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Gating of visual processing by physiological need

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Abstract

Physiological need states and associated motivational drives can bias visual processing of cues that help meet these needs. Human neuroimaging studies consistently show a hunger-dependent, selective enhancement of responses to images of food in association cortex and amygdala. More recently, cellular-resolution imaging combined with circuit mapping experiments in behaving mice have revealed underlying neuronal population dynamics and enabled tracing of pathways by which hunger circuits influence the assignment of value to visual objects in association cortex, insular cortex, and amygdala. These experiments begin to provide a mechanistic understanding of motivation-specific neural processing of need-relevant cues in healthy humans and in disease states such as obesity and other eating disorders.

Introduction

A key behavioral goal for the health and survival of an animal is the maintenance of bodily homeostasis. Brain networks have evolved to promote specific actions that will restore and maintain homeostasis. A foundational example involves the hunger-related hypothalamic circuitry that promotes food seeking and feeding behaviors during states of acute or upcoming energy deficit. Hunger can bias neural processing in higher-order brain regions such as cortex and amygdala. These regions serve many purposes, and are unlikely to contain dedicated ‘hunger circuits’ per se. However, they can be recruited during states of energy deficit to optimize the search for sources of food, by biasing attention towards food-associated stimuli in the environment (Figure 1A). Indeed, attentional capture by cues predicting energy-dense foods is a notion familiar to anyone who has walked through a grocery store when hungry [1,2]. This once-useful adaptation can be counterproductive in modern Western society, where high-fat and high-sugar foods are more readily available, and

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food advertisements are inescapable. Emerging basic and clinical research in humans and rodents is beginning to elucidate the brain regions, circuits, and mechanisms that drive this hunger-dependent biasing of responses to visual food cues.

Hunger-dependent neural responses to visual food cues in humans

Humans have highly-evolved visual systems that can identify motivationally-relevant stimuli in cluttered environments. For example, attention to, and perception of food-associated visual cues is enhanced during states of hunger [3]. Using fMRI in hungry subjects, many studies have demonstrated stronger neural responses to food-related images vs. other images containing similar low-level visual features. Such effects are pronounced in visual association areas including inferotemporal cortex, parahippocampal gyrus, and fusiform gyrus (involved in complex object recognition), with lesser effects observed in primary visual cortex (Figure 1B) [4–8]. Critically, the enhanced responses to food-associated images are no longer present when the same subjects are scanned again following meal consumption. Moreover, enhancement of food cue responses can scale with level of hunger and with the caloric content of the associated food [7,9].

Brain areas not directly involved in visual processing, per se, also exhibit visual food cue response biases in hungry human subjects. These structures include limbic areas (amygdala and nucleus accumbens), gustatory and visceral areas (insular cortex), areas involved in executive function (prefrontal cortex and orbitofrontal cortex), and areas controlling bodily homeostasis (hypothalamus) [4–6,9–11]. Many of these areas activated by visual food cues are similarly activated by the taste or smell of food [8]. Food cue response enhancement in these areas is also reduced following meal consumption.

Human neuroimaging studies of food cue responses have also provided useful clinical insights, as patients with eating disorders demonstrate abnormal neural responses to food cues in both hungry and sated states. For example, anorexia patients, even when hungry, demonstrate reduced food cue responses in visual areas as compared to healthy controls [12]. In contrast, subjects suffering from obesity or other eating disorders can show enhanced responses to food cues in visual areas and in insular cortex that persists even following a meal [4,13,14]. One study even found that amygdala responses to high-calorie food during satiety could predict future weight gain [11].

Human neuroimaging studies involve indirect estimates of activity using measurements pooled across tens of thousands of neurons of varying functional properties, morphology, chemical makeup, and projection identity. Thus, while these studies uncover important information regarding the brain regions involved, they provide limited information about circuit mechanism and local population dynamics. A better understanding of the cellular and circuit mechanisms underlying these hunger-dependent responses to food cues may facilitate interpretation of human neuroimaging studies and enable targeting of specific cell types and pathways for treatment of obesity and eating disorders. Studies addressing this phenomenon using extracellular recordings from single neurons in non-human primates [15], while insightful, are limited by recording yield and duration. New tools and approaches for recording large numbers of single neurons across extended periods of time in mice are

beginning to enable more detailed investigation of visual processing in the context of different homeostatic need states.

