EPPENDORF 2007 WINNER

Neural Circuits Underlying Chemical Perception

The olfactory circuit in fruit flies is mapped out by combining genetic tools with in vivo measurements of neural activity.

Rachel I. Wilson

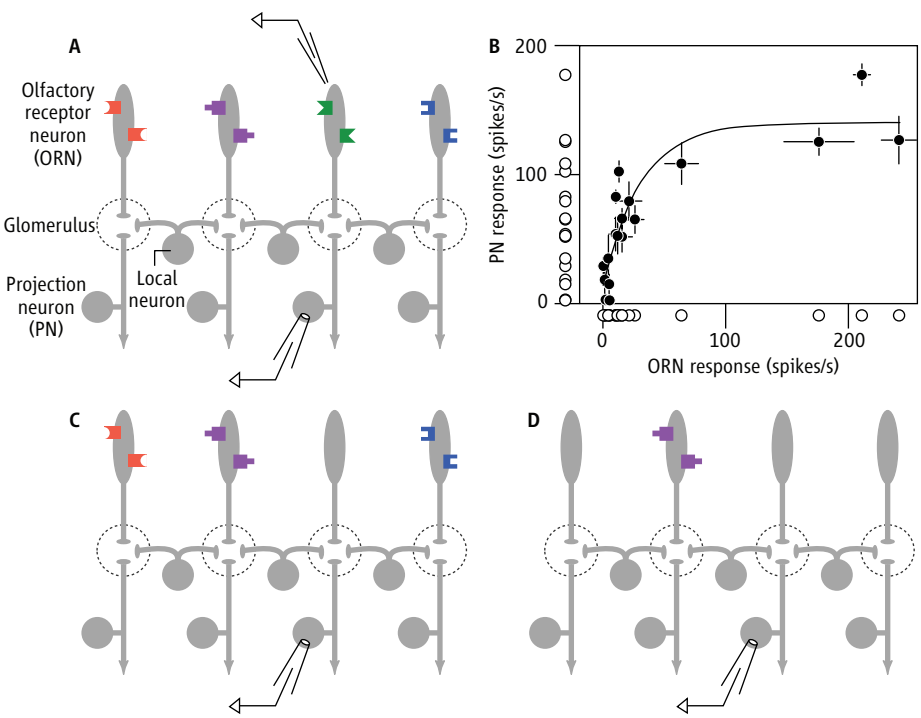
Eppendorf and *Science* are pleased to present the prize-winning essay by Rachel Wilson, the 2007 winner of the Eppendorf and *Science* prize for Neurobiology.

The air around us is full of chemical signals—plumes of smelly molecules floating in the breeze. Most animals are constantly alert to these olfactory cues. Odors can signal the quality of a food source, the location of a danger zone, or the sexual status of a potential mate. Initially, these signals are transduced by receptor neurons in the nose (or in insects, by receptor neurons in the antennae). Olfactory information is then passed to the brain via a series of electrical impulses in the axons of these neurons. Importantly, individual types of olfactory receptor neurons (ORNs) are not dedicated to sensing a particular odor. Instead, each ORN type can respond to multiple different odors (*1*). This confers an enormous coding capacity on the olfactory system. Thus, in order to identify an odor, the brain must decode a distributed pattern of impulses from a diverse population of receptor inputs.

My lab's goal is to understand how the brain solves this problem. Our mission is simplified by the beautiful organization of the olfactory system: All the ORNs expressing the same odorant receptor gene project their axons to the same compartment (termed a glomerulus) in the brain (*2*). Each second-order neuron in the brain receives direct input from just a single ORN type. Individual glomeruli thus represent discrete processing channels (see the figure, panel A). Glomeruli are also interconnected by local neurons, although the function of these lateral connections is not well understood. Recently, we performed a series of experiments asking what computations occur within an individual processing channel and how lateral connections contribute to these computations.

These questions are technically difficult to address in the vertebrate olfactory bulb. Therefore, we turned to the fruit fly *Drosophila melanogaster*. The fly antennal lobe shares the basic organization of the olfactory bulb, but is comparatively simpler, with only ~50 glomeruli as compared to ~1000 in mice (*3*, *4*). We can genetically label neurons that are either pre- or postsynaptic to specific glomeruli, allowing us to monitor activity in identified cells. In collaboration with colleagues at the California Institute of Technology, I recently developed techniques for making electrophysiological recordings from single neurons in the adult *Drosophila* brain in vivo (*5*). This allows us to exploit the sensitivity of electrophysiological recording techniques in a simple and genetically tractable invertebrate nervous system.

