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Review

Overlapping Brain Circuits for Homeostatic and Hedonic Feeding

Mark A. Rossi[1] and Garret D. Stuber[1,2,3,*]
[1]Department of Psychiatry
[2]Neuroscience Center
[3]Department of Cell Biology and Physiology
University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA
*Correspondence: gstuber@med.unc.edu
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Central regulation of food intake is a key mechanism contributing to energy homeostasis. Many neural circuits that are thought to orchestrate feeding behavior overlap with the brain's reward circuitry both anatomically and functionally. Manipulation of numerous neural pathways can simultaneously influence food intake and reward. Two key systems underlying these processes—those controlling homeostatic and hedonic feeding—are often treated as independent. Homeostatic feeding is necessary for basic metabolic processes and survival, while hedonic feeding is driven by sensory perception or pleasure. Despite this distinction, their functional and anatomical overlap implies considerable interaction that is often overlooked. Here, we argue that the neurocircuits controlling homeostatic feeding and hedonic feeding are not completely dissociable given the current data and urge researchers to assess behaviors extending beyond food intake in investigations of the neural control of feeding.

Tightly regulating energy intake is necessary for survival of all animals. A critical component of energy balance is the ability to obtain and consume food sufficient to meet ongoing metabolic demands. The neurocircuits controlling feeding behavior are thought to be disrupted in pathologies of hypophagia (e.g., resulting in anorexia nervosa) or hyperphagia (e.g., resulting in obesity). In other pathologies, such as substance abuse, the neural circuits traditionally thought to control feeding may be co-opted by drugs of abuse, suggesting overlapping feeding and reward circuitry within the brain. The cells most closely linked to facilitating feeding are intermingled with the cells most closely linked to reward-guided behavior. A comprehensive understanding of these systems will greatly facilitate our understanding of pathologies that rely on feeding and reward circuits. Here, we pose the question of whether such circuits are indeed dissociable and should ultimately be considered separately given the current data and accepted approaches.

For more than half a century, scientists have struggled to understand the intermingled neural basis of reward and feeding (Berridge, 1996; Hoebel and Teitelbaum, 1962; Margules and Olds, 1962; Wise, 2004). Despite early recognition that feeding and reward are intimately linked, these two topics have frequently been examined in isolation for practical reasons. For example, studies have looked at the contribution of particular brain regions to body weight regulation, energy expenditure, and food intake (for review, see Elmquist et al., 1999; Morton et al., 2006), while others focused on the role of neuronal populations in reward-guided behavior (Corbett and Wise, 1980; Morris et al., 2006; Schultz, 2002), but relatively few have considered the two together (Castro et al., 2015; Saper et al., 2002) (Table 1). Despite much progress toward understanding how certain parts of the brain contribute to either feeding or reward, questions of motivated behavior continue to be framed in terms of *homeostatic feeding*—food intake that is necessary to maintain typical body weight and metabolic function—or *hedonic feeding*—food intake driven by sensory perception or pleasure. These distinctions can be helpful to guide first-pass efforts to define basic functional elements of integrated neural circuits; however, homeostatic and hedonic feeding systems are likely both activated during all feeding situations. The degree to which each is activated may shift depending on the type of food (i.e., palatable or aversive) and the physiological state of the animal (i.e., starvation).

The anatomical interconnectedness, as well as the functional consequences of perturbation, of classical homeostatic and hedonic neurocircuits suggests that they contribute to a more complex motivational system. With a few notable exceptions discussed below, optogenetic or chemogenetic activation of appetite-stimulating cells often produces rewarding phenotypes (a preference or willingness to work for stimulation), whereas activating appetite-inhibiting cells tends to be aversive (avoidance of stimulation) (Jennings et al., 2013a, 2015). Here, we will discuss anatomical and functional evidence to support the claim that homeostatic and hedonic feeding circuits are not presently dissociable from one another. We have divided the relevant brain regions into three broad categories: ventricular, intermediate, and monoaminergic. Ventricular neurons are those cells that are positioned adjacent to the third ventricle, regulate food intake, densely express receptors for a variety of circulating hormones, and project to downstream "intermediate" targets. Intermediate neurons are those cells implicated in feeding that are positioned downstream of ventricular cells. Intermediate cell groups can provide synaptic feedback onto ventricular neurons and interact heavily with one another. Determining anatomical and physiological links between ventricular neurons and postsynaptic, molecularly defined intermediate neurons is still an active area of research, but we have included discussion of

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Table 1. Acute Manipulations of Molecularly and Anatomically Defined Neurons that Influence Food Intake Also Affect Appetitive Behavior

Area	Cell Type	Manipulation		Food Intake	Appetitive Behavior	References
Arc	AgRP	ChR2, Gq, Gs, TRPV1	↑	+	+/–	Aponte et al., 2011; Krashes et al., 2011; Atasoy et al., 2012; Betley et al., 2015; Dietrich et al., 2015; Chen et al., 2016; Nakajima et al., 2016
	AgRP	Gi	↓	–	?	Krashes et al., 2011
	POMC	ChR2 (extended), Gq (chronic)	↑	–	?	Aponte et al., 2011; Zhan et al., 2013
	POMC	Gi (24 hr intake)	↓	+	?	Atasoy et al., 2012
	TH	ChIEF	↑	+	?	Zhang and van den Pol, 2016
	Vglut2	Gq	↑	–	?	Fenselau et al., 2017
	Vglut2	Gi	↓	+	?	Fenselau et al., 2017
	Oxtr	Gq	↑	–	?	Fenselau et al., 2017
PVN	SIM1	Gi	↓	+	?	Atasoy et al., 2012
	TRH	Gq	↑	+	?	Krashes et al., 2014
	PACAP	Gq, Gs	↑	+	?	Krashes et al., 2014; Nakajima et al., 2016
	MC4R	Gq	↑	–	?	Garfield et al., 2015
	MC4R	Gi	↓	+	?	Garfield et al., 2015
CeA	PKCδ	Gi, eNpHR3.0	↓	+	?	Cai et al., 2014a
	PKCδ	ChR2	↑	–	/	Cai et al., 2014a
	Tac2	ChR2	↑	/	?	Cai et al., 2014a
	Crf	ChR2	↑	/	?	Cai et al., 2014a
	Sst	eArch3.0	↓	/	?	Kim et al., 2017
	Crf/Nts/Tac2	eArch3.0	↓	/	?	Kim et al., 2017
	Nts	eArch3.0	↓	/	?	Kim et al., 2017
	Tac2	eArch3.0	↓	/	?	Kim et al., 2017
	Vgat	ChR2	↑	+	?	Han et al., 2017
	Htr2a	ChR2	↑	+	+	Douglass et al., 2017
	Htr2a	eNpHR3.0	↓	–	/	Douglass et al., 2017
PBN	CGRP	Gq, ChR2	↑	–	?	Carter et al., 2013
	CGRP	Gi	↓	+	?	Carter et al., 2013
	MC4R	Gi	↓	+	?	Garfield et al., 2015
LHA	MC4R	Gq	↑	/	?	Garfield et al., 2015
	Vglut2	ChR2	↑	–	–	Jennings et al., 2013a
	Vglut2	eArch3.0	↓	+	+	Jennings et al., 2013a
	Vgat	Gq, ChR2	↑	+	+	Jennings et al., 2015; Navarro et al., 2016
	Vgat	Gi, eArch3.0	↓	–	–	Jennings et al., 2015; Navarro et al., 2016
	Orexin	Gq	↑	+	?	Inutsuka et al., 2014
VTA	Vgat	ChR2	↑	–	–	Tan et al., 2012; van Zessen et al., 2012
NAc	D1R	eArch3.0	↓	+	?	O'Connor et al., 2015
	D2R	eArch3.0	↓	/	?	O'Connor et al., 2015
PFC	D1R	ChR2	↑	+	?	Land et al., 2014
	D1R	eNpHR3.0	↓	–	?	Land et al., 2014

Appetitive behavior was limited to place preference and self-stimulation behavior. Note that manipulations are grouped by whether they putatively increase (↑) or decrease (↓) neuronal output, but different manipulations that have similar net effects on cellular activity are not necessarily equivalent to each other. +, increase; –, decrease; /, no effect; +/–, increase or decrease depending on experimental conditions; ?, effect unknown.

