

## **Un(learning) pain by consequences. Development of the learning theory of placebo effects**

As Kurt Lewin once wrote, “there is nothing so practical as a good theory”. Indeed, theories enable us to prioritize certain research directions, formulate predictions, determine whether a new finding integrates with existing research results or not, and therefore require further investigations, among others. Unfortunately, in recent years, focus on the empirical investigation has been observed in psychology that is not accompanied by an equally deep interest in theory development. It has been even suggested recently that the lack of theories is one of the main factors responsible for the so-called “replication crisis” facing psychology, i.e., many scientific study results are difficult or even impossible to reproduce. A similar focus on an empirical rather than a theoretical investigation is observed in the field of placebo studies.

Placebo is a pharmacologically inert substance (e.g., a sugar pill, a saline injection) that may produce significant effects on health. When the effect is positive, it is called the placebo effect, in contrast to the negative effect, called the nocebo effect. Although placebo effects are observed in many medical conditions, they are most often studied in pain. When the placebo results in pain reduction, the observed effect is called placebo hypoalgesia. On the other hand, when the placebo produces pain worsening, this effect is called nocebo hyperalgesia.

The question arises, how is it possible that an inert substance produces such significant effects on health? There is growing evidence that placebo responses are the results of learning. For example, when somebody has experienced pain reduction after the application of a potent pain killer in the form of a white, round pill, they may also experience pain reduction in the future when they are administered placebo in a similar way, i.e., white, round pill, however containing no pain killer. This is an example of the learning process called classical conditioning in which a formerly neutral stimulus (in this case, a placebo) becomes able to induce a response (in this case, a pain relief) initially induced by another stimulus (in this case, a pain killer). The second learning process that may be responsible for the induction of placebo and nocebo effects is observational learning. In this process, an individual’s responses are shaped by observing others’ responses. For example, if one sees a person who takes a placebo and experiences pain relief, they may experience similar pain relief as a result of a placebo application.

There is accumulating evidence that both classical conditioning and observational learning may induce placebo and nocebo effects. A few theoretical accounts of placebo effects have also been proposed, which include those learning processes. However, those accounts are either focused on one of the learning processes and thus do not analyze their mutual relationships or do not fully reflect the current state of the art in the field. Most importantly, they do not include the third basic learning process, i.e., operant conditioning. In this process, a behavior (e.g., taking a placebo) that is followed by a reward (e.g., attention from others, pain relief) occurs more often in the future, while a behavior followed by a punisher (e.g., pain, withdrawal of attention from others) occurs rarer. Surprisingly, operant conditioning was not considered as a mechanism of placebo effects until very recently. Indeed, only one study has been conducted so far in which placebo analgesia was induced by operant conditioning. Moreover, no previous study to date has analyzed placebo and nocebo effects induced by all three learning processes.

Thus, before we start developing the theory, we must first learn more about placebo and nocebo effects induced by operant conditioning as well as on the mutual relationships between placebo hypoalgesia and nocebo hyperalgesia induced by operant conditioning, classical conditioning, observational learning as well as verbal suggestions which are also commonly used to elicit placebo and nocebo effects. To do so, we will conduct five experimental studies and the review of the current state of the art in the field of placebo hypoalgesia and nocebo hyperalgesia induced by classical conditioning, observational learning, and verbal suggestions. Although pain is a subjective phenomenon, participants’ pain ratings may not fully reflect this experience. Thus, in our experiments, we will not only rely on subjective pain ratings but also record galvanic skin response and heart rate variability as more objective measures of pain.

Based on the results of our research as well as the research conducted by other investigators, we will first develop preliminary assumptions of the learning theory of placebo effects and then, after critical appraisal, the final version of the learning theory.

We believe that our project results will help better understand the role of the learning processes in the induction of placebo and nocebo effects. We also believe that the knowledge on the role of those processes in placebo and nocebo effects will contribute to the development of effective pain management methods based on those learning processes, which will be of help for people suffering from pain.