GREAT EXPECTATIONS

THE PLACEBO EFFECT TURNS SOCIAL CUES AND BELIEFS INTO A HEALING SUPERPOWER. IS IT POSSIBLE TO HACK OUR MINDSETS TO CREATE PERSONALIZED PLACEBOS?

By Alan Morantz
Photographs by Naama Stern

The ritual begins before you even swallow the pill. You sit in a pristine medical office where diplomas hang in alignment and speak with a doctor whose confident manner and pressed white coat radiate authority. She explains your treatment with empathy and confidence, describing how the medication will target your condition. She types out the prescription on her computer and sends it to your pharmacist. Even the pharmacy visit reinforces the gravity — the careful instructions about timing and dosage, the child-proof bottle with its official label. When the first pill hits your tongue, neural networks, primed by dozens of subtle cues suggesting relief is imminent, fire up, and feel-good neurotransmitters, like endorphins and dopamine, are released.

Once seen as props of medical hucksters, placebos have been shown to have as much therapeutic value as the active ingredients of some conventional drugs. Cognitive neuroscientist Rotem Botvinik-Nezer wants to harness that power to strengthen the effectiveness of traditional treatments.

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Triggering the placebo effect is a challenge, says Botvinik-Nezer, an Azrieli Early Career Fellow. Genes, personality, the nature of the doctor-patient relationship and other factors predispose us to be more or less susceptible to the placebo effect.

As researchers have documented, this elaborate theatre of health care — the clinical settings, the medical authority, the dispensing of treatment — may have as much therapeutic value as the active ingredients of conventional drugs themselves. This is the placebo effect in action, and it can be significant: In one study of almost 200 randomized clinical trials, about half of the typical overall treatment effects were attributed to placebo response, with much of the rest coming from the drug effect.

Yet, for many, the very word "placebo" still carries a whiff of flim-flammery. Two hundred years ago, placebos were seen as parlour tricks or props of scam artists and medical hucksters. Early researchers seemed to conjure therapeutic effects from items such as metal rods, "magnetized" trees and hickory ash, though few took those accounts seriously. In the Victorian Age, doctors used sugar pills as pacifiers to soothe patients' minds and calm their feverish imagination — knowing it was unlikely anything good could come of pharmacologically inert substances.

Research over the last decades has identified real brain-body responses to classic placebos like sugar pills and contextual cues like visits to a doctor's office. But placebos are rarely considered in clinical practice. That's largely because health care practitioners view them as problematic, says cognitive neuroscientist Rotem Botvinik-Nezer, an assistant professor in the psychology department of The Hebrew University of Jerusalem. Deceiving patients goes against the bedrock principle of informed consent.

"I think it's a big miss," says Botvinik-Nezer. "Placebo effects are about the brain's ability to translate beliefs into physiological responses. The fact that we can induce internal processes for healing through placebos cannot be a problem."

An Azrieli Early Career Faculty Fellow, Botvinik-Nezer leads a lab that studies how beliefs are formed and updated, and how they influence behaviour, perception and health. In her mind, the unwillingness of the medical world to embrace the possibilities of the placebo effect in the overall treatment of patients is a lost opportunity. If the placebo effect could be harnessed, she says, it could strengthen our ability to heal ourselves and boost the efficacy of existing medications. "What if we could make any treatment work better just by shaping belief?" she asks.

The placebo effect doesn't require deceptive sugar pills or saline injections to work. It does, however, need the right social cues, beliefs and expectations — a set of triggers that differs from person to person. Is there a way to hack those contextual cues and expectations to create a personalized placebo effect? One that doesn't require a fake treatment and that can pass the ethics test? Botvinik-Nezer is well on the way to finding out.

Over the past three decades of research, placebos have been shown to offer a clinically significant benefit for a wide range of conditions, not only relating to pain, anxiety and depression but also to asthma, allergies, hypertension and immune deficiencies. (This does not suggest that placebos are necessarily an alternative to conventional drugs for these conditions.) Placebos have been shown to reduce pain and muscle rigidity for patients with Parkinson's disease — in some trials, they were responsible for a 20 to 30 per cent improvement in motor scores, though they don't affect the progression of the disease.

We also know a lot more about how these effects come about. Neuroscientists have used modern neuroimaging techniques such as functional MRI to observe real-time brain activity after a placebo is administered. They've discovered that placebos can change brain activity in ways similar to active pharmacological treatments. When people are primed to expect relief from pain, the prefrontal cortex, which involves expectation, decision-making and cognitive control, shows increased activity. Neurotransmitters such as endorphins, the brain's natural opioids, and dopamine, associated with reward and motivation, are released.

