and autophagasome formation (Krols et al., 2016). Moreover, proteins involved in ER-mitochondrial contacts have been implicated in diseases including Alzheimer's disease, frontotemporal dementia, and amyotrophic lateral sclerosis (Krols et al., 2016). This suggests that future work in other cell types will uncover additional disease-relevant functions of ER-mitochondrial contacts beyond PtdSer transfer.

Finally, the discrepancy among fly, mouse, and human cell models of PD is one that should be addressed by future work in the field of PD research. *Drosophila* research has been at the forefront for understanding the *in vivo* functions of Pink1 and Parkin, and it will be important to understand why mouse models have not fully recapitulated the phenotypes seen in flies or in patients. The possibility remains that compensatory mechanisms in mice could protect against Pink1 or Parkin loss (Whitworth and Pallanck, 2017), so investigating these mechanisms may be a productive line of inquiry for PD research. In addition, the work from this study also exemplifies the strength of validating pathological mechanisms in human cells and/or patient tissue whenever possible.

The current work of Valadas et al. (2018) is a compelling example of how cell-type-specific pathological mechanisms can explain multiple distinct symptoms arising from a single genetic deficit. Understanding these mechanisms in different cell types will therefore be essential to the development of fully effective therapies. To address non-motor symptoms like sleep dysfunction, the present findings about PtdSer depletion may be one entry point for a future therapeutic approach. Future studies employing cell-type-specific tools are likely to discover additional pathological mechanisms that could be promising therapeutic targets for both PD and other neurodegenerative diseases.

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Shining a Light on Olfactory Circuits

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How is odor information organized in the brain? In this issue of *Neuron*, Jeanne et al. (2018) pair optogenetics with electrophysiology to map functional connections between two olfactory brain regions. They suggest that lateral horn neurons encode "odor scenes" to represent biologically relevant odor environments.

The world is full of smelly objects, and the olfactory system needs to detect and respond to thousands, if not tens of thousands, of different volatile chemicals. How does the brain do this? Work by Jeanne et al. (2018) in this issue of *Neuron* sheds new light on this question.

Odorants are detected by odorant receptors expressed on the dendrites of olfactory neurons. Typically, olfactory sensory neurons (OSNs) express only a single type of odorant receptor. This defines the OSN's identity and ensures that it will report only the odor-induced activities of a single odorant receptor. Olfactory neurons that express the same receptor converge their axons to a region in the brain called a glomerulus. There are 50 glomeruli in the *Drosophila* brain, which together comprise the antennal lobe (AL). The AL is the primary

olfactory organizing brain region and acts to concentrate olfactory neuron signals into discrete organizing units. Glomeruli can act alone or send signals via excitatory and inhibitory local neurons to neighboring glomeruli. Much is known about the olfactory signals entering the AL (which odors activate which OSNs and hence which glomeruli), but far less is known about the olfactory information leaving the AL. The output neurons for the AL are olfactory projection neurons (PNs) (Figure 1). Typically, a PN innervates a single glomerulus and sends axons to the mushroom body calyx (for olfactory learning/memory) and to the lateral horn (for innate odor responses). The ~150 PNs in the *Drosophila* brain densely innervate the lateral horn, where they signal to ~1,400 lateral horn neurons (LHNs), the output neurons for this olfactory organizing center (Dolan et al., 2017; Frechter et al., 2018). LHNs are diverse, with ~250 different morphological types described so far, targeting various regions of the fly brain (Dolan et al., 2017; Frechter et al., 2018) (Figure 1).

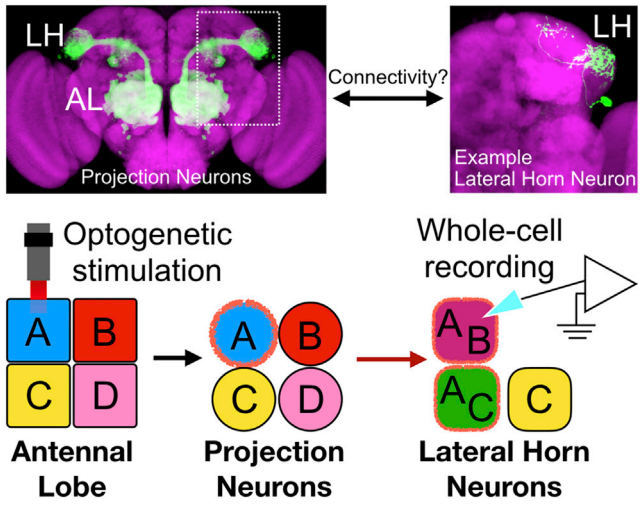

Figure 1. Mapping Functional Connections between Projection Neurons and Lateral Horn Neurons

In this issue of *Neuron*, Jeanne et al. (2018) mapped functional connections between PNs and LHNs and, as a result, provided new insights into how LHNs might organize odor information. To do this, they paired optogenetic stimulation of PNs with whole-cell patch electrophysiological recordings from a subset of GFP-labeled LHNs (Figure 1). Jeanne et al. (2018) took advantage of the organizing nature of the AL to optogenetically activate a glomerulus and thereby selectively activate the dendrites of genetically labeled PNs expressing the red-shifted channel rhodopsin ReaChR (Inagaki et al., 2014). A single LHN was recorded and labeled per experimental brain. Jeanne et al. (2018) collected 110 LHNs from paired optogenetic and electrophysiological recordings, and patched neurons were dye filled after recordings to allow their anatomy to be imaged and reconstructed.

