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NEURAL CIRCUITS

The influence of hunger

Hunger and other motivational states can alter the attention an individual pays to sensory cues that are relevant to that state. Alterations in sensory-cue-induced activity in the insular cortex have been implicated in this process; however, it is unclear how motivational states drive these changes. In a new study, Livneh *et al.* report a pathway from the hypothalamus to the insular cortex by which hunger-mediating hypothalamic agouti-related peptide-expressing ($AgRP^+$) neurons can modulate the insular cortex activity induced by food cues.

The authors first examined whether insular cortical activity is required for food-restricted mice to carry out a task in which they learn to distinguish between visual cues to obtain liquid food. They found that pharmacological inactivation of the insular cortex impaired the ability of the animals to respond to the food-paired cue, indicating that this region has a key role in eliciting appropriate behavioural responses to cues that predict food.

Owing to the deep, bone-obscured position of the insular cortex in the head, it has been impossible to image activity in this region in behaving animals. To overcome this problem, the authors used a reflective microprism and a virally expressed highly sensitive fluorescent calcium sensor to observe the activity of neurons in the superficial layers of the insula, revealing that many insular cortex neurons responded to both the food cue and to either licking or feeding in food-restricted mice. The authors therefore suggest that insular cortex neurons represent information about the likely gustatory and interoceptive outcomes of impending feeding.

The authors found that, in hungry mice, insular cortex neurons were much more likely to respond to food-related cues than to food-unrelated cues, and food-cue-responsive neurons were highly unlikely to respond to other cues. Moreover, satiation attenuated food-cue-elicited responses, indicating that hunger gates the responses of insular cortex neurons to food-related cues.

How does hunger modulate food-cue-induced responses in the insular cortex? Previous studies showed that activation of hypothalamic $AgRP^+$ neurons, which are involved in integrating caloric deficit signals from the periphery, can drive feeding. In the new study, chemogenetic activation of $AgRP^+$ neurons in satiated mice exposed to the food cue not only induced behavioural responses to food cues but also restored food-cue responsiveness in many insular cortex neurons. $AgRP^+$ neurons do not directly project to the insular cortex, so the authors used tracing methods to map the connections between these neurons and this brain region. They revealed a pathway that involves successive projections between inhibitory $AgRP^+$ neurons, the paraventricular thalamus (PVT), the basolateral amygdala (BLA) and the insular cortex.

The authors chemogenetically manipulated this pathway to test its function. Inhibition of PVT neurons (which should have the same effects as $AgRP^+$ neuron activation) promoted feeding in mice, whereas selective activation of PVT neurons projecting to the BLA, which should overcome the inhibition of these neurons by $AgRP^+$ inputs, reduced the behavioural responses to the food cue. Last, inhibition of BLA neurons projecting to the insular cortex attenuated responses to all cues in the task, particularly the food cue, indicating that it reduced bias to this cue.

Together, these data reveal a neural pathway whereby a motivational state can influence the processing of sensory cues in the insular cortex to elicit an appropriate behavioural response that satisfies the state-specific needs of the individual.

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> “hunger gates the responses of insular cortex neurons to food-related cues”

ORIGINAL ARTICLE Livneh, Y. *et al.* Homeostatic circuits selectively gate food cue responses in insular cortex. *Nature* **546**, 611–616 (2017)