Arc, arcuate nucleus of the hypothalamus; AgRP, agouti-related peptide; CeA, central nucleus of the hypothalamus; CGRP, calcitonin gene-related peptide; ChIEF, fast-closing mutated channelrhodopsin hybrid; ChR2, channelrhodopsin-2; Crf, corticotrophin releasing factor; D1R, d1-like dopamine receptor; D2R, d2-like dopamine receptor; eArch3.0, archaerhodopsin-3.0; eNpHR3.0, halorhodopsin-3.0; Gq, hM3Dq (Gq-coupled designer receptor exclusively activated by designer drug); Gi, hM4Dq (Gi-coupled designer receptor exclusively activated by designer drug); Htr2a, serotonin receptor 2a; Gs, Gs-coupled designer receptor exclusively activated by designer drug; LHA, lateral hypothalamic area; MC4R, melanocortin 4 receptor; NAc, nucleus accumbens; Oxtr, oxytocin receptor; PACAP, pituitary adenylate cyclase-activating polypeptide; PBN, parabrachial nucleus; PFC, prefrontal cortex; PKCδ, protein kinase C delta type; POMC, proopiomelanocortin; PVN, paraventricular nucleus of the hypothalamus; Sim1, single-minded 1; Sst, somatostatin; Tac2, tachykinin 2; TRH, thyrotropin-releasing hormone; TRPV1, transient receptor potential cation channel subfamily V member 1; Vgat, vesicular GABA transporter; Vglut2, vesicular glutamate transporter 2; VTA, ventral tegmental area.

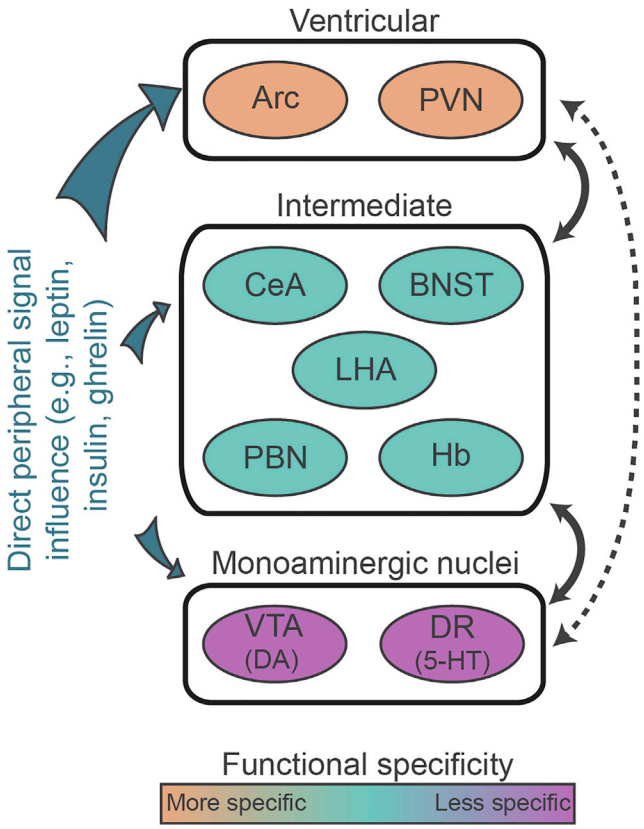

Figure 1. Circuits Involved in Feeding and Reward

Schematic illustration of ventricular, intermediate, and monoaminergic nuclei. There are strong reciprocal connections between ventricular and intermediate as well as intermediate and monoaminergic nuclei (indicated by solid lines). Direct connections between ventricular neurons and monoaminergic nuclei are relatively sparse or absent in adults (indicated by the dashed line). Ventricular neurons express receptors for peripheral signaling molecules implicated in feeding more densely than do intermediate and monoaminergic nuclei. Arc, arcuate nucleus; BNST, bed nucleus of the stria terminalis; CeA, central nucleus of the amygdala; DA, dopamine; DR, dorsal raphe; Hb, habenula; LHA, lateral hypothalamic area; NAc, nucleus accumbens; PBN, parabrachial nucleus; PFC, prefrontal cortex; PVN, paraventricular nucleus of the hypothalamus; VTA, ventral tegmental area; 5-HT, 5-hydroxytryptamine.

the evidence where available. Monoaminergic neurons are found downstream and positioned to receive input from intermediate neurons, but direct input from ventricular neurons is sparse (Figure 1). The functions of given cell groups appear to be relatively specific at the level of ventricular neurons; manipulations of these cells produce pronounced effects on energy homeostasis. Intermediate neurons have more general functions, contributing to reward and aversion as well as food intake and body weight regulation. At the most general level, monoaminergic neurons (i.e., mesolimbic dopamine neurons) are involved in arousal, movement, motivation, and many other adaptive functions. We consider each of these levels and how they contribute to feeding behavior in turn.

The arrangement of neurons discussed here is one of many possible schemes that could be used when discussing complex neural systems. This simplified framework permits distillation of a rich literature, reaching back nearly a century, into a set of concepts that can be contained within a single manuscript. It is partially conceptual and does not imply that other connections do not exist between these brain regions. Although circulating hormones can directly affect cells throughout the brain, we have chosen hypothalamic ventricular cells as a starting point because they tend to express receptors for circulating feeding molecules such as insulin, leptin, and ghrelin more densely than do intermediate or monoaminergic structures (Hill et al., 1986; Scott et al., 2009; Zigman et al., 2006) and because they function most specifically in the regulation of feeding and related behaviors, although they likely have other important functions as well (discussed below). As with any classification system, there are limitations to this approach. In addition to signaling from peripheral hormones, ventricular neurons also receive synaptic input, originating primarily from intra-hypothalamic sources (Wang et al., 2015). However, whether the synaptic input reflects feedback mechanisms or whether it can independently drive activity is unclear. Moreover, the neuronal organization described in this review is a framework for understanding a common theme: neurons most closely related to homeostatic feeding directly and indirectly interface with circuits that influence reward and aversion. Finally, the cell types and projections discussed below represent only a subset of the cells that are known to exist within these regions. Other classes of cells may have unique molecular signatures, connectivity, and functions. The present discussion is limited to neurons that are known to be involved in feeding or reward processing, and functionally unrelated cell types and connections have been omitted for clarity.

Ventricular Neurons of the Hypothalamus

Arcuate Nucleus

Molecularly defined cell types in the arcuate nucleus of the hypothalamus (Arc) are often targeted as an "entry point" to homeostatic feeding circuits because they are strongly influenced by peripheral signals and perturbation robustly influences food intake. These neurons are located in the hypothalamus along the third ventricle and express receptors for many circulating molecules associated with homeostatic feeding, including leptin, ghrelin, and insulin (Cone, 2005; Hill et al., 1986; Scott et al., 2009; Varela and Horvath, 2012; Zigman et al., 2006). Because of their location and responsiveness to circulating hormones, much attention has been given to the cells within the Arc and their role in energy homeostasis. Two Arc neuron populations that are prominently studied in the context of homeostatic feeding exert opposing influences on food intake. They are typically characterized by their non-overlapping molecular expression profiles wherein one group expresses agouti-related peptide (AgRP) and another group expresses proopiomelanocortin (POMC). For comprehensive reviews, see Cone (2005), Elmquist et al. (1999), and Morton et al. (2006).

