But in most crystalline materials, the bonding between atoms or molecules is isotropic (has the same strength in all dimensions). These materials therefore spontaneously form as 3D objects, which makes it considerably more difficult to produce quasi-2D sheets. The only feasible way to make ultrathin sheets of these materials is to deposit a thin film on the flat surface of another crystalline starting material, and to monitor the process in real time at the atomic level. The grown film is said to be epitaxial if its unit cells align with the unit cells of the substrate.

For oxides, such techniques came to fruition in the late 1980s and early 1990s as a result of intensive research on copper oxides (cuprates) that exhibit high-temperature superconductivity. These cuprates have a layered structure, but are strongly bonded together, and so scientists explored their superconductivity by engineering layers in epitaxial thin films[6]. Perovskite oxides display a rich variety of potentially useful physical effects, including multiferroic behaviour and colossal magnetoresistance[7], due to electron–electron correlations (interactions) in the constituent transition-metal ions[8]. Up to now, these properties have generally been studied in thin films grown on top of a substrate.

Ji *et al.* now report that free-standing films of perovskite oxides can be made using a careful combination of a state-of-the-art technique for fabricating thin films, called molecular beam epitaxy (MBE), and a previously developed method[9] for exfoliating thin films from substrates (Fig. 1). The authors used MBE to 'spray paint' ultrathin epitaxial layers of a perovskite and a water-soluble buffer layer onto a substrate, so that the buffer layer is sandwiched between the perovskite oxide and the substrate. The thickness of the resulting perovskite oxide films could be controlled at the atomic level.

The authors freed square-millimetre-sized, single-crystal perovskite oxide films from the substrate by dissolving the buffer layer in water, and then transferred them onto a variety of other substrates, such as carbon substrates that contained micrometre-scale holes. Remarkably, the overall process could produce films near the extreme limit of thickness — a single unit cell. The researchers studied the membranes using scanning transmission electron microscopy, an imaging technique that can resolve single atoms and quantitatively determine their positions. Intriguingly, they observed that the thin film of bismuth ferrite undergoes an unexpected phase transition to form a different crystal lattice.

Ji and colleagues' findings demonstrate that free-standing films of perovskite oxides can be made at thicknesses that are less than a previously proposed critical limit[10] below which it was thought that the lattice of the film would collapse. A long-standing question for those working with 2D materials has been whether a minimum thickness is required to stabilize crystalline order. The new findings suggest that no such minimum thickness is needed for free-standing thin films of perovskite oxides.

Many questions are raised by this work. Ji and co-workers demonstrate the method for only two archetypical examples out of many possible perovskite oxides, which raises the questions of how broadly applicable it is to other oxides and what new phenomena might emerge in those systems. Moreover, now that it has been shown that perovskite oxides do not apparently need to have a fundamental minimum thickness, other fabrication methods for making thin films of these materials should also be explored.

Free-standing thin films are an ideal platform for studying certain materials' properties, such as phase transitions that occur only when materials are confined within a certain number of dimensions, or nanoscale elasticity in the absence of substrates. Free-standing specimens are especially useful for analytical studies that work in transmission mode (in which, for instance, light, X-rays or electrons are passed through a sample to analyse it), because the absence of a substrate prevents unwanted background signals from being produced that could interfere with the signal from the specimen. Ji and colleagues' work also opens up the technological potential of 2D perovskite oxides, because they can now be extensively studied in the way that intrinsically layered materials such as graphene have been. ■

Yorick A. Birkhölzer *and* **Gertjan Koster** *are at the MESA+ Institute for Nanotechnology, University of Twente, 7500 AE Enschede, the Netherlands.*
e-mail: g.koster@utwente.nl

1. Ji, D. *et al. Nature* **570**, 87–90 (2019).
2. Rijnders, G. & Blank, D. H. A. *Nature* **433**, 369–370 (2005).
3. Novoselov, K. S. *et al. Science* **306**, 666–669 (2004).
4. Manzeli, S., Ovchinnikov, D., Pasquier, D., Yazyvev, O. V. & Kis, A. *Nature Rev. Mater.* **2**, 17033 (2017).
5. Wang, L. & Sasaki, T. *Chem. Rev.* **114**, 9455–9486 (2014).
6. Logvenov, G., Gozar, A. & Bozovic, I. *Science* **326**, 699–702 (2009).
7. Hwang, H. Y. *et al. Nature Mater.* **11**, 103–113 (2012).
8. Imada, M., Fujimori, A. & Tokura, Y. *Rev. Mod. Phys.* **70**, 1039 (1998).
9. Lu, D. *et al. Nature Mater.* **15**, 1255–1260 (2016).
10. Hong, S. S. *et al. Sci. Adv.* **3**, eaao5173 (2017).

