

SUMMARY

Parkinson's disease is a chronic, progressive neurodegenerative disorder that presents a wide range of motor and non-motor symptoms. The disorder is characterized by several neuropathological features including the loss of dopaminergic cell in the substantia nigra, a crucial area in the brainstem. However, to date it is not fully understood how these observations are related to the pathophysiology over the decades of the disease. Measuring neuronal activity changes by neurophysiological investigations might unveil some of the underlying processes. Oscillatory activity patterns are altered in Parkinson's disease patients over the progression of the disease involving various brain areas. Besides cortex, selected nuclei of the basal ganglia are also investigated in patients undergoing functional neurosurgery. However, to get a better understanding over the interplay between the affected deep brain structures (the basal ganglia) and more superficial (cortical) brain areas, more extensive investigations would be desirable. Animal models offer a range of possibilities to investigate brain activity patterns associated with parkinsonism. In the present thesis, a rodent model of Parkinson's disease was used to describe how neurophysiological patterns alter in experimental parkinsonism in numerous parts of the basal ganglia-cortex loop.

The overall aim of this thesis was to describe the changing patterns of neuronal synchrony in response to experimentally induced dopaminergic cell loss in the rat between deep and superficial structures of the basal ganglia-cortex loop.

Chapter 1 gives a brief overview on altered neuronal oscillatory activity on Parkinson's disease patients and the rat model. Major characteristics of this neurodegenerative disorder are described, a simple overview of the most investigated anatomical circuitry, the basal ganglia is presented. The possibilities and limitations of investigating these circuitries in human subjects are described. As some of the limitations of these studies might be overcome with models, the most frequently used animal models of the disease are introduced. Next, a short overview is given on possible measurements of brain activity, more specifically brain oscillatory activity both in humans (electroencephalography - EEG, magnetoencephalography - MEG, electrocorticography - ECoG) and experimental animals (local field potentials - LFP, single units). The measurements resulting in continuous signal might be used to characterize local activity (power spectrum), coupling between distant brain areas (such as functional connectivity showing symmetrical correlation between brain areas) and causality (describing statistical likelihood of directional influences between brain areas). Next, changes of these oscillatory patterns in patients and animal models of Parkinson's disease are shortly reviewed. Neuronal oscillatory patterns are altered in Parkinson's disease and are to be associated with motor impairment, cognitive decline, and effectiveness of therapeutic interventions. Local and

interregional beta oscillatory activity is also increased in rodent models of Parkinson's disease, however several aspects of the disease related synchronization patterns (especially between far brain areas involving cortex and basal ganglia) are yet not well understood.

In the final section of Chapter 1, some, yet limitedly understood aspects of the basal ganglia-cortex neurophysiology are highlighted: how synchronized activity and directional influences between cortex and basal ganglia are affected by degeneration of the dopaminergic system in the freely moving behaving rat; how this may alter between various cortical areas of the two hemispheres, or cortical areas and basal ganglia (in particular subthalamic nucleus and striatum); how this develops over time throughout the development of dopaminergic cell loss remains to be investigated.

The studies presented in this thesis describe neurophysiological alterations in the freely moving, behaving rat model of Parkinson's disease (induced by unilateral administration of the selective neurotoxin 6-hydroxydopamine). With all experiments we used custom developed recording devices that enabled chronic recordings simultaneously from multiple brain structures including cortex and basal ganglia in the awake behaving rat before, during and after the development of dopaminergic cell loss. The presented studies investigated local neuronal oscillatory patterns (power spectrum), long distance synchronization patterns (functional connectivity) and directional influences (Granger causality) between various brain sites in intact and hemiparkinsonian rats.

Chapter 2 describes the changes of local and interregional neuronal synchronization in motor cortex and the basal ganglia during the development of dopaminergic degeneration in the rat model of Parkinson's disease. In this study, bilateral motor cortical areas and the subthalamic nucleus (component of the basal ganglia) was investigated in behaving (sitting and walking) rats. Local spectral power, interregional synchronization and directionality was computed from the local field potential recorded during and after the development of dopaminergic cell degeneration. After neurotoxin injection the first change in interregional synchronization was an increment in cortico-cortical synchronization. We observed increased bidirectional directional influences (Granger causality) in the beta frequency band between cortex and subthalamic nucleus within the lesioned hemisphere. In the walking condition, the neurotoxin lesion-induced changes in synchronization resembled that of the resting state, whereas the changes in Granger causality were less pronounced after the lesion. Based on the observations of a relatively preserved connectivity pattern of the cortex contralateral to the lesioned side and the early emergence of increased cortico-cortical synchronization during the development of the dopaminergic cell loss, it is concluded that the cortico-cortical synchronization might have a compensatory role.

Chapter 3 presents how local oscillatory activity and interregional synchronization alters in the hemiparkinsonian rat model between multiple cortical and striatal brain areas. Local field potentials were recorded in resting and walking states, before and after the unilateral neurotoxin injection. The interplay between cortex and basal ganglia was characterized by computing functional connectivity and directionality patterns within and between striatum (component of the basal ganglia) and six cortical sites in each hemisphere. In the hemiparkinsonian state we detected changes in the beta frequencies: increased oscillatory activity and enhanced coupling between cortical areas of the two hemispheres. These changes were more widespread at rest when compared to the walking condition. The directionality analysis revealed an increased drive from the non-lesioned towards the lesioned hemisphere (in particular to striatum), most prominently during walking. It is concluded that the directional influences between the two hemispheres that arose after the development of hemiparkinsonism might be a representation of a compensatory component of the dynamic interactions between the measured brain areas.

Chapter 4 complements findings of the previous study: it uses an analytical approach that enables more direct comparison between patterns detected in the rodent model and Parkinson's disease patients. Local field potentials were recorded simultaneously from 12 cortical areas and the left and right striatum before and after the dopaminergic cell loss. Subsequently spectral power and synchronization were computed between brain regions at rest and during locomotion. The results revealed an increase in relative beta power over a wide range of areas at rest, and in a limited number of areas during locomotion. Synchronization between brain regions was moderately increased in the beta frequency band. In addition, excessive gamma band synchronization was observed between many of the recorded brain regions in the resting condition. The conclusion is drawn that the changes in local oscillatory brain activity and synchronization between brain regions in hemiparkinsonian rats present several similar traits to the changes observed in Parkinson's disease patients.

In Chapter 5, the main findings of this thesis and possible future perspectives are discussed. Taken together the results, the rat model used in this thesis allowed to expand on findings of previous rodent studies. We presented dynamic interactions between hemispheres early on during the development of dopaminergic cell loss and between numerous brain areas (including cortical and subcortical sites) in the fully developed hemiparkinsonian state. Regarding human studies, the limitations of the model and patient data comparison are discussed. The similarities in synchronization patterns are noted, the potential role of the asymmetric dopamine load in the detected directionality patterns are mentioned. Then, the role of beta activity in local oscillations and interregional synchronization in parkinsonism is briefly summarized. It is suggested that beta activity/synchronization might also have a beneficial role in the dynamics of brain

oscillatory activity in parkinsonism, besides the antikinetic aspect formerly described in literature. Subsequently, several methodological considerations and future directions are discussed.

Taken together, this thesis presents a novel rodent model of Parkinson's disease that allows chronic, freely moving multielectrode measurements simultaneously from several structures of the basal ganglia-cortex loop. The results illustrate how such a model might extend our understanding of the dopamine depleted brain. The major conclusion of this thesis is that the impact of dynamic interactions (both symmetric and directional) between hemispheres are remarkably increased in the asymmetrically dopamine depleted brain.