For the 2008 study[3], around 100 flies were trained to associate food with a magnetic field that was roughly ten times the strength of Earth's, after which the flies were placed in a device (a two-choice tubular T-maze) used to examine behavioural preferences. Each of the two arms of the device was surrounded by a magnetic coil, but only one of these coils produced the learnt magnetic field. With broad-spectrum illumination (light with a wavelength of 300–700 nanometres), flies preferentially aggregated in the arm with the magnetic field. But when the blue–ultraviolet part of this spectrum (light with a wavelength of less than 420 nm) was removed, the flies distributed uniformly between the two arms, apparently oblivious to the magnetic field. Blue–ultraviolet light seems to be required for a magnetic sense that depends on Cry (ref. 1), and because Cry-deficient mutant flies failed to detect the magnetic field in broad-spectrum light, the authors concluded that *Drosophila*'s magnetic sense is Cry-based.

In the wake of this ground-breaking claim, a number of papers were published — some in high-profile journals — showing similar results (see references in ref. 4). The authors of the 2014 study[5] harnessed the ability of the fly to climb against gravity (negative geotaxis) to test the animal's magnetic sense, and found that in dim blue light, the climbing tendency was high in the absence of a static magnetic field, but poor when the field was present. With or without the field, climbing was poor in the absence of blue light or when Cry-deficient mutant flies were tested. These results support a Cry-based magnetic sense in *Drosophila*.

Bassetto and colleagues tried to replicate the two influential studies from 2008 and 2014 using the same strains of flies. They received blueprints of the apparatus used in 2008, which enabled them to manufacture an exact copy, and the authors of the 2014 paper supplied the actual apparatus used in their study.

In highly controlled conditions, with apparatus placed in an electromagnetically shielded chamber inside a non-magnetic building that blocked external background radiofrequency noise, Bassetto *et al.* rigorously repeated the 2008 study, testing 984 sets of 100 flies over 48 months (97,658 flies in total). The authors found no preference for magnetic fields in the T-maze experiment.

Likewise, when Bassetto and colleagues attempted to replicate the results of the 2014 study using almost 11,000 flies, they failed to detect a difference in fly climbing tendency in dim blue light either with or without an applied magnetic field. When they reassessed the statistical approaches and sample sizes used in the two earlier studies, Bassetto *et al.* concluded that most of the original results were probably false positives, indicating magnetic sensitivity where it didn't actually exist.

Bassetto and colleagues' study is incredibly rigorous, with extremely large sample sizes. It also used appropriate statistical methods and assumptions, and the experimenters were not told of the magnetic conditions used in each experiment. The work was performed in arguably the best-controlled environment for magnetic experimentation in the world, purpose-built to be free of magnetic artefacts and radiofrequency noise. Therefore, the results the authors obtained raise serious doubts about the presence of a magnetic sense in *Drosophila*.

But do the authors definitively debunk the existence of a magnetic sense in *Drosophila*? Possibly, although there are now at least 15 publications reporting that this sense does exist, with many indicating a Cry-based mechanism. Can all of them be wrong? Again, possibly — and for similar reasons — but this is a serious call to make. Exact replication is notoriously difficult because, for instance, the states of the flies (such as health, age or reproductive state) and environments (such as season, time of day, temperature or humidity) in the original and replicate experiments might have differed.

Nonetheless, Bassetto *et al.* have raised a major red flag over the likelihood of *Drosophila* having the capacity for magnetic sensing. Hopefully this will encourage further replication studies, as well as entirely new studies, to scrutinize the magnetic sense of *Drosophila* with the same level of rigour as the work undertaken by Bassetto and colleagues.

