frontiers FOR YOUNG MINDS

HEALTH
Published: 09 May 2019
doi: 10.3389/frym.2019.00060

LET US USE THE BRAIN TO HEAL

Haitham Hajjo and Asya Rolls*

The Ruth and Bruce Rappaport Faculty of Medicine, Technion–Israel Institute of Technology, Haifa, Israel

YOUNG REVIEWERS:


ARIEL
AGE: 10.5


EINAV
AGE: 12


GUY
AGE: 10


MAAYAN
AGE: 12


SHANI
AGE: 10.5


TAMAR
AGE: 10

Anyone who has a younger brother or sister probably knows about the magic of Band-Aids: put one on a scrape and the pain goes away! But we know that adhesive bandages do not really affect the pain; they only cover the wound. So why do they make us feel better? The way a Band-Aid helps your little brother or sister is an example of the placebo effect. *Placebo* is a pretend medicine, like a sugar pill, that, when given to a patient, actually makes them feel better and may even improve their condition. How does this happen? We now know that thoughts and emotions can affect the way our bodies respond to pain and sickness, as well as to treatments. In this article, we explain what the placebo effect is, how it was discovered, and how it has influenced medicine. We also explain the biological causes of the placebo effect, and how we could use it and its healing potential to create more effective treatments for many problems.

WHAT IS THE PLACEBO EFFECT?

A placebo is a medicine that has no physical effect in itself. So why are doctors and researchers so excited about it? How does it help patients, and how did it all start?

During World War II, soldiers wounded on the battlefield were in a great amount of pain. The medical staff gave them morphine, a painkiller that is still used today. At some point the morphine began to run out, and soldiers were left writhing in pain. There seemed to be no way of helping them—but then one of the nurses had a brilliant idea: she collected the empty morphine syringes, filled them with water, and injected the wounded soldiers. Amazingly, they soon felt less pain!

After the war, one of the doctors who had seen what the brilliant nurse did began to study the subject of placebos. He made some spectacular discoveries. It turns out that patients suffering from some diseases actually get better after receiving a placebo. *Pain* is one problem that responds very well to placebos. Like a Band-Aid on a child's injury, placebos can really ease pain, even pain after surgery. *Parkinson's* disease patients, who suffer from uncontrollable movements, improve greatly when they get placebo pills. *Asthmatic* and *allergic* people often respond very well to sugar pills or to inhalers that do not contain any active medicine. There are even *placebo surgeries*: the patient is taken into the operating theater and given general anesthetic, sometimes the surgeon even cuts the skin, but there is no actual surgery. It is astonishing to see how some patients' condition truly improves as a result of a fake surgery like that [1].

Many scientists have studied the psychological effects of placebos. One of the things they discovered was that the *size* of a pill has a large effect on the patient's response. A big pill affected patients more than a small pill, even though they both contained only sugar. The color of the medicine was also important: for example, a red pill affected patients differently than a blue pill. And, of course, one of the most important factors is the *price* of the medicine: the more expensive a placebo is, the more effective it is [2].

The use of placebos raises many ethical questions. When a doctor uses a placebo, you might say he or she is tricking the patient. Then again, the doctor is helping the patient by improving his or her condition without using chemicals, which cause side effects. Is not a doctor's first duty not to harm, but to heal as well as possible? In some countries, especially in Germany, the use of placebos is so common that it has become a complicated legal and ethical issue.

To sum up, the *placebo effect* is what happens when giving a patient fake medicine reduces their pain, makes them feel better, and improves their health (although sometimes not as effectively as real treatment, or not for a very long time). For many years, scientists have been fascinated by the healing power of placebos. This has been one of the greatest mysteries of science, and it shows us once again how thoughts and feelings can affect our health. There is no doubt that the placebo effect works; but to this day, nobody has discovered exactly how.

To explain what we do know, let us go back to the Band-Aid example.

