Journal Club

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Inhibitory Central Amygdala Outputs to Thalamus Control the Gain of Taste Perception

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Review of Veldhuizen et al.

The survival of an animal critically depends on its ability to identify nutrient-rich food and avoid harmful substances. Although olfactory cues and visual information contribute to these processes, the taste system is ultimately responsible for recognizing and discriminating between the different food qualities. The sensation of taste begins on the tongue, which contains specialized taste receptor cells that are sensitive to the five basic tastes (Yarmolinsky et al., 2009). In humans, taste information travels from the oral cavity to primary gustatory cortex [insular cortex (IC)] via the following three synapses: taste receptor cells to the rostral nucleus of the solitary tract (NST); NST to the gustatory thalamic nucleus [ventral posterior medial nucleus (VPM)]; and VPM to IC (Oliveira-Maia et al., 2011).

In addition to the valence (appetitive or aversive) of a tastant, its intensity is an important characteristic, because it reflects concentration and quantity. Differences in taste intensity perception across individuals have been suggested to underlie food preferences, diet, and risk for obesity (Prutkin et al., 2000). Despite investigations into the source of this variability, whether peripheral mechanisms (at the level of taste receptor cells) and/or central mechanisms (VPM, IC, and related gustatory brain regions) account for the variability remains unclear. Peripheral mechanisms have received support from some studies, including one reporting that individuals with higher taste bud densities reported some tastes as more intense than individuals with fewer taste buds (Miller and Reedy, 1990). Yet, such mechanisms are thought to be insufficient to explain individual differences in taste intensity perception (Feeney and Hayes, 2014). Nevertheless, central mechanisms remain underexplored. This is an important issue because knowing whether central mechanisms play a significant role in interindividual variability in taste perception could help us understand not only individual differences in food preferences and diet, but also how gustatory circuit dysfunction may contribute to obesity.

Veldhuizen et al. (2020) hypothesized that inhibitory output from the central amygdala to gustatory brain regions act as a central gain mechanism that influences taste intensity perception. This idea is supported by three previous findings: (1) patients who had undergone surgical resection of the anterior medial temporal lobe, particularly those involving the amygdala, had increased taste sensitivity and stronger ratings of perceived taste (Small et al., 1997, 2001), which hinted at an inhibitory influence from the amygdala; (2) in directed attention tasks, amygdala circuits regulate gain by assigning greater weights to salient sensory stimuli (Vuilleumier et al., 2004); and (3) Within the amygdala, the central nucleus is sensitive to changes in taste intensity perception, and this structure has reciprocal connectivity with all major gustatory regions (NST, VPM, IC; Small et al., 2003). To test their hypothesis, Veldhuizen et al. (2020) assessed blood oxygenation level-dependent (BOLD) responses to sweet, sour, salty, and bitter tastants in 28 healthy participants using psychophysiological measurements, regression, and dynamic causal modeling.

The first question Veldhuizen et al. (2020) addressed was whether amygdala responses to the different tastants covaried with the mean intensity rating across tastants. Using taste psychophysics, they found that intensity ratings of sweet, sour, and salty positively correlated with each other. Functional magnetic resonance imaging showed that these three tastants led to significant activation of IC, operculum, pre-central and post-central gyrus, left amygdala, cingulate cortex, and putamen, consistent with previous work (Veldhuizen et al., 2011). In support of their hypothesis, BOLD responses in the left central amygdala were associated with each participant's mean taste intensity rating, which was calculated as an average of the ratings for all three tastants. Associations between mean taste intensity rating and responses in bilateral cuneus were also observed.

The authors next asked whether the central amygdala was functionally coupled to major gustatory regions, such as NST, VPM, and IC, and other regions involved

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in taste processing. A psychophysiological interaction analysis followed by regression of the responses of significantly connected areas with the mean intensity rating revealed circuits between the amygdala and three regions, mediodorsal (MD) thalamus, VPM/pulvinar thalamus, and mid-temporal gyrus, that are influenced by taste sensitivity. Of these, gustatory VPM thalamus is a likely target region to participate in taste sensitivity, whereas contributions from MD thalamus and mid-temporal gyrus are unexpected.

