and reduces food intake, whereas the OVLT controls thirst, body temperature and fever[8]. As a result, it would not be surprising for both of these brain regions to be involved.

How might infection activate specialized neurons? Ilanges *et al.* propose that Adcyap1 neurons can be activated by peripheral immune molecules that are produced in the body when the immune system detects the presence of a pathogen. These molecules might cross the incomplete blood–brain barrier or activate peripheral vagal or spinal nerves that transmit information to the NTS and AP. Osterhout and colleagues showed that VMPO neurons express receptor proteins for molecules produced in response to a pathogen. They also found that infection-generated immune signals cross the blood–brain barrier and trigger local production of other molecules that facilitate the activation of VMPO and OVLT neurons[6]. The activated neurons stimulate downstream brain centres to orchestrate physiological and behavioural responses to infection.

A next step is to investigate the downstream brain areas triggered by activation of Adcyap1 neurons in the NTS and AP, and how they mediate the physiological responses that characterize sickness behaviours. Moreover, an open question is how the duration of the sickness response is controlled, and whether the same neuronal circuits are involved in mediating prolonged, chronic symptoms of viral infections, such as long COVID.

Amirah-Iman Hicks and **Masha Prager-Khoutorsky** are in the Department of Physiology, McGill University, Montreal, Quebec H3G 1Y6, Canada.
e-mail: masha.prager-khoutorsky@mcgill.ca

1. Konsman, J. P., Parnet, P. & Dantzer, R. *Trends Neurosci.* **25**, 154–159 (2002).
2. Harden, L. M., Kent, S., Pittman, Q. J. & Roth, J. *Brain Behav. Immun.* **50**, 322–333 (2015).
3. Ilanges, A. *et al. Nature* **609**, 761–771 (2022).
4. Lu, Y.-C., Yeh, W.-C. & Ohashi, P. S. *Cytokine* **42**, 145–151 (2008).
5. Ayres, J. S. & Schneider, D. S. *Annu. Rev. Immunol.* **30**, 271–294 (2012).
6. Osterhout, J. A. *et al. Nature* **606**, 937–944 (2022).
7. Daneman, R. & Prat, A. *Cold Spring Harb. Perspect. Biol.* **7**, a020412 (2015).
8. McKinley, M. J. *et al. The Sensory Circumventricular Organs of the Mammalian Brain* (Springer, 2003).
9. Quan, N. & Banks, W. A. *Brain Behav. Immun.* **21**, 727–735 (2003).

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Materials science

Interfaces boost strain response in layered oxides

David A. Egger

A structure with precisely engineered layers produces a giant strain in an electric field. The interplay between structural distortions and electric dipoles at the interfaces between layers could aid material and device design. **See p.695**

Water freezing into the intricate pattern of a snowflake is one of the most striking examples of the impact that temperature can have on a material. But temperature is not the only external parameter that can change the appearance and properties of a material: a snowball, for instance, is formed simply by compressing snow with one's hands. The shapes of some materials can even be modified by exposing them to an electric field, inducing electromechanical effects that can be used to build actuators and motors that move objects with high precision[1]. On page 695, Zhang *et al.*[2] report that a phenomenon of this kind, known as electrostriction, can be enhanced in certain oxide materials by imbuing them with interfaces that are engineered on an atomic scale.

Electrostriction describes the generation of strain in insulating materials subjected to an electric field. The interaction between the mechanical and electrical properties of a material is perhaps better known in the context of piezoelectricity, in which electric charge accumulates in a material in response to mechanical stress. But piezoelectricity is present only in materials that lack certain crystallographic symmetries, and it involves a linear relationship between strain and the electric field. By contrast, electrostriction is possible in crystals of all symmetries, and describes a strain that increases with the square of the electric field strength.

