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Dear 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 PNAS.

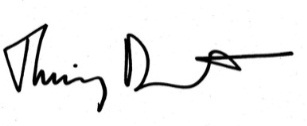
A key question in olfaction is: *How do animals perceive odors uniquely in different environmental conditions*? Distinct odors activate unique sets of olfactory receptor neurons (ORNs), suggesting that odors are encoded by the particular combination ORNs they excite – a “combinatorial code” for odor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

1. It is known that mutual inhibition between *Drosophila* projection neurons normalizes ORN responses, maintaining odor codes by preventing saturation (Olsen et al Neuron 66, 287, 2010). We find that this mechanism is enhanced by adaptation within individual ORNs, highlighting the importance of regulation at the very front-end of the olfactory circuit, well before signals are mixed downstream.
2. The Weber-Fechner law allows sensory systems to retain sensitivity by adjusting responses to the environment. This is straightforward for a single channel system. But the different type of olfactory receptors (Or) in *Drosophila* respond to many of the same compounds with different affinities, so adjusting all ORN responses for optimal sensitivity may require a precise balancing act. Our work shows that such fine-tuning is not necessary – a single adaptive mechanism, insensitive to particular odor identity because it depends on the activity of the Or ion channel rather than the identity of the Or (Nagel & Wilson Nat Neuro 14(2), 208, 2011), is highly adept at maintaining odor coding fidelity.
3. Our results hold for various decoding schemes, whether they reconstruct exact odor signals or learn associations among odors. We also find that front-end Weber-Fechner adaptation has benefits for primacy coding (Wilson et al. Nat Comm. 8, 1477, 2017).

As potential reviewers you may want to consider: Larry Abbott (Columbia University; [lfabbott@columbia.edu](mailto:lfabbott@columbia.edu)), Venkatesh Murthy (MCB Harvard; [vnmurthy@fas.harvard.edu](mailto:vnmurthy@fas.harvard.edu)), Rachel I. Wilson (Harvard Medical School; [rachel\_wilson@hms.harvard.edu](mailto:rachel_wilson@hms.harvard.edu)), and Elissa Hallem (UCLA; ehallem@ucla.edu). Because of potential conflicts of interests we request that it not be reviewed by A. Lazar, DG Luo, M. Stopfer or Y. Tu.

Thank you kindly for your consideration.

Sincerely yours,

  
Thierry Emonet

Associate Professor of Molecular, Cellular and Developmental Biology & Physics