Neural networks and brain tumors: the interplay between tumor, cognition, and epilepsy

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CHAPTER 1

GENERAL INTRODUCTION
The famous Hungarian writer Frigyes Karinthy stated that all people in the world are interconnected through at most five other persons in his short story ‘Chains’.\(^1\) Although this assertion was rather unfounded at the time, it turned out to lay the foundation of this thesis. Karinthy’s prediction was confirmed almost forty years later, by social psychologist Stanley Milgram, who showed that all people in the United States are connected through at most five others. This renowned ‘six degrees of separation’ experiment is discussed in the next chapter, but it is clear that the experiment widened a branch of science that had for the most part been reserved to mathematicians and physicists. Milgram’s work stirred up research into social relations using the mathematical framework of ‘network theory’. Network theory refers to the analysis of topological features in any type of system, which can therefore be applied to all complex networks alike, including social networks.

Over the past decades, it has become increasingly clear that all complex systems have similar organizational characteristics, whether it concerns social networks, biological networks of proteins, or technological networks such as the Internet. Almost all of these networks share an architecture featuring local specialization combined with global integration. These two aspects are also hallmarks of the brain: optimal brain functioning depends highly on specific, detailed processing of input at the one hand, while global integration of several brain areas at the other hand is equally pivotal for overall functioning. Network theory is therefore highly relevant for understanding the human brain in health and disease.

Ironically, Karinthy’s relevance to the subject of this thesis extends beyond his pioneering work on social networks: he was diagnosed with a brain tumor at the age of 46. The tumor was resected in 1936, which inspired him to write a book about his experiences with the disease and its treatment.\(^2\) Karinthy, whose writing was most famous for its absurd humor, never lost his wit and wrote: ‘I went from humorist to tumorist…’. Karinthy died of the consequences of his brain tumor in 1938, as do most brain tumor patients, unfortunately.

Primary brain tumors account for approximately 2% of the incidence of all cancer types. However, the mortality rates of brain tumor patients are many times higher than those of most frequently occurring types of cancer. The annual incidence of primary brain tumors, of which gliomas – originating from the supporting tissue in the brain – occur most frequently, varies from 7 to 19 cases per 100,000 people.\(^3,4\) Glioma patients almost invariably die as a consequence of their disease; the median survival ranges from ten years in relatively slow-growing tumors to only fourteen months in patients suffering from the most aggressive and infiltrative subtype. Most patients with intracranial tumors experience devastating symptoms of their disease. These often include epileptic seizures and functional decline in the form of cognitive deficits. The mechanisms by which brain tumors lead to these two burdensome symptoms remain to be elucidated at this time.

In this thesis, network theory is applied to the brain in order to shed light on this interplay between the triad of brain tumor – cognition – epilepsy.

**Aims and outline of this thesis**

The general aim of this thesis is to expand our understanding of the impact and consequences of brain tumors on the brain and its functioning as a whole. As described above, brain tumors can be accompanied by a range of behavioral manifestations, of which cognitive deficits and epilepsy occur most frequently and usually involve the whole brain.
However, the pathophysiology of these symptoms is still incompletely understood. Several aspects of our general but complex aim are therefore investigated separately in several sections, in which the triad of tumor – cognition – epilepsy is the central theme.

**Section I: Introduction**

Chapter 2 introduces the other chapters of this thesis in greater depth. A historical perspective of network theory is offered and key features of networks are explained. Also, concepts in the aforementioned triad are described in detail. Furthermore, this chapter outlines the status of network analysis and its relation with brain tumors, cognition, and epilepsy at the start of this thesis.

**Section II: Cognition**

In this section, the inter-correlations between cognition, functional connectivity, and networks are first studied: chapter 3 investigates whether cognitive performance is related to functional connectivity and/or network topology in a group of healthy participants. In chapter 4, cognitive performance in a large group of low-grade glioma (LGG) patients is determined. It is investigated whether these patients show poorer cognitive performance when compared to healthy controls. Secondly, we investigate whether radiotherapy has late detrimental effects on cognition in a longitudinal study design. Subsequently, cognition and functional connectivity are addressed in brain tumor patients: in chapter 5, we determine whether there is a correlation between functional connectivity and cognitive functioning within a sample of LGG patients.

