Understanding alcohol relapse through whole brain imaging

Addiction is a disease that affects circuits and brain areas involved in reward, stress, and self-control. Continued substance abuse can lead to dependence that is associated with a withdrawal symptom when drug availability is ceased, and increased intake upon relapse. Around 80% of adults are exposed to alcohol during their lifetime, yet less than 30% will develop an alcohol use disorder. It's difficult to explain how drug addiction develops over time. How similar exposure to alcohol can produce such different outcomes between individuals remains poorly understood. Drug related behaviors are encoded by maladaptive reward memories, which are associations between drug-predictive environmental stimuli (e.g. the smell and visual context) and drug reward. These pathological memories will also promote motivated behavioral routines including substance seeking, excessive consumption or craving. Rewriting or suppressing these memories remains currently one of the biggest challenges of neurobiology. Reconsolidation is a memory maintenance process - reactivated long-term memories destabilize and newly available information can update the memory. This memory destabilization requires adequate retrieval conditions such as memory-related cues that either provide novel information or confirm prediction. In our experiments we will use animal model of binge-like alcohol drinking. In binge-like alcohol drinking mice can drink alcohol voluntarily in a free access mode. This access is limited to a couple of hours per day. This model reflects a situation in humans when repeated episodes of excessive drinking, especially at an early age, are thought to cause a profound increase in the risk of developing an alcohol-related disorder. After the training, animals are deprived of alcohol and tested whether they develop strong craving and drink more alcohol in relapse. Our aim is to see what happens in the brain when animals are faced with an environmental cue that anticipates access to alcohol or immediately after they gain access to alcohol following long withdrawal. We will do it by visualizing c-Fos - a marker of neuronal response to new stimulus. We will perform whole optically cleared transparent brain imaging in light-sheet microscope. Such approach enables identifying all active cells with their anatomical annotation. Hundreds of pictures covering the whole brain will be processed as a single three-dimensional image. The c-Fos positive cells will be identified as single objects or groups which, in turn, form a 3D map of brain "hot spots". In our project we aim at identifying new candidate structure involved in alcohol relapse and brain response to alcohol-related environmental cue. We do hope that this will help to better understand events leading to development of addiction.