First, we asked what computations occur as information moves through the antennal lobe. We recorded odor responses in vivo from both ORNs and second-order neurons (termed projection neurons, or PNs; see the figure, panel A) corresponding to seven different glomeruli. We found that, for each glomerulus, the odor responses of PNs differ from the responses of their presynaptic ORNs. Whereas ORNs are somewhat narrowly tuned to odors, PNs are more broadly tuned. This distributes odor representations more efficiently within a PN's dynamic range (see the figure, panel B). We also found that, on average, the signal-to-noise



Decoding olfactory signals. (**A**) Recording from ORNs and their cognate PNs. Unlike the situation in this simplified cartoon, each glomerulus contains the axons of ~40 ORNs and the dendrites of about four PNs. (**B**) PN responses differ from the responses of their presynaptic ORNs. Plot shows the responses of ORNs and PNs corresponding to the same identified glomerulus (glomerulus DM1). Each black circle represents the response to a different odor, averaged across experiments (±SEM). Projecting the data onto each axis (white circles) illustrates that odor responses are distributed more uniformly in PN coding space than in ORN coding space. [Panel reproduced from (*6*)] (**C**) Silencing one type of ORN in order to observe lateral inputs onto its postsynaptic PNs. (**D**) Confining ORN input to one glomerulus in order to map its lateral inputs onto other glomeruli.

The author is in the Department of Neurobiology, Harvard Medical School, Boston, MA 02115, USA. E-mail: rachel_wilson@hms.harvard.edu

Published by AAAS

ratio of a PN's odor responses is better than that of an ORN's responses. Finally, we showed that these two transformations together can increase the separability of odor representations (*6*).

In these experiments, we focused on neurons responsive to "typical" odors (fruity odors, plant volatiles, and other odors representative of major chemical classes). Next, we asked whether odors with special behavioral relevance are processed in the same way as the "typical" odors. Other investigators had previously reported that one type of neuron in the antennae responds to cis-vaccenyl acetate, a *Drosophila* pheromone (*7*, *8*). We found that these ORNs are very narrowly tuned, responding to this pheromone but not to any other odors in our test set. In behavioral experiments, we found that genetically ablating these ORNs abolishes innate attraction to the pheromone. When we recorded from PNs postsynaptic to the glomerulus targeted by these ORNs, we found that, like their direct presynaptic inputs, these PNs are very narrowly tuned to cis-vaccenyl acetate. Thus, these PNs are unusual: They are exclusively dedicated to one ligand. This special circuit may ensure a tight connection between a pheromonal stimulus and a hardwired behavioral response (*9*).

Finally, returning to "typical" glomeruli, we asked how lateral connections shape PN odor responses. Here we exploited the fact that mutation of an odorant receptor gene silences all the ORNs that normally express that receptor. We reasoned that, by recording from a PN postsynaptic to silent ORNs, we could directly observe the effect of odor-evoked lateral inputs onto that PN (see the figure, panel C). Surprisingly, we found that lateral synaptic connections onto PNs are mainly excitatory. Control experiments showed that these connections exist in normal flies, not just mutants. We then genetically engineered flies where only one type of ORN is functional, and recorded from PNs postsynaptic to silent ORNs (see the figure, panel D) in order to map the pattern of connections from the functional receptors onto other glomeruli. This experiment showed that lateral excitatory connections are spatially widespread, heterogeneous in strength, and obey connectivity rules that are stereotyped across flies (*10*). At about the same time, another group independently discovered a new class of cholinergic local neurons in the fly antennal lobe (*11*), suggesting a possible cellular substrate for the excitatory connections we had found. These lateral excitatory connections may contribute to broad PN tuning. Alternatively, they may serve to bring all PNs transiently closer to their spike threshold whenever one receptor type is activated, thereby increasing their sensitivity.

