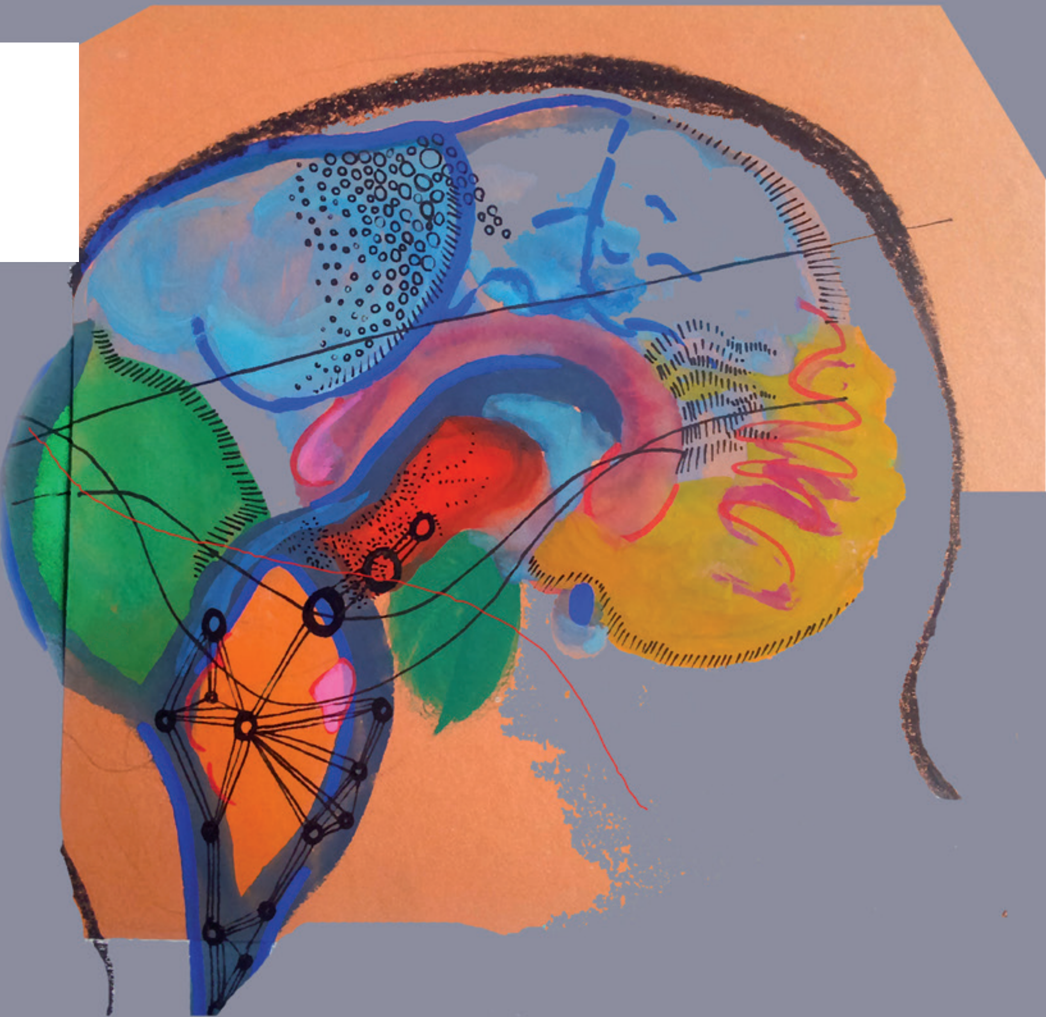
SPEAKING ON THE EDGE

The protection of cognition after glioma surgery in eloquent areas



Djaina Satoer

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SPEAKING ON THE EDGE:

The protection of cognition after glioma surgery in eloquent areas

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Voor mijn allerliefste oma

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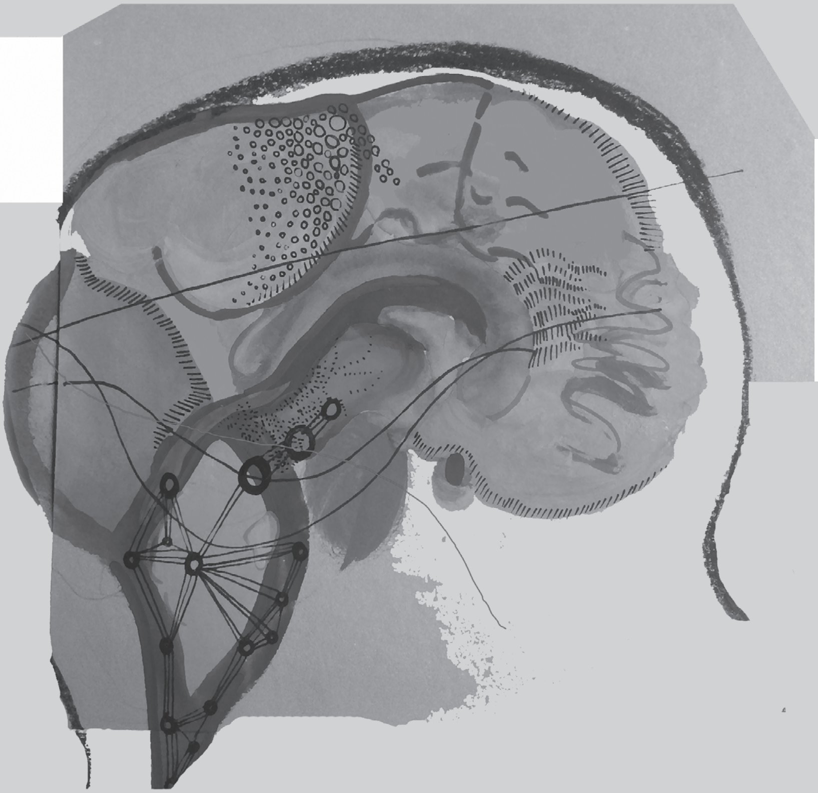