Two things that are very typical of children are: (1). They have a good memory, and (2). They get injured a lot. A child remembers that when he or she first got hurt, an adult put a Band-Aid on the wound and said that it would get better soon. After a while the wound healed and the pain went away, because of the natural healing process. The Band-Aid does not lessen the pain, but what the child remembers is that a Band-Aid was used and the pain went away. So the child makes the connection in his or her brain between the Band-Aid and the relief from pain. This is called *conditioning*: the brain thinks that two events are connected, or that one depends on the other.

WHAT IS CONDITIONING?

The most famous scientist to study conditioning was a Russian physiologist named Ivan Pavlov. When we eat, our bodies respond in several ways: the mouth produces saliva (spit) to make chewing and swallowing easier, the stomach produces acids to break down the food, and so on. Pavlov was interested in how the body responds to food, and this is what he studied in his experiments. However, in science, experiments often have unexpected results that lead to fascinating discoveries. Pavlov studied dogs. Each morning he rang a bell to call them to breakfast. After they had eaten, he measured the responses of their digestive system—for example, at which point they started salivating (producing saliva). Gradually he realized that to make saliva, the dogs did not even have to get the food: their mouths started to water as soon as he rang the bell, even if food did not follow. Why? Because the dogs had learnt that the ringing of the bell meant food. When they heard it ring, they expected food, and their bodies responded (Figure 1). Pavlov's experiment showed that thoughts can affect a dog's body. We humans respond in a similar way (has your mouth ever started to water when you heard the pizza guy at the door?) [3].

In the same way, the wounded soldiers in World War II thought they were getting morphine, and so they expected to feel less pain. This thought in itself lessened the pain, even though the injections contained only water.

But there is more. Doctors have discovered that placebos can work even when patients are told that they are receiving a new medicine, which they have never been exposed to before. This means that even if the patient has never had an experience that can help predict the outcome of the present (as with the child and the Band-Aid) the placebo effect can still take place, making the patient feel better and helping them heal. How does this happen?

Here there is another factor at work: *expectation*. When a patient is given a medicine, even an unfamiliar one, this might make

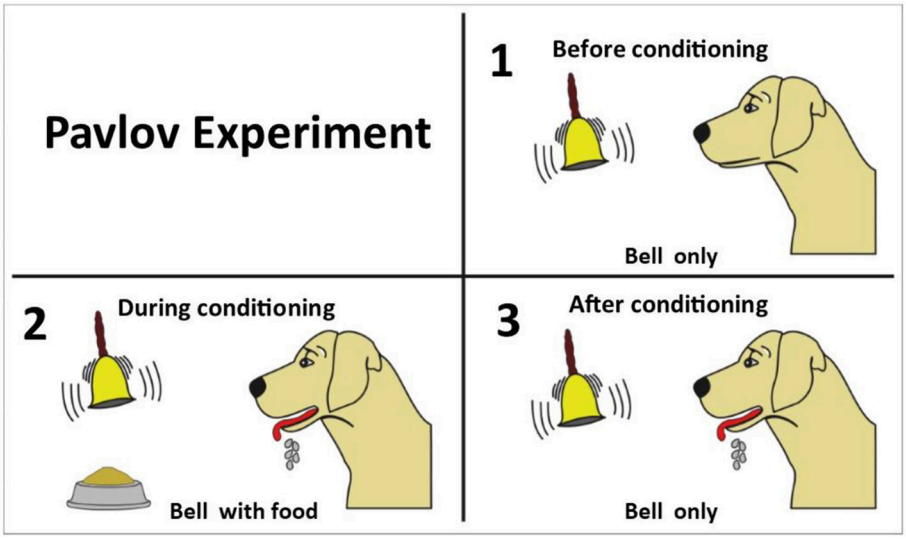


Figure 1

Pavlov's experiment. **1**. Before conditioning, the dogs salivated when they saw food, but had no special response to the ringing of a bell. **2**. During the conditioning process, Pavlov rang the bell each time he gave the dogs food. **3**. After conditioning, the dogs salivated when they heard the bell ring, even if they did not get food.

him or her think positive thoughts and expect an improvement. We think that these positive thoughts and expectations alone can help to reduce the pain, improve the patient's condition, and cure the disease.

