BRAIN SCIENCE PODCAST

With Ginger Campbell, MD

Episode #77

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Interview with Fabrizio Benedetti, MD, PhD, Author of *Placebo Effects: Understanding the Mechanisms in Health and Disease,* and *The Patient's Brain: The Neuroscience behind the Doctor-Patient Relationship*

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INTRODUCTION

Welcome to the *Brain Science Podcast*. This is Episode 77, and I am your host, Dr. Ginger Campbell. My guest today is Dr. Fabrizio Benedetti. Dr. Benedetti trained as both a physician and a clinical neurophysiologist, but he is also one of the world's leading researchers on the neurobiology of placebos. He studies what goes on in the brain when one is given a placebo—which an inert, or inactive treatment.

Before I get into the interview I want to thank Dr. Harriet Hall, at the *Science-Based Medicine* blog, for bringing Dr. Benedetti's research to my attention.

Also, since this is a fairly technical episode, I want to remind you that you can find a free episode transcript and links to references in my show notes at brainsciencepodcast.com. You do not need any specific background knowledge to understand and appreciate this discussion, but I will warn you that we start with a detailed conversation about what placebo effects are, and what they are not. Even if you are an experienced clinician, you will want to listen to this introductory information, because it turns out that what Dr. Benedetti studies is quite different than what you might expect.

The neurobiology of placebos is a complex, but fascinating subject, so I will be back after the interview to review the key ideas, and to expand on a few key points that we didn't have time to discuss. Be sure to listen all the way to the end of the episode.

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INTERVIEW

Dr. Campbell: Fabrizio, I want to thank you for being on the *Brain Science Podcast*. Welcome!

Dr. Benedetti: Thank you very much for your invitation.

Dr. Campbell: I like to always start out with my guests by asking them to tell me a little bit about themselves; and in your case, I am particularly interested in how you happened to end up devoting your career to studying this unusual area of placebos.

Dr. Benedetti: Well, actually it is not an unusual area, because 'placebo' is a term which is very much used in medicine—in the medical sciences. The difference is that when we talk about 'placebo' and 'placebo effect,' we talk about clinical trials methodology. That's the main difference. I mean the novel approach to the placebo effect is that today we are studying, and actually we are understanding the placebo effect from a neurobiological perspective. That's the main difference.

I got involved in placebo research because I am a doctor, and about 15 years ago I used to run different clinical trials, particularly in pain; not only in pain, but also in motor disorders like Parkinson's disease, like dementia, for example—dementia of the Alzheimer's type or other types of dementia. And I was really fascinated by the placebo effect; particularly by the placebo group. Those patients who got placebo actually sometimes got better and improved much better than the active treatment group. So, I was very interested to understand why the placebo group gets better compared with the active treatment group.

But in this regard, there was a very important paper which was published in 1978[1] from a group at UCSF. The names of the three authors are Levine, Gordon, and Fields. They used a neurobiological, actually a neuropharmacological approach to the placebo effect, because they described for the first time the blockade of the placebo response (the placebo analgesic response; I'm talking about placebo in analgesia); and they showed that naloxone—I mean by blocking the opiate receptors, it is possible to block placebo analgesia.

So, this 1978 paper was very influential to me. And so, I decided to start a new line of research by using a neurobiological, a neuropharmacological, a neuroimaging approach to the placebo phenomenon.

Dr. Campbell: Well, as a physician, I share your fascination with this. And it's actually one of the things that drew me to your work. The other thing was that this summer I was on a panel at a conference that was talking about this, sort of

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[1] Levine JD, Gordon NC and Fields, HL (1978) "The mechanisms of placebo analgesia." Lancet, 2, 654-7. (Abstract). See also a follow-up paper: Levine JD, Gordon NC, Bornstein JC, and H L Fields HL (1979) "Role of pain in placebo analgesia." Proc Natl Acad Sci 76(7): 3528–3531 (full text).

in the context of the misuse, in terms of alternative medicine groups whose treatments, such as homeopathy, are basically placebo effect, but are trying to exaggerate what that means.

But getting back to your work, I obviously discovered your work through your books; and I'm curious about why you started writing books—because I know that's a lot of work.

Dr. Benedetti: It's a lot of work, you're right. But it is really fascinating and particularly rewarding work. I like writing; I like writing, a lot. So, I decided to write, first, a book[2] with Oxford University Press, about placebo effects, of course, which is my main topic of research. And there is a second one, actually. The second one is *The Patient's Brain*, which describes the relationship between doctor and patients. I mean in general—a doctor, in general. It would be better to say 'of professionals and patients'—from a neurobiological perspective.

So, I decided to write these two books because I believe that today we are in a very good position to describe, from a biological and from an evolutionary approach, the doctor-patient relationship, and the placebo effect, itself.

Dr. Campbell: Who's your target audience for these books?

Dr. Benedetti: The audience is a mixed audience, actually: all physicians, of course; psychologists; I would say philosophers—particularly for the second one, *The Patient's Brain*. If you have a look at it, the approach to the doctor-patient relationship is quite unusual, because it is a sort of approach which starts from mind-body interaction—the mind-body problem. So, I think that the audience is mainly represented by physicians and psychologists, of course, but also by philosophers, and I would say anybody who is interested in the mind-body problem and the doctor-patient relationship—and social interactions, as well;

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[2] *Placebo Effects: Understanding the mechanisms in health and disease* (2009) by Fabrizio Benedetti

because, particularly in the second book, *The Patient's Brain*, the first one or two chapters are about evolution.

