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Neuroscience: Hacking development to understand sensory discrimination

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Fine sensory discrimination abilities are enabled by specific neural circuit architectures. A new study reveals how manipulating particular network parameters in the fly's memory centre, the mushroom body, alters sensory coding and discrimination.

Our brains are amazing classifiers. When sitting in a garden of flowers with your eyes closed, you can tell not just that you're smelling flowers, but that you're smelling roses and not violets. How does the brain make these fine sensory discriminations? Are the brains of good discriminators wired differently? In other words, what specific features of sensory circuits promote discrimination? And are there any trade-offs that determine a 'just right' skill level? A study by Ahmed *et al.*[1] reported in a recent issue of *Current Biology* tackled these questions using the power of *Drosophila* genetics.

A common circuit solution to neural classification problems is a so-called 'expansion layer' architecture. Here, a small number of sensory input channels project to a far larger number of expansion layer neurons, allowing sensory information to be represented combinatorially in a large-dimensional coding space. Sensory stimuli are then classified through learning by modifying the outputs of the expansion layer onto a smaller number of output neurons that represent the learned values of the specific neuronal combination generated by each of the input stimuli. This architecture evolved independently multiple times and resembles a structure used in machine learning called a perceptron[2]. In insects, the expansion layer architecture is found in a structure called the mushroom body, where the input layer is the olfactory

projection neurons, the expansion layer is the Kenyon cells, and the output layer is the mushroom body output neurons (MBONs) (Figure 1A).

Much theoretical work has investigated the computational effects of altering the number of neurons in the expansion layer ('cell number') and the number of inputs per expansion layer neuron ('input number'). For example, models have predicted that sensory discriminability would be improved by increasing the cell number or the selectivity of expansion layer neurons[3], and that discriminability is highest when the input number is relatively low (~7 inputs per Kenyon cell, in the fly mushroom body)[4]. However, these predictions have never been experimentally tested. Here, Ahmed *et al.* leveraged the power of *Drosophila* genetics to test the functional effects of altering the input number and cell number of the fly expansion layer system, the mushroom body.

They first evaluated the effect of changing the number of neurons in the expansion layer, i.e. the number of Kenyon cells. Previous work from the Clowney lab showed that the number of inputs that each Kenyon cell receives (input number) remains unchanged when either increasing or decreasing the number of Kenyon cells[5], meaning they could genetically change cell number without altering input number in the expansion layer. Using calcium imaging, the authors showed that increasing or decreasing the number of Kenyon cells did not significantly change their odour selectivity, and even flies with few Kenyon cells maintain sparse odour representations (Elkahlah *et al.*[5] and this study) (Figure 1B). It is possible that while reduced Kenyon cell numbers can maintain sparse odour representations of a limited number of odours, these animals might have an impoverished representation of the olfactory world — but this is harder to test experimentally. More surprisingly, MBON odour responses remained the same even when the number of Kenyon cells was increased. This result was unexpected because each MBON receives inputs from all Kenyon cells in its compartment, and suggests compensatory changes in the mushroom body inhibitory network or the strength of Kenyon cell to MBON connections[6,7].

Given the overall conservation of physiological responses of Kenyon cells and MBONs upon changes in the number of Kenyon cells, what is the behaviour of these animals with extreme cell numbers in their expansion layer? The authors showed that reducing the number of Kenyon cells did not affect learning, at least on an 'easy' learning task. Given that reducing cell number in the expansion layer of the cerebellum affects performance only on 'difficult', not 'easy' tasks[8], it will be interesting to test in the future whether flies with few Kenyon cells struggle on more difficult tasks (e.g., discriminating similar odours or detecting low odour concentrations). Conversely, increasing the number of Kenyon cells improved learning on an easy task (Figure 1B). The circuit bases for this improved learning remain unknown. The unchanged MBON activity upon increasing Kenyon cell number argues against a straightforward increase in feedforward excitation. Instead, the increased cell number, combined with whatever compensation keeps MBON activity the same, might result in more reliable signal transmission to MBONs.

The authors then tested the consequences of altering the second key parameter in the expansion layer, the input number, using clever genetic manipulations on Kenyon cells. The normal average input number is around ~6–8; the authors increased this to ~12 by using RNAi to knock down Tao, a kinase that reduces dendritic outgrowth[9], and they decreased input number to ~1 by overexpressing Dscam, an adhesion molecule that limits dendritic outgrowth through self-repulsion[10]. Combining these manipulations with calcium imaging experiments, Ahmed and colleagues showed that increasing the input number made Kenyon cells more responsive to odours — i.e. they were less selective. In

