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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 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 fine-tuning is not necessary. 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), is highly adept at maintaining odor coding fidelity.
2. We find that when combined with known downstream mechanisms – divisive normalization in the antennal lobe (Olsen et al Neuron 66, 287, 2010) and sparse connectivity to the mushroom body (Olsen et al Neuron 66, 287, 2010) – front-end Weber-Fechner adaptation contributes significantly to the robustness of the combinatorial code. This highlights the importance of regulation at the very front-end of the olfactory circuit, well before signals are mixed downstream.
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 the recently-proposed primacy coding hypothesis, in which odors are encoded by the set of earliest responding glomeruli (Wilson et al. Nat Comm. 8, 1477, 2017).

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

Thank you kindly for your consideration.

Sincerely yours,

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