**Section III: Epilepsy**

This section focuses on studies into (tumor-related) epilepsy, and how this frequently occurring symptom of brain tumors relates to functional connectivity and brain network architecture. The network correlates of this second hallmark of brain tumor symptomatology are thus determined. In chapter 6, the diagnosis of epilepsy, which still presents problems in a considerable number of patients, is investigated in detail. It is determined whether functional connectivity can be used as a predictor of diagnosis, and whether it is a more sensitive measure than currently used methods. A specific type of epilepsy, namely absence seizures, is addressed in chapter 7. It is investigated whether changes in connectivity and network architecture occur from seizure start to seizure termination. In chapter 8, a group of patients with focal epilepsy due to circumscribed lesions (some of which tumors) is compared to a group of healthy participants, in order to determine whether functional connectivity and network topology differ between these groups. In chapter 9, cross-sectional data of patients with medial temporal lobe epilepsy are used to investigate whether epilepsy duration (i.e. time since first seizure) has an impact on functional connectivity and network characteristics. Chapter 10 concerns a longitudinal study of brain tumor patients, who all suffer from epilepsy. These patients are followed for one year, in order to investigate whether functional connectivity and network topology change over time. Moreover, clinical features of the seizures are determined, in order to investigate whether these features are related to both functional connectivity and network architecture.
Section IV: Reversible damage

Changes in functional connectivity and network topology in brain tumor patients have been investigated in the previous sections. It remains to be seen how other types of brain lesions may influence the brain network. In this section, two chapters focus on reversibly lesioning the brain during the Wada test. In this procedure, one hemisphere of the brain is selectively sedated, in order to test memory performance of the non-sedated hemisphere. The Wada test is performed in patients suffering from pharmaco-resistant epilepsy in whom resection of one of the temporal lobes is considered, but it can also be seen as ‘shutting down’ one part of the brain. This experiment allows us to investigate whether acute sedation of parts of the brain induces changes in connectivity and network architecture. Chapter 11 describes whether changes in functional connectivity occur after unilateral injection of the sedative. Changing network topology during the procedure is then addressed in chapter 12. Functional correlates of network topology are also investigated, by means of memory performance during sedation.

Section V: Treatment

Section V focuses on treatment effects of neurosurgery in brain tumor patients. Changes in functional connectivity and network topology due to tumor resection are investigated in a group of patients with various brain tumor types. Chapter 13 determines whether changes in functional connectivity occur after neurosurgery in these patients. In chapter 14, we investigate whether network topology changes after tumor resection. Both chapters also relate these changes to postoperative clinical outcome in terms of seizure-freedom.

Section VI: Summary and General Discussion

In this final section, the results and methodological considerations of previous chapters are summarized. Furthermore, governing hypotheses and possible implications for future research and clinical practice are discussed.
CHAPTER 15

SUMMARY AND GENERAL DISCUSSION
The general aim of this thesis is to expand our understanding of the impact and consequences of brain tumors on the brain and its functioning as a whole. In order to accomplish this complex assignment, several lines of research have been described in the different sections in this thesis, mainly focusing on the triad of tumor - cognition - epilepsy that has been outlined in the introduction.

In **chapter 2**, a broad overview has been given of the state of the art of network theory, of cognition and epilepsy research in brain tumor patients, and of the interrelations between the former and the latter. Summarizing what was known at the start of this research yields the following: (a) the brain can be seen as a complex network, (b) healthy brains are characterized by the small-world principle, (c) brain tumors interfere with this 'optimal' brain network topology and functional connectivity, and (d) both cognition and epilepsy seem related to brain network topology. Now, what further insights have been gained in this thesis?

**Cognition**

In section II, a number of studies into aspects of cognition are described. Brain tumor patients often display global cognitive deficits, which is somewhat surprising for a focal lesion. However, the network perspective provides an alternative possibility: that changes in whole-brain network topology in brain tumor patients may be responsible for overall cognitive deterioration. The association between cognition and brain networks was first addressed in healthy participants in **Chapter 3**. In this chapter, functional connectivity (synchronization likelihood, SL) and particularly network topology of the brain as measured with MEG are correlated to cognitive performance in healthy participants. Better overall cognitive performance is related to increased clustering and increased small-world topology in several frequency bands, corroborating previous results: two other studies using MRI also show increased structural and functional small-world topology to be related to higher intelligence quotient.

