General introduction
1.1 Brain tumors

Brain tumors can be subdivided in primary and secondary brain tumors. Primary tumors originate from the intracranial structures (arising from neuronal, glial, leptomeningeal, pituitary or lymphocytic cells), whereas secondary brain tumors (metastases) derive from solid or hematological malignancies elsewhere in the body.

The symptoms produced by the tumor depend on the localization in the brain, on the size of the tumor and on the rate of tumor growth. A brain tumor may give rise to focal neurological deficits, cognitive deficits, epileptic seizures and symptoms of increased intracranial pressure.

1.1.1 Primary brain tumors

The incidence of primary brain tumors in the Netherlands is 6.5 per 100,000 for men and 4.4 per 100,000 for women. Of these, 80% are gliomas, tumors arising from the supporting glial tissue of the brain. The annual incidence is approximately 800 newly diagnosed patients in the Netherlands. Glial tumors are subdivided according to the tumor type and are graded on the basis of the most malignant area identified at histological examination, according to the World Health Organization (WHO) system. A WHO grade I glioma (e.g. pilocytic astrocytoma) is a brain tumor which predominantly occurs in children. A grade II glioma (low-grade astrocytoma or oligodendroglioma) is a tumor that shows an infiltrative growth pattern in combination with cytological atypia. A WHO grade III glioma (anaplastic astrocytoma, mixed oligoastrocytoma or oligodendroglioma) shows increased mitotic activity, anaplasia, and has infiltrative capability, whereas a grade IV glioma (glioblastoma multiforme) is the most malignant glioma with anaplasia, high mitotic activity, and additional microvascular proliferation and/or necrosis.

1.1.2 Low-grade gliomas (LGG)

Twenty to twenty-five% of the gliomas are low-grade, including astrocytomas, mixed oligoastrocytomas as well as oligodendrogliomas. These tumors mainly affect young adults and can be indolent for many years. The first presenting symptom in the majority of LGG patients is a seizure. Median survival of these patients is approximately 7 years. Patients with a low-grade oligodendroglioma tend to have a better prognosis with a median survival of 9-12 years. These tumors may remain clinically stable for many years, but some patients show rapid radiological progression with development of neurological symptoms. Patients with a low-grade glioma can be confronted with impairment in cognitive functioning, which tends to be global and cannot unequivocally be explained by tumor localization alone. Established negative prognostic factors for survival in low-grade glioma patients are age over 40 years, tumor diameter of more than 6 centimeters, tumor crossing the midline and neurological deficits. Several aspects of optimal treatment of low-grade gliomas are still a topic for debate. A “watch and wait” policy is justified in those patients without any of the aforementioned negative prognostic factors. The decision to operate both patients with 1 or more negative prognostic factors or with signs of clinical or radiological tumor progression beyond a biopsy for histological
verification of the tumor rests on the presumption that the extent of the resection might be a prognostic factor in the outcome of these patients.\textsuperscript{14-17}

Both radiotherapy and chemotherapy affect survival of low-grade glioma patients although the optimal timing for these treatment modalities also still is subject to debate. A recent study showed no effect of early radiotherapy on median survival although the 5-year progression free survival of patients in the early radiotherapy group was significantly longer when compared to those who received delayed radiotherapy (i.e. radiotherapy at time of progression).\textsuperscript{5} Data on health related quality of life and cognitive function were lacking in this study.

In the late 1980s Cairncross and Macdonald reported that anaplastic oligodendrogliomas were more chemo-sensitive than had been expected.\textsuperscript{18} Since then, many reports confirmed this observation and demonstrated that deletions of chromosome 1p and 19q are associated with increased responsiveness of anaplastic oligodendrogliomas to radiation therapy and chemotherapy.\textsuperscript{19-22} There is growing evidence that these deletions are also involved in tumor genesis and chemo-sensitivity of low-grade astrocytomas.\textsuperscript{23-26} During the last decade, several studies have explored upfront treatment of newly diagnosed low-grade glioma (in particular oligodendroglioma) with chemotherapy (either PCV (procarbazine, CCNU and vincristine), CCNU alone or Temozolomide) in relatively small groups of patients. A prolonged progression-free survival in some patients was observed.\textsuperscript{23,24,27,28} An EORTC trial is currently under way to compare the effect of radiotherapy versus the effect of Temozolamide on progression-free survival of patients with low-grade gliomas (EORTC 22033-26033).

\subsection*{1.1.3 High-grade gliomas}

The high-grade gliomas include the anaplastic astrocytoma, anaplastic oligodendroglioma, anaplastic oligo-astrocytoma and the glioblastoma multiforme.

