# Parallels and overlap: the integration of homeostatic signals by mesolimbic dopam...

Health & Medicine

# Introduction

Motivated behaviors are fundamentally rooted in homeostasis. To survive, animals, including humans, have adopted behavioral strategies to efficiently procure and ingest substances based on homeostatic perturbations, particularly deficits in body fluid (e. g., thirst) and energy balance (e. g., hunger). Historically, researchers have dichotomized physiological underpinnings of ingestive behaviors into “ homeostatic” and “ non-homeostatic” [occurring in the absence of need and based on positive feedback (e. g., reward; hedonic)] neural processes—that is, as separate mechanisms. Indeed, as this field progressed, there have been attempts to conceptualize these two constructs as a means through which to view maladaptive motivated behaviors, particularly behaviors underlying obesity development and drug addiction. As such, reward-related neural substrates are thought to override processes that maintain homeostatic balance ( 1 – 6 ). However, there is ambiguity when delineating the neural substrates that regulate “ homeostatic” vs. reward processes. Rather than separable concepts, there are in fact many overlapping and parallel pathways [see ( 7 – 15 ) for review]. Moreover, one system traditionally viewed as participating in reward-driven ingestive behavior—the mesolimbic dopamine system—now appears to be a central hub for directing behavior in responses to homeostatic challenges. This review focuses on a particular form of mesolimbic dopamine activity—the phasic activation of dopamine neurons and subsequent phasic release of dopamine in striatal terminal regions—and will consider what these signals mean for goal-directed behavior and how they may be tuned by perturbations in physiological state.

## Phasic Dopamine Signaling and Motivated Behaviors

Midbrain dopamine neurons in VTA and SNc (substantia nigra pars compacta) exhibit distinctive firing patterns involving a combination of regular, pacemaker-like firing, irregular single spikes, and occasional high-frequency trains of action potentials, known as bursts ( 16 – 20 ). Bursts are of particular interest as these brief neural activations lead to transient increases in dopamine concentration in terminal regions such as NAc, which via activation of D1 and D2 receptors, influence the excitability of striatal output neurons and regulate their plasticity ( 21 , 22 ). Collectively, the bursts of action potentials from dopamine cell bodies and the dopamine release associated with them ( 23 ) are termed “ phasic” dopamine signaling. These signals are further shaped at the cell body and terminals by dopamine D2 autoreceptor inhibition, dopamine synthesis and vesicular packaging, the ready-releasable pool of vesicles, the rate of dopamine reuptake by the dopamine transporter [for an excellent review, see ( 22 )], and cholinergic modulation of presynaptic release ( 24 – 26 ). For the purposes of this review, the primary focus will be on the preponderance of data that support phasic dopamine as critical for aspects of goal-directed behavior including reinforcement, associative strength, reward prediction, incentive motivation, value and utility ( 27 – 35 ).

Phasic dopamine signaling has frequently been studied in the context of motivated behaviors that result from positive reinforcement. For example, dopamine is thought to reinforce learned associations between predictive stimuli and primary reward ( 36 , 37 ). As motivated behaviors occur on subsecond timescale, phasic dopamine signaling has been implicated as a

driving mechanism through which mesolimbic circuitry regulates reward-seeking ( 38 – 44 ). Within the reward prediction error framework, phasic dopamine activity at the time of the outcome (e. g., sucrose reward) is determined by an animal's expectation. Importantly, when errors in expectation occur (e. g., the outcome is better or worse than predicted), phasic dopamine signaling at the time of reward responds with a brief change in activity, specifically a burst or pause in neuronal firing or a transient increase or suppression in dopamine release at terminal regions. Accordingly, associative strength grows steeply when differences exist between predictions and outcomes ( 38 , 43 – 45 ) and, based on these data, phasic dopamine has been commonly termed a " teaching" signal that has functional properties in mediating motivational aspects of behavior. In turn, phasic dopamine responses evoked by predictive cues act to incentivize approach and consumption ( 46 – 50 ).

However, the complex roles of phasic dopamine signaling extend beyond positive reinforcement. Indeed, as goal-directed behaviors for positive reinforcement are highly adaptive, forming associations between aversive stimuli and negative reinforcement is also essential for survival. Consideration of these complexities will be critical in understanding how mesolimbic dopamine signaling can regulate behaviors in response to homeostatic perturbation as well as how changes in physiological state can profoundly change neural computations within mesolimbic circuitry. In humans, expectation of pain relief (i. e., negative reinforcement) results in transient increases in NAc blood oxygen level-dependent (BOLD) activity as well as increased functional connectivity between the NAc and key

mesolimbic nodes (e. g., VTA and medial prefrontal cortex) ( 51 , 52 ). Similarly, in animals, mesolimbic dopamine also play a role in processing aversive stimuli. For example, pain relief in injured rats results in increased VTA dopamine activity as measured by c-Fos immunohistochemistry and detection of NAc dopamine with microdialysis ( 53 ). Moreover, in the same study, administration of analgesia in injured rats resulted in a conditioned place preference and these effects were blocked by pharmacological inhibition of the VTA. Other research has demonstrated that cues that are associated with the avoidance of punishment (e. g., foot shock) reliably increase NAc phasic dopamine release, while inescapable punishment results in a decrease in phasic dopamine release ( 54 ). Finally, aversive agents like oral quinine and systemic LiCl (lithium chloride) reduce phasic dopamine release in the NAc and the rapid encoding of these stimuli allow for plastic adaptations in subsequent behaviors ( 55 – 58 ).

Mesolimbic dopamine responses to aversive stimuli comprise a substantial amount of complexity and heterogeneity ( 56 ), for example, with populations of VTA dopamine neurons that are either excited or inhibited by aversive stimuli ( 59 ). Work from Ungless and colleagues using electrophysiology in anesthetized rats has identified regional variation in the VTA, with dorsally-located dopamine neurons inhibited and ventrally-located dopamine neurons excited by aversive or noxious stimuli, while a separate population of non-dopaminergic neurons are inhibited by the same aversive stimuli (in this case, tail pinch or foot shock) ( 60 , 61 ). Others have demonstrated that tail pinch in anesthetized animals increases phasic dopamine release within the dorsal striatum and NAc core while alleviation of

pain by removing the tail pinch increases dopamine release in the NAc shell —converging evidence for distinct neural populations that modulate positively and negatively valence states ( 62 ).

Given that feeding and drinking may be produced through negative reinforcement processes ( 63 – 67 ), it is key to determine whether physiological states can exert control over mesolimbic processes. Techniques such as pharmacology and human neuroimaging, while certainly valuable, lack the temporal resolution and specificity to observe the subsecond nature of motivated behaviors and their associated mechanisms within mesolimbic pathways. Similarly, the distinctions within behavioral processes (e. g., appetitive vs. consummatory behaviors) are often difficult to parse using methods that have low temporal resolution. Thus, the combination of real-time recordings (e. g., electrophysiology, fast-scan cyclic voltammetry, *in vivo* fiber photometry) along with precise control of behavioral and physiological outcomes (e. g., intraoral and intragastric delivery of stimuli) will be critical in understanding the interactions between behavior, physiological state, and mesolimbic phasic dopamine signaling.

## Physiological and Neural Control of Homeostasis

Homeostasis is tightly regulated by a multitude of peripheral physiological processes as well as actions within the brain. These peripheral processes include feedback from various organs (e. g., stomach and intestines; kidneys and vasculature), which use both neural (e. g., vagus nerve) and hormonal routes to relay information regarding homeostatic balance to central nodes that subsequently generate the appropriate behaviors poised to maintain

and reinstate homeostatic balance (e. g., eating, drinking). Here, were provide a brief overview of the central neural processes that are traditionally thought of as “ homeostatic” and how the mesolimbic system has gained prominence as a neural substrate that is sensitive to homeostatic perturbation.

## Feeding and Energy Balance

Energy balance is generally well-maintained by a variety of peripheral signals relating to hunger and satiety. However, feeding behaviors come with their own complexities that often deviate from traditional notions of homeostatic balance. Recent work has focused intensely on investigating digressions in homeostatic energy balance in the context of the obesity epidemic and these studies have been reviewed in a number of recent manuscripts ( 13 , 14 , 68 – 73 ). There is a rich body of literature examining neural controls of energy balance from the perspective of basic homeostatic control and perturbation as well as data suggesting that so-called “ homeostatic” neural substrates are capable of regulating “ reward” related feeding behaviors.

In states of hunger and satiety, hormonal mechanisms and post-ingestive effects on peripheral organs that are relayed to the central nervous system are often critical for initiating and halting feeding behaviors. Indeed, many feeding-related hormones readily enter the brain to control food intake and feeding behaviors. Hypothalamic and hindbrain nuclei have been focused on as primary targets for these hormonal and neural feeding signals. These two brain regions are traditionally associated with maintaining homeostatic energy balance, and their anatomical proximity to ventricular areas with a

permeable blood brain barrier allows for heightened sensitivity to circulating hormones. The pancreas-derived hormone, insulin, a critical hormone for blood glucose regulation, enters the brain to promote satiety and reduce feeding behaviors [reviewed in ( 74 )]. The adipose-derived satiety hormone, leptin, provides a robust satiety signal to hypothalamic and hindbrain nuclei ( 75 – 78 ). Similarly, the gut and hindbrain derived incretin and satiety hormone, glucagon-like peptide-1 (GLP-1), utilizes central processes to reduce food intake and feeding behavior [reviewed in ( 79 )]. Conversely, the stomach-derived hormone, ghrelin, interacts with hypothalamic circuitry to increase food intake ( 80 ).

Perhaps most interesting, however, is the ability of these feeding hormones to engage motivated behaviors via signaling to hypothalamic and hindbrain substrates. For example, insulin administration into the arcuate nucleus of the hypothalamus reduces sucrose self-administration ( 81 ) and ventricular insulin delivery blocks high-fat diet induced conditioned place preference ( 82 ). Leptin receptor signaling in the nucleus of the solitary tract (NTS) reduces food seeking and effort to work for food ( 83 ). Similarly, GLP-1R signaling in the lateral hypothalamic area (LHA) and NTS is critical for motivated responding for food and, interestingly, chronic GLP-1R knockdown in both these regions produces elevated responding for food reward ( 84 , 85 ). Ghrelin also acts on hypothalamic substrates to increase food motivated behaviors via direct ghrelin receptor activation and interactions with feeding-related neuropeptides ( 86 – 88 ). Importantly, these data suggest that homeostatic feeding signals act within hypothalamic and hindbrain nuclei to

not only regulate feeding based on metabolic deficits, but also regulate reward-seeking and goal-directed actions.

To uncover the underlying neural mechanisms that regulate these parallel homeostatic and reward-related phenomena, agouti-related peptide expressing (AgRP) neurons in the arcuate nucleus of the hypothalamus have received a considerable amount of attention, and tremendous effort has been dedicated to examine these substrates as key regulators of energy balance. Besides the classic notion that AgRP neurons convey hunger signals ( 89 ), the ability of these neurons to engage motivated behaviors is striking. Betley and colleagues performed an elegant study examining the type of motivational signal AgRP neurons relay ( 66 ). While feeding can be motivated by intrinsic rewarding properties of food (i. e., positive valence), there is also the possibility that AgRP neurons transmit negative valence signals (i. e., hunger). Indeed, consistent with production of negative affect, optogenetic activation of AgRP neurons was shown to cause avoidance of a flavored, non-nutritive gel as well as avoidance of a location paired with AgRP photostimulation. Overall, these data again reflect the integration between homeostatic perturbation and motivated behaviors where, in this case, animals seek out food in order to restore homeostatic balance, a behavior that is in part motivated by negative valence signals. Others have demonstrated that AgRP neurons are rapidly inhibited by just the sight of food independent of consumption ( 90 ). Given the role of AgRP neurons as interoceptive sensors of hunger states, these data are initially counterintuitive. However, the authors of this study propose that this anticipatory inhibition of AgRP neurons to sensory properties of food acts to

slow food-seeking behaviors once food has been found and in anticipation of restoration from caloric need. Thus, in addition to integrating signals relaying homeostatic state, AgRP neuron activity integrates learned associations with respect to food-related stimuli.

Absorption of nutrients and eventual post-ingestive consequences primarily act to engage satiety mechanisms, with hormonal signals described as one of several downstream outcomes. Alternatively, mechanisms that sense nutrients can profoundly influence motivated behaviors independently of hormonal modulation. For example, flavor-nutrient experiments have been enlightening in understanding the concept of appetition, where the post-ingestive consequences of calorie intake can induce goal-directed behaviors to further consume food. Studies from Sclafani and colleagues have demonstrated that pairing intragastric infusions of carbohydrates (e. g., glucose) or fat with particular flavors can lead to preferential intake of those flavors ( 91 – 95 ). There is still considerable debate about whether these food-seeking behaviors are engaged by sensing of nutrients at the level of the gut (e. g., by glucose transporters) or whether the nutrients are transported in the blood to act directly on the brain ( 96 – 98 ). What is remarkable is that these post-ingestive processes act independently of taste to engage neural processes that guide reward-seeking behaviors ( 99 – 103 ). Thus, in addition to hormonal processing, there is abundant evidence that the actions of nutrients in the periphery are critical for developing relationships between physiological state and motivated behaviors.

Taken together, these data suggest that the presumed “ homeostatic” processes of hunger and satiety are complex and capable of engaging behaviors that are often considered “ reward-related.” Moreover, the collective evidence is consistent with the theme that there are parallel and overlapping circuitries that integrate changes in physiological state with reward-seeking behaviors.

## Body Fluid Homeostasis

Body fluid homeostasis is tightly regulated as sodium deficit and dehydration pose highly threatening challenges to survival. Moreover, the rewarding value of fluids like water and hypertonic saline is heavily dependent on physiological state. A key example of this is the phenomenon of sodium appetite, where motivation to obtain and consume sodium changes drastically depending on body fluid balance. Indeed, sodium deprivation produces a robust, selective, and innate appetite for sodium that is in turn reflected in goal-directed behaviors to seek out and ingest sodium [see ( 104 ) for review]. For example, animals that have never before encountered a hypertonic sodium solution express powerful and preferential intake of it immediately upon sodium depletion ( 105 , 106 ). Other studies have demonstrated that sodium depleted animals will make operant responses for sodium or approach sodium-related cues ( 107 – 109 ). In addition to goal-directed behaviors for acquiring salt, sodium deplete animals show exclusively appetitive taste reactivity to intra-oral infusions of hypertonic sodium in comparison to sodium replete rats that exhibit a mixture of appetitive and aversive taste reactivity ( 110 ). Thus, in states of need, the appetitive value of sodium is profoundly augmented, thus providing an ideal

platform to study the impact of perturbations in homeostasis on goal-directed behaviors and reward encoding.

At the level of the central nervous system, decerebrated rats fail to produce behavioral responses to sodium depletion including increased sodium intake or frequency of saline-induced appetitive taste reactivity, relative to intact animals—suggesting an important role for forebrain structures in regulating behavioral outcomes to changes in body fluid homeostasis ( 111 ). More recent studies have revealed that a subpopulation of neurons in the NTS that express 11-β-hydroxysteroid dehydrogenase type 2 (HSD2) not only powerfully drive sodium appetite in sodium-replete mice, but also project to a number of forebrain regions that control motivated behaviors ( 112 , 113 ). Other research has shown that lesions to the central nucleus of the amygdala disrupt consummatory behaviors in response to sodium depletion ( 114 , 115 ), while lesions to the parabrachial nucleus result in attenuated licking to changing sodium concentrations in sodium depleted rats ( 116 , 117 ). In sodium-deprived states, synchrony has been shown between the lateral hypothalamus, central amygdala, and nucleus accumbens, thus providing evidence that these regions encode the appetitive properties of sodium and its associated goal-directed behaviors based on body fluid state ( 118 ). Collectively, these data emphasize the importance of forebrain neural substrates in body fluid homeostasis and provide a valuable foundation for researchers to use sodium appetite as a powerful means to measure behaviors dependent on physiological state in the context of mesolimbic dopamine signaling.

Intake of water, like sodium, is also highly dependent on an organism's current body fluid state—this is to be expected as thirst and sodium appetite are highly intertwined and act in concert to maintain body fluid homeostasis. Centrally, circumventricular organs play a critical role in detecting blood composition and osmolarity and, under appropriate conditions, generate water seeking and consumption. Indeed, stimulation of circumventricular organs (e. g., subfornical organ, SFO) results in robust water intake in water sated animals and neural activity in these regions is modulated by water intake ( 119 , 120 ). Interestingly, as the neural responses to water intake occur rapidly, it has been proposed that these processes are not directly controlled by changes in blood osmolarity (i. e., a direct response to homeostatic deficit) and are in fact an anticipatory response to changes in homeostatic balance. As such, activity in SFO nitric oxide synthase (NOS) expressing neurons is increased during water restriction and then promptly decreases seconds after subsequent water consumption ( 121 ). The decrease in SFO NOS neural activity occurs well before changes in blood osmolarity suggesting that the SFO is well equipped to anticipate changes in homeostasis. Moreover, data from the same group also suggests that suppressing activity of thirst-promoting SFO neurons is negatively reinforcing and that overall the state of thirst relays a negative-valence signal that motivates an animal to drink to terminate the aversive, thirsty state ( 67 ). These findings parallel studies on AgRP neurons of the arcuate nucleus and their responses to food and food restriction [as described above, ( 66 )]. Interestingly, effects of the thirst-promoting hormone, angiotensin II, may, in part, require learned associations between angiotensin II receptor signaling

and subsequent water intake ( 122 ). These data suggest that the central control of thirst is not limited to basic homeostatic responses and involves complex interactions between physiological state and forebrain processes that allow for the approach, consumption and reinforcement of water in order to restore body fluid homeostasis.