Chapter 1

General introduction

COGNITION AND COGNITIVE IMPAIRMENT

Cognitive impairment is a broad term to refer to a defect in brain function(s) related to the ability to think, concentrate, formulate thought and/or to solve problems. Cognitive impairments can be caused by several acquired brain diseases, such as stroke, traumatic brain injury, vascular infection, neurodegenerative disease or by a brain tumor. The profile and severity of cognitive disturbances may depend upon the nature of the brain lesion. The cognitive disease profile could be for instance diffuse, characterized with a global decline of cognitive functions resulting from damage to wide-spread areas in the brain, as in Alzheimer dementia. Other diseases, resulting from more region specific brain damage, may cause more pronounced deficits in a specific cognitive domain, such as language in stroke patients. Hence, the type of impairment can be related to the site of the lesion, such as pronounced disturbances in language and calculation in the dominant left hemisphere, and in the right hemisphere deficits in visual-spatial perception and direct attention. Data from neuroimaging studies, such as functional Magnetic Resonance Imaging (fMRI) and Diffuse Tensor Imaging (DTI) have played an important role in revealing that the classic topological view of functions (i.e. static organization) should be combined with a hodotopical view (i.e. adaptive and dynamic organization of functions)[1]. Several subcortical networks and also individual variability play an essential role in cognitive functions. Neuronal interactions underlie the dynamics and self-organization of cognitive and behavioral networks[2]. Apart from the static anatomical organization, language and other (non-linguistic) cognitive functions are distributed among multiple cortical and subcortical networks which could vary between individuals.

COGNITION IN GLIOMA PATIENTS

A less frequent but severe brain disease which can cause cognitive disturbances is a brain tumor. Brain tumors may arise from a tumor elsewhere in the body, i.e. a brain metastasis, or from the brain tissue itself, i.e. a primary brain tumor. The most frequent occurring primary brain tumors are gliomas. The incidence of newly diagnosed gliomas is about 5-7 per 100,000 each year in the Netherlands[3]. They consist of low grade gliomas (LGG) and high grade gliomas (HGG). LGGs are histologically classified as astrocytoma, oligodendroglioma, or mixed oligoastrocytoma (grade II defined by World Health Organization). HGGs are more aggressive and consist of anaplastic astrocytomas and glioblastomas (grades III and IV respectively). Despite a relatively stable state which can last for several years after diagnosis of LGGs, progression into a more aggressive form (anaplastic glioma or secondary glioblastoma) is inevitable. LGGs typically affect young adults, they are usually discovered by epileptic seizures and are often located in “eloquent areas” of the brain. These areas contain important functionality, this means that surgical access and resection increases chances of neurological damage. The most best known eloquent areas are the dominant temporal lobe (e.g. language function), both parietal lobes (e.g. sensorimotor functions, visuospatial abilities, reading and calculation), parts of the dominant frontal lobe (e.g. motor and language function), insula and basal ganglia (e.g. memory function). The severity and the type of cognitive disturbances may depend on size, localization and grade of the tumor. Because of the slow growth rate of LGGs (approx. 4 mm p/y)[4], reorganization of neurological functions may be facilitated, and probably therefore patients are only mildly impaired at neurological and/or cognitive level. Despite the absence of severe cognitive disturbances, which seems at first glance rather striking, patients and/or proxies often report differences and problems in daily life functioning (during anamnesis). For instance, they mention word-finding problems and reduced fluency of speech, general slowness, changes in short-term memory and/or difficulties in the planning of complex tasks. Some patients mention changes in cognitive functioning but they cannot describe exactly how their functioning has changed, and there are also patients who do not report cognitive problems at all.

LANGUAGE AND COGNITION

Little is known about the type, severity and extent of language and other cognitive disturbances in patients with LGG. In stroke patients, it is known that language disturbances (aphasia) are frequently accompanied by other cognitive disorders[5]. Only few researchers have structurally and prospectively analyzed cognitive brain functions in LGG patients. Because of the often imprecise complaints of the patients, it appears to be difficult during anamnesis to pinpoint the exact cognitive difficulties LGG patients cope with. See fragments 1 and 2 below of 2 patients for illustration.

