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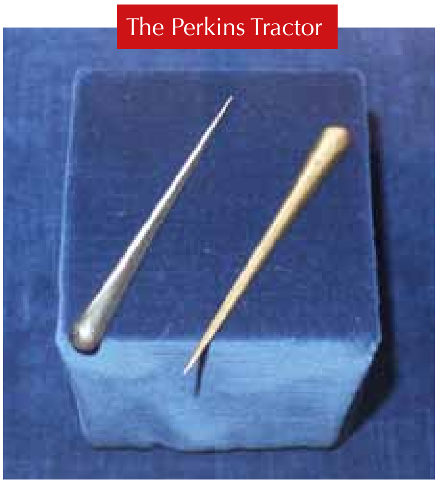
Just the placebo effect?

When your doctor prescribes you a tablet and you get better, was it really the drug or could it have been the colour of the tablet? **Andrew Brown** investigates the placebo effect.

In 1796, the American doctor Elisha Perkins patented his 'Perkins Tractor', which he claimed could 'draw off the noxious electrical fluid that lies at the root of all suffering'. Consisting of two metal rods, the device was waved over the patient's body. Reports of its curative powers caught the attention of British doctor John Haygarth who, in controlled experiments, showed that although the Perkins Tractor did indeed alleviate symptoms, so did a wooden copy. He was the first to show that a therapeutic response can be achieved by something pharmacologically inert – what we now call the placebo effect.

The placebo effect is often considered to be a psychological rather than a physiological phenomenon – patients only *think* they are better. But it

The Perkins Tractor



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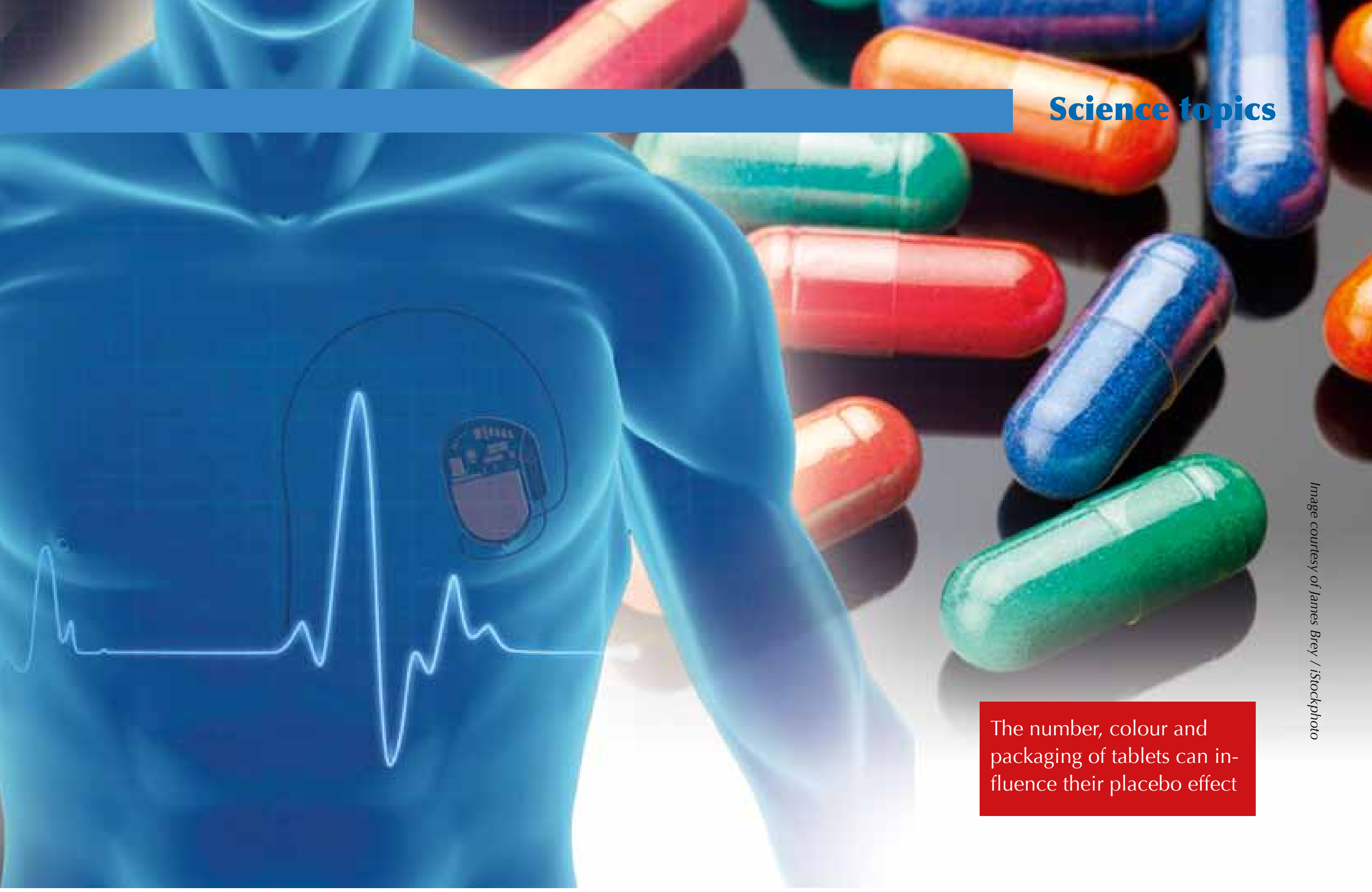
REVIEW