THE BRAIN AND THE IMMUNE SYSTEM

IMMUNE SYSTEM

A very sophisticated "policing" system that scans all over the body for invaders (such as viruses, bacteria and cancer cells) and fights them. It also scans the body for unhealthy cells, like cancer cells and eliminates them.

Our *brain*, as we all know, controls our thoughts and expectations. Our **immune system** is one of the most important systems that keep our body healthy. It is like an army made of a huge number of different cells, working together to fight disease and keep our body healthy and working properly.

Our laboratory team wanted to find out how these processes happen. How exactly can the brain affect the immune system? This is important because understanding of these processes can help us develop medicines and cure diseases.

REWARD SYSTEM

A network of nerve cells and other structures in the brain, which make us feel pleasure in response to certain things. The cells in this system use a substance called dopamine to communicate with each other. The secretion of dopamine leads to the feeling of pleasure.

Scientists can now identify some of the areas of the brain that are involved in various functions. One of such area is the **reward system**, which is responsible for the feeling of pleasure. Scientists have discovered that when a patient expects to feel better, this expectation "switches on" parts of the reward system. This is very interesting, but can it affect the body's healing processes?

For our research, we tried to simulate the placebo process, using laboratory animals (mice). First we used biological particles that, when injected into nerve cells, enable us to "switch" them on and off. We injected these particles very accurately into the nerve cells of the mice's reward system, so that we could activate and deactivate it. This activation of the reward system is very similar to what happens

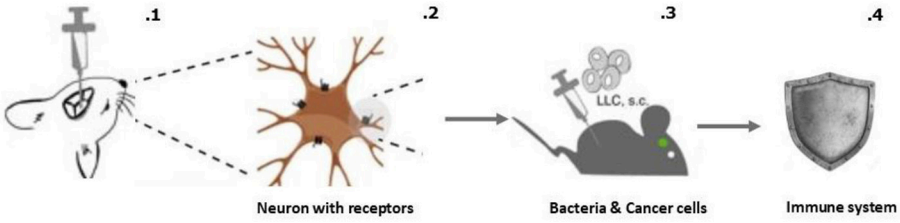


Figure 2

Figure 2

Activating the reward system in the brain made the immune system fight bacteria and cancer cells more effectively. **1**. We injected particles into the reward system area in the brain of the mice. **2**. These particles entered the nerve cells of the reward system, enabling us to control the cells. **3**. We then challenged the mice's immune system with bacteria or cancer cells. **4**. We saw that activating the reward system made the immune system work more effectively against bacteria and cancer cells.

in the brain when we expect something positive—like improvement as a result of medicine. We discovered that when we "switched on" the brain areas involved in positive feelings, such as expectations of healing, the immune system was also activated. It could then cope with diseases, for example, get rid of bacteria, in a better way. Our conclusion was that activating the reward system made the immune system fight bacteria more effectively [4] (Figure 2).

Another important role of the immune system is to fight cancer. After we saw that activating the brain's reward system made the immune system fight germs better, we wanted to find out whether this would also be true for cancer. Therefore, we challenged the immune system of the mice with cancer cells, and "switched on" the reward system in their brains. The result was similar: when the reward system was activated, the immune system worked better and killed more cancer cells [5] (Figure 2).

The next question we had to answer was: how does the reward system in the brain communicate with the immune system, which is located in various places in the body, some of which are very far from the brain? Our bodies have an "emergency" nervous system called the **sympathetic system**, which is part of the body's whole nervous system. The sympathetic nervous system usually goes into action when the body is under stress, like at times of sickness. It is made up of nerves that connect the brain to other parts and systems of the body—like the cardiovascular (heart and blood) system, the digestive system, and the immune system. The activity of the sympathetic system can affect what other parts of the body do—for example, when we exert ourselves, our heart beats faster. We found that activating the reward system affected this "emergency" sympathetic system—which then made the immune system cells fight harder against the cancer cells. How did this happen? [4, 5].

