KLAWE RZECZY; HEADHOT: MATTHEW PAUL D'AGOSTINO

‘Our thoughts can have a role in our experience of pain’

How exactly the placebo effect works is still a mystery, but neuroscientist **Luana Colloca** is trying to find the answers. She tells David Robson how what we know so far is transforming the way we treat pain

FOR a phenomenon that has been known about for hundreds of years, there is still much to learn about the placebo effect – when a person’s health improves after taking a dummy treatment like a sugar pill. It is thought that the expectation of a positive outcome is behind it, and that a negative expectation is involved in its unwelcome opposite, the nocebo effect, which is when symptoms worsen. But questions remain about exactly how the mind affects the body in this way and why some people experience the effect more strongly than others.

Luana Colloca is among those tackling such questions. A neuroscientist and the director of the Placebo Beyond Opinions Center at the University of Maryland School of Nursing in Baltimore, Colloca and her colleagues have shown how specific gene variants can shape the extent of someone’s placebo response. They are now looking into how best to harness such effects to help soothe pain, which could decrease the use of prescription opioid drugs and the risk of addiction to them. They are also exploring the use of virtual reality, with results published last year showing that it can successfully reduce perceived pain and anxiety levels.

Colloca has rounded up all the latest findings on the placebo and nocebo effects in a book that she has co-edited called *Placebo Effects Through the Lens of Translational Research*. She spoke to *New Scientist* about her work on pain relief, whether the placebo effect can help in treating mental health conditions and how it impacts the way we use wearable tech.

David Robson: Some people might imagine that placebo responses are fake or imaginary. What first persuaded you that they are real?
Luana Colloca: The placebo phenomenon is probably one of the oldest phenomena in the history of medicine, but also one of the most controversial. When I started researching this topic, I had a very sceptical approach. I had just achieved my medical licence and I was assigned as a PhD student to study placebo effects in Parkinson’s disease at the University of Turin in Italy. These patients had severe symptoms – tremors, rigidity and slow movement known as bradykinesia – and they were all candidates for deep brain stimulation, which consists of electrodes implanted in the subthalamic region, a bean-sized area that controls our movement and coordination. When we implanted the electrodes, we could record neuronal activities very precisely.

The patients had been receiving a drug by injection that increases brain dopamine levels and improves Parkinson’s symptoms. While undergoing the surgery, however, they were given an injection of a placebo, which they ›

believed was the real drug – and they saw the same improvements in their symptoms. Despite this having no active ingredient, their rigidity somehow unlocked or the tremor decreased, and they reported feeling better. Through the electrodes, you could see a change in the neuronal activity along with the motor changes. That was my epiphany.

Can the placebo effect be seen with any treatment?
Virtually any treatment can have a placebo component. In some cases, it is the positive mindset that improves the symptoms: the conscious belief that the saline solution or sugar pill is an active drug that will help. But it can also be the result of learning from a previous experience with a drug, through a process called conditioning.

One team, for example, looked at whether you could use a placebo to reduce the amount of immune suppressant drugs needed after a transplant. They asked patients who were taking an immune suppressant twice a day following a kidney transplant to take a placebo that looks identical at two additional times in the day. Without any active ingredient, the placebo dose showed the same suppressed immune response. When a placebo effect is learned, you don't need any conscious expectation of relief; in fact, a patient could be very negative but still experience some benefits.

What causes the effect?
Placebo responses depend on a sort of inner pharmacy – that is, the release of "endogenous" compounds by the body that resemble the active drugs we use to manage symptoms. Placebo pain relief, for example, comes from the release of endogenous opioids, cannabinoids and dopamine.

We have genes that determine the way these endogenous chemicals are processed. The *OPRM1* gene, for instance, encodes for the mu opioid receptor, while the *FAAH* and *COMT* genes encode for enzymes that break down cannabinoids and dopamine. Someone carrying one variant of one of these genes can display higher placebo effects compared with those carrying another. In our lab, we have shown that single nucleotide polymorphisms – variants at a single base position in our DNA – on these three genes can predict the magnitude of the placebo effect.

Of course, these genetic variants alone can't explain everything: we need to study how the environment and genes interact. Along these lines, we're also pursuing research into early life and adversity. One of our ongoing projects suggests that people who have experienced trauma in early life show a smaller placebo effect, and so we are interested to see the way that someone's life history might interact with their genetic variants to determine their placebo responses.

Surprising facts about the placebo effect

SCEPTICISM MAY REDUCE THE BENEFITS OF PSYCHOLOGICAL THERAPY
Almost all medical treatments have the potential to trigger some form of the placebo effect – meaning that sceptical beliefs could impair outcomes. This may be especially important for psychological therapies. The more someone expects to benefit from a treatment like cognitive behavioural therapy for conditions like depression, the more likely it is to improve their symptoms.

THE BENEFITS OF EXERCISE MAY DEPEND ON A PLACEBO RESPONSE
Physical activity can be beneficial for so many different conditions – from diabetes to heart disease and chronic pain – that some doctors describe exercise as a form of medicine. And this, too, includes a placebo component. According to a 2022 review of published studies, our expectations of the benefits of exercise can influence how it alters mood, self-esteem, cardiovascular fitness and blood pressure.