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1. Mouritsen, H. *Nature* **558**, 50–59 (2018).
2. Wehner, R. & Labhart, Th. *Experientia* **26**, 967–968 (1970).
3. Gegear, R. J., Casselman, A., Waddell, S. & Reppert, S. M. *Nature* **454**, 1014–1018 (2008).
4. Bassetto, M. *et al. Nature* **620**, 595–599 (2023).
5. Fedele, G., Green, E. W., Rosato, E. & Kyriacou, C. P. *Nature Commun.* **5**, 4391 (2014).
6. Johnsen, S., Lohmann, K. J. & Warrant, E. J. *J. Exp. Biol.* **223**, jeb164921 (2020).
7. Dreyer, D. *et al. Curr. Biol.* **28**, 2160–2166 (2018).
8. Engels, S. *et al. Nature* **509**, 353–356 (2014).
9. Meister, M. *eLife* **5**, e17210 (2016).
10. Malkemper, E. P. *et al. Commun. Biol.* **6**, 242 (2023).

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Allergies

The immunology that underlies picky eating

Marc E. Rothenberg

Humans can be picky eaters. One such behaviour is an aversion to food associated with food allergy. The immunological basis for this response has been uncovered in mice, revealing the role of neuroimmune connections. **See p.634 & p.643**

Allergic diseases are on the rise, affecting 30–40% of the global population[1]. Research often focuses on the illness and death associated with these and other immune-mediated diseases, but emerging evidence suggests that allergies also provide some protection and benefit. Food aversion, for instance, can limit exposure to harmful stimuli, acting as a defence strategy to prevent further damage. Yet how allergy and food aversion are connected mechanistically has been unclear. Writing in *Nature*, Plum *et al.*[2] (page 634) and Florsheim *et al.*[3] (page 643) report evidence in mice that the arm of the immune system involved in allergic responses communicates with the brain, and thereby leads to food avoidance.

The authors report that this avoidance response involves a neuroimmune pathway that requires antibody responses (relying on a type of antibody termed IgE). The pathway also depends on activation of a population of gut-resident immune cells called mast cells, which produce and release molecules called leukotrienes that are normally associated with promoting inflammation (Fig. 1).

The brain and immune system communicate readily through, for example, a system (called the efferent hypothalamic–pituitary–adrenal axis) that regulates production of a potent anti-inflammatory hormone called cortisol. This communication is bidirectional, and the immune system can activate structures outside the brain called afferent nerve fibres. These fibres are extensions of sensory neurons that connect to the brain and generate molecules called cytokines in the brain.

What is often unappreciated is that these biological responses can be altered through learning or conditioning — the brain can

