CHAPTER 10

Summary
SUMMARY

In chapter 1, clinical aspects of gliomas, a type of primary brain tumors with high mortality, are reviewed. Patients with a glioma or other (non-neoplastic) focal lesion suffer from severe symptoms that are still poorly understood, such as epilepsy and cognitive impairment. Modern network theory provides a framework that may improve our understanding of brain functioning in patients with brain tumors and other focal lesions. As a central theme in this dissertation, modern network theory is used to study the global impact of focal brain lesions and their neurosurgical treatment. This thesis aims to apply these methods to neurophysiological recordings of patients with focal lesions in order to provide insight into the pathophysiology of complex symptoms in patients with brain lesions. The following research questions are discussed:

I) How do brain tumors or other, (non-neoplastic) lesions disturb functional brain networks?

II) How does network topology relate to epilepsy and how does it relate to cognitive deficits?

III) How are functional networks and, as a consequence, epilepsy and cognitive performance, affected by neurosurgery?

In chapter 2, as a starting point of this dissertation, a broad overview is given of network theory and its application in neuroscience and neurology. Neurophysiological recordings such as electroencephalography (EEG), magnetoencephalography (MEG) and electrocorticography (ECoG), can be used to measure neural activity. These recordings can be used to characterize functional connectivity, which denotes the statistical interdependencies between elements of the system, for instance the synchronization of two simultaneously recorded EEG signals between different brain regions. Subsequently, functional brain networks can be analyzed using measures from network theory. Both in general and in the brain, an optimal network topology combines highly interconnected, specialized regions with global integration (a ‘small-world topology’). Functional connectivity in broad band (0.5-48 Hz) filtered neurophysiological recordings is decreased in patients with brain lesions, but different patterns are seen depending on the frequency band. It appears that the most significant disturbances are found in frequency bands below 10 Hz. In these lower frequencies, the small-world topology partly gets lost in patients with brain lesions, and alterations in functional connectivity are not restricted to the lesioned area. Importantly, these changes are related to cognitive deficits, and are affected by neurosurgical intervention. Moreover, functional connectivity increases during epileptic seizures, and interictal (i.e. in the period between two seizures) functional connectivity disturbances may be present in patients with lesional epilepsy. These changes seem to make the brain more vulnerable for the occurrence of epileptic seizures.

In section 2, a number of studies on local and global functional connectivity and functional networks in patients with brain lesions are described. Chapter 3 investigates the correlation between epilepsy duration, measured as time since the first seizure, and local functional connectivity as well as small-world characteristics, in the lesioned area. Average functional connectivity, measured with the phase-lag index (PLI), local clustering (a measure of local segregation), and average shortest path length (a measure of global integration) were studied in ECoG registrations from the temporal lobe of temporal lobe epilepsy (TLE) patients. Lower
Chapter 10 Summary

PLI, lower clustering coefficients, and lower small-world index in the broad frequency band (0.5-48 Hz) were correlated with longer epilepsy duration. This study showed that ongoing lesional epilepsy affects both the level of information exchange as well as the functional network organization in the affected temporal lobe of TLE patients. In chapter 4, global functional networks were reconstructed from preoperative resting-state magnetoencephalography (MEG) recordings in lesional epilepsy patients. Average functional connectivity strength and network topology were compared between patients with different histopathological lesions and healthy controls, and correlations with seizure frequency and cognitive deficits were explored. Low-grade glioma (LGG) patients showed decreased network synchronizability (i.e. stability of the synchronous state) and decreased global integration compared to healthy controls in the theta frequency range (4-8Hz). Patients with non-glial lesions (NGL) also showed decreased network synchronizability, as well as increased normalized average shortest path lengths, indicating a loss of global integration of information in the network. In contrast, networks of high-grade glioma (HGG) patients did not significantly differ from those of healthy controls. Altered global network characteristics correlated with seizure frequency in LGG patients, and with cognitive performance in both LGG and HGG patients. This chapter shows that the impact of lesions on functional networks differs between lesions with different histopathology, possibly due to variability in lesional growth pattern. Interestingly, decreased stability of the synchronous state in the theta band seems to make LGG patients more prone to the occurrence of seizures, whereas loss of global integration and stability of the synchronous state were related to cognitive decline. The correlation between network topology and seizure frequency is further explored in chapter 5. MEG recordings were made in glioma patients who were on levetiracetam monotherapy, directly after neurosurgery (T1), and six months later (T2). Higher theta band functional connectivity at T1 and T2 was related to a higher total number of seizures. Furthermore, a higher number of seizures was related to a less optimal, more random global network topology. No changes in global connectivity or network topology occurred over time. These results suggest that pathologically increased theta band connectivity is a hallmark of tumor-related epilepsy.