Neural mechanisms underlying hunger-dependent visual responses to food cues

To understand the effects of hunger and satiety on association cortical responses to visual food cues at cellular resolution, we performed two-photon calcium imaging of the activity of hundreds of neurons simultaneously in postrhinal cortex (POR, defined here as a specific retinotopically-organized area in mouse lateral association cortex [16]). These recordings were conducted in head-fixed mice performing a Go-NoGo task. Following training, mice can discriminate between arbitrary visual cues (drifting visual gratings) associated with food (liquid Ensure, a high calorie liquid meal replacement) or with other outcomes [17]. We found that, in hungry mice, the average response across neurons to learned food cues was stronger than to neutral cues in postrhinal cortex, but not in primary visual cortex. This enhancement was due to an increased magnitude of responses to food cues in individual neurons, and to an increase in the number of neurons responsive to the food cue. Importantly, this food cue response bias was abolished following feeding to satiety (Figure 2). These cellular recordings support a role for hunger state in modifying or gating the flow of specific sensory information through the visual system. We observed even stronger effects of hunger on visual food cue responses in insular cortex (InsCtx [18]). Here, both the hunger-dependent food cue bias and visual cue-evoked responses in many cells were entirely suppressed following satiation (Figure 2). In addition, previous work has shown that ongoing InsCtx activity is also modulated by hunger state [19]. The hunger-dependent enhancement of food cue responses in mouse visual association cortex and InsCtx recapitulates key findings from the human neuroimaging studies discussed above.

How does hunger modulate cortical areas such as POR and InsCtx? Genetic mouse models can provide new insights into how homeostatic signals bias cortical responses toward need-relevant stimuli, by enabling the use of cell type-specific circuit mapping and manipulation. Agouti-related peptide (AgRP) neurons constitute a powerful genetic entry point for evaluating putative pathways from hunger circuitry to cortex [20] (Figure 3A). Located in the arcuate nucleus of the hypothalamus, AgRP neurons are sensitive to hormonal signals of negative energy balance, and demonstrate high levels of activity during food restriction and lower levels following meal consumption [21–23]. Consistent with these findings, direct activation of AgRP neurons drives food seeking and feeding behaviors [24,25], and inhibition or ablation of AgRP neurons results in hypophagia [23,25,26]. We found that activation of AgRP neurons in sated mice restored engagement and accurate performance in a visual discrimination task for food rewards and, furthermore, restored food cue-evoked activity patterns in InsCtx (Figure 3B) [18]. This finding could shed light on previous studies in humans in which ghrelin administration restores enhanced food cue responses in cortex and amygdala [27], as ghrelin potently activates AgRP neurons (Figure 3C, [22,28,29]; for further discussion of the hypothalamic circuitry that drives feeding behaviors, see Andermann and Lowell, 2017).

We recently combined cellular imaging and circuit mapping to uncover a specific pathway from hypothalamic AgRP neurons to InsCtx via paraventricular thalamus (PVT; involved in feeding and other reward-related behaviors [30–32]) and basolateral amygdala (BLA; involved in encoding the value of learned cues [18,33–37]; Figure 3A). Specific manipulations revealed that components of this pathway were important for food cue responses in InsCtx, and for behavioral responses to food cues. The above pathway is, to our knowledge, the first to causally link hypothalamic interoceptive neurons to cortical circuits, and thus provides a starting point for further elucidation of the circuit mechanisms underlying need state-dependent enhancement of visual processing. In future, it will be important to define the roles of additional pathways relaying signals to cortex and amygdala from AgRP neurons and from other sources (e.g., visceral inputs, satiety centers [20,38]).