AgRP-expressing neurons are found exclusively in the Arc and are critically important for feeding in mice. It is generally thought that AgRP neuron output represents an orexigenic, appetite-stimulating signal, as these neurons are activated by fasting. In humans, AgRP expression is negatively correlated with body mass index (Alkemade et al., 2012). Genetic ablation of AGRP neurons causes anorexia and starvation in adult mice despite the fact that neonatally ablated mice develop normally (Gropp et al., 2005; Luquet et al., 2005). In fed mice, acute

optogenetic (Betley et al., 2013) or chemogenetic stimulation induces feeding and food-directed behavior that mimics the behavior of fasted mice (Aponte et al., 2011; Krashes et al., 2011; Nakajima et al., 2016). AgRP neurons co-express genes for neuropeptide Y (*Npy*) (Hahn et al., 1998) and γ-aminobutyric acid (GABA) (Tong et al., 2008), and axon terminals co-release AgRP, Npy, and GABA. They send mostly non-overlapping, long-distance projections throughout the forebrain, hypothalamus, and hindbrain (discussed in detail below) (Betley et al., 2013). AgRP neurons express receptors for and are responsive to a variety of locally produced and circulating molecules including leptin, ghrelin, Npy, and melanocortins (Cone, 2005). Interestingly, optogenetic activation of AgRP neurons promotes feeding only after a relatively long latency (on the order of minutes), despite the finding that the presentation of food rapidly inhibits their activity (Betley et al., 2015; Chen et al., 2015). The rapid inhibition in the absence of consumption may be driven by ascending midbrain and hindbrain signals or through poly-synaptic cortical sensory inputs, though the mechanism is unknown.

POMC neurons are intermingled with and have similar efferent and afferent connectivity to AgRP neurons (Cone, 2005; Wang et al., 2015). It is not known if, like AgRP neurons, individual POMC neurons send long-distance projections to only one target region or if individual neurons send axon collaterals to multiple targets. Arc POMC neurons are thought to functionally oppose AgRP neurons. They tend to co-express β-endorphin and cocaine-amphetamine-regulated transcript and are responsive to circulating hormones including leptin and insulin (Cheung et al., 1997; Cone et al., 2001; Cowley et al., 2001). Leptin, which suppresses appetite, is thought to activate POMC neurons because acute administration induces expression of the immediate early gene *Fos* (Elias et al., 1999) and increases *Socs3* mRNA (Bjørbaek et al., 1999), suggesting activation of negative feedback intracellular pathways in these cells. Ablation of POMC neurons causes hyperphagia and obesity in mice (Gropp et al., 2005; Zhan et al., 2013). Prolonged activation of these cells suppresses feeding via melanocortin receptor activation and reduces body weight (Aponte et al., 2011; Zhan et al., 2013), while prolonged inhibition potentiates food intake (Atasoy et al., 2012). The POMC product, α-melanocyte-stimulating hormone (α-MSH), agonizes melanocortin-4 receptors (MC4R). Deletion of MC4R causes obesity in mice (Huszar et al., 1997), and mutations of MC4R are thought to underlie some forms of obesity in humans (Vaisse et al., 2000). AgRP acts as an inverse agonist of the MC4R (Nijenhuis et al., 2001), suggesting that AgRP and POMC neurons share common downstream targets. Arc POMC neurons are also locally inhibited by AgRP neurons. However, this inhibition is not necessary for AgRP-evoked feeding (Atasoy et al., 2012). Together with the observations that acute optogenetic activation of POMC somata fails to reduce feeding, while extended activation is effective, these results demonstrate that Arc AgRP and POMC neurons differentially influence feeding. However, the mechanisms underlying their functional differences are largely unclear. Since AgRP neurons synapse locally onto POMC neurons and both populations have similar long-range targets, balance between these two opposing systems is likely necessary to maintain energy homeostasis.

Although much research has focused on Arc AgRP and POMC neurons in feeding and energy homeostasis, an additional orexigenic neuron population has recently been identified in the Arc. Optogenetic activation of tyrosine hydroxylase (TH)-expressing neurons in Arc drives food intake in fed mice. These cells detect the orexigenic hormone ghrelin and excite AgRP neurons while inhibiting POMC neurons (Zhang and van den Pol, 2016). Furthermore, oxytocin-receptor-expressing glutamatergic (OXTR-Vglut2) neurons in the Arc rapidly promote satiety via synergistic effects with POMC neurons on postsynaptic MC4R-expressing neurons (Fenselau et al., 2017). Still, little is known about the synaptic connectivity and endogenous activity patterns of these non-canonical feeding neurons.

A notable exception to the phenomenon in which orexigenic neuron stimulation is rewarding and anorexogenic neuron stimulation is aversive involves the activation of AgRP neurons, which produces either aversive or rewarding phenotypes depending on the timing of stimulation with respect to food availability (Figure 2A). Following pairing of one side of a chamber with optogenetic activation of AgRP neurons in the absence of food, mice gradually learn to avoid the stimulation-paired side, displaying conditioned avoidance. One explanation for this is that AgRP neurons guide behavior via a negative-valence signal, which is used by the brain to actively avoid particular locations or environmental stimuli (Betley et al., 2015). If the AgRP neuronal signal drives the perception of hunger, it stands to reason that promoting a feeling of hunger without delivering food would be unpleasant. However, mice will lever-press to deliver AgRP stimulation if food is present and will continue self-stimulating even if food is removed. Importantly, mice fail to acquire robust self-stimulation if initial training is conducted in the absence of food (Chen et al., 2016). These paradoxical results demonstrate that the rewarding properties of AgRP neuron activation depend on the presence of food. While more work is needed to determine the mechanisms underlying this phenomenon, both phenotypes must depend on interactions with downstream targets to influence behavior. An interesting question is whether the rewarding or aversive effects of AgRP neuron stimulation depend on mesolimbic dopamine since dopaminergic circuitry mediates reward and aversion (Lammel et al., 2012).

Paraventricular Nucleus

One of the many long-range output targets for Arc AgRP and POMC neurons is the paraventricular nucleus of the hypothalamus (PVN). It sits adjacent to the third ventricle dorsal to the Arc and is implicated in a wide range of behaviors including feeding, drinking, maternal behavior, and temperature regulation via descending projections to the hindbrain and spinal cord (Insel and Harbaugh, 1989; Leibowitz, 1978; Lu et al., 2001; Stanley and Leibowitz, 1984). Microinjection of Npy into the PVN induces feeding in rats, which can be attenuated by concurrent injection of an MC4R agonist (Cowley et al., 1999). Optogenetic activation of AgRP fibers projecting to PVN recapitulates feeding induced by projection-agnostic AgRP cell body stimulation (Atasoy et al., 2012), and activation of OXTR-Vglut2 projections from Arc to PVN rapidly inhibits feeding (Fenselau et al., 2017). Chemogenetic inhibition of single-minded 1 (*Sim1*)-expressing neurons, postsynaptic targets of AgRP neurons within the PVN, promotes food intake (Atasoy et al., 2012). Similarly,