Fragment 1 (original) – no cognitive complaints, epileptic seizures
Patient 77: female, 31 years old, education VMBO

Investigator: "heeft u klachten op cognitief gebied zoals we dat noemen dus taal geheugen…"
Patient 77: "nee heb ik eigenlijk nog niet, problemen mee"
Investigator: "want waaraan heeft u gemerkt ja dat u uiteindelijk deze eh hersentumor heeft"
Patient 77: "ik heb het eigenlijk gemerkt doordat ik eh twee jaar geleden epileptische aanvallen kreeg"

Fragment 1 (translation)

Investigator: "do you have complaints at the level well, at cognitive level as we call it, so language, memory…"
Patient 77: "no I don't have problems with it yet"
Investigator: "so how did you notice , the existence of this brain tumor"

Patient 77: "well I noticed eh because I suffered from epileptic seizures 2 years ago"

Fragment 2 (original) – no clear cognitive complaints
Patient 93: male, 36 years old, education hogeschool

Investigator: "dus u heeft eigenlijk geen problemen cognitief?"
Patient 93: "nou het gaat niet zo snel als het zou moeten gaan, ik heb het idee dat ik iets trager ben"
Investigator: "dat snap ik, maar verder heeft u eigenlijk geen klachten"
Patient 93: "nee"

Fragment 2 (translation)

Investigator: "so you don't have any complaints, cognitively?"
Patient 93: "well, it doesn't go as fast as it should go, I have the idea that I am a bit slower"
Investigator: "I understand, but apart from that you don't have other complaints"
Patient 93: "no"

Consequently, the traditional clinical neurological tools or brief neuropsychological instruments, such as Karnofsky Performance Score and Mini Mental State Examination, used to evaluate the cognitive status of LGG patients, were not sufficiently sensitive to detect cognitive impairments[6, 7]. Therefore, for a long time, an in-depth examination of cognitive deficits in these patients was ignored. Recently, more elaborate neuropsychological testing did reveal the existence of cognitive deficits. One or more impairments were present in almost all of these patients at different cognitive levels, such as in the domains of language, memory, attention and the executive functions[8-10].

It is evident that language and the other cognitive skills are not completely separate functions. Primary non-linguistic cognitive mechanisms may be the source for linguistic impairments, as has been shown for working memory and attention[11, 12]. Subsequently, primary language disorders are reported to influence capacities in non-linguistic domains such as problem solving[13]. The relation between language and other cognitive functions is illustrated by the fact that patients with a persisting aphasia after stroke had a worse performance in more cognitive domains than aphasic stroke patients with a relatively good recovery[13, 14]. At the same time, the fact that the same study shows that non-linguistic impairments were present in both persisting and recovered aphasia patients in the year after stroke[14] indicates that the relation between aphasia and other cognitive disorders is not very pronounced. In a clinical setting, there is an ongoing debate on the feasibility of measuring cognitive functions in the presence of language impairments. A relevant observation in this respect is that only a minority (25%) of the variance in non-linguistic performance can be accounted for by auditory comprehension[15]. Nearly all research on the relation between language and other cognitive disorders is based on the performance of patients with a stroke, neurodegenerative diseases or developmental disorders. In one study with glioma patients, our subjects of research, it was found that language performance (naming) did not affect performance on other cognitive tests[16]. Hence, the use of extended standardized neuropsychological tests in the different cognitive domains is mandatory to better identify and understand the cognitive profile of this patient group.

SPONTANEOUS SPEECH IN GLIOMA PATIENTS

Adequate spontaneous speech in a conversational situation requires an integration of meaning, sound and syntax to bring "the message across". The most suitable way to evaluate the quality of communication is a quantitative analysis of "aphasic symptoms" in the spontaneous speech, as already demonstrated in other clinical populations[17]. An interview setting with open questions (e.g. during clinical examination) seems to be the best opportunity to elicit as much speech as possible in order to measure conversational skills resembling daily life and subsequently to evaluate the conversational difficulties LGG patients encounter.

A decrease of everyday language skills is a well-known complaint of these patients and their proxies, but when tested, the usual language tasks such as naming and category fluency do not always reveal abnormalities, nor do they capture all the communication problems encountered by the patients. Apparently, the interpretation of formal language tasks in relation to daily conversation is not clear. As mentioned before, patients (or their proxies) point out changes in fluency of their speech, causing problems in their daily communication. This lack of fluency may have different causes, such as word-finding difficulties or an inability to maintain focused on the topic of conversation. See fragments 3 and 4 for illustration.

Fragment 3 (original) – word-finding and problems maintenance topic conversation
Patient 57: female, 51 years old, education primary school

Patient 57: "ja moet soms toch wel eens eh denken voor eh even voor eh een woord hé? namen meestal maar bijvoorbeeld ik ik zit nu ergens over te praten en dan kan ik bijvoorbeeld opeens kwijt zijn waar we het over hadden"

Fragment 3 (translation)

Patient 57: "yes have to think eh for a eh a while eh for a word, right? names mostly but for instance I I am now talking about something and all of a sudden I have lost the topic of our conversation"

Fragment 4 (original) – clear word-finding complaints
Patient 79: male, 63 years old, education university

Patient 79: "ja kijk iedereen heeft wel eens denk ik dat je een woord aan het zoeken bent hè? van ja hoe hoe hoe zat dat ook alweer maar echt zo dat ik een blokkade heb dat v(..) dat viel mij op en dat was eh wat ik zeg twee keer door de telefoon met name en dan die keer dus dat ik bij die eh longarts zat dat ik echt niet meer uit mijn woorden kon komen"

Fragment 4 (translation)

Patient 79: "yes well, I guess everyone is looking for a word now and then right? what what what was it again but really a speech arrest I experienced that struck me, that was eh what I said twice on the telephone and in particular that time when I was sitting at the pulmonologist I really couldn't find the right words."