The work described in this chapter is one of the first studies to report on gender differences in resting-state network topology: women have less clustering and shorter path length than men in the delta band, suggesting greater efficiency but also more random network topology. Previous studies have suggested that gender differences in connectivity and network topology may be present during execution of cognitive tasks. However, gender differences during resting-state have rarely been investigated. Recently, anatomical gender differences with respect to network architecture have been reported, corroborating our finding of shorter path length in women. The cause of this gender effect remains to be elucidated: hormonal differences may influence network development differentially in men and women. These and our results combined indicate that gender is to be taken into account when investigating connectivity and networks in the brain.

In the following **chapter 4**, cognition is longitudinally investigated in a group of LGG patients. On average six years after diagnosis, these patients showed significantly decreased cognitive abilities when compared to healthy participants, but no differences were found between patients who had been treated with RT and those who had not. The research described in chapter 4 is performed another six years later, on average twelve years after diagnosis. Patients still prove to have significant cognitive deficits when compared to healthy controls. Furthermore, differences are found between patients who underwent radiotherapy and patients who did not. The radiotherapy group deteriorates...
significantly between six and twelve years after diagnosis, while the radiotherapy naïve group remains stable with respect to cognitive performance. No other studies have followed patients for as long as twelve years after diagnosis, and most studies using shorter follow-up times found no widespread cognitive differences between patients treated with radiotherapy and patients who did not undergo radiotherapy. Our results suggest that patients who undergo radiotherapy as primary treatment may indeed be at greater risk for cognitive deficits on the long run. Unfortunately, no neurophysiological time series were recorded in these patients, preventing us from relating cognitive deficits to network alterations.

The last chapter of the first section (chapter 5) investigates the correlation between resting-state MEG-based functional connectivity and cognitive functioning in a group of LGG patients and healthy controls. Results replicate previous findings, namely that these patients perform significantly poorer than healthy controls on almost all cognitive tests. Furthermore, patients show increased functional connectivity (SL) in the delta, theta, and lower gamma frequency bands when compared to controls, while connectivity in the lower alpha band is decreased. These results in part corroborate previous studies, which also report increased low-frequency SL in a group of varying brain tumor patients. However, a decrease in connectivity in the higher frequency bands has also been reported in these studies, which contradicts results in the gamma frequency in this chapter.

Other studies have reported changes in network topology in the previously mentioned cohorts of brain tumor patients. In a group of patients with varying tumor histopathology, decreased clustering and decreased path length (i.e. a more random network architecture) are reported. In contrast, the application of graph analysis to the LGG patients' data of chapter 5 shows opposite results in the theta band, namely increased clustering and thus more regular network topology. Possible explanations for these differences in both functional connectivity and network topology relate to the included patient sample (a homogeneous group of LGG patients versus a more heterogeneous sample of brain tumor patients) and the comparison that was made with healthy controls (matched to patients versus significantly different in age). Future studies should elucidate the pattern and direction of differences in connectivity and network topology between specific types of brain tumors and healthy participants.

Nevertheless, it is clear from this section that functional connectivity and network topology are indeed pivotal for cognitive functioning in healthy people: increased small-world topology (i.e. high clustering and short path length) are related to higher IQ and better cognitive performance. Moreover, both cognitive performance and functional connectivity are disturbed in LGG patients, and correlations exist between these two phenomena. Brain tumor patients consistently show pathologically increased connectivity particularly in the lower frequency bands (delta, theta), which is related to poorer cognitive functioning. Now, how does the frequently occurring symptom of epileptic seizures relate to connectivity and networks?

**Epilepsy**

To address this question, we performed five studies that further exemplify the importance of functional connectivity and network topology for (tumor-related) epilepsy. The first of these, chapter 6, describes the value of functional connectivity (SL based on the interictal EEG) as a predictor of diagnosis after a first event that is suspected of being an epileptic
seizure in a large group of patients. It is shown that patients who are later diagnosed with epilepsy have significantly higher theta band SL than those patients who are not diagnosed with epilepsy. Increased connectivity in this frequency band has been reported before in epilepsy patients when compared to healthy participants. It is interesting to note that only connectivity in the theta frequency range (4 to 8 Hz) differed between patients and healthy participants, the meaning of which has become clearer throughout further studies described in this thesis.