- Biology
- Medicine
- Ethics
- Interdisciplinary
- Ages 16+

Although the word 'placebo' is probably familiar to most people, the chances are that not many really know what it is. The author helps the reader to understand what the placebo effect is and what it does, including the complex ways in which it helps patients get better.

This article will be of most benefit to the study of the nervous system in upper secondary-school biology. The suggested classroom activities will be particularly useful for teachers. The questions provided would be suitable for biology students in whole-class discussion sessions, small-group projects or even individual homework assignments. Since the content of the article is not purely scientific but also touches on ethical issues, it could provide excellent discussion material for psychology and social science classes.

Michalis Hadjimarcou, Cyprus



The number, colour and packaging of tablets can influence their placebo effect

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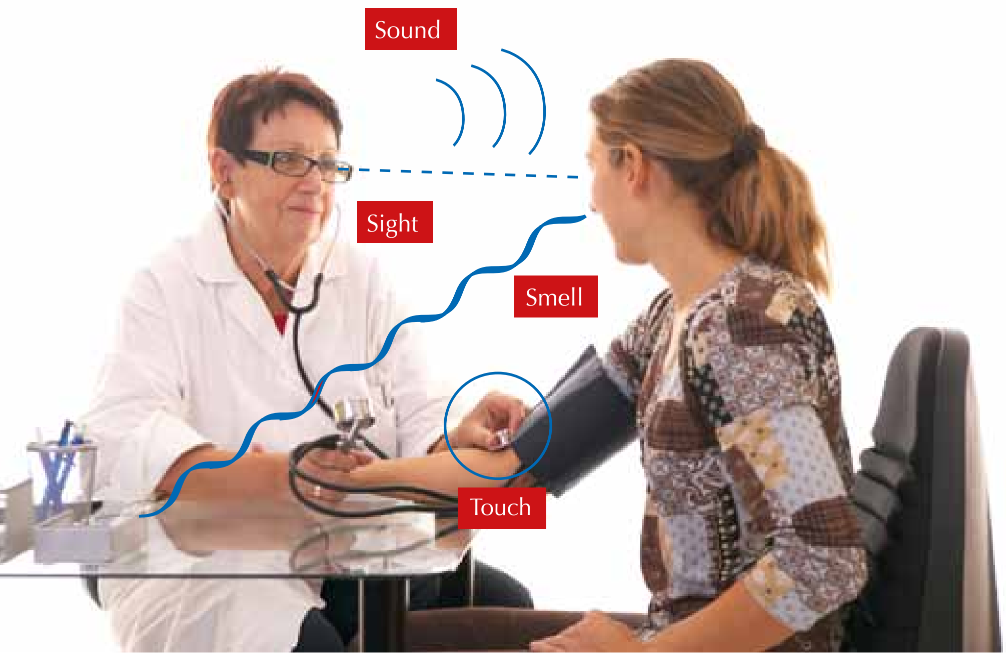