One particularly interesting relay, or gate, in the pathway described above is the basolateral amygdala complex (BLA). BLA responses to food cues are enhanced by hunger [6,10,11,39], and can encode the value of salient visual stimuli [33,34,37]. Moreover, reinforcer devaluation tasks demonstrate that the BLA plays a role in updating the value of stimuli based on selective satiation on a specific reinforcer [33,40]. These studies suggest that the amygdala may be involved in reducing the motivational value of visual food cues in cortex following restoration of energy balance via feeding to satiety. In particular, reciprocal loops between the lateral and basolateral amygdala and cortex may serve to bias sensory processing of motivationally-salient stimuli [17,41–43]. We recently found that hunger-dependent enhancement of cortical responses to food cues may be mediated in part by direct amygdalo-cortical projections: 1) amygdala feedback to POR showed a marked hunger-dependent enhancement of responses to food-associated cues [17], and 2) chemogenetic silencing of amygdalar inputs to InsCtx selectively blunted responses to learned visual food cues in InsCtx [18].

Surprisingly, need state-dependent processing of salient sensory cues has also been observed at the level of hypothalamic neurons that regulate energy balance and hunger drive. For example, three different groups recently demonstrated that AgRP neuron activity is rapidly reduced within seconds by sensory cues predicting food availability [21,29,44]. This drop in AgRP neuron activity in response to food-predicting cues was attenuated when mice were sated [29]. Similarly, rapid sensitivity to food cues was reported in arcuate nucleus proopiomelanocortin (POMC) neurons [21,29] and in leptin receptor-expressing GABAergic neurons in the dorsomedial hypothalamus [45]. However, the predictive cues in these studies were not strictly visual, because food presentation likely engages multiple sensory modalities. Using a visual discrimination task, we have shown that AgRP population activity is suppressed by an initially arbitrary visual stimulus that becomes associated with food availability [18]. The rapid drop in AgRP neuron activity in response to cues predicting food availability likely allows the animal to rapidly anticipate the eventual state of increased satiety following consumption of the associated food and absorption of nutrients, thereby preventing overconsumption [20]. However, at the level of understanding homeostatic biasing of cognitive circuits, these findings add complexity, as they reject the strict view of slow and steady homeostatic inputs to cognitive circuitry. Nevertheless, during receipt of very small rewards, as occurs during the operant visual discrimination task described above,

transient changes in AgRP neuron activity are quite small relative to the overall difference in tonic activity levels between hungry and sated states [18].

Perspectives and Future Directions

Many of the same limbic and cortical circuits recruited during states of energy deficit to enhance representations of visual food cues also likely enhance non-visual sensory cues associated with food. For example, human subjects show enhanced neural responses to olfactory food cues in many of the same areas as visual food cues (Figure 1B) [8]. Odor processing in the olfactory bulb of rodents is also modulated by hunger state [46]. Moreover, ghrelin injection can reduce odor detection thresholds, while leptin, a satiety-related hormone released by adipose tissue, can decrease neural activity in the olfactory bulb in response to food odors [47,48]. Future studies could examine whether the circuitry described in Figure 3A also plays a role in hunger-dependent modulation of responses to cues of other sensory modalities.

Learned cues that predict reward (e.g. cues related to drugs of abuse) can also drive enhanced responses across many of the same brain areas, perhaps by hijacking the circuits normally used to drive attention towards physiologically-relevant cues [49]. For example, human neuroimaging results contrasting cocaine- and food-predicting cues show similar, but not identical, brain-wide response patterns [50]. Further, other need states may similarly shape visual processing of need-relevant cues. For example, studies in water-restricted humans find enhanced neural responses to water-predicting cues in association cortex and insular cortex [51,52]. Future studies could assess whether amygdalo-cortical reciprocal loops and/or other brain regions play similar roles in recruitment of cognitive resources in the context of different homeostatic and hedonic drives [44,53].