NEUROSCIENCE

Closing in on what motivates motivation

The neurotransmitter dopamine facilitates learning, motivation and movement. Evidence of its release independently of the activity of dopamine-producing neurons in rat brains forces a rethink of dopamine regulation. **See Article p.65**

MARGARET E. RICE

Dopamine is a neurotransmitter molecule that influences brain pathways that are involved in motivation, movement, cognition and reward-driven learning. How it contributes to such varied behaviours is the subject of ongoing investigation. On page 65, Mohebi *et al.*[1] shed light on how dopamine release is regulated in the rat brain to accomplish different functions.

Dopamine is produced by neurons located in the midbrain, in regions known as the ventral tegmental area (VTA) and the substantia nigra pars compacta. The long axons of these neurons extend to other parts of the brain, including the nucleus accumbens, the dorsal striatum and the prefrontal cortex. Within these target sites, the axons branch extensively[2] to form a structure known as an arbor. The textbook description of dopamine signalling suggests that the activation of dopamine-producing neurons in the midbrain generates electrical signals that travel along their axons to their target regions, where they cause a dopamine release that is 'broadcast' throughout the territories covered by the axonal arbors. This concept is fundamental to current ideas about how reward-based learning occurs: an unexpected reward leads to an increase in the activity of dopamine neurons that is assumed to transmit a dopamine signal throughout the target regions to facilitate learning[3,4].

Yet dopamine release in the target regions is more complicated than its textbook description. For example, it can be regulated locally by neurotransmitters and other molecules[5]. Moreover, studies in animals of the activity of dopamine neurons using an imaging approach to monitor the activity of dopamine neurons or a microelectrode method to assess dopamine release indicate that an unexpected reward can cause the predicted increase in the activity of the axonal arbor, and dopamine release in the nucleus accumbens[6,7]. However, these features are absent in the neighbouring dorsal striatum[6,7], providing an argument against a role for dopamine as a universal broadcast signal.