The cells of the immune system must constantly renew themselves, so that they can be ready for new challenges. For example, when bacteria invade our body, we need more immune cells. That is one of the reasons why we have a store of **stem cells**. Stem cells can become almost any kind of cell that the body needs. They are stored in a space at the center of our bones which is filled with **bone marrow**. The nerves of the sympathetic nervous system reach the bone marrow,

SYMPATHETIC SYSTEM

The "emergency" system that controls our body. It mediates the "fight or flight" response that we experience under stress, and tells the body to, for example, run from an enemy, or to fight a disease. The sympathetic system influences other systems in our body, such as the cardiovascular (heart and blood) system, the digestive system, and the immune system.

STEM CELLS

Special cells that can develop into various kinds of cells.

BONE MARROW

A substance inside the bones. It contains the stem cells that develop into our immune cells.

Figure 3

Activating the reward system in the brain affects the sympathetic nervous system. The nerves reach the bone marrow, where immune cells are developed. As a result, the new immune cells are more aggressive—because the reward system was activated.

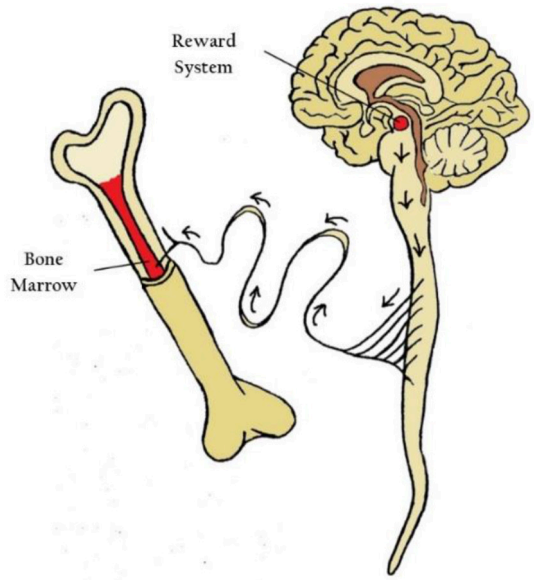


Figure 3

just as they reach every other part of the body. Therefore, they can influence what kind of immune cells develop in the bone marrow. In short, when we "switched on" the reward system in the brain, it affected the sympathetic nervous system, which reached the bone marrow and caused the new immune cells to be more aggressive and effective (Figure 3). This was why the immune cells became better at reducing cancerous tumors [5].

SUMMARY

Science just begins to explain how thoughts and emotions can influence our immune system and our health. It could open up new possibilities for treating diseases. Based on these and other findings, we could try to use new technologies to activate various areas of the brain and help cure diseases. There are many recent technologies which we might use to control brain activity, such as special helmets that generate a magnetic field aimed at a specific area of the brain. There are even special computer games meant to activate specific areas of the brain in a certain way.

Remember that this research is only the tip of the iceberg. Every experience, thought, or feeling, activate many processes in the brain and the body, and we do not fully understand most of them yet. These experiences affect each individual brain differently, and not everyone responds to placebos the same way. So, there is still a lot of work to do before we figure out the mechanisms of the placebo effect. In the meantime, it seems that the sentence "*It is all in your head*" is not just a figure of speech: it is a scientific statement that has a huge influence on our health and bodies.

ACKNOWLEDGMENT

The authors would like to thank Ph.D. student Maria Krot for drawing and editing the illustrations in this article.