The first question to address with this dataset was how to organize these LHNs. Should they be organized by morphology or by response characteristics? To address this, Jeanne et al. (2018) recorded LHN odor responses from intact flies followed by reconstruction of LHN morphology. They confirmed that LHNs that shared neuronal morphologies also shared odor response profiles. This suggested that clustering their 110 LHNs by morphology would be a good way to organize their data. As such, an LHN type was defined by its morphology, and the 110 LHNs clustered into 39 morphological types.

The next step was correlating LHN types to glomerular connectivity. While the 39 morphological LHN types were indeed similarly connected to AL glomeruli, their connectivity pattern to each glomerulus was not identical, exhibiting a moderate correlation coefficient of 0.6. Jeanne et al. (2018) explain this moderate correlation as a biological error rate between LHNs and the large number of glomeruli. That is, with 50 possible glomeruli connecting to each LHN, even a 5% error rate in connectivity of identical neurons would reduce correlations to 0.7. Nonetheless, these findings raise many interesting possibilities. As Jeanne et al. (2018) suggested, reduced correlations might reflect changes to connections due to differences in environmental stimuli within each individual. Intriguingly, this similar, but not identical, connectivity among individuals (presumably by otherwise identical PN-LHN pairs) could be a source of individuality in odor responses. This could enable flexibility in the olfactory circuit to allow differential and adaptive behavioral responses even in animals of identical genotypes.

Do all 50 glomeruli equally contribute to connections with LHNs? Or are some glomeruli overrepresented, meaning that they are connected to more LHNs than others? And if so, what may be the biological relevance of such glomerular overrepresentations? Jeanne et al. (2018) indeed found that some glomeruli are overrepresented in their connections to LHNs. These glomeruli (VA1d, VA1v, DC3, and VA6) are activated by narrowly tuned odorant receptor neurons. This suggests that they may impart specific and particularly relevant information to LHNs. For example, VA1d is activated by social pheromones and could indicate the presence of other animals within an olfactory context.

The ultimate question Jeanne et al. (2018) aimed to address is how do LHNs organize and encode olfactory information. Many LHNs have diverse morphologies, and many could be connected to a large number of glomerular PNs. At one extreme, the connectivity of glomeruli to LHNs could be completely independent. The fact that glomerulus A contacts LHN type 1 would have no bearing on whether glomerulus B, C, or D will also contact LHN type 1. In this case, each LHN receives a completely unique connectivity pattern. To investigate this, Jeanne et al. (2018) created a similarity matrix between glomeruli based on LHNs responses. Interestingly, they found that certain glomeruli were more often paired together than would be expected by chance alone. That is, if an LHN type 1 is connected by glomerulus A, there was a much higher probability that it

would also be connected by PNs innervating glomeruli B and C (Figure 1). This begins to establish patterns of connectivity between the AL and the lateral horn. The simplest prediction on how this might occur is if paired glomeruli are essentially receiving similar olfactory information from similar biologically relevant odors (such as pheromones), and the activated PNs from these two glomeruli further share highly similar morphologies. In this manner, odor A and odor B represent similarly relevant mating pheromones detected by different olfactory receptors, and as such, they will impart similar olfactory information to the lateral horn. In this case, it makes sense that glomerulus A and glomerulus B would show highly correlated connectivity patterns as they would be expected to share PN morphologies. This was indeed found for a small subset of glomeruli (e.g., DA1 and DL3 glomeruli both respond to the male pheromone cis-vaccenyl acetate, and their PNs share similar morphology). However, for the most part, this was not the case. When OSN or PN activity profiles (from prior studies: Hallem and Carlson, 2006; Badel et al., 2016) were mapped onto the glomerular similarity matrix, there was only a weak correlation between glomerular activities due to odor responses and glomerular connectivity patterns to LHNs. This suggests that the pattern of glomerular connectivities (glomeruli A and B more often connecting to LHN 1) is not likely driven by similarities in odor responses. So what is the meaning of the observed glomerular-to-LHN connectivity patterns?

To gain insight into this question, Jeanne et al. (2018) carefully examined the glomerular similarity matrix and identified 21 pairs of glomeruli that were most often found functionally connected to the same LHN. By graphically showing these relationships (i.e., DM1-DM2-VA3), a new organizing pattern began to emerge. While the odorants predicted to activate these glomerular networks might be quite different (e.g., ethyl hexanoate activates DM2 while 2-phenyl ethanol activates VA3), they shared what Jeanne et al. (2018) defined as an "odor scene." An odor scene describes an ethological and biologically relevant olfactory environment. For example, one odor scene activates a glomerular network characterized by fruit/yeast odors and anti-bacterial odors and together constitutes an ideal location for oviposition. Another odor scene activates a glomerular network characterized by responses to social and mating pheromones and anti-bacterial plant odors. This might constitute an ideal location for mating. This is an intriguing finding as it suggests that LHNs might encode odor qualities that emerge by the combination of biologically relevant parts and thus might direct innate behaviors by representing biologically relevant odor environments. Furthermore, the behavioral interpretation of a complex environment could be directed by weighing the activities of LHNs underlying different odor scenes. It is likely that more odor scene networks might be identified as additional glomeruli-LHN connectivity patterns are established.

The work by Jeanne et al. (2018) offers an exciting new perspective on how LHNs might encode olfactory information. However, much remains to be done. A caveat for this work is that connectivity patterns were generated in an *ex vivo* prep that differs from wild-type brains by a lack of spontaneous firing of olfactory neurons and the absence of excitatory and inhibitory local signaling in the AL. For this study, aimed at identifying direct connections between glomeruli and LHNs, these caveats are acceptable. Nonetheless, it will be interesting to compare these glomerular connectivity and LHN networks to *in vivo* studies (Frechter et al., 2018). This might reveal, for example, an increase in connectivity between groups of glomeruli, an expansion of the number of odor scenes, or even more complexity in LHN signaling.

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