Other natural, non-homeostatic drives may also employ similar mechanisms to drive attention towards salient environmental cues. A recent study demonstrated that oxytocin, a neuropeptide implicated in social interaction, can directly modulate neural activity in the olfactory bulb of mice, enhancing signal-to-noise during odor coding [54]. Oxytocin also enhances representations of pup calls in auditory cortex of mothers [55]. We speculate that, for a given sensory modality, modulation of activity occurs at those stages in the sensory processing hierarchy which contain unambiguous representations of need-relevant objects in the environment. As such, modulation may occur at earlier stages for olfactory, gustatory, and auditory processing than for visual processing (hence the increased hunger-dependent modulation in POR *vs.* V1). While we have focused on mammalian brain areas involved in food cue processing, impressive efforts to elucidate circuitry linking need states and sensory processing in animal models with somewhat simpler circuitry promise to yield important insights [56,57].

We have illustrated how basic physiological need states may provide important and tractable entry points into understanding the roles of cortex in cognition. We suggest that an evolutionarily-conserved role of cortex is to help meet essential homeostatic needs of the body, by adding flexibility and context-dependence to sensory perception, memory, and decision-making in a dynamic world.

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** Of outstanding interest

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Highlights

- Hunger drives attention towards visual food-associated cues
- In humans, neural response biases to food cues emerge in higher-order cortex and amygdala
- In mice, cellular imaging reveals similar population biases, but local response diversity
- Specific pathways between hypothalamus, amygdala, and cortex underlie these biases