The results described in chapter 6 indicate that SL in the theta band is indeed both specific and sensitive when classifying patients with and without epilepsy, even when using the first interictal EEG. Up till now, the use of the EEG when diagnosing epilepsy has been limited to visual assessment of so-called ‘interictal epileptiform discharges’ (IEDs). However, sensitivity is quite low using this method (35 percent in our study). By using theta band SL in addition to visual inspection, the sensitivity of predicting diagnosis could be increased to 58 percent. Furthermore, accurate classification of patients in the absence of IEDs was 76 percent, while the neurologist stands empty-handed when only using visual inspection. These findings suggest that functional connectivity may be a useful additional tool to differentiate between patients who indeed suffer from epilepsy and need to be treated with AEDs, and patients who will not have another seizure and thus do not have epilepsy. The clinical value of theta band connectivity in epilepsy diagnosis should be addressed in future, prospective studies, but the current results are promising.

In the following chapter 7, network changes are described during absence seizures in children, as measured with EEG. Previous research has shown that functional connectivity tends to increase during seizures, although this hypersynchronization may be preceded by (local) desynchronization. Indeed, results of our study show increased SL in all frequency bands when comparing the ictal with the pre-ictal network structure, corroborating previous literature. Furthermore, both clustering and path length increase as the seizure starts, indicating that the functional brain network becomes more regular, which has also been reported before. This means that the pre-ictal network topology is more random than the ictal network architecture. Several studies have suggested that random networks are highly vulnerable to runaway hypersynchronization, and more random interictal network topology has been reported previously in (animal) model studies as well. The question remains: does the interictal network topology of human epilepsy patients differ from the healthy population?

The remaining three chapters in this section attempt to answer this question, focusing on interictal network characteristics of patients suffering from (tumor-related) epilepsy. In chapter 8, functional connectivity (i.e. PLI) and weighted network topology are investigated in a group of patients suffering from focal epilepsy due to circumscribed brain lesions (half of which are brain tumors) and compared to healthy participants. No differences in functional connectivity are found between patients and controls. However, lesional epilepsy patients do show increased clustering in the theta and lower alpha band as compared to healthy participants, and a tendency towards increased theta band path length is also found. This increase in clustering and path length is also reported by another group. These two studies suggest that interictal network topology in epilepsy patients are more regular than those of healthy controls. However, contrasting results have been published: decreased clustering and path length were reported in previously described unweighted MEG-based networks in brain tumor patients, and in fMRI-based functional networks of epilepsy patients, indicating a more random interictal topology in patients. The
reason for this discrepancy remains unknown, but methodology of network analysis may play an important part. Furthermore, the global aspect of clustering and path length could be a limitation, as local differences in network topology may cancel each other out. We will address this discrepancy to greater depth in the last part of this discussion.

Furthermore, this study is the first to report differences in functional connectivity and network topology between different types of brain tumors. HGG patients have significantly higher upper gamma band PLI than patients with LGG or benign lesions. Network topology also differs between groups, particularly in the theta band. HGG patients show the least alterations in network topology, while LGG patients and patients with benign lesion have significantly abnormal network architecture when compared to healthy controls, suggesting that slowly growing tumors and stationary lesions may induce more extensive reorganization than tumors that grow rapidly. Furthermore, epileptic seizures occur in a much higher percentage of LGG patients than HGG patients, which may also influence connectivity and network topology. The specifics and the clinical significance of these differences remain to be investigated in future studies.

In addition to differences between patients and healthy controls, associations between network topology and epilepsy characteristics are found in lesional epilepsy patients. Increasing theta band path length is related to longer epilepsy history, higher seizure frequency, and AED polytherapy, indicating that more regular interictal network topology is related to more severe epilepsy. These findings contrast several model studies, which suggest that more random network topology would be related to higher vulnerability to seizures. The level of measurement and network methodology may in part explain these differences. Regardless of these contradictions, our results illustrate that network topology in patients is of functional importance in terms of epilepsy. Furthermore, particularly the theta band again proves to play a pivotal role in epilepsy.