Although this definition suggests that many materials exhibit electrostriction, the magnitude of the effect is often small. To be useful for electromechanical applications,

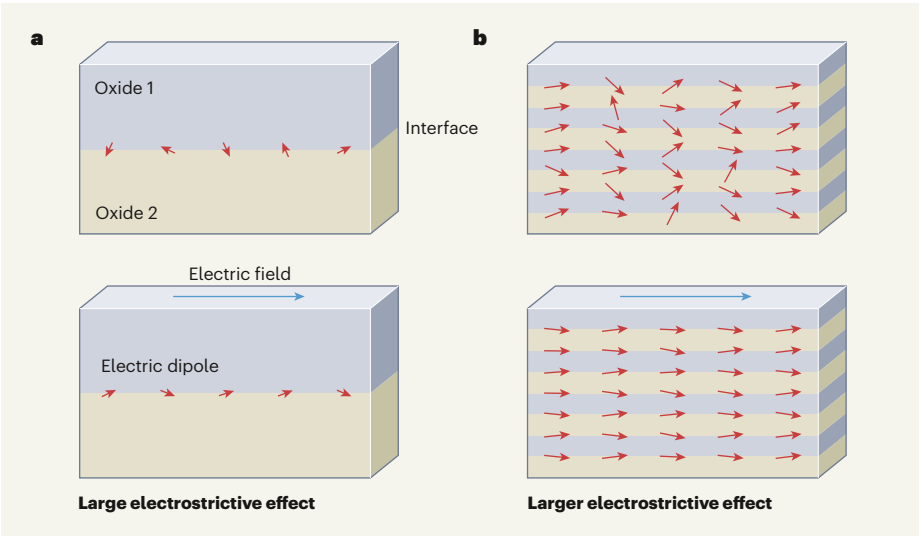

Figure 1 | Extraordinary electrostriction in a layered oxide structure. Zhang *et al.*[2] demonstrated that alternating, ultrathin layers of two oxide compounds could be engineered to achieve unprecedented electrostriction — an effect in which strain is generated in a material by an applied electric field. **a,** The authors found that the interfaces between the oxide layers induced local structural distortions (not shown) that made it easier for electric dipoles (red arrows) to align with an external electric field, thereby increasing the magnitude of the electrostriction. **b,** Reducing the thickness of the oxide layers had the effect of enhancing the structural distortions and dipoles at the interface. By assembling a structure comprising many ultra-thin layers, and thus many enhanced interfacial dipoles, Zhang *et al.* produced a material characterized by a very large electrostrictive effect.

electrostriction must therefore be tuned through careful material design. Most existing materials that exhibit a large electrostriction coefficient (the property that quantifies the effect) contain lead, which is toxic, so lead-free compounds displaying pronounced electrostriction are highly sought after[3].

Aside from polymeric materials[4], tailored oxide substances, such as compounds containing gadolinium and cerium[5] and some bismuth-based materials[6], are particularly promising candidates. Now, Zhang *et al.* have shown that electrostriction can be enhanced in such oxides by engineering them to contain artificial interfaces. The resulting materials have electrostriction coefficients that are approximately 1,500 times larger than those reported previously for these oxides.

In his Nobel lecture in 2000, physicist Herbert Kroemer argued that "the interface is the device", in reference to the key role of interfaces in structures built from inorganic semiconductor materials (see go.nature.com/3bhbsjs). This sentiment now seems more relevant than ever: interfaces in certain oxide compounds have already been shown to induce unexpected piezoelectricity[7], and new physical phases have started to emerge at these interfaces[8]. Zhang and colleagues' success takes these concepts to another level and is the next chapter in this story.

The authors engineered artificial structures by layering oxide films as thin as approximately one nanometre (Fig. 1). The films alternated between one kind of oxide and another, and the number of interfaces was shown to influence the structural and electrostrictive properties of the material. By varying the thickness of the layers, and thereby tuning the number of alternating oxide interfaces, the authors succeeded in achieving an extremely large electrostriction coefficient.

Through a powerful combination of structural characterization and molecular-dynamics simulations, Zhang *et al.* found evidence to suggest that the thickness of pairs of oxide films was key to the enhanced electrostriction. Specifically, reducing this thickness gave rise to atomic processes in the materials that couple mechanical and electrical effects. Their simulations showed that, as the thickness was decreased, atoms at the interfaces were less likely to be fixed in space. This gave them a freedom that distorted the local structure of the material, inducing a strain that was detected in the authors' experiments.

