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Neural circuit mechanisms underlying emotional regulation of homeostatic feeding

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Abstract

The neural circuits controlling feeding and emotional behaviors are intricately and reciprocally connected. Recent technological developments, including cell type-specific optogenetic and chemogenetic approaches, allow for functional characterization of genetically-defined cell populations and neural circuits in feeding and emotional processes. Here, we review recent studies that have utilized circuit-based manipulations to decipher the functional interactions between neural circuits controlling feeding and those controlling emotional processes. Specifically, we highlight newly-described neural circuit interactions between classical emotion-related brain regions, such as hippocampus and amygdala, and homeostatic feeding circuitry in the arcuate nucleus and lateral hypothalamus. Together, these circuits will provide a template for future studies to examine functional interactions between feeding and emotion.

Behavioral Interactions Between Feeding and Emotion

Since feeding is essential for survival, the brain has evolved multiple overlapping mechanisms to assure adequate levels of food intake during changing energy demands [1–4]. Ultimately, the decision to eat is controlled by neuronal activity in distributed feeding centers that primarily reside in the hypothalamus, hindbrain, and limbic brain regions [1–4]. These feeding centers are anatomically connected with broadly distributed brain regions that convey emotional information. Consistently, feeding and emotions are known to be interrelated on a behavioral level [5]. For example, psychiatric disorders are often associated with changes in feeding behavior and metabolic disorders including obesity are associated with an increased risk for developing mood and anxiety disorders [6–8]. However, the anatomy and function of the underlying neural circuits that govern interactions between feeding and emotion remain largely underexplored. Here, we review newly-described neural circuits in mice that are responsible for assigning emotional valence to feeding. Particularly, we will discuss how distinct hypothalamic feeding neurons bidirectionally communicate with emotional circuitry to control emotional aspects of feeding behavior.

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Regulation of Diverse Emotional Behaviors by Arcuate Feeding Neurons

It is well recognized that the arcuate nucleus of the hypothalamus (ARC) has a primary role in feeding [1–4]. For example, chemogenetic (glossary) and optogenetic activation of ARC neurons expressing *agouti-related protein* (ARC^{AGRP}) increases feeding in sated mice [9, 10]. Selective activation of ARC^{AGRP} neuronal projections to either paraventricular hypothalamus (PVH), lateral hypothalamus (LH), or anterior bed nucleus of the stria terminalis (αBNST) was sufficient to rapidly increase food intake in sated animals [11–13], while activation of ARC projections to other brain regions involved in emotion, such as periaqueductal gray (PAG) and the central nucleus of the amygdala (CeA) did not increase feeding [11, 12]. Interestingly, chemogenetic and optogenetic manipulation of ARC^{AGRP} neurons also potently modulated diverse emotional and motivational behaviors including emotional valence, anxiety, aggression, and fear-related behaviors [14–19]. A series of recent studies suggest that ARC^{AGRP} neurons modulate emotional processes in an effort to suppress competing emotional states and prioritize motivational drives towards food acquisition [14, 15, 19]. For example, although mice normally avoid areas associated with danger or threats, during food deprivation or activation of ARC^{AGRP} neurons, mice approached fear-associated (such as areas previously paired with shocks) or threat-associated (paired with predator scents) areas to obtain food [14, 15, 19]. Together, these findings suggest that ARC^{AGRP} neurons, in addition to promoting feeding, are involved in modulating motivational states in accordance with changing energy demands and environmental conditions.

Although the neural circuits governing ARC^{AGRP} neural regulation of emotional behaviors remain incompletely resolved, a circuit mediating the role of ARC^{AGRP} neurons in aggression was recently described [15]. In this study, the authors found that chemogenetic activation of ARC^{AGRP} neurons in sated mice recapitulated the reduced fear, aggression, and anxiety-related behaviors observed in fasted mice [15, 16]. Further experiments determined that ARC^{AGRP} neurons projected to and inhibited neuropeptide Y receptor type 1 expressing (NPY^{R1}) neurons in medial amygdala (MEA) to both evoke feeding in a free access feeding paradigm and reduce aggressive behavior in the resident-intruder assay [15]. The NPY1R neurons in MeA project to neurons localized in posterior BNST (pBNST) to evoke aggression-related behaviors. In this manner, ARC^{AGRP} neurons project to MeA to inhibit downstream neural circuits that promote aggression. These results provide an excellent template for future studies to investigate the circuit mechanisms governing the role of additional ARC^{AGRP} projections in emotional processes as similar circuit tracing and behavioral approaches can be utilized to decipher the precise ARC^{AGRP} neuron circuits that mediate anxiety or fear-related behaviors. For example, the diverse projection targets of ARC^{AGRP} neurons to brain regions involved in fear and anxiety, including amygdala and periaqueductal gray (PAG), may partially underlie the function of these neurons in these emotional processes [11, 20]. In particular, inhibitory projections from ARC^{AGRP} neurons to the PAG may suppress fear or anxiety-related responses by inhibiting PAG neurons which promote fear and anxiety, although this hypothesis requires further testing [21].

