News & views

Neuroscience

What happens to a lonely fly

Joel D. Levine

The fruit fly *Drosophila melanogaster* is a social animal. Flies kept in chronic social isolation have now been found to show dysregulated sleep and feeding patterns, casting light on how prolonged absence of social contact affects health. **See p.239**

The neuroscientist Bruce McEwen wrote[1] in 2002 that stress is the foremost public-health issue of our times, and that "when activated chronically it can cause damage and accelerate disease". Many stressors are of a social nature, and McEwen[1] and others (see go.nature.com/3s3b4kw) noted with concern that certain social pressures, such as poverty, inadequate education and violent crime, can contribute to the development of illnesses such as cancer, diabetes and depression. However, little is understood about how these social pressures translate to disease. On page 239, Li *et al.*[2] present a fascinating and creative approach to modelling the effects of social context on an individual's health, using the fruit fly *Drosophila melanogaster*.

McEwen's view was that a strong community sets the stage for health, and that social isolation can lead to sickness. The American Psychological Association has published surveys that agree (see go.nature.com/3s7dqic). These indicate that more than 60% of US adults have gained or lost weight during the COVID-19 pandemic. Mental-health problems, including disruption to sleep, have also risen during this period, which, along with increased social distancing, has been marked by a heightened incidence of sexual harassment and racial tensions[3] (see also go.nature.com/3s3b4kw). The pandemic thus serves as a wake-up call to us to find new strategies for ensuring the health of society.

Although the fly might seem an unlikely contributor to investigations into the effects of social environment, there are now at least two decades of research indicating that flies respond to their social context[4]. This research tells us that social context shapes, and is shaped by, neural and cognitive function and levels of gene expression. Social experience and the composition of social groups influence flies' susceptibility to disease as well as many of their behaviours, including mating, eating and sleeping[5,6]. These features of a fly's life are influenced by its genetics and its social experience, but what happens when the fly is alone?

Li *et al.* establish the fly as a model for studying effects of social isolation. They investigate flies maintained in groups (Fig. 1a) and flies maintained in acute or chronic isolation — for 1–3 or 5–7 days, respectively. They show that, compared with flies kept in acute isolation or in groups, those kept in chronic isolation display disruption to their sleep patterns and eat twice as much food (Fig. 1b). These differences in behaviour are accompanied by changes in the expression of 214 genes assayed from whole fly heads, including many genes associated with biological pathways of sleep.

Li *et al.* focused on two of these genes: one encoding the protein limostatin, a hormone that is upregulated in the head in response to starvation, and the other encoding drosulfakinin, a peptide released in the head that is downregulated in response to starvation. Intriguingly, the expression pattern of these genes under conditions of social isolation mimicked that seen in starved flies, despite constant food availability. Thus, in the fly, social isolation mimics starvation. This observation is reminiscent of findings of a study in humans showing that social isolation produces food-craving responses in the midbrain that are similar to those induced by hunger[7].

The authors identified a cluster of limostatin-expressing P2 neurons in the central complex of the fly brain, and showed that they contribute to the effects of social isolation in flies. These cells, which have previously been called fan-shaped-body columnar neurons[8], extend projections that connect with tangential sleep-promoting neurons of the fan-shaped body, a structure in the centre of the fly brain[8,9]. P2 neurons were previously characterized[10] by their expression of a peptide called NPF, which is related to a peptide in mammals called NPY that is associated with feeding and social behaviour. However, the function of

