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Feeding behavior survival circuit: anticipation & competition

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A decision to eat or not to eat can be beneficial or detrimental to an organism, depending on internal and external conditions. Because feeding is essential for survival, as it replenishes energy and nutrients, in safe environments, its expression is prioritized over other behaviors. Under threat, responding to danger is a higher priority for survival and feeding is paused even in hungry states. Thus, successful expression of feeding behavior requires adaptive control that utilizes cognitive processes to dynamically assess and update internal drives and environmental changes. Recently identified key circuit components, which are important in anticipatory responding based on food memories and predictions and in resolving feeding versus threat avoidance competition, will be discussed within a connectional schema.

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Introduction

Organisms must feed to survive. They also need to avoid danger and adjust feeding behavior (foraging and consumption) accordingly. A decision to eat or not to eat, therefore, reflects both the internal drives and external conditions. In safe environments, when energy and nutrient resources are low or their depletion is anticipated, feeding takes priority over other behaviors. Conversely, under imminent threat, real or anticipated, attending and responding to danger takes priority over replenishing energy and nutrients, and feeding is halted even in hungry states. Accordingly, successful expression of feeding is coordinated with other survival behaviors (e.g. defensive), and is regulated in response to actual and expected events (e.g. energy and nutrients usage/gains, danger, reward).

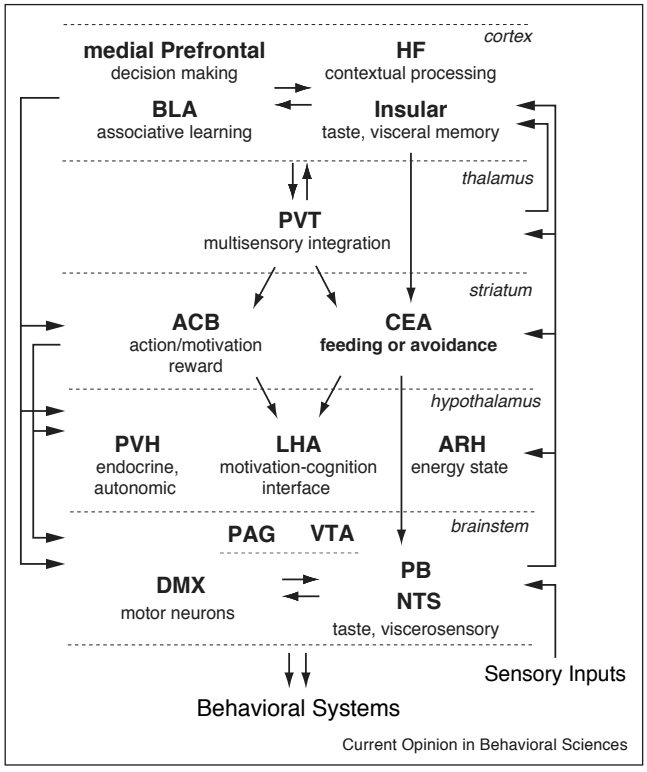
The assessments of internal and external environments that guide feeding behavior engage cognitive processes, including learning and memory and decision-making. These computations are complex but do not require consciousness; they can occur in the absence, or independent, of conscious awareness and the fundamental principles are conserved across mammals. Consequently, research findings in animal models have improved our understanding of the neural mechanisms underlying human feeding control and its dysregulation (e.g. [1,2]). Notable progress has been made in uncovering the neural mechanisms mediating physiological control of food consumption, in the context of energy metabolism and body weight regulation [3]. In contrast, much remains unknown about the neural mechanisms mediating adaptive control of feeding behavior. In part, this is due to scarcity of prior behavioral investigations combined with neural analyses, and in part due to methodological limitations and complexity of the underlying neural substrates. Recent methodological advancements with optogenetics and chemogenetics have enabled cell-specific manipulations within functional circuits in behaving animals [4,5]. Novel circuit mechanisms underlying adaptive control of feeding behavior that were revealed with these approaches are highlighted here within an established connectional schema. These findings are interpreted within the concept of survival circuits that was put forward by LeDoux and others [6–8].