The ability of ARC^{AGRP} neurons to modulate emotional behaviors has important implications. Namely, the suppression of fear [14, 15, 19], aggression [15], and anxiety

behavior [14–16] likely facilitates more proactive and risky food seeking behaviors during times of negative energy balance, supported by a recent study showing that chemogenetic activation of ARC^{AGRP} neurons increases foraging behavior [16]. Meanwhile, suppression of fear and aggression may conserve energy production during times of hunger or nutrient scarcity. In the case of fear-associated behaviors, activation of the prototypical “fight or flight” pathway is energy costly as confronting an aggressor or fleeing from a threat would require valuable energy resources that must be conserved during times of negative energy balance. Therefore, ARC^{AGRP} neurons appear to promote positive energy balance via distributed actions that both promote feeding and conserve energy resources.

Lateral Hypothalamus Modulates the Mesolimbic Reward Circuitry

Along with arcuate nucleus (ARC), lateral hypothalamus (LH) is well-recognized as a “feeding center” in the brain. Much of LH’s effect on feeding has been attributed to the close association between LH and ventral tegmental area (VTA) of the mesolimbic reward system [22]. Of particular importance to emotion and feeding, disruption in the mesolimbic dopamine system consisting of nucleus accumbens and VTA is linked to changes in mood and emotions [23–25]. However, the functional interactions between hypothalamic feeding circuitry and mesolimbic reward pathways remain unclear.

Recent studies, however, have provided new insights into the interactions between LH and the mesolimbic reward system by manipulating genetically defined LH projections to VTA [26, 27]. For example, optogenetic stimulation of LH projections to VTA drove mice to compulsively cross a shock grid to obtain sucrose rewards in a pavlovian conditioning approach task [26]. In this task, an audiovisual cue was paired with the delivery of a sucrose reward, and mice were first trained to associate cues with reward delivery and upon cue presentation, cross an inactive shock grid to obtain sucrose rewards. Following the training, sucrose port entries were recorded during a baseline period where cues were delivered in the absence of shocks. Port entries were then recorded with an active shock grid in response to cue presentation both with and without optogenetic stimulation of LH projections to VTA. Generally, mice learn to inhibit appetitive responses towards reward-associated cues in the presence of learned cue-shock associations. However, optogenetic stimulation of LH inputs to VTA selectively increased the likelihood of mice crossing an active shock grid to obtain sucrose rewards following cue presentation. By contrast, optogenetic inhibition of LH inputs to VTA reduced compulsive sucrose seeking behaviors [26]. Stimulation of the same circuit did not affect feeding during baseline trials in the absence of foot shocks, suggesting that LH inputs to VTA specifically control compulsive food-seeding [26]. From a therapeutic perspective, such a circuit has major advantages as approaches that target this specific circuit pathway may be able to selectively affect maladaptive compulsive forms of feeding while maintaining normal energy homeostasis and feeding. Indeed, optogenetic inhibition of LH projections to VTA did not impact basal levels of food intake in hungry mice during a free access feeding paradigm [26].

It was demonstrated that LH projections to VTA that control compulsive sucrose seeking contain both excitatory and inhibitory synaptic inputs [26]. Interestingly, selective stimulation of LH GABAergic inputs to VTA increased basal food intake in sated mice

while stimulation of LH glutamatergic inputs did not affect basal feeding, suggesting that GABAergic and glutamatergic inputs to VTA exert distinct functions in basal and compulsive feeding [26]. Therefore, compulsive sucrose seeking seems to rely on the concerted efforts of both GABAergic and glutamatergic inputs to VTA while GABAergic inputs to VTA are sufficient to drive feeding in sated animals. In addition to the role of LH GABAergic projections to VTA in feeding, these projections also potently modulate emotional behaviors. For example, in a real time place preference assay, optogenetic stimulation of LH GABAergic inputs to VTA promoted approach behaviors and was rewarding as mice actively preferred locations paired with optogenetic stimulation of this projection pathway [27]. On a functional level, LH GABAergic projections to VTA inhibited the activity of local GABAergic interneurons in VTA, subsequently activating VTA dopamine neurons [27]. Consistently, stimulation of LH GABAergic inputs in VTA robustly increased dopamine levels in the nucleus accumbens, indicating that LH GABAergic projections to VTA likely increase feeding by activating mesolimbic VTA-NAc dopamine projections [27].

Taken together, LH GABAergic neurons robustly increase appetitive and consummatory feeding [28, 29] in large part by stimulating the mesolimbic dopamine reward pathway [26, 27]. Of interest to emotions, optogenetic manipulation of VTA dopaminergic neurons [30] or their projections to NAc [24] controls depressive-related behaviors in animal models of depression, such as chronic social defeat stress. Given that changes in feeding behavior are common in mood and anxiety disorders [5–8], further studies are needed to investigate functional interactions between the LH feeding and mesolimbic reward circuitry in the context of emotion-related pathological conditions including mood and anxiety disorders.