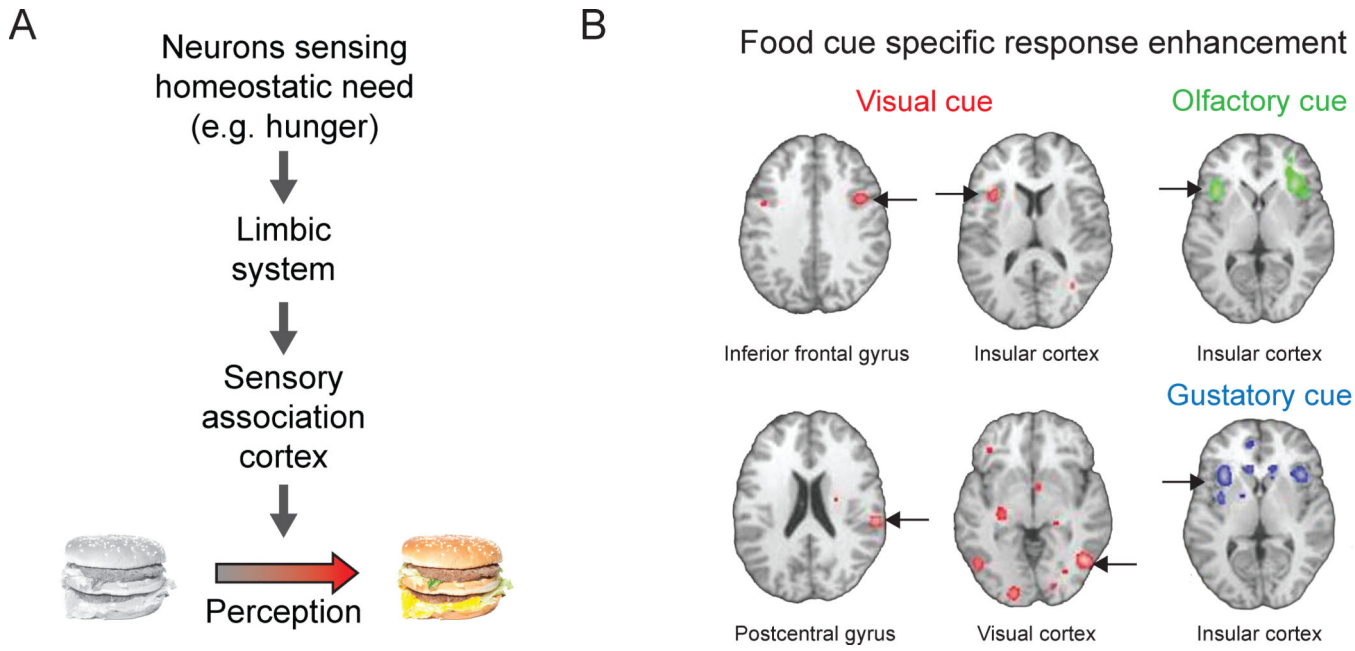

Figure 1. Physiological needs bias processing of salient visual cues

A. To help meet the changing needs of our bodies, we direct our attention and neural processing towards relevant sensory cues in the environment. A specific physiological or homeostatic need is sensed by specialized neurons in the brain that coordinate complex search and consummatory behaviors to satisfy the need. This need state is relayed through limbic structures to cortical areas that process environmental stimuli, enhancing representations of salient objects (i.e., those relevant to the current physiological need). For example, hunger is a powerful homeostatic drive that biases visual processing towards food-associated sensory cues, such as images of cheeseburgers. B. A meta-analysis across human neuroimaging studies shows hunger-dependent enhancement of responses to visual food cues (red regions, *left* and *middle columns*) in many brain areas, including in association cortex (fusiform gyrus and parahippocampal gyrus) and insular cortex. Responses to other stimuli predicting food, including odors (*top right*) and tastes (*bottom right*), are also affected by hunger state in insular cortex. Pseudocolored pixels indicate brain regions with significant response enhancement in states of hunger vs. satiety. Modified from Obesity, 22, C. Huerta, P. Sarkar, T. Duong, A. Laird, and P. Fox, Neural bases of food perception: Coordinate-based meta-analyses of neuroimaging studies in multiple modalities, 1439–1446, 2014, with permission from John Wiley and Sons.