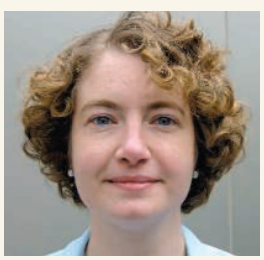
Taken together, our results show that a major transformation of olfactory signals occurs in the antennal lobe, and that integration across different glomerular channels begins here, in the first relay of the olfactory system. More broadly, these studies demonstrate the feasibility of deconstructing a simple neural circuit using genetic tools combined with in vivo measurements of neural activity. Decades ago, experiments in an invertebrate model organism (the squid) yielded key insights into how nerve cells produce electrical impulses; these experiments in *Drosophila* illustrate how invertebrates are helping neuroscientists bridge the conceptual gap between cells and circuits to understand the logic of neural computations.

References

1. B. Malnic, J. Hirono, T. Sato, L. B. Buck, *Cell* **96**, 713 (1999).
2. P. Mombaerts, *Nat. Rev. Neurosci.* **5**, 263 (2004).
3. E. A. Hallem, J. R. Carlson, *Trends Genet.* **20**, 453 (2004).
4. C. I. Bargmann, *Nature* **444**, 295 (2006).
5. R. I. Wilson, G. C. Turner, G. Laurent, *Science* **303**, 366 (2004).
6. V. Bhandawat, S. R. Olsen, M. L. Schlief, N. W. Gouwens, R. I. Wilson, *Nat. Neurosci.*, published online October 7 2007, http://dx.doi.org/10.1038/nn1976.
7. P. Clyne, A. Grant, R. O'Connell, J. R. Carlson, *Invert. Neurosci.* **3**, 127 (1997).
8. P. Xu, R. Atkinson, D. N. Jones, D. P. Smith, *Neuron* **45**, 193 (2005).
9. M. L. Schlief, R. I. Wilson, *Nat. Neurosci.* **10**, 623 (2007).
10. S. R. Olsen, V. Bhandawat, R. I. Wilson, *Neuron* **54**, 89 (2007).
11. Y. Shang, A. Claridge-Chang, L. Sjulson, M. Pypaert, G. Miesenbock, *Cell* **128**, 601 (2007).

10.1126/science.1151362

2007 Grand Prize Winner



The author of the prize-winning essay, **Rachel Wilson**, received her AB degree in chemistry from Harvard in 1996. She began her training as a neurophysiologist with Helmut Haas at Heinrich-Heine-Universität in Düsseldorf and continued as a graduate student with Roger Nicoll at the University of California, San Francisco. In her graduate work, she showed that endogenous cannabinoids act as retrograde messengers at hippocampal synapses. In 2001, she joined Gilles Laurent's laboratory at the California Institute of Technology as a postdoctoral fellow. There, in collaboration with another postdoctoral fellow, Glenn Turner, she developed methods for performing whole-cell recordings from neurons in the adult *Drosophila* brain in vivo. In 2004, she joined the Department of Neurobiology at Harvard Medical School. Her laboratory uses small neural circuits to study fundamental principles of sensory processing.

Finalist

Marianne Hafting Fyhn, for her essay, "The Grid Map in the Brain." Dr. Fyhn was born in Morehead City, North Carolina, USA, and grew up in Bergen, Norway. She did her undergraduate studies in biology at the Universities of Bergen, Oslo, and Tromsø before completing her master's thesis at the University of Tromsø in 1999 with work in Arctic biology at Spitsbergen. In 2000 she started her graduate work in neurobiology at the Centre for the Biology of Memory under the supervision of Dr. May-Britt and Dr. Edvard Moser at The Norwegian University for Science and Technology, Trondheim. She performed in vivo recordings of spatially modulated neurons from the hippocampus and entorhinal cortex of freely behaving rats and discovered "grid cells," which are neurons in entorhinal cortex with a remarkable hexagonal activity pattern. Since receiving her Ph.D. in 2005, she has been a postdoctoral fellow at the Centre for the Biology of Memory. Dr. Fyhn is a hiking, mountaineering, and fishing enthusiast. She has two small children with whom she enjoys outdoor activities.

CREDIT: (RIGHT) TORKEL HAFTING

For the full text of Dr. Fyhn's essay and for information about applying for next year's awards, see *Science* Online at www.sciencemag.org/feature/data/prizes/eppendorf/eppenprize.shtml.