach–avoidance behavior (Box 3).

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