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Figure 1: The psychosocial context consists of a diversity of factors that are symbolic of the fact that a therapy is being performed. A physical placebo (such as a sugar pill) may constitute only one of these factors. In the scene shown here, many of the patient's senses (sight, smell, touch and hearing) are bombarded by stimuli

is far more than that, as clinical trials have testified. In a Swedish trial of heart patients, for example, those in the placebo control group were given an identical pacemaker to those in the treatment group, but unbeknown to them, the device was switched off. After three months, astonishingly, the symptoms of patients in *both* groups had improved. More astonishing still, the researchers were able to measure the improvement in the patients in the placebo control group as an increase in the flow of blood from the heart (Linde et al., 1999).

So what is going on? As Fabrizio Benedetti, professor of physiology and neuroscience and a world authority on the placebo effect, explains: "the placebo effect is a real neurobiological phenomenon, where something happens in the patient's brain". It is triggered not by the ingredients of the placebo itself, but by what it symbolises. In a clinical setting, there are many symbolic factors, which Benedetti refers to collectively as the 'psychosocial context' (Figure 1): "The sight

Reprinted from de la Fuente-Fernández R, Stoessl AJ (2002) The placebo effect in Parkinson's disease. Trends in Neuroscience **25(6)**: 302-306. doi: 10.1016/S0166-2236(02)02181-1. Copyright 2002, with permission from Elsevier

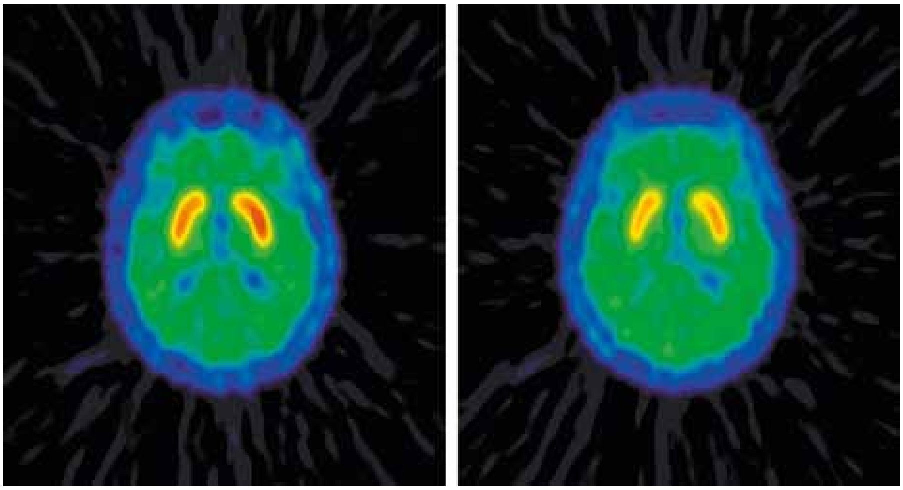


Figure 2: When sufferers of Parkinson's disease, whose brains have low levels of dopamine, are told that their motor function will improve, they release substantial amounts of dopamine in a region of the brain called the dorsal striatum (de la Fuente-Fernández & Stoessl, 2002). The figure shows PET (positron emission tomography) scans of the brain of a Parkinson's patient, showing the amount of radiolabelled raclopride – a compound that competes with dopamine for dopamine receptors – before (a) and after (b) administration of a placebo. The less intense red colour in (b) indicates an increase in the level of dopamine, which inhibits raclopride from binding

and words of the doctor, the smell of the drugs, the hospital machinery: all of these sensory and social stimuli tell the patient that the therapy is being performed." The patient's resulting expectation of a therapeutic effect elicits the placebo effect.