PETS CAN EXPERIENCE A FORM OF THE EFFECT
In the early 2000s, scientists conducting clinical trials for dog epilepsy discovered a curious phenomenon: the animals given a new drug had fewer seizures, but so, mysteriously, did those given placebo pills. We don't know why this was, but one possibility is that the use of pills changes an owner's behaviour, which benefits the dog. If so, it is a kind of placebo by proxy.

Animals can also benefit from conditioning, in which the brain and body start reacting in a certain way to a real drug – and then continue to respond if it is swapped for a placebo pill. **DR**

A lot of your work on placebos has centred on pain. Addiction to opioid painkillers is still a huge health crisis. Could a better understanding of the placebo effect help us to reduce dependence on such drugs?
My colleagues and I hope so, along with a general shift in the perception of pain management. We now know that there is a strong "descending pain modulatory system", a kind of top-down processing which means that our thoughts can have a role in our experience of pain. For example, research shows that catastrophising thoughts – such as "there's nothing I can do to reduce the intensity of my pain" and "it's never going to get any better" – can amplify distress and reduce placebo effects. Cognitive behavioural therapy can help people to reframe their experiences and reduce catastrophising, which, in turn, reduces the intensity of the pain that they are experiencing. Someone may not be able to eliminate their pain entirely, but they can aim to reduce it to do the activities that are so meaningful for them.

The idea now is to create personalised pain management. We could identify the people who can manage their pain with non-pharmaceutical approaches and so limit the use of prescribed opioids to those who don't respond to the other pain therapeutics. The best treatment for you may be very different to the best treatment for me.

Have you tried this approach?
In one study, we worked with multi-trauma patients – people who have any kind of injury that you can imagine. We went to the bedsides and told them that "opioids are important in this condition, but we don't expect you to be on opioids for the rest of your life". We gave them this 20-minute education about the full spectrum of pain treatments and they started needing less opioids to treat their pain while they were still in the hospital. We need a multidimensional approach – there isn't a single pill that will treat all pain.


SHUTTERSTOCK/DAVID PERERAS

Some of your research looks at using virtual reality to improve people's pain and anxiety about their symptoms. How does that work?
Virtual reality can be therapeutic. By ourselves, we can't detach from the pain and anxiety we are experiencing. Through virtual reality, however, you can turn someone's attention away from the symptoms they are experiencing with strong visual stimulation and three-dimensional sounds. You can even add smell sensations along with the goggles. Together, this multisensory stimulation helps modulate the brain's perception of pain and other symptoms. It's cost-effective, accessible to most patients and free of the side effects associated with medication, so it has great potential as a tool for chronic pain.

When we offered immersive VR at the hospital bedside, we saw reductions in perceived pain and anxiety, along with changes in objective measures of the nervous system that signal distress. It's unbelievable the engagement we've seen through our research at Maryland: no matter the age, sex or ethnicity, the participants wanted to try it.

Can placebo effects influence treatments for mental health conditions?
There is considerable debate about the potential differences in efficacy of placebo versus mental health therapeutics. There's a very robust literature on the large placebo effects in the treatment of depression with antidepressant drugs, but there is a huge gap in our knowledge for other conditions, such as bipolar disorder and schizophrenia. We do know that there's a relatively small placebo response in obsessive-compulsive disorder, so the effects of our expectations are not universal across all mental health conditions.

> "Virtually any treatment can have a placebo component"

Several factors contribute to placebo responses in mental health conditions, such as expectations and interactions with the physician. Specifically, expectations related to treatment efficacy and side effects could be manipulated to optimise clinical outcomes and reduce side effects. There is growing evidence that expectations during treatment can affect responses to pharmacological and non-pharmacological treatments, including cognitive training, responses to psychedelics and psychotherapy.

Using virtual reality can help reduce levels of pain and anxiety

Wearable tech now gives us a huge amount of information about our health. Does the way we interpret this affect whether it helps us or not?
In general, it's positive to pay attention to our bodies, but for people who tend to catastrophise, it could become detrimental. There have been cases of people running to hospital because they notice their heart rate is high or they see a different spike in their neural recordings, or they might become neurotic about their sleep if they don't get the perfect number of hours.

It's not just wearable technology: patients can now have access to their clinical notes online, information that wouldn't have been available before. Doctors need to be mindful of the potential for this information to create nocebo effects that harm patients.

How has your understanding of the placebo response influenced your own life and how you deal with your own health issues?
My research on placebo, and perhaps more importantly on nocebo, has influenced my perspective on medicine. Understanding the power of beliefs and expectations has made me more attuned to the role of verbal and non-verbal language in patient-doctor communication. Personally, I've become more mindful of the potential impact of these framing effects on my own interactions with patients and study participants, fostering a more careful approach.

The knowledge I've gained about placebo and nocebo effects has shaped how I approach my own health. I consciously incorporate positive thinking and conditioning into my own lifestyle, recognising the potential benefits they may have on overall well-being and healthy habits. When I feel pain, for example, I use a non-steroidal anti-inflammatory pill with a positive mindset, and I feel better with low dosages. It's not about substituting these practices for full-dose treatment, but rather complementing them with positive thinking and other placebo-based strategies. ▮

David Robson is a science writer and author of *The Expectation Effect: How your mindset can transform your life*. He is based in London