LH GABAergic Neurons Receive Inputs from Emotional Circuitry

Given that LH GABAergic neurons potently regulate feeding and emotional processes, synaptic inputs to these neurons are also likely to regulate feeding and emotional behavior since integrated synaptic strength controls neural activity. LH GABAergic neurons receive synaptic inputs from brain regions classically involved in emotion-related behaviors including lateral septum [31] and nucleus accumbens [23], and manipulation of these inputs to LH regulates feeding. For example, a recent study utilized a closed-loop optogenetic stimulation protocol to investigate the role of nucleus accumbens dopamine type 1 receptor expressing neurons (NAc^{D1R}) and their inputs to LH in feeding [32]. In this study, ongoing feeding was detected in real-time to detect when a mouse licked at least three consecutive times from a sucrose dispensing port and following three consecutive sucrose port licks, optogenetic stimulation of NAc^{D1R} inputs to LH was provided for 500 ms. Remarkably, the authors found that selective optogenetic stimulation of the NAc^{D1R} to LH pathway rapidly suppressed ongoing feeding [32], and further circuit tracing approaches were utilized to determine that NAc^{D1R} neurons release GABA to selectively inhibit orexigenic LH GABAergic neurons [32]. Additional work is necessary to explore the role of this circuit pathway in emotional processes, such as anxiety and depressive behaviors. However, it is noteworthy that NAc^{D1R} neurons have previously been linked to emotion-related feeding disturbances [33, 34]. For example, synaptic transmission onto NAc^{D1R} neurons was altered following a chronic restraint stress induced-anorexia model [33]. Given that NAc^{D1R}

neurons control feeding behaviors [32, 34] and are altered in emotion-related feeding disorders [33], NAc^{D1R} neurons and their projections to LH GABAergic neurons may in part underlie the association between depressive disorders and altered feeding states. Further studies utilizing rodent animal models of emotional disorders may shed additional light into the role of this circuit pathway in pathological forms of feeding behavior.

Another recently identified origin of inhibitory inputs to LH GABAergic neurons consists of septal GABAergic neurons that relay appetitive suppressive information to LH GABAergic neurons [35]. Similar to NAc^{D1R} neurons, synaptic and neural alterations in the septal nucleus are also implicated in emotion-based feeding disorders [36–38]. In particular, inhibition of lateral septum neurons blocked stress-induced reductions in food intake [38], although it remains unclear if septal GABAergic projections to LH GABAergic neurons are involved in the role of lateral septum in stress-induced alterations in feeding, or other components of emotional behavior. However, given that septum both modulates feeding [35, 39–41] and affective behaviors [31], septal inputs to LH appear poised to govern emotional components of feeding behavior.

In summary, synaptic inputs from lateral septum and nucleus accumbens modulate the activity of LH GABAergic neurons [32, 35]. LH GABAergic neurons in turn project to VTA to potently stimulate the mesolimbic dopamine reward circuitry and drive appetitive and approach behaviors [27]. Further studies are needed to determine if cell type-specific inputs to LH GABAergic neurons are altered during pathological forms of emotion-related feeding disorders since LH GABAergic neurons are well positioned between neural circuits controlling emotional behaviors and those controlling homeostatic and hedonic feeding states.

LH Glutamatergic Neurons Reduce Feeding via Connections with Emotional Circuitry

Contrasting to the orexigenic role of LH GABAergic neurons, glutamatergic neurons in the LH exert negative effects on feeding [42, 43]. For instance, optogenetic stimulation of LH glutamatergic neurons reduced feeding and was aversive while selective ablation of LH glutamatergic neurons increased food intake [42, 43]. The acute appetite-reducing effect of LH glutamatergic neurons appears to be independent of projections to VTA as selective optogenetic stimulation or inhibition of LH glutamatergic projections to VTA did not affect basal feeding, although this circuit pathway was aversive in a real time place preference assay [27]. In addition to VTA, LH glutamatergic neurons project to lateral habenula (Lhb), a brain region involved in reward and depressive behavior [43, 44]. Optogenetic stimulation of glutamatergic LH to Lhb projections decreased food intake in sated mice when provided free access to a palatable liquid diet and promoted aversion in a real-time place preference assay [43]. Of note, lateral habenula also projects to VTA, suggesting that LH glutamatergic inputs to Lhb may be another indirect pathway for LH neurons to control the activity of VTA neurons [22, 43].

Meanwhile, the synaptic inputs to LH glutamatergic neurons also imply a role for these neurons in emotional regulation of feeding as LH glutamatergic neurons receive inhibitory

inputs from the bed nucleus of the stria terminalis (BNST), a key subcortical brain region involved in relaying stress and emotion-related information to limbic structures [45–47]. Selective optogenetic stimulation of BNST GABAergic inputs onto LH glutamatergic neurons robustly and rapidly increased food intake in well-fed mice [42]. Interestingly, a separate study reported that optogenetic stimulation of BNST projections to LH reduced anxiety-related behavior in the open field test and elevated plus maze test of anxiety behavior [46], indicating that BNST projections to LH also control anxiety behavior. However, the postsynaptic population in LH mediating the anxiolytic role of BNST to LH projections remains unknown. Since LH glutamatergic and LH GABAergic neurons have opposite functions in feeding and emotion-related behaviors [22, 26–29, 35, 42, 43], it appears that different emotion centers in brain (NAc, BNST, septum) selectively target opposing cell types in the LH to bi-directionally control feeding and emotion-related behaviors. Further studies are needed to determine if these cell type-specific projections to distinct postsynaptic neurons in LH are static in nature or if these connections are altered under diverse metabolic and emotional conditions. Also, it is important to note that other distinct cell populations in the LH, such as neurotensin (NTS) and orexin (OX) neurons, are also involved in the regulation of feeding and emotional processes [48–51], although the precise afferent and efferent inputs to these cell types and the role of these circuits in emotional components of feeding remain underexplored.