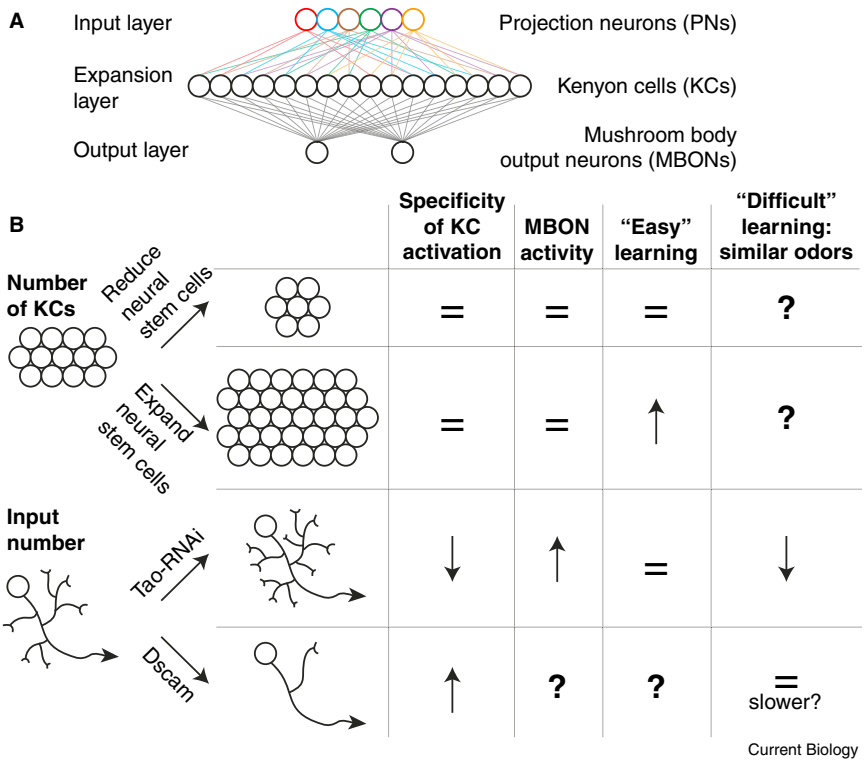

Figure 1. Manipulating network parameters in an expansion layer circuit changes sensory coding and discrimination.
(A) Schematic of an expansion layer neural circuit architecture with generic labels (left) and mushroom body-specific labels (right). (B) Summary of results from Ahmed *et al.*[1] and Elkahlah *et al.*[5]. Diagrams: circles represent Kenyon cell somata; branched structures are Kenyon cell dendrites where each "claw" at the end of a dendritic branch receives a projection neuron (PN) input; the arrowhead shows the axon continuing out of the frame. Upward arrow: increased activity or higher memory scores. Downward arrow: decreased activity or lower memory scores. =, no effect observed; ?, experiment not done.

contrast, decreasing the input number made Kenyon cells less responsive — i.e. they were more selective and their population odour representations were sparser (Figure 1B). These experiments demonstrated that input number, not cell number, determines Kenyon cells' odour selectivity.

As predicted by theoretical studies[2–4] and consistent with past results[11], when Kenyon cells were less selective due to higher input number, flies could perform an easy task where they learned to discriminate between dissimilar odours, but they could not learn a more difficult discrimination task that used similar odours (Figure 1B). At the other end, when Kenyon cells were more selective due to lower input number (i.e. sparser), flies could perform the difficult discrimination tasks, but appeared somewhat slower than control flies to choose the correct odour, suggesting slower evidence accumulation[12]. In the future it will be interesting to test if flies with sparser-than-normal Kenyon cells outperform control flies at very difficult discrimination tasks (using odours even more similar than those used here), as predicted theoretically[2]. It is possible that improving discrimination may require using a more subtle reduction in input number than the extreme reduction used here, which might be so drastic that it impairs odour detection. One caveat to these experiments is that the genetic manipulations used have other effects beyond affecting input number: the manipulation to reduce input number (Tao-RNAi) also reduces the number of Kenyon cells by ~25% and causes defects in axon guidance. However, the fact that Tao-RNAi flies learn normally on the easy task argues against major defects in mushroom body circuitry.

This work raises the questions of whether there is an optimal cell and input number for expansion layers, and if so, what are the trade-offs, and if these are species-specific or more general. Ahmed *et al.*[1] found that increasing cell number in the expansion layer improves memory, at least on easy discrimination tasks, suggesting that *Drosophila melanogaster* may not have reached the optimal number of Kenyon cells to maximise memory. Neurons are energetically expensive[13], so insect brains are likely under pressure to keep the number of Kenyon cells to the minimum required, with ecological needs likely driving Kenyon cell number variation across insect species, from 2,000 per hemisphere in *Drosophila* to 175,000 in honeybees[14].

