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Dear *eLife* Editors,

We are pleased to submit the manuscript "**Front-end Weber-Fechner gain control enhances the fidelity of combinatorial odor coding**" by N. Kadakia and T. Emonet for consideration in *eLife* as a Research Advance to our recent paper "Gorur-Shandilya S et al. **eLife**, 6:e27670 (2017)". In the 2017 paper we reported that *Drosophila* olfactory receptor neurons (ORNs) adapt their gain with respect to mean signal intensity according to the Weber-Fechner law of psychophysics. Here we examine theoretically the consequence of this finding for combinatorial coding.

A key question in olfaction is: How do animals perceive odors uniquely in different environmental conditions? Distinct odors activate unique sets of olfactory receptor neurons (ORNs), suggesting a "combinatorial code" for odor identity. But environmental changes such as fluctuations in odor intensity or the presence of background odors may scramble these codes. Here we show that front-end gain adaptation with Weber-Fechner scaling, recently characterized by us and others in Drosophila ORNs, contributes significantly to preserving combinatorial odor codes. Our work is significant in that:

1. The Weber-Fechner law allows sensory systems to remain responsive by adjusting sensitivity to the mean stimulus intensity in the environment. This is straightforward for a single channel system. But what about a multi-channel system? In *Drosophila*, different ORNs respond to many of the same compounds with different affinities. Adjusting all ORN responses for optimal sensitivity may therefore require a precise balancing act. Our work shows that such <u>fine-tuning is not necessary</u>. A single adaptive mechanism, that depends on the activity of the channel rather than on the identity of the Or it expresses (Nagel & Wilson Nat Neuro 14(2), 208, 2011), can maintain odor coding fidelity when odors mix with backgrounds and fluctuate rapidly.
2. We find that ORN adaptation enhances the impact of known downstream neural transformations, in the antennal lobe (Olsen et al, Neuron 2010) and mushroom body (Litwin-Kumar et al, Neuron 2017), which help maintain neural representations of odor identity. Thus, ORN adaptation promotes odor recognition, as it reduces information loss <u>before these downstream transformations</u> are enacted. Indeed, we find that for some classification tasks, regulation within individual neurons can be just as important as connectivity between them.
3. Our results are robust. They require no odor- or ORN-specific parameter tuning. They <u>hold for various decoding schemes</u>, whether reconstructing exact odor signals or learning associations among odors. They also extend the recently-proposed primacy coding hypothesis, which posits that odors are encoded by the set of earliest responding glomeruli (Wilson et al, Nat Comm 2017).
4. Our study is of interest to the broad readership of *eLife*: Weber's Law exists in vision, touch, and audition, and is viewed as a mechanism to maintain sensitivity across signal <u>intensities</u>. Here we suggest a new way of thinking about it. In a multi-channel sensory system, it helps preserve combinatorial codes, which are signatures of signal <u>identity</u>.

As potential reviewers we suggest: Venkatesh Murthy (MCB Harvard; vnmurthy@fas.harvard.edu), Dmitry Rinberg (NYU; dmitry.rinberg@nyulangone.org), and Rachel I. Wilson (Harvard Medical School; rachel_wilson@hms.harvard.edu). Because of potential conflicts of interests, we request that our manuscript not be reviewed by Aurel Lazar, Dong-Gen Luo, or Yuhai Tu.

Thank you kindly for your consideration.

Sincerely yours,
Thierry Emonet
Associate Professor of Molecular, Cellular and Developmental Biology & Physics