Taken together, there is abundant evidence suggesting that changes in physiological state, particularly those that threaten survival, can profoundly influence motivated behaviors and reward-seeking. This has critical implications for understanding the neural control of these processes and provides a platform through the interaction between homeostatic perturbation and its eventual effects on the mesolimbic dopamine system can be studied.

## Modulation of Mesolimbic Pathways by Changes in Physiological State

The mesolimbic dopamine system represents a neurobiological substrate that can adapt and respond to a variety of conditions that extend well beyond stimulus-reward associations. The data described below provide support for the hypothesis that mesolimbic phasic dopamine signaling through VTA-NAc pathways is poised to respond to changes in physiological state and is a prime example of a neural substrate that integrates both homeostatic and reward processes.

### The Impact of Hunger on Mesolimbic Dopamine Signaling

Hunger is undoubtedly one of the most potent drivers of goal-directed behaviors, and a vast amount of research takes advantage of hunger as a

primary means to study reward-seeking and motivated behaviors. However, it should be emphasized that hunger can powerfully modulate phasic mesolimbic dopamine signaling, can alter goal-directed behaviors toward rewards other than food (e. g., drugs of abuse), and can fundamentally impact the neurophysiology of dopamine neurons. For example, in experiments from Wilson and colleagues, rats were placed in a chamber where access to a palatable liquid meal was restricted by a wire mesh screen. After 10 min, the screen was removed, and the animal was allowed to consume the meal for 20 min. Critically, this task allowed the experimenters to use microdialysis to measure NAc dopamine levels while separating anticipatory (10 min pre-meal period) and consummatory (20 min meal access) behaviors. The results of these experiments revealed that when well-trained animals were food-deprived during a test session, there was a significant increase in NAc dopamine levels during both the anticipatory and consummatory phase of this task, relative to control rats fed *ad libitum* ( 123 ). While the authors of this study claimed that NAc dopamine release is more attributable to consummatory aspects of feeding given that they observed a more robust response during the consummatory phase of their task, the temporal resolution of microdialysis fails to capture subsecond, phasic dopamine signaling in response to food cues. Regardless, this study introduced the importance of hunger states in modulating mesolimbic dopamine signaling. Indeed, food restriction can both increase dopamine neuron firing rate ( 19 ) and reduce dopamine reuptake ( 124 ) and, in addition, food-restricted rats show enhanced extracellular dopamine release in response to extended sucrose intake ( 125 ) [however, see ( 126

)]. Further studies have shown that chronic food restriction results in enhanced burst firing of SNc dopamine neurons, augmentation of cocaine-induced burst firing and, remarkably, persistence of this increased burst firing even after animals are refed ( 127 ). Finally, phasic NAc dopamine release evoked by sugar pellets is elevated in food-restricted rats, relative to *ad libitum* fed rats, as discussed in more detail below ( 128 ). These results have critical implications for how changes in energy balance, in this case the state of hunger, impact the physiological properties of dopamine neurons. Importantly, these findings suggest that homeostatic perturbation can (1) sensitize phasic dopamine signaling to enhance reward seeking for substances critical for survival and (2) alter phasic dopamine signaling to potentially enhance maladaptive reward seeking for substances of abuse.

As described above, alterations in energy balance can potently modulate neurobiological processes within mesolimbic neural pathways. Indeed, these changes can have a robust impact not only on goal-directed behaviors for natural rewards (e. g., food), but also enhance behavioral sensitivity toward other rewarding substances, such as drugs of abuse. Moreover, these processes are a clear example of how mechanisms that are designed to respond to homeostatic perturbations can be molded into behaviors that are maladaptive and viewed as “ reward-related.” In an experiment using a model of drug relapse, rats were trained to self-administer heroin via lever presses, which was followed by a 14-day abstinence period where the rats were removed from operant chambers and underwent either mild food restriction or were allowed *ad libitum* food access. During test sessions in which the levers were available but no reward was administered (i. e.,

extinction parameters), food restricted rats exhibited enhanced heroin-seeking behaviors, as reflected by increased lever responses, relative to food sated rats. Furthermore, these effects can be modulated by both duration of food restriction or re-feeding. As such, reduced duration of food restriction and re-feeding attenuates this enhanced heroin-seeking behavior ( 129 ). Importantly, these data suggest that depending on the physiological state of an organism, it is possible to tune the sensitivity of mesolimbic mediated reward-seeking behaviors. Indeed, using the same behavioral paradigm, D'Cunha and colleagues demonstrated that food restricted animals exhibit increased extracellular dopamine levels in the NAc shell (measured via microdialysis) in response to the heroin-associated context (i. e., self-administration operant chambers) in comparison to sated animals. Interestingly, these effects are attenuated in response to NAc shell D1 receptor blockade, suggesting a putative role of NAc shell D1 receptor signaling in modulating hunger mediated heroin-seeking behaviors ( 130 ). These observations can be seen across other drugs of abuse and by using different reward-related behavioral paradigms. Indeed, with nicotine self-administration, the highest level of self-administration behavior can be seen in animals with the greatest degree of food and weight restriction ( 131 ). Furthermore, food restricted rats show enhanced conditioned place preference (CPP) to cocaine, relative to *ad libitum* fed rats, with food restriction potentiating both the acquisition and the expression of cocaine-induced CPP ( 132 ). Thus, in support of the data described above, food restriction and energy balance have potent effects not only on the

expression of reward-seeking behaviors, but also the acquisition of goal-directed behaviors for natural rewards and a variety of drugs of abuse.

## Body Fluid Homeostasis and Mesolimbic Dopamine Signaling

While much work has focused on the mesolimbic system in the context of food reward [( 27 , 29 , 133 ) for examples], the role of phasic dopamine signaling in body fluid homeostasis is less well understood. However, it is important to emphasize again here that the dependency of the appetitive value of sodium or water on body fluid homeostatic state allows researchers to precisely examine the interaction between perturbations in physiological state with mesolimbic dopamine signaling and goal-oriented behaviors.

Several studies have provided a glimpse into the role of dopamine signaling in controlling body fluid homeostasis and drinking behaviors ( 134 – 137 ). However, few have utilized real-time recording techniques to examine (1) the effects of body fluid balance on mesolimbic pathways; (2) how changes in body fluid balance influence different components of motivated behaviors (i. e., appetitive vs. consummatory); and (3) the neurobiological mechanisms that underlie state dependent mesolimbic dopamine signaling. Early lesion studies using knife cuts demonstrated that cuts medial to the striatum result in severe dopamine depletion as well as persistent eating and drinking deficits, while cuts through the ventral and posterior portions of the striatum, while still impairing animals, had less severe consequences ( 134 ). Given the clear disadvantages of knife cut lesions, it is difficult to fully attribute these behavioral effects to striatal dopamine. However, in a separate study, more selective lesions of SNc-striatal dopamine pathways using 6-hydroxydopamine attenuated drinking behaviors in response to the thirst

promoting hormone, angiotensin II ( 135 ). In pharmacological studies, dopamine receptor blockade has mixed effects. As such, systemic dopamine D2 receptor blockade was shown by one group to decrease the latency to stop drinking ( 136 ), while others showed that similar antagonism produces only modest reductions in total licking during a drinking session ( 137 ). Thus, while these data suggest a putative role of the mesolimbic dopamine system in directing drinking in response to perturbations in body fluid homeostasis, basic pharmacology and lesion studies fail to capture the subsecond processes involved in phasic dopamine responses to perturbations in body fluid homeostasis.

To carefully parse the temporal, behavioral, and mesolimbic components involved in body fluid homeostasis, recent studies from our laboratory combined real-time recording of NAc dopamine release via fast-scan cyclic voltammetry with intraoral delivery of hypertonic saline during varying states of body fluid homeostasis ( 138 ). First, naive rats that had never experienced hypertonic saline were divided into 3 groups: sodium replete, deplete, or re-replete (sodium deplete, then allowed to restore sodium balance). Critically, upon intraoral delivery of hypertonic saline, only sodium deplete animals exhibited a robust, phasic increase in NAc dopamine release and this effect was absent in both replete and re-replete animals. These data are consistent with previous work demonstrating that (1) the rewarding value of sodium is highly dependent on the physiological state of the animal and (2) that animals need not have previous experience with either sodium depletion or hypertonic saline for sodium depletion to alter the value of hypertonic saline. More importantly, these data provide strong evidence that

VTA-NAc phasic dopamine signaling encodes the rewarding value of sodium in a state-dependent manner. Given the importance of VTA-NAc phasic dopamine in encoding discrepancies between predicted and actual outcomes, this study next examined whether cues associated with intraoral hypertonic saline are also capable of evoking phasic dopamine responses. Interestingly, the training history of the rats was critical. Phasic dopamine responses to sodium paired cues from rats trained only under replete conditions, were absent even when rats were subsequently tested under deplete conditions. On the contrary, phasic dopamine responses from rats trained under deplete conditions were robust when also testing under deplete conditions. However, this response appeared flexible and was absent in rats trained under deplete conditions and tested under replete conditions. Thus, both innate and learned responses to sodium are intimately connected with the physiological state of the animal. Moreover, the findings implicate an important role of VTA-NAc phasic dopamine in guiding goal-directed behaviors based on perturbations in body fluid homeostasis.

## Homeostatic Signals are Relayed to Mesolimbic Pathways

Based on the work described above, changes in physiological state and homeostatic perturbation have a key role in modulating mesolimbic pathways and their relevant behavioral outputs. What remains unclear are the gating mechanisms that (1) provide information regarding physiological state to the mesolimbic system and (2) how mesolimbic pathways integrate and relay this information. Fortunately, there are many investigations that provide insight into the mechanisms linking peripheral signals (e. g., hormonal signaling; post-ingestive feedback) and mesolimbic circuitry

(discussed in Section Homeostatic signals are relayed to mesolimbic pathways) as well as the transmission of homeostatic signals through central relays to mesolimbic pathways (Section Neuronal inputs to mesolimbic pathways that regulate homeostasis).

## Direct Hormonal Influences on the Mesolimbic Pathway

Receptors for a multitude of feeding related hormones are expressed throughout the brain including key nodes within the mesolimbic pathway ( 77 , 139 – 143 ). This provides one potential and relatively straightforward mechanism through which perturbations in homeostasis might directly influence mesolimbic physiology. For example, pharmacological activation of GLP-1Rs in the VTA, NAc core, and NAc shell reduces palatable food intake and body weight ( 144 ) and affects responses to drugs of abuse ( 145 – 147 ). Moreover, GLP-1R action within the VTA can alter phasic dopamine signaling as, in our laboratory, we demonstrated that LiCl-induced reductions in stimulated phasic dopamine release can be attenuated by GLP-1R blockade ( 58 ) and that ventricular injections of the GLP-1R agonist, exendin-4, can reduce cocaine-induced phasic dopamine signaling in the NAc core ( 148 ). These effects appear to be due, in part, to altered excitatory drive onto dopamine cell bodies as GLP-1R activation does not alter evoked NAc phasic dopamine release as measured in *ex vivo* brain slices ( 149 ). Other satiety hormones, including amylin and leptin, which have effects on food intake and related behaviors, are also capable of modulating phasic dopamine signaling. Indeed, in addition to VTA amylin receptor activation reducing food intake and food motivated behaviors, amylin receptor signaling in the VTA also reduces NAc core phasic dopamine release ( 150 ).

Moreover, NAc core D1/D2 dopamine receptor activation partially rescues the food intake suppressive effects of VTA amylin receptor activation ( 151 ). It remains possible, though, that some of the effects of amylin may be either indirect, through action in the area postrema or via the calcitonin receptor ( 152 ). VTA amylin signaling also synergistically acts with leptin receptor signaling, where combined activation of receptors for these hormones in the VTA produces weight loss and hypophagia ( 153 ). Leptin receptor signaling in the VTA, similar to the other satiety peptides described above, can independently control energy balance and food motivated behaviors. Intra-VTA administration of leptin reduces food intake, while knockdown of VTA leptin receptors results in hyperphagia and heightened sensitivity to palatable foods ( 154 ). The sustained weight loss from VTA manipulation is yet another example of overlap between the role of the VTA in homeostatic and reward-related functions.

Interestingly, leptin and insulin signaling in the VTA can also reduce excitatory synaptic transmission on to dopamine neurons, attenuate VTA dopamine concentration, and reduce food motivated behaviors ( 154 – 159 ). Leptin can also exert its effects on cocaine-seeking behaviors via attenuation of cocaine-induced increases in NAc dopamine levels ( 160 ) and also reduces dopamine neuron activity ( 154 ). Furthermore, *ob/ob* mice, which lack a functional leptin gene have reduced responses to the psychostimulant, amphetamine, and have reduced dopamine release in NAc ( 155 ). Overall, these data demonstrate that leptin not only has an impact on mesolimbic pathways but is also physiologically critical for the expression of goal-directed behaviors (for either nutritive or non-nutritive substances) and

appropriate functioning of phasic dopamine signaling. However, in the case of insulin, there are a few inconsistencies. In response to insulin, while some have described attenuated VTA dopamine concentration and reduced excitatory synaptic transmission ( 156 – 158 ), others have demonstrated increases in dopamine neuron activity and striatal dopamine release ( 161 , 162 ). In light of this, the net effect of insulin on phasic dopamine activity remains unclear. One intriguing proposal is that local NAc circuits have a critical role in modulating insulin-mediated phasic dopamine signaling ( 162 ). This represents a key mechanism through which VTA and NAc dopamine signaling can independently use homeostatic signals to regulate state-dependent goal-directed behaviors.

Like satiety hormones, peripheral hunger signals can also directly act within VTA-NAc dopamine systems. Ghrelin, a stomach-derived hormone that induces feeding in sated rats (and thus is considered a peripheral “ hunger hormone”), not only has receptors expressed in the VTA and NAc ( 142 ), but also alters phasic dopamine signaling and food motivated behaviors. Physiologically, ghrelin action in the VTA increases dopamine neuronal firing, synaptic plasticity, and NAc dopamine turnover ( 163 ). Pharmacological manipulations have demonstrated that intra-VTA and NAc shell delivery of ghrelin can increase food intake, however, only VTA ghrelin receptor signaling is effective in increasing food motivated behaviors (i. e. operant responding for food reward) ( 164 , 165 ). One possible explanation for this is divergent circuitry from the VTA to other feeding relevant brain regions (e. g., LHA, dorsal striatum). Our laboratory has explored the effects of central ghrelin signaling on phasic dopamine release in the NAc. In awake, behaving

*ad libitum* fed rats, delivery and consumption of sugar pellets reliably evoked modest phasic dopamine release in the NAc core; this release was significantly greater in food-restricted rats. Importantly, the effect of food restriction was recapitulated in *ad libitum* fed rats that were given intracerebroventricular ghrelin during the recording session. Interestingly, this effect was recapitulated by delivery of ghrelin to the LH (targeting orexin positive neurons) but not the VTA directly ( 128 )—supporting multi-synaptic processes in driving phasic dopamine signaling. Furthermore, ghrelin's ability to potentiate phasic dopamine release extends beyond primary food reward, as central administration of ghrelin can also increase NAc phasic dopamine responses to food-predictive cues ( 166 ). Thus, by integrating hormonal signals directly within VTA-NAc pathways, mesolimbic dopamine signaling can relay information relating to both hunger and satiety states to then guide goal-directed behaviors.

## Post-ingestive Caloric Sensing and Cues That Predict Calories

Besides the role of hormonal signaling within mesolimbic dopamine pathways, other post-ingestive consequences of nutrient consumption can impact central neural substrates and subsequently guide goal-directed behaviors. In regards to the neural correlates that mediate caloric sensing and cues associated with calories, mesolimbic dopamine neurons again arise as potential nodes that integrate and relay post-ingestive information.