But the psychosocial context can also determine the strength and type of placebo effect. For example, the number, colour and even the packaging of tablets influence their effects (for details of the research behind these observations, see the online supporting information[w1]). In a US study in which half of the participants were given an inert sugar pill and half were given sham acupuncture (the needles did not actually pierce the skin), the sham acupuncture was significantly better at relieving pain than the sugar pill, whereas the pill helped patients sleep (Kaptchuk, 2006).

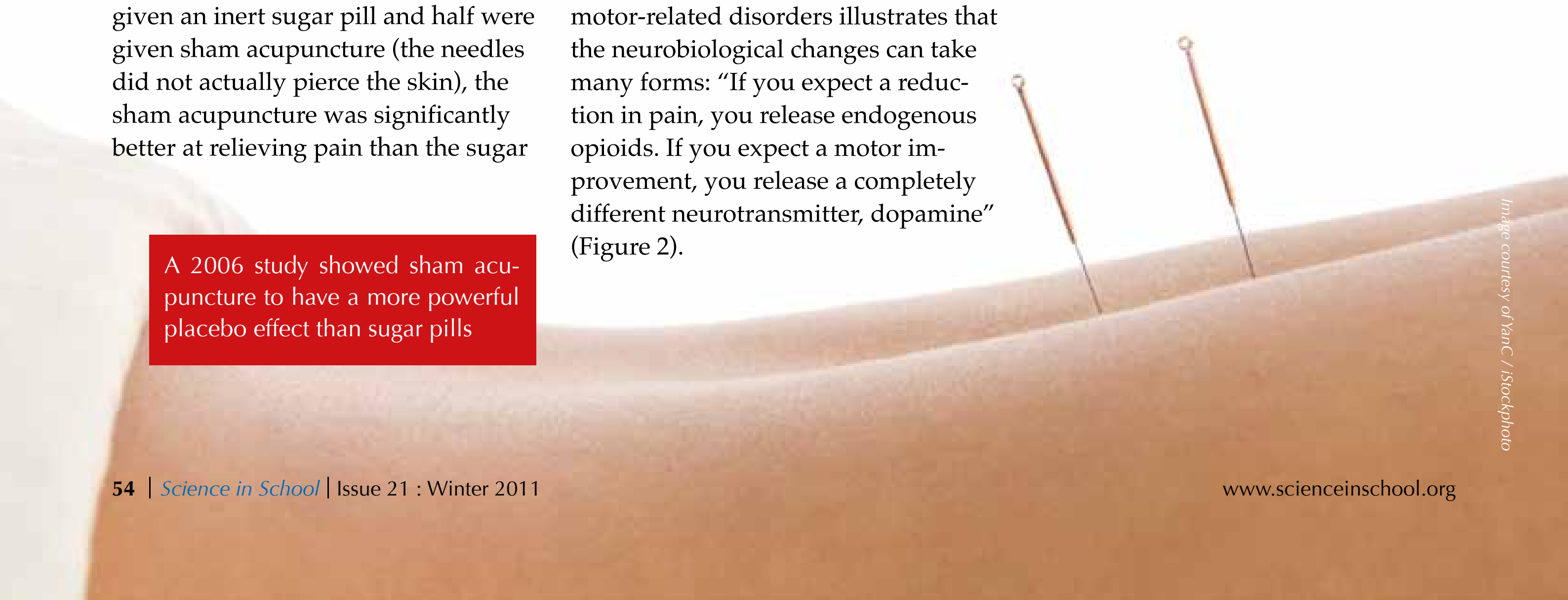
So how does the psychosocial context cause neurobiological changes in the brain? When a patient expects a therapeutic treatment, neurotransmitters are released. These bind to their corresponding receptors, prompting the release of further molecules in the brain and other organs, among them hormones, immune mediators and more neurotransmitters, which all cause far-reaching physiological changes that can generate a therapeutic effect.

Benedetti's work on pain and motor-related disorders illustrates that the neurobiological changes can take many forms: "If you expect a reduction in pain, you release endogenous opioids. If you expect a motor improvement, you release a completely different neurotransmitter, dopamine" (Figure 2).