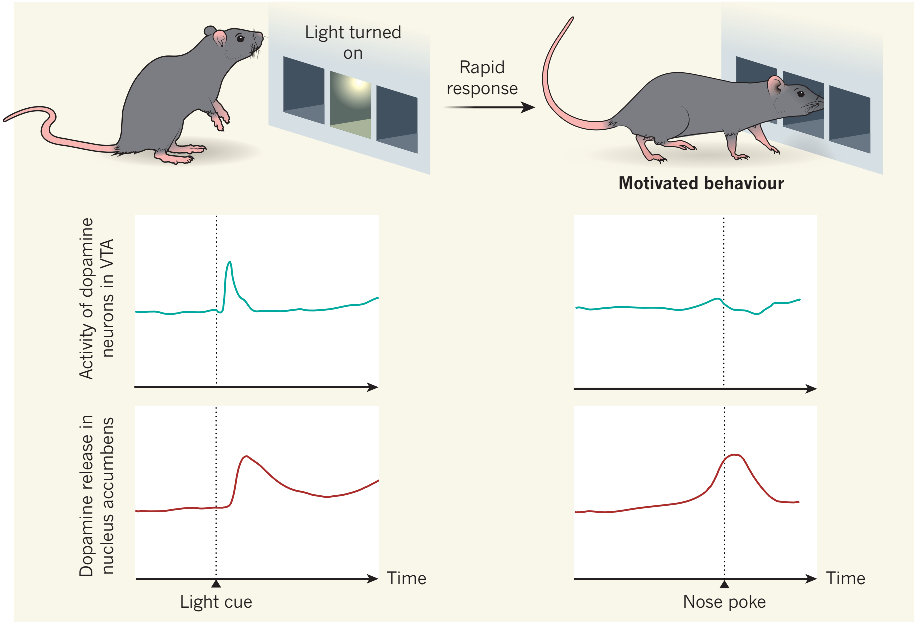


Figure 1 | Neuronal activity and dopamine release in the rat brain. In the bandit task, freely moving rats poke their noses into a central port in response to a light cue (shown). The animals stay there until a sound cue prompts them to move to an adjacent port, where they make a nose poke for which they might receive a food reward in a separate port (not shown). Mohebi *et al.*[1] recorded the activity of neurons that produce dopamine (a neurotransmitter molecule) in the ventral tegmental area (VTA) of the rat brain during this task, as well as the release of dopamine by these neurons in another region of the brain, the nucleus accumbens. In response to the light cue, the authors observed a common feature of reward-driven learned behaviour: an increase in neuronal activity and in dopamine release, which fits the widely held model of dopamine release depending on the activation of dopamine-producing neurons. They also found that dopamine release ramped up during the rat's motivated approach to the central port, which is where the animal makes a nose poke to start the task. Unexpectedly, however, this was not accompanied by an increase in the activity of dopamine neurons.

In addition to reward-dependent increases in dopamine release, dopamine release in the nucleus accumbens ramps up slowly[8–13] as an animal approaches a reward site, before it obtains a reward. The amount of dopamine that is released during this ramping-up phase provides information about the value of the anticipated reward and motivates the amount of effort that the animal makes to attain it.

Most previous studies that tracked dopamine release during motivated behaviours used freely moving animals. By contrast, experiments that recorded the activity of dopamine neurons typically studied animals whose heads were held in a fixed position owing to technical constraints. Mohebi *et al.* took the key step of recording both neuronal activity and dopamine release in freely moving rats, although both properties were not recorded in the same animals.

The authors studied animals that were engaged in a behavioural task called a bandit task. The experimental apparatus used has ports into which a rat can poke its nose (Fig. 1). The central port is illuminated at the start of the task, which provides a cue for the animal to make a nose poke into that port, and then to stay in position until a sound cue prompts it to make a nose poke into one of the adjacent ports. Nose pokes into a neighbouring port might result in a food reward from a separate food port. The animal could therefore learn, for example, that a particular port was associated with a high probability of a food reward.

Mohebi *et al.* observed that, when the rate of reward increased, there was also an increase in the animals' response rate, with a decrease in the time taken by the animal to start the task by making a nose poke into the central port after receiving the light cue. An increased response rate indicates that the animals are more motivated to take part in the task. Using a microdialysis technique to assess extracellular concentrations of dopamine in the brain revealed a pattern of dopamine elevation in distinct areas that correlated with reward availability during the task.

Dopamine increases were observed in the nucleus accumbens core, but not in the adjacent nucleus accumbens shell or in the dorsal striatum. Dopamine elevation was recorded in a part of the prefrontal cortex called the ventral prelimbic cortex, but a rise in dopamine levels was not observed in other areas of the prefrontal cortex. These data should put to rest the prevailing view that increased activity of dopamine neurons in response to rewards, or to cues that predict reward delivery, causes the broadcast of a dopamine signal to all of the brain regions that these neurons target.

The regions of the rat brain that showed an increase in dopamine release correspond to the human nucleus accumbens and ventromedial prefrontal cortex. In human brain-imaging

50 Years Ago

With all the excitement and preparation at Cape Kennedy for the launch of Apollo 11, NASA'S biosatellite programme is easily overlooked. But soon after June 18, NASA will launch Biosatellite III carrying a 14 pound adolescent male pigtail monkey trained for the flight and implanted with apparatus at the University of California, Los Angeles … The monkey will certainly be heavily instrumented. Monitors will record wave patterns from ten areas of his brain, eye movements, heart action and respiration, take measurements at four sites in the circulatory system, record changes in bone and muscle and observe performance in two behavioural tests for which the monkey can earn two thirds of his daily rations … It is some indication of the rush to put man in space that the recordings of the monkey's brain activity during weightlessness will be the first ever made by NASA.