I start from the evolution of defense mechanisms in unicellular organisms—many, many, many years ago. That's very interesting, because the doctor-patient relationship is sort of a social mechanism of defense. And this social mechanism of defense has evolved from unicellular organisms. Of course, a unicellular organism actually is interested in withdrawal; for example, a part of the cell withdraws from the noxious stimulus in a social interaction. The behavior is, of course, much more complex, but the meaning of the response is exactly the same.

Dr. Campbell: Survival.

Dr. Benedetti: Survival, and withdrawal from a noxious stimulus, of course—from a noxious and, more in general, from a dangerous stimulus.

Dr. Campbell: I enjoyed *The Patient's Brain*. I actually have to admit that there are a couple of chapters in there I haven't had a chance to read yet, but I'm looking forward to reading the rest of the book. I sort of focused on the therapeutics chapter, Chapter 6, because that included what seemed to me as some updates from the book, *Placebo Effects*.

Dr. Benedetti: Yes, you are right.

Dr. Campbell: I want to focus today on some of the experiments you've done, but first I think that we probably should talk a little bit about definitions. You use the phrase, 'placebo effects,' on purpose—as opposed to 'the placebo effect.' Do you want to talk a little bit about why you emphasize this idea?

Dr. Benedetti: Which kind of idea?

Dr. Campbell: The idea that 'placebo effects' is a plural—that there's more than one.

Dr. Benedetti: Well, the title of my first book, yes, is plural—'*Placebo Effects*,' not '*The Placebo Effect*,' because there is not a single placebo effect, but many. The reason for that is that there are many placebo responses, there are many placebo effects because there are different mechanisms, and these different mechanisms occur in different conditions—in different medical conditions and different therapeutic interventions.

So, for example, we cannot talk about 'the placebo effect.' You cannot ask the question: what is the mechanism of the placebo effect. It would be better to ask: what are the different mechanisms across a variety of conditions—of medical conditions and therapeutic interventions—because there are actually many, many mechanisms.

Sometimes a placebo effect takes place because there is expectation. The patient expects a therapeutic benefit, and this kind of expectation actually has an effect on the brain and the body. The connection between expectation and real improvement that may occur is due at least to two mechanisms; you see that there is not a single mechanism.

The first mechanism is a reduction of anxiety. And this is not surprising at all, because if you tell a patient, 'Now your pain is going to decrease; now I am going to give you a powerful pharmacological agent and your pain is going to decrease in the next few minutes,' actually this a powerful anxiolytic procedure. So, sometimes there is a reduction in anxiety in the patient.

There is also another mechanism, which is another link between expectation—what you expect and what you get. The link is the activation of a reward mechanism; in particular, from a neurobiological point of view, the activation of the nucleus accumbens. The nucleus accumbens is a very important region in the brain in which there is a release of dopamine. When you expect a reward there is an activation of the nucleus accumbens and a release of dopamine.

This is not only true for the placebo effect, it is true for natural rewards; natural rewards in animals, including man, of course. Natural rewards are food, water, sex (sex is a powerful reward), money (money, in human beings, of course, not in animals; money is a cultural reward). And all these rewards activate the nucleus accumbens.

When you give a placebo—and actually when you give any drug, or any medical treatment—the reward is the treatment itself; the reward is the expectation that in a few minutes you will feel better. So, the clinical improvement, the clinical benefit is a reward in the same way as food, sex, and money are rewards which activate the nucleus accumbens.

There are many other mechanisms, actually. I mentioned only a couple of mechanisms: reduction in anxiety and activation of reward mechanisms. But there is one more important mechanism, which is learning. Actually a placebo response is a learning phenomenon.

If you give a placebo for the first time to a patient, sometimes there could be a response, some other times there is no response; sometimes the response is statistically significant, some other times it is not. But if you give a placebo after repeated effective therapies—for example, if you give morphine on Monday, and if you give morphine again on Tuesday, and morphine again on Wednesday, but on Thursday you replace morphine with a placebo, well, you can bet that almost 100% of patients will respond. So, learning is very, very important.

And in conclusion, the reason why I prefer to use the term, 'placebo effects'—the plural—is that there is not a single mechanism. Sometimes the patients feel better after placebo administration because there is a reduction of anxiety. But some other times their improvement has nothing to do with anxiety; it is because there is an activation of the reward mechanism. And some other times neither anxiety nor reward mechanisms are involved, but the patients feel better because it is a sort of learning mechanism.

Dr. Campbell: Could you spend a few minutes talking about what you do not mean by 'placebo effects'— in other words, the stuff that needs to be eliminated to look at the true placebo effect?

Dr. Benedetti: Yes, that's a very important question; and it is a very complex issue, because to the clinical trialist and to the neurobiologist—to the neurophysiologist—a placebo effect, or placebo response, means two different things. To the clinical trialist, a placebo effect means any improvement which may take place after placebo administration. To the neurobiologist, a placebo response, or placebo effect means only something active in the brain happening after placebo administration: learning, anxiety reduction, activation of reward mechanisms. In fact, when you give a placebo—and, actually, when you give any drug, not only a placebo—the improvement that may take place after placebo or drug administration can be due to plenty of factors.

For example, it could be spontaneous remission. This is a very common error in clinical trials; a very common mistake: you give a placebo or you give a drug just before the reduction of a symptom, and you believe that the placebo or the drug was effective, but actually the pain or the symptom would have vanished anyway. So, spontaneous remission is not a placebo effect.

There is another factor in clinical trials, for example; we call it 'regression to the mean.' Regression to the mean is a statistical phenomenon in which, when there is a second evaluation of the symptom, usually the patient tends to the mean of the general population. This is statistics; it is not a real improvement.

There is another factor which is quite important in clinical trials in which an improvement may take place, and this factor is bias—both experimentalists' and patients' bias. For example, usually the patient tends to please the experimenter, because he or she is involved in a clinical trial, he or she receives many attentions, so usually there is a tendency to please the experimenter, to please the doctor. This is not a real placebo response; this is just bias.