Survival circuits: a brief overview of connectional organization

Anatomical connections in rodents indicate that the neural systems underlying mammalian survival behaviors are similarly organized [9,10]. Within each circuitry, physiological and environmental sensory inputs could converge with cognitive, hedonic and behavioral state information at multiple stages of processing. The expression of each behavior is accompanied with appropriate physiological (endocrine, autonomic) responses and their coordinated expression is orchestrated through hypothalamic systems. These circuitries could cross-communicate, and have access to sensory and motor brainstem areas, cognitive processing via cortical and hippocampal systems, and action and reward control via striatal systems [9,10].

The connectional patterns further suggest that the incoming and processed information could be shared across the forebrain-brainstem components, via converging or parallel pathways (Figure 1). Similarly, each circuit's outputs (cognitive, behavioral, physiological) could be initiated after different stages of processing. Consequently, distinct

Figure 1



Feeding behavior neural network.
The diagram depicts the organization of the connections that mediate adaptive control of feeding behavior. For clarity, some brains areas are not shown (e.g. pallidal regions) and only select areas and connections that were discussed in the text are represented. Abbreviations: ACB-nucleus accumbens; ARH-arcuate nucleus of the hypothalamus; BLA-basolateral area of the amygdala; CEA-central nucleus of the amygdala; DMX-dorsal motor nucleus vagus nerve; HF-hippocampal formation (includes hippocampal proper and subiculum); LHA-lateral hypothalamic area; NTS-nucleus of the solitary tract; PAG-periaqueductal gray; PB-parabrachial nucleus; PVH-paraventricular hypothalamic nucleus; PVT-paraventricular thalamic nucleus; VTA-ventral tegmental area.

functional circuitries may be recruited within a broader connectional network, depending on the type of input (physiological, cognitive) and levels of processing, from innate (reflex) to highly integrated (predictive). For instance, when survival depends on rapid control of feeding—to enhance food seeking and consumption under starvation or to pause these behaviors when encountering a proximal danger—relatively simple, reflex-type circuitries may be engaged [11], similar to the patterns observed in defensive behaviors [12,13]. Under other circumstances, more complex computations within an integrated circuitry determine the expression of feeding behavior. These processes involve continuous assessments of internal and external environments and updating through cognitive processes (learning and memory, decision-making, planning) about ongoing and expected changes.

Anticipatory regulation of feeding: learning and memory integration across the network

The ability to regulate an ongoing behavior in anticipation of future events is clearly advantageous to survival. Regulation of feeding in anticipation of future energy changes is also advantageous physiologically, as it should minimize the extent of homeostatic perturbations [14]. Adaptive regulation is based on prior experience but how learning and memory are integrated within the feeding circuitry has not been clear. Recent work demonstrated that hypothalamic neurons are critical for food memory encoding and recall, and that acquired predictions are dynamically updated across the feeding circuitry.

Hypothalamus: food memories and predictions

In a recent study, Sharpe *et al.* [15••] demonstrated with optogenetic methods in a novel GAD-Cre rat that the lateral hypothalamic GAD-expressing (LHA^{GABA}) neurons are required for cue-food learning and memory. They manipulated the LHA^{GABA} neurons during a Pavlovian conditioning task, where cue-food associations were assessed by the cue's ability to drive food seeking (food receptacle approach). Temporally selective silencing of the LHA^{GABA} neurons during the cue presentations disrupted the acquisition and memory of cue-food associations. These findings are consistent with prior evidence that the LHA is recruited during cue-food learning acquisition [16] and that the LHA^{GABA} neurons are critical in the control of feeding behavior ([17–19]. Indeed, the LHA may function as a motivation-cognition interface within the feeding network [20].