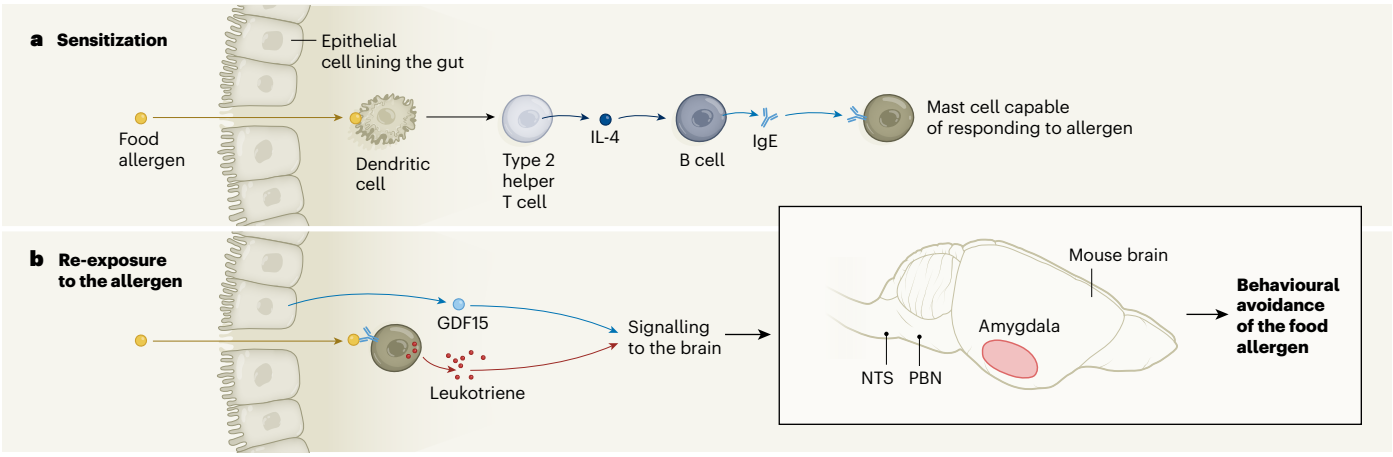

Figure 1 | Immune response involved in a food-aversion behaviour associated with food allergy. Plum *et al.*[2] and Florsheim *et al.*[3] investigated the development of an allergic reaction to food in mice. **a**, If a food in the gut crosses epithelial cells and enters gut tissue, this can trigger an allergic response. Sensitization to the allergen requires various immune cells and signalling molecules. Dendritic cells capture the allergen and activate type 2 helper T cells, which release the cytokine protein IL-4. This triggers immune cells called B cells to release a type of antibody called IgE, which is capable of recognizing the specific allergen. This IgE binds to a mast cell. **b**, If the animal encounters this allergen subsequently, the mast cell releases molecules called leukotrienes, and epithelial cells release a protein called GDF15. These factors eventually lead to activation of brain regions known as the nucleus of tractus solitarius (NTS), the external lateral parabrachial nucleus (PBN) and the amygdala, which process signalling inputs to drive behavioural responses. This sequence of events might explain how mice avoid eating food containing the allergen.

modify the response, as was investigated by Ivan Pavlov (perhaps best known for studying conditioning responses in dogs)[4]. For example, rodents can be trained to develop an allergic response, including activation and release of inflammatory molecules by mast cells, when exposed to a stimulus such as an audiovisual cue in the absence of a toxic substance (allergen)[5]. Furthermore, a behaviour such as avoidance of specific foods can be set up in parallel with an immune response to that food[4].

Similarly to other manifestations of allergy, such as sneezing, itching or vomiting, which counteract immediate exposure to an allergen, food aversion protects the host by facilitating subsequent avoidance to a toxin. The interactions between behaviour, the brain and the immune system in this context are an emerging area of research. Insights into this process have broad implications for both health and disease, including the possibility that the mind can be harnessed to improve a disease state in the absence of specific therapy (through what is often referred to as the placebo effect). However, although evidence for an immunological basis for food-avoidance behaviour has been reported[4], the operational mechanisms have remained elusive.

Both research teams provide fundamental insight into the mechanisms that underlie these aversion responses. The two groups induced a food allergy in mice by injecting a food allergen, the egg protein ovalbumin, in the presence of an immune-system stimulant (called an adjuvant). They then re-exposed the animals to the allergen through the gut. The authors found that immunological sensitization resulted in the mice avoiding the allergen when given a choice between drinking water alone and drinking water containing the allergen.

Plum *et al.* demonstrate that the allergen-specific avoidance behaviour depended on mast cells. Mice that were genetically engineered to have mast-cell deficiencies did not develop an avoidant response. Furthermore, gut mast cells were activated during the phase in which the avoidance behaviour was acquired. Development of such behaviour after allergen exposure was also subject to genetic control, because it was affected by the genetic background of the mouse strains used.

Furthermore, avoidance was promoted by the same cytokine (IL-4) as that required by type 2 helper T cells — the cells of the adaptive branch of the immune system that were induced by the initial exposure to the allergen. Aversion was also promoted by IgE, which is known to sensitize mast cells to allergens[6]. Notably, inhibiting production of leukotrienes impaired avoidance.

Florsheim *et al.* demonstrate allergen avoidance with multiple experimental regimens, including two food-allergy models (using two different adjuvants) and a non-food-allergy model involving food sensitization by means of lipopolysaccharide molecules — bacterial-wall components that stimulate immune responses. The authors report long-term aversion responses (exceeding 48 weeks) after allergen sensitization, and also provide evidence for the roles of mast cells, IL-4 and IgE. Their work excludes a role for the vagus nerve (the main nerve that controls involuntary body functions), or direct allergen sensing by sensory neurons. Allergen exposure activated specific regions of the brain (the nucleus of tractus solitarius, the external lateral parabrachial nucleus and the central amygdala) that are associated with processing sensory-neuron signals involved in learning.

