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Current Opinion in Neurobiology

Gating of visual processing by physiological need

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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 visual 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.

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Current Opinion in Neurobiology 2018, **49**:16–23

This review comes from a themed issue on **Neurobiology of behavior**

Edited by **Kay Tye** and **Nao Uchida**

https://doi.org/10.1016/j.conb.2017.10.020

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 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.

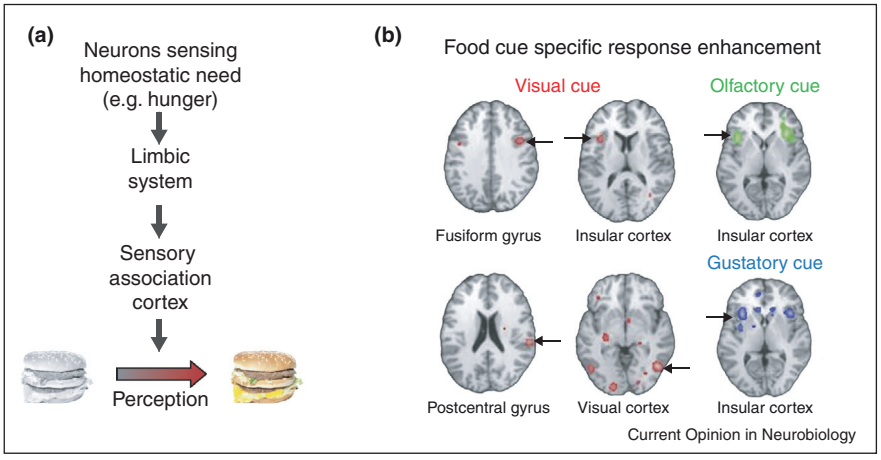
Hunger-dependent neural responses to visual food cues in humans

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 versus 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) [4–7,8••]. 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) [4–6,9,10,11•]. 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

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 versus satiety. Reprinted from Huerta *et al*. [8••] with permission from John Wiley and Sons.

reduced food cue responses in visual areas as compared to healthy controls [12]. By 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, a putative mouse homolog to human parahippocampal gyrus, 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