In the neurosurgical literature there are some reports on a reduced spontaneous speech after glioma resection in the Supplementary Motor Area (SMA syndrome). This area, located high in the frontal lobe, is classically related to the planning and initiation of motor function, and not to language function[18]. Since spontaneous speech is difficult to evaluate with routine language tests such as naming and repetition, there is a need for an adequate tool to analyze and evaluate spontaneous speech. From clinical practice, it is known that damage to the SMA in relation to motor function shows almost always rapid and complete restoration, therefore surgery in this part of the brain is regarded as a low risk procedure[19]. However, the impact of (surgical) damage to the SMA on language function is largely unknown, and neither is the extent and speed of recovery. Research in this area requires detailed spontaneous speech analyses to elucidate the characteristics of this speech deficit.

GLIOMA SURGERY IN ELOQUENT AREAS

As LGGs are often located in eloquent areas, surgery may be associated with an unacceptable risk for serious neurological impairment. Therefore many of these tumors were deemed inoperable and consequently a "wait and scan" policy was applied for patients with such a diagnosis. Despite their slow growth rate, transformation to HGG is unavoidable and outcome will eventually be fatal. Median survival in LGG patients is between 5-8 years. However, surgical treatment is highly important to acquire tumor tissue for correct histological diagnosis and several studies have reported an improved prognosis after radical surgical resection of the tumor in an early stage[20].

For this reason, during the last 2 decades, surgery under general anesthesia for patients with gliomas became more frequently favored over a "wait and scan" approach. Preoperative non-invasive techniques such as Magnetic Resonance Imaging (MRI), functional MRI and Diffusion Tensor Imaging (DTI) are used to determine localization of the tumor and its proximity to functional areas. It appeared however, that neurosurgical decisions based solely on non-invasive neuroimaging techniques were not sufficient, because it was not possible to differentiate between essential cortical areas or regions which could be functionally compensated[21]. Therefore, intraoperative functional mapping by means of Direct Electrocortical Stimulation (DES) in awake glioma surgery was introduced. DES is a real-time technique to detect cortical eloquent areas, subcortical white matter bundles and deep grey nuclei by means of a bipolar electrode[22]. In addition to preoperative neuroimages, DES can be used to induce a "transient lesion" to reveal critical functional brain areas. This combination of techniques supports the neurosurgeon in optimizing the surgical treatment plan. Duffau et al.[23] among others demonstrated that, with DES, it was possible to extend the surgical indications for LGG resection (operating in or nearby eloquent areas), to improve the quality of the resection, and to decrease the number of neurological deficits in comparison to classic surgery under general anesthesia[24-27]. To our knowledge, only 1 study showed a slightly better (but not significant) outcome after classic surgery compared to awake craniotomy[28]. However, they did not apply DES during surgery, but stopped the resection when the patient showed language disturbances. A recent large meta-analysis revealed that patients operated without DES were more at risk for late postoperative neurologic problems than patients operated with DES[29]. Nonetheless, a disadvantage of DES concerns the possibility of false-positives or false-negatives, caused by fatigue of the patient, intraoperative epileptic seizures, and brain shift during surgery, which could lead to inadequate tumor resection. To avoid false-positives or false-negatives, delicate intraoperative language tasks are necessary, which must be assessed preoperatively to determine baseline. Presently, the combination of preoperative neuroimaging and awake brain surgery using direct electrocortical and subcortical stimulation is regarded the gold standard treatment strategy in LGG patients[30]. In order to maximize tumor resection while preserving cognitive function and consequently Quality of Life (QoL), the most appropriate and efficient intraoperative language tasks still need to be determined. Therefore structured and prospective long-term collection of data on cognitive function in these patients is mandatory.

EFFECTS OF GLIOMA SURGERY ON COGNITION AND QUALITY OF LIFE

Even though maximal preservation of functions is pursued, it has been demonstrated that glioma surgery may deteriorate existing cognitive disturbances or even induce new cognitive impairments. Based on experience and literature studies, it is known that most of these deficits are transient and recover spontaneously within 3 months. The majority of these studies, however, based their conclusions on basic neurological screening tests or on tasks limited to only one cognitive domain[10, 31-33]. Studies in which more extensive tasks were administered showed mixed results on cognitive outcome; both cognitive recovery as well as decline in comparison to the preoperative baseline level are reported[10, 16, 34, 35]. Hence it remains unclear whether spontaneous recovery indeed occurs within 3 months in the different cognitive domains. Due to brain plasticity, recovery of brain functions may take place at least until 1 year after surgery[36]. Therefore, follow-up longer than the traditional 3-month postoperative period, with an elaborate neuropsychological examination is necessary to determine possible permanent effects of glioma surgery on cognition. In addition, tumor or treatment related risk factors, such as tumor grade, volume, extent of resection and adjuvant therapy that are known to have potential influence on cognitive change should also be taken into account[37, 38].

Maintenance of Quality of Life (QoL) is an essential outcome measure in glioma treatment. Although QoL is a multidimensional concept referring to a patient's well-being and satisfaction with life, influenced by physical, emotional and social components associated with the disease in question, intact cognition is considered to be an essential part in QoL experience[39, 40]. It is known that patients with a brain tumor rate their QoL lower than healthy controls[41]. This can be caused by the disease itself, the treatment, prognosis at the moment of examination or by a combination of these aspects[42]. The influence of radio- and chemotherapy received a lot of attention in relation to QoL. In brain tumor patients epilepsy burden, cognition, depression, fatigue and emotional distress are the most relevant aspects associated with QoL[43-46]. Although cognition is generally assumed to be associated with QoL, a direct relation between objective cognitive test results and a subjective QoL rating has not been reported yet. This may again be explained by the use of brief neurological screening tests to assess cognition[47]. To better understand this predictive relation, more extensive neuropsychological testing combined with (global) QoL rating before and after surgery must be conducted. Investigation of QoL and its relation to cognition and emotional factors in glioma patients is crucial, as preservation of QoL could improve survival function[43]. The neurosurgical effects, in terms of possible postoperative damage, on QoL, however, are not entirely understood. As QoL is a wide-spread concept, our aim was to clarify the early effect of glioma surgery in eloquent areas on a global QoL rating as a first step towards broader research.