In section 3, the effects of interventions on functional connectivity and network organization are studied. In chapters 6 and 7, MEG recordings were projected on the standardized AAL atlas using beamforming, hereby providing an anatomical framework for this analysis. In chapter 6, functional connectivity changes within six months after surgery are studied in resting-state networks (RSN) of LGG patients, which are subnetworks with a known correlate to cognitive tasks. Lower alpha band connectivity in the default mode network (DMN) was increased after surgery, and this increase was related to improved verbal memory functioning. Similarly, right frontoparietal network (FPN) connectivity in the upper alpha band was increased after resection, which correlated with improved attention, working memory and executive functioning. These findings indicate that, at the source level, increased alpha band RSN functional connectivity in MEG recordings correlates with improved cognitive outcome after resective surgery. Chapter 7 studies functional connectivity and functional network alterations related to epilepsy outcome after surgery. Functional neural network analysis is a promising technique for more accurate identification of the target areas for epilepsy surgery, but a better understanding of the correlations between functional network characteristics changes due to surgery and postoperative seizure status is required. These correlations were explored in a longitudinal magnetoencephalography (MEG) recordings of 20 lesional epilepsy patients. Resting-state MEG recordings were obtained at baseline (preoperatively; T0), and at 3-7 (T1) and 9-15 months after resection (T2). Functional networks were characterized with a new approach based upon the minimum spanning tree (MST), that might represent a critical backbone of information flow in weighted networks. We found a significant positive
correlation between functional connectivity in the lower alpha band and seizure frequency at T0, especially in regions where lesions were located. MST leaf fraction, a measure of integration of information in the network, was significantly increased between T2 and T0, only for the seizure-free patients. Finally, betweenness centrality, a measure of hub-status, decreased between T0 and T2 in seizure free patients in regions that were anatomically close to resection cavities. These results increase insight into functional network changes in successful epilepsy surgery and might eventually be utilised for optimization of neurosurgical approaches.

Chapter 8 describes a study of temporary sedation of one hemisphere with intra-arterial amobarbital, which was used to simulate a reversible brain lesion. The intra-arterial amobarbital procedure (IAP or Wada test) is used to determine language lateralization and contralateral memory functioning in patients eligible for temporal lobe resection because of pharmaco-resistant epilepsy. During selective sedation of one hemisphere, functioning of the contralateral hemisphere was assessed by means of neuropsychological tests. Whole-brain network topology changed significantly after amobarbital injection: local clustering decreased in all frequency bands, while average shortest path lengths decreased in the theta and lower alpha band, indicating a shift towards a more random network topology. Network characteristics after injection of amobarbital were correlated with memory score: higher theta band small-world index and increased upper alpha path length were related to better memory scores. The whole-brain network topology in patients eligible for epilepsy surgery becomes more random and less optimally organized after selective sedation of one hemisphere. Furthermore, memory functioning after injection was related to network topology, indicating that functional performance is related to topological network properties of the brain.

In section 4, a modeling study is described that was performed to integrate and interpret the empirical findings from the previous sections. More specifically, chapter 9 aims to explain how focal lesions cause global alterations in functional brain networks, and the hypothesis is tested that interactions of damaged tissue with remaining brain areas globally affect functional connectivity. Local polymorphic delta activity (PDA), which typically characterizes EEG/MEG recordings of patients with cerebral lesions, was modeled and functional connectivity alterations were studied in an anatomic realistic model of human brain activity. Lesions were created by 1) altering parameters of individual neural masses in order to create PDA (i.e simulating acute focal brain damage); 2) combining this PDA with weakening of structural connections (i.e. simulating brain tumors), and 3) fully deleting structural connections (i.e. simulating a complete neurosurgical resection). Effects of these lesions on functional connectivity for remote regions were quantified using the synchronization likelihood while discarding direct connections with the lesioned areas. Not only structural disconnection but also PDA (in the context of intact structural connections) in itself caused functional connectivity decreases, and, interestingly, functional connectivity between regions that were not lesioned was also decreased. The specific pattern of connectivity alterations differed between lesion types. PDA in regions with a central role in the structural network had bigger impact than PDA in more isolated regions. These findings demonstrate that altered activity in damaged brain tissue, as measured with EEG/MEG, may cause global alterations in brain connectivity.