Finally, the authors wanted to know whether inhibitory output from the amygdala establishes effective connectivity with the identified brain regions involved in taste sensitivity. To answer this question, they examined changes in connectivity between these regions in relation to the mean intensity rating using Bayesian model estimation, which revealed inhibitory connections originating from the left amygdala to bilateral MD and VPM/pulvinar thalamic nuclei. Interestingly, this analysis also found bidirectional connections between MD and VPM/pulvinar thalamus, suggesting that a functional network of the amygdala–MD thalamus–VPM/pulvinar thalamus plays a critical role in determining mean taste intensity ratings. Subsequent analyses showed that connections from amygdala to left VPM/pulvinar thalamus and right MD thalamus, as well as from right VPM/pulvinar to right MD thalamus, contributed the most to the predictive model. Therefore, consistent with their hypothesis, the strength of inhibitory connections from the amygdala to multiple thalamic nuclei is able to predict individual variation in taste intensity perception; specifically, greater inhibition predicts lower taste intensity perception.

In summary, Veldhuizen et al. (2020) identified specific central amygdala neural circuits in humans that act as a gain mechanism for taste intensity perception. Because peripheral mechanisms cannot account for across-tastant intensity perception, it is clear that central mechanisms play a major role in this feature of taste processing. An intriguing question is whether the gain mechanism arises in central amygdala or these responses are downstream of an earlier mechanism. Taste information reaches the central amygdala via two routes, directly from IC and from NST (Schiff et al., 2018). Because IC represents taste quality using a distributed population code (Avery et al., 2020), and both IC and their outputs to thalamus are activated as a function of taste intensity (Spetter et al., 2010; Yeung et al., 2016), it is reasonable to speculate that IC may modulate taste intensity perception. A notable observation by the authors was that although IC responses vary with tastant concentration, their activity does not reflect the perception of taste intensity across tastants. Since IC responses do not encode taste intensity perception, and because the first synapse in the ascending gustatory pathway, NST, also did not show taste intensity-modulated responses, the reported central gain mechanism most likely arises in central amygdala itself. It would be worthwhile in the future to understand how IC and NST inputs together give rise to this taste gain mechanism in central amygdala.

The amygdala gain mechanism functions through its connections with two distinct thalamic nuclei (VPM and MD) and the mid-temporal gyrus. VPM receives gustatory input from NST and in turn projects to IC, and, based on rodent experiments, is thought to help establish baseline firing of IC neurons and taste encoding (Samuelsen et al., 2013). Therefore, inhibitory outputs from the amygdala are in a perfect position to regulate the transfer of gustatory information from VPM thalamus to IC. In contrast to VPM, the role of MD thalamus in taste processing remains unknown, despite the presence of reciprocal connectivity with IC in rodents (Shi and Cassell, 1998). Given the well documented role of MD thalamus in selectively routing and synchronizing behaviorally relevant sensory information to specific cortical networks depending on task demands (Saalmann, 2014), it is possible that central amygdala inputs to MD thalamus regulates taste stimuli processing by coordinating necessary attentional functions. If so, it would mean that distinct central amygdala outputs underlie different processes relevant for taste intensity perception: central amygdala to VPM thalamus for taste intensity coding; and central amygdala to MD thalamus for taste salience coding. This is an exciting possibility, which may be clarified by future studies using optogenetic circuit manipulations in other species (e.g., rodents) during taste-specific behavioral assays. Like MD thalamus, mid-temporal gyrus is not part of the standard taste pathway. Although most studies have focused on its role in language, visual perception, and semantic memory, it has previously been associated with taste quality processing (Crouzet et al., 2015). One possibility is that central amygdala inputs to mid-temporal gyrus reflects processes related to taste quality, which could also be involved in taste intensity perception. Additional studies are required to uncover the contributions of this circuit in taste processing, both in rodents and in human participants.

In conclusion, the study by Veldhuizen et al. (2020) fills a critical gap in our understanding of the neural circuits underlying individual differences in taste perception. The projections from the central amygdala are unlikely to be the only pathways involved in this variability, however. Indeed, Veldhuizen et al. (2020) also found that the cuneus was significantly associated with taste perception. Given that cuneus receives visual information and its connectivity with amygdala is modulated by visual–olfactory integration processes (Stickel et al., 2019), it is possible that this circuit also supports visual–gustatory integration. This should be further examined in future studies. Interestingly, another visual region, the pulvinar, also exhibited functional connectivity with the amygdala during taste perception. Although this structure has received limited attention in taste studies, along with the cuneus, it may support visual processes that help taste perception. Future work using noninvasive imaging tools that have superior spatial resolution will clarify the exact role of regions such as the pulvinar in taste perception.

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