Stimuli received by the body induce neuronal adaptations that are crucial for environmental adaptation. Those induced by addictive substances can be pathological. Most of them are reversible, but in susceptible individuals (about 10-20%), they can lead to permanent changes in the structure and function of synapses, as well as to central nervous system dysfunctions such as dysregulation of the mesocorticolimbic circuit (a key element of the reward system, which plays an important role in the regulation of emotions, motivation, and cognitive processes related to reward and punishment). Opioid addiction, particularly to fentanyl, a very strong painkiller, is one of the most severe health threats, including the high mortality rate due to overdoses. The immense potency of fentanyl, its improper use as a prescription drug, and its availability on the black market contribute to the spread of this addiction, which has reached epidemic levels in some country. Available therapies, primarily substitution therapies (methadone and buprenorphine treatment), alleviate symptoms and reduce harm but do not lead to complete recovery. The likely cause of the limited effectiveness of these therapies is that they target the consequences rather than the causes and are unable to reverse the key neuroplastic changes induced by drugs that are essential for the development of addiction. Recently, the concept of psychotherapy supported by psychedelics has been reconsidered. It is based on the assumption that psychedelics stimulate neuroplasticity, and in a state of increased plasticity, the brain is more susceptible to modifications, which can support psychotherapy for mental disorders, particularly in the area of compulsive behavioral patterns.

Our initial findings suggest that psilocybin may interact with genes linked to opioid addiction, with miRNA playing a key role in this process. Furthermore, our analysis points to a potential connection between psilocybin's effects and the hormonal system, highlighting the importance of considering sex differences in these interactions.

Despite the growing interest in psilocybin for treating CNS disorders, including those induced by psychoactive substances, there is a lack of basic research on the mechanisms of its potential therapeutic effects on one of the most dangerous addictions—fentanyl addiction. In this rapidly developing research area, our project will provide comprehensive studies at both the molecular and behavioral levels. We plan to use a simple model to study the mechanisms by which addictive substances induce long-lasting neuronal changes—sensitization and tolerance. Their development will be monitored using locomotor activation (LA) test and ultrasonic vocalization (USV) responses in appetitive and aversive pathways. USV is a way for laboratory rodents to express emotions, with positive or negative emotions being expressed at different frequencies. These tests will also assess the impact of psilocybin administered at different stages of the sensitization/tolerance process on modulating these effects. One group will receive psilocybin before sensitization is induced to determine whether it can prevent the development of neuroadaptive changes induced by fentanyl. The potential of psilocybin to block neuroplastic changes is important due to its potential to prevent the development of addiction in individuals receiving chronic pain therapy. Another group will receive psilocybin after the development of sensitization/tolerance, after which the rats will be exposed to the environment where they had received fentanyl to extinguish drug-related associations. Based on responses to context and a fentanyl-priming dose, the ability of psilocybin to support the extinction of neuroadaptive changes induced by repeated fentanyl administrations will be assessed. Due to sex differences in responses to fentanyl and psilocybin, as well as increased susceptibility to addiction in women, the study will be conducted on both male and female rats, taking into account the estrous cycle phase. Biological changes will be assessed in brain areas critical for addiction development based on the analysis of parameters related to the activity of opioid, dopaminergic, serotonergic, glutamatergic, reproductive systems, and the analysis of neuroplasticity markers. Integrated bioinformatics analysis will contribute to a better understanding of the factors involved in processes related to fentanyl addiction and the mechanisms associated with the therapeutic effects of psilocybin.