**Chapter 9** investigates the correlation between duration of epilepsy (i.e. time since first seizure), functional connectivity (PLI), and network topology within the temporal lobe in MTLE patients by using ACoG recordings. In contrast to the results in chapter 8, it is shown that increased connectivity, higher clustering coefficients, and higher small-world index (all in the broadband) are associated with shorter duration of epilepsy. These findings indicate that network topology in the temporal lobe becomes more random as the duration of epilepsy increases, corroborating findings from some of the previous work (chapter 7 and 114,276) but contradicting other studies (chapter 8 and reference 257). However, the current study differs from these studies with regard to the network modalities that were measured: only connectivity and network topology of the temporal lobe were investigated in this chapter, while other studies took the whole brain into account. Local differences in connectivity in epileptic brains have been reported previously, which corroborate these findings.224

Chapter 9 describes a cross-sectional study, but changes in network topology in a longitudinally followed cohort of patients are also reported in this thesis. In **chapter 10**, a group of brain tumor patients suffering from epilepsy is followed over the course of their disease and treatment. Patients are included after tumor resection, and all patients use the same AED (levetiracetam). They are followed with MEG recordings up to one year after neurosurgical intervention. Results show that there are no changes in either functional connectivity or network topology during the year following tumor resection. This is remarkable, as seizure frequency does decrease significantly and patients undergo several types of tumor-treatment (i.e. chemotherapy and/or radiotherapy). Unfortunately, no other
studies have investigated connectivity and network topology over time, denouncing comparison to other work.

Associations between the theta band and epilepsy characteristics are found again in these brain tumor patients: higher theta band connectivity is related to increased number of total seizures at the first and second time points, corroborating our results from chapter 6 and chapter 13. Also, higher number of seizures is associated with longer path length and higher edge weight correlation in the theta band, indicating that a less optimal, more random network topology is related to a greater number of seizures.

Reversible damage

In previous chapters, we have demonstrated that brain tumors and stationary other types of lesions that cause epilepsy are accompanied by changes in functional connectivity and network topology. In the following two subsequent studies, the effects of a reversible ‘lesion’ on the brain are investigated. The EEGs recorded before and during the Wada test, or intra-arterial amobarbital procedure (IAP), were used for both studies. In chapter 11, changes in functional connectivity after injection of the sedative are reported. Results show that connectivity increases within the hemisphere that is injected. However, connectivity within the contralateral hemisphere and also interhemispherical connectivity changes after sedation, depending on the frequency band that is analyzed. In the lower bands, both interhemispherical and within-hemisphere connectivity decrease significantly, while the opposite is true for the higher frequencies. These results are comparable to what seems to happen in brain tumor patients (see chapter 5), and indicate once more that a focal lesion has significant impact on the brain as a whole.

The influence of the IAP on network topology is discussed in chapter 12. It is shown that the whole-brain network becomes more random after injection of amobarbital in all frequency bands. Moreover, theta band network topology is correlated to memory performance during sedation: increased small-world topology is associated with better memory functioning. These results confirm the functional correlate of network architecture that has been reflected on in section II. They show again that the brain can be seen as a network, and that any functional alteration in one part of the network is accompanied by changes throughout the whole system. But: what happens to the brain network after a commonly applied treatment modality in brain tumor patients, namely (partial) tumor resection?

Treatment

We investigated a patient population comprising of tumor patients with several types of histopathological diagnoses with MEG before and after neurosurgical intervention. Some of these patients underwent biopsy only, while gross total tumor resection was achieved in others. All patients suffered from epileptic seizures before the operation. In chapter 13, functional connectivity (PLI) is calculated, and related to postsurgical outcome in terms of seizure-freedom. Results show that theta band interhemispherical connectivity decreases after surgery. This result is highly interesting, particularly when combining these findings with results of chapter 5, in which we reported LGG patients to have increased functional connectivity in (amongst others) the theta band. The decrease in theta band connectivity could speculatively be a ‘normalization’ of the pathologically increased connectivity that is
found in brain tumor patients. This idea is further supported by the clinical association that is reported in chapter 13: a greater decrease in theta band connectivity is associated with seizure-freedom after surgery, while patients who show only a small decrease or increase of connectivity in this frequency band still tended to suffer from seizures.

Chapter 14 describes changes in network topology after tumor resection in the same group of brain tumor patients. After surgery, patients’ network architecture had more small-world characteristics in the lower alpha band, as indicated by increased clustering and small-world-index. Interestingly, this change was significantly present in the group of patients who did not have seizures after neurosurgical intervention, while patients still having seizures did not show changes in network topology after resection. Although it remains unknown why the lower alpha band is implicated in this study while other work points towards the importance of the theta frequency range, it is clear that (more optimal) network topology is related to functional status in terms of epilepsy.

