Resting state functional networks (RSN) are often used to characterize patient cognitive state or as disease biomarkers. However, so far only a few studies considered functional networks in rats and that was under anesthesia and using fMRI, seriously limiting their applicability and translational potential. Here we propose to use a novel high density 3D printed flexible silicone implant to identify and characterize EEG-based functional connectivity in freely moving rats and study its resilience and responses to different conditions, stimuli and drugs. Combining expertise of four teams in animal surgery, human and animal pharmaco-EEG (NIMH), brain implants (MHH, NIMH), realistic head phantoms (BUT), analytical methods for field potentials (NENCKI, BUT, NIMH, MHH) and building on prior collaboration **we will establish a standard for high-throughput systematic EEG-based functional connectivity biomarkers for rats with high translational potential and broad applicability in translational pharmaco-EEG research**.

Despite the fact that neuropsychiatric disorders show only minor CNS structural abnormalities, they are accompanied by disrupted network activity and impaired information processing. These relatively discrete changes have been identified over the past few decades along with the development of multiple neuroimaging methods and advances in signal analysis. Based on these methods, for example, schizophrenia is now viewed as a large-scale networks disconnection syndrome, depression as a state with an overly constrained and rigid pattern of functional brain network activity, etc. The translation of these concepts down to animals have been slow. This is unfortunate since the animal studies offer more possibilities of invasive manipulations. Here we propose the combination of the computational approaches used in humans with the traditional methods used in animals to open up a much wider window to understand neurobiology of the brain processes and increase translational validity.

The costs and challenges of animal fMRI convince us that EEG-based methods are optimal solution to the challenge of characterizing brain states in behaving animals. To achieve standardization of EEG-based functional connectome analysis in rats, increase throughput and maximize data uptake (and so minimize the number of animals needed) we will use a novel flexible implant developed by the German partner to record data from animals on standardized electrode grids (akin to 10-20 EEG setup of humans). This will allow us to collect data 1) from freely moving animals, 2) distinguish between behavioral activity and inactivity (resting state) and sleep and 3) minimize invasiveness and thus suffering and prolonged convalescence via 4) collecting high quality data from the head´s surface without the need of skull penetration and brain injuries. 5) Furthermore using chronic biocompatible and flexible electrode implants that can serve in longitudinal studies including animal growth phases and enable crossover design which results in numbers on animals saved. Last but not least, while human EEG studies are following standardized principles of recording and data processing and international societies have published corresponding guidelines, nothing comparable is available for the animals [2]. This standardization is particularly important in pharmaco-EEG, where there is an important interplay with external variables, such as the. Not surprisingly, the International Pharmaco-EEG Society (IPEG), a leading expert society in the field, has the creation of guidelines for methodological standardization of animal EEG studies as one of their major priorities.

Each of the partners will contribute in their specific domain. The Czech sites have expertise in psychopharmacology and pharmaco-EEG focused on translational research as well in forward modeling and measurements of electric characteristics of tissues and 3D objects. The team has made significant achievements in EEG translational methodology of computing 3D spline mapping, functional connectivity and source localization in rats. The current proposal will focus on data acquisition from animals and tightly collaborate with the German site on improving the EEG implant, and with Polish site on adaptation of computational methods of large scale networks and performing translational comparisons.

The Polish team has experience with 1. forward and inverse modeling of electric field propagation in the brain, including finite element modeling of tissue with inhomogeneous and anisotropic conductivity; 2. multimodal data integration and co-registration of data with brain atlases; 3. neuroinformatics experience, including development of open source scientific packages; 4. development of dynamics-based connectivity methods. Their role will be analytical and computational integration of source reconstruction and connectivity methods to maximize reliability and stability of developed new connectivity-based biomarkers to increase their chances for translation.

The German site is leading in fabrication technologies for chronically biocompatible silicone implant systems which include wiring, electronics and connectors as a whole. The contribution will be the development of highly flexible recording implants that 1. meet individual anatomies where necessary, 2. grow with the animals, 3. have a hugging functionality towards the convexity of the rats´ skulls and 4. allow a higher electrode density as can be achieved with conventional wiring.