Effects of ketamine optical isomers on motivation and decision-making in rats using deep learning for behavioral analysis: the role of sigma-1 receptors and ventral striatal dopamine

Motivation is defined as vigorous, goal-directed behavior. When impaired, the vigor of response decreases, and the effort required to achieve a goal feels greater than it actually is. Motivational impairments are a key feature of apathy, which often accompanies conditions like depression, neurodegenerative disorders, and post-COVID fatigue syndrome. As these conditions become more prevalent, motivational impairments are emerging as a global issue. No effective treatments have been developed apart from high-risk psychostimulants. While conventional antidepressants may seem like a solution, they often worsen apathy, which is their side effect. The pathomechanism of apathy is still unclear, but research indicated that it may be rooted in decreased mesolimbic dopamine, which underlies motivation and pleasure.

(*S*)-ketamine and (*R*)-ketamine are optical isomers of ketamine – a potent antidepressant. While (*S*)-ketamine is already available as a clinically approved medication, (*R*)-ketamine has only recently been studied in humans. Both compounds increase striatal dopamine via mechanisms different from classical psychostimulants and activate sigma-1 receptors, further regulating dopamine release. Previous studies also demonstrated that the sigma-1 receptor partly mediates the antidepressant-like effect of ketamine in rodents. However, while (*S*)-ketamine is a stronger dopaminergic enhancer, (*R*)-ketamine is a more potent S1R receptor agonist. This distinction is key for treating impaired motivation and apathy, as dopaminergic neurotransmission drives motivation, and sigma-1 receptors can regulate this process. This suggests that both compounds may differently affect motivation and show various efficacies in reducing apathy symptoms. Previous research has not yet addressed either this issue or the impact of sigma-1 receptor agonists on motivation. This represents a significant research gap that is addressed by the proposed project.

The project will investigate whether (*S*)-ketamine and (*R*)-ketamine can enhance vigor and effort-based choices in a rat model of motivational impairment. The project will also examine whether specific agonists of sigma-1 receptors (DTG and PRE-084) can improve motivation and whether their selectivity at the sigma-1/2 receptor affects behavioral efficacy. After determining the efficacy of these compounds, the project evaluates whether sigma-1 agonists can further modulate the motivational effects of (*S*)-ketamine and (*R*)-ketamine and whether this effect is driven via increased ventral striatal dopamine.

To assess the behavioral effects of the tested compounds, the project employs operant tasks involving food-motivated learning to measure response vigor and decision-making based on effort in rats. In these tasks, rats will press a lever to receive palatable food or choose between exerting effort or receiving less-valued food for free. Another test will assess whether the tested compounds affect food preference and consumption. Tetrabenazine, which inhibits dopamine release, will be used to model impaired motivation in rats. The test will be video and audio-recorded. Videos will be analyzed using deep learning algorithms (DeepLabCut, SimBA) to capture additional behavioral patterns and estimate decision-making strategies. Rats vocalize ultrasounds when rewarded or stressed, so the audio analysis will help determine how rats react to different types of food and whether tested compounds can change the pattern of ultrasonic vocalization. To determine if the efficacy of the compounds depends on ventral striatal dopamine, its concentration will be measured using microdialysis in freely moving rats.

The results of this project will show whether (*S*)-ketamine can be an antidepressant with a potential pro-motivational effect, possibly expanding research on its therapeutic uses. Additionally, the findings may indicate that (*R*)-ketamine offers advantages over (*S*)-ketamine, supporting further clinical research. By exploring the role of the sigma-1 receptor in motivation, the project can identify new targets for apathy treatment and suggest new mechanisms for driving motivation.