Editor's Note: These short, critical reviews of recent papers in the *Journal*, written exclusively by graduate students or postdoctoral fellows, are intended to summarize the important findings of the paper and provide additional insight and commentary. For more information on the format and purpose of the Journal Club, please see http://www.jneurosci.org/misc/ifa_features.shtml.

Odorless Trigeminal Stimulus CO₂ Triggers Response in the Olfactory Cortex

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Review of Carlson et al.

The olfactory cortex is separated from the outside world by only two synapses, without any relay and filter in the thalamus. The piriform cortex (PCX), part of the olfactory cortex, has been shown to play a role in odor perception, as well as in odor association and learning (Wilson and Sullivan, 2011). Nevertheless, little is known about how olfactory signals coming from the olfactory bulb (OB) are integrated in the olfactory cortex.

The PCX is composed of three layers and can be divided into two regions: the anterior PCX receives more afferents from the OB and has fewer association fibers than the posterior PCX (Bekkers and Suzuki, 2013). The anterior PCX receives not only olfactory signals, but also input from trigeminal nerve (Brand, 2006), which conveys mechanical, thermal, chemical, and/or nociceptive information. At high concentrations, most odorants can elicit intranasal sensations of burning, tingling, or pickling (Doty et al., 1978). Moreover, the odorless trigeminal stimulant, carbon dioxide (CO₂), when presented with low concentration odors, can increase pungency ratings of the odors (Cain and Murphy, 1980). In addition, imaging techniques in humans have shown that even pure trigeminal stimuli,

such as CO₂, evoke activity in the PCX (Albrecht et al., 2010). There therefore appears to be interplay between the olfactory and trigeminal systems (Brand, 2006): non-olfactory trigeminal sensations may converge with odor information in the PCX and this convergence may influence odor perception.

In a recent study, Carlson et al. (2013) used multi- and single-unit *in vivo* electrophysiological recordings from anesthetized mice to study integration of olfactory and trigeminal stimulations in the anterior PCX. They compared the activity elicited by odor (low concentration of isopentyl acetate) to that elicited by trigeminal stimuli (CO₂). Low odor concentrations failed to evoke trigeminal sensation and therefore allowed the authors to study responses to olfactory stimuli independently. High odor concentration (4 Torr) or CO₂ allowed them to selectively study responses to trigeminal stimuli.

The authors showed that the activity of 26.3% of recorded PCX neurons was modulated by presentation of CO₂ alone. One-third of these neurons were also activated by odors. Among the neurons responding to isopentyl acetate (11.8% of all neurons), a substantial proportion was also sensitive to CO₂ stimulation (9.2% of all neurons). CO₂-evoked activity was not found in the whole olfactory cortex, however. For example, in the olfactory tubercle (another region of the olfactory cortex), activity in only 3.5% of recorded neurons was modulated by CO₂ presentation. Convergence of inputs to the PCX might explain how the presentation of CO₂

together with a low-concentration odor can change the pungency ratings of the odor.

Carlson et al. (2013) also found that the temporal dynamics of activation in PCX neurons was different for trigeminal versus odor stimulation. Whereas odors triggered an increase in the firing rate during stimulus presentation, the response to trigeminal stimulation occurred at stimulation offset, reaching peak of magnitude ~1 s after the stimulus, independent of CO₂ concentration or stimulus duration.

Carlson et al. (2013) next took advantage of the population of neurons responding with specific temporal dynamics to both odor and trigeminal stimulations to study the ability of odor to elicit intranasal trigeminal sensations. While recording PCX neurons exhibiting both odor and trigeminal-related activity, they applied different concentrations of odor (1–4 Torr of isopentyl acetate) or CO₂ (25–100%). Interestingly, at 4 Torr odor concentration, numerous single units displayed an offset response as found when CO₂ was presented. The authors concluded that the offset response could be generalized to different trigeminal stimuli. More interestingly, these results are the first electrophysiological evidence for a switch from odorant to trigeminal sensation when odors are presented at high concentrations.

