Neuro 204, Referee's report – Week 5, [your name here] SAMPLE 2

J. McGann et al. (2005) **Odorant representations are modulated by intra- but not inter-glomerular presynaptic inhibition of olfactory sensory neurons.** *Neuron* 48:1039-1053.

The glomerular layer of the olfactory bulb constitutes the first stage where information from olfactory receptor neurons (ORNs) is organized and processed. The projection from ORNs to glomeruli is extremely convergent with on average several thousands ORNs converging onto each glomerulus of the mammalian olfactory bulb. Each of the several thousand of ORNs expressing the same odor receptor converges onto one or a few glomeruli in the olfactory bulb. Thus, at the level of sensory input to the olfactory bulb, odor receptor identity is mapped across the surface of the olfactory bulb with the glomeruli serving as the anatomical units of this map. In addition, each glomerulus can be discretely activated in an odorant-specific manner which suggests that these discrete anatomical structures also serve as functional units in representing odor information. Recent studies have shed light on the complexity of the synaptic network in the glomerular layer which raises questions about the various roles this network plays in processing olfactory information.

One glomerular processing pathway that has attracted much attention is that mediating presynaptic inhibition of transmitter release from ORNs. This is achieved by multiple synaptic pathways including depression intrinsic to the presynaptic terminal and GABA- and dopaminergic inhibition. For instance, feedback inhibition within a glomerulus can occur when ORNs excite GABA-ergic periglomerular interneurons (PG cells) which in turn presynaptically inhibit further ORN input. However, PG cells can also be activated by other sources like mitral and tufted cell dendrites from the same glomerulus and short-axon cells from neighboring glomeruli. What is the impact of presynaptic inhibition on glomerular processing and more generally, what is its role in odor coding?

In the present study, McGann et al. investigated these questions and characterized the properties and functional role of presynaptic inhibition in ORNs. They employed a genetically encoded probe for neural activity, synapto-pHluorin, which permits to monitor transmitter release from ORNs through fluorescence emission during vesicle exocytosis (Bozza et al, 2004). They first worked with in vitro slice preparations to characterize different ways in which ORN transmitter release is modulated by previous activity. They then concentrated on two inhibitory pathways, namely intraglomerular feedback inhibition and lateral interglomerular inhibition, to determine the role each plays in modulating the representation of odors in vivo.

Both slice and in vivo experiments lead the authors to similar conclusions. In particular, they show that the magnitude of ORN input to the glomerulus is strongly modulated by intraglomerular feedback inhibition but very weakly or not at all by lateral interglomerular inhibition. From this observation, the authors conclude that the inhibition of ORNs is mainly driven by glomerular interneurons *within* the same glomerulus and that presynaptic inhibition *between* glomeruli does not appear to be strong enough to significantly affect spatial patterns of odorant-evoked input in vivo. The authors also show that blocking presynaptic inhibition has little effect on spatial patterns of odorant-evoked input in vivo and only causes an increase of the amplitude of odorant-evoked input to glomeruli. This suggests that the predominant role of presynaptic inhibition in odor coding is gain control of input to the olfactory bulb.

This study should be appropriate for publication in Neuron following revision, and deserves high priority. Indeed, the above findings are very interesting and have important implications in the field. They allow a better understanding of how this single processing step – presynaptic inhibition – shapes glomerular activity patterns by characterizing both functional organization of

presynaptic inhibition in vitro and its effects on odor representations in vivo. The lack of presynaptic inhibitory effect between glomeruli implies that the mapping of odors in the olfactory bulb is mostly determined by the "initial" convergence of ORNs onto glomeruli rather than by postsynaptic processing. In light of this, presynaptic inhibition is not involved in shaping the pattern of odorant-evoked input but instead serves to modulate the strength of this input. Interestingly, the weak presynaptic inhibition between glomeruli suggests that the PG cells excited by short-axon cells intervene in postsynaptic but not presynaptic inhibitory connections. The authors monitored neural activity via synapto-pHluorin which is a new exciting approach that leads to exceptional resolution and is applied very well in both in vitro and in vivo preparations. This study will be of great interest to readers interested in sensory processing and more generally to people with interest in neural coding and imaging.

hajor issue will require revision:

1. The authors claim that interglomerular inhibition plays no role in odorant coding although this conclusion is only weekly supported by their results. In their in vivo experiments indeed, they made the assumption that if interglomerular inhibition took place, odorant-evoked signal in a test glomerulus would be suppressed when its neighbor was coactivated by a different odorant. However, this is a very strong assumption made on the circuitry underlying interconnected glomeruli and one could argue that this assumption does not hold necessarily for all glomeruli. For instance, it has been shown that short-axon cells give rise to a rich and extensive interglomerular axonal network which projects to glomeruli up to several hundred micrometers distant. The authors subsequently failed to find evidence arguing in favor of substantial interglomerular inhibition. However, they only used six different odorant pairings with in addition the very restrictive condition of seeing no-overlap between glomeruli activated by each odorant of one pair. Considering the high dimensionality of odorant space, this negative result is certainly not sufficient to rule out any role played by interglomerular inhibition and the authors should be more careful in their interpretation. Indeed, in their in vitro experiments, they obtained a suppression ratio for glomeruli less than 400 um from an activated neighbor which, albeit weak, was statistically significant. Although the preparation was different (in vivo vs. in vitro), the evidence brought by the in vivo experiments is certainly not convincing enough. It would be a substantial improvement to test a larger number of odorant pairs for evidence of interglomerular inhibition.

Minor issue:

2. The authors mention that the synapto-pHluorin signal in olfactory bulb slices was much smaller than that observed in vivo. They explain this discrepancy by differences in ORN activation evoked by electrical versus odorant stimulation. In order to better compare results from both protocols, it would certainly be useful to design an electrical stimulation paradigm that results in synapto-pHluorin signals that are similar in strength to those measured in vivo with odorant stimulation. Indeed, electrical stimulation evokes single volleys of *synchronous* action potentials in a small subset of ORNs near the electrode, whereas odorant stimulation results in *prolonged* activation of many ORNs innervating a glomerulus.