"But the crucial question" explains Benedetti, "is *how* what the brain expects can trigger a specific release of neurotransmitters." At present, he admits that we have no definitive answer to this, but two mechanisms have been studied particularly closely (Figure 3):

1. Classical (or Pavlovian) conditioning: an unconscious mechanism. Benedetti explains: "If you are given a placebo for the first time, usually there is a small response or no response. But if, for example, you inject morphine five days in a row and on the sixth day you replace it with a saltwater placebo, you can bet that one hundred percent of the patients will respond to the placebo." The patients' brains have been conditioned to respond to the injection by producing molecules that interact with the same targets as morphine. A region of the brain called the dorsolateral prefrontal cortex may be crucial in the conditioning response (Figure 4).
2. A two-part conscious mechanism:
   a) The expectation of reward: the patient expects that his or her condition will improve, activating the reward network in a region of the brain called the nucleus accumbens – part of the same region that is activated with the expectation of food, sex, money or even humour (Figure 4; Hayes, 2010).

A 2006 study showed sham acupuncture to have a more powerful placebo effect than sugar pills



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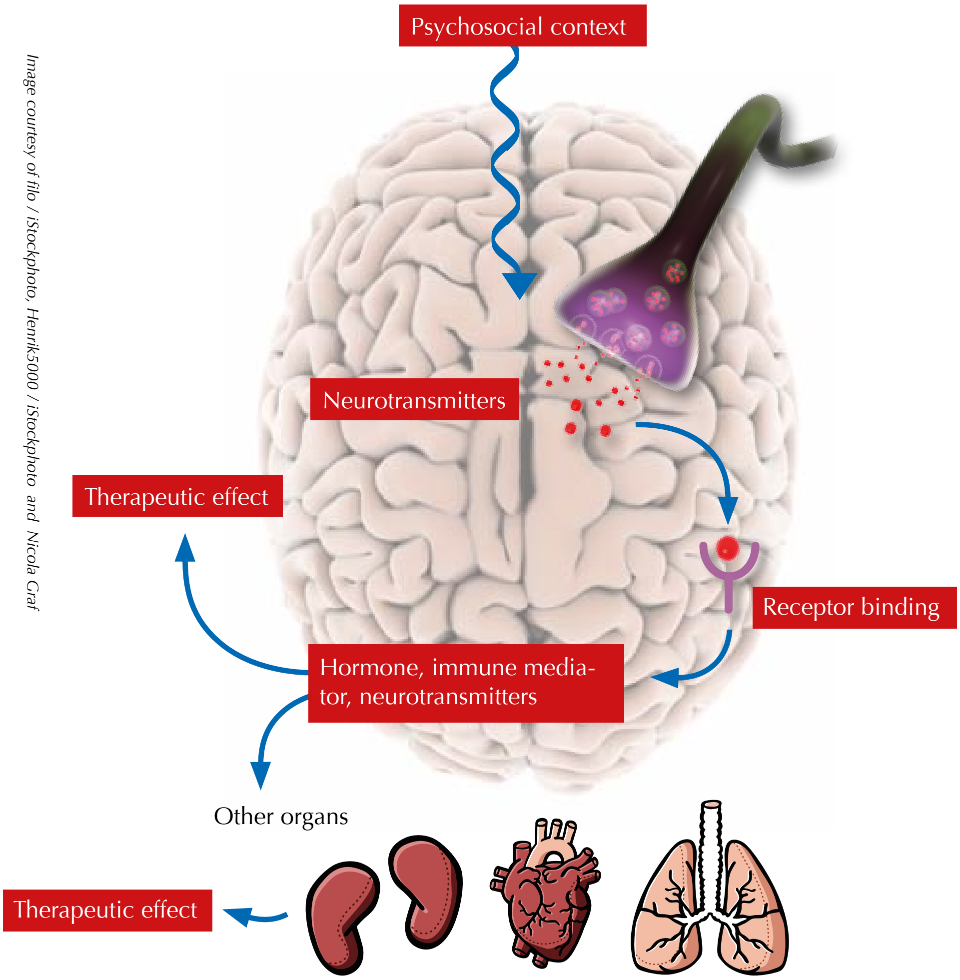