For example, if you ask a patient, just before placebo administration or just before drug administration, 'Please rate your pain from 0, which means no pain, to 10, which means unbearable pain,' if he or she says, '7,' and then you give a placebo and you ask again, 'Rate your pain,' and now he or she says, '6,' is this a real reduction? I'm not sure. I mean probably it is a sort of bias; it is a sort of ambiguous response. Ambiguity is very, very important.

So, in conclusion, there are many factors in a clinical trial: spontaneous remission, regression to the mean, experimentalists' and patients' biases. These are not placebo effects. This has nothing to do with the placebo response—the real placebo response. The real placebo response, the real placebo effect is a psychobiological phenomenon. It is something active happening in the brain after placebo administration: like learning, like anxiety reduction, and such like.

Dr. Campbell: But the things you just mentioned—regression to the mean, biases, and spontaneous remission—are actually the things that, when we do a clinical trial, we are trying to filter out, to determine whether or not our active treatment really works. So, they are, you might say, intentionally part of the placebo groups' data when you're doing a clinical trial. I guess, as you said in both of your books, that means that clinical trials are not a good way to study the actual placebo effects—because that's not their goal. So, what do you do to actually get rid of these things you just told me about, and find out the mechanisms of the real placebo effects?

Dr. Benedetti: Well, you can do a lot of things. First and foremost what you have to do is to study a placebo response in the laboratory setting, not in the clinical trial setting; because, as you said, actually you cannot rule out spontaneous remission in a clinical trial. It is very important to stress that the clinical trial and, usually, drug companies, are interested in the possible difference between the new drug—the new therapy—and the placebo; but they are not interested to understand why there is an improvement in the placebo group. The only thing they are interested in—I am referring to drug companies and clinical trialists, of course—what they are interested in is the difference: if the new drug or the new non-pharmacological therapy is better than a placebo, so it means that it works.

If you want to study the mechanism, or if you want to study, not so much the active treatment group, but you want to study the placebo group, you have to move from the clinical trial setting to the laboratory setting. By 'the laboratory setting,' I mean that you have to bring the patients into the laboratory; you have to study them for only a few hours. For example, if you want to perform a brain imaging study, or if you want to perform a neuropharmacological study, just to describe the biochemical pathways which are involved in the placebo effect, you have to study the patient; or otherwise you can also study a healthy volunteer, and healthy subjects in the lab.

So, as you said before, and as I say in my books, the clinical trial setting is not a good model to understand the biological and the psychological mechanisms of the placebo effect, because many things happen in a clinical trial, and so you cannot use the appropriate controls to rule out spontaneous remission, to rule out regression to the mean, to rule out experimentalists' and patients' bias. So, if we want to understand the mechanisms in what is going on in the patient's brain when you give a placebo, when you give either a positive or a negative verbal suggestion, you have to study the patient or the healthy subjects in the laboratory. This is very, very important.

Dr. Campbell: And you described in your book—I think you called it the 'balanced trial.'

Dr. Benedetti: 'Placebo balanced design.'

Dr. Campbell: Yes. Would you talk about that for just a minute? And then we can go into some of your experiments. I just think that's a good way of illustrating the difference of how your trials would be designed, compared to say a clinical trial; because what you do in this balanced trial is something we couldn't do in a clinical trial.

Dr. Benedetti: Yes, you are correct. The balanced placebo design is quite interesting, but it is also quite expensive, because actually you need four groups of patients, not only two groups of patients. The balanced placebo design is quite fascinating because you can study and, hopefully, understand the influence of verbal suggestions—expectations—on the action of drugs.

The balanced placebo design, after all, is very simple, because you have four groups of patients. The first group of patients receives placebo, but it is told it is the active drug. The second group receives placebo, and it is told it is actually the placebo; so, it is told the truth. The third group receives the active treatment, and it is told it is placebo. And the fourth group receives the active treatment, but it is told it is the active treatment.

You see, it is a sort of combination between what you get and what you are told. In this way you can study the modulation of the drug action by verbal suggestion. Just imagine a situation in which you give an active treatment, but you tell the patient, 'Now I am going to give you a placebo.' This means that the patient does not expect any effect, because he or she is told that it is a placebo, not the real drug. So, this makes a really big difference.

There is a beautiful brain imaging study which was performed in the United States at the National Institute on Drug Abuse, by Nora Volkow. They gave methylphenidate to cocaine abusers[3]. It makes a big difference if you give the methylphenidate and you tell the patient, 'This is methylphenidate,' or, 'This is a placebo.' The difference is as large as 50% of the metabolic response of the brain; which means that if you give methylphenidate and you measure metabolic activity in the brain of cocaine abusers, there is a reduction of the effect, compared to methylphenidate with the verbal suggestion that it is methylphenidate.

So, this means that expectation makes a big difference. There is a sort of additive effect between expectation—between this psychological component—and the real pharmacodynamic effect of the drug.

Dr. Campbell: Right.

Dr. Benedetti: So, this is the balanced placebo design, basically. It has been used mainly in all those situations, all those medical conditions in which the psychological component is supposed to be large; like tobacco, for example, like alcohol, and drug abuse, as well. And so, the balanced placebo design has very much been used in these medical conditions.

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Dr. Campbell: I want to talk about some of the experimental findings. And you have alluded to a few of them. We're running a little bit short on time, compared to what I was expecting, so I'm going to skip pain for right now—I'll come back to it if we have time—and ask you to talk about the experiments with Parkinson's disease, because I think these are really fascinating, and this is information that

[3] Volkow, ND, Wang JG, Ma Y, Fowler JS, Zhu W, Maynard L et al. (2003) Expectation enhances the regional brain metabolic and the reinforcing effects of stimulants in cocaine abusers. Journal of Neuroscience, 23, 11261–8. (Full Text)

most of my listeners really won't know anything about. Can you talk about that? I'm talking about the deep brain stimulation, and what you've seen with the single-neuron recordings.

