Summary

Finding genes that influence cognitive abilities has proven difficult, because many genes are involved with small effect sizes. One approach to this problem is to focus on endophenotypic traits that mediate genetic influences on cognition. Since endophenotypes are closer to the gene action than cognitive traits, genes underlying endophenotypes may be easier to find. Neuronal oscillations in the gamma-frequency band (30–100 Hz) are implicated in several cognitive functions and, therefore, a potential source of endophenotypes. For the research in this thesis, we measured local field potentials (LFPs) in acute hippocampal slices from common inbred mouse strains during spontaneous activity and carbachol-induced oscillations, using 64-channel multi-electrode arrays. Our aims were 1) to thoroughly characterize hippocampal network activity with quantitative traits, 2) to estimate the heritability and genetic correlations of these traits, 3) to perform a genome wide scanning for genes that influence these traits, and 4) to search for behavioral and cognitive traits with which the hippocampal traits are correlated. These steps were taken to investigate which hippocampal network activity traits can be used as endophenotypes for behavioral or cognitive traits.

We characterized the hippocampal activity with classical (amplitude, frequency, inter-regional correlation and phase relations) and non-classical (DFA exponent, oscillation burst life-time, Langevin parameters, cross-frequency phase-locking) methods. The heritability of the derived traits ranged from 5–20%. We found that some traits had a very low genetic correlation between them, which suggests that they have different genetic underpinning and, therefore, also may be involved in different aspects of cognition.

The use of BXD recombinant inbred mouse strains allowed for genome wide scans for genes influencing the hippocampal traits. A systems genetic approach combining QTL mapping and correlation with gene expression was applied to search for novel gene candidates. This led to the identification of eight genes for the traits derived with the classical methods, including Plcb1, a phospholipase that is known to influence hippocampal oscillations. We also identified two genes that code for calcium channels, Cacna1b and Cacna1e, which mediate presynaptic transmitter release and have not been shown to regulate hippocampal network activity previously.

Finally, genetic correlations between the hippocampal activity traits and a wide range of behavioral traits were computed. The amplitude of the hippocampal oscillations appeared to be genetically correlated with several measures of mice exploring a novel environment. The identified candidate genes potentially influence hippocampus-related behavioral functions by shaping hippocampal network activity.

Taken together, this thesis provides proof-of-principle that oscillations recorded in vitro may be used to identify behaviorally relevant endophenotypes and their underlying genes.