Newly-Identified Hippocampal and Amygdala Feeding Circuits

As discussed above, primary feeding centers localized in ARC and LH, in addition to regulating feeding, also modulate emotional processes. On the other hand, emotion-related brain regions including hippocampus and amygdala modulate feeding behavior [5]. For instance, the hippocampal formation (HPC) has been classically implicated in emotional behaviors, including anxiety and depressive behavior [52–55]. In addition to the hippocampus' role in emotion, numerous lines of evidence support a role for hippocampus, and in particular its ventral pole (vHPC), in feeding behavior [56]. For example, feeding-related peptides (e.g., ghrelin, leptin, and glucagon-like peptide 1) signal in hippocampus to modulate feeding and synaptic plasticity [57–62]. Orexigenic ghrelin signaling in vHPC increases feeding behavior [60, 61], while anorexigenic leptin [58] or glucagon like-peptide 1 (GLP-1) [57] signaling in vHPC reduces feeding. Although the hippocampus was previously known to bi-directionally influence feeding [56, 63, 64], until recently the precise neural circuits responsible for hippocampal control of feeding remained unclear.

One putative neural circuit that contributes to the role of vHPC in feeding was recently described [60]. In this study, the authors utilized food entrainment feeding paradigms to restrict food access to a four-hour period each day for 8 consecutive days. During this paradigm, pharmacological blockade of the ghrelin receptor (GHSR) in vHPC decreased food intake while vHPC ghrelin administration facilitated feeding [60, 61]. Further anterograde track tracing and immunohistological approaches determined that vHPC GHSR neurons project to LH orexin neurons and pharmacological blockage of this projection pathway blocked the orexigenic effect of vHPC ghrelin signaling in conditioned feeding responses [60]. While these findings are interesting, the precise neural circuits connecting vHPC ghrelin neurons to orexin neurons in the LH remain to be determined as vHPC

projects directly to LH as well as indirectly through NAc, BNST, and LS [54, 56, 65]. Furthermore, given that ventral hippocampal leptin and GLP-1 signaling have been reported to decrease feeding behavior [57, 58], additional work is needed to determine the downstream neural circuits connecting hippocampal leptin and GLP-1 signaling to primary feeding circuitry in the hypothalamus or elsewhere.

A second recent report suggests an additional neural circuit pathway by which vHPC may control feeding [65]. In this study, free access feeding behavior was assayed in well fed mice following optogenetic and/or chemogenetic activation of vHPC neurons and their downstream projection targets. Consistent with previous reports that hippocampus exerts a tonic inhibitory effect on feeding behavior [64, 66, 67], chemogenetic activation of excitatory glutamatergic neurons in vHPC reduced food intake during a free-access feeding paradigm in *ad libitum* fed mice [65]. Further optogenetic manipulations and circuit tracing experiments determined that vHPC projections to the lateral septum are sufficient to acutely reduce dark period food intake [65]. Additional studies are needed to independently validate the significance of vHPC inputs to LS and LH in various metabolic states and experimental conditions. Furthermore, given that vHPC modulates emotional processes, such as anxiety and fear [52, 55, 68], the functional interactions between vHPC projections controlling emotional behaviors [54, 69, 70] and those controlling feeding remain unknown. One possibility is that vHPC modulates feeding by directly and indirectly projecting to downstream cell populations involved in energy homeostasis (e.g., LS, BNST, LH, NAc) while vHPC controls emotional behaviors by projecting to downstream brain regions involved in emotion (e.g., amygdala, cortex, BNST, LS). Supportively, vHPC projections to nucleus accumbens [54] and cortex [70] were recently shown to mediate depressive-related behaviors and fear conditioning, respectively, indicating that different vHPC projections may control distinct behaviors.

In addition to ventral hippocampus, the amygdala has classically been connected to emotional behaviors, including fear and anxiety behaviors [21, 71]. Given the close association between feeding and emotion [5], there is great interest in determining if amygdala circuits contribute to these interactions. Indeed, abundant evidence indicates a role for amygdala in feeding behavior [63, 72, 73], although the underlying neural circuits governing the amygdala's role in feeding remained inconclusive. Recent findings, however, have provided new insights into the functional amygdalar circuits that govern feeding behavior and suggest that the amygdala is well positioned to integrate feeding-related inputs from hypothalamus, hindbrain, and cortex to regulate feeding.

