enhancement is a crucial step towards cooling molecules using evaporative cooling, a powerful technique for driving hot particles from a system to reduce its temperature.

The two papers report types of resonance that are distinct in character from those observed in other systems. Both teams used the quantum properties of molecules, applying the complexity of the molecules' internal states and the way they can be coupled to applied fields. And they both addressed a crucial gap in this line of research: the ability to flexibly control inelastic and elastic collisions between ultracold molecules. They also provide benchmarks for future calculations in theoretical quantum chemistry.

Despite sharing many features, the two techniques are distinct. The Feshbach resonance reported by Park *et al.* is enticing from a fundamental point of view, because it seems to prove that long-lived metastable complexes of two NaLi molecules can exist, despite the fact that the molecules are chemically reactive. This is unexpected, and indicates that collisional processes are not entirely understood – even for simple molecules. By contrast, Chen and colleagues' field-linked resonances are appealing because they can be applied to non-magnetic molecules and are highly controllable using microwave radiation. Such capabilities are widely sought after, and could be applied to other ultracold molecules to offer a general technique for creating molecular quantum matter and controlling chemical reactions.

In the past two decades, it has become possible to prepare ultracold molecules in precisely controlled quantum states. Manipulating polar molecules, such as those used by both sets of authors, is of particular interest, because it would enable new forms of exotic quantum matter[10,11], including certain superfluids (materials that flow without friction) and supersolids (their spatially ordered counterparts). However, such control would require molecular gases to be driven to even lower temperatures and higher densities – enough to enhance interactions and grant access to many-body quantum phases – than are currently accessible.

The findings of both teams could prove key to reaching these goals. Because the concepts described by the authors are broadly applicable, it is exciting to anticipate similar findings with other ultracold molecules. We can hope that many further developments will be built on these results, and will yield fascinating insights into ultracold chemistry and molecular many-body physics.

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1. Park, J. J., Lu, Y-K., Jamison, A. O., Tscherbul, T. V. & Ketterle, W. *Nature* **614**, 54–58 (2023).
2. Chen, X.-Y. *et al. Nature* **614**, 59–63 (2023).
3. Chin, C., Grimm, R., Julienne, P. & Tiesinga, E. *Rev. Mod. Phys.* **82**, 1225 (2010).
4. Yang, H. *et al. Science* **363**, 261–264 (2019).
5. Son, H. *et al. Science* **375**, 1006–1010 (2022).
6. Chin, C. *et al. Phys. Rev. Lett.* **94**, 123201 (2005).
7. Bause, R., Christianen, A., Schindewolf, A., Bloch, I. & Luo, X.-Y. *J. Phys. Chem. A* https://doi.org/10.1021/acs.jpca.2c08095 (2023).
8. Avdeenkov, A. V. & Bohn, J. L. *Phys. Rev. Lett.* **90**, 043006 (2003).
9. Schindewolf, A. *et al. Nature* **607**, 677–681 (2022).
10. Carr, L. D., DeMille, D., Krems, R. V. & Ye, J. *New J. Phys.* **11**, 055049 (2009).
11. Baranov, M. A., Dalmonte, M., Pupillo, G. & Zoller, P. *Chem. Rev.* **112**, 5012–5061 (2012).

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Neuroscience

Dual role for dopamine in shaping spontaneity

Dorgham Khatib & Genela Morris

The neurotransmitter dopamine has well-established roles in reward-driven behaviours, such as searching for food. The discovery that it also shapes spontaneous behaviour reveals parallels between these two phenomena. **See p.108**

Some actions that people take are geared towards specific goals, and others are triggered by stimuli in the environment. However, much of our time is spent in spontaneous, self-motivated activity, which often takes the form of habitual actions. Although research has revealed a lot about how deliberate behaviours are learnt, much less is known about the way in which spontaneous behaviour is organized and turned into habits. Markowitz *et al.*[1] show on page 108 that spontaneous behaviour in mice is regulated by dopamine, a neurotransmitter that is better known for its role in reinforcing rewarding actions.

The authors studied the brain mechanism by which action elements (stereotypical motions such as turning left or pausing during running) are combined into spontaneous behaviour. They focused on the dorsolateral striatum (DLS), a key brain region involved in the selection, refinement, sequencing and control of actions as they form habits[2]. Dopamine released in the DLS reinforces and invigorates rewarding actions[3,4]; Markowitz *et al.* asked whether it might also have a role in unplanned, unstructured behaviour.