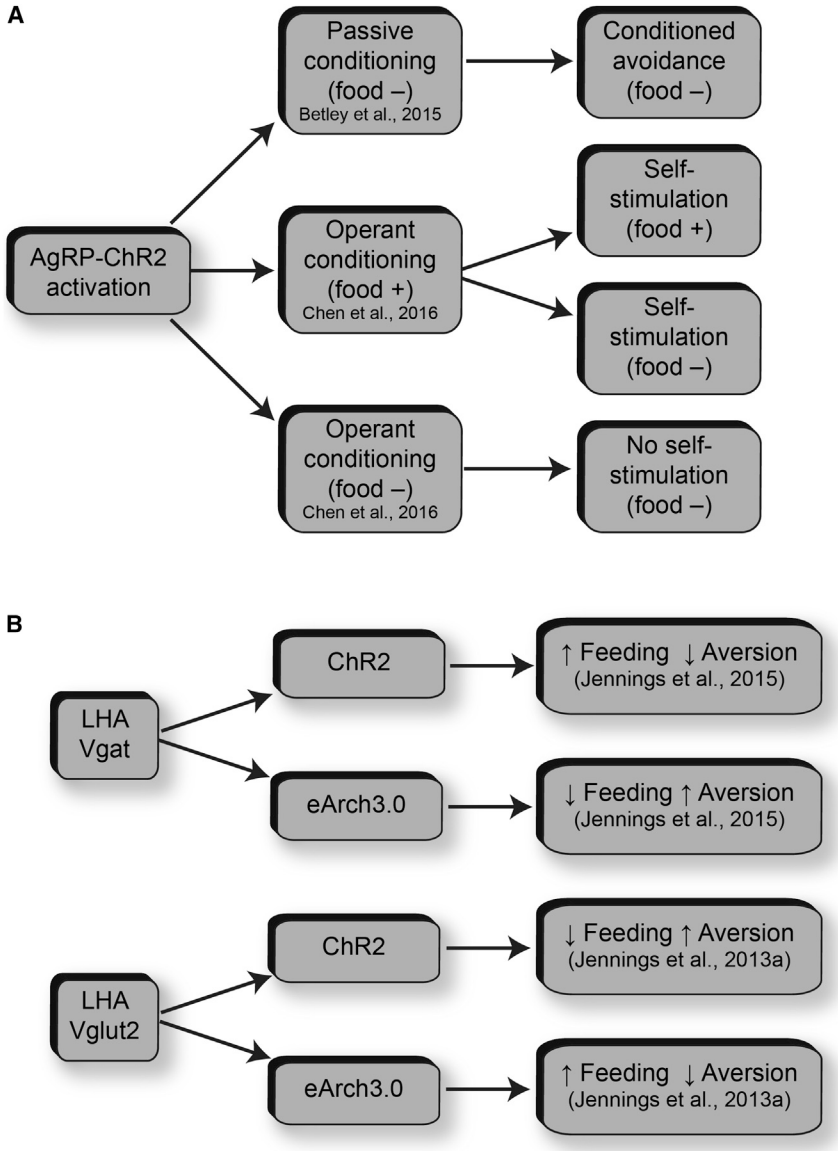

Figure 2. Functional Heterogeneity within Molecularly Defined Hypothalamic Neuronal Populations

(A) Arc AgRP neurons promote context-dependent aversion or reward. Depending on the availability of food, mice will either avoid or lever-press for AgRP stimulation.

(B) Anatomically intermingled, functionally opposing LHA neurons influence feeding and reward.

targeted ablation of PVN-Sim1 neurons produces hyperphagia and obesity (Xi et al., 2013), while chemogenetic activation of MC4R-expressing neurons, a target of both AgRP and POMC neurons, suppresses feeding (Garfield et al., 2015). Optogenetic activation of MC4R-expressing neuronal projections from PVN to PBN suppresses food intake, but interestingly mice do not avoid stimulation in a conditioned place preference assay, suggesting that activation of this pathway is not aversive (Garfield et al., 2015). Paradoxically, an excitatory, orexigenic projection emanating from the PVN and projecting to AgRP neurons in the Arc has recently been described (Krashes et al., 2014), yet how this projection integrates with other cell groups is unclear.

Exactly how the interactions between ventricular neurons and downstream targets coordinate behavior is murky. However, both Arc and PVN neurons project to brain areas that influence a variety of motivated behaviors and ultimately interface with midbrain dopamine neurons. Through higher-order interactions, ventricular neurons gain functions that extend far beyond homeostatic feeding.

Intermediate Areas

We next consider intermediate neurons that are located in discrete anatomical targets that receive axonal innervation from Arc and PVN populations. Intermediate neurons provide feedback to ventricular cells and are highly interconnected with other intermediate and monoaminergic neurons. These cell groups are implicated in both reward processing and feeding as well as other processes that have largely been studied outside the context of feeding behavior. Here, we focus the discussion on the bed nucleus of the stria terminalis (BNST), central amygdala (CeA), parabrachial nucleus (PBN), and lateral hypothalamic area (LHA), but note that this is not an exhaustive list of potential intermediate targets. In general, ablation, electrical stimulation, or pharmacological perturbation of these areas can affect both feeding and reward phenotypes as well as stress and anxiety. However, these anatomically defined regions are heterogeneous in cell type and connectivity, the details of which are largely unknown. Much work is needed to determine the functional relationships between molecularly defined neuronal populations.

PBN

The pontine PBN is often studied for its role in gustation and taste processing. It receives gustatory input via projections from the nucleus of the solitary tract. Lesions of the PBN disrupt the ability to acquire conditioned taste aversion while sparing conditioned flavor preference (Reilly et al., 1993). Electrophysiological recordings show that PBN neurons are reciprocally connected with CeA and LHA and respond to a variety of tastants (Li et al., 2005). Together, these results suggest that in addition to relaying taste information to forebrain structures, PBN is also critical for learning about taste.

The PBN receives synaptic input from both AgRP and POMC neurons as well as other intermediate populations (Betley et al.,

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2013; Carter et al., 2013; Stachniak et al., 2014; Williams and Elmquist, 2012; Wu et al., 2009). It is thought that the inhibitory drive from AgRP neurons onto PBN cells suppresses feelings of malaise that can influence food intake and reward-directed behavior. When inhibition from ventricular neurons is removed by genetically eliminating GABA release from AgRP neurons, the resulting hyperactivity of PBN halts feeding (Wu et al., 2009, 2012). In agreement with these results, PBN neurons respond to malaise (Swank and Bernstein, 1994) and can alter the rewarding properties of food (Söderpalm and Berridge, 2000). Interestingly, PBN neurons that encode calcitonin gene-related peptide (CGRP) exhibit Fos induction that is inversely related to food intake. Acute activation of PBN-CGRP neurons or their projections to CeA suppresses feeding (Carter et al., 2013). Acute inhibition of somata or projections to CeA restores feeding during conditions that suppress appetite but does not induce feeding in sated mice (Campos et al., 2017; Carter et al., 2013). Of relevance to the present discussion, PBN neurons send long-distance projections to LHA, ventral tegmental area (VTA), PVN, BNST, CeA, and nucleus accumbens (NAc) (Fulwiler and Saper, 1984; Moga et al., 1990; Pritchard et al., 2000), thus positioning this area to integrate input related to energy needs from ventricular neurons with visceral signals (i.e., visceral malaise) to tune goal-oriented behavior. Indeed, optogenetic stimulation of MC4R-expressing neurons projecting from PVN to PBN ($MC4R^{PVN \rightarrow PBN}$) suppresses food intake. Unlike other intermediate populations, which tend to be either anorexigenic and aversive or orexigenic and appetitive, hungry mice prefer $MC4R^{PVN \rightarrow PBN}$ stimulation (Garfield et al., 2015), though the broader circuit mechanisms underlying this phenomenon are unknown.