While the experiments by Carlson et al. (2013) provided new insights into the temporal and spatial integration of odorant and trigeminal stimulation by the olfactory cortex, they also raise questions regarding the underlying network and the biological relevance of an offset activation

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by trigeminal stimulant. Until now, few studies described the electrophysiological activation of the PCX following odor presentation (Bekkers and Suzuki, 2013). It is known that responses in the anterior PCX consist of a burst of activity time-locked to the onset of odor inhalation. Among others, Miura et al. (2012) showed that the activation of the PCX is more strongly correlated to inhalation than to the onset of odor presentation. Strikingly, in some cases, the offset response to trigeminal stimulus seemed also to be synchronized with the inhalation phase of respiration when the stimulus was no longer present (Carlson et al., 2013, their Fig. 3A). Whereas the authors showed that CO₂ presentation did not alter respiratory frequency, it would be interesting to study more deeply the putative correlation between trigeminally evoked activity and inhalation.

The response of some PCX neurons to both odor and trigeminal stimuli led Carlson et al. (2013) to propose that the modified pungency rating of odors by CO₂ may be explained by integration processes in the PCX. This interpretation is possible, but it is important to note that the related network is still poorly understood. Trigeminal ganglion neurons are unique among primary sensory neurons in having two axonal branches entering the CNS at widely distant points. The trigeminal nerve projects to the trigeminal nuclei, which in turn project to the amygdala and the thalamus, but some trigeminal collaterals also directly project to the olfactory epithelium (nasal cavity) and to the OB (Brand, 2006). Both these pathways should be activated by CO₂ presentation, and which contributes to activity induced in the PCX by CO₂ and high odor concentration remains unclear. Because the OB receives both direct input from odor sensory neurons and trigeminal input, integration could occur at the OB level, upstream of PCX. It would therefore be valuable to record the response of mitral cells in the OB to trigeminal stimulation.

As discussed above, the trigeminally evoked activity in PCX neurons is an off-

set response. The physiological relevance and cellular mechanisms underlying this offset response in the PCX remain to be investigated. These may be similar to those proposed to explain the offset response in other sensory systems, including the visual (Bair et al., 2002) and auditory (Kasai et al., 2012) systems. In the case of the auditory system, offset neurons of the inferior colliculus are thought to encode sound duration and the offset response has been proposed to result from postinhibitory rebound excitation dependent on intrinsic membrane properties (Kasai et al., 2012). Further studies using patch-clamp recording of PCX neurons would be necessary to determine whether postinhibitory rebound underlies the offset response in PCX. Moreover, the analyses performed by Carlson et al. (2013) and the low spontaneous activity of PCX neurons did not allow them to detect a putative inhibition during the stimulus that might trigger the offset responses. A more audacious hypothesis is that the low activity in PCX neurons observed upon the presentation of a high odor concentration resulted from an inhibitory activity related to the trigeminal component of the stimulation. From the different electrophysiological recording traces shown by Carlson et al. (2013), one may wonder if we are facing a homogeneous population of neurons. Kasai and colleagues (2012) showed that offset neurons in the auditory system represent a heterogeneous population: some of them were described as pure “offset” neurons (as found in Fig. 3A, middle, in Carlson et al., 2013), whereas others displayed both onset and offset activation (as found in Fig. 5B in Carlson et al., 2013). Among this last group, Kasai et al. (2012) observed two discharge patterns during the onset period: neurons displayed either a sustained or a phasic activity. It would therefore be of interest to more thoroughly investigate the offset patterns of neurons activated by trigeminal stimulation in the PCX.

In conclusion, Carlson et al. (2013) showed electrophysiological evidence for activation of neurons from the piriform

cortex by an odorless trigeminal stimulant. Moreover, they described the pattern of activation of piriform cortex neurons upon this stimulation. Strikingly, whereas response to odor occurred during odor presentation, response to trigeminal stimulants appeared after the stimulus presentation, in the offset period. Importantly, this study gives strong new insights into the modulation of odor perception by trigeminal stimulants and highlights the particular role of the piriform cortex in multisensory integration of information.

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