Dr. Benedetti: Well, in Parkinson's disease, basically there are two approaches. The first approach is through PET—positron emission tomography. The second approach is through recording from single neurons during the implantation of electrodes for the surgical treatment—deep brain stimulation—of Parkinson's disease. In the first case, if you use PET, and you measure dopamine release in the striatum—which is a region of the brain which is pretty important in Parkinson's disease …

There is a beautiful study which was published in 2001[4] by a Canadian group in Vancouver. They found that after placebo administration actually there is a huge release of dopamine in the nucleus accumbens. Just to give you an idea of this huge release of dopamine, there is an increase in extracellular dopamine as large as 200%—which is really huge. To make a comparison with a drug, that corresponds, more or less, to a full dose of amphetamine. This happens in the striatum. And this release of dopamine has a dramatic effect on the activity of neurons in the basal ganglia.

We approached this problem by using single-unit—single neuronal—recordings during the implantation of electrodes in Parkinson's disease. And in Parkinson's patients we implanted electrodes (I am both a basic and clinical neurophysiologist, so I also perform intraoperative neurophysiology); and during the implantation of a couple of electrodes in the subthalamic nuclei—the left and the right subthalamic nucleus—in Parkinson's patients, we were able to record from single neurons just before, during, and right after placebo administration. And what we found was that after this huge release of dopamine in the striatum

[4] de la Fuente-Fernández R, et al. (2001) Expectation and Dopamine Release: Mechanism of the Placebo Effect in Parkinson's Disease. *Science* **293**, 1164. (Abstract)

there is a dramatic change in neuronal activity in the brains of the Parkinson's patients.

Just to summarize what is going on in the basal ganglia, there is a dramatic decrease of the activity of neurons in the subthalamic nucleus, but there is a dramatic increase of activity in the thalamus—in the motor thalamus. This increase in the motor thalamus is reflected in an increase in the motor cortex, and the subsequent improvement in motor symptoms, which are typical of Parkinson's disease. Now we know part of the circuit of the neuronal network which is involved which is modified by placebo administration in Parkinson's disease.

Dr. Campbell: To make sure I have this clear, normally—or, I guess, 'normally' is a bad word—in a Parkinson's patient the subthalamic nuclei is overactive?

Dr. Benedetti: Yes, that's correct.

Dr. Campbell: And then, when you use the stimulator, it decreases the activity of these neurons, and that leads to motor improvement. And when you use placebo, you can see that same effect?

Dr. Benedetti: Yes, absolutely correct. Just let me explain again in a few words. Deep brain stimulation intervention means that you stimulate the subthalamic nucleus, and the stimulation of the subthalamic nucleus leads to a decrease in the activity of neurons. If you give a placebo, you can get the very same effects.

Dr. Campbell: And the placebo in this case is telling the patient that the stimulator is firing, when it's really not?

Dr. Benedetti: No. In this case, in this paper—probably you're referring to the paper published in *Nature Neuroscience* in 2004[5]—in that case the placebo was a subcutaneous injection of saline solution (and, of course, saline solution is not an anti-Parkinson's agent) along with verbal suggestions of motor improvement.

Dr. Campbell: OK. But the patient already has the electrodes, because they have the stimulator in place.

Dr. Benedetti: Yes. In this case the electrodes are not used for stimulation, but are used to record from single neurons.

Dr. Campbell: OK.

Dr. Benedetti: So, we have the electrodes in the subthalamic nucleus, which, later on, will be used to stimulate. But we give a placebo; the electrodes are used to record from single neurons. We record from single neurons. We give the subcutaneous injection with saline solution, which is the placebo, along with verbal suggestion of motor improvement, and we record what is going on in the neurons of the subthalamic nucleus.

Dr. Campbell: OK, this is very significant, though, because nobody has done any of these kinds of actual recordings in studying placebo effects, before this experiment. Would that be accurate?

Dr. Benedetti: Yes. That was the first demonstration of the placebo effect at the level of single neurons.

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[5] Benedetti F, Colloca L, Torre E et al. (2004) Placebo-responsive Parkinson patients show decreased activity in single neurons of the subthalamic nucleus. *Nature Neuroscience*, **7**, 587-88. (Abstract)

Dr. Campbell: So then, later on, did you use the same patients or similar patients to do the experiment that I was thinking about—the one where the patient thinks that the stimulator is on, when it's really not?

Dr. Benedetti: Those are different patients, actually; because we also use a different procedure. I mean we study the placebo response in Parkinson's disease with different approaches. Probably you are referring to our series of papers in which the placebo was the stimulator on or off.

Dr. Campbell: Yes, that's the one I was thinking of.

Dr. Benedetti: Yes. That's another experiment; that's correct. In that case the placebo is not the subcutaneous injection of saline solution, but in that case—that's another study—the placebo is the stimulator which is off, but the patient believes it is on.

Dr. Campbell: Right. And you saw similar results.

Dr. Benedetti: Yes, we see similar results. And in that case we can also study the nocebo effect[6], which is the opposite phenomenon. So, you expect a negative outcome, and actually what you get is a real negative outcome. In that case the placebo—in Parkinson's disease; in Parkinson's patients—the placebo is that you turn the stimulator off, but the patients believe it is on. The nocebo is the opposite situation: you turn the stimulation on, but actually the patient believes it is off. Sometimes it is sufficient—this expectation; the belief of the patients—to reduce the effect of deep brain stimulation. If you stimulate the subthalamic nucleus, and if you switch on the stimulator but the patient does not know anything, because he believes that the stimulator is still off, this belief reduces the effect of DBS—of deep brain stimulation.