Extended Amygdala

The extended amygdala comprises distinct nuclei that have historically been implicated in anxiety, stress, and fear learning (Cassell et al., 1999). Two components of the extended amygdala that are involved in both reward and feeding are the BNST and the CeA. These areas receive input from ventricular neurons and have diverse projections to intermediate and monoaminergic targets.

The BNST is a critical mediator of anxiety and fear learning that acts in coordination with other amygdaloid nuclei to regulate physiological responses to threats (Walker et al., 2003). Chemical lesions of BNST prevent rats from expressing anxiety-like behavior following aversive foot shock conditioning (Hammack et al., 2004). Electrical stimulation induces aggressive behavior in cats (Shaikh et al., 1986), potentiates anxiety-like behavior, and elevates plasma corticosterone in rats (Casada and Dafny, 1991; Dunn, 1987). Although limited attention has been given to its role in feeding, manipulations of BNST circuitry can have profound effects on food intake and reward. Optogenetic activation of AgRP fibers within the BNST evokes food intake in fed mice (Betley et al., 2013). Similarly, optogenetic activation of GABAergic BNST efferent projections to the LHA induces feeding and reward-related behaviors (Jennings et al., 2013a). It is commonly thought that inhibition of food intake by stress is mediated by corticotrophin-releasing factor (CRF). Antagonizing CRF2 receptors within the BNST potentiates feeding following restraint stress (Ohata and Shibasaki, 2011), but the role of BNST CRF is unlikely to be limited to feeding (Kash et al., 2015). Many of the details underlying the synaptic relationships between ventricular and intermediate neurons within the BNST remain to be elucidated. Presently, the postsynaptic targets of AgRP neurons within the BNST are unknown. However, feeding induced by stimulation of BNST-projecting AgRP neurons is not affected by simultaneous inhibition of putative downstream MC4R neurons within the BNST (Garfield et al., 2015).

Importantly, the BNST also receives convergent input from a variety of regions implicated in reward and anxiety phenotypes, including the amygdala, hippocampal formation, prefrontal cortex (PFC), and VTA (Weller and Smith, 1982). Chemogenetic activation of Npy1R-expressing neurons, downstream targets of AgRP neurons within the medial amygdala that project to BNST, suppresses food intake and increases territorial aggression (Padilla et al., 2016). BNST neurons project to LHA (Jennings et al., 2013a) and the VTA (Jennings et al., 2013b). These projections can influence anxiety states and reward phenotypes (reviewed by Stamatakis et al., 2014). The present data suggest that the BNST is a critical modulator of stress and anxiety responses and may inhibit food intake in order to bias behavior toward defensive action.

The CeA is an amygdaloid nucleus involved in regulating fear and anxiety responses. Lesions of the CeA disrupt Pavlovian learning and the expression of conditioned fear responses (e.g., freezing, elevated heart rate, and elevated arterial pressure), whereas electrical stimulation produces bradycardia and reduces blood pressure (Baxter and Murray, 2002; Kapp et al., 1979, 1982). Although it is primarily studied in the context of fear learning and anxiety, the CeA can also influence food intake. CeA neurons receive direct input from both AgRP and Arc POMC neurons. In contrast to the BNST, activation of AgRP projections within the CeA fails to induce feeding in sated mice (Betley et al., 2013), but administration of an MC4R antagonist directly into the CeA potentiates feeding in rats (Kask and Schiöth, 2000). Together, these results suggest that Arc POMC neurons may uniquely influence feeding via CeA projections, though this remains to be tested. Recent work has shown that molecularly and anatomically distinct neuron populations within the CeA may selectively control unique aspects of feeding and reward (Kim et al., 2017). A subset of CeA neurons (protein kinase C-δ neurons) are activated by anorexigenic signals, and optogenetic inhibition drives food intake (Cai et al., 2014a). Optogenetic activation of CeA neurons expressing serotonin receptor 2a or their axons within the PBN facilitates food intake and promotes approach (Douglass et al., 2017). Unique CeA outputs may also differentially contribute to feeding and reward-related behaviors. Indeed, descending GABAergic projections from CeA to the periaqueductal gray control prey pursuit while projections to the reticular formation control jaw movements associated with feeding in mice (Han et al., 2017). Much work is needed to understand why lesions of the CeA have relatively little effect on energy homeostasis and reward-directed behavior, yet acute manipulations influence food intake and food-directed behavior. A more detailed understanding of the synaptic connectivity and molecular profiles of CeA neurons will help to shed light on these issues.

In addition to afferents from ventricular neurons, the CeA also receives synaptic input from many cortical, thalamic, and intra-amygdala cells (Samson et al., 2005) and projects to BNST, LHA, NAc, and ascending neuromodulatory cell groups in the

midbrain and hindbrain (Sah et al., 2003). As such, the CeA is well positioned to modify and coordinate fear and anxiety behaviors as well as reward seeking and feeding. Given its established role in modulating anxiety states (Tye et al., 2011), one possibility is that the CeA integrates diverse inputs to select behaviors based on the current state of the organism and ensure proper physiological arousal. When threats are perceived, CeA-mediated fear behaviors may dominate by suppressing feeding and other competing drives, likely in coordination with the BNST. This possibility remains to be directly tested.

LHA

The LHA is a critical link between feeding and reward. The cells located here receive input from ventricular neurons and have diverse efferent and afferent connections with reward circuitry. Both AgRP and Arc POMC neurons project to LHA (Wang et al., 2015) and these same projections can be activated by the satiety signal, leptin (Elias et al., 1999). Historically, the LHA was treated as a ''feeding center'' based on the finding that ablation produces hypophagia and starvation (Anand and Brobeck, 1951a, 1951b), whereas electrical stimulation elicits feeding (Hoebel and Teitelbaum, 1962; Margules and Olds, 1962). However, these results have been difficult to interpret because LHA manipulations also have profound effects on motivation and reward phenotypes (Carr and Simon, 1984; Hoebel and Teitelbaum, 1962; Stuber and Wise, 2016; Teitelbaum and Epstein, 1962). Rodents and primates reliably self-stimulate for electrical stimulation of the LHA at the same sites that elicit feeding (Margules and Olds, 1962; Rolls et al., 1980). Similarly, both deprivation state and the administration of circulating satiety signals such as insulin, glucagon, or leptin can modify the rate of LHA self-stimulation (Abrahamsen et al., 1995; Balagura and Hoebel, 1967; Carr and Wolinsky, 1993; Fulton et al., 2000). The mechanisms underlying electrical self-stimulation are multifaceted, though, as it can have divergent effects on proximal or distal sites, is not cell-type specific, and can influence fibers of passage.

