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Navigating flexibly on the fly

For most of us, maintaining a sense of direction is something we only notice when disoriented. Imagine arriving at a subway station. As you emerge at street level you are completely turned around, but only for a few seconds. All it takes is the sight of a familiar landmark, and your mental map "clicks" back into place and you know where you are heading.

How do landmarks update our sense of direction, often without us consciously realizing?

This question had remained unanswered for any organism. Until recently. My colleagues and I used the fruit fly *Drosophila melanogaster* to obtain a mechanistic view into this process[1]. We uncovered how visual landmarks are incorporated into a brain's internal compass, creating a sense of direction tethered to the external world.

Insects sense direction like us

In most mammals, head direction cells serve as an internal compass that track the direction the animal faces in real time[2]. In 2015, it was discovered that cells in the insect central complex serve a similar function[3,4]. However, unlike the salt-and-pepper organization seen in mammals, the fly compass network has an orderly ring-shaped topology, comprised of individual compass neurons called E-PG neurons[5]. These neurons tile sectors of the ring, carrying a sustained "bump" of neural activity[3,6]. This activity bump behaves like the needle of a compass, circling around as the fly turns[3].

In darkness, self-movement signals rotate the bump proportionally to the fly's angular velocity[7,8]. As with our own sense of direction in complete darkness, errors quickly accumulate without landmarks to keep the compass true.

How is this error-prone self-motion-based estimate reconciled with changing external landmarks to generate a coherent sense of direction? We discovered that associative synaptic plasticity allows visual cues to be mapped onto the compass network, creating a sense of direction that is both accurate and flexible. This was possible by combining the advanced genetic toolkit in flies with accessibility to whole-cell electrophysiology during behavior[9,10].

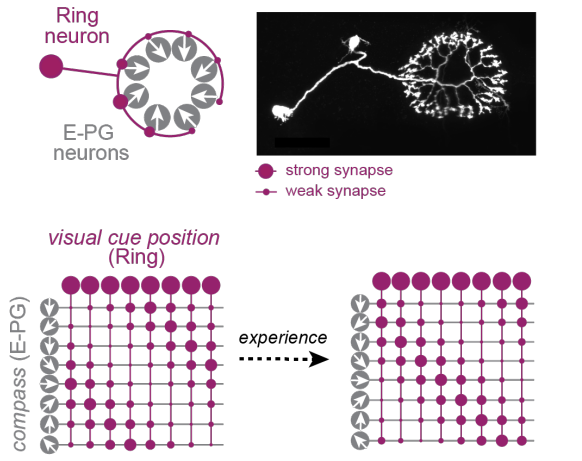

Figure 1: Visual inputs to the compass
Each visual ring neuron contacts every E-PG neuron. We propose that associative plasticity of ring → E-PG synapses mediates remapping when visual surroundings change.

From visual signals to compass coordinates

Anatomy was our first hint that this network is plastic. Visual information enters the compass via inhibitory neurons called ring neurons[11–13]. Ring neuron visual responses tile the fly's field of view and collectively convey information about surrounding cues[13–16]. Each ring neuron sends a circular axon that synapses with every E-PG neuron[17]. At first, this all-to-all connectivity was puzzling. If all ring → E-PG synapses were equivalent, then each E-PG neuron would receive the same visual drive, essentially discarding positional information. Alternatively, this wiring diagram may represent a set of potential connections with patchy functional connectivity (Fig. 1).

To test this, I isolated the drive from visual cues onto E-PG neurons by performing *in vivo* whole-cell electrophysiology from individual E-PG neurons while presenting visual cues to the fly in an LED arena[18]. Consistent with the visual drive coming directly from inhibitory ring neurons, visual cues often evoked synaptic inhibition, and ring neurons were required for visual inhibition. Each E-PG neuron received visual inhibition from some locations and not others, confirming that functional connectivity was patchy.

Nature or nurture?

Notably, we could not predict an E-PG neuron's visual tuning based on its anatomical position, as different flies exhibited different visual maps. This could be explained either by fixed idiosyncratic differences between individuals or from connectivity changes during an individual's lifetime.

The explanation that visual inputs were plastic was intriguing. A mid-1990s theoretical model proposed how associative plasticity could tether rat head direction cells to landmarks[19]. This model used an all-to-all wiring diagram similar to our observations. The core idea is that associative plasticity selectively "wires together" compass neurons with visual neurons. By taking a mental "snapshot" of each panoramic angle, the compass incorporates landmark information such that each heading direction associates with the view from that particular angle.

The compass initially relies on error-prone self-movement information and improves as the network "learns" consistent surroundings, with self-movement and landmark signals integrated to create a more accurate direction estimate. We reasoned that visual plasticity must occur rapidly to be useful, and we should be able to observe changes within an experiment.

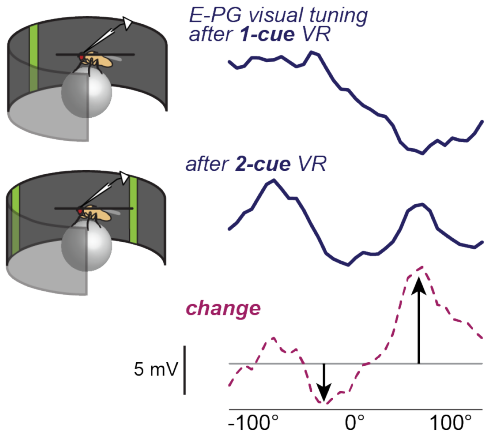

Figure 2: Inputs to compass neurons are plastic
Example of how E-PG visual responses, measured using whole-cell recordings, can change with experience. Switching the fly from 1-cue to 2-cue virtual reality (VR) leads to changes in E-PG visual tuning.

New surroundings alter the compass

To test adaptation to changing surroundings, we measured the compass network using calcium imaging while the fly explored in virtual reality. The fly walked on an air-cushioned ball, initially with a single bright cue guiding its exploration. Next, we presented two identical cues, 180° apart—an ambiguous scene given its symmetry.

In the two-cue world, the compass became unstable, alternating between two coordinate systems. After this experience, the compass continued alternating, even back in a one-cue world where the scene was no longer ambiguous.

The compass stabilized after minutes, sometimes into a new coordinate frame often re-oriented by 180°. This demonstrates that experience can alter the mapping between visual cues and the compass, providing the first evidence for ring → E-PG synapse plasticity.

To more directly test changes of visual input to E-PG neurons, we used whole-cell electrophysiology. Within minutes, we could observe visual drive remapping to match the structure of the two-cue world (Fig. 2).

This finding suggests that associative plasticity enables experience to alter ring → E-PG neuron connectivity. In a companion study, Kim et al. obtained complementary evidence for associative plasticity using optogenetics and calcium imaging[20].

Visual inputs to compass neurons are plastic

Our key discovery supports theoretical models describing how navigational networks establish a stable mental map using associative plasticity to learn consistent sensory cues during exploration[19,21–25]. Both head direction and grid cell networks are hypothesized to use such an algorithm, but it has not been possible to directly test this in mammals. Our results provide direct experimental evidence for this type of unsupervised learning at the level of synaptic potentials *in vivo*.

Despite 50 years of important research detailing mechanisms of synaptic plasticity[26–28], it remains a challenge to directly relate synaptic phenomena to spatial learning. These experiments illustrate how invertebrate research can provide that link.

So even if you are still lost when exiting the subway, we may soon understand why.

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