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[6] Benedetti F, Lamotte M, Lopiano L and Colloca L (2007) When words are painful--Unravelling the mechanisms of the nocebo effect. *Neuroscience*, 147, 260-71 (Abstract)

Dr. Campbell: I don't think we can underestimate the importance of these studies, because I think the average physician thinks that placebo effects are totally at the cortical level—pain, for example; we perceive pain at the cortical level—and I don't think the average physician realizes that the placebo effect could be happening deep down in our brain. Even if expectation is involved, this is a recording deep in the brain—correct?

Dr. Benedetti: Yes, I think you are correct, because very often there is misunderstanding and misconception about what placebo effect is. As you said before, the average physician believes it is something happening at the level of the cortex; for example, at the level of subjective perception, like pain. This was actually the main criticism until several years ago; and the main criticism was that the main experimental model was pain. And you know that pain is a subjective experience, so it is subject to bias, it is subject to a lot of psychological influences.

But right after pain, Parkinson's disease (not only Parkinson's disease, but the immune system, as well; the endocrine system, as well; the cardiovascular system, as well) has been used as a model. And we have learned in the past few years that what we have seen for pain is also true for Parkinson's disease, the immune system, the endocrine system, and so forth. So, there has been a shift in the intellectual approach to the placebo effect by many physicians, because what we have learned is that pain is not a special case, subjective symptoms are not a special case; we see the very same effect for the motor systems, like Parkinson's disease, or release of immune mediators, as far as the immune system is concerned.

[music]

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Dr. Campbell: Let's talk a little bit about the—would it be fair to call the immune system an example of an unconscious placebo effect?

Dr. Benedetti: Yes, that's quite an interesting topic—I mean the unconscious placebo response.

Dr. Campbell: Those are different mechanisms, right?

Dr. Benedetti: Yes, absolutely. Well, actually there are two types of responses: conscious and unconscious placebo responses. When we talk about conscious placebo responses, actually we talk about expectation. So, you have to trust your doctor, you have to believe in the therapy you are getting, you have to expect, consciously, something. But there is also an unconscious placebo response. The mechanism is completely unconscious; what we call 'classical conditioning,' or 'Pavlovian conditioning,' from Ivan Pavlov.

I can try to explain with an example which is quite straightforward. For example, when you give an aspirin pill, there is the active agent inside the pill, which is the acetylsalicylic acid, and there is a psychosocial context. So, what is the psychosocial context of an aspirin pill? For example, the psychosocial context is its shape, its color. An aspirin pill usually is white and is round. So, if you associate the shape and the color of a pill with the pharmacodynamic effect of the pharmacological agent which is inside the pill, after many associations you can bet that any pill which is round and white can produce the very same effects of the pharmacological agent which is inside the pill.

So, this is completely unconscious. This is an unconscious mechanism. You don't need to believe your doctor; you don't need to trust the therapy you are receiving. It is a completely unconscious association between two stimuli: the pharmacodynamic action of the drug on the one hand, and on the other hand, the psychosocial context, for example, the shape and the color of the pill.

Dr. Campbell: Then in unconscious placebo effects, though, that are based on classical conditioning, this has been demonstrated in animals also?

Dr. Benedetti: Oh, yes; it is demonstrated in animals, as well. It is interesting that one of the first neurobiological approaches to the placebo response was published in *Science* in 1962[7]. The title of the paper was, "The Biology of the Placebo Effect in the Rat." That approach, that experiment was quite interesting, because the experimenters gave a pharmacological agent interfering with motor behavior, many times; but at a given point during the experiment they replaced the real pharmacological agent with saline solution or with distilled water. And they found the very same response as with the previous drug, interfering with motor response.

Probably this is one of the first studies to use this neurobiological approach in animals. So, in animals there are strong, powerful, robust placebo responses; but there is a main difference that in animals the mechanism is classical conditioning, is Pavlovian conditioning, it is not expectation, of course. It is very difficult to say that a rat has expectation about the therapeutic benefit. So, it is a completely unconscious mechanism.

Dr. Campbell: Actually, I guess this is a leading question. I want to lead you into the study you described of how, when you're dealing with an unconscious mechanism like the immune system, expectations can't affect the results. You just talked about how, in pain, if the person thinks they're not getting the pain

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[7] Herrnstein RJ, (1962) Placebo Effect in the Rat. Science 138, 677-678. (Abstract)

medicine, then even real pain medicine may not work as well. But that's not true when you're dealing with an unconscious effect, like say a drug that affects your immune system. Could you talk about that a little bit? Because it illustrates the importance of a difference between those two mechanisms.

Dr. Benedetti: Yes, that's true. As far as we know today, these two mechanisms—on the one hand, expectation, which is a conscious mechanism; and on the other hand, conditioning, which is unconscious—can be involved in different situations. In general, we can say today that conscious expectations are important for conscious physiological functions, like pain, like motor performance. On the other hand, we can say that unconscious—classical—conditioning is more important for unconscious physiological functions, like hormone secretion, like activation of different immune mediators.

I would like to give you an example—a very quick example[8]. If you tell a patient, 'Now I'm going to give you a drug which will increase your GH—growth hormone—so, your GH will increase, because this effect is due to the drug I'm going to give you,' these verbal suggestions and expectation of GH increase have no effect. This is not surprising at all, of course. But if you perform a conditioning—a pharmacological preconditioning procedure—for example, you give a drug increasing GH on the first day, and you give the very same drug on the second day, both days you can see, not surprisingly, an increase in GH; but on the third day you replace the drug with a placebo, now you can see a placebo increase of GH.