From *Nature* 7 June 1969

100 Years Ago

The American seaplane N.C.4 has completed its flight to England, *via* the Azores and Portugal, and arrived at Plymouth at 1:26 p.m. G.M.T. last Saturday. The honour of the first Atlantic crossing by air thus falls to the Americans, though the yet greater honour of the first direct flight from continent to continent remains to be won. The feat accomplished by the N.C.4 clearly illustrates the advantage of the seaplane for long flights over the ocean, owing to its ability to alight on the water in any calm locality and carry out minor repairs, if necessary. Even in mid-Atlantic such an aircraft would have a fair chance to rectify some slight defect and proceed on its course, whereas an aeroplane is certain to be useless for further flight if forced to descend on the water.

From *Nature* 5 June 1919

studies, changes in activity in these regions are observed that correlate with the subjective value of rewards in decision-making tasks[14]. This offers a hint that Mohebi and colleagues' findings might have relevance across species.

The authors found that neuronal activity in the VTA of rats was unaffected by an increase in the reward rate, however, suggesting that the motivation-related dopamine release is dissociated from the activation of dopamine neurons. To test this hypothesis, the authors examined dopamine release in the rat nucleus accumbens using a method for the rapid imaging of dopamine release[15] that enables monitoring on a subsecond timescale, rather than the timescale of minutes that is possible with microdialysis.

As expected, the authors found that cues for reward availability, as well as the reward itself, were linked to an increase in the activity of dopamine neurons in the VTA (Fig. 1). These cues were also associated with an increase in dopamine release in the nucleus accumbens (the only brain region that was examined for dopamine release in this experiment) that serves as a learning signal to influence future behaviour.

As the reward rate increased, extracellular dopamine levels ramped up progressively as the rats approached either the central port or the port where food was dispensed, which is consistent with dopamine driving the motivation, as has been proposed previously[8–13]. However, there was no ramping up of the activity of dopamine neurons in the VTA (Fig. 1). This evidence for dopamine release in the absence of an increase in activity in dopamine neurons provides further support for the authors' model that neuronal activity and dopamine release can be dissociated. Importantly, these data point to the possibility of a local regulation of dopamine release that is independent of the activity of dopamine neurons. The power of such local regulation[5] is familiar to those who study the cells and circuits of the striatum.

Unanswered by Mohebi and colleagues' study is which local factors in the nucleus accumbens might generate the ramped-up increases in dopamine release — or, in other words, what it is that motivates motivation. One possibility might be the release of the neurotransmitter acetylcholine from cells called cholinergic interneurons[16,17]. Of course, if the authors had reported evidence to support this, then the key question would have become which parts of the brain are conveying information about motivation to those neurons. Mohebi *et al.* report that there is a ramping up of activity of some non-dopamine neurons in the VTA before the animal carries out a nose poke. Perhaps those neurons have a role in facilitating dopamine release, which could be a topic for future research.

As well as providing evidence for the textbook view that a spike in the activity of dopamine neurons is accompanied by dopamine release, albeit not in all target regions, the unexpected observation of dopamine release in the absence of activity of dopamine neurons provides a new depth of understanding of dopamine signalling in the brain. Like the ramping up of dopamine, this is bound to provide the motivation for more work. ■

Margaret E. Rice *is in the Department of Neurosurgery and the Department of Neuroscience and Physiology, New York University School of Medicine, New York, New York 10016, USA.*
e-mail: margaret.rice@nyu.edu

1. Mohebi, A. *et al. Nature* **570**, 65–70 (2019).
2. Matsuda, W. *et al. J. Neurosci.* **29**, 444–453 (2009).
3. Schultz, W. *J. Neurophysiol.* **80**, 1–27 (1998).
4. Fiorillo, C. D., Tobler, P. N. & Schultz, W. *Science* **299**, 1898–1902 (2003).
5. Sulzer, D., Cragg, S. J., Rice, M. E. *Basal Ganglia* **6**, 123–148 (2016).
6. Howe, M. W. & Dombeck, D. A. *Nature* **535**, 505–510 (2016).
7. Brown H. D., McCutcheon, J. E., Cone, J. J., Ragozzino, M. E., Roitman, M. F. *Eur. J. Neurosci.* **34**, 1997–2006 (2011).
8. Phillips, P. E., Stuber, G. D., Heien, M. L., Wightman, R. M. & Carelli, R. M. *Nature* **422**, 614–618 (2003).
9. Roitman, M. F., Stuber, G. D., Phillips, P. E., Wightman, R. M. w& Carelli, R. M. *J. Neurosci.* **24**, 1265–1271 (2004).
10. Wassum, K. M., Ostlund, S. B. & Maidment, N. T. *Biol. Psychiatry* **71**, 846–854 (2012).
11. Howe, M. W., Tierney, P. L., Sandberg, S. G., Phillips, P. E. & Graybiel, A. M. *Nature* **500**, 575–579 (2013).
12. Hamid, A. A. *et al. Nature Neurosci.* **19**, 117–126 (2016).
13. Syed, E. C. *et al. Nature Neurosci.* **19**, 34–36 (2016).
14. Bartra, O., McGuire, J. T. & Kable, J. W. *NeuroImage* **76**, 412–427 (2013).
15. Patriarchi, T. *et al. Science* **360**, eaat4422 (2018).
16. Threlfell, S. *et al. Neuron* **75**, 58–64 (2012).
17. Cachope, R. *et al. Cell Rep.* **2**, 33–41 (2012).