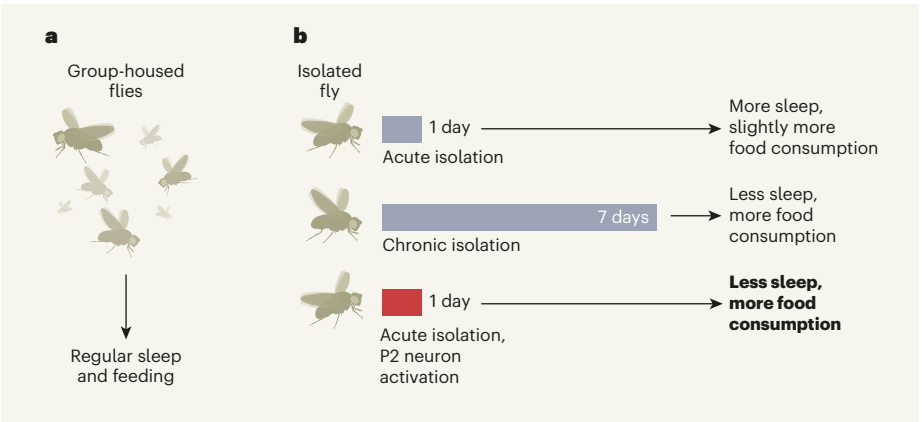

Figure 1 | The effects of isolation on the fruit fly *Drosophila melanogaster*. a, Flies typically live in social groups. **b**, Li *et al.*[2] found that when flies were acutely isolated (for a day), the insects showed increased sleeping time and slightly increased food consumption. However, when flies were chronically isolated (for seven days), they displayed sleep loss and ate substantially more food than did group-housed flies. The authors found that, in flies that were acutely isolated, artificially activating a cluster of neuronal cells called P2 neurons in the upper part of the brain led to behavioural changes mimicking those observed in chronically isolated flies. P2 neurons extend projections to the fan-shaped body of the fly brain, where other neurons control feeding and sleeping (not shown). Together, these findings suggest that P2 neurons might become more active with, and thus 'track' the duration of, periods of isolation, leading to behavioural changes with time.

P2 neurons was previously not clear.

When the authors silenced the P2 neurons, the behavioural effects of social isolation disappeared, suggesting that the circuit formed by P2 neurons projecting into the fan-shaped body mediates these effects. Artificial activation of P2 neurons in acutely isolated flies resulted in these flies eating more and sleeping less, similar to chronically isolated flies without the artificial activation (Fig. 1b). This result suggests that P2 neurons might track the duration of isolation and, as the interval of isolation increases, update the neurons that regulate sleep and feeding. In other words, P2 neurons might function as a timer.

Proving this 'timer' model would require detailing the relationship between the strength of P2 activation and the duration of social isolation. Although not proven, this model suggests that P2 neurons affect the social state of an individual, an idea that could serve as a foundation for future studies to examine the effects of neural circuitry on social state and physiological measures. It might be, for example, that P2-neuron activation predicts the amount of sleep an individual gets or the number of matings it attempts[11].

Drosophila exhibit collective behaviour, a social-network structure and hallmarks of culture[12–14]. Li and colleagues' investigation is an example of a growing number of studies in flies[4] showing that manipulating social context modulates individual behaviour, physiology and gene expression in group members. Li *et al.* have thus begun to unravel the relationship between social context, social experience and homeostasis at the neuronal and molecular levels.

I was fascinated by this study because of the similarities uncovered by Li *et al.* between the effects of isolation on *Drosophila* and the effects of stress on human mental health. By virtue of our common evolutionary ancestry with this insect, the fly has already helped us to understand the mechanisms underlying development, learning and disease in humans[15]. From an evolutionary perspective, *D. melanogaster* serves as a fount of ancestral wisdom. Crucially, models such as the one proposed by Li and colleagues might lead to a greater understanding of mental illness in people, and could inform the development of new ways to treat isolation and, by extension, craving and addiction. But even as we wait for the fly to help us combat the complex effects of social isolation, Li and colleagues' study reminds us that there are benefits to everyday interactions with others.