And this occurs irrespective of what the patient expects. For example, after this preconditioning procedure, if you give a placebo, along with verbal suggestions of decrease, there is an increase anyway. So, this means that expectation has no effect on unconscious physiological functions. It is a completely unconscious

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[8] Discussed on pages 203-4 in *The Patient's Brain: The neuroscience behind the doctor-patient relationship* by Fabrizio Benedetti (2011)

mechanism. What you expect does not matter; what matters is the previous conditioning you performed.

Dr. Campbell: And similar results have been obtained with immune system type experiments. True?

Dr. Benedetti: Yes.

Dr. Campbell: What I thought about when I read this was the idea that was popular back in the early, I guess it was in the '80s, when some people were trying to treat cancer by visualization—telling people to visualize that their immune system was attacking their cancer. It seems to me that these results indicate that that approach would probably not work.

Dr. Benedetti: Yes. I agree; I very much agree. That's more quackery; it's not a real approach. This is a very important point. Probably we can return to this point later; but this is a very important point. I am a doctor, it is true, but I am mainly a neurophysiologist, so I use the placebo response as a model to understand how our brain works. I am not sure that in the future it will have a clinical application. This is a very important point—a translational research: can we use placebo in routine clinical practice?

Well, sometimes it works; but that's not the important problem. The important thing right now is to understand how our brain works. And I would say the placebo response is a fascinating phenomenon, because it is a sort of melting pot of concepts, of ideas for neuroscience. So, if you use a placebo response, you can understand a lot of brain functions, like anxiety, like social learning, classical conditioning, reward mechanisms, and so forth. So, the clinical application is—I think in English you say it is a 'different kettle of fish.'

Dr. Campbell: But I do think that this information is important for clinicians; especially what you've found about expectation and how it can affect our active treatment. Just the fact that giving somebody real pain medicine, when they don't know they're getting it, decreases its effectiveness, that's a big deal. I'm an emergency room physician. I've been talking about this stuff with my nurses, saying things to them like, 'This is why it's important to tell the patient when you give them the pain shot,' and, 'What you tell them really matters.'

You were talking earlier about how some of the effects are decreased anxiety and stimulation of the reward circuitries. I've been talking to them about this, not in so much detail, but to say that explains why patients seem to get better as soon as you give them the shot, even though you know the shot didn't work that fast. Nurses have a tendency to think that that means maybe the patient was faking, or something. So, I've been saying to them that's not what's going on; it's just showing that there are other things going on that work faster. So, I think understanding this stuff could be very important to clinicians—both psychologists and physicians.

Dr. Benedetti: Oh, definitely. Yes, of course, it is very important. I would say that the take-home message for clinicians, for physicians, for all health professionals is that their words, behaviors, attitudes are very important, and move a lot of molecules in the patient's brain. So, what they say, what they do in routine clinical practice is very, very important, because the brain of the patient changes sometimes. As you said, of course, there is a reduction in anxiety; but we know that there is a real change. There is a real change in the patient's brain which is due to—in a single sentence, we can call it the 'ritual of the therapeutic act.'

The ritual of the therapeutic act is very complex. In the ritual of the therapeutic act there is a doctor; in the ritual of the therapeutic act there are drugs, there are syringes. Sometimes there are very complex machines, like an MRI machine, for example. All these social and sensory stimuli constitute what we call the 'ritual of the therapeutic act;' and the ritual of the therapeutic act communicates and tells the patients that a therapy is being performed. And this is very important because it induces expectation in the patient. So, absolutely, it is very, very important for a clinician.

What I meant before is that some people all over the world are trying to use a real placebo procedure in routine clinical practice. And I would say that in this sense it is very difficult to say right now whether or not there will be a real clinical application. I'll try to explain better.

For example, many people, including my group actually, are trying to use this conditioning mechanism to the advantage of the patient. Just imagine a conditioning procedure: for example, in cancer pain, what you want to do is to enhance the analgesic effect, but you also want to administer small doses of morphine, for example—of narcotics in general.

So, what you can do using a conditioning placebo protocol, you can give morphine, for example, for three, four, five days in a row, and then you replace morphine with a placebo, for example one or even a couple of days. Then you reinforce, again with morphine—with the real pharmacological agent—and then you replace again the pharmacological agent with placebo. With this placebo conditioning procedure, in the long run you can reduce the intake of toxic drug, like morphine.

For example, in 2001 we ran an experiment like this in routine clinical practice in postoperative pain, and we were able to reduce bupenorphine by a little more than 30%—33%, 34%. You can use this conditioning mechanism in routine clinical practice, but it's not easy to say right now whether or not there will be a real therapeutic paradigm, a real therapeutic protocol using placebos in routine clinical practice.[9]

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[9] Pollo A, Amanzio M, Arslanian A, Casadio C, Maggi G and Benedetti F (2001) Response expectancies in placebo analgesia and their clinical relevance. *Pain*, **93**, 77-84

Dr. Campbell: Yes, I can see that; and I can see why that could be very complicated. For example, if you're working with a cancer patient and you're doing that, and the cancer patient, for whatever reason, doesn't have a good placebo response—they're a person in the group who, that component isn't very big in them—and on the days they're not getting the real pain medicine they may be having more pain, which not only is undesirable, but also maybe leads to anxiety. Maybe they think on that day that they're getting worse, because their pain is getting worse. I can see how this could be a very complex issue.

Dr. Benedetti: Yes, it's very complex, of course.