Several investigations have determined that animals can, independently of taste, use the post-ingestive consequences of nutrient consumption (e. g., carbohydrates and fat) to generate cue-reward associations and that these processes are in part modulated by mesolimbic phasic dopamine signaling (

97 , 99 , 167 – 171 ). For example, while animals are able to generate preferences for both sucrose and non-nutritive saccharin in comparison to water, sucrose preference is substantially greater than saccharin even when matched for sweetness. This is further emphasized in operant conditioning tasks, where animals are more inclined to lever press for nutritive substances (e. g., sucrose) over non-nutritive sweeteners such saccharin or sucralose. Importantly, in *trpm5-/-* mice, which lack sweet taste transduction, these behavioral outcomes persist only with sucrose, albeit with slower temporal occurrence. These results further suggest that motivated behaviors can occur independently of hedonic value, although hedonic value certainly acts synergistically with nutritional value ( 169 ). Furthermore, using fast-scan cyclic-voltammetry, this study revealed greater phasic dopamine signals in the NAc core to delivery of sucrose pellets than to saccharin pellets, suggesting that mesolimbic phasic dopamine is capable of encoding the nutritive value of substances ( 169 ). This is further supported by studies that examined cued associations with nutritive or non-nutritive rewards. From our laboratory, in rats conditioned to associate cues with the delivery of either sucrose or saccharin pellets, we found that sucrose cues evoked greater phasic dopamine release in the NAc core, relative to saccharin cues. Importantly, this difference was greatest when sucrose and saccharin were presented on alternate days during conditioning—giving rats the opportunity to distinguish between post-ingestive consequences of each type of reward. When the nutritive value of these rewards was masked by presenting saccharin and sucrose pellets within the same session, the attenuation of phasic dopamine release to the saccharin cues, relative to sucrose cues, was

reduced although, interestingly, was not abolished ( 170 , 172 ). Overall, these data suggest that while the encoding of hedonic taste value plays a role in modulating phasic dopamine signaling, nutritive value of rewards also contributes strongly to these processes.

Interestingly, mesolimbic dopamine can be highly sensitive to the precise caloric content of nutrients. Fat, similar to sucrose and glucose, also elicits post-ingestive feedback mechanisms that influence goal-directed behaviors ( 171 , 173 – 175 ). When fat is delivered intragastrically, dorsal striatal dopamine levels increase in parallel with increasing caloric density of fat infusions, and dopamine receptor blockade impairs an animal's ability to regulate caloric intake ( 176 ). These data suggest that mesolimbic dopamine signaling not only regulates caloric sensing, but also relays a signal reflecting the magnitude of caloric content.

The mechanisms regulating caloric sensing and hormonal regulation of energy balance, while intertwined, can also exhibit dissociable processes. In experiments involving intragastric infusions of glucose, disruption of glucose metabolism with intravenous 2-DG was shown to reduce striatal dopamine levels. Interestingly, this reduction was rescued with subsequent intravenous glucose administration ( 168 ). In a separate study, delivery of low concentrations of glucose into hepatic-portal vein was shown to increase spontaneous phasic dopamine release events in the NAc shell ( 97 ). Thus, in addition to peripheral hormonal signals, which relay homeostatic state and taste information encoding hedonic value, peripheral nutrient sensing and

post-ingestive feedback signals are also critical mechanisms that regulate mesolimbic dopamine signaling in response to homeostatic perturbation.

The data described above have covered dopamine signaling in response to calories in both the dorsal and ventral striatum—brain regions that have been previously attributed to dissociable functions in regards to motivated behaviors ( 177 ). Indeed, recent evidence has suggested that dorsal and ventral striatal dopamine pathways are differentially modulated by caloric content and hedonic value. As such, intake of non-nutritive sucralose was shown to increase ventral striatal dopamine levels, however, increases in dopamine within the dorsal striatum only occurred when sucralose intake was paired with intragastric glucose. Moreover, when intragastric glucose infusions were paired with the taste of a bitter compound, ventral striatal dopamine was unresponsive, relative to baseline, while dorsal striatal dopamine levels were augmented ( 103 ). Taken together, these results provide evidence for separate striatal circuits that regulate hedonic value or post-ingestive reinforcement. However, questions remain regarding whether hedonic value and caloric value are processed either through distinct dorsal vs. ventral striatal pathways or via integrated pathways within these brain regions. Regional specificity of phasic dopamine signals remains a subject of intense study ( 178 – 180 ).

## Neuronal Inputs to Mesolimbic Pathways That Regulate Homeostasis

While physiological state information can be relayed to the mesolimbic system directly via hormones, the VTA and NAc also receive extensive neuronal projections from a multitude of neural substrates that are involved

in processing homeostatic information. This provides an alternative, yet complementary, mechanism through which physiological state information is integrated prior to being transmitted to the mesolimbic dopamine system.

## Hindbrain Inputs

Hindbrain neural processes are capable of modulating goal-oriented behaviors and reward ( 83 , 84 , 144 ). Thus, it is unsurprising that homeostatic information that is relayed to hindbrain neural substrates can be transmitted to mesolimbic dopamine pathways. Indeed, the NTS has a direct projection to both VTA and NAc (181) and homeostatic feeding circuits, such as GLP-1 expressing neurons in the NTS, provide input to the VTA ( 144 ). Interestingly, NTS GLP-1R activation alters the expression of dopamine-related genes in the VTA ( 182 ). These data suggest that, besides direct homeostatic signaling to mesolimbic circuitry, these signals can be initially gated by hindbrain processes before being relayed to the mesolimbic circuits. Further support for this hypothesis can be observed in animals with lesions to the area postrema (AP) and parabrachial nucleus (PBN) - while amylin receptor activation can reduce VTA stimulated dopamine release in the NAc in control animals, these effects are abolished in animals with either AP or PBN lesions ( 152 ).

Brainstem subregions that regulate body fluid homeostasis also have projections to the mesolimbic pathway. Within the NTS, a subset of neurons expressing 11-β-hydroxysteroid dehydrogenase type 2 (HSD2) are particularly sensitive to sodium depletion and signals that relay sodium deficiency ( 112 ) and in turn project to the AP ( 183 ). While these HSD2 neurons have sparse projections to the VTA, there are monosynaptic VTA

projections to the pre-locus coeruleus (pre-LC) and external lateral PBN (PBel-inner) ( 184 ). Importantly, within the pre-LC and PBel-inner, sodium sensitive neurons that express Forkhead box protein 2 (FoxP2) have direct projections to the VTA. Thus, one logical pathway through which sodium deficiency and body fluid homeostasis is relayed to mesolimbic pathways is via a polysynaptic pathway that traverses through NTS/AP HSD2 neurons → Pre-LC/PBel-inner FoxP2 neurons → VTA dopamine neuron circuitry ( 104 ).

## Midbrain Inputs

Besides hindbrain projections, the VTA also receives extensive input from midbrain substrates that regulate homeostatic processes. In particular, the lateral dorsal tegmental area (LDTg) projections to the VTA ( 185 , 186 ) have been identified as one pathway that regulates homeostatic functions and goal-directed behaviors. Additionally, the LDTg is critical for maintaining both burst and tonic firing of VTA dopamine neurons ( 187 , 188 ). Interestingly, animals can be trained to self-administer optogenetic activation of LDTg inputs to the VTA ( 189 ), which in turn increases NAc dopamine levels ( 190 ). Additionally, excitation of cholinergic or glutamatergic LDTg input to the VTA produces conditioned place preference for opioids ( 191 ). Overall, these data provide support for LDTg to VTA pathways in modulating reward, however, whether homeostatic changes can mediate this pathway remains understudied. Nonetheless, the LDTg is anatomically poised to use homeostatic signals. The LDTg receives input from the NTS ( 192 ) and expresses receptors for hormones that regulate energy balance ( 140 , 141 ). Recent data have also demonstrated that GLP-1 ( 193 ) and amylin receptor activation ( 193 ) in the LDTg reduces food

intake and motivated behaviors. Collectively, midbrain LDTg input to the VTA is critical for VTA function, and this system reflects yet another parallel pathway through which homeostasis and reward interact.

Other midbrain inputs to the VTA, including the pedunculopontine tegmental nucleus (PPTg) can modulate goal-directed behaviors and putative homeostatic functions. For example, the PPTg sends cholinergic and glutamatergic input to the VTA ( 194 – 196 ), modulates burst firing of VTA neurons ( 197 ), and interacts with the VTA, along with other limbic structures, to regulate reinstatement of cocaine seeking ( 198 ). In the context of homeostasis, others have demonstrated that PPTg lesions block food conditioned place preference in food-sated, but not food-deprived rats ( 199 ). Moreover, melanin-concentrating hormone (MCH) and orexin producing neurons from the LHA send projections to the PPTg ( 200 ), although the role of this pathway in modulating energy balance is unknown. Thus, while the PPTg appears to have putative roles in regulating homeostatic balance and goal-directed behaviors, the precise interactions between PPTg, homeostatic perturbations, and phasic dopamine signaling remains to be determined.

## Forebrain Inputs

Hypothalamic nuclei in the forebrain, as we have briefly discussed, consist of classic homeostatic neural regulators. In parallel with hindbrain and midbrain pathways, hypothalamic brain regions, in particular the lateral hypothalamic area (LHA), send direct and reciprocal projections to the 3 , 201 – 207 ) and provide another set of circuits through which homeostatic signals can be relayed to the mesolimbic dopamine system. Several studies have delved

into the role of LHA-VTA pathways in reward related behaviors, while others have assessed the relationship between homeostatic LHA signaling and the VTA. Photostimulation of GABAergic LHA-VTA pathways results in increased NAc dopamine release and promotes approach behaviors ( 208 ). Interestingly, animals will self-administer photostimulation of LHA-VTA pathways, an effect that is mediated by neurotensin transmission ( 203 ). Polysynaptic pathways to the NAc can also modulate reward seeking. For example, LHA CART (cocaine and amphetamine regulated transcript) neurons that project to the paraventricular thalamic nucleus (PVT) promote reward behaviors, which can then be attenuated by glutamate receptor blockade in the NAc shell ( 209 ).

In the context of homeostatic regulation, there have been some efforts to delineate the relationship between hormonal signals, the LHA, and VTA dopamine signaling. The LHA contains a subpopulation of neurons that produce orexin, a neuropeptide that interacts with feeding hormones and drugs of abuse ( 80 , 210 – 223 ), which then project to many sites throughout the brain, the VTA among them. It has been demonstrated *in vitro* that leptin administration can reduce excitatory synaptic strength between LHA orexin neurons and the VTA and that these effects can be attenuated by fasting or high-fat diet induced obesity ( 224 ). Additionally, energy balance can be regulated through LHA neurotensin neurons that also express leptin receptors. These in turn modulate local LHA orexin neurons that subsequently impact mesolimbic pathways ( 225 ). Finally, we have demonstrated in our laboratory that the hyperphagic effects of central ghrelin administration can be blunted by intra-VTA administration of orexin

receptor antagonist and that ghrelin injected directly into LHA recapitulates the effect of ICV ghrelin on phasic dopamine signaling whereas, interestingly, intra-VTA ghrelin does not ( 128 ).

Neurons in the LHA are also sensitive to levels of circulating nutrients and this may be a route by which nutritional value is relayed to mesolimbic circuitry ( 226 – 229 ). Along these lines, MCH neurons in LHA are excited by physiological increases in extracellular glucose ( 228 ). These neurons project to VTA and optogenetic activation of their terminals biases preference for the non-nutritive sweetener, sucralose, relative to sucrose. Interestingly, co-activation of these terminals while mice are drinking water is not sufficient to shift their preference away from sucrose, indicating that taste is involved and is presumably integrated with nutritive value as relayed by MCH neuron activation. In addition, the same manipulation, activation of MCH neuron terminals in VTA, elevates dopamine levels in NAc ( 230 ). Collectively, the data described above are a prime example of how reward-seeking is modulated by changes to physiological state and, moreover, show how hypothalamic to VTA circuits can act in concert with hindbrain and midbrain VTA pathways to dynamically regulate homeostatic responses and goal-directed behaviors.

Growing evidence now supports forebrain structures involved in executive functions such as learning, memory, and decision making, as sites for homeostatic signaling ( 14 , 231 – 233 ). Of particular interest are pathways originating from the ventral subregion of the hippocampus (vHP), which have been shown to interact with phasic dopamine signaling ( 234 ) as well as to

integrate homeostatic signals ( 235 – 237 ). For example, ghrelin administration to the vHP increases food intake and reward seeking and increases phosphorylated tyrosine hydroxylase within the NAc ( 236 ). Further studies have demonstrated that vHP ghrelin signaling requires downstream communication to LHA orexin neurons ( 238 ), providing putative evidence for a polysynaptic pathway between the vHP, LHA, and VTA. The vHP also has the capability of bidirectionally modulating feeding behaviors, as GLP-1R signaling in the vHP potently reduces food intake and motivated behaviors ( 237 ). Additionally, these effects are mediated by vHP to medial prefrontal cortex pathways (mPFC) ( 239 ). The mPFC to NAc projections have been implicated in a variety of phasic dopamine-related functions ( 240 – 243 ) and mPFC dopamine signaling has been shown to have a role in modulating energy balance and feeding ( 242 ). Together, these data provide another polysynaptic pathway (e. g. VTA→mPFC→NAc) through which homeostatic perturbation might impact phasic dopamine signaling. Overall, these data emphasize the notion that pathways that regulate homeostasis and goal-directed behaviors are remarkably complex, and the degree to which information regarding physiological state is relayed to mesolimbic dopamine pathways is not limited to peripheral, hindbrain, or midbrain input.

## Conclusions and Considerations

In the current review, we have emphasized the notion that there is substantial overlap between homeostatic and reward-related neural processes. More specifically, existing data support complex, dynamic, and parallel neural pathways that integrate physiological state and goal-directed

behaviors. Accordingly, mesolimbic phasic dopamine signaling represents one of many central mechanisms through which these integrative processes can occur.

However, many questions remain to be addressed. First, the intricacies between phasic burst firing of VTA dopamine cell bodies and terminal dopamine release in the NAc are under evaluation. While we have described heterogeneity of VTA dopamine neurons in processing positive vs. negative valence, the electrophysiological activity of individual NAc neurons is also intimately tuned to either rewarding or aversive stimuli and can be shaped toward cues that predict these stimuli ( 244 ). Of course, while VTA dopamine neuron activity and phasic burst firing of VTA neurons robustly mediates terminal dopamine release and reuptake ( 22 , 245 ), several investigations have proposed the notion that NAc neurons are capable of modulating terminal release of dopamine independently of VTA cell bodies ( 24 – 26 ). For example, optogenetic activation of NAc cholinergic interneurons increases extracellular dopamine ( 25 , 26 ) that is in turn modulated by the endocannabinoid system and prefrontal cortical afferents to the NAc ( 245 ). In the context of homeostatic modulation of phasic dopamine signaling, we have briefly described the effects of insulin on NAc dopamine release. Data from Stouffer and colleagues have emphasized the role of cholinergic interneurons (which express insulin receptors) in modulating the insulin-mediated increases in dopamine levels within the striatum ( 162 ). Collectively, the possibility of local NAc circuitry and NAc input from other brain regions in modulating dopamine release should be a focal topic in conjunction with perturbations in homeostasis.

Next, we have described the ability of phasic dopamine signaling to respond to a variety of different perturbations to homeostasis, however, whether the responses of the mesolimbic dopamine system to varying physiological states utilizes overlapping or distinct output pathways is unknown. Given the variety of inputs to the VTA, as we have described above, it seems highly likely that these inputs are capable of engaging distinct subpopulations of VTA neurons whose signals are subsequently integrated to generate a specific behavioral outcome. For example, in the case of feeding and energy balance, it would be enlightening to determine whether the receptors for feeding hormones are co-expressed on the same neuronal populations within the VTA and how anorexigenic and orexigenic peptides interact through local VTA circuits to impact phasic dopamine signaling. In a similar vein, the degree to which perturbations in body fluid homeostasis can impact mechanisms regulating energy balance at the level of the VTA should also be examined. Eating and drinking are intimately linked and it is well known that eating stimulates thirst and dehydration induces anorexia [excellently reviewed in ( 246 )]. Moreover, temporal differences in signaling pathways between this mixture of hormones might also affect these interactions. Indeed, what is left to be reconciled is the slow temporal action of peripheral hormone or nutrient signaling to the brain, relative to the rapid subsecond actions of phasic dopamine signaling.

In light of the data presented here, the endogenous relevance of phasic dopamine signaling in regulating behavioral responses to homeostatic perturbations requires further study. We briefly describe work that attributes phasic dopamine signaling as a “ teaching signal” that strengthens

associations and guides behaviors toward stimuli that are advantageous for an animal. Indeed, some have argued that phasic dopamine signaling is in large part mediating approach/appetitive behaviors toward cues associated with high subjective utility (e. g., incentive salience) as opposed to consummatory behaviors ( 47 , 50 ). The question that remains, however, is how the robust influence of homeostatic perturbation on phasic dopamine signaling subsequently impacts particular behavioral components that are related to motivation and goal direction. One possibility is that homeostatic need states tune phasic dopamine signaling to engage appetitive behaviors toward stimuli that are relevant for the need state. For example, in a sodium deplete state, this physiological state might tune phasic dopamine signaling to engage appetitive behaviors for obtaining sodium, while responses for food reward are attenuated. Whether VTA-NAc pathways are physiologically relevant for these behavioral outputs remains to be seen. Thus, for future studies, researchers might use loss-of-function experiments (e. g., optogenetic inhibition of dopamine neurons) to determine what characteristics of goal-directed behaviors (e. g., appetitive, consummatory) are impacted during varying states of need.