The most common and most aggressive high-grade glioma is the glioblastoma multiforme. The mean age of onset for glioblastoma is higher than for anaplastic astrocytoma (50 years vs. 40 years) and there is a male preponderance (sex ratio: 3:2).\textsuperscript{29} High-grade gliomas can present with neurological deficits related to the localization of the tumor as well as with signs of increased intracranial pressure (e.g., headache, vomiting, disturbed vigilance) or with epileptic seizures.

The median survival ranges from approximately 14 months in patients with a glioblastoma multiforme up to 5 years in anaplastic oligodendroglioma.\textsuperscript{30} Age, WHO performance status and the need for dexamethasone before the start of the combined therapy are independent prognostic factors in the outcome of patients with a glioblastoma multiforme.\textsuperscript{31} The goal of surgery is histological verification of the tumor on the one hand and cytoreduction on the other hand. Cytoreduction may result in alleviation of symptoms but the study of Sanai and Berger also showed that more extensive resection is associated with a longer life expectancy.\textsuperscript{32} Radiotherapy of glioma has been shown to be effective in several studies,\textsuperscript{33-37} although the clinical condition of the patient and his life expectancy have to be taken into account.

Nowadays, there is an important role for chemotherapy in the treatment of patients with a glioblastoma multiforme. In 2005, the results of an EORTC trial were published, comparing the
effect of radiotherapy combined with chemotherapy (temozolomide) followed by six adjuvant cycles of chemotherapy with the effect of radiotherapy alone. This study showed that the median survival of the patients who were treated with the combination of chemotherapy and radiotherapy was slightly better than the median survival of the combined treatment group (12 versus 14 months), and – more importantly – that the number of patients with a more than two-year survival increased from 10 to 26%. The authors concluded that the addition of temozolomide to radiotherapy for newly diagnosed glioblastoma multiforme resulted in a clinically meaningful and significant survival benefit with minimal additional toxicity.

Very interesting is the epigenetic silencing of the MGMT (O6-methylguanine-DNA methyltransferase) DNA-repair gene by promoter methylation compromising DNA repair which has been associated with longer survival in patients with glioblastoma receiving alkylating (BCNU and CCNU) or methylating agents (temozolomide). Whether there is an effect of this combined modality treatment in anaplastic astrocytoma will be evaluated in a new EORTC trial (26053-22054), that is currently under way.

1.2 Impact of a brain tumor on health-related quality of life (HRQoL) and neurocognitive function

During the last decades, studies evaluating new treatment protocols for brain tumor patients mainly focused on response measures, such as overall survival (OS) and progression free survival (PFS). Nowadays, it is generally recognized that the choice of treatment should include the evaluation of its effect on HRQoL. Since the treatment of primary brain tumors is not curative, morbidity during the remaining survival time is of major importance for both the patient and his or her care taker(s).

In the course of the disease the majority of the primary brain tumor patients are confronted with neurocognitive deficits, which can be induced by the tumor, the associated epilepsy and anti-epileptic drugs as well as by tumor treatment. These cognitive deficits may have a negative impact on HRQoL.

1.2.1 Health-related quality of life

HRQoL is a multidimensional construct which should encompass information of the tumor and its treatment on the patient’s usual or expected physical, psychological and social well-being, and is therefore important to measure in cancer patients as one of the secondary outcome measures. There are various scales to evaluate the HRQoL: these can be subdivided into generic and cancer-specific scales.

An example of a generic HRQoL questionnaire is the SF-36, which is a short-form health survey with 36 questions. It yields an 8-scale profile of functional health and well-being scores, respectively physical functioning, role limitations caused by physical functioning, bodily pain, general health perceptions, vitality, social functioning, role limitations caused by emotional problems, and general mental health. The raw scores are converted linearly to 0 to 100 scales, with higher scores representing better functioning. In addition to individual SF-36 scale
scores, two higher-order component scores can be calculated, a Physical Component Scale and a Mental Component Scale.

To assess brain tumor-specific symptoms issues, the generic SF-36 can be accompanied by the Brain Cancer Module (BCM 20), which is an example of a cancer specific scale. The BCM 20 contains five multi-item scales consisting of either future uncertainty, visual disorder, motor dysfunction, communication deficit, and emotional distress. It also contains 7 single items (headache, seizures, drowsiness, hair loss, itching, weakness in the legs, and difficulties with bladder control). Raw scores of the BCM 20 can be linearly converted to 0 to 100 scale scores, with higher scores representing lower levels of functioning. There are several cancer-specific HRQoL questionnaires, for instance the Cancer rehabilitation evaluation system-short form (CARES-SF), the City of Hope Quality of Life (Cancer Patient Version), the Daily Diary Card, the FACT-G with an additional version of the FACIT for brain tumors (FACT-Br), and the Functional Living Index-Cancer (FLIC).

