susceptible to damage from muscle activity. Some of these mutations may also disrupt titin's ability to recoil during muscle contraction[6].

In their analysis, Herman *et al.*[2] considered only rare, protein-truncating *TTN* variants (occurring with a frequency of less than 1%). So, how these mutations interact with the more common, non-truncating *TTN* mutations — such as those that change a single amino acid — or with cardiomyopathy-associated variants of other genes remains to be evaluated. Modelling the cumulative effect of multiple gene variants on the heart's physiology will require more sophisticated analyses.

The authors' data suggest that massively parallel sequencing is more sensitive than Sanger sequencing in detecting *TTN* variants. A reason for this could be that this type of sequencing determines a given sequence many more times than the older technique. This repeated sequencing, or possibly the analyses used to align the resulting sequences, may be more suited to the repetitive nature of *TTN*. In the immediate future, DNA microarrays designed to capture specific exons on the basis of bioinformatic identification[7] could be used to analyse *TTN* variants. However, such microarrays should be carefully evaluated for their use in DCM diagnostics, as the boundaries of some of the *TTN* exons are incompletely defined in the most commonly used databases (those of the National Center for Biological Information in Bethesda, Maryland, and the University of California, Santa Cruz). Alternative approaches involving whole-genome sequencing might therefore be favoured for DCM diagnostics.

The actual outcome of DCM-related mutations, however, depends on the rest of an individual's genetic make-up and on environmental factors. For example, the effects of protein-disrupting *TTN* variants would be expected to be worse when combined with factors such as dysfunctional heart valves or hypertension. Interestingly, in the present study[2], men with *TTN* mutations had more severe DCM than women. Male hearts may be more sensitive to *TTN* mutations because they are normally larger than female hearts, and a larger heart faces greater strain and pressure.

Herman and colleagues' observation that a few of the control individuals carry titin-disrupting gene variants indicates that there are likely to be additional genetic or environmental factors that enhance the disease-causing potential of these mutations. Alternatively, these symptomless individuals might carry other gene variants that actively suppress the effects of the *TTN* mutations. For example, gene variants that drive increased degradation of the mutated *TTN* messenger RNA, or of the truncated titin, could reduce the amount of the damaged protein in the heart, and thereby limit the negative effects of *TTN* mutations. So, for a small percentage of people, life with less titin may not be too bad.

Diagnosing the genetic basis of DCM provides useful information that could guide therapy, especially when there is a risk of life-threatening — but treatable — irregular heart rhythms[8]. Most diagnostic testing now relies on sequencing many genes at once, as there are few clinical clues that reduce the number of candidate genes. However, given the frequency of titin-disrupting variation reported by Herman and colleagues, mutations in *TTN* now emerge as primary causes of, or highly potent contributors to, cardiomyopathy. ■

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1. Dellefave, L. & McNally, E. M. *Curr. Opin. Cardiol.* **25,** 198–204 (2010).
2. Herman, D. S. *et al. N. Engl. J. Med.* **366,** 619–628 (2012).
3. Miller, M. K., Granzier, H., Ehler, E. & Gregorio, C. C. *Trends Cell Biol.* **14,** 119–126 (2004).
4. Gerull, B. *et al. Nature Genet.* **30,** 201–204 (2002).
5. Gautel, M. *Pflügers Arch.* **462,** 119–134 (2011).
6. Nagueh, S. F. *et al. Circulation* **110,** 155–162 (2004).
7. Bamshad, M. J. *et al. Nature Rev. Genet.* **12,** 745–755 (2011).
8. van Rijsingen, I. A. *et al. J. Am. Coll. Cardiol.* **59,** 493–500 (2012).

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CONDENSED-MATTER PHYSICS

A duo of graphene mimics

The synthesis of analogues of graphene by two different means provides insight into the origins of massless particles and paves the way for studies of materials with exotic topological properties. SEE LETTERS P.302 & P.306

JONATHAN SIMON & MARKUS GREINER

When a particle is constrained to move in a honeycomb-lattice structure, its properties change dramatically: it behaves as though it has no mass and travels at the speed of light. Such particles, known as massless Dirac fermions, were first observed[1,2] in atomic graphene in work that spawned a frenzy of research into its properties, both to understand the fundamental science and for technological applications. In a pair of letters published in this issue, Gomes *et al.*[3] (page 306) and Tarruell *et al.*[4] (page 302) describe how, for the first time, they have created synthetic analogues of graphene in two different systems.