Finally, the interaction between sex differences, homeostasis, and phasic dopamine signaling requires extensive examination. Several recent studies have demonstrated that the effects of central homeostatic signaling are sex dimorphic. For example, female rats have higher levels of LHA ghrelin receptor expression than males, and acute blockade of LHA ghrelin receptors in females, but not males, reduces food intake, body weight, and food seeking behaviors ( 88 ). Central GLP-1R activity also reveals sex

dimorphism, where broad activation of GLP-1Rs results in greater suppression in food motivated behaviors in female compared to male rats along with interactions with estrogen signaling ( 247 ). Interestingly, these results appear to vary depending on brain region, as LHA GLP-1R knockdown or blockade increases food motivation only in male rats ( 85 ). Examination of sex differences in body fluid homeostasis are also in progress. Recent studies have revealed an effect of sex on thirst, including increased water intake in male rats compared to female rats in response to angiotensin II ( 248 ), a lack of desensitization to repeated angiotensin II administration in female rats ( 249 ), and interactions of thirst and estrogens ( 250 ). Thus, future work should examine whether these sex dimorphisms in homeostatic regulation are reflected in mesolimbic phasic dopamine signaling.

While questions remain, a putative mechanism arises whereby neurons in the VTA are readily able to burst fire in response to homeostatic perturbation and the presence of state-relevant stimuli (e. g., food, cues predicting food); this in turn modulates the degree to which phasic dopamine increases occur in striatal targets—in particular the NAc. The result of the phasic increase could be to alter ongoing NAc activity as well as plasticity in the service of guiding motivated behaviors. Future research conducted with a special emphasis on the impact of physiological state on mesolimbic dopamine signaling will be critical in furthering our understanding of maladaptive behaviors with the eventual goal of effectively treating prominent health issues such as obesity and drug addiction.

## Author Contributions

TH, JM, and MR conceived the scope of the manuscript. TH generated drafts. JM and MR provided critical discussion, edits and comments. TH, JM, and MR approved the final version of the manuscript.

## Funding

This work was supported by the National Institutes of Health [DA025634 (MR)].

## Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## References

1. Margules DL, Olds J. Identical " feeding" and " rewarding" systems in the lateral hypothalamus of rats. *Science* (1962) 135: 374–5. doi: 10. 1126/science. 135. 3501. 374

PubMed Abstract | CrossRef Full Text | Google Scholar

2. Weingarten HP. Conditioned cues elicit feeding in sated rats: a role for learning in meal initiation. *Science* (1983) 220: 431–3.

PubMed Abstract | Google Scholar

3. Kelley AE, Baldo BA, Pratt WE. A proposed hypothalamic-thalamic-striatal axis for the integration of energy balance, arousal, and food reward. *J Comp Neurol* . (2005) 493: 72–85. doi: 10. 1002/cne. 20769

PubMed Abstract | CrossRef Full Text | Google Scholar

4. Zheng H, Lenard NR, Shin AC, Berthoud HR. Appetite control and energy balance regulation in the modern world: reward-driven brain overrides repletion signals. *Int J Obes.* (2009) 33 (Suppl. 2): S8–13. doi: 10. 1038/ijo. 2009. 65

PubMed Abstract | CrossRef Full Text | Google Scholar

5. Berridge KC, Ho CY, Richard JM, Difeliceantonio AG. The tempted brain eats: pleasure and desire circuits in obesity and eating disorders. *Brain Res* . (2010) 1350: 43–64. doi: 10. 1016/j. brainres. 2010. 04. 003

PubMed Abstract | CrossRef Full Text | Google Scholar

6. Kenny PJ. Common cellular and molecular mechanisms in obesity and drug addiction. *Nat Rev Neurosci* . (2011) 12: 638–51. doi: 10. 1038/nrn3105

PubMed Abstract | CrossRef Full Text | Google Scholar

7. Hoebel BG, Teitelbaum P. Hypothalamic control of feeding and self-stimulation. *Science* (1962) 135: 375–7. doi: 10. 1126/science. 135. 3501. 375

PubMed Abstract | CrossRef Full Text | Google Scholar

8. Hernandez L, Hoebel BG. Feeding and hypothalamic stimulation increase dopamine turnover in the accumbens. *Physiol Behav* . (1988) 44: 599–606. doi: 10. 1016/0031-9384(88)90324-1

PubMed Abstract | CrossRef Full Text | Google Scholar

9. Kelley AE, Berridge KC. The neuroscience of natural rewards: relevance to addictive drugs. *J Neurosci* . (2002) 22: 3306–11. doi: 10. 1523/JNEUROSCI. 22-09-03306. 2002

PubMed Abstract | CrossRef Full Text | Google Scholar

10. Saper CB, Chou TC, Elmquist JK. The need to feed: homeostatic and hedonic control of eating. *Neuron* (2002) 36: 199–211. doi: 10. 1016/S0896-6273(02)00969-8

PubMed Abstract | CrossRef Full Text | Google Scholar

11. Palmiter RD. Is dopamine a physiologically relevant mediator of feeding behavior? *Trends Neurosci* . (2007) 30: 375–81. doi: 10. 1016/j. tins. 2007. 06. 004

CrossRef Full Text | Google Scholar

12. Lutter M, Nestler EJ. Homeostatic and hedonic signals interact in the regulation of food intake. *J Nutr* . (2009) 139: 629–32. doi: 10. 3945/jn. 108. 097618

PubMed Abstract | CrossRef Full Text | Google Scholar

13. Ferrario CR, Labouebe G, Liu S, Nieh EH, Routh VH, Xu S, et al. Homeostasis meets motivation in the battle to control food intake. *J Neurosci* . (2016) 36: 11469–81. doi: 10. 1523/JNEUROSCI. 2338-16. 2016

PubMed Abstract | CrossRef Full Text | Google Scholar

14. Liu CM, Kanoski SE. Homeostatic and non-homeostatic controls of feeding behavior: distinct vs. common neural systems. *Physiol Behav* . (2018) 193(Pt. B): 223–31 doi: 10. 1016/j. physbeh. 2018. 02. 011

PubMed Abstract | CrossRef Full Text | Google Scholar

15. Rossi MA, Stuber GD. Overlapping brain circuits for homeostatic and hedonic feeding. *Cell Metab* . (2018) 27: 42–56. doi: 10. 1016/j. cmet. 2017. 09. 021

PubMed Abstract | CrossRef Full Text | Google Scholar

16. Grace AA, Bunney BS. Intracellular and extracellular electrophysiology of nigral dopaminergic neurons−1. Identification and characterization . *Neuroscience* (1983) 10: 301–15. doi: 10. 1016/0306-4522(83)90135-5

PubMed Abstract | CrossRef Full Text | Google Scholar

17. Grace AA, Bunney BS. Intracellular and extracellular electrophysiology of nigral dopaminergic neurons−2. Action potential generating mechanisms and morphological correlates . *Neuroscience* (1983) 10: 317–31. doi: 10. 1016/0306-4522(83)90136-7

PubMed Abstract | CrossRef Full Text | Google Scholar

18. Grace AA, Bunney BS. The control of firing pattern in nigral dopamine neurons: burst firing. *J Neurosci* . (1984) 4: 2877–90. doi: 10. 1523/JNEUROSCI. 04-11-02877. 1984

PubMed Abstract | CrossRef Full Text | Google Scholar

19. Marinelli M, Rudick CN, Hu XT, White FJ. Excitability of dopamine neurons: modulation and physiological consequences. *CNS Neurol Disord Drug Targets* (2006) 5: 79–97. doi: 10. 2174/187152706784111542

PubMed Abstract | CrossRef Full Text | Google Scholar

20. Marinelli M, Mccutcheon JE. Heterogeneity of dopamine neuron activity across traits and states. *Neuroscience* (2014) 282: 176–97. doi: 10. 1016/j. neuroscience. 2014. 07. 034

PubMed Abstract | CrossRef Full Text | Google Scholar

21. Surmeier DJ, Carrillo-Reid L, Bargas J. Dopaminergic modulation of striatal neurons, circuits, and assemblies. *Neuroscience* (2011) 198: 3–18. doi: 10. 1016/j. neuroscience. 2011. 08. 051

PubMed Abstract | CrossRef Full Text | Google Scholar

22. Sulzer D, Cragg SJ, Rice ME. Striatal dopamine neurotransmission: regulation of release and uptake. *Basal Ganglia* (2016) 6: 123–48. doi: 10. 1016/j. baga. 2016. 02. 001

PubMed Abstract | CrossRef Full Text | Google Scholar

23. Owesson-White CA, Roitman MF, Sombers LA, Belle AM, Keithley RB, Peele JL, et al. Sources contributing to the average extracellular concentration of dopamine in the nucleus accumbens. *J Neurochem* . (2012) 121: 252–62. doi: 10. 1111/j. 1471-4159. 2012. 07677. x

PubMed Abstract | CrossRef Full Text | Google Scholar

24. Cachope R, Mateo Y, Mathur BN, Irving J, Wang HL, Morales M, et al. Selective activation of cholinergic interneurons enhances accumbal phasic dopamine release: setting the tone for reward processing. *Cell Rep* . (2012) 2: 33–41. doi: 10. 1016/j. celrep. 2012. 05. 011

PubMed Abstract | CrossRef Full Text | Google Scholar

25. Threlfell S, Lalic T, Platt NJ, Jennings KA, Deisseroth K, Cragg SJ. Striatal dopamine release is triggered by synchronized activity in cholinergic interneurons. *Neuron* (2012) 75: 58–64. doi: 10. 1016/j. neuron. 2012. 04. 038

PubMed Abstract | CrossRef Full Text | Google Scholar

26. Cachope R, Cheer JF. Local control of striatal dopamine release. *Front Behav Neurosci* . (2014) 8: 188. doi: 10. 3389/fnbeh. 2014. 00188

PubMed Abstract | CrossRef Full Text | Google Scholar

27. Roitman MF, Stuber GD, Phillips PE, Wightman RM, Carelli RM. Dopamine operates as a subsecond modulator of food seeking. *J Neurosci* . (2004) 24: 1265–71. doi: 10. 1523/JNEUROSCI. 3823-03. 2004

PubMed Abstract | CrossRef Full Text | Google Scholar

28. Cheer JF, Aragona BJ, Heien ML, Seipel AT, Carelli RM, Wightman RM. Coordinated accumbal dopamine release and neural activity drive goal-

directed behavior. *Neuron* (2007) 54: 237–44. doi: 10. 1016/j. neuron. 2007. 03. 021

PubMed Abstract | CrossRef Full Text | Google Scholar

29. Day JJ, Roitman MF, Wightman RM, Carelli RM. Associative learning mediates dynamic shifts in dopamine signaling in the nucleus accumbens. *Nat Neurosci* . (2007) 10: 1020–8. doi: 10. 1038/nn1923

PubMed Abstract | CrossRef Full Text | Google Scholar

30. Tsai HC, Zhang F, Adamantidis A, Stuber GD, Bonci A, De Lecea L, et al. Phasic firing in dopaminergic neurons is sufficient for behavioral conditioning. *Science* (2009) 324: 1080–4. doi: 10. 1126/science. 1168878

PubMed Abstract | CrossRef Full Text | Google Scholar

31. Day JJ, Jones JL, Wightman RM, Carelli RM. Phasic nucleus accumbens dopamine release encodes effort- and delay-related costs. *Biol Psychiatry* (2010) 68: 306–9. doi: 10. 1016/j. biopsych. 2010. 03. 026

PubMed Abstract | CrossRef Full Text | Google Scholar

32. Saunders BT, Robinson TE. The role of dopamine in the accumbens core in the expression of Pavlovian-conditioned responses. *Eur J Neurosci* . (2012) 36: 2521–32. doi: 10. 1111/j. 1460-9568. 2012. 08217. x

PubMed Abstract | CrossRef Full Text | Google Scholar

33. Steinberg EE, Keiflin R, Boivin JR, Witten IB, Deisseroth K, Janak PH. A causal link between prediction errors, dopamine neurons and learning. *Nat Neurosci* . (2013) 16: 966–73. doi: 10. 1038/nn. 3413

PubMed Abstract | CrossRef Full Text | Google Scholar

34. Schultz W, Carelli RM, Wightman RM. Phasic dopamine signals: from subjective reward value to formal economic utility. *Curr Opin Behav Sci* . (2015) 5: 147–54. doi: 10. 1016/j. cobeha. 2015. 09. 006

PubMed Abstract | CrossRef Full Text | Google Scholar

35. Berke JD. What does dopamine mean? *Nat Neurosci* . (2018) 21: 787–93. doi: 10. 1038/s41593-018-0152-y

CrossRef Full Text | Google Scholar

36. Schultz W. Behavioral dopamine signals. *Trends Neurosci* . (2007) 30: 203–10. doi: 10. 1016/j. tins. 2007. 03. 007

PubMed Abstract | CrossRef Full Text | Google Scholar

37. Schultz W. Updating dopamine reward signals. *Curr Opin Neurobiol* . (2013) 23: 229–38. doi: 10. 1016/j. conb. 2012. 11. 012

PubMed Abstract | CrossRef Full Text | Google Scholar

38. Hollerman JR, Schultz W. Dopamine neurons report an error in the temporal prediction of reward during learning. *Nat Neurosci* . (1998) 1: 304–9. doi: 10. 1038/1124

PubMed Abstract | CrossRef Full Text | Google Scholar

39. Carelli RM. The nucleus accumbens and reward: neurophysiological investigations in behaving animals. *Behav Cogn Neurosci Rev* . (2002) 1: 281–96. doi: 10. 1177/1534582302238338

PubMed Abstract | CrossRef Full Text | Google Scholar

40. Carelli RM. Nucleus accumbens cell firing and rapid dopamine signaling during goal-directed behaviors in rats. *Neuropharmacology* (2004) 47 (Suppl. 1): 180–9. doi: 10. 1016/j. neuropharm. 2004. 07. 017

PubMed Abstract | CrossRef Full Text | Google Scholar

41. Colombo M. Deep and beautiful. The reward prediction error hypothesis of dopamine . *Stud Hist Philos Biol Biomed Sci* . (2014) 45: 57–67. doi: 10. 1016/j. shpsc. 2013. 10. 006

PubMed Abstract | CrossRef Full Text | Google Scholar

42. Lak A, Stauffer WR, Schultz W. Dopamine neurons learn relative chosen value from probabilistic rewards. *Elife* (2016) 5: e18044. doi: 10. 7554/eLife. 18044

PubMed Abstract | CrossRef Full Text | Google Scholar

43. Schultz W. Dopamine reward prediction-error signalling: a two-component response. *Nat Rev Neurosci* . (2016) 17: 183–95. doi: 10. 1038/nrn. 2015. 26

PubMed Abstract | CrossRef Full Text | Google Scholar

44. Schultz W. Predictive reward signal of dopamine neurons. *J Neurophysiol* . (1998) 80: 1–27. doi: 10. 1152/jn. 1998. 80. 1. 1

PubMed Abstract | CrossRef Full Text | Google Scholar

45. Montague PR, Dayan P, Sejnowski TJ. A framework for mesencephalic dopamine systems based on predictive Hebbian learning. *J Neurosci* . (1996) 16: 1936–47. doi: 10. 1523/JNEUROSCI. 16-05-01936. 1996

PubMed Abstract | CrossRef Full Text | Google Scholar

46. Robinson TE, Berridge KC. The neural basis of drug craving: an incentive-sensitization theory of addiction. *Brain Res Rev* . (1993) 18: 247–91. doi: 10. 1016/0165-0173(93)90013-P

PubMed Abstract | CrossRef Full Text | Google Scholar

47. Berridge KC. From prediction error to incentive salience: mesolimbic computation of reward motivation. *Eur J Neurosci* . (2012) 35: 1124–43. doi: 10. 1111/j. 1460-9568. 2012. 07990. x

PubMed Abstract | CrossRef Full Text | Google Scholar

48. Berridge KC, Robinson TE. Liking, wanting, and the incentive-sensitization theory of addiction. *Am Psychol* . (2016) 71: 670–9. doi: 10. 1037/amp0000059

PubMed Abstract | CrossRef Full Text | Google Scholar

49. Difeliceantonio AG, Berridge KC. Dorsolateral neostriatum contribution to incentive salience: opioid or dopamine stimulation makes one reward cue more motivationally attractive than another. *Eur J Neurosci* . (2016) 43: 1203–18. doi: 10. 1111/ejn. 13220

PubMed Abstract | CrossRef Full Text | Google Scholar

50. Salamone JD, Pardo M, Yohn SE, Lopez-Cruz L, Sanmiguel N, Correa M. Mesolimbic dopamine and the regulation of motivated behavior. *Curr Top Behav Neurosci* . (2016) 27: 231–57. doi: 10. 1007/7854_2015_383

