REPLY TO SEMELIDOU AND SKOULAKIS:

"Short-term" habituation has multiple distinct mechanisms

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The Letter by Semelidou and Skoulakis (1) questions the congruence of our model (2) with current experimental evidence of olfactory habituation. We thank the authors for their Letter and would like to make three points in response.

1) Re: "and is independent of the mushroom bodies, unlike what the authors propose." To clarify, our model studied the effect of antennae lobe (AL) habituation on the mushroom body (MB) downstream. We did not propose that 30-min habituation itself occurs in, or requires, the MB. Indeed, we directly followed the mechanism proposed by Das et al. (3), where the locus of habituation is at the synapses between local inhibitory neurons and projection neurons (PNs) in the AL. We then computationally modeled the effect of PN habituation on downstream Kenyon cells, which receive input from PNs.

2) Re: "Importantly, osmotactic attenuation in Drosophila can occur not only after the prolonged 30-min stimulation, but also after a 4-min odor exposure as shown in a 2018 publication." Our paper focuses strictly on the mechanism for 30-min odor habituation (3). We completely agree, and we acknowledge in our paper that there are multiple circuits involved in habituation across multiple timescales. For example, we discuss habituation on the order of milliseconds at the odorant receptor level (4–9); we discuss long-term habituation on the order of days (3); and we suggest potential involvement of the lateral horn, a region of the *Drosophila* brain believed to be responsible for innate behaviors. We regretfully missed Semelidou et al. (10), which found direct evidence for another type of habituation happening at an even shorter-term (4-min odor exposure) and using a different mechanism than the one we studied, involving the lateral horn. We apologize for this omission.

3) Re: "the term 'short-term olfactory habituation' cannot be used to describe both olfactory habituation to 4- and 30-min odor exposure, a revised unified nomenclature is clearly necessary." We agree that the nomenclature "short-term" is overloaded. We followed the terminology of Das et al. (3), but we agree that future works should use better terms to distinguish among the many "short-term" timescales of habituation.

We hope this discussion helps clarify the contribution of our paper; i.e., algorithmically modeling the effect of 30-min habituation in the antennae lobe on downstream mushroom body activity. We thank Semelidou and Skoulakis for their Letter and their praise of our model, and we hope insights from the model can help untangle other forms of habituation in the olfactory system.

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The authors declare no competing interest.

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