Recent reports demonstrate that amygdala is directly responsive to hindbrain satiety information. Following meal consumption vagal nerve inputs from the gut converge on neurons in the nucleus of the solitary track (NTS). NTS projects to another key hindbrain satiety center, the parabrachial nucleus (PBN) [74–77]. Neurons in the outer external lateral subdivision of PBN (PBelo) expressing the gene encoding calcitonin gene-related peptide (CGRP) are recruited downstream of NTS following conditions that suppress feeding, such as visceral satiety input [76–78]. Interestingly, optogenetic activation of PBelo CGRP neuronal projections to the lateral capsule of the central nucleus of the amygdala (CeL) reduces feeding, indicating that amygdala neurons directly respond to hindbrain satiety

circuits to reduce feeding [78]. However, the role of this circuit pathway in emotional processing remains unclear. A recent report suggests that a specific subset of neurons in CeL might mediate the role of this amygdala sub-region in feeding behavior [79]. Specifically, GABAergic neurons in CeL expressing protein kinase C-δ (PKC-δ) responded to diverse anorexigenic signals [79] in a similar manner as described for PBN CGRP neurons [77–79]. Consistently, real-time feeding assays revealed that optogenetic activation of CeL PKC-δ neurons profoundly reduced feeding in both food-deprived and well-fed mice, while optogenetic inactivation of these neurons increased feeding [79]. Although the amygdala controls anxiety behaviors [21, 71], optogenetic activation of CeL PKC-δ neurons did not alter anxiety-related behaviors in the open field or elevated plus maze test [79]. However, given that CeL PKC-δ neurons suppress conditioned fear-related behaviors [21, 80] and central amygdala mediates aversive cue-induced suppression of feeding [73], further work is needed to determine how distinct cell populations in the central amygdala mediate physiological and pathological forms of feeding and/or fear-related behaviors.

Along with the central nucleus of the amygdala, neurons within the medial basolateral amygdala (mBLA) and medial nucleus of the amygdala (MeA) also contribute to feeding behavior [15, 81]. For example, excitatory neurons in the mBLA receive input from D1 type dopamine receptor expressing neurons in the prefrontal cortex (PFC^{D1R}) and optogenetic stimulation of this pathway increased food intake during an overnight free access feeding paradigm [81]. Within the neighboring medial nucleus of amygdala, chemogenetic activation of neuropeptide Y 1 receptor (NPY1R) expressing neurons both reduced feeding during dark period free access feeding assays and evoked aggression in a resident-intruder assay [15]. In light of these findings, it appears that multiple discrete amygdala sub-regions, including mBLA, CeL, and MeA, contribute to feeding behavior in functionally distinct manners. Further work is needed to fully decipher how the distinct amygdala sub-regions integrate various feeding related information and ultimately relay this input to the hypothalamic feeding circuitry to control feeding behavior. Nonetheless, distinct amygdala neurons integrate feeding-related information from hindbrain satiety centers, ARC^{AGRP} neurons, and higher order cortical brain regions to modulate feeding behavior, as depicted in Figure 1.

Although hippocampal and amygdalar circuits control fear and anxiety behaviors [21, 53, 54, 69–71, 80] and feeding behavior [15, 60, 65, 79, 81], the functional interactions between the hippocampal and amygdalar circuits controlling emotion and feeding remain largely unknown. One possibility is that neural circuits in hippocampus and/or amygdala are involved in detecting a real or perceived threat and acutely suppressing feeding behavior to divert motivational needs towards combating apparent environmental threats. Further studies are needed to fully investigate how the recently described hippocampal and amygdalar feeding circuits interact with the known functions of these structures in anxiety and fear-related behaviors during competing or changing motivational drive states.

Concluding Remarks and Future Perspectives

It has been proposed that emotions evolved to reinforce behaviors that promote survival [82]. Since feeding is essential for survival, neural circuit overlap between brain regions controlling feeding and emotions is hardly surprising. At the neural circuit level, key

hypothalamic feeding centers (such as ARC and LH) are bi-directionally connected to brain regions that convey emotional information, including vHPC, amygdala, VTA, NAc, LS, and BNST (Table 1). These bidirectional connections modulate both feeding and emotional processes including anxiety, fear, and aggressive behavior. We propose that emotional circuits interact with feeding circuits to modulate feeding and motivational states in accordance with constantly changing metabolic demands and environmental conditions. Future work may utilize novel advances in whole brain activity mapping and/or imaging approaches, such as Clarity [83, 84], to further probe the distributed communication between feeding and emotion hubs in response to changes in feeding or emotional state (see Outstanding Questions). For example, chemo/optogenetic approaches may be combined with whole brain imaging techniques and functional neuroanatomy to more completely identify functional interactions between hypothalamic feeding neurons and diverse emotion centers. These studies should expand the knowledge of interactions between feeding and emotional neural circuits beyond the level of the individual neural circuit connections described above and towards a more holistic expanded view of neural circuit interactions during functional feeding behaviors or emotional processes. Meanwhile, no widely successful clinical treatment options exist for certain emotion-related feeding disorders, such as anorexia nervosa [85]. Therefore, an increased understanding of the basic neural circuitry underlying interactions between feeding and emotion is likely necessary for the development of new pharmacological treatments for emotion-related feeding disorders.