As has been discussed previously (DiLeone et al., 2003; Stuber and Wise, 2016), there is considerable molecular and anatomical heterogeneity within the LHA. This, along with the dramatic effects that coarse manipulations have on feeding and reward phenotypes, has made the LHA a prime target for applications of molecular and genetic tools. Because manipulations of many cell types have robust effects on both food intake and self-stimulation, interpreting the present data in a binary fashion as either ''feeding'' or ''reward'' related is fraught with problems. Recent evidence suggests that mostly non-overlapping populations of LHA neurons contribute differentially to reward and aversion as well as feeding (Figure 2B). Acute activation of LHA glutamatergic neurons suppresses feeding and drives aversion (Jennings et al., 2013a), while genetic ablation potentiates food intake and weight gain (Stamatakis et al., 2016), suggesting these cells as a negative regulator of feeding and reward. LHA glutamatergic neurons predominantly project to the lateral habenula (LHb). Though it is not traditionally thought of as a feeding center, manipulations of the LHb can influence food intake. Optogenetic inhibition of LHA glutamatergic afferents within the LHb promotes food intake and reward-related behaviors (Stamatakis et al., 2016), and optogenetic activation of LHb efferents within the ventral midbrain produces behavioral avoidance and suppresses consummatory behavior (Stamatakis and Stuber, 2012). LHA GABAergic neurons, another substantial LHA cell group, are intermingled with and seem to functionally oppose glutamatergic cells. Acute activation of LHA GABA cells enhances motivation for food, drives food consumption, and is rewarding (Jennings et al., 2015; Navarro et al., 2016), while acute inhibition or genetic ablation reduces food intake and is aversive (Jennings et al., 2015; Navarro et al., 2016). Similarly, acute activation of an adjacent GABAergic population located in the zona incerta promotes approach and food intake with a preference for palatable foods (Zhang and van den Pol, 2017). Emerging evidence suggests that activity of LHA GABA neurons may also be required for learning about cue-reward relationships in rats (Sharpe et al., 2017). LHA GABAergic neurons comprise heterogeneous subpopulations that may be functionally distinct. Chemogenetic activation of the subset of LHA GABA neurons expressing the neuropeptide galanin potentiates motivated feeding for palatable foods without affecting chow intake (Qualls-Creekmore et al., 2017). Another subset of LHA GABA neurons express pancreas duodenum homeobox 1 (*Pdx1*) and project to the PVH. Optogenetic activation of this pathway promotes food intake in fed mice (Wu et al., 2015). Orexin/hypocretin neurons of the LHA are also thought to contribute to reward and feeding. Their activity is reduced immediately following food consumption (González et al., 2016). Acute activation of LHA orexin neurons, which project to the VTA, potentiates reward seeking for both drugs and food (Harris et al., 2005; Inutsuka et al., 2014). Orexin/hypocretin neurons may more generally control arousal, though (Mahler et al., 2014). There are also overlapping subsets of neurons within the LHA that express melanin-concentrating hormone (MCH) (Domingos et al., 2013) or leptin receptors (Leinninger et al., 2009) and project to the VTA to influence dopamine release and intake of palatable foods.

The LHA receives input from the BNST (Jennings et al., 2013a) and VTA (Taylor et al., 2014), two regions that are heavily implicated in the control of positive and negative behavioral states. Furthermore, LHA projections to the LHb (Stamatakis et al., 2016), VTA (Nieh et al., 2015, 2016), and locus coeruleus (Laque et al., 2015) can influence feeding and reward. Together, the anatomical connectivity and nuanced functions of molecularly defined cell types within the LHA suggest that this area may contribute broadly to regulating motivation that is directed toward feeding.

The specific synaptic connectivity between ventricular and intermediate neurons (and within distinct intermediate neuron populations) is still largely unknown. Arc AgRP and POMC neurons innervate many of the same intermediate areas and likely have antagonistic effects on downstream targets. Ventricular neurons can influence—either through direct innervation or through poly-synaptic connections with intermediate neurons—the activity of canonical reward and aversion brain regions.

Monoaminergic Systems

Monoaminergic systems (i.e., dopamine and serotonin) are crucial for myriad behaviors, and manipulations of these cells can have profound effects on feeding and reward phenotypes.

Because direct connections between ventricular neurons and monoaminergic neurons are sparse, indirect connections via intermediate cell groups likely orchestrate functional interactions.

Dopamine has long been implicated as a critical mediator of goal-directed behavior and learning. Rats and mice readily learn to selectively self-stimulate (Adamantidis et al., 2011; Ilango et al., 2014; Rossi et al., 2013; Tsai et al., 2009; Witten et al., 2011) and avoid optogenetic inhibition (Danjo et al., 2014; Ilango et al., 2014) of midbrain dopamine neurons. Optogenetic activation of VTA GABAergic neurons, which reduces dopamine release, inhibits licking for sucrose and promotes aversion (Tan et al., 2012; van Zessen et al., 2012). Destruction of dopaminergic neurons causes profound deficits in feeding, movement, motivation, and learning. In addition to its established role in reward, dopamine signaling is also a critical component of voluntary feeding and motivated behavior in general. Intracranial self-stimulation sites, which depend on dopamine release, have often been found to promote feeding and depend on the current satiety state of the subject (Abrahamsen et al., 1995; Adamantidis et al., 2011; Carr and Wolinsky, 1993; Jennings et al., 2013a; Stuber et al., 2011). Moreover, ablation of dopaminergic neurons (Ungerstedt, 1971) or selective disruption of dopamine production causes hypoactivity and aphagia in mice (Zhou and Palmiter, 1995). Circulating signals such as ghrelin and leptin can also influence the activity of dopaminergic systems (Palmiter, 2007), although hormone receptor expression is much lower than in ventricular populations. Acute administration of the orexigenic peptide ghrelin excites VTA dopamine neurons in rodents (Abizaid et al., 2006; Cone et al., 2014) and increases blood oxygen level-dependent (BOLD) responses to food pictures in the ventral midbrain and striatum in healthy volunteers (Malik et al., 2008). In mice, the anorexigenic protein leptin can directly and indirectly influence the activity of VTA dopamine neurons and reduce food intake (Domingos et al., 2011; Fulton et al., 2006; Hommel et al., 2006; Leinninger et al., 2009).

The mesolimbic dopamine system is also strongly influenced by intermediate neurons. Direct connections between ventricular neurons and dopaminergic cells are quite sparse and functional interactions probably rely heavily on intermediate relays. Though direct inhibition of dopamine neurons by AgRP neurons has not been demonstrated in adult animals, AgRP neurons can modify VTA dopaminergic plasticity and dopamine-dependent behaviors during development (Dietrich et al., 2012), and acute activation of AgRP neurons in adult mice mediates a variety of non-food-related behaviors, including anxiety and stereotypy (Dietrich et al., 2015). It has recently been shown that palatable food can promote feeding even in AgRP-impaired mice, an effect that is dependent on dopaminergic signaling (Denis et al., 2015), despite the sparseness of direct AgRP to VTA projections. The circuit mechanisms governing these effects are unclear, though they likely depend on at least one intermediate connection linking AgRP and mesolimbic dopaminergic signaling. Ventral tegmental dopaminergic neurons receive input from many intermediate regions, including the PBN (Coizet et al., 2010). PBN afferents can inhibit putative dopaminergic neurons, which probably requires local interneurons since PBN neurons are glutamatergic (Coizet et al., 2010). In addition to the PBN, VTA dopaminergic neurons receive input from LHA, CeA, and BNST and send dense projections to the NAc and PFC (Beier et al., 2015). Both of these primary efferent targets of VTA dopamine fibers exert high-level control over food seeking and goal-directed action.