For the second key parameter of expansion layers, input number for each Kenyon cell, Ahmed *et al.*[1] found that either increasing or decreasing input number worsens performance, consistent with models predicting that ~7 inputs per Kenyon cell is optimal[4]. Is this number common across species or does it depend on species-specific ecological needs? A recent pre-print reported that in three closely related *Drosophila* species with divergent ecological niches, input number per Kenyon cell is conserved across species, although the identity of the inputs has changed in an ecologically dependent way[15]. This finding suggests that closely related species might have evolved higher discriminability towards ecologically relevant odours at the expense of less important ones while maintaining a common circuit blueprint. However, the circuit blueprint, too, has changed over longer evolutionary timescales. For example, locusts (last common ancestor with flies 350 million years ago) have a much larger input number: each Kenyon cell receives input from ~400 projection neurons[16], suggesting a different scheme for maintaining Kenyon cell selectivity[4].

The work of Ahmed *et al.*[1] beautifully illustrates how extensive knowledge of developmental genetics can enable specific manipulations to test long-standing theoretical computational predictions in neuroscience, an approach that promises to bear more fruit in the future.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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Plant–microbe interactions: Plant-exuded *myo*-inositol attracts specific bacterial taxa

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Plants exude a plethora of metabolites that transform the microbiome composition. Initiated from genome-wide association studies of either a plant or a bacterium, two new studies dissect the impact of plant-secreted *myo*-inositol on recruitment of certain bacterial taxa by *Arabidopsis*.

Plants grow in concert with microbes, contributing to the fitness of all interacting species. Plant roots exude a series of metabolites, depending on their developmental stage, in the soil and therefore influence the composition of the surrounding microbes, either specifically attracting distinct microbial species or allowing the catabolism of the metabolites and therefore the presence or growth of microbiome members[1]. Therefore, the genetic context of the plant and its microbiome, collectively the plant hologenome, defines the overall fitness of the interacting species. Tracing the molecular and chemical factors behind plant–microbe interactions can be inspired by genome-wide association studies (GWAS) that reveal the genetic context of either the plant or microbes potentially contributing to the intricate interactions between the plant and its microbiome. Two new studies in this issue of *Current Biology* provide vigorous examples of how genetic variability of either a plant host or a microbiome species determines plant–microbe interaction success[2,3] (Figure 1).

In one of the new studies, O'Banion and colleagues[2] dissect a previously generated (holo)metatranscriptome dataset on developing xylem and mature leaf tissues of poplar trees and its microbiome[4] to identify the single nucleotide polymorphisms (SNPs) of the plant that correlate with the abundance of two bacterial genera, *Pantoea* and *Streptomyces*. Thorough analysis of the xylem-based GWAS dataset revealed that genes with SNPs encoding distinct transporters of *myo*-inositol correlate with these two bacterial genera. *Pantoea* was associated with the *INT1* gene, which encodes a tonoplast-localized transporter of *myo*-inositol, while the *Streptomyces* network correlated with the *PMT5* gene, encoding a transporter of various polyols and monosaccharides, including *myo*-inositol, across the plasma membrane. Motivated by these correlations detected in field-grown plants and microbiomes, the authors tested isolates of *Pantoea* and *Streptomyces* for their root colonization abilities using axenic soft-agar grown *Arabidopsis* seedlings harboring specific mutations for *myo*-inositol transport. As expected, *Pantoea* displayed reduced root colonization of *Arabidopsis* plants with *int1* disruption, while *Streptomyces* exhibited reduced establishment on the roots of *pmt5* mutant plant seedlings. Reassuringly, supplementation of *myo*-inositol rescued the mutant root colonization deficit of the bacterial strains but did not increase root colonization levels when wild-type Col-0 plants were used.

In the other new study, Sánchez-Gil and colleagues[3] employed a microbe-centered genetic trait analysis in which they identified that *Pseudomonas* isolates that display the highest colonization of *Arabidopsis* roots grown in an axenic soil system carry the *iol* gene cluster, encoding inositol catabolism in bacteria. Specifically, *Pseudomonas simiae* WCS417 and *Pseudomonas protegens* CHA0 displayed the strongest colonization of the root fraction without the soil (i.e., a combination of root and rhizoplane, the root's inner part and the surface zone, respectively), while the other *Pseudomonas* isolates (*Pseudomonas capeferrum* WCS358, *Pseudomonas fluorescens* RS158, and *Pseudomonas* sp. WCS317) that lacked the complete *iol* gene cluster had reduced colonization of the root structures, in spite of comparable abundance in the rhizosphere and bulk soil compartments. In addition to the *iol* gene cluster, the two *Pseudomonas* isolates were also enriched for genetic traits related to siderophore biosynthesis. Subsequently, the authors tested a *P. protegens* mutant lacking the *iol* gene cluster, which demonstrated significantly diminished *Arabidopsis* root colonization in the axenic soil system when initially mixed with the wild-type strain, but displayed comparable root colonization when either