Outstanding Questions

- Since ARC^{AGRP} neurons modulate fear, anxiety, and aggression, what specific downstream targets mediate these effects and under what conditions?
- How do newly-described LH feeding circuits interact with mesolimbic reward circuitry in the context of pathological conditions associated with mood and anxiety disorders?
- Amygdala and ventral hippocampus modulate feeding via connections with hypothalamic and/or hindbrain brain regions. How do these neural circuits interact with the ventral hippocampal and amygdala circuits controlling fear and anxiety behaviors? Do potential circuit interactions downstream of the hippocampus and/or amygdala link “higher level” emotional processes with appropriate feeding behavioral responses?
- Emerging evidence suggests broad and diverse connections between primary feeding circuits in hypothalamus and emotional brain structures. How are these distributed networks altered during feeding and/or emotional behaviors? Can these connections be functionally analyzed and understood beyond the level of individual circuits?

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Glossary

Chemogenetics
A behavioral neuroscience approach that utilizes designer receptors exclusively activated by designer drugs (DREADDs) that couple to intracellular signaling pathways to selectively activate or inhibit defined neuronal cell-types. Targeted neurons are activated or inhibited via injection of a blood brain barrier-permeable ligand that selectively binds to these receptors to activate intracellular signaling pathways.

Optogenetics
A behavioral neuroscience approach that utilizes microbial opsins and light to selectively activate or inhibit genetically defined cell-types.

Free Access Feeding Paradigm
Animals are provided non-conditional access to food during feeding behavior measurements.

Resident-Intruder Assay
A behavioral test of aggressive behavior in which an unfamiliar male rodent is introduced into the cage of another male rodent and aggressive behavior, such as attack behaviors, are recorded and quantified.

Negative Energy Balance
When energy expenditure exceeds energy intake.

Real-Time Place Preference Assay
Behavioral assay of aversion in which exploratory activity is recorded in an arena and stimulation or inhibition of a circuit pathway is selectively coupled with exploration of one half of the arena. The preference for each side of the arena is determined during real time exploration and scored as a measure of aversive behavior.

Chronic Social Defeat Stress
Rodent animal model of stress-induced depressive behavior in which rodents are exposed to multiple days of intermittent physical attack by a dominant mouse followed by more extended sensory contact (but not physical contact) with a dominant mouse.

Chronic Restraint Stress
Animal model of stress induced behavior abnormalities in which rodents are physically restrained for multiple days.

Open Field Test (OFT)
Test of locomotor behavior and anxiety behavior in which activity in an open field is measured and quantified. The time spent in the center of the arena relative to the corner of the arena is scored as a measure of anxiety-related behavior, with increased time in the center indicating reduced anxiety behavior.

Elevated-Plus Maze (EPM)

Test of anxiety-related behavior. Exploratory activity is scored in a maze that consists of two arms of equal distance. One arm is enclosed by walls while the other arm is exposed and not enclosed by arms. The relative amount of time that the animal spends in the exposed, anxiety-provoking arms, vs. the enclosed arms is scored as a measure of anxiety-related behavior.

Ghrelin
Stomach derived peptide secreted during times of hunger to drive feeding behavior.

Leptin
Adipose tissue derived satiety peptide that is secreted in proportion to fat stores.

Glucagon-Like Peptide 1
Satiety-promoting peptide secreted by neurons in the hindbrain and gastrointestinal track (GI track).

Clarity
A tissue clearing method that produces transparent brain tissue, facilitating whole-brain imaging across broadly distributed brain regions.

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Trends

- Distinct ARC^{AGRP} neuron circuits regulate feeding and diverse emotional states. These circuits modulate multiple emotional processes in accordance with changing energy demands and environmental conditions to promote positive energy balance.
- $LH^{GABAergic}$ and $LH^{glutamatergic}$ neurons exert opposing effects on feeding behavior and emotional behavior. These neurons control feeding via bi-directional interactions with emotional circuitry, including bed nucleus of the stria terminalis (BNST), septum, lateral habenula, and ventral tegmental area.
- Hippocampus regulates feeding via neural circuit interactions with the lateral septum and lateral hypothalamus, although additional neural circuit mechanisms remain unknown.
- Amygdala circuits integrate homeostatic inputs from hypothalamus, cognitive inputs from prefrontal cortex, and visceral inputs from hindbrain satiety centers to modulate feeding.