PubMed Abstract | CrossRef Full Text | Google Scholar

51. Keltner JR, Furst A, Fan C, Redfern R, Inglis B, Fields HL. Isolating the modulatory effect of expectation on pain transmission: a functional magnetic resonance imaging study. *J Neurosci* . (2006) 26: 4437–43. doi: 10. 1523/JNEUROSCI. 4463-05. 2006

PubMed Abstract | CrossRef Full Text | Google Scholar

52. Baliki MN, Geha PY, Fields HL, Apkarian AV. Predicting value of pain and analgesia: nucleus accumbens response to noxious stimuli changes in the presence of chronic pain. *Neuron* (2010) 66: 149–60. doi: 10. 1016/j. neuron. 2010. 03. 002

PubMed Abstract | CrossRef Full Text | Google Scholar

53. Navratilova E, Xie JY, Okun A, Qu C, Eyde N, Ci S, et al. Pain relief produces negative reinforcement through activation of mesolimbic reward-

valuation circuitry. *Proc Natl Acad Sci USA* . (2012) 109: 20709–13. doi: 10. 1073/pnas. 1214605109

PubMed Abstract | CrossRef Full Text | Google Scholar

54. Oleson EB, Gentry RN, Chioma VC, Cheer JF. Subsecond dopamine release in the nucleus accumbens predicts conditioned punishment and its successful avoidance. *J Neurosci* . (2012) 32: 14804–8. doi: 10. 1523/JNEUROSCI. 3087-12. 2012

PubMed Abstract | CrossRef Full Text | Google Scholar

55. Roitman MF, Wheeler RA, Wightman RM, Carelli RM. Real-time chemical responses in the nucleus accumbens differentiate rewarding and aversive stimuli. *Nat Neurosci* . (2008) 11: 1376–7. doi: 10. 1038/nn. 2219

PubMed Abstract | CrossRef Full Text | Google Scholar

56. Mccutcheon JE, Ebner SR, Loriaux AL, Roitman MF. Encoding of aversion by dopamine and the nucleus accumbens. *Front Neurosci* (2012) 6: 137. doi: 10. 3389/fnins. 2012. 00137

PubMed Abstract | CrossRef Full Text | Google Scholar

57. Twining RC, Wheeler DS, Ebben AL, Jacobsen AJ, Robble MA, Mantsch JR, et al. Aversive stimuli drive drug seeking in a state of low dopamine tone. *Biol Psychiatry* (2015) 77: 895–902. doi: 10. 1016/j. biopsych. 2014. 09. 004

PubMed Abstract | CrossRef Full Text | Google Scholar

58. Fortin SM, Chartoff EH, Roitman MF. The aversive agent lithium chloride suppresses phasic dopamine release through central GLP-1 receptors. *Neuropsychopharmacology* (2016) 41: 906–15. doi: 10. 1038/npp. 2015. 220

PubMed Abstract | CrossRef Full Text | Google Scholar

59. Matsumoto M, Hikosaka O. Two types of dopamine neuron distinctly convey positive and negative motivational signals. *Nature* (2009) 459: 837–41. doi: 10. 1038/nature08028

PubMed Abstract | CrossRef Full Text | Google Scholar

60. Ungless MA, Magill PJ, Bolam JP. Uniform inhibition of dopamine neurons in the ventral tegmental area by aversive stimuli. *Science* (2004) 303: 2040–2. doi: 10. 1126/science. 1093360

PubMed Abstract | CrossRef Full Text | Google Scholar

61. Brischoux F, Chakraborty S, Brierley DI, Ungless MA. Phasic excitation of dopamine neurons in ventral VTA by noxious stimuli. *Proc Natl Acad Sci USA* . (2009) 106: 4894–9. doi: 10. 1073/pnas. 0811507106

PubMed Abstract | CrossRef Full Text | Google Scholar

62. Budygin EA, Park J, Bass CE, Grinevich VP, Bonin KD, Wightman RM. Aversive stimulus differentially triggers subsecond dopamine release in reward regions. *Neuroscience* (2012) 201: 331–7. doi: 10. 1016/j. neuroscience. 2011. 10. 056

PubMed Abstract | CrossRef Full Text | Google Scholar

63. Hull CL. *Principles of Behavior: An Introduction to Behavior Theory* . Oxford: Appleton-Century. (1943).

Google Scholar

64. Sidman M. Avoidance conditioning with brief shock and no exteroceptive warning signal. *Science* (1953) 118: 157–8.

PubMed Abstract | Google Scholar

65. Berridge KC. Motivation concepts in behavioral neuroscience. *Physiol Behav* . (2004) 81: 179–209. doi: 10. 1016/j. physbeh. 2004. 02. 004

PubMed Abstract | CrossRef Full Text | Google Scholar

66. Betley JN, Xu S, Cao ZFH, Gong R, Magnus CJ, Yu Y, et al. Neurons for hunger and thirst transmit a negative-valence teaching signal. *Nature* (2015) 521: 180–5. doi: 10. 1038/nature14416

PubMed Abstract | CrossRef Full Text | Google Scholar

67. Leib DE, Zimmerman CA, Poormoghaddam A, Huey EL, Ahn JS, Lin YC, et al. The Forebrain thirst circuit drives drinking through negative reinforcement. *Neuron* (2017) 96: 1272–81. e4. doi: 10. 1016/j. neuron. 2017. 11. 041

PubMed Abstract | CrossRef Full Text | Google Scholar

68. Grill HJ, Kaplan JM. Interoceptive and integrative contributions of forebrain and brainstem to energy balance control. *Int J Obes Relat Metab Disord.* (2001) 25 (Suppl. 5): S73–77. doi: 10. 1038/sj. ijo. 0801917

PubMed Abstract | CrossRef Full Text | Google Scholar

69. Grill HJ, Hayes MR. The nucleus tractus solitarius: a portal for visceral afferent signal processing, energy status assessment and integration of their combined effects on food intake. *Int J Obes.* (2009) 33 (Suppl. 1): S11–15. doi: 10. 1038/ijo. 2009. 10

PubMed Abstract | CrossRef Full Text | Google Scholar

70. Kanoski SE, Davidson TL. Western diet consumption and cognitive impairment: links to hippocampal dysfunction and obesity. *Physiol Behav* . (2011) 103: 59–68. doi: 10. 1016/j. physbeh. 2010. 12. 003

PubMed Abstract | CrossRef Full Text | Google Scholar

71. Grill HJ, Hayes MR. Hindbrain neurons as an essential hub in the neuroanatomically distributed control of energy balance. *Cell Metab* . (2012) 16: 296–309. doi: 10. 1016/j. cmet. 2012. 06. 015

PubMed Abstract | CrossRef Full Text | Google Scholar

72. Petrovich GD. Forebrain networks and the control of feeding by environmental learned cues. *Physiol Behav* . (2013) 121: 10–8. doi: 10. 1016/j. physbeh. 2013. 03. 024

PubMed Abstract | CrossRef Full Text | Google Scholar

73. Mietlicki-Baase EG, Hayes MR. Amylin activates distributed CNS nuclei to control energy balance. *Physiol Behav* . (2014) 136: 39–46. doi: 10. 1016/j. physbeh. 2014. 01. 013

PubMed Abstract | CrossRef Full Text | Google Scholar

74. Vogt MC, Bruning JC. CNS insulin signaling in the control of energy homeostasis and glucose metabolism - from embryo to old age. *Trends Endocrinol Metab* . (2013) 24: 76–84. doi: 10. 1016/j. tem. 2012. 11. 004

PubMed Abstract | CrossRef Full Text | Google Scholar

75. Elmquist JK, Elias CF, Saper CB. From lesions to leptin: hypothalamic control of food intake and body weight. *Neuron* (1999) 22: 221–32. doi: 10. 1016/S0896-6273(00)81084-3

PubMed Abstract | CrossRef Full Text | Google Scholar

76. Pinto S, Roseberry AG, Liu H, Diano S, Shanabrough M, Cai X, et al. Rapid rewiring of arcuate nucleus feeding circuits by leptin. *Science* (2004) 304: 110–5. doi: 10. 1126/science. 1089459

PubMed Abstract | CrossRef Full Text | Google Scholar

77. Scott MM, Lachey JL, Sternson SM, Lee CE, Elias CF, Friedman JM, et al. Leptin targets in the mouse brain. *J Comp Neurol* . (2009) 514: 518–32. doi: 10. 1002/cne. 22025

PubMed Abstract | CrossRef Full Text | Google Scholar

78. Li Z, Kelly L, Heiman M, Greengard P, Friedman JM. Hypothalamic amylin acts in concert with leptin to regulate food intake. *Cell Metab* . (2015) 22: 1059–67. doi: 10. 1016/j. cmet. 2015. 10. 012

PubMed Abstract | CrossRef Full Text | Google Scholar

79. Kanoski SE, Hayes MR, Skibicka KP. GLP-1 and weight loss: unraveling the diverse neural circuitry. *Am J Physiol Regul Integr Comp Physiol* . (2016) 310: R885–95. doi: 10. 1152/ajpregu. 00520. 2015

PubMed Abstract | CrossRef Full Text | Google Scholar

80. Olszewski PK, Li D, Grace MK, Billington CJ, Kotz CM, Levine AS. Neural basis of orexigenic effects of ghrelin acting within lateral hypothalamus. *Peptides* (2003) 24: 597–602. doi: 10. 1016/S0196-9781(03)00105-0

PubMed Abstract | CrossRef Full Text | Google Scholar

81. Figlewicz DP, Bennett JL, Aliakbari S, Zavosh A, Sipols AJ. Insulin acts at different CNS sites to decrease acute sucrose intake and sucrose self-administration in rats. *Am J Physiol Regul Integr Comp Physiol* . (2008) 295: R388–94. doi: 10. 1152/ajpregu. 90334. 2008

PubMed Abstract | CrossRef Full Text | Google Scholar

82. Figlewicz DP, Bennett J, Evans SB, Kaiyala K, Sipols AJ, Benoit SC. Intraventricular insulin and leptin reverse place preference conditioned with high-fat diet in rats. *Behav Neurosci* . (2004) 118: 479–87. doi: 10. 1037/0735-7044. 118. 3. 479

PubMed Abstract | CrossRef Full Text | Google Scholar

83. Kanoski SE, Alhadeff AL, Fortin SM, Gilbert JR, Grill HJ. Leptin signaling in the medial nucleus tractus solitarius reduces food seeking and willingness to work for food. *Neuropsychopharmacology* (2014) 39: 605–13. doi: 10. 1038/npp. 2013. 235

PubMed Abstract | CrossRef Full Text | Google Scholar

84. Alhadeff AL, Mergler BD, Zimmer DJ, Turner CA, Reiner DJ, Schmidt HD, et al. Endogenous glucagon-like peptide-1 receptor signaling in the nucleus tractus solitarius is required for food intake control. *Neuropsychopharmacology* (2017) 42: 1471–9. doi: 10. 1038/npp. 2016. 246

PubMed Abstract | CrossRef Full Text | Google Scholar

85. Lopez-Ferreras L, Richard JE, Noble EE, Eerola K, Anderberg RH, Olandersson K, et al. Lateral hypothalamic GLP-1 receptors are critical for the control of food reinforcement, ingestive behavior and body weight. *Mol Psychiatry* (2018) 23: 1157–68. doi: 10. 1038/mp. 2017. 187

PubMed Abstract | CrossRef Full Text | Google Scholar

86. Toshinai K, Date Y, Murakami N, Shimada M, Mondal MS, Shimbara T, et al. Ghrelin-induced food intake is mediated via the orexin pathway. *Endocrinology* (2003) 144: 1506–12. doi: 10. 1210/en. 2002-220788

PubMed Abstract | CrossRef Full Text | Google Scholar

87. Perello M, Sakata I, Birnbaum S, Chuang JC, Osborne-Lawrence S, Rovinsky SA, et al. Ghrelin increases the rewarding value of high-fat diet in an orexin-dependent manner. *Biol Psychiatry* (2010) 67: 880–6. doi: 10. 1016/j. biopsych. 2009. 10. 030

PubMed Abstract | CrossRef Full Text | Google Scholar

88. Lopez-Ferreras L, Richard JE, Anderberg RH, Nilsson FH, Olandersson K, Kanoski SE, et al. Ghrelin's control of food reward and body weight in the lateral hypothalamic area is sexually dimorphic. *Physiol Behav* . (2017) 176: 40–9. doi: 10. 1016/j. physbeh. 2017. 02. 011

PubMed Abstract | CrossRef Full Text | Google Scholar

89. Cone RD. Anatomy and regulation of the central melanocortin system. *Nat Neurosci* . (2005) 8: 571–8. doi: 10. 1038/nn1455

PubMed Abstract | CrossRef Full Text | Google Scholar

90. Chen Y, Lin YC, Kuo TW, Knight ZA. Sensory detection of food rapidly modulates arcuate feeding circuits. *Cell* (2015) 160: 829–41. doi: 10. 1016/j. cell. 2015. 01. 033

PubMed Abstract | CrossRef Full Text | Google Scholar

91. Elizalde G, Sclafani A. Flavor preferences conditioned by intragastric polycose infusions: a detailed analysis using an electronic esophagus preparation. *Physiol Behav* . (1990) 47: 63–77. doi: 10. 1016/0031-9384(90)90043-4

PubMed Abstract | CrossRef Full Text | Google Scholar

92. Drucker DB, Ackroff K, Sclafani A. Flavor preference produced by intragastric polycose infusions in rats using a concurrent conditioning procedure. *Physiol Behav* . (1993) 54: 351–5. doi: 10. 1016/0031-9384(93)90122-V

PubMed Abstract | CrossRef Full Text | Google Scholar

93. Drucker DB, Ackroff K, Sclafani A. Nutrient-conditioned flavor preference and acceptance in rats: effects of deprivation state and nonreinforcement. *Physiol Behav* . (1994) 56: 701–7. doi: 10. 1016/0031-9384(94)90230-5

PubMed Abstract | CrossRef Full Text | Google Scholar

94. Ackroff K. Learned flavor preferences. The variable potency of post-oral nutrient reinforcers. *Appetite* (2008) 51: 743–6. doi: 10. 1016/j. appet. 2008. 05. 059

PubMed Abstract | CrossRef Full Text | Google Scholar

95. Myers KP. The convergence of psychology and neurobiology in flavor-nutrient learning. *Appetite* (2018) 122: 36–43. doi: 10. 1016/j. appet. 2017. 03. 048

PubMed Abstract | CrossRef Full Text | Google Scholar

96. Ackroff K, Yiin YM, Sclafani A. Post-oral infusion sites that support glucose-conditioned flavor preferences in rats. *Physiol Behav* . (2010) 99: 402–11. doi: 10. 1016/j. physbeh. 2009. 12. 012

PubMed Abstract | CrossRef Full Text | Google Scholar

97. Oliveira-Maia AJ, Roberts CD, Walker QD, Luo B, Kuhn C, Simon SA, et al. Intravascular food reward. *PLoS ONE* (2011) 6: e24992. doi: 10. 1371/journal. pone. 0024992

PubMed Abstract | CrossRef Full Text | Google Scholar

98. Zukerman S, Ackroff K, Sclafani A. Post-oral appetite stimulation by sugars and nonmetabolizable sugar analogs. *Am J Physiol Regul Integr Comp Physiol* . (2013) 305: R840–853. doi: 10. 1152/ajpregu. 00297. 2013

PubMed Abstract | CrossRef Full Text | Google Scholar

99. De Araujo IE, Oliveira-Maia AJ, Sotnikova TD, Gainetdinov RR, Caron MG, Nicolelis MA, et al. Food reward in the absence of taste receptor signaling. *Neuron* (2008) 57: 930–41. doi: 10. 1016/j. neuron. 2008. 01. 032

CrossRef Full Text | Google Scholar

100. Touzani K, Bodnar R, Sclafani A. Activation of dopamine D1-like receptors in nucleus accumbens is critical for the acquisition, but not the expression, of nutrient-conditioned flavor preferences in rats. *Eur J Neurosci* . (2008) 27: 1525–33. doi: 10. 1111/j. 1460-9568. 2008. 06127. x

CrossRef Full Text | Google Scholar

101. Touzani K, Bodnar RJ, Sclafani A. Dopamine D1-like receptor antagonism in amygdala impairs the acquisition of glucose-conditioned flavor preference

in rats. *Eur J Neurosci* . (2009) 30: 289–98. doi: 10. 1111/j. 1460-9568. 2009. 06829. x

PubMed Abstract | CrossRef Full Text | Google Scholar

102. Touzani K, Bodnar RJ, Sclafani A. Acquisition of glucose-conditioned flavor preference requires the activation of dopamine D1-like receptors within the medial prefrontal cortex in rats. *Neurobiol Learn Mem* . (2010) 94: 214–9. doi: 10. 1016/j. nlm. 2010. 05. 009