Another hypothalamic area, the arcuate nucleus (ARH) is considered a primary sensory relay for energy balance signals. It contains two sets of neurons, orexigenic, AgRP (NPY/GABA) and anorexigenic, POMC/CART. These neurons respond to energy signals (e.g. adipose-released hormone, leptin), GI-derived satiety signals (e.g. CCK), and food deprivation (ghrelin) in opposite ways to ultimately stimulate or inhibit food consumption, respectively [3]. Intriguingly, these neurons respond rapidly upon food presentation during a meal, which suggests they are dynamically guided by predicted, rather than actual, meal-associated changes. Chen *et al.* [21••] found that in fasted mice, the activity of the AgRP (NPY/GABA) neurons was high, as expected, but it decreased as soon as food was presented and eating began. The opposite was found for the POMC/CART neurons. When food was removed during a meal, these patterns were reset, activity of AgRP neurons increased, while POMC/CART neurons decreased.

According to these patterns, the ARH neurons may be critical during the food seeking rather than consumption phases of feeding behavior (additional evidence reviewed in [3]). In that regard, Livneh *et al.* [22••] demonstrated in mice that the AgRP neurons regulate food seeking

induced by food cues and processing within the insular cortex, according to hunger state. They found that the AgRP neurons reach the insular cortex via relays in the paraventricular thalamus (PVT) and the basolateral amygdala (BLA). Interestingly, at least the PVT and insular components of that circuitry also guide flexible behavioral control under competing cognitive drives.

Insular cortex, paraventricular thalamus & central amygdala: behavioral guidance during flexible, anticipatory responding

Mammals, from rodents to primates, show innate preference for sweet over biter tastes, indicated by acceptance and rejection swallowing patterns, respectively [23]. These biases likely reflect hardwired survival strategies, as typically sweet tastes signal nutrients while bitter tastes predict decayed foods. The input and output components of the basic circuitry for these responses—the sensory (taste) and motor (controlling orofacial muscles) neurons—are located in the brainstem [10]. Accordingly, rats with the brainstem disconnected from the forebrain can respond reflexively to accept sweet and reject bitter tastes [24]. Without the brainstem-forebrain communications, however, these rats cannot integrate prior experience and respond in a flexible way [24]. It has been known for a long time that the insular cortex is important for taste integration and memory [25,26], but the circuitry through which it guides feeding behavior based on taste-associated memory has not been clear. A recent study demonstrated that its pathway to the central nucleus of the amygdala (CEA) is necessary in guiding flexible anticipatory responding when different cues predict appetitive (sweet) or aversive (bitter) tastes [27••].

In mice, Schiff *et al.* [27••] identified an excitatory monosynaptic connection from the insular cortex to the lateral CEA, somatostatin and PKCδ neurons. They demonstrated that the insular-CEAl pathway is required during a go/no-go task, where mice respond to one cue to receive a sweet (sucrose) liquid and withhold responding to another cue in order to avoid a bitter (quinine) liquid. Bilateral inhibition of the transmission within the insular-CEAl pathway, with the tetanus toxin light chain expressed in a Cre-dependent manner, impaired correct responding, most notably during the no-go trials when animals suppress licking in response to the quinine cue. These manipulations specifically impacted adaptive control, when behavioral choice is guided by cues, but not when mice responded to increased concentration of quinine. Activation of the insular-CEAl pathway by photostimulation was sufficient to induce lick suppression and place aversion and to serve as a negative reinforcer (instead of quinine).

The CEA is well positioned to coordinate suppression of feeding behavior in anticipation of multifaceted aversive outcomes. In addition to the insular cortex, it receives cortical inputs from the BLA, PFC and HF [28], as well as inputs from the brainstem sensory and feeding areas (reviewed in [29•]). Some of these inputs have been shown to selectively promote appetitive or avoidance behaviors. Optogenetic stimulation of distinct BLA pathways (from neurons expressing Rspo2 or Ppp1r1b) to the CEA, induced freezing or self-stimulation [30••]. The BLA inputs to the mPFC (prelimbic area), which could potentially reach the CEA, bias the expression of defensive behaviors [31]. The BLA-mPFC pathways are topographically organized and distinct subsystems may differently bias appetitive and aversive behaviors [32,33].

The CEA is also connected with the PVT [34,35], which mediates adaptive responding when food reward- and danger cue-induced behaviors are pitted against each other. Choi and McNally [36••] demonstrated that chemogenetic silencing of the PVT selectively interfered with balancing the expression of food seeking (lever presses and approach to food receptacle) and threat avoidance (freezing), but did not impact the expression of either behavior alone or bias the balance in one direction.