Atomic graphene is a single layer of carbon atoms organized into a honeycomb structure. The new graphene analogues[3,4] share this honeycomb topology and offer substantial advantages in manipulation and readout of material properties over what is possible with atomic graphene. Gomes *et al.*[3] assembled 'molecular graphene' from individually placed carbon monoxide (CO) molecules, and studied the bizarre effects that arise from small variations in the material's lattice structure (Fig. 1a,b). Tarruell *et al.*[4] show that a clever arrangement of laser beams (an optical lattice) produces a honeycomb structure to confine an ultracold gas of potassium atoms, and investigated how the lattice structure controls the mass of the atoms (Fig. 1c,d).

The first step in studying a graphene analogue is to show that its particles are massless. In everyday life, an object's mass is measured by weighing it on a scale. That is impossible for an extremely light object such as an electron, particularly when its mass is inextricably tied to the material in which it resides. Gomes and colleagues[3] circumvented this difficulty by studying the energy gap between the valence and conduction energy bands in their molecular graphene. This quantity reflects the energy required to create an electron–hole pair out of the vacuum (where a hole is a charge carrier created by the absence of an electron), and thus the electron's mass. The authors measured the gap using scanning tunnelling microscopy and spectroscopy, and observed no separation between the valence and conduction bands — only a sharp dip at the Dirac point, at which the bands touch. The dip indicates a vanishing number of quantum states at zero energy, and the absence of a gap is a clear signature of massless Dirac fermions.

Having established the existence of massless electrons in their molecular graphene, Gomes and colleagues employed their exquisite control of the material to study how slight modifications to the lattice geometry change the properties of its resident electrons. First, they introduced a periodic arrangement known as a Kekulé structure to reimbue their massless Dirac fermions with mass, and detected this mass through the appearance of an energy

gap in the material's electron-energy spectrum. They then showed that a distortion of the lattice structure, akin to squeezing it along several axes, makes the electrons act as if they are in a magnetic field[5]. The appearance of an isolated, zero-energy quantum state in the presence of this apparent field serves as striking confirmation of the existence of massless Dirac fermions in the molecular graphene.

Meanwhile, Tarruell and colleagues[4] demonstrated that the potassium atoms in their material behave as massless Dirac fermions by watching them undergo a transition between the conduction and valence bands. Such transitions require substantial energy input for particles that have mass, to overcome the particles' rest mass and bridge the energy gap. But for a massless particle there is no energy gap, so the particle can move freely between valence and conduction bands at the Dirac point.

Holding a massless Dirac fermion near a Dirac point in order to observe transitions between bands would be extremely challenging in the solid state, because motional damping is difficult to control, and scattering off lattice impurities and phonons (quasiparticles associated with lattice vibrations) regularly randomizes the Dirac fermions' momentum. Ultracold atomic gases in optical lattices are ideally suited to overcoming this problem, as the atoms move without dissipation in extremely clean and tightly controlled environments[6].