PubMed Abstract | CrossRef Full Text | Google Scholar

103. Tellez LA, Han W, Zhang X, Ferreira TL, Perez IO, Shammah-Lagnado SJ, et al. Separate circuitries encode the hedonic and nutritional values of sugar. *Nat Neurosci* . (2016) 19: 465–70. doi: 10. 1038/nn. 4224

PubMed Abstract | CrossRef Full Text | Google Scholar

104. Fortin SM, Roitman MF. Physiological state tunes mesolimbic signaling: Lessons from sodium appetite and inspiration from Randall R. *Sakai Physiol Behav* . (2017) 178: 21–7. doi: 10. 1016/j. physbeh. 2016. 11. 021

PubMed Abstract | CrossRef Full Text | Google Scholar

105. Richter CP. Increased salt appetite in adrenalectomized rats. *Am J Physiol Legacy Content* (1936) 115: 155–61. doi: 10. 1152/ajplegacy. 1936. 115. 1. 155

CrossRef Full Text | Google Scholar

106. Geran LC, Spector AC. Anion size does not compromise sodium recognition by rats after acute sodium depletion. *Behav Neurosci* . (2004) 118: 178–83. doi: 10. 1037/0735-7044. 118. 1. 178

CrossRef Full Text | Google Scholar

107. Quartermain D, Miller NE, Wolf G. Role of experience in relationship between sodium deficiency and rate of bar pressing for salt. *J Comp Physiol Psychol* . (1967) 63: 417–20. doi: 10. 1037/h0024611

PubMed Abstract | CrossRef Full Text | Google Scholar

108. Krieckhaus EE, Wolf G. Acquisition of sodium by rats: interaction of innate mechanisms and latent learning. *J Comp Physiol Psychol* . (1968) 65: 197–201. doi: 10. 1037/h0025547

PubMed Abstract | CrossRef Full Text | Google Scholar

109. Robinson MJ, Berridge KC. Instant transformation of learned repulsion into motivational “ wanting”. *Curr Biol* . (2013) 23: 282–9. doi: 10. 1016/j. cub. 2013. 01. 016

PubMed Abstract | CrossRef Full Text | Google Scholar

110. Berridge KC, Flynn FW, Schulkin J, Grill HJ. Sodium depletion enhances salt palatability in rats. *Behav Neurosci* . (1984) 98: 652–60. doi: 10. 1037/0735-7044. 98. 4. 652

PubMed Abstract | CrossRef Full Text | Google Scholar

111. Grill HJ, Schulkin J, Flynn FW. Sodium homeostasis in chronic decerebrate rats. *Behav Neurosci* . (1986) 100: 536–43. doi: 10. 1037/0735-7044. 100. 4. 536

PubMed Abstract | CrossRef Full Text | Google Scholar

112. Geerling JC, Loewy AD. Aldosterone-sensitive neurons in the nucleus of the solitary: efferent projections. *J Comp Neurol* . (2006) 498: 223–50. doi: 10. 1002/cne. 20993

PubMed Abstract | CrossRef Full Text | Google Scholar

113. Jarvie BC, Palmiter RD. HSD2 neurons in the hindbrain drive sodium appetite. *Nat Neurosci* . (2017) 20: 167–9. doi: 10. 1038/nn. 4451

PubMed Abstract | CrossRef Full Text | Google Scholar

114. Galaverna OG, Seeley RJ, Berridge KC, Grill HJ, Epstein AN, Schulkin J. Lesions of the central nucleus of the amygdala. I: effects on taste reactivity, taste aversion learning and sodium appetite . *Behav Brain Res* . (1993) 59: 11–7. doi: 10. 1016/0166-4328(93)90146-H

CrossRef Full Text | Google Scholar

115. Seeley RJ, Galaverna O, Schulkin J, Epstein AN, Grill HJ. Lesions of the central nucleus of the amygdala. II: effects on intraoral NaCl intake . *Behav Brain Res* (1993) 59: 19–25. doi: 10. 1016/0166-4328(93)90147-I

PubMed Abstract | CrossRef Full Text | Google Scholar

116. Spector AC, Grill HJ, Norgren R. Concentration-dependent licking of sucrose and sodium chloride in rats with parabrachial gustatory lesions. *Physiol Behav* . (1993) 53: 277–83.

PubMed Abstract | Google Scholar

117. Scalera G, Spector AC, Norgren R. Excitotoxic lesions of the parabrachial nuclei prevent conditioned taste aversions and sodium appetite in rats. *Behav Neurosci* . (1995) 109: 997–1008. doi: 10. 1037/0735-7044. 109. 5. 997

PubMed Abstract | CrossRef Full Text | Google Scholar

118. Tandon S, Simon SA, Nicolelis MA. Appetitive changes during salt deprivation are paralleled by widespread neuronal adaptations in nucleus accumbens, lateral hypothalamus, and central amygdala. *J Neurophysiol* . (2012) 108: 1089–105. doi: 10. 1152/jn. 00236. 2012

PubMed Abstract | CrossRef Full Text | Google Scholar

119. Oka Y, Ye M, Zuker CS. Thirst driving and suppressing signals encoded by distinct neural populations in the brain. *Nature* (2015) 520: 349–52. doi: 10. 1038/nature14108

PubMed Abstract | CrossRef Full Text | Google Scholar

120. Augustine V, Gokce SK, Lee S, Wang B, Davidson TJ, Reimann F, et al. Hierarchical neural architecture underlying thirst regulation. *Nature* (2018) 555: 204–9. doi: 10. 1038/nature25488

PubMed Abstract | CrossRef Full Text | Google Scholar

121. Zimmerman CA, Lin YC, Leib DE, Guo L, Huey EL, Daly GE, et al. Thirst neurons anticipate the homeostatic consequences of eating and drinking. *Nature* (2016) 537: 680–4. doi: 10. 1038/nature18950

PubMed Abstract | CrossRef Full Text | Google Scholar

122. Postolache M, Santollo J, Daniels D. Associative learning contributes to the increased water intake observed after daily injections of angiotensin II. *Physiol Behav* . (2017) 179: 340–5. doi: 10. 1016/j. physbeh. 2017. 07. 005

PubMed Abstract | CrossRef Full Text | Google Scholar

123. Wilson C, Nomikos GG, Collu M, Fibiger HC. Dopaminergic correlates of motivated behavior: importance of drive. *J Neurosci* . (1995) 15: 5169–78.

PubMed Abstract | Google Scholar

124. Patterson TA, Brot MD, Zavosh A, Schenk JO, Szot P, Figlewicz DP. Food deprivation decreases mRNA and activity of the rat dopamine transporter. *Neuroendocrinology* (1998) 68: 11–20. doi: 10. 1159/000054345

PubMed Abstract | CrossRef Full Text | Google Scholar

125. Avena NM, Rada P, Hoebel BG. Underweight rats have enhanced dopamine release and blunted acetylcholine response in the nucleus accumbens while bingeing on sucrose. *Neuroscience* (2008) 156: 865–71. doi: 10. 1016/j. neuroscience. 2008. 08. 017

PubMed Abstract | CrossRef Full Text | Google Scholar

126. Pothos EN, Creese I, Hoebel BG. Restricted eating with weight loss selectively decreases extracellular dopamine in the nucleus accumbens and alters dopamine response to amphetamine, morphine, and food intake. *J Neurosci* . (1995) 15: 6640–50. doi: 10. 1523/JNEUROSCI. 15-10-06640. 1995

PubMed Abstract | CrossRef Full Text | Google Scholar

127. Branch SY, Goertz RB, Sharpe AL, Pierce J, Roy S, Ko D, et al. Food restriction increases glutamate receptor-mediated burst firing of dopamine neurons. *J Neurosci* . (2013) 33: 13861–72. doi: 10. 1523/JNEUROSCI. 5099-12. 2013

PubMed Abstract | CrossRef Full Text | Google Scholar

128. Cone JJ, Mccutcheon JE, Roitman MF. Ghrelin acts as an interface between physiological state and phasic dopamine signaling. *J Neurosci* . (2014) 34: 4905–13. doi: 10. 1523/JNEUROSCI. 4404-13. 2014

PubMed Abstract | CrossRef Full Text | Google Scholar

129. D'cunha TM, Sedki F, Macri J, Casola C, Shalev U. The effects of chronic food restriction on cue-induced heroin seeking in abstinent male rats. *Psychopharmacology* (2013) 225: 241–50. doi: 10. 1007/s00213-012-2810-1

PubMed Abstract | CrossRef Full Text | Google Scholar

130. D'cunha TM, Daoud E, Rizzo D, Bishop AB, Russo M, Mourra G, et al. Augmentation of heroin seeking following chronic food restriction in the rat:

differential role for dopamine transmission in the nucleus accumbens shell and core. *Neuropsychopharmacology* (2017) 42: 1136–45. doi: 10. 1038/npp. 2016. 250

PubMed Abstract | CrossRef Full Text | Google Scholar

131. Donny EC, Caggiula AR, Mielke MM, Jacobs KS, Rose C, Sved AF. Acquisition of nicotine self-administration in rats: the effects of dose, feeding schedule, and drug contingency. *Psychopharmacology* (1998) 136: 83–90. doi: 10. 1007/s002130050542

PubMed Abstract | CrossRef Full Text | Google Scholar

132. Zheng D, Cabeza De Vaca S, Carr KD. Food restriction increases acquisition, persistence and drug prime-induced expression of a cocaine-conditioned place preference in rats. *Pharmacol Biochem Behav* . (2012) 100: 538–44. doi: 10. 1016/j. pbb. 2011. 10. 021

PubMed Abstract | CrossRef Full Text | Google Scholar

133. Wanat MJ, Kuhnen CM, Phillips PE. Delays conferred by escalating costs modulate dopamine release to rewards but not their predictors. *J Neurosci* . (2010) 30: 12020–7. doi. org/10. 1523/JNEUROSCI. 2691-10. 2010

CrossRef Full Text | Google Scholar

134. Alheid GF, Mcdermott L, Kelly J, Halaris A, Grossman SP. Deficits in food and water intake after knife cuts that deplete striatal DA or hypothalamic NE

in rats. *Pharmacol Biochem Behav* . (1977) 6: 273–87. doi: 10. 1016/0091-3057(77)90026-0

CrossRef Full Text | Google Scholar

135. Sumners C, Woodruff GN, Poat JA. Effects of specific dopamine lesions and dopamine receptor sensitivity on angiotensin II- and carbachol-induced thirst in rats. *Psychopharmacology* (1981) 73: 180–3. doi: 10. 1007/BF00429214

PubMed Abstract | CrossRef Full Text | Google Scholar

136. Snodgrass SH, Allen JD. Effect of dopamine agents on schedule- and deprivation-induced drinking in rats. *Pharmacol Biochem Behav* .(1987) 27: 463–75. doi: 10. 1016/0091-3057(87)90350-9

PubMed Abstract | CrossRef Full Text | Google Scholar

137. Horvitz JC, Richardson WB, Ettenberg A. Dopamine receptor blockade and reductions in thirst produce differential effects on drinking behavior. *Pharmacol Biochem Behav* . (1993) 45: 725–8. doi: 10. 1016/0091-3057(93)90531-W

PubMed Abstract | CrossRef Full Text | Google Scholar

138. Cone JJ, Fortin SM, Mchenry JA, Stuber GD, Mccutcheon JE, Roitman MF. Physiological state gates acquisition and expression of mesolimbic reward prediction signals. *Proc Natl Acad Sci USA* . (2016) 113: 1943–8. doi: 10. 1073/pnas. 1519643113

PubMed Abstract | CrossRef Full Text | Google Scholar

139. Marks JL, Porte DJr, Stahl WL, Baskin DG. Localization of insulin receptor mRNA in rat brain by in situ hybridization. *Endocrinology* (1990) 127: 3234–6. doi: 10. 1210/endo-127-6-3234

PubMed Abstract | CrossRef Full Text | Google Scholar

140. Sexton PM, Paxinos G, Kenney MA, Wookey PJ, Beaumont K. In vitro autoradiographic localization of amylin binding sites in rat brain. *Neuroscience* (1994) 62: 553–67. doi: 10. 1016/0306-4522(94)90388-3

PubMed Abstract | CrossRef Full Text | Google Scholar

141. Merchenthaler I, Lane M, Shughrue P. Distribution of pre-pro-glucagon and glucagon-like peptide-1 receptor messenger RNAs in the rat central nervous system. *J Comp Neurol* . (1999) 403: 261–80.

PubMed Abstract | Google Scholar

142. Zigman JM, Jones JE, Lee CE, Saper CB, Elmquist JK. Expression of ghrelin receptor mRNA in the rat and the mouse brain. *J Comp Neurol* . (2006) 494: 528–48. doi: 10. 1002/cne. 20823

PubMed Abstract | CrossRef Full Text | Google Scholar

143. Cork SC, Richards JE, Holt MK, Gribble FM, Reimann F, Trapp S. Distribution and characterisation of Glucagon-like peptide-1 receptor expressing cells in the mouse brain. *Mol Metab* . (2015) 4: 718–31. doi: 10. 1016/j. molmet. 2015. 07. 008

PubMed Abstract | CrossRef Full Text | Google Scholar

144. Alhadeff AL, Rupprecht LE, Hayes MR. GLP-1 neurons in the nucleus of the solitary tract project directly to the ventral tegmental area and nucleus accumbens to control for food intake. *Endocrinology* (2012) 153: 647–58. doi: 10. 1210/en. 2011-1443

PubMed Abstract | CrossRef Full Text | Google Scholar

145. Sirohi S, Schurdak JD, Seeley RJ, Benoit SC, Davis JF. Central & peripheral glucagon-like peptide-1 receptor signaling differentially regulate addictive behaviors. *Physiol Behav* . (2016) 161: 140–4. doi: 10. 1016/j. physbeh. 2016. 04. 013

PubMed Abstract | CrossRef Full Text | Google Scholar

146. Hernandez NS, O'donovan B, Ortinski PI, Schmidt HD. Activation of glucagon-like peptide-1 receptors in the nucleus accumbens attenuates cocaine seeking in rats. *Addict Biol* . (2017) doi: 10. 1111/adb. 12583. [Epub ahead of print].

PubMed Abstract | CrossRef Full Text | Google Scholar

147. Hernandez NS, Ige KY, Mietlicki-Baase EG, Molina-Castro GC, Turner CA, Hayes MR, et al. Glucagon-like peptide-1 receptor activation in the ventral tegmental area attenuates cocaine seeking in rats. *Neuropsychopharmacology* (2018) 43: 2000–8. doi: 10. 1038/s41386-018-0010-3

PubMed Abstract | CrossRef Full Text | Google Scholar

148. Fortin SM, Roitman MF. Central GLP-1 receptor activation modulates cocaine-evoked phasic dopamine signaling in the nucleus accumbens core. *Physiol Behav* . (2017) 176: 17–25. doi: 10. 1016/j. physbeh. 2017. 03. 019

PubMed Abstract | CrossRef Full Text | Google Scholar

149. Mietlicki-Baase EG, Ortinski PI, Reiner DJ, Sinon CG, Mccutcheon JE, Pierce RC, et al. Glucagon-like peptide-1 receptor activation in the nucleus accumbens core suppresses feeding by increasing glutamatergic AMPA/kainate signaling. *J Neurosci* . (2014) 34: 6985–92. doi: 10. 1523/JNEUROSCI. 0115-14. 2014

PubMed Abstract | CrossRef Full Text | Google Scholar

150. Mietlicki-Baase EG, Mcgrath LE, Koch-Laskowski K, Krawczyk J, Reiner DJ, Pham T, et al. Amylin receptor activation in the ventral tegmental area reduces motivated ingestive behavior. *Neuropharmacology* (2017) 123: 67–79. doi: 10. 1016/j. neuropharm. 2017. 05. 024

PubMed Abstract | CrossRef Full Text | Google Scholar

151. Mietlicki-Baase EG, Reiner DJ, Cone JJ, Olivos DR, Mcgrath LE, Zimmer DJ, et al. Amylin modulates the mesolimbic dopamine system to control energy balance. *Neuropsychopharmacology* (2015) 40: 372–85. doi: 10. 1038/npp. 2014. 180

PubMed Abstract | CrossRef Full Text | Google Scholar

152. Whiting L, Mccutcheon JE, Boyle CN, Roitman MF, Lutz TA. The area postrema (AP) and the parabrachial nucleus (PBN) are important sites for salmon calcitonin (sCT) to decrease evoked phasic dopamine release in the nucleus accumbens (NAc). *Physiol Behav* . (2017) 176: 9–16. doi: 10. 1016/j. physbeh. 2017. 03. 023

PubMed Abstract | CrossRef Full Text | Google Scholar

153. Mietlicki-Baase EG, Olivos DR, Jeffrey BA, Hayes MR. Cooperative interaction between leptin and amylin signaling in the ventral tegmental area for the control of food intake. *Am J Physiol Endocrinol Metab* . (2015) 308: E1116–122. doi: 10. 1152/ajpendo. 00087. 2015

PubMed Abstract | CrossRef Full Text | Google Scholar

154. Hommel JD, Trinko R, Sears RM, Georgescu D, Liu ZW, Gao XB, et al. Leptin receptor signaling in midbrain dopamine neurons regulates feeding. *Neuron* (2006) 51: 801–10. doi: 10. 1016/j. neuron. 2006. 08. 023

PubMed Abstract | CrossRef Full Text | Google Scholar

155. Fulton S, Pissios P, Manchon RP, Stiles L, Frank L, Pothos EN, et al. Leptin regulation of the mesoaccumbens dopamine pathway. *Neuron* (2006) 51: 811–22. doi: 10. 1016/j. neuron. 2006. 09. 006

PubMed Abstract | CrossRef Full Text | Google Scholar

156. Mebel DM, Wong JC, Dong YJ, Borgland SL. Insulin in the ventral tegmental area reduces hedonic feeding and suppresses dopamine

concentration via increased reuptake. *Eur J Neurosci* . (2012) 36: 2336–46. doi: 10. 1111/j. 1460-9568. 2012. 08168. x

PubMed Abstract | CrossRef Full Text | Google Scholar

157. Labouebe G, Liu S, Dias C, Zou H, Wong JC, Karunakaran S, et al. Insulin induces long-term depression of ventral tegmental area dopamine neurons via endocannabinoids. *Nat Neurosci* . (2013) 16: 300–8. doi: 10. 1038/nn. 3321

PubMed Abstract | CrossRef Full Text | Google Scholar

158. Liu S, Labouebe G, Karunakaran S, Clee SM, Borgland SL. Effect of insulin on excitatory synaptic transmission onto dopamine neurons of the ventral tegmental area in a mouse model of hyperinsulinemia. *Nutr Diabetes* (2013) 3: e97. doi: 10. 1038/nutd. 2013. 38

PubMed Abstract | CrossRef Full Text | Google Scholar

159. Thompson JL, Borgland SL. Presynaptic leptin action suppresses excitatory synaptic transmission onto ventral tegmental area dopamine neurons. *Biol Psychiatry* (2013) 73: 860–8. doi: 10. 1016/j. biopsych. 2012. 10. 026

PubMed Abstract | CrossRef Full Text | Google Scholar

160. You ZB, Wang B, Liu QR, Wu Y, Otvos L, Wise RA. Reciprocal Inhibitory Interactions Between the Reward-Related Effects of Leptin and Cocaine.