Furthermore, Florsheim *et al.* show that allergen exposure induced dose-dependent production of the hormone GDF15 by epithelial cells in the gut. Consistent with the mechanism of avoidance behaviour uncovered, GDF15 production was dependent on IL-4, IgE and the blocking of leukotrienes. GDF15 can bind to its receptor in the nucleus of tractus solitarius and the area postrema, a region of the brain involved in eliciting nausea in response to noxious stimuli[7]. Interestingly, neutralizing GDF15 prevented food aversion.

These two studies deepen our understanding of the neuroimmune system. Although limited to mice, the findings suggest that the same allergy mediators (IgE, mast cells and leukotrienes) that elicit immediate allergic responses also offer a sensing function, providing a mechanism by which the nervous system can evaluate environmental factors, including food. The evidence indicates the involvement of specific brain regions, particularly those involved in processing sensing signals into behavioural responses, and that the effects are mediated by GDF15. Immediate GDF15 production by gut epithelial cells occurred after allergen ingestion, but the underlying mechanism is unknown. How the brain elicits the avoidance response is also an open question.

Might these findings be relevant to humans? Several human disorders are associated with food aversion, including cancer, anorexia nervosa and food allergy[8]. In the case of food allergy, aversion is typically specific to distinct food types, similar to the mouse findings reported. The protective effect of food avoidance in an individual with a food allergy is a form of Pavlovian conditioning that might

help to avert exposure to an environmental danger. However, food aversion can be harmful if the allergy no longer exists or when it interferes with oral immunotherapy — a way of treating a food allergy by the reintroduction of increasing amounts of allergy-triggering foods[9].

Humans have a greater capacity for learning than do mice, and thus food avoidance probably involves more-complex learning in humans than the simple behavioural conditioning seen in rodents. Unlike humans with food allergies, mice with an experimentally induced food allergy do not completely avoid the allergen. Instead, the animals studied by the authors ingested low volumes of allergen-embedded drinking water, probably triggering a minor response. Furthermore, it is interesting to speculate that underlying immune-mediated mechanisms might contribute to food choices even in individuals who show no overt signs of allergy.

These findings might prompt further testing of potential treatments because drugs are available that precisely target identified allergy mediators. Omalizumab, an antibody that blocks IgE, is approved for the treatment of conditions such as asthma and, on the basis of early clinical studies, shows promise for treating food allergy[10]. Dupilumab is a clinically approved antibody that blocks IL-4 signalling. Furthermore, the types of leukotriene identified by Plum *et al.* and Florsheim *et al.* are readily blocked by clinically available drugs that interfere with the molecules' synthesis or with receptor-mediated signalling. In addition, a mast-cell-depleting antibody is in early clinical development[11]. Beyond anti-allergy therapeutic strategies, GDF15-based drugs are being tested in preclinical animal models[12].

Memory is a feature shared by the brain and the immune system, although the mechanisms involved differ vastly. The latest findings identify the importance of immunological memory, mediated by a classic allergic response, in acting as a primer for food aversion. Whether direct memory in the brain is also involved remains to be determined.

The mechanism of food aversion uncovered by the two studies is a notable leap forward in our understanding of the molecular and cellular bases of the neuroimmune connections involved in behavioural conditioning. Plum *et al.* and Florsheim *et al.* thereby provide a new meaning to picky eating.