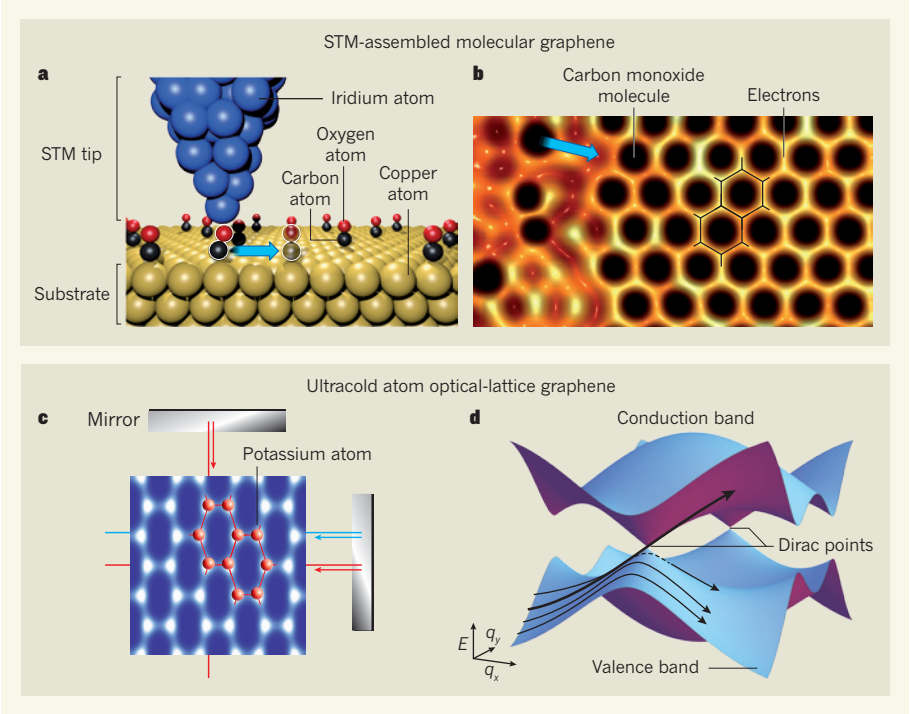
Tarruell and co-workers took advantage of these features in their work. They started with a cloud of fermionic (half-integer spin) potassium atoms in the valence band. These atoms exhibited a spread in momentum due to the Pauli exclusion principle, according to which two or more fermionic particles cannot occupy the same quantum state. The authors then subjected the atomic cloud to a magnetic-field gradient that gently accelerated the atoms, slowly varying their momentum. In this setting, any atom whose momentum trajectory crosses a Dirac point should be transferred to the conduction band (Fig. 1d).

Tarruell *et al.* elegantly observed the existence of Dirac points by imaging the momentum distribution of their cloud. They achieved this by allowing the cloud to expand and then taking an image of its spatial distribution, noting that atoms in the cloud that have more momentum move more quickly in this expansion. Before the acceleration, the atoms are distributed smoothly around zero momentum, whereas after acceleration the distribution has gaps corresponding to atoms that have been transported through a Dirac point, and hence transferred to the conduction band.

To address the question of how the Dirac fermions arise, Tarruell and colleagues smoothly tuned the energy potential of their structure to transform the underlying honeycomb lattice, which has two Dirac points, into a dimer lattice, which has none. To probe for the existence of Dirac points in each lattice, they accelerated the potassium atoms and measured the fraction of atoms transferred to the conduction band. What they find is an impressive verification of a theoretically predicted topological phase transition[7–9]: the atom fraction transferred drops abruptly to zero at precisely the point at which the dimer lattice forms and the two Dirac points merge and annihilate one another.

These studies[3,4] pave the way for a new realm of condensed-matter physics, in which materials with exotic topological properties can be built to order from the ground up. However, some of the most interesting properties arise when interactions between particles cause them to self-organize into intricate patterns determined by the laws of quantum mechanics. To this end, it will be essential to suppress the role of the copper substrate underlying Gomes and colleagues' material, because it screens out the repulsive Coulomb interaction between the electrons and limits the electrons' lifetime.

By contrast, the ultracold atoms described by Tarruell *et al.*[4] are extremely long lived and can exhibit strong interactions, but so far have been studied only in synthetic magnetic fields[10] that are not strong enough to investigate the physics of highly correlated Dirac fermions. Much stronger fields should be achievable through temporal modulation of the Dirac points[11]. Once these limitations are overcome, the techniques developed by Tarruell, Gomes and their colleagues should point the way to a new generation of quantum materials. ■



A.B. H. MANOHARAN *ET AL.*; C.D. J.S. & M.G.