ORIGINAL SOURCE ARTICLE

Ben-Shaanan, T. L., Azulay-Debby, H., Dubovik, T., Starosvetsky, E., Korin, B., Schiller, M., et al. 2016. Activation of the reward system boosts innate and adaptive immunity. *Nat. Med.* 22:940–4. doi: 10.1038/nm.4133

REFERENCES

1. Beecher, H. K. 1955. The powerful placebo. *J. Am. Med. Assoc.* 159:1602–6.
2. Rajagopal, S. 2006. The placebo effect. *Psychiatr. Bull.* 30:185–8. doi: 10.1192/pb.30.5.185
3. Pavlov, I. P., and Anrep, G. V. 1928. *Conditioned Reflexes: An Investigation of the Physiological Activity of the Cerebral Cortex*. London: Oxford University Press.
4. Ben-Shaanan, T. L., Azulay-Debby, H., Dubovik, T., Starosvetsky, E., Korin, B., Schiller, M., et al. 2016. Activation of the reward system boosts innate and adaptive immunity. *Nat. Med.* 22:940–4. doi: 10.1038/nm.4133
5. Ben-Shaanan, T. L., Schiller, M., Azulay-Debby, H., Korin, B., Boshnak, N., Koren, T., et al. 2018. Modulation of anti-tumor immunity by the brain's reward system. *Nat. Commun.* 9:2723. doi: 10.1038/s41467-018-05283-5

SUBMITTED: 28 March 2019; **ACCEPTED:** 12 April 2019;
PUBLISHED ONLINE: 09 May 2019.

EDITED BY: Idan Segev, Hebrew University of Jerusalem, Israel

CITATION: Hajjo H and Rolls A (2019) Let Us Use the Brain to Heal. Front. Young Minds 7:60. doi: 10.3389/frym.2019.00060

CONFLICT OF INTEREST STATEMENT: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

YOUNG REVIEWERS

ARIEL, AGE: 10.5

Hello, my name is Ariel, I live in Jerusalem, Israel. My hobbies are: to play piano, play at my grandma and grandpa's house playstation, and travel around the world while making new friends. My dreams are to visit Argentina and work as a scientist.

EINAV, AGE: 12

I do not like pizza, but I love broccoli. I have a twin sister. I study in a gifted class and especially like literature. I have been studying for 6 years in the acting studio. At the Sydney Lights Festival, the entire city was illuminated with the colors I chose.

GUY, AGE: 10

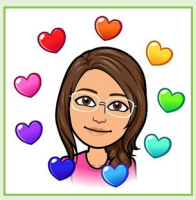
I hate school and I like snakes and riding my bike. I practice capoeira and aikido. When I am grown up, I wish to be a pilot.

MAAYAN, AGE: 12

I study in a gifted class. I was born in the United States and I lived in Australia for a year. I have a twin sister, and I have twin cats. The first solid food I ate was sushi. I am in a gymnastics class. I like to hike and swim except when there are leeches or fish in the water.

SHANI, AGE: 10.5

I am a fifth grade student at Alona elementary school. I participate in a program for gifted children. I love reading, especially Harry Potter books and I talk a lot! I love scientific experiments, cooking, baking, and experimenting with cooking and baking. I do not like cleaning the kitchen! I love riding roller blades and jumping on the trampoline. I love chocolate and I hate getting up in the morning. I love cats!



TAMAR, AGE: 10

I love reading and hate doing homework. My favorite dish is chocolate cake with hot chocolate inside, and I really dislike tomatoes. One of my dreams is becoming an actress.

AUTHORS

HAITHAM HAJJO

A medical student at the Technion's Faculty of Medicine. Part of the M.D./Ph.D. program in which I combine life science research with medical studies. I do my research in the labs of Professor Asya Rolls and Professor Naama Geva-Zatorsky, and I am interested in the interaction between the brain and the microbiota, the intestinal microbial population that plays an important role in maintaining normal

functioning of the body. Besides my studies, I really like classical Arabic poetry, hiking, and meeting new people.

ASYA ROLLS

I never knew I wanted to be a scientist, I just always enjoyed learning new things and biology fascinated me. Today I am a scientist at the Technion's Faculty of Medicine and my lab deals with the question of how thoughts and emotions affect the ability of the body to cope with disease. We try to understand phenomena, such as the placebo effect, in which people are cured with dummy drugs (such as a sugar pill). We explore what brain activity can produce these phenomena and how the brain directs healing processes in the body. I love to watch movies, I hate to get bored and I have two children, Uri and Anna, whom I hope will do something that excites them in life. *rolls.asya@gmail.com