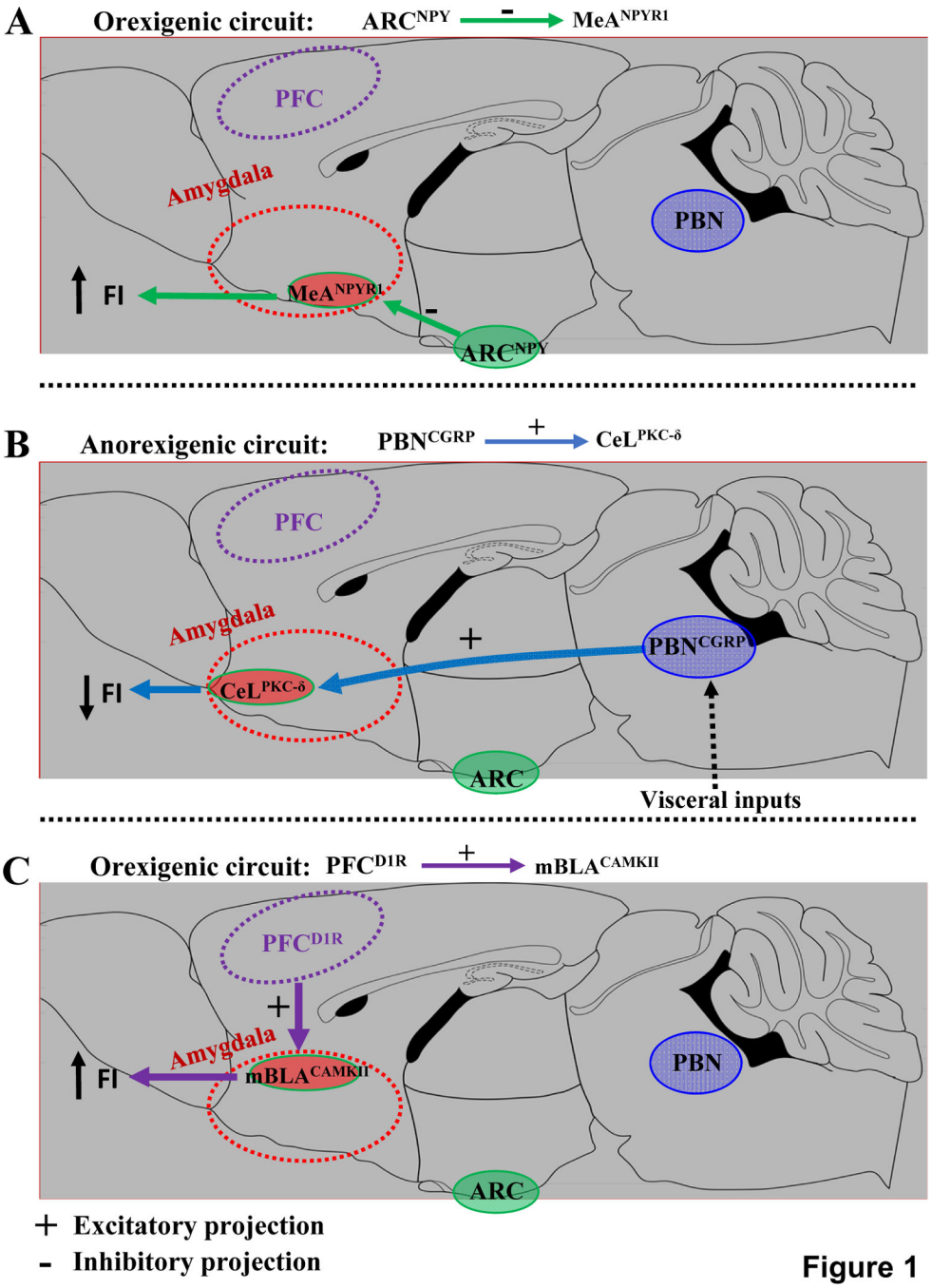

Figure 1. Amygdala Integrates Homeostatic, Cognitive, and Visceral Inputs to Control Feeding

Distinct neural populations within the amygdala control feeding by integrating input from homeostatic, visceral, and cognitive centers. (**A**) Hypothalamic input conveying homeostatic energy state information is transferred to the amygdala via inhibitory projections from ARC^{NPY} neurons to NPYR1 expressing neurons in MeA to increase food intake (FI). (**B**) Visceral inputs suppresse food intake, at least in part, by directly or indirectly activating PBN^{CGRP} excitatory neurons that project to neurons in the CeL that express PKC-δ. (**C**) Neurons in the mPFC which express the dopamine receptor 1 (D1) project to and activate

excitatory CAMKII neurons in mBLA to increase food intake. The projections downstream of the amygdala that ultimately control feeding remain unknown, although they may involve projections to hypothalamic and/or hindbrain feeding centers. CGRP (calcitonin gene-related peptide), NPY (neuropeptide Y), NPYR1 (neuropeptide Y receptor type 1), PKC (protein kinase C), CAMKII (Calcium/calmodulin-dependent protein kinase II), D1 (dopamine receptor type 1), CeL (amygdala central nucleus, lateral division), mBLA (medial basolateral amygdala), vHPC (ventral hippocampus), PFC (prefrontal cortex).