Ingestion of sugars and palatable foods is known to increase striatal dopamine release (Hajnal et al., 2004; Hernandez and Hoebel, 1988; Rada et al., 2005; Roitman et al., 2004, 2008; Small et al., 2003), and the dopaminergic system is altered in obese humans and in animal models of obesity (Volkow et al., 2011). Striatal dopamine D2 receptor availability is inversely correlated with obesity in humans and rats (Johnson and Kenny, 2010; Wang et al., 2001), and lentiviral-mediated knockdown of D2 receptor expression makes rats more susceptible to weight gain when allowed to consume calorically dense food (Johnson and Kenny, 2010). While chronic D2 receptor blockade potentiates weight gain (Cope et al., 2005), D2 receptor knockout mice are not obese (Baik et al., 1995). Similarly, microinfusions of D1- or D2-slective dopamine receptor antagonists into the NAc fail to affect food intake in rats (Baldo et al., 2002). Thus, specific functions of dopamine receptors per se in acute feeding are open to interpretation. One possibility is that altered dopamine receptor expression is an effect of obesity resulting from pathological dopamine release. The observed changes related to obesity and chronic antipsychotic administration may reflect compensatory changes of other circuit nodes and not necessarily causal involvement of dopamine receptors (Palmiter, 2007). Chronic food restriction in rats decreases extracellular dopamine in NAc (Pothos et al., 1995). Aphagia resulting from genetic disruption of dopamine production can be rescued by restoration of dopamine signaling in the dorsal or ventrolateral, but not the ventromedial, striatum (Darvas et al., 2014; Hnasko et al., 2006; Szczypka et al., 2001). Gastric infusion of glucose increases dopamine release in both the dorsal striatum and NAc. Intriguingly, optogenetic activation of D1 receptor-expressing neurons in the dorsal striatum, but not the NAc, overrides the satiating effects of such an intra-gastric load, while genetic ablation of these neurons produces the opposite effect (Han et al., 2016). Although the mechanisms linking gastric glucose sensing with dopamine release are not fully understood, these results highlight the notion that dopamine signaling within distinct striatal compartments is functionally heterogeneous.

While dorsal striatal dopamine is critical for the ability to feed and sense glucose, NAc dopamine seems to be critical for the motivation to feed. When dopamine fibers innervating the NAc are selectively destroyed, rats become unwilling to exert effort to obtain food despite being physically capable of eating and performing instrumental actions (Aberman and Salamone, 1999). Because of this, it has been proposed that NAc dopamine invigorates and motivates behavior independently of primary effects on appetite (Salamone and Correa, 2012) and may function similarly to a gain signal. However, dopamine-deficient mice that have dopamine production virally restored in the dorsal striatum show similar instrumental responding for food and comparable break points on a progressive ratio task (Robinson et al., 2007). The willingness to exert effort for food in these mice that is absent in NAc dopamine-depleted mice may be due to differences in experimental timing. In viral restoration experiments, mice recover for months prior to testing, whereas dopamine-depleted rats are tested within weeks of surgery. This extra time may allow the dorsal striatum to co-opt NAc functions.

Alternatively, viral rescue within the dorsal striatum yields low levels of dopamine in the NAc, which may be sufficient to rescue motivational deficits. Interestingly, acute optogenetic activation of dopamine D1 receptor-expressing projections from NAc to LHA halts feeding, while inhibition potentiates consummatory behavior (O'Connor et al., 2015). In addition to dopaminergic input, neurons within the NAc receive dense glutamatergic innervation from thalamic and cortical regions that convey information related to gustation and executive function. Thus, the NAc may integrate high-level descending signals with information pertaining to homeostatic needs to direct behavior toward relevant goals (Kelley, 2004).

Another major target of VTA dopamine projections is the PFC. In humans, BOLD responses within the frontal cortex are positively correlated with the pleasantness of flavors (de Araujo et al., 2003). In rats, aspiration of medial PFC (mPFC) produces finickiness while having relatively little impact on the ability to feed (Kolb and Nonneman, 1975). Similarly, excitotoxic lesions of mPFC have little effect on energy homeostasis and body weight (Davidson et al., 2009). However, dopamine is released in the mPFC during consumption of palatable foods (Bassareo and Di Chiara, 1997; Hernandez and Hoebel, 1990). Furthermore, a subset of fasting-activated mPFC neurons expressing dopamine D1 receptors, presumed to be direct downstream targets of VTA dopamine axons, bidirectionally drive food intake (Land et al., 2014). How mPFC influences on food intake and reward-guided behavior integrate with its established role in executive function, cognitive control, and learning (reviewed by Miller and Cohen, 2001) remains to be determined.

In addition to the mesolimbic dopaminergic system, serotonergic (5-hydroxytryptamine, 5-HT) neurons located in the dorsal raphe nucleus are highly interconnected with both intermediate and monoaminergic neurons (Muzerelle et al., 2016; Ogawa et al., 2014; Pollak Dorocic et al., 2014) and contribute to feeding. In general, pharmacological manipulations that increase 5-HT availability tend to decrease feeding, while reducing 5-HT has the opposite effect (for detailed reviews, see Blundell, 1986; Simansky, 1996). Mice lacking 5-HT2C or 5-HT1B receptors are hyperphagic and obese (Bouwknecht et al., 2001; Tecott et al., 1995), and these receptors are thought to permit suppression of feeding via interactions with Arc AgRP and POMC neurons (for discussion of this, see Sohn et al., 2013). However, systemically agonizing 5-HT2C receptors does not impact daily food intake or body weight in mice (Zhou et al., 2007). *In vivo* calcium imaging reveals that serotonergic neurons increase their activity during food consumption as well as social interactions (Li et al., 2016); however, relatively few 5-HT neurons show Fos induction following food ingestion (Takase and Nogueira, 2008), and blockade of 5-HT signaling within the nucleus of the solitary tract is associated with increased feeding following AgRP neuron ablation (Wu et al., 2012). Optogenetic activation of dorsal raphe Pet-1 neurons, which release both glutamate and 5-HT, is rewarding, promoting place preference and self-stimulation (Liu et al., 2014). Importantly, optogenetic activation of 5-HT neurons within the dorsal raphe can also increase patience (Miyazaki et al., 2014), anxiety (Ohmura et al., 2014), and pain sensitivity (Cai et al., 2014b). Given its disparate functions and wide anatomical distribution, it has been hypothesized that serotonin may underlie basic behavioral arousal or attention (Robbins, 1997). Though serotonin is able to influence feeding, affecting food intake may be one of many consequences of perturbation of this system.

Concluding Remarks

The neurocircuits that may bias behavior toward either homeostatic or hedonic feeding are largely intertwined and overlapping. Assignment of specific cell types and brain regions to one category or the other is often unhelpful. Together, the systems involved in hedonic and homeostatic aspects of feeding provide a means by which the nervous system can dynamically coordinate intake of "rewarding" stimuli in order to meet metabolic demands and ensure survival. Because food is essential, it is unsurprising that so many neuron populations that facilitate food intake also promote rewarding phenotypes and those that suppress appetite are aversive. Ventricular neurons of the hypothalamus represent an entry point by which peripheral signals reflecting the metabolic state of the animal can robustly and efficiently influence the nervous system to ultimately orchestrate behavior. The neurons located in the Arc and PVN integrate information from circulating hormones and instruct intermediate targets to initiate or cease the process of acquiring sustenance. Intermediate neurons located in subcortical structures function more generally, integrating input pertaining to various needs, including feeding, mating, and safety. They ultimately influence monoaminergic neurons, which are very general in function. Monoaminergic neurons (i.e., mesolimbic dopamine) are involved in motivation and can influence food intake. However, in conjunction with their downstream targets, they are also involved in numerous other processes including executive function and learning about the environment.

Recent technological advances have allowed researchers to probe functional neurocircuits *in vivo* with unprecedented precision. Specifically, optogenetic and chemogenetic tools have shed light onto the functional heterogeneity within anatomically defined brain regions (Tables 1 and 2). Such tools have made it possible to begin to answer the question of whether the AgRP neuronal output represents a positive- or negative-valence signal (Figure 2A), and they have greatly facilitated disentangling the functional heterogeneity of the LHA (Figure 2B) among many other brain regions. Because of the dual outcomes (hyperphagia/reward or hypophagia/aversion) of some acute manipulations, it is important to measure both feeding and reward phenotypes. Note the frequency of question marks in Tables 1 and 2.