The European Organization for Research and Treatment of Cancer (EORTC) initiated a research program to develop an integrated, modular approach for evaluating the quality of life of patients participating in international clinical trials (EORTC QLQ-C30). It incorporates nine multi-item scales: five functional scales (physical, role, cognitive, emotional, and social); three symptom scales (fatigue, pain, and nausea and vomiting), a global health and quality-of-life scale and several single-item symptom measures. The intention is that the QLQ-C30 will be supplemented by more specific subscales (‘modules’) to assess aspects of QoL of particular importance to specific subgroups of patients (e.g. the aforementioned Brain Cancer Module (BCM-20)).

Although brain tumors are often associated with a rapid functional decline and with poor survival rates, patients diagnosed with a LGG, as well as patients diagnosed with a HGG may enjoy relatively long periods of progression free survival. An earlier study showed that patients with LGG in comparison with patients suffering from low grade hematological malignancies experienced a worse QoL.

Relatively little is known on HRQoL during the disease course of patients with high-grade gliomas. Although one might intuitively expect a decrease in HRQoL in the course of the disease, this does not necessarily have to be the case. A recent EORTC study showed that newly-diagnosed GBM patients do not report lasting negative effects of tumor treatment with radiotherapy plus concomitant and adjuvant temozolomide on HRQoL, and even demonstrated a slight improvement after diagnosis, up till 6 months after they started the actual treatment.

Evaluation of the HRQoL is of major importance for the assessment of direct as well as long-term effects of a brain tumor and its treatment. Disease remission in the mid- to long-term survivors of the disease may be accompanied by a return to normal levels of functioning and well-being.
1.2.2 Neurocognitive function

In the course of their disease, the majority of glioma patients are confronted with impairment in neurocognitive function.\textsuperscript{7,47-51} Both the prevalence of neurocognitive deficits and changes in the course of the disease are highly variable between various studies, due to differences in patient and tumor characteristics, differences in treatment options, study design and the use of different screening instruments.\textsuperscript{52}

Most of the studies on neurocognitive function in brain tumor patients pertain to those with low-grade glioma and studies may have used insensitive screening instruments for this specific patient population, such as the Folstein’s Mini-Mental State Examination (MMSE) which is a widely used standardized short cognitive screening battery used to screen for dementia and which is not sensitive to other neurological disorders. The MMSE also does not take the education level into account, which means that a highly educated person may have a high score on the test although there are significant cognitive deficits. Another reason is the effect of aphasia on the results of the MMSE. Thirdly, in a more extensive test battery, the time to perform tasks is taken into account which is not the case in the MMSE. By using a more extensive neurocognitive test set, it is possible to detect small changes in a variety of neurocognitive parameters within one patient in the course of the disease. Neurocognitive summary measures can be calculated from such an extensive neurocognitive test battery, and further (based on the performance of healthy controls) it is possible to detect deficits in different neurocognitive domains. Tumor progression, tumor directed treatment, epilepsy and the use of antiepileptic drugs can influence neurocognitive function negatively, although tumor treatment, on the other hand, can also alleviate deficits.

The characterization of tumor- and treatment-related cognitive sequelae is important in both low- and high-grade glioma patients. Although glioma patients can remain clinically stable and without obvious neurological deficits after the initial diagnosis, neurocognitive deficits may have very serious and long lasting impact in various domains during the gained survival time: in the way the patients take care of themselves, in their leisure time and in their social and working life.

Brain tumor patients may suffer from reduced attentional functioning, working memory, psychomotor speed and executive functioning.\textsuperscript{12} The origin of these neurocognitive deficits in glioma patients is not completely understood. One might expect that the cognitive deficits simply reflect the specialized functions of the local brain regions that are affected by the disease (‘local destruction’). However, in slowly growing (low-grade) glioma, cognitive effects of local tissue destruction may be clinically unnoticed for a very long time. It appears that the neurocognitive deficits these patients are suffering from are more diffuse than one would expect on the basis of the localized lesion. It is thought that neurocognitive deficits depend on large-scale dynamical neural systems,\textsuperscript{53-61} and it is expected that the high prevalence of neurocognitive deficits in brain tumor patients is caused by diffuse changes in the network organization induced by the tumor, by tumor-related epilepsy and by tumor and epilepsy treatment (‘global disruption’).
Important aspects of pathophysiological processes underlying neurocognitive decline can be studied with functional imaging techniques such as functional Magnetic resonance imaging (fMRI), Positron emission tomography (PET), Electroencephalography (EEG) and Magnetoencephalography (MEG).