How these effects are triggered is not straightforward. Our genes, our personality, the nature of our relationship with our doctor, the severity of our condition — all these factors and many more may predispose us to be more or less susceptible to the placebo effect. As a result, scientists are finding it challenging to pinpoint who might respond to certain placebos, or even when.

Still, they try. Some researchers focus on identifying the typical placebo responder, hoping to reliably replicate what makes this responder so open to the effect. Others focus on the intervention, trying to find a standard protocol to induce placebo effects by modifying the information individuals receive in the clinical setting. The findings have been unsatisfying. Studies summarizing the broad literature suggest that a placebo responder does not exist, and others show there is no one-size-fits-all script.

At the core, Botvinik-Nezer says, the patient needs to be in the right mindset to be receptive to the placebo effect. So it becomes an old-fashioned communication issue: What is the right message that would resonate with a particular patient? To one person, a general explanation of a medication may be reassuring, while to another, it may come across as vague. Some may prefer relatable examples, others technical information. "If that's the case," says Botvinik-Nezer, "then individual differences are not a problem to control for, they are a feature to design for. But if the key is to match the message to the person, how do we actually do it at scale in the real world?"

Botvinik-Nezer is now taking the first step to addressing that challenge in online experiments. She and her students collect information from study participants: demographic profile, personality traits, beliefs, emotional states. Is the person extroverted? Does she have a high fear of pain? Is he conscientious? They combine the data set from each participant with information about the (fictional) treatment, and then ask the AI chatbot ChatGPT to design a brief explanation of the treatment that would be most persuasive for the specific individual.

Her objective is to see whether this process boosts expectations — whether people given personalized descriptions of a drug expect it to work better than those who were given non-personalized explanations, or explanations that were personalized for someone else.

There are years of research ahead, but if the process proves its worth, how would it look in practice? Imagine going to your medical clinic to get relief from a bad run of anxiety. Once you check in, an AI chatbot asks you a series of questions about yourself and your condition. You then see the doctor, who decides on a prescription and asks the AI chatbot to prepare an explanation of the drug that is tailored to your communication preferences. Before you leave, you "meet" with the AI chatbot and receive your tailored information. The chatbot also shows you a video explaining how the drug will alleviate the anxiety and when and how to use it. Oh, and the chatbot would be happy to answer any of your questions.

This approach will not work equally well on all conditions. The placebo effect has been shown to be strong for pain, depression and anxiety, and less so for conditions such as obsessive-compulsive disorder or schizophrenia. But it is progress toward the ideal of personalized medicine.

"Matching the right person to the right treatment is already becoming reality," says Botvinik-Nezer. "But we should go one step forward. We can personalize the belief that the treatment works. By shaping beliefs, we can make medicine truly personal."

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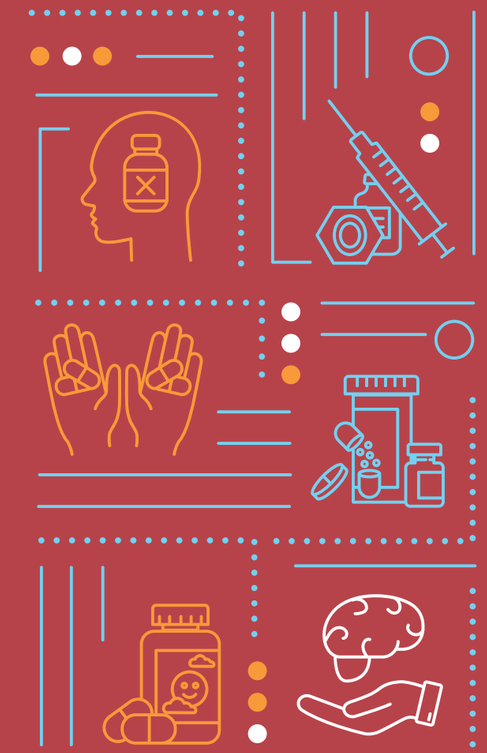
Botvinik-Nezer was first exposed to neuroscience during her undergraduate years at Tel Aviv University (TAU). She later completed her PhD at TAU's Sagol School of Neuroscience. "At Tel Aviv University, I actually wanted to study placebos, but there were no labs in Israel doing placebo research in humans," she says. "When I got closer to the postdoc, I looked for a leading placebo lab to go to, and then I moved to Tor Wager's lab at Dartmouth College."

It was a great choice. Wager is one of the world's leading placebo researchers, and moving her family to the Ivy League school in Hanover, New Hampshire, gave her a chance to explore placebo effects and how expectations and beliefs are shaped with the most experienced colleagues and most advanced equipment.