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Figure 3: The placebo effect: from psychosocial context to therapeutic response. The psychosocial context tells the patient's brain to expect a therapeutic effect. As a result, neurobiological events occur in the brain via unconscious and / or conscious mechanisms, bringing about the release of effector molecules. These cause physiological changes in the brain and other organs that can generate a therapeutic effect

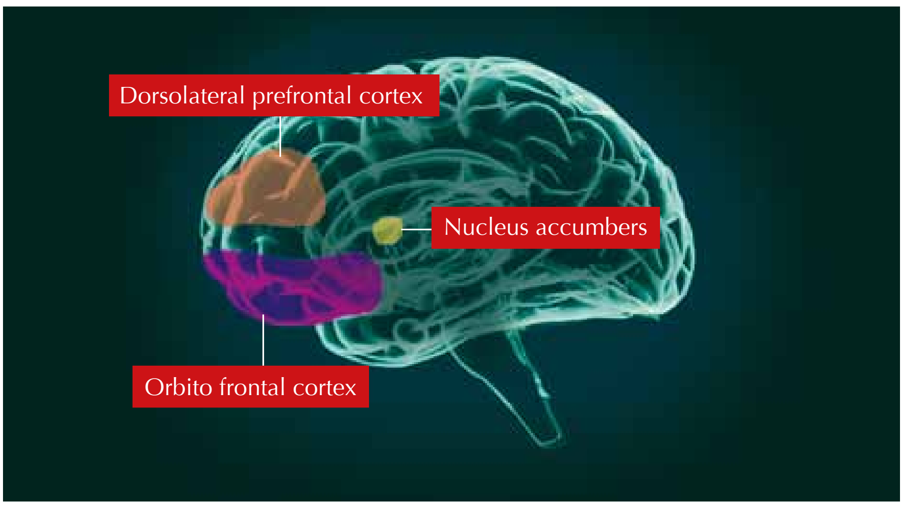

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Figure 4: Schematic side-view of the brain showing the regions involved in the conditioning response (dorsolateral prefrontal cortex) and the reward and anxiety response (nucleus accumbens and orbitofrontal cortex, respectively) during the placebo effect

b) Anxiety modulation: this occurs via the brain's anxiety network, which spans many regions, such as the orbitofrontal cortex. "If I give you a treatment and tell you your pain is going to decrease, your anxiety will decrease, triggering the release of neurotransmitters in your brain," Benedetti says.

Both the anxiety and reward networks control many biochemical pathways and associated organs. In the switched-off pacemaker study, the heart condition of the patients in the placebo group is thought to have improved because they were less anxious and produced lower levels of catecholamine stress hormones, known to alter heart function.

Placebo research is still in its infancy; perhaps the most exciting future research will focus on the placebo effect in conventional medicine. Benedetti has already begun, looking at the placebo effect of *real* drugs. For example, in one trial, he found that an injection of the powerful analgesic metamizol was effective in reducing patients' post-operative pain, whereas a hidden administration of the drug (via a pre-laid tube) was completely ineffective (Colloca & Benedetti, 2005). The analgesic effect of the open injection was therefore entirely due to the placebo effect.

This is revolutionary: the idea that the efficacy of drugs can be affected so profoundly by the context in which they are given. For the medical profession, the challenge will be to make the most effective and ethical use of the placebo effect.

Acknowledgement

This article is based on an interview and a lecture[w2] given at the European Molecular Biology Laboratory (EMBL), in Heidelberg, Germany, by Fabrizio Benedetti, professor of physiology and neuroscience at the University of Turin Medical School and at the National Institute of Neuroscience in Italy.

CLASSROOM ACTIVITY

Topics for discussion

- Would it be ethical for doctors to prescribe a placebo for their patients?
- Should conventional medicine make more use of the placebo effect?
- How might the placebo effect give credence to ineffective alternative therapies?
- One of your friends claims to have invented a treatment for spots. How would you design an experiment to test whether the observed improvement is due to the treatment itself or to the placebo effect?
- What can you find out about the negative counterpart of the placebo effect, known as the *nocebo effect*, whereby negative expectations can cause unpleasant symptoms, in the absence of a physical cause?
- Some people are classed as good 'placebo responders' whereas others are not. What might be the evolutionary advantage of being a good placebo responder?