Functional MRI is based on the increase in blood flow to the local vasculature that accompanies neural activity in the brain. This increase results in a corresponding local reduction in deoxyhemoglobin because the increase in blood flow occurs without an increase of similar magnitude in oxygen extraction. Thus deoxyhemoglobin can be referred to as an endogeneous contrast enhancing agent. Changes in the blood oxygen level-dependent (bold) response in both resting state and during task/no-task situations can be used in the evaluation of underlying mechanisms of neurocognitive function in patient groups or in healthy controls.

PET imaging (positron emission tomography) also makes use of the fact that increase in neural activity results in an increase in regional cerebral blood flow (rCBF). which gives the opportunity to measure within a resting state and during various neurocognitive tasks. Electroencephalography (EEG) and magnetoencephalography (MEG) are distinct methods of which the EEG measures electrical activity generated by extracellular currents in the brain, while MEG detects magnetic fields related to intracellular currents.

2. Neurophysiological methods

As described in the previous paragraph, neurocognitive functioning in glioma patients can be affected by the tumor and by the treatment of the tumor, as well as by tumor-related epilepsy and anti-epileptic drugs, as described in chapter 1.2.2., and can be assessed by neuropsychological tests. The underlying pathophysiological mechanisms in the brain responsible for these neurocognitive deficits have not been elucidated. We hypothesize that neurocognitive functioning is reflected by the functional integration as measured with MEG. The observed MEG changes are thought to be the intermediate between the effect of tumor and tumor-related treatment on the one hand ("input") and neurocognitive deficits ("output") on the other hand (figure 1).

2.1 Magnetoencephalography (MEG)

Magnetoencephalography (MEG) is a neuroimaging technique that allows the recording of magnetic fields generated by brain activity. In 1968, David Cohen performed the first recording using 1 sensor. Nowadays, it is possible to make recordings from the whole brain with 150 or more sensors simultaneously (‘whole head MEG’).

The MEG detects the magnetic field generated by intracellular neuronal currents, in contrast to the electroencephalogram (EEG), which corresponds to the activity generated by the extracellular currents. The tiny magnetic field, in the order of femtotesla (10⁻¹⁵ tesla), generated by the brain can be detected by the low temperature superconducting quantum interference devices (SQUIDS) which can transform the time-varying magnetic field into time-varying voltage. MEG can have a much higher spatial density than EEG. Furthermore, MEG does
not need a reference electrode and for this reason is more suitable for estimating rhythm synchronization. A third advantage is that the magnetic field is less distorted by the skull and the scalp than in EEG registrations. Other functional neuroimaging techniques, such as fMRI and PET are more accurate in the precise localization of activity and therefore have a higher spatial resolution, but these techniques have a much lower temporal resolution compared to MEG.

2.2 Functional connectivity

Synchronization of neuronal activity plays an important role in the integrated activity of different brain areas. The understanding of this integration is important in the context of information processing in the healthy and diseased brain. The functional interactions are studied by computing synchronization of time series of activity from the different brain regions. Statistical interdependencies between such time series are referred to as ‘functional connectivity’. The ‘effective connectivity’ on the other hand refers to the direct influence of one neural entity on a second, which means that functional connectivity does not necessarily imply a causal link whereas the effective connectivity does.

The functional integration can be computed both at rest or during a task. Recent fMRI research has shown that the no-task resting state is stable and active and is characterized by activation of a ‘default’ network, which is suspended in case of specific goal-directed
behaviour. Besides the default network more different patterns during rest can be found with potential functional relevance consisting of regions which are known to be involved in visual and auditory processing, motor and executive functioning, and memory.\textsuperscript{63} Resting state functional connectivity has been studied with EEG and MEG in different brain disorders, such as Alzheimer’s disease,\textsuperscript{65-69} Parkinson’s disease,\textsuperscript{70,71} and multiple sclerosis.\textsuperscript{72} It has recently been shown in patients with Alzheimer’s disease and Parkinson’s disease that resting state connectivity is a reliable indicator of neuropsychological functioning.\textsuperscript{67,69-71} Previously, these time series of magnetic field strengths were quantified with linear techniques such as coherence, a normalised measure of linear correlation as a function of frequency.\textsuperscript{73,74} Measures of statistical interdependencies between time series which are sensitive to both linear and non-linear interdependencies are the phase synchronization,\textsuperscript{75} synchronization likelihood (SL)\textsuperscript{76} and the phase lag index (PLI).\textsuperscript{77}