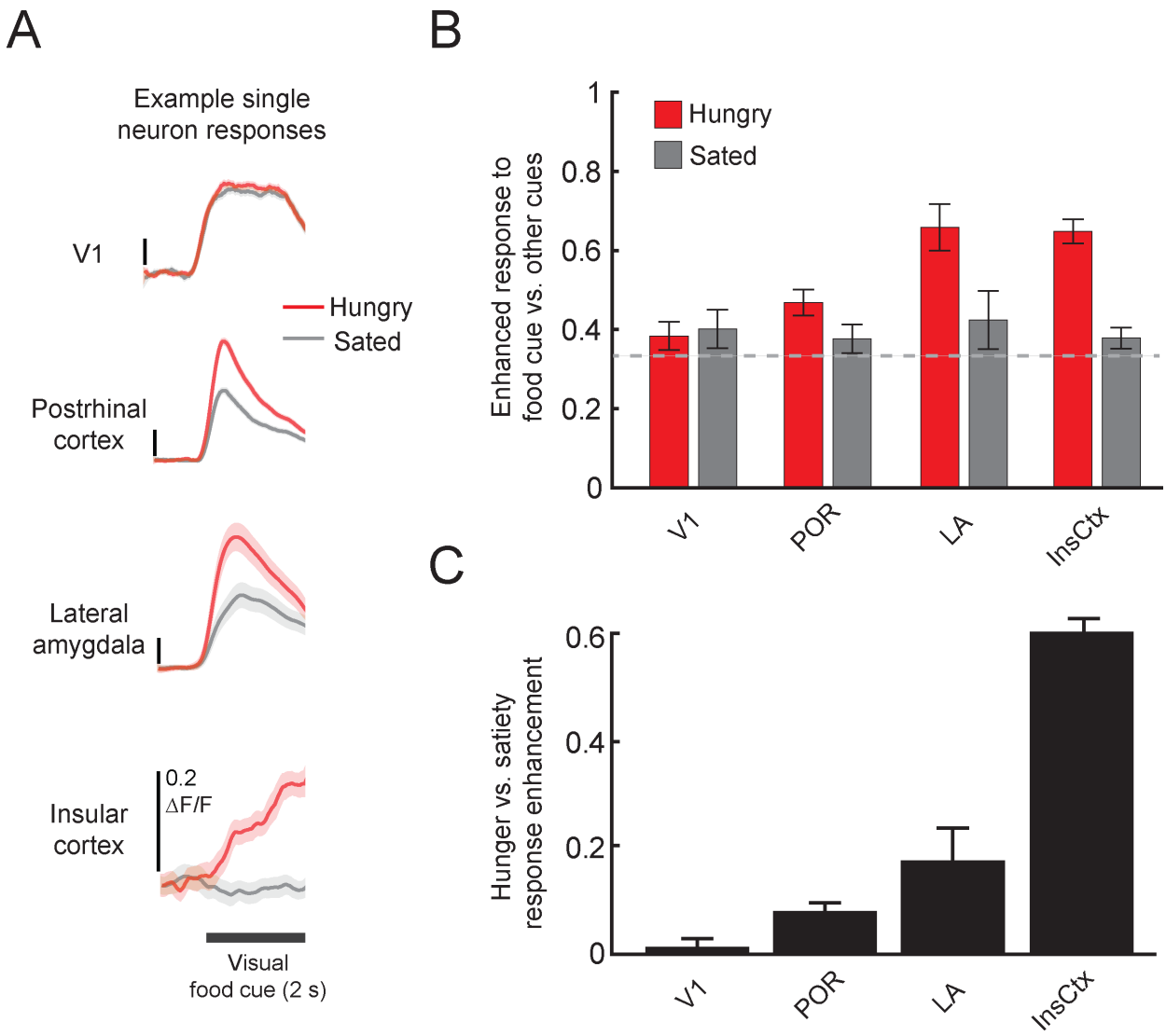

Figure 2. Cellular imaging of enhanced responses to food cues in food-restricted mice

A. Average food cue-evoked calcium response timecourses using two-photon imaging in mouse primary visual cortex (V1), postrhinal cortex (POR), lateral amygdala (LA; recorded from lateral amygdala axons in postrhinal cortex), and insular cortex (InsCtx). Neurons in POR, LA, and InsCtx tended to show increased activity in response to the same visual food-predicting cue when mice were hungry *vs.* after a period of feeding to satiety. ΔF/F: fractional change in fluorescence of the GCaMP6 calcium indicator. Mean +/− s.e.m. across trials. Reprinted from Neuron 91, C. Burgess, R. Ramesh, A. Sugden, K. Levandowski, M. Minnig, H. Fenselau, B. Lowell, and M. Andermann, Hunger-Dependent Enhancement of Food Cue Responses in Mouse Postrhinal Cortex and Lateral Amygdala, 1154–1169, 2016 with permission from Elsevier. B. At the population level, V1 did not show a bias towards food cues *vs.* neutral or aversive cues (food cue bias = (food cue response)/(sum of responses to all 3 visual cues); no bias = 0.33), regardless of hunger state. However, POR, LA, and InsCtx all showed a bias towards the food cue when the mice were hungry. Similar to findings from human neuroimaging studies, this bias was not present when mice were

sated. C. Food cue response enhancement between sated and hungry states increases from V1 to POR, LA, and InsCtx. Hunger-satiety modulation index = $(\text{Response}_{\text{Hungry}} - \text{Response}_{\text{Sated}})/(\text{Response}_{\text{Hungry}} + \text{Response}_{\text{Sated}})$.

