

Ketamine is a drug that has been used for over 60 years to model psychoses. Over the past 10 years there has been a surge of clinical studies reporting ketamine is an effective treatment for depression. Despite international efforts seeking to understand ketamine's mechanisms of action, how ketamine affects brain networks is poorly understood.

Brain activity can be investigated in many different ways. One of the most widely used techniques is to measure electrophysiological activity, such as brain oscillations and individual spiking of neurons. Recent years have witnessed a surge of interest in high frequency oscillations (HFO), also known as ripples, considered important for their roles in health and disease. In awake rodents, we have shown that low doses of ketamine produce fast brain rhythms termed high-frequency oscillations (HFO, 130-180 Hz). Many international groups have confirmed that this class of drugs increase HFO in diverse cortical and subcortical. However, whether this is a brain-wide phenomenon or related to particular neuronal circuits remains unclear. This proposal builds on our series of recent papers demonstrating the olfactory bulb (OB) is an important generator of ketamine-dependent HFO in the brain. However, important questions remains, for example does sensory input drive this rhythm and can the OB impose it on other brain regions, and potentially throughout the brain.

The proposal outlined here builds on 3 previously successful grant proposals. Here we seek to develop our findings based on our previous work and pilot studies to test novel our ideas. The specific hypotheses we intend to test are: 1) *Sensory nares input drives ketamine-dependent HFO in the OB*. This is particularly important given that nasal respiration can drive HFO in the brain and that intranasal administration of ketamine is used clinically. Ketamine receptors have also been identified in the nasal epithelia and as such binding at this site is likely to produce changes in olfactory-related circuits; 2) *Anterior piriform cortex is a generator of ketamine-dependent HFO driven by the OB*. The piriform cortex receives input from the OB, and can in turn project back to the OB to control rhythm "gain" in this region. It is not known whether this region, or other olfactory areas are able to generate ketamine-dependent HFO which is important to understand the networks and potential functional relevance of this rhythm. One striking aspect of ketamine-dependent HFO is its fast frequency, typically around 150 Hz, which overlaps with effective frequencies used in deep-brain stimulation clinically in depressed patients. We will examine whether ketamine indeed does mimic deep brain stimulation by examining unit activity in olfactory brain regions and also whether deep brain stimulation mimics effects of ketamine.

To test these hypotheses we will use state-of-the-art silicon probe electrodes, local brain infusions, and behaviour measures. We will carry out recordings using freely moving rats and also ketamine-xylazine anesthetised rats where a similar type of HFO can be recorded. This is particularly important for ethical reasons since some of experiments can now be conducted under anesthesia. We have a laboratory dedicated to in vivo electrophysiology and the necessary surgical and analytical experience to complete this project in the given time-frame. We also have several established collaborations in place at the Mossakowski Institute, our partner, for the brain imaging part of the proposal.

Given international efforts for a better understanding of how ketamine works our findings will be of broad interest. The work also has clear societal impact and interest to neuropharmacologists, preclinical researchers, neural network modellers and clinicians. Our findings will be disseminated at international conferences and open access publications in at least two major international journals. Wherever possible we will make our data freely available for secondary use by other researchers. Our findings will have major impact for understanding how ketamine affects a fundamental brain network which will contribute to improved understanding of ketamine's psychoactive properties with particular relevance to depression and schizophrenia.