*Neuropsychopharmacology* (2016) 41: 1024–33. doi: 10. 1038/npp. 2015. 230

PubMed Abstract | CrossRef Full Text | Google Scholar

161. Konner AC, Hess S, Tovar S, Mesaros A, Sanchez-Lasheras C, Evers N, et al. Role for insulin signaling in catecholaminergic neurons in control of energy homeostasis. *Cell Metab* . (2011) 13: 720–8. doi: 10. 1016/j. cmet. 2011. 03. 021

PubMed Abstract | CrossRef Full Text | Google Scholar

162. Stouffer MA, Woods CA, Patel JC, Lee CR, Witkovsky P, Bao L, et al. Insulin enhances striatal dopamine release by activating cholinergic interneurons and thereby signals reward. *Nat Commun* . (2015) 6: 8543. doi: 10. 1038/ncomms9543

PubMed Abstract | CrossRef Full Text | Google Scholar

163. Abizaid A, Liu ZW, Andrews ZB, Shanabrough M, Borok E, Elsworth JD, et al. Ghrelin modulates the activity and synaptic input organization of midbrain dopamine neurons while promoting appetite. *J Clin Invest* . (2006) 116: 3229–39. doi: 10. 1172/JCI29867

PubMed Abstract | CrossRef Full Text | Google Scholar

164. Skibicka KP, Hansson C, Egecioglu E, Dickson SL. Role of ghrelin in food reward: impact of ghrelin on sucrose self-administration and mesolimbic

dopamine and acetylcholine receptor gene expression. *Addict Biol* . (2012) 17: 95–107. doi: 10. 1111/j. 1369-1600. 2010. 00294. x

PubMed Abstract | CrossRef Full Text | Google Scholar

165. Skibicka KP, Shirazi RH, Rabasa-Papio C, Alvarez-Crespo M, Neuber C, Vogel H, et al. Divergent circuitry underlying food reward and intake effects of ghrelin: dopaminergic VTA-accumbens projection mediates ghrelin's effect on food reward but not food intake. *Neuropharmacology* (2013) 73: 274–83. doi: 10. 1016/j. neuropharm. 2013. 06. 004

CrossRef Full Text | Google Scholar

166. Cone JJ, Roitman JD, Roitman MF. Ghrelin regulates phasic dopamine and nucleus accumbens signaling evoked by food-predictive stimuli. *J Neurochem* . (2015) 133: 844–56. doi: 10. 1111/jnc. 13080

PubMed Abstract | CrossRef Full Text | Google Scholar

167. Mark GP, Smith SE, Rada PV, Hoebel BG. An appetitively conditioned taste elicits a preferential increase in mesolimbic dopamine release. *Pharmacol Biochem Behav* . (1994) 48: 651–60. doi: 10. 1016/0091-3057(94)90327-1

PubMed Abstract | CrossRef Full Text | Google Scholar

168. Ren X, Ferreira JG, Zhou L, Shammah-Lagnado SJ, Yeckel CW, De Araujo IE. Nutrient selection in the absence of taste receptor signaling. *J Neurosci* . (2010) 30: 8012–23. doi: 10. 1523/JNEUROSCI. 5749-09. 2010

PubMed Abstract | CrossRef Full Text | Google Scholar

169. Beeler JA, Mccutcheon JE, Cao ZF, Murakami M, Alexander E, Roitman MF, et al. Taste uncoupled from nutrition fails to sustain the reinforcing properties of food. *Eur J Neurosci* (2012) 36: 2533–46. doi: 10. 1111/j. 1460-9568. 2012. 08167. x

PubMed Abstract | CrossRef Full Text | Google Scholar

170. Mccutcheon JE, Beeler JA, Roitman MF. Sucrose-predictive cues evoke greater phasic dopamine release than saccharin-predictive cues. *Synapse* (2012) 66: 346–51. doi: 10. 1002/syn. 21519

PubMed Abstract | CrossRef Full Text | Google Scholar

171. Tellez LA, Ferreira JG, Medina S, Land BB, Dileone RJ, De Araujo IE. Flavor-independent maintenance, extinction, and reinstatement of fat self-administration in mice. *Biol Psychiatry* (2013) 73: 851–9. doi: 10. 1016/j. biopsych. 2013. 02. 028

PubMed Abstract | CrossRef Full Text | Google Scholar

172. Mccutcheon JE. The role of dopamine in the pursuit of nutritional value. *Physiol Behav* . (2015) 152: 408–15. doi: 10. 1016/j. physbeh. 2015. 05. 003

PubMed Abstract | CrossRef Full Text | Google Scholar

173. Sclafani A, Touzani K, Ackroff K. Ghrelin signaling is not essential for sugar or fat conditioned flavor preferences in mice. *Physiol Behav* . (2015) 149: 14–22. doi: 10. 1016/j. physbeh. 2015. 05. 016

CrossRef Full Text | Google Scholar

174. Sclafani A, Touzani K, Ackroff K. Intragastric fat self-administration is impaired in GPR40/120 double knockout mice. *Physiol Behav* . (2015) 147: 141–8. doi: 10. 1016/j. physbeh. 2015. 04. 031

PubMed Abstract | CrossRef Full Text | Google Scholar

175. Kraft TT, Huang D, Lamagna S, Warshaw D, Natanova E, Sclafani A, et al. Acquisition and expression of fat-conditioned flavor preferences are differentially affected by NMDA receptor antagonism in BALB/c and SWR mice. *Eur J Pharmacol* . (2017) 799: 26–32. doi: 10. 1016/j. ejphar. 2017. 01. 034

PubMed Abstract | CrossRef Full Text | Google Scholar

176. Ferreira JG, Tellez LA, Ren X, Yeckel CW, De Araujo IE. Regulation of fat intake in the absence of flavour signalling. *J Physiol* . (2012) 590: 953–72. doi: 10. 1113/jphysiol. 2011. 218289

PubMed Abstract | CrossRef Full Text | Google Scholar

177. Yin HH, Ostlund SB, Balleine BW. Reward-guided learning beyond dopamine in the nucleus accumbens: the integrative functions of cortico-basal ganglia networks. *Eur J Neurosci* . (2008) 28: 1437–48. doi: 10. 1111/j. 1460-9568. 2008. 06422. x

PubMed Abstract | CrossRef Full Text | Google Scholar

178. Brown HD, Mccutcheon JE, Cone JJ, Ragozzino ME, Roitman MF. Primary food reward and reward-predictive stimuli evoke different patterns of phasic dopamine signaling throughout the striatum. *Eur J Neurosci* . (2011) 34: 1997–2006. doi: 10. 1111/j. 1460-9568. 2011. 07914. x

PubMed Abstract | CrossRef Full Text | Google Scholar

179. Lammel S, Ion DI, Roeper J, Malenka RC. Projection-specific modulation of dopamine neuron synapses by aversive and rewarding stimuli. *Neuron* (2011) 70: 855–62. doi: 10. 1016/j. neuron. 2011. 03. 025

PubMed Abstract | CrossRef Full Text | Google Scholar

180. Xiao L, Priest MF, Nasenbeny J, Lu T, Kozorovitskiy Y. Biased oxytocinergic modulation of midbrain dopamine systems. *Neuron* (2017) 95: 368–84. e5. doi: 10. 1016/j. neuron. 2017. 06. 003

PubMed Abstract | CrossRef Full Text | Google Scholar

181. Rinaman L. Ascending projections from the caudal visceral nucleus of the solitary tract to brain regions involved in food intake and energy expenditure. *Brain Res* . (2010) 1350: 18–34. doi: 10. 1016/j. brainres. 2010. 03. 059

PubMed Abstract | CrossRef Full Text | Google Scholar

182. Richard JE, Anderberg RH, Goteson A, Gribble FM, Reimann F, Skibicka KP. Activation of the GLP-1 receptors in the nucleus of the solitary tract

reduces food reward behavior and targets the mesolimbic system. *PLoS ONE* (2015) 10: e0119034. doi: 10. 1371/journal. pone. 0119034

PubMed Abstract | CrossRef Full Text | Google Scholar

183. Sequeira SM, Geerling JC, Loewy AD. Local inputs to aldosterone-sensitive neurons of the nucleus tractus solitarius. *Neuroscience* (2006) 141: 1995–2005. doi: 10. 1016/j. neuroscience. 2006. 05. 059

PubMed Abstract | CrossRef Full Text | Google Scholar

184. Shin JW, Geerling JC, Stein MK, Miller RL, Loewy AD. FoxP2 brainstem neurons project to sodium appetite regulatory sites. *J Chem Neuroanat* . (2011) 42: 1–23. doi: 10. 1016/j. jchemneu. 2011. 05. 003

PubMed Abstract | CrossRef Full Text | Google Scholar

185. Lammel S, Lim BK, Ran C, Huang KW, Betley MJ, Tye KM, et al. Input-specific control of reward and aversion in the ventral tegmental area. *Nature* (2012) 491: 212–7. doi: 10. 1038/nature11527

PubMed Abstract | CrossRef Full Text | Google Scholar

186. Watabe-Uchida M, Zhu L, Ogawa SK, Vamanrao A, Uchida N. Whole-brain mapping of direct inputs to midbrain dopamine neurons. *Neuron* (2012) 74: 858–73. doi: 10. 1016/j. neuron. 2012. 03. 017

PubMed Abstract | CrossRef Full Text | Google Scholar

187. Lodge DJ, Grace AA. The laterodorsal tegmentum is essential for burst firing of ventral tegmental area dopamine neurons. *Proc Natl Acad Sci USA* . (2006) 103: 5167–72. doi: 10. 1073/pnas. 0510715103

PubMed Abstract | CrossRef Full Text | Google Scholar

188. Chen L, Lodge DJ. The lateral mesopontine tegmentum regulates both tonic and phasic activity of VTA dopamine neurons. *J Neurophysiol* . (2013) 110: 2287–94. doi: 10. 1152/jn. 00307. 2013

PubMed Abstract | CrossRef Full Text | Google Scholar

189. Steidl S, Veverka K. Optogenetic excitation of LDTg axons in the VTA reinforces operant responding in rats. *Brain Res* . (2015) 1614: 86–93. doi: 10. 1016/j. brainres. 2015. 04. 021

PubMed Abstract | CrossRef Full Text | Google Scholar

190. Steidl S, O'sullivan S, Pilat D, Bubula N, Brown J, Vezina P. Operant responding for optogenetic excitation of LDTg inputs to the VTA requires D1 and D2 dopamine receptor activation in the NAcc. *Behav Brain Res* . (2017) 333: 161–70. doi: 10. 1016/j. bbr. 2017. 06. 045

PubMed Abstract | CrossRef Full Text | Google Scholar

191. Steidl S, Wang H, Ordonez M, Zhang S, Morales M. Optogenetic excitation in the ventral tegmental area of glutamatergic or cholinergic inputs from the laterodorsal tegmental area drives reward. *Eur J Neurosci* . (2017) 45: 559–71. doi: 10. 1111/ejn. 13436

PubMed Abstract | CrossRef Full Text | Google Scholar

192. Cornwall J, Cooper JD, Phillipson OT. Afferent and efferent connections of the laterodorsal tegmental nucleus in the rat. *Brain Res Bull* . (1990) 25: 271–84. doi: 10. 1016/0361-9230(90)90072-8

PubMed Abstract | CrossRef Full Text | Google Scholar

193. Reiner DJ, Leon RM, Mcgrath LE, Koch-Laskowski K, Hahn JD, Kanoski SE, et al. Glucagon-like peptide-1 receptor signaling in the lateral dorsal tegmental nucleus regulates energy balance. *Neuropsychopharmacology* (2018) 43: 627–37. doi: 10. 1038/npp. 2017. 225

PubMed Abstract | CrossRef Full Text | Google Scholar

194. Oakman SA, Faris PL, Kerr PE, Cozzari C, Hartman BK. Distribution of pontomesencephalic cholinergic neurons projecting to substantia nigra differs significantly from those projecting to ventral tegmental area. *J Neurosci* . (1995) 15: 5859–69. doi: 10. 1523/JNEUROSCI. 15-09-05859. 1995

PubMed Abstract | CrossRef Full Text | Google Scholar

195. Charara A, Smith Y, Parent A. Glutamatergic inputs from the pedunculopontine nucleus to midbrain dopaminergic neurons in primates: Phaseolus vulgaris-leucoagglutinin anterograde labeling combined with postembedding glutamate and GABA immunohistochemistry. *J Comp Neurol* . (1996) 364: 254–266.