The group studied mice engaged in spontaneous behaviour in an open arena in the dark, devoid of external cues or rewards. To visualize the release of dopamine in the DLS, they used a real-time imaging technique called fibre photometry, along with proteins designed to fluoresce in response to binding by dopamine. Cameras captured the animals' behaviour in 3D, and a previously developed machine-learning algorithm[5] then classified the various behavioural sequences of the mice into action elements, which the authors refer to as syllables.

Markowitz *et al.* showed that behavioural syllables were reliably associated with bouts of dopamine release into the DLS – similar to the pattern observed in reward-learning situations. The fluctuations in dopamine had two effects on behaviour, on two timescales (Fig. 1). First, high levels of dopamine release were followed within seconds by increased variability in the actions performed by the mice. Thus, on the immediate timescale, dopamine promotes randomness. Second, syllables that coincided with a large release of dopamine were more likely to be repeated in the subsequent minutes than were those associated with lower levels of the neurotransmitter. Thus, in the long term, dopamine serves to reinforce spontaneous actions.

To ascertain causality, the researchers performed stimulation experiments in which they artificially induced dopamine release when specific, pre-chosen syllables (including 'walk' and 'pause and turn') were detected. This reproduced both scales of effect: after dopamine stimulation, the mouse performed the chosen syllables more frequently; and immediately after stimulation, behaviour became more variable.

What are the consequences of these seemingly contradictory effects of dopamine on behaviour? The shaping of behaviour benefits from both reinforcing well-travelled paths and trying new trajectories – a combination that ensures a repertoire that is robust but also flexible. This effect resonates with a well-known challenge to the theory of reinforcement learning, known as the exploration–exploitation trade-off[6,7]: should a hungry animal return to a known feeding site, or should it explore in the hope of finding a

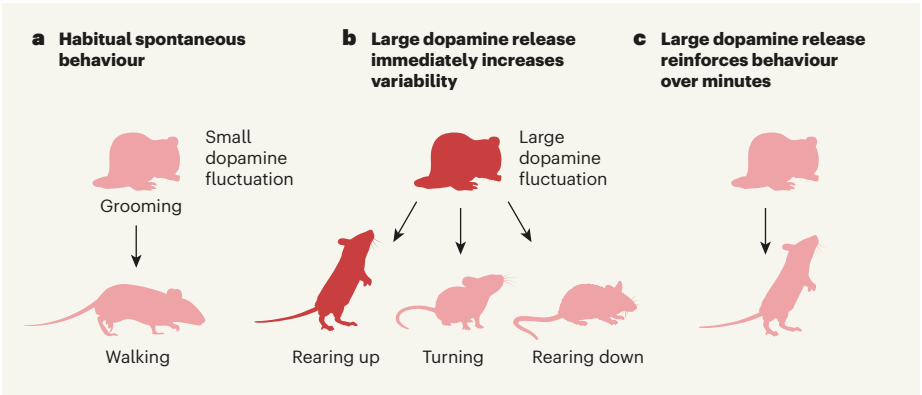

Figure 1 | How dopamine curates routine behaviour. a, Markowitz *et al.*[1] report that, when a mouse is engaged in a sequence of spontaneous behaviour, switches between elements of activity called syllables (such as grooming and walking) are accompanied by small fluctuations in the release of the neurotransmitter dopamine (indicated by pink colouring). **b**, A large dopamine fluctuation (red) induces immediate variability in subsequent syllables. **c**, The large fluctuation also reinforces behaviour, making it more likely that a syllable that coincides with a large dopamine release (here, grooming) will be used again. Presumably, whichever of the subsequent variable syllables also coincides with a large dopamine release (here, rearing up) becomes reinforced too, forming a new routine behaviour, although this was not explicitly tested.

better food source? Various theoretical solutions for resolving this trade-off have been proposed[8,9], but they typically deal with the quantity (how much) and quality (how) of exploration. In the context of spontaneous behaviour, Markowitz and colleagues' findings — with random exploratory behaviour taking place immediately after dopamine release — might offer a surprising answer for the dynamics (when) of exploration. Whether this phenomenon occurs in the context of reward learning is an open question; however, it stands to reason that, after a reward, a sated animal can afford the risk of venturing away from the safety of known actions.