SUMMARY

The conclusive effects of glioma surgery in eloquent areas and the potential tumor- and/or treatment related effects on cognition and global QoL of the patient remain uncertain. Better understanding of impact of glioma surgery on the well-being of the patient is highly needed in order to choose the best treatment strategy. Maintenance of cognitive functioning is one of the most important outcome measures in glioma surgery, as (mild) cognitive disturbances may negatively affect patients' functioning and experience of daily life.

AIM OF THE STUDY AND OUTLINE OF THIS THESIS

The aim of this study is to determine the effects of awake surgery in eloquent areas in patients with a presumed low grade glioma. Using an extensive neuropsychological test protocol, a spontaneous speech analysis and global QoL rating, the short and long-term effects on cognition, language functions and quality of life were assessed in a large cohort of consecutive glioma patients. Extensive data analysis was performed and the following questions have been addressed in this thesis:

What is known about the impact of glioma surgery on the patients' cognitive functions?
A systematic review on the effects of glioma surgery in eloquent areas on cognition is provided. Sensitive tests for cognitive change will be discussed and it will be clarified, as revealed so far, whether glioma surgery in eloquent areas is a safe method to preserve cognitive functions (Chapter 2).

What are the early and late effects of glioma surgery on cognitive functions, language and global QoL?
The early effects of glioma surgery on cognition are reported, as measured with tests assessing the main cognitive domains of language, memory, attention, the executive functions and visuospatial abilities (Chapter 3).

The quality of verbal communication before and 3 months after surgery is measured by means of a detailed spontaneous speech analysis. The additional value of the assessment of daily conversation is demonstrated, next to several standardized language tasks, as usually assessed in glioma patients (Chapter 4).

The early effects of glioma surgery on global QoL, cognition and emotional factors are addressed. In addition, the predictive value of cognitive performance and emotional factors on postoperative QoL will be discussed (Chapter 5).

The long-term course of cognitive recovery in a single patient who developed a language deficit during glioma surgery near the Supplementary Motor Area is described. The clinical relevance of an analysis of daily speech and neuropsychological testing will be underlined (Chapter 6).

The long-term effects on cognitive performance until 1 year after glioma surgery are presented, as measured with an extensive neuropsychological test protocol in a large group of consecutive glioma patients (Chapter 7).

Finally, the main findings of the study will be outlined, as well as the clinical implications and suggestions for future research (Chapter 8) followed by a summary of the results of this thesis (Chapter 9).

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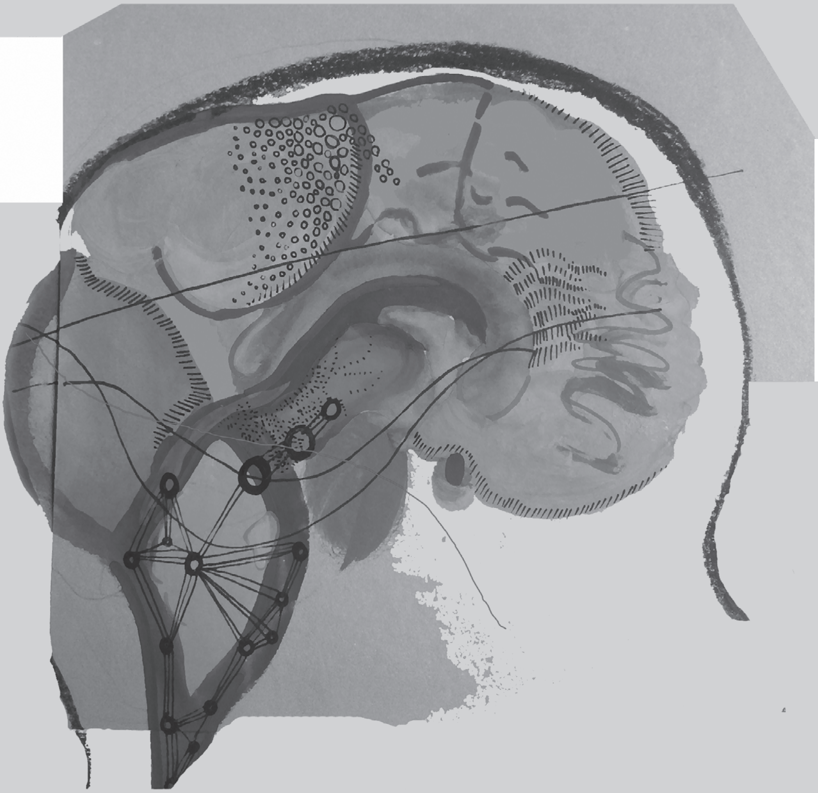


Chapter 2

Glioma surgery in eloquent areas, can we preserve cognition? A systematic review

ABSTRACT

Background. Cognitive preservation is crucial in glioma surgery, as it is an important aspect of daily life functioning. Several studies claimed that surgery in eloquent areas is possible without causing severe cognitive damage. However, this conclusion was relatively ungrounded due to the application of brief neurological tools, the analysis of cognitive tests only postoperatively, heterogeneous treatment or analyses in patients with different tumor histopathology.