Implications for future research

The work that is described in this thesis promotes a network theoretical approach towards the brain and in particular the brain that is invaded by a tumor. When these studies started, methods of investigating functional connectivity and network topology were scarce and use of this theoretical framework for brain research was rather novel. Luckily, network theory and its application to neuroscience have gained considerable attention during the course of this work. Findings from the studies that comprise this thesis are encouraging with respect to the functional correlates and clinical application of network theory in both healthy people and patients. In brain tumor patients specifically, the application of network theory seems to advance our understanding of how a localized tumor gives rise to global cognitive deficits and whole-brain hypersynchronization. However, we are still only beginning to unravel the true implications of network topology of the brain. Some gaps and limitations of the work described in this thesis should be noted and could aid in designing future studies.

First of all, the choice of methodology when investigating connectivity and network architecture in the brain is still debated upon. Several methods of calculating functional connectivity are available. In this thesis, the phase lag index and synchronization likelihood are used, either separately or concurrently. These two measures, although both an index for connectivity, are very different in essence and are likely to assess different aspects of correlations between time series. Although the type of measurement of functional connectivity does not seem to influence some of the reported results, different results are also found when using different connectivity measures (e.g. chapter 14). Other research groups have used a whole range of other measures, many of which have been compared in a recent methodological paper. However, even when considering this paper, it remains unclear which measures are best under which conditions.

Network construction based on neurophysiological time series is also different across publications and is possibly even more problematic to reliably decide upon than connectivity. Network topology is based on the measure of functional connectivity that is used, hereby introducing a first arbitrary component. Furthermore, it is not yet clear whether weighted or unweighted network analysis is superior. In unweighted network analysis, all information on edge strength is discarded. Moreover, setting a threshold in order to render the graph binary is arbitrary and setting a fixed threshold poses problems
when comparing groups with different connectivity strength. The latter disadvantage can in part be controlled by not using a fixed threshold of connectivity, but by choosing an average number of connections per node (k or degree). However, this method still does not guarantee comparability across networks of different size or average connectivity: raising k in a more sparsely or less strongly connected network will lead to a difference in the connections that are considered in the analysis. In this case, the sparser network will almost certainly become more random than the network it is compared to. The benefit of weighted networks exists in the inclusion of all available information, which is why it is also used increasingly in neuroscience. However, this method may also induce a higher level of noise to the analysis, by including connections with a very low weight. Recently, authors have been using both weighted and unweighted methods concurrently, by first thresholding all connectivity values until a set percentage of connections is left. Subsequently, the remainder of the correlations is used for weighted network analysis.92

This thesis focuses on two features of networks, namely the clustering coefficient and average path length, that are described by Watts and Strogatz in their seminal Nature paper.7 The formulation of these network variables signified a giant leap for network theory in the field of neuroscience as well as in other scientific areas, as they were easy to apply and almost immediately led to interesting results (see chapter 2). However, a critical look at the small-world network as the framework that is used in this thesis and other recent studies induces a feeling of insufficiency. Although clustering and path length are obviously very important for network organization and also for brain functioning, it is becoming increasingly clear that other network characteristics are also pivotal in this respect. It has recently been stated that assortativity (i.e. the network equivalent of ‘the rich getting richer’, see chapter 2) may also be important in the brain.157 Assortativity (which is equivalent to degree correlation or edge weight correlation) is only indirectly assessed in some chapters of this thesis, but extensive research into this characteristic of network may elucidate some more of the mechanism underlying the triad of tumor – cognition – epilepsy. Another up and coming measure in network theory is ‘modularity’.42 This term refers to the extent to which subclusters or modules that can be differentiated in the entire network. Such a module is characterized by high connectivity within itself, while connections between modules are few. Modularity could therefore subserve both specialization and integration, which are both needed for optimal brain functioning. Several studies in healthy participants have shown that the brain is indeed organized in functional modules, and five to seven modules have consistently been reported,392-394 but studies on anatomical modularity have not been performed as yet. Furthermore, investigation of modules can also yield additional information on the role that different brain areas have in the network. ‘Hubs’ have been mentioned in chapter 2, but they have only rarely been related to brain tumors, cognition, or epilepsy. One model study reports hubs to be highly important in propagation of hypersynchronization in simulated neural networks,261 but further information is lacking. With respect to modules, nodes (or brain areas) that are highly interconnected within one module can be differentiated from those areas that are links between several modules. In the only study investigating modularity with MEG in a patient population, MEG recordings of five patients suffering from absence epilepsy were compared to recordings of five healthy participants.282 Results showed that patients have fewer modules than healthy controls. While within-module connectivity does not differ between groups, patients’ between-module connectivity is higher in several brain areas.
These results indicate that some areas of the brains of epilepsy patients are more likely to be activated by several different modules, hereby putatively increasing synchronizability and thus seizure vulnerability of the network. Future studies should aim at elucidating the role of both structural and functional modularity in the healthy as well as in the diseased brain.