Table 1

Overview of recently described CNS feeding circuits

Feeding Circuit	Impact on Feeding	Refs
NAc^{D1R} > LH^{GABA}	Inhibitory inputs from NAc rapidly reduce feeding by inhibiting LH^{GABA} neurons.	[32]
PVT^{GLUT} > NAc	Glucose sensitive neurons in paraventricular thalamus that are activated in response to low glucose concentrations increase sucrose seeking behaviors by providing excitatory inputs to neurons in NAc.	[86]
$Septum^{GABA}$ > LH^{GABA}	GABAergic neurons in septum reduce feeding by providing inhibitory synaptic connections to LH GABAergic neurons.	[35]
$BNST^{GABA}$ > LH^{GLUT}	GABAergic neurons in BNST selectively project to glutamatergic neurons in LH to increase feeding.	[42]
ARC^{AGRP} > aBNST	ARC^{AGRP} neurons provide inhibitory GABAergic input to neurons in anterior BNST to increase feeding.	[11]
ARC^{AGRP} > PVH^{MC4R}	ARC^{AGRP} neurons increase feeding by inhibiting postsynaptic melanocortin 4 receptor-expressing neurons in PVH.	[11,89,97]
ARC^{oxtr} > PVH^{MC4R}	Glutamatergic neurons in ARC that express the oxytocin receptor activate MC4R-neurons in PVH to rapidly suppress feeding.	[87]
ARC^{AGRP} > LH	Inhibitory GABAergic projections from ARC^{AGRP} neurons to the lateral hypothalamus rapidly increase feeding.	[11, 89]
ARC^{AGRP} > PVT	ARC^{AGRP} projections to paraventricular thalamus increase feeding, albeit to a lesser extent than ARC^{AGRP} projections to aBNST, PVH, and LH.	[11]
ARC^{AGRP} > PBN^{CGRP}	Hunger driving ARC^{AGRP} neurons project to and inhibit visceral satiety controlling PBN^{CGRP} neurons to increase ongoing food intake.	[77]
ARC^{AGRP} > MeA^{NPY1R}	ARC^{AGRP} neurons project to and inhibit neurons expressing the NPY 1 receptor in the medial amygdala to increase feeding.	[15]
ARC^{TH} > PVH	Tyrosine hydroxylase expressing neurons in ARC locally inhibit ARC^{POMC} neurons and postsynaptic neurons in PVH to increase feeding.	[88]
PVH^{MC4R} > LPBN	MC4R-expressing neurons in PVH provide excitatory glutamatergic input to LPBN neurons that do not co-express CGRP. This excitatory input suppresses feeding.	[89]
$PVH^{Glutamate}$ > ARC^{AGRP}	Subsets of excitatory neurons in PVH expressing thyrotropin-releasing hormone (TRH) and pituitary adenylate cyclase-activating polypeptide (PACAP) increase feeding via excitatory connections to ARC^{AGRP} neurons.	[90]
PVH^{SIM1} > vlPAQ/DR	Silencing of excitatory synaptic input from PVH to ventrolateral periaqueductal gray (vlPAQ) and dorsal raphe complex (DR) increases feeding, suggesting that these projections are involved in suppressing food intake.	[91]
$vDMH^{LepR}$ > ARC^{AGRP}	GABAergic leptin receptor expressing-neurons in the ventral dorsomedial nucleus of the hypothalamus inhibit ARC^{AGRP} neurons to reduce feeding.	[92]
PBN^{CGRP} > CeAlc	Glutamatergic projections from PBN^{CGRP} neurons to the laterocapsular division of the central nucleus of the amygdala reduce feeding.	[78]
RMg/ROb^{5HT} > NTS	Serotonin (5HT) projections from the raphe magnus (RMg) and raphe obscurus (ROb) act on postsynaptic 5HT3 receptors in NTS to reduce feeding.	[75]
NTS^{CCK} > PVH^{MC4R}	Neurons in NTS that express cholecystokinin (CCK) project to PVH^{MC4R} neurons to reduce feeding.	[93]
$NTS^{CCK, DBH}$ > PBN^{CGRP}	Two molecularly distinct but functionally convergent excitatory pathways from NTS to PBN^{CGRP} neurons reduce feeding. One pathway consists of NTS neurons that express CCK and another consists of noradrenergic neurons expressing dopamine β-hydroxylase (DBH).	[94]
$mPFC^{D1R}$ >$mBLA^{CamKII}$	Medial prefrontal cortex neurons expressing the dopamine D1 receptor project to CamKII positive neurons in mBLA to increase feeding.	[81]
$vHPC^{Glutamate}$ > LS	Glutamatergic neurons in ventral hippocampus project to lateral septum to reduce feeding.	[65]
$vHPC^{GHSR}$ > LH^{orexin}	Connections between ghrelin receptor expressing-neurons in ventral hippocampus and orexin receptor expressing-neurons in LH mediate vHPC ghrelin regulated control of feeding behavior.	[60]

Feeding Circuit	Impact on Feeding	Refs
LH^{GABA} > VTA^{GABA}	GABAergic neurons in LH project to inhibitory GABAergic interneurons in VTA to increase feeding. This projection disinhibits VTA dopamine neurons, increasing their firing rate.	[27]
LH^{GABA} > PVH	GABAergic neurons in LH project to PVH to increase feeding.	[95]
$LH^{Glutamate}$ > Lhb	Glutamatergic neurons in LH project to neurons in lateral habenula to decrease feeding.	[43]
BF^{Ach} > ARC	Acetylcholine neurons in the basal forebrain reduce feeding by projecting to neurons in the arcuate nucleus. The specific postsynaptic target neuron in ARC remains unknown.	[96]