Objective. To elucidate the short and long-term effects of glioma surgery on cognition by identifying all studies who conducted neuropsychological tests pre- and postoperatively in glioma patients.

Methods We systematically searched the electronic databases Embase, Medline OvidSP, Web of Science, PsychINFO OvidSP, PubMed, Cochrane, Google Scholar, Scirius and Proquest aimed at cognitive performance in glioma patients pre- and postoperatively.

Results. We included 17 studies with tests assessing the cognitive domains: language, memory, attention, executive functions and/or visuospatial abilities. Language was the domain most frequently examined. Immediately postoperatively, all studies except one, found deterioration in 1 or more cognitive domains. In the longer term (3-6/6-12 months postoperatively) the following tests showed both recovery and deterioration compared to preoperative level: naming and verbal fluency (language), verbal word learning (memory) and Trail Making B (executive functions).

Conclusion. Cognitive recovery to the preoperative level after surgery is possible to a certain extent, however the results are too arbitrary to draw definite conclusions. More studies with longer postoperative follow-up with tests for cognitive change are necessary for a better understanding of the conclusive effects of glioma surgery on cognition.

INTRODUCTION

In the Netherlands, the incidence of newly diagnosed primary brain tumors is 5-7 per 100,000 of which 20% are low grade gliomas (LGG)[1]. LGGs are mostly revealed by epileptic seizures and/or by mild cognitive complaints. LGGs often reside in the so-called "eloquent areas" of the brain. However, due to the slow growth rate of LGGs, i.e. 4 mm p/y[2], the brain is assumed to be able to reorganize the functions at risk for impairment (e.g. language or motor)[4]. Therefore severe neurological and/or cognitive disturbances are assumed to be relatively rare. Currently, the gold standard treatment for LGG is awake surgery with direct electrocortical stimulation to preserve functions. Recent publications show that, with this technique, maximal resection percentages with minimal neurological deficits can be attained[5]. Currently, the specific effects of glioma surgery on higher cognitive functions, such as language, memory, attention and executive functions, however, are not entirely clear.

There is a vast body of literature with reports on the neurological outcome of patients operated on for brain diseases, such as meningiomas, cavernomas, ependymomas, metastases and gliomas in eloquent areas[6-10]. These studies have provided knowledge about the tremendous neural plasticity of the brain during the recovery period after surgical intervention. The general observation is that postoperative deterioration (such as aphasia) is transient and recovers within 3 months. However, there is no real evidence for this assumption related to cognition. Mostly, individual cases were presented but no solid group analyses were conducted[11-16]. Moreover, the majority of these studies used brief neurological screening tools, such as MMSE and/or KPS, or limited language tasks, such as naming[4, 17-19].

Some neurosurgical studies investigated cognition more thoroughly with extensive tests after diagnosis[20, 21] or after (mixed) surgical treatment (before adjuvant therapy)[22-28]. They highlighted impairments in language and attention/executive functioning. Their results, however, did not provide insight into the effects of surgery, because cognition was investigated on only 1 time point, i.e. pre- or postoperatively. In other studies, neuropsychological tasks were conducted, but heterogenenous tumor treatment was applied, such as combinations of stereotactic biopsy, total resection, chemo- and/or radiotherapy[29-31], or heterogeneous tumor groups were taken together for analysis[32-35].

Several investigators already pointed out the relevance of extensive cognitive testing in glioma patients before surgery with a follow-up[36-39]. However, detailed complete analyses on the effects of extensive surgery on the main cognitive domains, such as language, memory, attention, executive functions and visuospatial abilities is not standard procedure in patients with eloquent area gliomas.

The aim of this systematic review is to search the literature to identify the current status of short and longer term effects of glioma surgery in eloquent areas on different cognitive functions, language, memory, attention/executive functions and visuospatial abilities. As a result, patients can be better prepared for their prognosis and sensitive tasks for cognitive change might be revealed, which is essential information for clinical practice.

METHODS

Search strategy

Our goal was to identify all publications reporting cognitive status in adult glioma patients before and after surgery until July 1st 2013. A double negation filter on "children" was utilized to minimize the results on pediatric literature. We systematically searched the electronic databases Embase, Medline OvidSP, Web of Science, PsychINFO OvidSP, PubMed, Cochrane, Google Scholar, Scirius and Proquest (see Appendix I, which illustrates the search string).

Study selection criteria

All titles and abstracts were reviewed by the first author (DS). Firstly, irrelevant studies were excluded. Then any study reporting on cognition was included for full-text screening. Subsequently we eliminated studies describing patients treated with biopsy, neurological status, heterogeneous tumors (and metastases) and heterogeneous treatment. Publications included in our study concerned an adult patient population with gliomas treated for extensive surgery in eloquent areas who underwent neuropsychological testing (with standardized tests) both before and after surgery. Difficult cases were discussed with 2 co-authors (EV and CD).