Silencing the PVT did not completely reverse the balance between food seeking and threat avoidance, indicating that additional areas within the critical circuitry contribute to the computations that resolve the outcome of these competitions. These additional areas could exert influence by impacting the PVT targets, notably two striatal regions, the nucleus accumbens (ACB) and CEA [34,35,37]. Prior, influential work has established the ACB in motivational and hedonic control of feeding behavior, and provided the foundation for its interactions with the LHA and ventral pallidum [38,39]. Recent work found that the ACB dopamine D2 receptor–expressing neurons inhibit food-reward seeking under innate threat, and their responses were guided by the LHA orexin/hypocretin neurons [40•]. The PVT receives inputs from the mPFC and hippocampal formation [41], which could concurrently influence the ACB and CEA [42–46].

Central amygdala circuitry in resolving feeding versus threat avoidance competition

Cessation of eating under threat is adaptive, as it enables the expression of defensive behaviors. The CEA is necessary for cessation of food consumption in response to innate and learned threats, as well as satiety signals [29•,47,48]. To effectively inhibit feeding behavior, the CEA is structurally well positioned to engage multiple pathways that would simultaneously impact hypothalamic and brainstem targets [29•]. The CEA is also well positioned to receive physiological and environmental sensory inputs from different stages of processing, including integrated information from cortical and thalamic areas (discussion above, Figure 1). Functional activation patterns during fearcue induced anorexia suggest that the CEA circuitry coordinates conflict resolution when threat

avoidance competes with food consumption [29•]. In accordance with an integrative role in adaptive control of survival behaviors, the CEA has been shown to coordinate the expression of prey hunting and biting behaviors through divergent pathways [49].

The CEA also drives food consumption [29•] and Douglass *et al.* [50•] showed that the serotonin receptor 2a-expressing (CEA^{Htr2a}) neurons are critical. The activity of these neurons increased during food consumption and their bidirectional manipulations modulated intake accordingly. The effects of these manipulations were reinforcing, based on food and place preference and self-stimulation assays. This study also identified that CEA^{Htr2a} neurons inhibit local and brainstem targets that suppress food consumption, the $CEA^{PKC\delta}$ neurons [48], and the parabrachial nucleus [51]. Thus, the CEA substrates underlying the drives to consume or avoid food may compete at multiple targets.

The CEA neurons are exceedingly diverse [30••,52,53] and determining how they are organized locally and at their targets remains an important inquiry. Another area of pressing interest is determining individual differences that lead to dysregulation and maladaptive behaviors. In that regard, there are profound sex differences in anorexia nervosa, and in animal models of threat (fear cue) induced short-term anorexia female rats show enhanced inhibition of feeding compared to males [54–56]. There are also sex differences in the mPFC recruitment during inhibition of feeding under threat, as well as under a cognitive drive to eat [29•,57]. That work highlights the mPFC circuitry, as a potential source of vulnerability to maladaptive control of feeding.

Concluding remarks

Adaptive control of feeding behavior is essential for survival. The underlying mechanisms require interactions between cognitive, hedonic, and physiological systems. Accordingly, these processes are supported by a highly integrated and exceedingly complex neural circuitry. The schematic in Figure 1 illustrates multiple anatomical pathways that could support distinct functional circuitries during adaptive control of feeding behavior, depending on the type of input (physiological, cognitive) and a degree of processing (shorter versus longer and more integrated loops between sensory inputs and behavioral outputs for reflexive versus cognitive control). Recently identified circuit components that are important during anticipatory regulation of feeding and during competition with other survival behaviors are conceptualized within this framework (Figure 1). Displayed are novel findings that hypothalamic neurons participate in formation of food memories and that acquired predictions are dynamically updated across the feeding network, and that the central amygdala circuitry resolves feeding and threat avoidance competition. The outlined network may serve as a blueprint for future work investigating adaptive regulation of feeding, as well as for potential sites of dysregulation when hunger and other survival drives compete.

Conflict of interest statement

Nothing declared.

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