The placebo response: science versus ethics and the vulnerability of the patient

FABRIZIO BENEDETTI

Department of Neuroscience, University of Turin Medical School and National Institute of Neuroscience, Corso Raffaello 30, 10125 Turin, Italy

In the past few years there has been a terrific increase in our knowledge of the mechanisms of the placebo response. Through both a neuropharmacological and a neuroimaging approach, researchers have investigated the very nature of the placebo phenomenon across a variety of medical conditions, ranging from pain to motor disorders and from immune system diseases to anxiety and depression (1-3).

The placebo response is an intriguing topic, for it has to do with complex mental events such as expectations, beliefs, trust and hope. The very mental act of trusting a doctor and believing in a therapy may trigger an intricate cascade of biochemical events that, in turn, may change the perception of a symptom or even the course of a disease. It goes without saying that one of the most important factors that triggers expectations and beliefs is represented by verbal suggestions, so that the neurobiology of the placebo response can be somehow rephrased as the neurobiology of suggestion as well as the neurobiology of expectation (1).

What we have learned over the past years is that verbally induced expectations may activate different neurotransmitters (4-7). For example, in pain, opioids, cannabinoids, dopamine and cholecystokinin are involved in different circumstances, and they can modulate pain perception in different directions. Positive verbal suggestions lead to positive expectations that, in turn, activate either opioid or cannabinoid systems (analgesic placebo response). Conversely, negative verbal suggestions lead to negative expectations which activate cholecystokinin and deactivate dopamine (hyperalgesic nocebo response). These biochemical events are likely to take place, at least in part, in a pain modulating network that involves both cortical and subcortical regions, e.g. the dorso-lateral prefrontal cortex, the anterior cingulate cortex and the periaqueductal grey, as well as in the reward circuit, particularly the nucleus accumbens (8).

On the basis of these recent insights, it is clear that the placebo response represents an excellent model to understand mind-body interactions, whereby a complex mental activity can change body physiology. Psychiatry and psychology, as disciplines investigating mental events, are at the very heart of the problem, for they use words and verbal suggestions to influence the course of a disease. Psychiatry, for example, has in its hands at least two therapeutic tools: words and drugs. Interestingly, what has emerged from recent placebo research is that words and drugs may use the very same mechanisms and the very same biochemical pathways (9). Morphine binds to mu opioid receptors, but verbal

suggestions of pain reduction may activate the same receptors. Likewise, cannabis binds to cannabinoid receptors, but suggestions of pain decrease may act on the same receptors. And also, anti-Parkinson agents bind to dopamine receptors, but verbal suggestions of motor improvement activate the same dopamine receptors in the very same brain areas. Therefore, the crucial concept is that, when a drug is administered, the same receptorial pathway can be activated in two different ways: by the drug itself and by the expectation of the drug.

Verbal suggestions are not the only means to induce expectations. The whole therapeutic setting (health professionals, medical instruments, hospital environment) represents what can be called the ritual of the therapeutic act. Indeed, drugs are less effective without therapeutic rituals. The hidden administration of drugs, whereby a pharmacological agent is administered unbeknownst to the patient, is less effective compared to an open administration in full view of the patient (10-12). In the hidden condition, the patient has no expectations of improvement, so that the global drug effect is reduced. In other words, the patient's expectations and beliefs add to the pharmacodynamic effect of drugs.

This new scientific knowledge leads us to better understand how our brain works and what kind of strategies it uses during social interactions. In fact, this special social encounter with the doctor (the healer) may trigger a number of mechanisms in the patient's brain which *per se* can be therapeutic. Therapeutic rituals are crucial in this sense. The mere act of performing a therapy may have biological and therapeutic effects, a kind of evolutionary mechanism that is likely to have evolved from social grooming in apes and altruistic behavior in early hominids (13). An individual who trusts a member of his own social group, whether a shaman or a modern doctor, has surely an advantage over those who lack this mental disposition. This pure social interaction can, in some circumstances, be as powerful as the action of a pharmacological agent.

The very existence of these trust- and belief-related features of mankind raise a number of problems and ethical concerns for the medical profession and, more in general, for our society. Although ethical issues related to the placebo response have long been known and debated (14,15), the most recent insights into the neurobiology of the placebo response have boosted some ethical concerns further. In fact, what is emerging today from a strict scientific stand-

point is that the very ritual of the therapeutic act can change the patient's brain, thus anybody who performs a therapeutic ritual can influence the physiology of the patient's brain and obtain positive effects. If a syringe filled with distilled water and handled by a doctor may induce expectations of benefit, then the same expectations can be induced by talismans, mascots and bizarre rituals carried out by quacks and shamans.

The tight relationship between the growing eccentric healing practices and the recent biological advances in placebo research is shown by the growing tendency to refer to the effects of placebos as real biological phenomena that need to be triggered and enhanced by a variety of odd, weird, and bizarre procedures. Particularly in very recent times, right after the experimental demonstration that endogenous opioids and cannabinoids can be activated by placebos (1,5), I personally was deluged with requests and proposals of new bizarre procedures, concoctions, talismans and mascots that could possibly enhance expectations, beliefs, trust and hope.

By surfing on the web, it is possible to realize that many websites have taken the biological effects of placebos as a sort of justification for bizarre therapeutic rituals. Many healers claim that after all there is no difference between a sugar pill and a talisman if one wants to deceive a patient and see if he/she will have a positive response. Deception is at the very heart of a placebo procedure, and indeed it makes no difference if this deception comes from a doctor or a quack or a shaman. From this perspective, many argue, any procedure that increases expectations and beliefs would be justified, no matter where it comes from. According to this worrisome view, any healer should strive to explain and clarify the purpose of his/her ritual, namely, the stimulation of chemicals in the patient's brain which are beneficial in a variety of conditions. This conception is supported by the recent rigorous science of placebo, which itself gives credibility to the enhancement of expectations with biological effects.

To prevent this disconcerting and upsetting perspective, there are three possible solutions. First, we could stop placebo research because of its potential consequences. When the neuroscientist studies the neurobiology of the placebo response, he wants to unravel the brain mechanisms of a human foible and a vulnerable trait that represent per se the very heart of human social interactions (13). In this sense, science risks to be exploited in the wrong way and, paradoxically, the neurobiological advances can turn into a regression of medicine to past times, when the eccentricity and oddity of the therapies were the rule. Second, we can accept that expectations can be enhanced with any means available and by anybody through bizarre and odd practices, a perspective that would surely be very dangerous. Third, if we do not want to adopt these extreme positions, we must develop new ways to communicate the results of placebo research. This is not an easy task, for scientific advances will inevitably go against ethical concerns as we will learn more

and more about the biology of a vulnerable aspect of mankind.

I think psychiatry and psychology are disciplines that are more involved in these ethical issues than others, because mental disorders such as depression, anxiety and somatoform pain are those conditions for which people more often refer to bizarre practices and to unscrupulous healers. Therefore, the new neurobiology of suggestion and placebo faces the ethical dilemma of what to do. The study of the biology of foibles and vulnerable aspects of mankind, and particularly of patients, may unravel new mechanisms of how our brain works, but it may have a profound negative impact on our society as well, and requires good communication between science, ethics and media.

I believe some of the most important questions we will need to answer are: What is the ethical limit to increase expectations? Can we accept every means available, whether a sugar pill or a talisman? What about a patient who trusts talismans but not pills and injections? Is it acceptable to use a talisman to activate his brain chemicals? These questions presage a worrisome future for medicine.

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