Figure 1 | Two approaches to making graphene analogues. **a**, Gomes *et al.*[3] assembled molecular graphene using a scanning tunnelling microscope (STM), the tip of which is made of iridium atoms, to individually position (blue arrow) carbon monoxide (CO) molecules in a hexagonal pattern on a copper substrate. **b**, STM image of the partially assembled graphene. Electrons are repelled from the hexagonally arranged CO molecules and forced to move on a honeycomb grid (black lines). The blue arrow indicates the path of a CO molecule as it is positioned. **c**, Tarruell *et al.*[4] generated a honeycomb optical lattice for confining ultracold potassium atoms through a combination of two interfering laser beams (red) and a third separate beam (blue), all retro-reflected by mirrors. The resulting intensity pattern is shown overlaid, with the intensity maxima shown in white and the tunnelling pathways between maxima emphasized by red lines. **d**, To observe the existence of Dirac fermions, the authors[4] accelerated potassium atoms in the material's valence energy band and found that those that pass through a Dirac point are transferred to the conduction band. The plot displays the electron energy (E) as a function of its momenta in the x and y directions (q_x and q_y) for both bands. The arrows denote the paths of the potassium atoms through momentum space.

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1. Novoselov, K. S. *et al. Nature* **438,** 197–200 (2005).
2. Zhang, Y., Tan, Y.-W., Stormer, H. L. & Kim, P. *Nature* **438,** 201–204 (2005).
3. Gomes, K. K., Mar, W., Ko, W., Guinea, F. & Manoharan, H. C. *Nature* **483,** 306–310 (2012).
4. Tarruell, L., Greif, D., Uehlinger, T., Jotzu, G. & Esslinger, T. *Nature* **483,** 302–305 (2012).
5. Levy, N. *et al. Science* **329,** 544–547 (2010).
6. Bloch, I., Dalibard, J. & Zwerger, W. *Rev. Mod. Phys.* **80,** 885–964 (2008).
7. Hasegawa, Y., Konno, R., Nakano, H. &

Kohmoto, M. *Phys Rev. B* **74,** 033413 (2006).
8. Wunsch, B., Guinea, F. & Sols, F. *New J. Phys.* **10,** 103027 (2008).
9. Montambaux, G., Piéchon, F., Fuchs, J.-N. & Goerbig, M. O. *Phys. Rev. B* **80,** 153412 (2009).
10. Lin, Y.-J., Compton, R. L., Jiménez-García, K., Porto, J. V. & Spielman, I. B. *Nature* **462,** 628–632 (2009).
11. Kitagawa, T., Berg, E., Rudner, M. & Demler, E. *Phys. Rev. B* **82,** 235114 (2010).

NEUROSCIENCE

How brains learn to control machines

After training, animals and humans can make their thoughts interact directly with computers. A study provides evidence that the corticostriatal system of the brain is essential for this learning process. SEE LETTER P.331

DAVID T. BLAKE

Brain–machine interfaces have a rich history in the sci-fi genre: in *The Matrix* films, human brains are plugged into a computer-based simulation that then becomes their 'reality'. But using our thoughts to directly control computers or other devices is not just in the realm of fantasy. Monkeys can learn to use visual cues to instruct a brain–machine interface to move a robotic arm or a computer cursor[1,2]. And electrode arrays were implanted into the brain of a paralysed man in 2006, enabling him to control an artificial arm, to move a cursor on a computer screen and even to open e-mail[3]. Over time, an individual learns to improve their control over the brain–machine interface by modifying the activity of their brain, but how this happens is not well understood. On page 331 of this issue, Koralek *et al.*[4] report that the corticostriatal system of the brain is involved in learning mental actions and skills that do not involve physical movement, such as those required for control of brain–machine interfaces*.

The corticostriatal system has a unique pattern of connectivity that enables sensory inputs to be associated with appropriate motor or cognitive responses[5]. It consists of a cortical component, the primary motor cortex, that exerts control over muscles, and a striatal component, the basal ganglia, that receives direct inputs from the motor cortex. The basal ganglia are involved in a wide range of learning conditions and are crucial to the motor deficits observed in Parkinson's and Huntington's diseases. Both corticostriatal components have a role in the learning and execution of physical skills requiring movement.