This strain, in turn, had a pronounced effect on the electric dipoles in the material, because it induced them to become stronger and to adopt a spatial configuration that made it easier to orient them in an external electric field (Fig. 1). This configuration effectively gave rise to the extraordinary electrostrictive effect observed in Zhang and colleagues' oxides. The findings therefore provide key insights into the interplay between subtle, interface-induced structural changes and the behaviour of electric dipoles in materials comprising ultrathin oxide layers.

It is tempting to compare the structural distortions observed by Zhang *et al.* with symmetry-breaking phenomena that can occur in bulk materials, far away from interfaces. A pertinent example arises in halide perovskite materials, which also exhibit pronounced electrostriction and are promising candidates for converting solar energy into electricity. Local fluctuations in the arrangement of atoms in these materials are thought to underlie some of their fascinating physical properties[9], so investigating the role of fluctuations that potentially occur at interfaces, and how they couple to symmetry-breaking phenomena and strain variations, could well inform our understanding of both systems.

Although Zhang and colleagues' study focuses on a single model system, the authors attempted to apply their design strategy to other materials — with encouraging results. This demonstrates that tuning electrostriction through the engineering of atomic-scale interfaces in oxide materials is a promising route to the fabrication of compounds with advanced electromechanical functionalities. Potential future applications of materials of this kind include nanometre-scale sensors and actuators, which could be used in biomedical technologies or in sonar devices for marine navigation, for example.

Implementation of these structures on a scale that is large enough to be commercially viable remains as fascinating as it is challenging. One particularly thought-provoking issue concerns the stability of the materials and their interfaces, because Zhang *et al.* found that chemical intermixing at the oxide interfaces (indicating a loss of stability) coincided with decreased electrostriction. This effect will be particularly relevant for future efforts to integrate electrostrictive structures into actual devices. Wiring these multilayered compounds to other materials will create even more interfaces than they contain alone, and the intermixing effect could pose a problem. Then again, as Kroemer would no doubt remind us, such interfaces are also 'the device', so perhaps integration will be yet another chance to improve performance.

David A. Egger is in the Department of Physics, Technical University of Munich, 85748 Garching, Germany.
e-mail: david.egger@tum.de

1. Uchino, K. *Piezoelectric Actuators and Ultrasonic Motors* (Springer, 1997).
2. Zhang, H. *et al. Nature* **609**, 695–700 (2022).
3. Cross, L. E., Jang, S. J., Newnham, R. E., Nomura, S. & Uchino, K. *Ferroelectrics* **23**, 187–191 (1980).
4. Zhang, Q. M., Bharti, V. & Zhao, X. *Science* **280**, 2101–2104 (1998).
5. Korobko, R. *et al. Adv. Mater.* **24**, 5857–5861 (2012).
6. Yavo, N. *et al. Adv. Funct. Mater.* **26**, 1138–1142 (2016).
7. Yang, M.-M. *et al. Nature* **584**, 377–381 (2020).
8. Ramesh, R. & Schlom, D. G. *Nature Rev. Mater.* **4**, 257–268 (2019).
9. Schilcher, M. J. *et al. ACS Energy Lett.* **6**, 2162–2173 (2021).

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Pharmacology

Two-drug trick to block systemic toxicity

Matthias P. Wymann & Chiara Borsari

When combined, two drugs alter the activity of a protein complex called target of rapamycin complex 1 such that it is inhibited in the brain but not the body, enabling the treatment of brain tumours in mice without systemic toxicity. **See p.822**

Medicinal chemists and pharmacologists dream about how drugs might be directed specifically to selected organs. A particularly challenging target is the brain: many drugs do not pass easily through the blood–brain barrier (BBB), or are actively pumped out of the brain. The situation is complicated further when a drug to be delivered also shows body-wide (systemic) adverse effects. One such drug is rapamycin, which blocks tumour growth, but is also used as an immunosuppressant during organ transplantation[1]. Rapamycin and its semi-synthetic derivatives, dubbed rapalogs, inhibit a protein complex called target of rapamycin complex 1 (TORC 1). On page 822, Zhang *et al.*[2] present an innovative chemical approach to confine the action of rapalogs to the brain, and thereby eliminate undesirable systemic effects such as immunosuppression. They combine a high-affinity rapalog (RapaLink-1) with a newly developed molecule (RapaBlock) that prevents TORC1