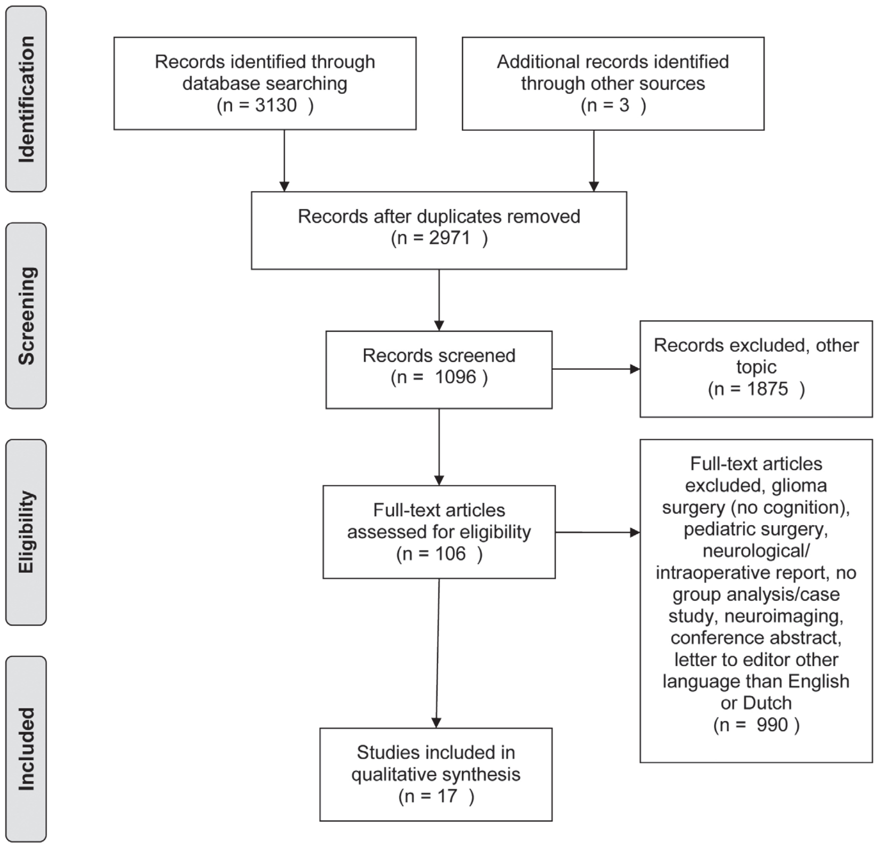
RESULTS

The electronic search resulted in 3130 publications. Three articles were identified by additional "hand-searching" the reference lists (total: 3133). After title and abstract screening, 162 were duplicates and 1875 articles were excluded because of irrelevance. Three-hundred-fourteen articles discussed glioma surgery, but not cognition or concerned pediatric literature. Six-hundred-seventy-six articles were excluded due to: neurological and/or intraoperative reports, no group analysis/case studies, focus on neuroimaging, conference abstract, letter to editor, other language than Dutch or English. Hundred-six full-text publications were evaluated of which finally 17 articles were selected (see Figure 1).

Included studies

We identified 17 articles (2006-2013) in which cognitive performance was assessed in glioma patients with an extensive test battery pre- and postoperatively, with or without further follow-up. The sample size ranged from 7 to 226 patients (of which a subgroup was analyzed)[39, 40]. The interval after tumor resection was different. Nine studies investigated cognition in the immediate postoperative phase, of which 7 conducted a follow-up (range 3 days-6

Figure 1. Flowchart of search results



months)[40-48]. Six articles conducted a postoperative examination between 3 months and 12 months[49-54], and another designed a prognostic study in which tasks were revealed associated with postoperative relapse in cognition[39, 55]. Eleven studies compared a postoperative follow-up moment to preoperative baseline level[42-46, 49-54] Follow-up moments ranged from 1-5 days to 3 years[40, 51]. The most common times of measurement were immediately and 3-6 months postoperatively. Two studies did not report on the exact follow-up time (Sarubbo et al.[51] only mentioned a follow-up of 3 years in the title, but did not provide specifications in the article) nor on specific statistical methods to investigate performance[49, 51]. Five articles discussed cognitive outcome of patients with specific tumor location (e.g. mesial frontal lobe, temporal lobe, insular lobe, uncinate fasciculus, arcuate fasciculus)[40, 43, 44, 47, 50]. The remaining studies included patients with gliomas in mixed eloquent areas, i.e. the frontal, temporal, parietal and/or occipital lobes. Table 1 shows details of the studies we identified.

Table 1. Study design

Author	Year	Surgical intervention	Immediate Postop testing	Follow-up testing	Tumor grade	N
Bello et al.	2006	awake surgery	Yes	1 month and 3 months	LGG + HGG	88
Teixidor et al.	2007	awake surgery	Yes	3 months	LGG	23
Yoshii et al.	2008	awake surgery	No	Yes, but not clear	LGG* + HGG	31
Chainay Hanna et al.	2009	surgery	Yes	3, 7 days	LGG	7
Campanella et al.	2009	surgery	Yes	No	LGG + HGG	20
Talacchi et al.	2011	(sub)total surgery	Yes	No	LGG + HGG	29
Papagno et al.	2011	awake surgery	Yes	3 months	LGG + HGG	44
Sarubbo et al.	2011	awake surgery	No	3 years	LGG	12
Wu et al.	2011	awake surgery	No	Yes, but not clear	LGG + HGG	33
Matavalli et al.	2012	awake surgery	Yes	No	LGG	22
Papagno et al.	2012	awake surgery	Yes	3 months	LGG + HGG	226**
Zhao et al.	2012	awake surgery	Yes	3-6 months	LGG + HGG	20
Santini et al.	2012	awake surgery	Yes	3-6 months	LGG + HGG	22
Satoer et al.	2012	surgery	No	3-4 months	LGG + HGG	28
Moritz-Gasser et al. (sub-study 2)	2012	awake surgery	No	6-12 months	LGG	12
Moritz-Gasser et al.	2013	awake surgery	Yes	6 months	LGG	8
Satoer et al.	2013	awake surgery	No	3-4 months	LGG + HGG	27

LGG=low grade glioma, HGG=high grade glioma. *=Also meningiomas were included, but this group could be separated from glioma patients in our analysis.**=At least one follow-up at 3 months was collected for 117 patients.