PubMed Abstract | Google Scholar

196. Oakman SA, Faris PL, Cozzari C, Hartman BK. Characterization of the extent of pontomesencephalic cholinergic neurons' projections to the thalamus: comparison with projections to midbrain dopaminergic groups. *Neuroscience* (1999) 94: 529–47. doi: 10. 1016/S0306-4522(99)00307-3

PubMed Abstract | CrossRef Full Text | Google Scholar

197. Floresco SB, West AR, Ash B, Moore H, Grace AA. Afferent modulation of dopamine neuron firing differentially regulates tonic and phasic dopamine transmission. *Nat Neurosci* . (2003) 6: 968–73. doi: 10. 1038/nn1103

PubMed Abstract | CrossRef Full Text | Google Scholar

198. Schmidt HD, Famous KR, Pierce RC. The limbic circuitry underlying cocaine seeking encompasses the PPTg/LDT. *Eur J Neurosci* . (2009) 30: 1358–69. doi: 10. 1111/j. 1460-9568. 2009. 06904. x

PubMed Abstract | CrossRef Full Text | Google Scholar

199. Bechara A, Van Der Kooy D. A single brain stem substrate mediates the motivational effects of both opiates and food in nondeprived rats but not in deprived rats. *Behav Neurosci* . (1992) 106: 351–63. doi: 10. 1037/0735-7044. 106. 2. 351

CrossRef Full Text | Google Scholar

200. Hong EY, Yoon YS, Lee HS. Differential distribution of melanin-concentrating hormone (MCH)- and hypocretin (Hcrt)-immunoreactive

neurons projecting to the mesopontine cholinergic complex in the rat. *Brain Res* . (2011) 1424: 20–31. doi: 10. 1016/j. brainres. 2011. 09. 051

PubMed Abstract | CrossRef Full Text | Google Scholar

201. Rodaros D, Caruana DA, Amir S, Stewart J. Corticotropin-releasing factor projections from limbic forebrain and paraventricular nucleus of the hypothalamus to the region of the ventral tegmental area. *Neuroscience* (2007) 150: 8–13. doi: 10. 1016/j. neuroscience. 2007. 09. 043

PubMed Abstract | CrossRef Full Text | Google Scholar

202. Hahn JD, Swanson LW. Distinct patterns of neuronal inputs and outputs of the juxtaparaventricular and suprafornical regions of the lateral hypothalamic area in the male rat. *Brain Res Rev* . (2010) 64: 14–103. doi: 10. 1016/j. brainresrev. 2010. 02. 002

PubMed Abstract | CrossRef Full Text | Google Scholar

203. Kempadoo KA, Tourino C, Cho SL, Magnani F, Leinninger GM, Stuber GD, et al. Hypothalamic neurotensin projections promote reward by enhancing glutamate transmission in the VTA. *J Neurosci* . (2013) 33: 7618–26. doi: 10. 1523/JNEUROSCI. 2588-12. 2013

PubMed Abstract | CrossRef Full Text | Google Scholar

204. Haemmerle CA, Campos AM, Bittencourt JC. Melanin-concentrating hormone inputs to the nucleus accumbens originate from distinct hypothalamic sources and are apposed to GABAergic and cholinergic cells in

the Long-Evans rat brain. *Neuroscience* (2015) 289: 392–405. doi: 10. 1016/j. neuroscience. 2015. 01. 014

PubMed Abstract | CrossRef Full Text | Google Scholar

205. Nieh EH, Matthews GA, Allsop SA, Presbrey KN, Leppla CA, Wichmann R, et al. Decoding neural circuits that control compulsive sucrose seeking. *Cell* (2015) 160: 528–41. doi: 10. 1016/j. cell. 2015. 01. 003

PubMed Abstract | CrossRef Full Text | Google Scholar

206. O'connor EC, Kremer Y, Lefort S, Harada M, Pascoli V, Rohner C, et al. Accumbal D1R neurons projecting to lateral hypothalamus authorize feeding. *Neuron* (2015) 88: 553–64. doi: 10. 1016/j. neuron. 2015. 09. 038

PubMed Abstract | CrossRef Full Text | Google Scholar

207. Woodworth HL, Brown JA, Batchelor HM, Bugescu R, Leinninger GM. Determination of neurotensin projections to the ventral tegmental area in mice. *Neuropeptides* (2018) 68: 57–74. doi: 10. 1016/j. npep. 2018. 02. 003

PubMed Abstract | CrossRef Full Text | Google Scholar

208. Nieh EH, Vander Weele CM, Matthews GA, Presbrey KN, Wichmann R, Leppla CA, et al. Inhibitory Input from the Lateral Hypothalamus to the Ventral Tegmental Area Disinhibits Dopamine Neuron *s* and Promotes Behavioral Activation. *Neuron* (2016) 90: 1286–98. doi: 10. 1016/j. neuron. 2016. 04. 035

PubMed Abstract | CrossRef Full Text | Google Scholar

209. Choudhary AG, Somalwar AR, Sagarkar S, Rale A, Sakharkar A, Subhedar NK, et al. CART neurons in the lateral hypothalamus communicate with the nucleus accumbens shell via glutamatergic neurons in paraventricular thalamic nucleus to modulate reward behavior. *Brain Struct Funct* . (2018) 223: 1313–28. doi: 10. 1007/s00429-017-1544-6

PubMed Abstract | CrossRef Full Text | Google Scholar

210. Haynes AC, Jackson B, Chapman H, Tadayyon M, Johns A, Porter RA, et al. A selective orexin-1 receptor antagonist reduces food consumption in male and female rats. *Regul Pept* . (2000) 96: 45–51. doi: 10. 1016/S0167-0115(00)00199-3

PubMed Abstract | CrossRef Full Text | Google Scholar

211. Willie JT, Chemelli RM, Sinton CM, Yanagisawa M. To eat or to sleep? Orexin in the regulation of feeding and wakefulness . *Annu Rev Neurosci* . (2001) 24: 429–58. doi: 10. 1146/annurev. neuro. 24. 1. 429

PubMed Abstract | CrossRef Full Text | Google Scholar

212. Rodgers RJ, Ishii Y, Halford JC, Blundell JE. Orexins and appetite regulation. *Neuropeptides* (2002) 36: 303–25. doi: 10. 1016/S0143-4179(02)00085-9

PubMed Abstract | CrossRef Full Text | Google Scholar

213. Thorpe AJ, Kotz CM. Orexin A in the nucleus accumbens stimulates feeding and locomotor activity. *Brain Res* . (2005) 1050: 156–62. doi: 10. 1016/j. brainres. 2005. 05. 045

PubMed Abstract | CrossRef Full Text | Google Scholar

214. Borgland SL, Taha SA, Sarti F, Fields HL, Bonci A. Orexin A in the VTA is critical for the induction of synaptic plasticity and behavioral sensitization to cocaine. *Neuron* (2006) 49: 589–601. doi: 10. 1016/j. neuron. 2006. 01. 016

PubMed Abstract | CrossRef Full Text | Google Scholar

215. Thorpe AJ, Doane DF, Sweet DC, Beverly JL, Kotz CM. Orexin A in the rostrolateral hypothalamic area induces feeding by modulating GABAergic transmission. *Brain Res* . (2006) 1125: 60–6. doi: 10. 1016/j. brainres. 2006. 09. 075

PubMed Abstract | CrossRef Full Text | Google Scholar

216. Borgland SL, Chang SJ, Bowers MS, Thompson JL, Vittoz N, Floresco SB, et al. Orexin A/hypocretin-1 selectively promotes motivation for positive reinforcers. *J Neurosci* . (2009) 29: 11215–25. doi: 10. 1523/JNEUROSCI. 6096-08. 2009

PubMed Abstract | CrossRef Full Text | Google Scholar

217. Parise EM, Lilly N, Kay K, Dossat AM, Seth R, Overton JM, et al. Evidence for the role of hindbrain orexin-1 receptors in the control of meal size. *Am J*

*Physiol Regul Integr Comp Physiol* . (2011) 301: R1692–99. doi: 10. 1152/ajpregu. 00044. 2011

PubMed Abstract | CrossRef Full Text | Google Scholar

218. Barson JR, Morganstern I, Leibowitz SF. Complementary roles of orexin and melanin-concentrating hormone in feeding behavior. *Int J Endocrinol* . (2013) 2013: 983964. doi: 10. 1155/2013/983964

PubMed Abstract | CrossRef Full Text | Google Scholar

219. Cason AM, Aston-Jones G. Role of orexin/hypocretin in conditioned sucrose-seeking in rats. *Psychopharmacology* (2013) 226: 155–65. doi: 10. 1007/s00213-012-2902-y

PubMed Abstract | CrossRef Full Text | Google Scholar

220. Sakurai T. The role of orexin in motivated behaviours. *Nat Rev Neurosci* . (2014) 15: 719–31. doi: 10. 1038/nrn3837

PubMed Abstract | CrossRef Full Text | Google Scholar

221. Sheng Z, Santiago AM, Thomas MP, Routh VH. Metabolic regulation of lateral hypothalamic glucose-inhibited orexin neurons may influence midbrain reward neurocircuitry. *Mol Cell Neurosci* . (2014) 62: 30–41. doi: 10. 1016/j. mcn. 2014. 08. 001

PubMed Abstract | CrossRef Full Text | Google Scholar

222. Bentzley BS, Aston-Jones G. Orexin-1 receptor signaling increases motivation for cocaine-associated cues. *Eur J Neurosci* . (2015) 41: 1149–56. doi: 10. 1111/ejn. 12866

PubMed Abstract | CrossRef Full Text | Google Scholar

223. Bernstein DL, Badve PS, Barson JR, Bass CE, Espana RA. Hypocretin receptor 1 knockdown in the ventral tegmental area attenuates mesolimbic dopamine signaling and reduces motivation for cocaine. *Addict Biol* . (2017). doi: 10. 1111/adb. 12553. [Epub ahead of print].

PubMed Abstract | CrossRef Full Text | Google Scholar

224. Liu JJ, Bello NT, Pang ZP. Presynaptic regulation of leptin in a defined lateral hypothalamus-ventral tegmental area neurocircuitry depends on energy state. *J Neurosci* . (2017) 37: 11854–66. doi: 10. 1523/JNEUROSCI. 1942-17. 2017

PubMed Abstract | CrossRef Full Text | Google Scholar

225. Leinninger GM, Opland DM, Jo YH, Faouzi M, Christensen L, Cappellucci LA, et al. Leptin action via neurotensin neurons controls orexin, the mesolimbic dopamine system and energy balance. *Cell Metab* . (2011) 14: 313–23. doi: 10. 1016/j. cmet. 2011. 06. 016

PubMed Abstract | CrossRef Full Text | Google Scholar

226. Levin BE, Routh VH, Kang L, Sanders NM, Dunn-Meynell AA. Neuronal glucosensing: what do we know after 50 years? *Diabetes* (2004) 53: 2521–8. doi: 10. 2337/diabetes. 53. 10. 2521

CrossRef Full Text

227. Burdakov D, Luckman SM, Verkhratsky A. Glucose-sensing neurons of the hypothalamus. *Philos Trans R Soc Lond B Biol Sci* . (2005) 360: 2227–35. doi: 10. 1098/rstb. 2005. 1763

PubMed Abstract | CrossRef Full Text | Google Scholar

228. Kong D, Vong L, Parton LE, Ye C, Tong Q, Hu X, et al. Glucose stimulation of hypothalamic MCH neurons involves K(ATP) channels, is modulated by UCP2, and regulates peripheral glucose homeostasis. *Cell Metab* . (2010) 12: 545–52. doi: 10. 1016/j. cmet. 2010. 09. 013

PubMed Abstract | CrossRef Full Text | Google Scholar

229. Karnani MM, Apergis-Schoute J, Adamantidis A, Jensen LT, De Lecea L, Fugger L, et al. Activation of central orexin/hypocretin neurons by dietary amino acids. *Neuron* (2011) 72: 616–29. doi: 10. 1016/j. neuron. 2011. 08. 027

PubMed Abstract | CrossRef Full Text | Google Scholar

230. Domingos AI, Sordillo A, Dietrich MO, Liu ZW, Tellez LA, Vaynshteyn J, et al. Hypothalamic melanin concentrating hormone neurons communicate the nutrient value of sugar. *Elife* (2013) 2: e01462. doi: 10. 7554/eLife. 01462

PubMed Abstract | CrossRef Full Text | Google Scholar

231. Sweeney P, Yang Y. An excitatory ventral hippocampus to lateral septum circuit that suppresses feeding. *Nat Commun* . (2015) 6: 10188. doi: 10. 1038/ncomms10188

PubMed Abstract | CrossRef Full Text | Google Scholar

232. Kanoski SE, Grill HJ. Hippocampus Contributions to Food Intake Control: Mnemonic, Neuroanatomical, and Endocrine Mechanisms. *Biol Psychiatry* (2017) 81: 748–56. doi: 10. 1016/j. biopsych. 2015. 09. 011

PubMed Abstract | CrossRef Full Text | Google Scholar

233. Sweeney P, Yang Y. Neural circuit mechanisms underlying emotional regulation of homeostatic feeding. *Trends Endocrinol Metab* . (2017) 28: 437–48. doi: 10. 1016/j. tem. 2017. 02. 006

PubMed Abstract | CrossRef Full Text | Google Scholar

234. Legault M, Rompre PP, Wise RA. Chemical stimulation of the ventral hippocampus elevates nucleus accumbens dopamine by activating dopaminergic neurons of the ventral tegmental area. *J Neurosci* . (2000) 20: 1635–42. doi: 10. 1523/JNEUROSCI. 20-04-01635. 2000

PubMed Abstract | CrossRef Full Text | Google Scholar

235. Kanoski SE, Hayes MR, Greenwald HS, Fortin SM, Gianessi CA, Gilbert JR, et al. Hippocampal leptin signaling reduces food intake and modulates food-

related memory processing. *Neuropsychopharmacology* (2011) 36: 1859–70. doi: 10. 1038/npp. 2011. 70

PubMed Abstract | CrossRef Full Text | Google Scholar

236. Kanoski SE, Fortin SM, Ricks KM, Grill HJ. Ghrelin signaling in the ventral hippocampus stimulates learned and motivational aspects of feeding via PI3K-Akt signaling. *Biol Psychiatry* (2013) 73: 915–23. doi: 10. 1016/j. biopsych. 2012. 07. 002

PubMed Abstract | CrossRef Full Text | Google Scholar

237. Hsu TM, Hahn JD, Konanur VR, Lam A, Kanoski SE. Hippocampal GLP-1 receptors influence food intake, meal size, and effort-based responding for food through volume transmission. *Neuropsychopharmacology* (2015) 40: 327–37. doi: 10. 1038/npp. 2014. 175

PubMed Abstract | CrossRef Full Text | Google Scholar

238. Hsu TM, Hahn JD, Konanur VR, Noble EE, Suarez AN, Thai J, et al. Hippocampus ghrelin signaling mediates appetite through lateral hypothalamic orexin pathways. *Elife* (2015) 4: e11190 doi: 10. 7554/eLife. 11190

PubMed Abstract | CrossRef Full Text | Google Scholar

239. Hsu TM, Noble EE, Liu CM, Cortella AM, Konanur VR, Suarez AN, et al. A hippocampus to prefrontal cortex neural pathway inhibits food motivation

through glucagon-like peptide-1 signaling. *Mol Psychiatry* (2017). doi: 10. 1038/mp. 2017. 91. [Epub ahead of print].

PubMed Abstract | CrossRef Full Text | Google Scholar

240. Carr DB, Sesack SR. Projections from the rat prefrontal cortex to the ventral tegmental area: target specificity in the synaptic associations with mesoaccumbens and mesocortical neurons. *J Neurosci* . (2000) 20: 3864–73. doi: 10. 1523/JNEUROSCI. 20-10-03864. 2000

PubMed Abstract | CrossRef Full Text | Google Scholar

241. Francois J, Huxter J, Conway MW, Lowry JP, Tricklebank MD, Gilmour G. Differential contributions of infralimbic prefrontal cortex and nucleus accumbens during reward-based learning and extinction. *J Neurosci* . (2014) 34: 596–607. doi: 10. 1523/JNEUROSCI. 2346-13. 2014

PubMed Abstract | CrossRef Full Text | Google Scholar

242. Land BB, Narayanan NS, Liu RJ, Gianessi CA, Brayton CE, Grimaldi DM, et al. Medial prefrontal D1 dopamine neurons control food intake. *Nat Neurosci* . (2014) 17: 248–53. doi: 10. 1038/nn. 3625

PubMed Abstract | CrossRef Full Text | Google Scholar

243. Hill DF, Parent KL, Atcherley CW, Cowen SL, Heien ML. Differential release of dopamine in the nucleus accumbens evoked by low-versus high-frequency medial prefrontal cortex stimulation. *Brain Stimul* . (2018) 11: 426–34. doi: 10. 1016/j. brs. 2017. 11. 010

PubMed Abstract | CrossRef Full Text | Google Scholar

244. Roitman MF, Wheeler RA, Carelli RM. Nucleus accumbens neurons are innately tuned for rewarding and aversive taste stimuli, encode their predictors, and are linked to motor output. *Neuron* (2005) 45: 587–97. doi: 10. 1016/j. neuron. 2004. 12. 055

PubMed Abstract | CrossRef Full Text | Google Scholar

245. Venton BJ, Seipel AT, Phillips PE, Wetsel WC, Gitler D, Greengard P, et al. Cocaine increases dopamine release by mobilization of a synapsin-dependent reserve pool. *J Neurosci* (2006) 26: 3206–9. doi: 10. 1523/JNEUROSCI. 4901-04. 2006

PubMed Abstract | CrossRef Full Text | Google Scholar

246. Zimmerman CA, Leib DE, Knight ZA. Neural circuits underlying thirst and fluid homeostasis. *Nat Rev Neurosci* . (2017) 18: 459–69. doi: 10. 1038/nrn. 2017. 71

PubMed Abstract | CrossRef Full Text | Google Scholar

247. Richard JE, Anderberg RH, Lopez-Ferreras L, Olandersson K, Skibicka KP. Sex and estrogens alter the action of glucagon-like peptide-1 on reward. *Biol Sex Differ* (2016) 7: 6. doi: 10. 1186/s13293-016-0059-9

PubMed Abstract | CrossRef Full Text | Google Scholar

248. Santollo J. Sex differences in angiotensin II-stimulated fluid intake. *Exp Physiol* . (2017) 102: 1380–4. doi: 10. 1113/EP086518

PubMed Abstract | CrossRef Full Text | Google Scholar

249. Santollo J, Volcko KL, Daniels D. Sex differences in the behavioral desensitization of water intake observed after repeated central injections of angiotensin II. *Endocrinology* (2018) 159: 676–84. doi: 10. 1210/en. 2017-00848

PubMed Abstract | CrossRef Full Text | Google Scholar

250. Santollo J, Marshall A, Curtis KS, Speth RC, Clark SD, Daniels D. Divergent effects of ERalpha and ERbeta on fluid intake by female rats are not dependent on concomitant changes in AT1R expression or body weight. *Am J Physiol Regul Integr Comp Physiol* . (2016) 311: R14–23. doi: 10. 1152/ajpregu. 00102. 2016

CrossRef Full Text | Google Scholar