Ketamine is a drug of abuse, which has been used to model schizophrenia in rats and humans for nearly 70 years. Recently it has successfully been used as medication for treatment-resistant depression. Brain activity may be examined through a myriad of methods, one of them being the recording of electrophysiological activity. This can be done by using electrodes, which may be implanted into a specific area of the brain to measure local field activity (LFP). Although ketamine has various applications, it is unknown how this compound achieves its effects.

Ketamine injections lead to the generation of very fast brain rhythms termed “high-frequency oscillations” (HFO, 130-180Hz) in many rat brain regions. Importantly, a similar activity has also been reported in cats, mice and recently humans. Our previous studies have shown, that one of the main sources of this brain rhythm is the olfactory bulb (OB), which is a brain area responsible for processing stimuli related to breathing and the sense of smell. Thus, there is a possibility, that the nasal epithelium, which is a layer inside our nasal cavity responsible for smell, may be associated with the generation of ketamine-dependent fast rhythms. The goal of this project is to understand the role the nasal epithelium plays in the generation of ketamine-dependent fast rhythms in the OB and other brain regions of rats. Gaining a better understanding of the underlying mechanisms of the impact ketamine has on the brain may lead to the development of more efficient antidepressant medication.

To achieve this aim I will firstly develop and validate a rat model of nasal epithelial damage and anosmia. This will be done by infusing gadolinium chloride into the nose of the rats. The damage done to the nasal epithelia will be tested using a well-validated test of smell (hidden cookie test). The rats will be implanted with electrodes so I can monitor the respiration rhythm (slower brain rhythms associated with nasal breathing, 1-10 Hz) which correlates with sniffing and direct olfactory input to the OB. I predict that damage to the nasal epithelium would disrupt this natural rhythm. In a separate group of rats, I will perform histological analyses of the olfactory epithelium at different time points to determine the extent of the visible damage, and whether the epithelium regenerates over time.

My preliminary research on small groups of rats has shown, that gadolinium anosmia lasts between 8-10 days. Histology results have shown distinct damage done to the nasal epithelium in gadolinium rats, compared to the control group. Furthermore, the ketamine-fast brain rhythm disappears and the respiration rhythm power is decreased along with evoking of anosmia. With time, as the anosmia dissipates, the respiration rhythm and fast brain rhythm (in response to ketamine) recover. This suggests, that the nasal epithelium is connected with the generation of these activities.

This project will help understand how ketamine affects core brain activity, and to what extent the nasal epithelia can drive abnormal ketamine rhythms in the rat brain. Given that similar activity has been recently reported in humans, the findings from this study have clear translatable value. This is potentially important since this circuit has not been investigated previously, and as such targeting the nasal epithelia could represent a useful drug target directly affecting brain activity.