2.3 Graph theoretical analysis of complex brain networks

The synchronization processes are believed to play an important role in coordinated and integrated activity to optimize information processing between widely distributed brain areas and can therefore be best described from the perspective of a network theory. The functional connectivity of the brain is probably evolved to optimize information processing and to support high dynamical complexity at the one hand and to be “cost efficient” on the other hand. It remains unclear whether changes in the mean level of coupling are also associated with changes in the global organization of functional networks. The modern theory of networks originated with the discovery of small-world networks in 1998 and scale-free networks in 1999. Watts and Strogatz introduced a simple model of a one-dimensional network on a ring. Starting from a ring lattice with $n$ nodes (e.g. vertices) and $k$ links (e.g. edges) (which is called the degree of a network) per vertex, each edge becomes rewired randomly with the probability $p$. By increasing probability $p$, more edges become rewired until the probability $p$ becomes 1. A graph with a probability $p = 0$ represents a complete ordered graph or lattice whereas a graph is completely random at a probability $p = 1$. Intermediate networks represent graphs with a probability $p$ which lies between 0 and 1 and these so-called ‘small-world’ networks seems to be crucial in the aforementioned optimized information processing.\textsuperscript{78} Watts and Strogatz formulated two measures to describe a graph. These parameters are the so-called “clustering coefficient” and the “path length”. The clustering coefficient (C) is a measure of the local structure, indicating the proportion of neighbouring vertices that are interconnected. The path length (L) describes the global integration by measuring the mean number of steps to go from one vertex to another vertex. By computing these two parameters, networks can be described from regular (in which there is a high local interconnectedness characterized by a high C and a long path length) to a completely random network (with a low local clustering characterized by a low C and a short path length). The intermediate graph or so-called small-world network combines the high local interconnectedness of a regular network and a short path length of a random network.\textsuperscript{78} Figure 2 shows the three different graphs.

Many networks (social networks, neural network of the C. Elegans and man-made networks
such as the architecture of the power grid system in the USA) show characteristics of “small-world networks”. The specific architecture of these “small-world networks” seems to be optimal for information processing in the brain.79,80

Graph theoretical properties of neural networks have been studied before in healthy subjects,81-85 and in patients with brain pathology such as Alzheimer’s disease (AD).69,86 These studies show a small-world configuration of the neural network in healthy subjects and a more random network organization in the AD population. Brain tumor patients have a localized lesion but show global cognitive deficits: for that reason it is interesting to study their network organization.

Fig 2. Three different graphs in the model of Watts and Strogatz.
References

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Outline of this thesis
The purpose of thesis is to assess the impact of primary brain tumors on Health-related quality of life (HRQoL) and on neurocognitive functioning in the course of the disease. In order to find an explanation for the diffuse neurocognitive decline, the effects of brain tumors on underlying functional networks in the brain were investigated.

In chapter 3, we describe HRQoL and neurocognitive functioning of newly diagnosed high-grade glioma patients. In chapter 3.1 we evaluate HRQoL of patients with a long-term survival and compare these results with HRQoL of patients with a short-term survival. In chapter 3.2 neurocognitive function of high-grade glioma patients during follow-up and during tumor recurrence is evaluated.

The neurocognitive deficits that are found in brain tumor patients are more global than can be explained on the basis of the localized lesion. In chapter 4 we describe the use of functional imaging techniques to evaluate underlying mechanisms of these widespread changes in neurocognitive functions. Cognitive function depends on large-scale dynamical neural systems, and it is expected that the deficits found in brain tumor patients are caused by diffuse changes in the network organization induced by the tumor, by tumor-related epilepsy and by tumor treatment.

In chapter 4.1, the results of a MEG study are described, in which functional connectivity in patients with a variety of brain tumors is studied. These results are compared to the results in healthy controls. In chapter 4.2 the spatial organization and strength of the underlying networks in the same patient population were evaluated.

Subsequently, we tested our hypothesis of widespread changes in network organization to be associated with neurocognitive function in low-grade glioma patients, since the majority of these patients do suffer from global neurocognitive deficits. In chapter 5, we describe the results of our analysis of the MEG registrations of these low-grade glioma patients and matched healthy controls. In chapter 5.1, the results of the power analysis and the correlation of these changes with neurocognitive function are described. The differences in functional connectivity between the LGG patients and healthy controls are described in chapter 5.2. The results on the neurocognitive tests in the low-grade glioma patients are correlated with the functional connectivity. In chapter 5.3 we analyze the specific architecture of the network organization in low-grade glioma patients and compare this to the same matched healthy control population. We were able to correlate neurocognitive functioning with the strength and spatial organization of the network.