Dr. Campbell: I do have a lot of listeners who are physicians, and psychologists, and other people who take care of patients, including nurses—who are, of course, very important—but a lot of them are also just regular people. What would you think that the implication is to those of us maybe coming from the point of view of a patient? Because each one of us could, at some point in our lives, be on the patient end of this. What are the implications for the patient?

Dr. Benedetti: Well, that's a tough question. It's not easy to answer, because the therapeutic effect after placebo administration very much depends on the doctor, on the nurse, or other professionals. It does not depend on the patient, really.

Dr. Campbell: What about knowledge? Does your research imply that if a person gets a diagnosis, that it is good for them to learn more about their disease?

Dr. Benedetti: Yes, diagnosis is another very important issue; negative diagnosis, particularly. The communication by physicians, the communication of negative diagnosis, like cancer, for example, is really powerful, and they induce a really powerful nocebo effect. For example, a mild pain can turn into a severe pain after a severe diagnosis, because there is, for example, an increase of the focus of attention on the part of the body where the cancer is located.

And so, of course communication is very, very important. But unfortunately this doesn't depend on the patients; it very much depends on health professionals. That's a very important issue. I would like to say that it is very important to teach communication to medical students—placebo effects and doctor-patient relationship to medical students. At least here in Europe, we feel this problem a lot—it is very, very important—with the knowledge about the importance of communication, of negative diagnosis, of the administration of the therapy, of the surgical procedure. That's very, very important. It increases the relationship, the interaction, the communication between health professionals and patients, of course.

There is one more thing. You talk about knowledge about the treatment, knowledge about the therapy. Very quickly, just in 30 seconds: We used a completely different approach through study of placebo effect (probably you know about that); the hidden administration— open and hidden administration. If you give a hidden injection of morphine—which means that the patient does not know that anything is being given; this means that the patient does not expect anything—the effect of morphine is reduced.

So, this hidden administration of drugs and, more in general, the hidden administration of medical treatments, is a very important issue, because it stresses the importance and it emphasizes the importance of communication and knowledge about the therapy. So, we have to enhance the expectations of the patients in order to enhance the effect of the therapy—the treatments that we give in routine medical practice.

Dr. Campbell: Yes. And unfortunately, I don't know about Europe, but here in the United States the system is really not designed for that; it's getting worse and worse, because the less time doctors have with their patients, this is what gets lost. That's why I think it's very important to get this information out there, that this is as important as having effective treatments; we have to have effective interactions with our patients.

We're just about out of time. Is there anything else you'd like to share before we stop, Fabrizio?

Dr. Benedetti: I don't think so. Actually, when you start talking about placebo effects, you can approach the placebo response from so many perspectives. You can talk about everything: you can talk about medicine, you can talk about ethics, you can talk about neurobiology, you can talk about philosophy. So, I think one hour is not enough to cover all the issues which are involved.

Dr. Campbell: I agree; absolutely. But I think that you've given my listeners a wonderful introduction to your field; and I really do appreciate you taking the time to talk with me.

Dr. Benedetti: Thank you very much.

[music]

I want to thank Dr. Benedetti again for talking with me about the neurobiology of placebos. I hope this conversation has given you a good introduction.

Now I want to take a few minutes to review and expand on Dr. Benedetti's remarks. The focus of our conversation was the study of placebos as a tool for understanding how our brains work. But, of course, this is a relatively new development. Historically, placebos have been an important component in what has come to be known as the 'randomized clinical trial.' As we mentioned during the interview, these sorts of trials are intended to determine whether treatments really work.

The idea is that problems like bias can be eliminated by comparing a treatment group with a placebo group, where both groups are treated identically, except for that the treatment group gets the drug and the other group gets a placebo—an inert substance. According to Dr. Benedetti's first book, *Placebo Effects*, the first use of a placebo was in a study done in 1834 [10], in which homeopathic treatment was compared to a placebo which was made from potatoes, thus beginning a long line of studies that show that homeopathy's effectiveness is equal to a placebo.

But getting back to what's going on in the brain, as we mentioned during the interview, clinical trials are not designed to discover the mechanisms of placebo effects. For that, we need to go into the lab with a different experimental protocol. In the interview, we talked about two protocols that are used to study placebo effects.

One is the balanced placebo study, where there are four groups: two groups which get placebo, and two groups which get active treatment; where half the groups are told that they got active treatment, and the other two groups are told that they got placebo—so all four possibilities. Even without added expense, it's not hard to see why this wouldn't be practical in a clinical setting.

The second protocol, which Dr. Benedetti mentioned briefly near the end of the interview, is the use of hidden administration of both drugs and placebos. In this situation it's not particularly surprising that placebo effects are reduced; but the most significant finding is that hidden administration actually reduces the effectiveness of active treatments. Thus, as Dr. Benedetti said, the take-home message for clinicians is that our words, behavior, and attitudes are very important, and as he said, "... move a lot of molecules in the patient's brain."

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[10] Actually sham treatments were used to discredit both mesmerism and "perkinism" (a treatment with metal rods) early in the 19th century. However, Armand Trousseau appears to have introduced the use of inert pills (placebo pills) in 1834. (the original paper was in French). See *Placebo Effects: Understanding the mechanisms in health and disease* by Fabrizio Benedetti, page 4.

Now, I want to return to the subject of pain. Even though we didn't have time to talk much about pain, it is the most intensely studied area with regards to placebos, and a great deal has been uncovered about the mechanisms of placebo pain relief. First, as Dr. Benedetti mentioned, expectation makes a big difference.

Remember that we mentioned that a hidden administration of real pain medicine is less effective. This is true whether the real medicine is a narcotic or a non-narcotic pain medicine. Also, because placebo analgesia can be blocked by giving naloxone (also known as Narcan), which is an opiate antagonist, or opiate blocker, it appears that the endogenous opiate pathways are involved in placebo analgesia.

