Ruprecht-Karls-Universität Heidelberg
Medizinische Fakultät Mannheim
Dissertations-Kurzfassung

Combining Optogenetics and fMRI to Study Cerebral Networks in Animal Models

Autor: Philipp Lebhardt
Institut / Klinik: Zentralinstitut für Seelische Gesundheit Mannheim (ZI)
Doktorvater: Prof. Dr. A. Sartorius

Functional magnetic resonance imaging is a well-established technique to examine brain activity and networks in animal models. In contrast to electrophysiology, optogenetics enables the control of specific cell types. A second advantage is that optogenetic stimulation can trigger excitatory as well as inhibitory effects.
This study investigated optogenetic manipulation of neuronal activity and connectivity changes in mice and rats, using fMRI as an analytical method. The work addresses (1) glutamate release in mice and its use as a neurotransmitter and (2) oxytocin release in rats and its impact on neuronal networks. In fMRI, changes of metabolism and blood flow are described by the hemodynamic response function. The influence of the optogenetic stimulation on the hemodynamic response function was examined and characterized for both species.
In the first part, glutamatergic neurons in the left hippocampus of mice were optogenetically stimulated via channelrhodopsin-2. Sham animals, without virus injection, were used as a control group to study unspecific effects induced by the laser stimulation. In transgenic (α-CamKII-Cre) mice, the direct hippocampal activation was investigated as well as its projections to other regions. Additionally, the impact of the dorsal-ventral position of the optical fiber on the hippocampal-prefrontal projections was investigated.
We could demonstrate that the hemodynamic response measured in the hippocampus of mice reached its maximum earlier compared to the hemodynamic response function in humans. An explanation for this observation may be the smaller body size and the faster metabolism of mice. A highly significant increase of the BOLD signal was found for the optogenetic stimulation of glutamatergic neurons in the left hippocampus and its projecting areas, like the contralateral hippocampus and prefrontal regions. Furthermore, a negative correlation of prefrontal activation and the fiber depth was measured, which may be explained by the larger amount of stimulated neurons.
In the second part, we optogenetically stimulated oxytocin-releasing neurons either in the amygdala or in the paraventricular nucleus of rats. We hypothesize that changes in the oxytocin associated networks of the basal ganglia and the olfactory system should result from the optogenetic stimulation. Long-term changes in connectivity were investigated. Therefore, changes in correlations between different brain regions were calculated using the resting-state measurements before and after the optogenetic stimulation. Moreover, seed regions of defined functional networks were determined and voxel-based changes in resting-state correlation to the seed region were investigated. Additionally, short-term connectivity changes were examined in a psychophysiological interaction analysis as well as the direct activation induced by the laser stimulation.
We found that both channelrhodopsin-2 groups showed increased connectivity in the olfactory and basal ganglia networks compared to the control group. However, no short-term network changes were observed comparing the laser on and laser off condition. This might be explained by the hormonal characteristics of oxytocin, leading to a more global and prolonged response.
To summarize, this thesis demonstrates the successful combination of optogenetics and fMRI as a tool for basic neuropsychiatric research. It proves the successful manipulation, not only of single neurons, but also of neuronal networks in vivo by optogenetic stimulation.