Since then, Botvinik-Nezer has been a prolific researcher, filling in the blanks of what is known about the placebo effect. One noteworthy study, published in 2024 in *Nature Communications*, involved the largest ever sample of participants in a placebo functional MRI study. She and her colleagues found a clear difference between the behavioural and neural effects of the placebo — between the sensation of pain and how that pain is interpreted in the brain.

Wager is impressed by what Botvinik-Nezer has accomplished to date. "She has made seminal contributions to the study of placebo



effects," he says. "This work identifies different stages of pain-related processing in the brain, identifying later systems that are susceptible to expectations and beliefs and earlier systems that are immune to them. This research will be important for understanding both the power and limitations of beliefs and expectations."

While Botvinik-Nezer has made her mark as a basic scientist, her work with personalized placebo effects takes her in a more practical direction. It also raises challenges. For one, basic science is about probing for causal relationships. "But with the new work, I'm not trying to see if there's an effect. I'm trying to boost it," she says. "My aim in this line of research is not to look for the truth but to find a way to make something work. And it's very different in how you design your experiments, how you look at the results, what is okay or not okay to do in your science."

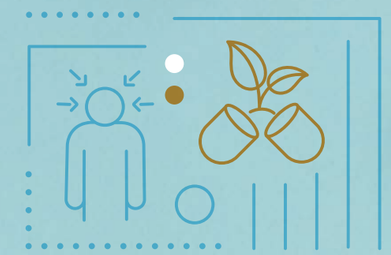
There is also the question of open science, one of her core professional values. Botvinik-Nezer has been involved in multiple large-scale collaborative projects testing and advancing open science practices across different fields. (As Wager says, "Rotem has put in tons of extra work to make valuable fMRI datasets and computational models available to the scientific community, even before the primary papers are published in many cases.") With more practical research, there can be pressure to limit the sharing of data to discourage others from prematurely commercializing the research. Building fences around her data is not something Botvinik-Nezer is used to doing.

These are tough issues to grapple with as a young scientist, navigating the journey from basic to applied science and back again. But she can lean on mentors such as Tor Wager, colleagues in her department and a strong community of scholars in Israel ("The amazing thing about the Azrieli grant is that it gets you not just funding, but also a wonderful community and lots of support").

Botvinik-Nezer also understands the high stakes involved. She regularly points to the underwhelming performance of the biggest pharmaceutical companies that attempt to develop drugs for brain disorders. One after another, companies have cut back or shuttered their neuroscience departments, in part because of the challenge of outperforming the placebo effect in clinical trials.

"Imagine spending billions of dollars to develop a new treatment only to find out that a sugar pill works just as well," says Botvinik-Nezer. "Huge amounts of money, resources, working hours, invested in developing drugs that failed clinical trials. Was it all wasted? Maybe not. Maybe we've learned something crucial. That, sometimes, the strongest medicine is not in the pill. It's in the brain, in our own beliefs, in our own expectations. Maybe now is the time to harness this power to boost the effect of active treatments." ▲●■

Botvinik-Nezer is now testing whether an AI chatbot can design an explanation of a proposed treatment that would be most persuasive for a specific individual. Her objective is to see whether this process boosts a patient's expectations of success.



SUGAR PILLS WITH A TWIST

Open-label placebos are placebo treatments given to patients with full transparency — patients are explicitly told they are receiving an inactive treatment, like a sugar pill or saline solution, that can still help them feel better through placebo effects.

The concept challenges the assumption that placebo effects require deception or belief in receiving real medication. Instead, open-label placebo research explores whether people can benefit from placebo treatments even when they know exactly what they're getting. It's not as unusual as it sounds: We listen to a scary campfire story and experience real fear and physiological reactions like goosebumps, despite knowing the ghost story is fake.

Research on open-label placebos has shown promising results across several conditions:

Irritable bowel syndrome (IBS): Some of the strongest evidence comes from IBS studies, where patients taking drugs clearly labelled as "placebo pills" and explained as inactive showed significant symptom improvements compared to no-treatment control groups.

Depression and anxiety: Studies have found modest but meaningful improvements in depressive symptoms when an open-label placebo is used alongside usual care, though effects are generally smaller than with antidepressants.

Chronic pain: Research suggests open-label placebos can provide pain relief, particularly when combined with a strong therapeutic relationship and clear explanation of how placebo effects work.

Cancer-related fatigue: Some studies have shown open-label placebos can help reduce fatigue in cancer survivors.

To work, open-label placebos require the proper conditioning (previous positive experiences with pills), expectancy effects (being told that placebos work) and the therapeutic ritual of taking medication. The provider-patient relationship and how the treatment is presented are also important factors.

The research is still new and evolving. Effect sizes are typically modest, and there is ongoing debate about the best protocols, patient selection and ethical considerations. The field is actively investigating which conditions respond best and how to maximize benefits of open-label placebos while maintaining transparency. ▲●■