

## The nocebo effect as a model to understand anxiety mechanisms

The nocebo effect is a phenomenon that is opposite to the placebo effect, whereby expectation of a negative outcome may lead to the worsening of a symptom. Thus far, its study has been limited by ethical constraints, particularly in patients, as a nocebo procedure is *per se* stressful and anxiogenic. It basically consists in delivering verbal suggestions of negative outcomes so that the subject expects clinical worsening. Although some natural nocebo situations do exist, such as the impact of negative diagnoses upon the patient and the patient's distrust in a therapy, the neurobiological mechanisms have been understood in the experimental setting under strictly controlled conditions. As for the placebo counterpart, the study of pain has been fruitful in recent years to understand both the neuroanatomical and the neurochemical bases of the nocebo effect. Recent experimental evidence indicates that negative verbal suggestions induce anticipatory anxiety about the impending pain increase, and this verbally-induced anxiety triggers the activation of cholecystokinin (CCK) which, in turn, facilitates pain transmission. CCK-antagonists have been found to block this anxiety-induced hyperalgesia, thus opening up the possibility of new therapeutic strategies whenever pain has an important anxiety component. The reward neuronal network has been found to be involved in the nocebo effect as well. In fact, whereas the placebo response is associated to the activation of dopamine and opioids in the nucleus accumbens, the nocebo response is associated to a de-activation of both dopamine and opioids. All these findings may help understand some of the mechanisms of anticipatory anxiety.