A third unknown factor in the current thesis relates to the impact of lesion type on network dynamics. Different patient populations are described in several of the chapters, but it is not yet clear whether for instance the development of gliomas is accompanied by other network alterations than lesions such as MTS. Within the lesional epilepsy patients, chapter 8 describes differences in network architecture between patients with HGG and patients with either LGG or benign lesions. It is conceivable that HGG, which grow relatively fast, leave less room for adaptation of the environment than the slow or not growing other types of lesions. From chapters 11 and 12, we can deduce that changes in functional network topology occur as fast as 30 seconds after sedation of one part of the brain, while tumor resection may also change functional network architecture for longer periods of time according to chapters 13 and 14. However, chapter 10 shows that network architecture is remarkably stable over longer periods of time in a group of brain tumor patients undergoing several types of treatment. Of course, the heterogeneity of the patient population may cancel out changes and reduces statistical power. However, the question remains in which time-scales plasticity occurs in the brain, and which lesions induce most plastic effects. A recent study has investigated functional connectivity and network topology in one patient who suffered a stroke in the right capsula interna and in eight healthy participants. Increased path lengths were found in the patient in the beta and gamma bands as compared to healthy controls, indicating that small-world topology decreases after stroke. Another study reports on changing network properties of the brain after stroke measured by fMRI. In this paper, patients’ motor networks were investigated longitudinally for a year after the stroke occurred. Results indicated that the motor network became more and more random over time, of which the authors suggest that an initially less optimized configuration is involved in regaining function. Possibly, a random outgrowth of functional connections is started after an acute lesion such as stroke, after which rehabilitation shapes the connections that are pruned or maintained. However, this study still does not clarify differences in plasticity according to lesion type. When the mechanisms underlying plasticity in different types of lesions could be elucidated using network theory, estimation of functional prognosis after for instance stroke or after neurosurgery might be improved.

One of the most consistent findings in this thesis concerns the role of theta band connectivity and network topology in brain tumor patients, (tumor-related) epilepsy, and cognitive (dys)functioning. The theta band represents an oscillatory pattern that has for long been thought to emanate from the hippocampal structures, after which it spreads to the outer layers of the brain. However, later studies have shown that other regions of the brain may also generate theta oscillations in certain cognitive states. As reviewed in chapter 10, there are numerous indications from network studies as well as neuron-specific papers that the theta band is important for both cognition and epilepsy. However, the specifics of the associations in the triad of tumor – cognition – epilepsy remain to be targeted in appropriate studies.

Lastly, clinical applications of network theory in neurological practice seem to be approaching as research proceeds. Chapter 6 shows that connectivity analysis may be a
useful addition to visual inspection of the EEG when diagnosing epilepsy. If this method
indeed proves to be an accurate diagnostic tool, patients could be treated accordingly or
may be reassured. Another paper shows that the functionality of brain tissue can
accurately be assessed with connectivity analysis.109 Moreover, connectivity is a good
predictor of post-operative functional outcome: in this study, areas with relatively low
connectivity could be resected without serious clinical consequences. Finally, two studies
using ACoG recordings of MTLE patients undergoing epilepsy surgery suggest that
connectivity peaks can predict the area of the temporal lobe that is most important in
seizure generation and propagation.146,152 When this area is resected, patients are more
often rendered seizure-free afterwards. Again, this finding suggests that epilepsy surgery
(and also tumor surgery) when tailored according to connectivity patterns could lead to
improved outcome, now in terms of seizure-freedom.

The results of studies in this thesis introduce physiological measures that may explain and
relate several important issues in neuro-oncology: functional deficits (i.e. cognitive
deterioration, epileptic seizures), plasticity, deterioration, and rehabilitation during the
course of the disease, and treatment-effects may all be related to functional connectivity
and the brain’s network topology. In the future, current measures of patients’ status (such
as progression-free survival, overall survival) may be replaced by these measurable
properties of the brain, which are relatively easy to determine and can be applied at any
time during the course of the disease. Ultimately, we hereby aim to apply our knowledge of
the brain’s connectivity and network topology to clinical practice.