Because so much has been published[11] about these opiate pathways, I wanted to make sure that their importance is not overshadowed by some of the other mechanisms that we discussed, such as anxiety reduction, reward mechanisms, and learning. It is reasonable to assume that if we are studying conscious physiological processes, some combination of these mechanisms will be involved.

An interesting demonstration of the role of expectation was published by Linde in 2007[12]. This was a study of sham acupuncture vs. real acupuncture. This study showed that it really didn't matter whether the patients got real acupuncture or sham acupuncture; what mattered was whether they thought they were getting real acupuncture[13].

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[11] See both of Benedetti's books for numerous references.

[12] Linde K, Witt CM, Streng A et al. (2007) The impact of patient expectation in four randomized control trials of acupuncture in patients with chronic pain. *Pain*, **128**, 264-71. (Abstract)

[13] Bausell RB, Lao L, Bergmans, Lee WL and Berman BM (2005) Is acupuncture analgesia an expectancy effect? Preliminary evidence based on participants perceived assignments in two-placebo-controlled trials. *Evaluation and the Health Professions*, **28**,9-26.

Clarification: Linde's study indicated that that the best predictor of a good response was whether the patient believed that acupuncture was an effective treatment. It was actually Bausell (2005) who showed that those who believed they were getting real acupuncture had the best responses. Both studies support the conclusion that the effectiveness of acupuncture represents a placebo effect related to expectation.

Now, one reason I didn't ask Dr. Benedetti to talk about pain was that I wanted to make sure that we had time to talk about his work with Parkinson's disease. I want to emphasize several key ideas here. While we can still classify Parkinson's disease as affecting conscious processes, there are several ways in which the research differs from that done with pain.

First of all, it involves motor function, rather than perception. Second, even without the single-neuron recordings, it is possible to measure motor improvement with an objective scale—which overcomes the common objection that placebo responses are just figments of the patient's imagination, or 'all in their head,' so to speak.

The single-cell recordings are significant, not only because they represent an objective measurement of a placebo effect, but because, as I mentioned before, they're occurring deep in the brain, in the subthalamic nuclei. This area of the brain is outside of conscious control. This means that even placebo effects that involve conscious processes can lead to changes in parts of the brain beyond consciousness.

This brings me to an even more intriguing phenomenon: the fact that unconscious placebo effects have been measured in both humans and in animals. An interesting example in animals was found in a study of dogs, which involved the injection of morphine. When you inject dogs with morphine, it causes them to salivate. In this one experiment, the dogs were given morphine injections for several days, and then they were given a placebo shot, and the same salivation was observed—thus, the placebo effect[14].

Now, when it comes to humans, the key idea is to remember that when we are studying unconscious physiological processes, expectation plays no role. If you

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[14] Collins KH and Tatum AL (1925). A conditioned reflex established by chronic morphine poisoning. *American Journal of Physiology*, **74**, 14-15. For more references see page 201 of *Placebo Effects: Understanding the mechanisms in health and disease* by Fabrizio Benedetti.

give someone an immune suppressive drug, but you tell them that it's going to have the opposite effect, this does not have any effect on the drug's immune suppression. It does not change the placebo response. This is a very important distinction because, remember, if you are dealing with a conscious process, like pain, you can actually reduce the effect of the active treatment with negative suggestions.

This distinction is also potentially significant when one is trying to interpret the results of clinical trials, because it may partly explain why the numbers for so-called 'placebo responders' vary so widely. It's not one-third, like some of us were taught in medical school. Given the relative role of conscious processes, it's not surprising that placebo responses tend to be very high in studies about depression. On the other hand, the respiratory system represents an interesting contrast.

If you give someone a placebo breathing treatment, they will often describe a significant subjective improvement; but the objective measurements of their respiratory functions do not improve. In other words, there's no objective placebo response. But here again, you can begin to appreciate Dr. Benedetti's comments about the complexity of applying placebo in a clinical context. I hope you can see why it would be unethical to give a placebo to a person who was in severe respiratory distress.

A common misunderstanding is that the placebo response is only a subjective phenomenon in the patient's head. But I hope today's conversation has convinced you that what is going on in the brain is much more than that. Besides, even the real placebo responses studied by Dr. Benedetti are not just in the brain. There is evidence that placebo analgesia may be having effects at the level of the spinal cord, and obviously, placebos involving immune and hormone functions have effects in the body.

Even so, I think the study of placebo responses is an example of the relevance of neuroscience. If you are involved in patient care, I want to encourage you to read Dr. Benedetti's latest book, *The Patient's Brain*. Both *The Patient's Brain* and *Placebo Effects* are written in an academic style that includes extensive references. But, don't forget, you can find the references that are mentioned in this episode at brainsciencepodcast.com.

Of course, most of you are not clinicians, but I encourage you to share this episode with your physician or therapist, because I think it is really important that this research reach a wider audience.

As always, you can send me feedback at docartemis@gmail.com. And if you haven't been to the website, brainsciencepodcast.com, I hope you will visit, because, like I said before, we do have extensive show notes and references, including episode transcripts, there, as well as links to things like our Facebook Fan page, and information about how you can donate to help support the podcast. So, there's a lot more on the website than there is for the typical podcast website.

Finally, don't forget to check out my other podcast, *Books and Ideas*. I'm going to be releasing a new episode of *Books and Ideas* later this month. It is an interview with Carol Tavris, the author of *Mistakes Were Made (But Not By Me)*.

Thanks again for listening. I look forward to talking with you again very soon.

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*Both of Dr. Benedetti's books contain extensive references. I suggest you consult these books for the details of the experiments mentioned in this podcast.

Transcribed by Lori Wolfson
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