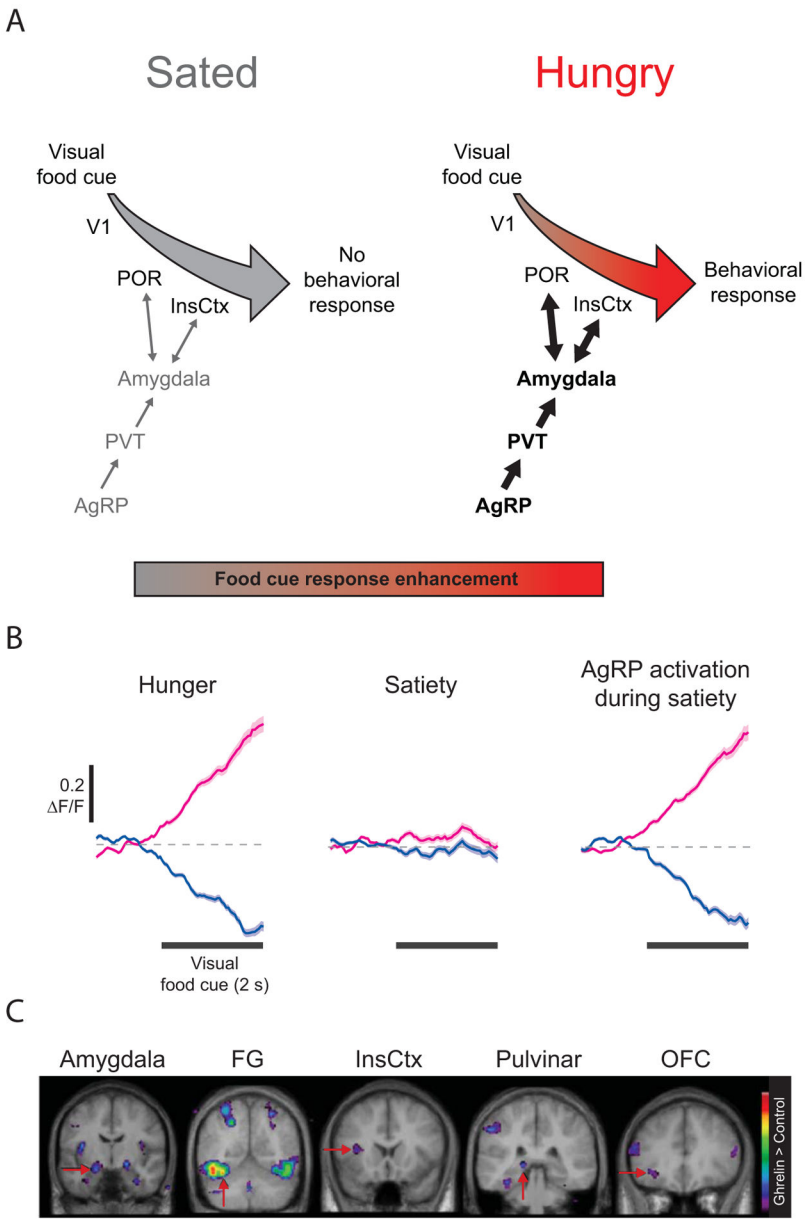

Figure 3. Circuits regulating hunger-dependent enhancement of responses to visual food cues

A. Circuit mapping experiments in mice have begun to trace the network of brain areas responsible for hunger-dependent visual processing of food-associated cues. Agouti-related peptide (AgRP) neurons in the arcuate nucleus of the hypothalamus respond to caloric deficiency and drive feeding-related behaviors. This hunger drive is transmitted via the paraventricular thalamus (PVT) to the basolateral amygdala, which in turn exhibits reciprocal connections with postrhinal cortex (POR) and insular cortex (InsCtx). This connectivity integrates information about hunger state with the learned value of food-predicting cues, thereby enhancing responses to motivationally-salient visual stimuli and guiding behavioral choices upon presentation of food cues. Similar circuitry may be recruited by other need states (e.g. thirst, salt appetite) and may be hijacked by maladaptive

drives, such as during drug seeking. B. Pharmacogenetic activation of AgRP neurons in sated mice was sufficient to restore InsCtx neuronal responses to visual food cues to levels observed in hungry mice. Subsets of InsCtx neurons responded to a visual food cue with either an increase (magenta) or decrease (blue) in activity when the mice were hungry. These responses were largely abolished when the mice were sated, but could be restored by activation of AgRP neurons. Reprinted with permission from Nature Publishing Group. C. Ghrelin administration in humans, which induces hunger, is also sufficient to induce enhanced responses to food cues *vs.* neutral cues, likely through actions on AgRP neurons. Colored pixels indicate the t-statistic for regions with significantly stronger responses to food images *vs.* scenery. Modified from Cell Metabolism, 7, S. Malik, F. McGlone, D Bedrossian and A. Dagher, Ghrelin modulates brain activity in areas that control appetitive behavior, 400–408, 2008, with permission from Elsevier. V1: primary visual cortex, FG: fusiform gyrus, OFC: orbitofrontal cortex.