

## **From pain to paraesthesia: response-generalization of the nocebo effect**

Pain is a phenomenon that affects millions of people around the world. Although in its essence it plays a biological role -it protects the body from further injury- as a result of various abnormalities, it sometimes turns into a chronic pain and becomes maladaptive. It becomes a problem that significantly reduces the quality of life, affecting physical as well as psychological aspects of life. People affected by pain seek help from various specialists. The information received from health professionals often has a major impact on the further development of the symptoms. Positive, reassuring advice may improve physical function and increase the effects of treatment, while negative messages may suppress the effects of treatment and contribute to the deterioration of the patient's condition. These phenomena are known in the literature as placebo (lat. placere – I shall please) and nocebo (lat. nocere – I shall harm). Awareness of the occurrence of these phenomena and their positive (placebo) and negative (nocebo) effects are important for clinical practice. The past decade has allowed us to look at the mechanisms of placebo and nocebo effects from a behavioral point of view, which has contributed, among other things, to a line of experimental research indicating that placebo effects are reactions that may be subject to laws associated with learning.

The process of learning is closely related to the phenomenon of generalisation, which may be considered in two categories: stimulus and response generalization. Both phenomena can be illustrated using examples taken from behavioural therapy for children with autism, which aims to enforce the desired behaviour, e.g. hanging a jacket on a hanger when returning home. This can be done, for example, by connecting a stimulus (hanger) with behaviour (hanging up the jacket). Stimulus generalization will occur when encountering not only the trained hanger but also another, similar one, and this will result in the expected behavior, i.e. hanging up the jacket. The response generation in turn will occur, when a given stimulus triggers the desired reaction, as well as another, similar to it, e.g. hanging up a cap or removing shoes.

The **stimulus** generalization is well studied in terms of the generalization of human anxiety or pain-related fear of a painful movement. There are also reports suggesting the possibility of inducing a placebo response by **stimulus** generalization. However, there are no reports on the possibility of a **response** generalisation of the placebo/nocebo. Is it possible to transfer the nocebo response from one reaction (e.g. increased pain) to another (e.g. paresthesia)? If so, how potent can it be?

This project, consisting of three experiments, is attempting to answer the above questions. In the first experiment, the pain experience caused by a direct current will be manipulated by nocebo suggestion. It will then be assessed whether the induced hyperalgesia, i.e. increased sensitivity to pain, will be generalised to other symptoms, e.g. paresthesia (a tingling-like sensation), induced by an electrical current with different parameters. In the second experiment, the modification of the pain sensation induced by the direct current will be the result of classical conditioning without suggestion (hidden conditioning). The experimental manipulation will concern only the painful sensation. Then, changes in paresthesia caused by ischemia resulting from compression of the blood pressure cuff, which was not manipulated experimentally, will be assessed. In the third experiment, both pain and paresthesia will be caused by pressure from a blood pressure cuff. Modulation of pain sensation will be achieved by one of these manipulations: verbal suggestion, classical conditioning, or combined verbal suggestion with conditioning. Subsequently, the influence of changes in pain sensation on paresthesia will be assessed. The experimental plan has a gradient structure in two dimensions. The first one refers to an increasing manipulation influence (suggestion; conditioning; suggestion, conditioning, conditioning plus suggestion). The second one refers to an increasingly distant response in terms of characteristics. In the first experiment, the nocebo response applies to two currents with different properties that cause pain and tingling, respectively. In the second, tingling caused by the current is replaced by 'tingling' (paresthesias) caused by experimentally induced ischemia. In the third, the pain caused by the current is replaced by the pain caused by the pressure similar to paresthesia.

The knowledge gained from this project will allow for a deeper understanding of the mechanisms of the nocebo effect formation and the strength of its impact through generalization on other symptoms. Also, the results will provide a basis for understanding the generalization of the placebo effect. As there is currently a gap in research on the generalization of the placebo response, this project may contribute to a new direction of research in this field. It is also the first attempt to induce the nocebo effect in paresthesias.