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1. McEwen, B. & Lasley, E. N. *The End of Stress As We Know It* (Dana, 2002).
2. Li, W. *et al. Nature* **597**, 239–244 (2021).
3. Bourassa, C., McKay-McNabb, K. & Hampton, M. *Can. Woman Stud.* **24**, 23–29 (2004).
4. Schneider, J., Atallah, J. & Levine, J. D. *Adv. Genet.* **77**, 59–78 (2012).
5. Dawson, E. H. *et al. Nature Commun.* **9**, 3574 (2018).
6. Sokolowski, M. B. *Neuron* **65**, 780–794 (2010).
7. Tomova, L. *et al. Nature Neurosci.* **23**, 1597–1605 (2020).
8. Hulse, B. K. *et al.* Preprint at bioRxiv https://doi.org/10.1101/2020.12.08.413955 (2020).
9. Donlea, J. M., Thimgan, M. S., Suzuki, Y., Gottschalk, L. & Shaw, P. J. *Science* **332**, 1571–1576 (2011).
10. Lee, G., Bahn, J. H. & Park, J. H. *Proc. Natl Acad. Sci. USA* **103**, 12580–12585 (2006).
11. Lee, C. R., Chen, A. & Tye, K. M. *Cell* **184**, 1500–1516 (2021).
12. Ramdya, P. *et al. Nature* **519**, 233–236 (2015).
13. Schneider, J., Dickinson, M. H. & Levine, J. D. *Proc. Natl Acad. Sci. USA* **109**, 17174–17179 (2012).
14. Danchin, E. *et al. Science* **362**, 1025–1030 (2018).
15. Bellen, H. J., Tong, C. & Tsuda, H. *Nature Rev. Neurosci.* **11**, 514–522 (2010).

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Metabolism

Dietary fructose expands the gut and aids fat uptake

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Feeding mice high-fructose corn syrup, a widely used sweetener in human diets, has been found to drive an increase in the surface area of the gut that is associated with enhanced absorption of dietary nutrients and weight gain. **See p.263**

The incidence of obesity has been steadily increasing, tripling globally between 1975 and 2016, at a high cost to public health[1]. Obesity predisposes individuals to various diseases, including cancer, and the number of obesity-associated deaths globally each year[1] (estimated at 2.8 million) is similar in scale to the reported COVID-19-associated deaths in the ongoing pandemic. Although fat-rich diets have taken much of the blame for the rise in obesity, excess consumption of processed sugars, and high-fructose corn syrup (HFCS) in particular, is strongly implicated in diet-induced obesity. Whether and how fructose causes obesity in humans remains a hotly debated question[2,3]. In a report on page 263 that should make one think twice before gulping down sugar-sweetened drinks with fatty snacks, Taylor *et al.*[4] propose that HFCS promotes obesity by boosting the ability of the intestine to absorb nutrients.

"Avoiding sugary drinks altogether might be a good start to curbing obesity."

Evidence has emerged[5–8] that the small intestine acts as the gatekeeper for the mammalian body against the harmful effects of fructose, the main one being the aberrant accumulation of fat (termed steatosis) in the liver. Moderate amounts of fructose — for example, those ingested when consuming fruits — are taken up and broken down by intestinal cells. Excess amounts, such as those that might be ingested after drinking a sugary beverage, overwhelm the intestine's absorptive capacity and the fructose either 'leaks' into the bloodstream to reach the liver intact, or it spills over from the small intestine and reaches the colon[5].

The breakdown of fructose in cells starts with its conversion to fructose 1-phosphate (F1-P). This modification involves the transfer of a phosphate group to fructose from the energy-providing molecule ATP, through the action of the enzyme ketohexokinase (KHK). Excess fructose in the liver fuels high KHK activity, which is thought to stimulate the expression of lipid-synthesis genes by diverse mechanisms[9]. The depletion of KHK in the liver of mice is enough to prevent fructose-induced liver steatosis[6].

Fructose that ends up in the colon is broken down by resident bacteria to produce molecules that can then fuel lipid synthesis in the liver[7]. Furthermore, fructose increases intestinal 'leakiness', a condition in which loose connections between gut cells enable ingested nutrients, and toxins from bacteria in the colon, to escape to the liver, where they activate inflammatory signals from immune cells that boost steatosis[8]. Therefore, excess fructose harms the liver both directly and indirectly through changes in the intestine.

Taylor and colleagues' study reveals that fructose has a previously unknown effect on the structure of the intestine (Fig. 1). Previous work[10] had shown that HFCS promotes metabolic pathways that support the formation of colon tumours, so the authors wondered what consequences a HFCS-rich diet might have for