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and a chemical sense in Drosophila*

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Reply to Hettinger: Olfaction is a physical and a chemical sense in *Drosophila*

We would like to thank Dr. Hettinger (1) for his positive comment on our results showing that flies can discriminate isotopes by smell and are capable of cross-learning between odors sharing a molecular vibration. Our article (2) demonstrated the presence of a physical (vibrational) component to odor character necessitating a vibration-sensing mechanism, the nature of which was not addressed experimentally and remains to be elucidated. We suggest that it likely involves inelastic electron tunneling, because this is consistent with our experimental data and with Brookes et al. (3), who have shown that an inelastic tunneling mechanism in olfaction is physically plausible. As pointed out by Luca Turin, this odorant detection mechanism does not require generation of free electrons by NADPH (4) and offers a potential explanation to why most enantiomer pairs smell identical. Further, Takane and Mitchell (5) have found IR spectra to be good predictors of odor character.

In our article, we described data obtained for *Drosophila* olfaction; we did not discuss or extend our findings to vertebrate olfactory systems or claim that humans can smell isotopes. Hence, a description of how the deuterated odors we use smell to humans is unnecessary. Several of the issues repeated here with respect to human olfaction were originally raised by Dr. Hettinger in the journal *Chemical Senses* in 2008 and answered by one of us (6). We seize this opportunity to point out the following: the change in C-H stretch frequency upon substitution by deuterium is indeed large, but its effect on odor character would be proportional to the intensity of the deuterium peak as measured by fly olfactory receptors, which is unknown at this stage and may be small, but nevertheless our experiments show that flies can consistently detect it.

The notion that smell, like hearing and color vision, may be a spectral sense is indeed attractive, but this does not make it

true. We have shown that in *Drosophila* one component of odorant recognition is conferred by molecular vibration, and this clearly implies a vibration-sensing mechanism. Another component to odor character could be the shape of the odorant molecules. If so, then olfaction in *Drosophila* combines both chemical (shape) and spectral (vibrations) components and may be evolutionarily intermediate between the purely spectral senses (vision and hearing) and a purely chemical one (taste). We further speculate that it is possible that vibration and shape sensing are used differentially for detection of different odors. This, Dr. Hettinger argues, requires a continuous odor space, which he dismisses. However, this is at odds with the fact that odor character requires multiple descriptors (rosy, musky, woody, etc.), and their relative prominence in related odors often varies in a strikingly continuous fashion. Finally, as Dr. Hettinger points out, using vibrations to detect isotopes is likely not very important to *Drosophila*. However, because all molecules vibrate, sensing molecular vibrations may be as useful to flies as it was to chemists until NMR and mass spectrometry came along.

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The authors declare no conflict of interest.

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