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1. Pawankar, R., Canonica, G. W., Holgate, S. T. & Lockey, R. F. (eds) in *The WAO White Book on Allergy* 12 (World Allergy Org., 2011).
2. Plum, T. *et al. Nature* **620**, 634–642 (2023).
3. Florsheim, E. B. *et al. Nature* **620**, 643–650 (2023).
4. Hadamitzky, M., Lückemann, L., Pacheco-López, G. & Schedlowski, M. *Physiol. Rev.* **100**, 357–405 (2020).
5. MacQueen, G., Marshall, J., Perdue, M., Siegel, S. & Bienenstock, J. *Science* **243**, 83–85 (1989).
6. Valent, P. *et al. Theranostics* **10**, 10743–10768 (2020).
7. Lockhart, S. M., Saudek, V. & O'Rahilly, S. *Endocr. Rev.* **41**, bnaa007 (2020).
8. Bernstein, I. L. *Nutrition* **15**, 229–234 (1999).
9. Sabouraud, M. *et al. Arch. Pediatr.* **28**, 319–324 (2021).
10. Dantzer, J. A., Kim, E. H., Chinthrajah, R. S. & Wood, R. A. *J. Allergy Clin. Immunol.* **151**, 1–14 (2023).
11. Terhorst-Molawi, D. *et al. Allergy* **78**, 1269–1279 (2023).
12. Xiao, Q.-A., He, Q., Zeng, J. & Xia, X. *Biomed. Pharmacother.* **146**, 112582 (2022).

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Climate-change ecology

The great melt will shape unprotected ecosystems

Nicolas Lecomte

Glaciers should be prioritized in conservation agendas — and soon. Analysis suggests that glaciers could lose around half their area by the century's end, with uncertain consequences for postglacial ecosystems. **See p.562**

Glacier shrinkage is driving one of the most rapid ecosystem shifts on Earth: as anthropogenic climate change causes glaciers to recede, the future of species that have adapted to glacial conditions remains unclear. A comprehensive spatial analysis that quantifies and anticipates this transformation has so far been lacking. But on page 562, Bosson *et al.*[1] project that glaciers outside the Antarctic and Greenland ice sheets could lose as much as half of their area by 2100. Their estimation that around half of these glacier areas are currently unprotected underscores the urgent need for enhanced climate-change mitigation and conservation measures.

Last year, the United Nations issued a resolution declaring 2025 as the International Year of Glaciers' Preservation, and emphasizing the importance of conserving these pristine ecosystems (see go.nature.com/3kfxmkx). Bosson and colleagues have responded to this call for immediate action by using the most precise model for glacier change[2] to quantify the impact of warming under different scenarios of greenhouse-gas emissions[3]. If emissions are cut to net zero by 2050, the authors predict that around 80% of the glaciated area they studied would remain in 2100. This fraction drops to half in a high-emissions scenario brought on by a tripling of emissions by 2075.

The implications of these predictions are far-reaching. But it is not yet clear how glaciers can be adequately safeguarded[4] — and it is perhaps even less obvious how best to protect the existence, function and benefits of glacial ecosystems[5], as well as those that will emerge in postglacial areas[6–8]. Bosson and colleagues' study opens up promising avenues for investigating the upcoming ecological changes.

Postglacial ecosystems hold tremendous potential for carbon sequestration, and research into these systems — although still in its infancy — is crucial for identifying their role as future carbon sinks. However, the development of functional postglacial ecosystems can be extremely slow and complex: slow, because it can take millennia[9], much longer than the agenda of any conservation plans; and complex, because species can respond to change positively, negatively or not at all (see, for example, ref. 10). Indeed, an understanding of the ecological processes involved is only now beginning to emerge, but their inherent complexity is already clear, and evident in the fact that several trajectories for recolonizing postglacial areas exist, even on the scale of individual glaciers[11].

Yet Bosson *et al.* estimate that, not only will deglaciation be rapid, but future deglaciated areas will also span a diverse range of biomes — from the size of Nepal to Finland — encompassing terrestrial, freshwater and even marine habitats. Such vast emergence on a relatively short timescale will add to the complexity of glacial dynamics and will increase the challenge of glacier conservation (see, for example, ref. 12).

There are several benefits associated with these predictions. First, newly deglaciated areas can already harbour plant life. For example, a remarkable discovery revealed a population of bryophytes (mosses) and associated microorganisms that had been buried under ice for 400 years[13].

Second, deglaciated areas could offer refuge for species seeking new homes, and habitats adjacent to glaciers could support such recolonization.