While these tools have been invaluable in defining functional circuit nodes embedded within complex neural tissue, their limitations must be considered when interpreting results. Viral transduction, for example, can introduce unexpected variability into experiments. Seemingly small differences in injection location, virus preparation, or subject age may have a large impact on the experimental results. It is important to consider the quantitative relationship between viral transduction and behavioral outcomes (for a detailed discussion, see Sternson et al., 2016). Moving forward, bulk manipulations alone may be insufficient to disentangle whether or how particular cells contribute to homeostatic or hedonic feeding behavior. This is, in part, because the outcomes of bulk activation or inhibition within interconnected circuits can be difficult to predict and can create

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Table 2. Acute Manipulations of Molecularly and Anatomically Defined Long-Distance Projections that Influence Food Intake Also Affect Appetitive Behavior

Area of Origin	Projection	Manipulation		Food Intake	Appetitive Behavior	References
Arc	AgRP→BNST	ChR2	↑	+	?	Atasoy et al., 2012; Betley et al., 2013; Garfield et al., 2015
	AgRP→PVN	ChR2	↑	+	?	Betley et al., 2013; Garfield et al., 2015
	AgRP→LHA	ChR2	↑	+	?	Betley et al., 2013; Garfield et al., 2015
	AgRP→CeA	ChR2	↑	/	?	Betley et al., 2013
	AgRP→PBN	ChR2	↑	/	?	Betley et al., 2013
	Oxtr→PVN	ChR2	↑	–	?	Fenselau et al., 2017
PVN	Sim1→PAG	Gi	↓	+	?	Stachniak et al., 2014
	Sim1→PBN	Gi	↓	/	?	Stachniak et al., 2014
	MC4R→PBN	ChR2	↑	–	+	Garfield et al., 2015
BNST	Vgat→LH	ChR2	↑	+	+	Jennings et al., 2013a
	Vgat→LH	eArch3.0	↓	–	–	Jennings et al., 2013a
	Vgat→VTA	ChR2	↑	/	+	Jennings et al., 2013a; Jennings et al., 2013b
	Vglut2→VTA	ChR2	↑	/	–	Jennings et al., 2013b
CeA	Vgat→PAG	ChR2	↑	+ (prey pursuit)	?	Han et al., 2017
	Vgat→RF	ChR2	↑	+ (chewing)	?	Han et al., 2017
	Htr2a→PBN	ChR2	↑	+	+	Douglass et al., 2017
PBN	CGRP→CeA	ChR2	↑	–	?	Carter et al., 2013
	CGRP→CeA	Gi	↓	+	?	Carter et al., 2013
	CGRP→BNST	ChR2	↑	/	?	Carter et al., 2013
LHA	Vglut2→lHb	eNpHR3.0	↓	+	+	Stamatakis et al., 2016
	LHA→VTA	ChR2	↑	+	?	Nieh et al., 2015
	LHA→VTA	eNpHR3.0	↓	/	?	Nieh et al., 2015
	Vglut2→VTA	ChR2	↑	/	–	Nieh et al., 2015; Nieh et al., 2016
	Vgat→VTA	ChR2	↑	+	+	Nieh et al., 2015; Nieh et al., 2016
	Vglut2→VTA	eNpHR3.0	↓	/	?	Nieh et al., 2016
	Pdx1→PVH	ChR2	↑	+	?	Wu et al., 2015
LHb	LHb→RMTg	ChR2	↑	–	–	Stamatakis and Stuber, 2012
NAc	D1R→LHA	ChR2	↑	+	?	O'Connor et al., 2015
	D2R→LHA	ChR2	↑	/	?	O'Connor et al., 2015
	GAD→LHA	ChR2	↑	–	?	O'Connor et al., 2015

Conventions are the same as Table 1 except arrows indicate putative effects on presynaptic activity but do not necessarily indicate the direction of change in postsynaptic output. Arc, arcuate nucleus of the hypothalamus; AgRP, agouti-related peptide; BNST, bed nucleus of the stria terminalis; CeA, central nucleus of the hypothalamus; CGRP, calcitonin gene-related peptide; ChR2, channelrhodopsin-2; D1R, d1-like dopamine receptor; D2R, d2-like dopamine receptor; eArch3.0, archaerhodopsin-3.0; eNpHR3.0, halorhodopsin-3.0; Gi, hM4Dq (Gi-coupled designer receptor exclusively activated by designer drug); Htr2a, serotonin receptor 2a; LHA, lateral hypothalamic area; LHb, lateral habenula; MC4R, melanocortin 4 receptor; NAc, nucleus accumbens; Oxtr, oxytocin receptor; PAG, peri-aqueductal gray; PBN, parabrachial nucleus; Pdx1, pancreas duodenum homeobox 1; PVN, paraventricular nucleus of the hypothalamus; RMTg, rostromedial tegmental nucleus; Sim1, single-minded 1; Vgat, vesicular GABA transporter; Vglut2, vesicular glutamate transporter 2; VTA, ventral tegmental area.

ambiguity about whether some functions attributed to particular neurons are related to unintended effects on downstream targets. Furthermore, synchronous activation of large groups of neurons is unlikely to capture the nuanced activity patterns that have been observed *in vivo*. It is therefore important that researchers carefully consider stimulation parameters to most closely approximate endogenous activity patterns. One potential way to address this is to record neural activity of relevant circuitry to identify and isolate subsets of neurons that selectively encode discrete aspects of behavior. Continued advancement in deep brain imaging will undoubtedly identify unique functional groups of neurons. Such populations may be defined by anatomical connections and molecular profiles. The traditionally singular molecular markers currently used to define cell types may be insufficient to specify functional units within complex, intertwined circuits. Combinatorial viral approaches allow expression of exogenous proteins in cell types that are defined by two or more features (Fenno et al., 2014). Combined with a more detailed understanding of the molecular profile of individual cells by leveraging high-throughput single-cell sequencing approaches, it may eventually be possible to identify pathways that selectively contribute to feeding.

Here, we have highlighted the major nodes involved in feeding, but our list is not exhaustive. Because so many areas and circuits may be involved in feeding and reward, some of which may not be known yet, it is important for researchers to screen for these phenotypes in a non-biased manner to determine relevant brain regions and cell types. The anatomy of the systems discussed here has been simplified for relevance to feeding, but it is important to note that intermediate and monoaminergic neurons receive input from disparate brain regions that are involved in a variety of motivated behaviors (e.g., anxiety and social behavior). The cells contributing to these behaviors may influence intermediate and monoaminergic pathways to suppress feeding in necessary situations (Burnett et al., 2016) independently of the activity of ventricular neurons. The details of such drive competition are largely unknown, but may involve selective tuning of the activity of intermediate neuron populations.

As a result of the dual role that intermediate and monoaminergic neurons play in guiding homeostatic and hedonic feeding, it is easy to imagine how they might be co-opted by drugs of abuse or unhealthy foods to the detriment of the organism. The circuits implicated in obesity and drug addiction overlap substantially with those that control typical feeding (Castro et al., 2015; Volkow et al., 2011). Elucidating the precise neurocircuits controlling unique aspects of feeding and reward seeking will be critical to understanding pathological behavior. Thus, when considering therapeutics for obesity, it is important not to immediately discount drugs that affect the reward system, as they may also have profound impact on food intake and energy homeostasis.

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