The dual effect observed by Markowitz *et al.* is consistent with what we know about the physiological changes that dopamine brings about in the DLS, and in the striatum in general. Like other neuromodulators and neurotransmitters, dopamine acts on DLS neurons by binding to specialized receptor proteins. Dopamine binding has two effects. It causes a slow cascade of events resulting in the long-term plasticity of active neuronal circuits[10,11], perhaps underlying the reinforcement of spontaneous behaviour. And it leads to an immediate increase in the excitability of the subgroup of DLS neurons that promotes actions, together with a decrease in the excitability of the subgroup that inhibits actions[12–14], perhaps underlying the increased variability seen by the authors. This is a prime example of how larger-scale complex processes can be reduced to mechanisms that are grounded in basic cellular physiology.

The current study provides valuable insights into the moulding of continuous everyday behaviours, and highlights previously unknown functions of dopamine. A next step will be to determine what triggers the dopamine fluctuations. Dopamine release might be controlled locally within the DLS[15], or might be regulated by the nucleus-housing cell bodies of dopamine neurons, which are located in the midbrain. Because the DLS is only one target of midbrain dopamine, the latter scenario could indicate that changes in dopamine levels are also communicated to other brain areas, with further effects on behaviour. The fluctuations might be 'noise' that hijacks the existing reinforcement-learning circuitry to ensure a wide repertoire of natural behaviours, or could be somehow related to the actions themselves.

Finally, it will be interesting to determine whether neuronal activity in the DLS itself influences dopamine release, creating a feedback loop. Clearly, the authors' findings are a promising sign that further discoveries await.

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1. Markowitz, J. E. *et al. Nature* **614**, 108–117 (2023).
2. Yin, H. H. & Knowlton, B. J. *Nature Rev. Neurosci.* **7**, 464–476 (2006).
3. Howe, M. W. & Dombeck, D. A. *Nature* **535**, 505–510 (2016).
4. Menegas, W., Akiti, K., Amo, R., Uchida, N. & Watabe-Uchida, M. *Nature Neurosci.* **21**, 1421–1430 (2018).
5. Wiltschko, A. B. *et al. Nature Neurosci.* **23**, 1433–1443 (2020).
6. Sutton, R. S. & Barto, A. G. *Reinforcement Learning: An Introduction* 2nd edn (MIT Press, 2018).
7. Kaelbling, L. P., Littman, M. L. & Moore, A. W. *J. Artif. Intell. Res.* **4**, 237–285 (1996).
8. Averbeck, B. B. *PLoS Comput. Biol.* **11**, e1004164 (2015).
9. Wilson, R. C., Geana, A., White, J. M., Ludvig, E. A. & Cohen, J. D. *J. Exp. Psychol. Gen.* **143**, 2074–2081 (2014).
10. Reynolds. J. N. J., Hyland, B. I. & Wickens, J. R. *Nature* **413**, 67–70 (2001).
11. Reynolds, J. N. J. *et al. Nature Commun.* **13**, 1296 (2022).
12. Surmeier, D. J., Ding, J., Day, M., Wang, Z. & Shen, W. *Trends Neurosci.* **30**, 228–235 (2007).
13. Lahiri, A. K. & Bevan, M. D. *Neuron* **106**, 277–290 (2020).
14. Hernández-López, S. *et al. J. Neurosci.* **20**, 8987–8995 (2000).
15. Threlfell, S. *et al. Neuron* **75**, 58–64 (2012).

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Genetics

Fast-evolving DNA drives human brain development

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Regions of the human genome that evolved rapidly after the separation between hominins and chimpanzees have now been charted. They contain genomic elements that are unique to humans and are linked to neurodevelopment and disease.

What are the genetic changes that separate humans from chimpanzees? The discovery that there is little difference between these species in terms of protein-coding DNA sequences has led to the hypothesis that the genomic changes responsible for human-specific traits are mainly evident in the non-protein-coding region of the genome[1]. Writing in *Cell*, Mangan *et al.*[2] report that the most rapidly evolving of these non-coding regions are related to human-specific neurodevelopment and disease. The work provides insights into how we differ from our great-ape ancestors.

So far, most studies of human-specific evolution have examined either coding DNA or non-coding regions that are highly evolutionarily conserved in all vertebrates, but mutated at a faster rate in humans than in other species[3]. These genetic sequences, named human accelerated regions (HARs), mostly reflect existing regulatory elements in DNA that have evolved more rapidly in humans[4,5]. However, highly conserved regions make up only about 5% of the human genome[4].