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Web references

w1 – More details of studies on the placebo effect are available to download from the *Science in School* website: www.scienceinschool.org/2011/issue21/placebo#resources

w2 – A video of Fabrizio Benedetti's lecture is available on the EMBL website (www.embl.de) or via the direct link: http://tinyurl.com/3tc4tf5

Resources

For a two-part radio programme by doctor and science writer Ben Goldacre on the placebo effect and its implications for conventional medicine, see: www.bbc.co.uk/radio4/science/placebo.shtml

For mp3 versions, see www.badscience.net

For a review of Ben Goldacre's book *Bad Science*, which includes a fascinating chapter on the placebo effect, see:

Hayes (2011) Review of *Bad Science*. *Science in School* **18**. www.scienceinschool.org/2011/issue18/badscience

For a brilliant article about the havoc wreaked by the placebo effect on the pharmaceutical industry, see:

Silberman S (2009) Placebos are getting more effective. Drugmakers are desperate to know why. *Wired Magazine*. Visit the *Wired Magazine* website (www.wired.com/magazine) or use the direct link: http://tinyurl.com/mwlxfp

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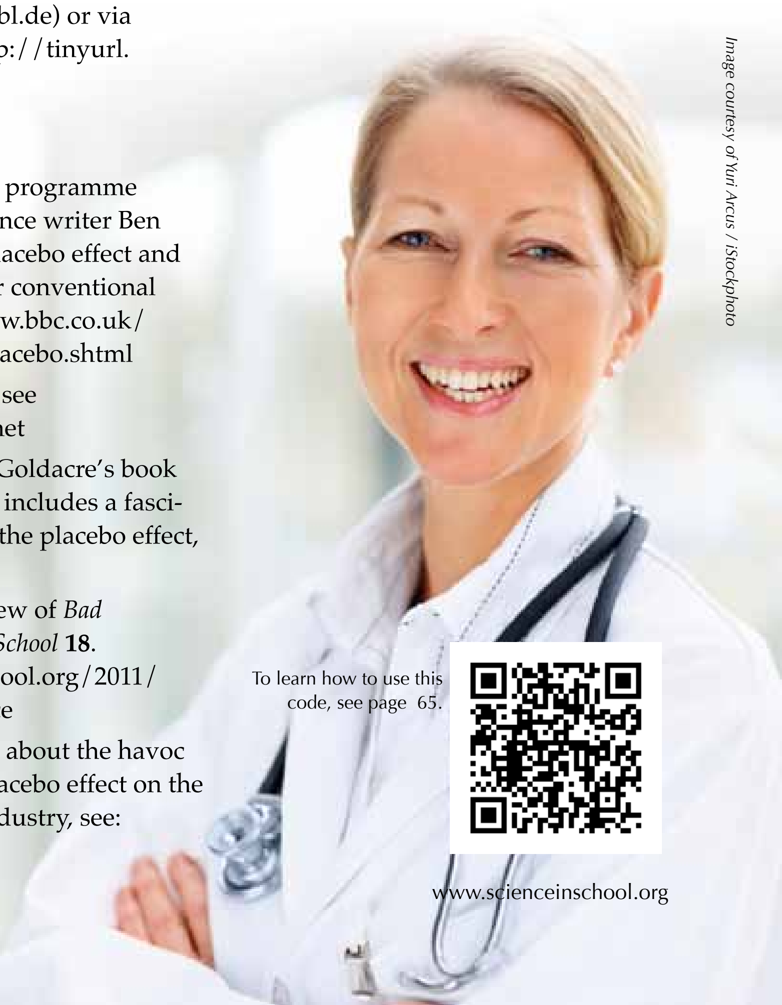
Andrew Brown recently graduated from the University of Bath, UK, with a degree in molecular and cellular biology. During his course, he took a year out to work for the agrochemical company Syngenta where he specialised in light and electron microscopy. He now works as an intern for *Science in School*, based at the European Molecular Biology Laboratory, in Heidelberg, Germany.



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