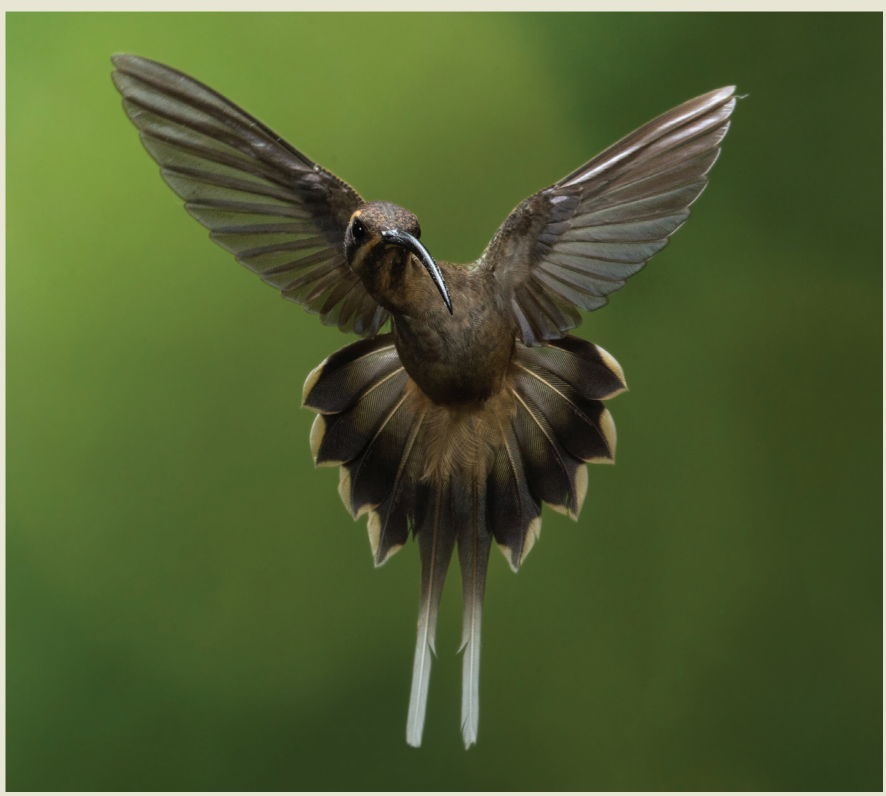
This article was published online on 22 May 2019.

EVOLUTION

Look and learn

Like humans, hummingbirds are vocal learners: they can adapt their vocalizations by listening to others. Vocal learning might have evolved from the ability to learn movements from others. If this is true, vocal learners should also be able to learn movements by watching one another. Writing in *Proceedings of the Royal Society B*, Araya-Salas *et al.* provide evidence for social learning of complex movements in long-billed hermit hummingbirds (*Phaethornis longirostris*; M. Araya-Salas *et al. Proc. R. Soc. B* **286**, 20190666; 2019).

Male hummingbirds sing and perform elaborate visual displays to attract mates and defend their territory. The authors found that each community of hummingbirds has its own variants of the songs and displays, indicating social learning of both. These observations support the theory that vocal learning evolved from general motor learning. **Natasha Bray**



CHRISTOPHER JIMENEZ NATURE PHOTO/GETTY