It was known that the learning of abstract (non-physical) skills, such as controlling a brain–machine interface, required the motor cortex, but it was not clear whether the striatal component was also involved. To address this issue, Koralek and colleagues[4] implanted electrodes in the cortex and striatum of live rats to record neuronal activity. The authors then set up a brain–machine interface (Fig. 1) in which a tonal sound with a specific pitch was automatically played to the animal depending on the measured activity of two groups of cortical neurons. The pitch of the sound increased if the first group of neurons was more active than the second group, and decreased if the second group was the more active. If the pitch got high enough, the rat earned a sugar-water reward; if the pitch dropped enough, then the animal received a food pellet.

Over a two-week period, the rats achieved a high level of proficiency at earning each reward. The researchers carried out a similar experiment with another set of animals, with the difference that no sound was played. In this case, the rats did not learn to alter activation of the two groups of neurons to earn rewards, which confirmed the necessity of the auditory feedback. The animals that did learn developed a synchrony between the activity of their motor cortex and that of their striatum during task performance that was absent before learning. In a sense, the task learning caused the cortex and striatum to work in harmony. This synchrony is perhaps not entirely surprising, as it is known that the striatum and cortex are active and display similar temporal patterns of activity in a wide range of motor and cognitive procedures[6].

Were the rats controlling the brain–machine interface in an intentional and goal-directed fashion? In a human brain–machine interface, we would simply ask the subject if they had a conscious knowledge that they were controlling an external interface. In the case of laboratory animals, such direct feedback is not possible, but Koralek *et al.* got part of the answer through clever experimental design. The authors gave sugar water to the rats before training, so that the animals were only motivated to get the food pellet afterwards. However, if the task performance were habitual and unintentional, the rats would not know how to earn one specific reward and not the other. What happened was that the animals did learn how to get the food pellet and not the sugar water, and this was associated with the change in brain activity predicted for goal-directed, intentional behaviour.

To assess the necessity for the striatum in the learning task, Koralek *et al.*[4] repeated their experiments using genetically modified mice[7] in which NMDA receptors were specifically inactivated in the striatum. NMDA receptors are required for normal functioning of the cortex–striatum connections, and so the genetically modified mice should have a greatly reduced ability to coordinate the two brain regions. Indeed, the authors observed that the mice could not learn how to achieve

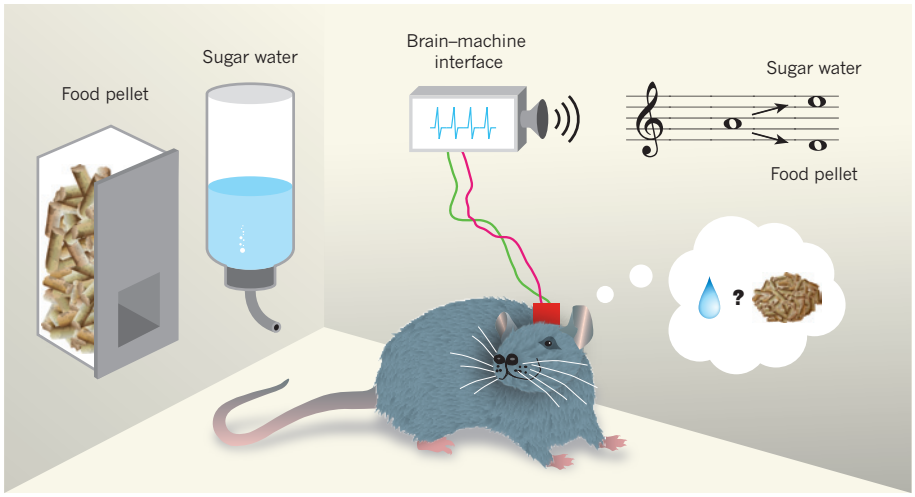

Figure 1 | Music to my brain. Koralek *et al.*[4] implanted electrodes into the brains of live rats to record the neuronal activity of the motor cortex and the striatum. Depending on certain features of motor-cortex activity, a tonal sound with a specific pitch was automatically generated. The rats learnt to make the pitch of the sound rise or fall by modifying their brain activity, as they were rewarded with either sugar water or food pellets, respectively, if the pitch changed enough. By using genetically modified mice in similar experiments, the authors showed that activity of the striatum was required for the animals to learn the task.

*This article and the paper[4] under discussion were published online on 4 March 2012.