Neuropsychological protocol

All studies investigated the language domain. Eight studies investigated 1-2 cognitive domains, and the remaining 9 studies examined 3-4 other different cognitive domains, i.e. memory, attention and executive functions and/or visuospatial abilities (or other). The most frequently used tests for assessing language functions concerned: object naming and verbal fluency (category and letter), for memory: verbal word learning (encoding, recall and recognition), verbal/digit span, for attention and executive functions: Trail Making Test (TMT) A, B. See Table 2 for specifics on conducted tasks per domain.

Cognitive baseline and outcome

At preoperative level (T1), 8 studies conducted a statistical group analysis compared to a normative group and 6 provided percentages to indicate impairments[39, 41-48, 50, 52-54]. Two studies reported individual scores[51, 55] and 1 study presented a mean of the tasks without mentioning the normative threshold[48].

The neuropsychological preoperative findings were as follows; language deficits: 12 studies, memory deficits: 3 studies, attention/executive functioning deficits: 3 studies, visuospatial domain: 1 study, and 1 study mentioned subnormal cognition without specifying the domains/tasks. Only 3 studies identified no preoperative cognitive deficits[44, 48, 54]. In sum, the majority of the studies found preoperative deficits in 1 or more cognitive domains.

Nine studies statistically compared immediate postoperative versus preoperative (T2-T1) cognitive level in the following domains; language: all studies, memory: 6, attention/executive functions: 4, visuospatial abilities: 3. In the immediate postoperative phase, 7/9 studies (78.8%) found a deterioration in the language domain[40, 42-46, 48], 2/6 (33.3%) found a decline in the memory domain[44, 45], and 3/4 (75%) in the executive functions[41, 44, 45]. Only 1 study found an improvement in the language domain (with Aphasia Quotient, AQ)[47].

Six studies investigated the recovery course between the immediate postoperative phase and a follow-up test-moment (T2-T3). Most studies reported no significant difference in performance on tests for language, memory, attention/executive functions or visuospatial abilities. Only 3 studies reported significant improvement in: language (naming[45] verbal fluency [44] and AQ[47]), memory (verbal word learning[45]) and attention/executive functions (TMTA, B[44]) .

Eleven studies compared a follow-up test-moment to preoperative level (T3-T1). One study indicated no statistically significant worsening or improvement[51]. In the longer term, 5 studies reported no significant differences in the language domain between T3-T1 suggesting an improvement to preoperative level of the defective functions in the immediate postoperative phase, in particular in language (naming, verbal fluency, sentence comprehension), but also in memory (verbal word learning), and executive functioning (TMTB)[42, 44-46, 48]. Six studies, however, still reported a significant cognitive deterioration in 1 or more domains at follow-up compared to preoperative baseline level, in the domains: language (naming, verbal fluency), memory (verbal word learning) and executive functions (TMTB)[40, 44, 50, 52-54]. Only 1 study found a significant improvement in the memory domain (verbal word learning, recall) compared to preoperative baseline level[52].

In short, cognitive disorders in the main cognitive domains are frequently observed preoperatively followed by, for the majority of studies, a decline in the immediate postoperative phase in 1 or more domains. Language and executive functions seemed to be the most frequently impaired functions direct postoperatively, although also improvement of a general Aphasia Quotient was found. Nearly no significant changes are mentioned between the direct postoperative phase and the follow-up, apart from 3 studies who found improvement in language, and/or memory and attention/executive functioning[44, 45]. However, compared to the preoperative level, half of the studies mentioned an equal performance whereas deterioration was found in the other studies, apart from an improvement in memory[52]. See Table 2 for detailed preoperative cognitive status and postoperative outcome and see Figure 2 for a summary of sensitive tasks short-term postoperatively (T2-T1), during course (T3-T2) and longer term postoperatively (T3-T1). In addition, overlapping tests with both recovery and deterioration are indicated.

Table 2. Neuropsychological protocol and outcome

		Neuropsychological test battery				Outcome			
Study		**Language**	**Memory (verbal and nonverbal)**	**Attention / executive functions**	**Visuospatial**	**-**	**+**	**=**	**Remarks**
Bello et al.	2006	- Naming (people, actions, objects)	-Verbal Span						
		- Category Fluency							
		- Letter Fluency							
		- Repetition (word, non-word, sentence)							
		- Comprehension (word, sentence)							
Baseline	*T1*	- Object naming				x			
		- Sent. Compr.							
		- Letter Fluency							
Follow-up	*T1-T2*	- Object naming				x			
		- Letter Fluency							
		- Sentence comprehension							
	T2-T3								
	T1-T3	- Object naming						x	
		- Letter Fluency							
		- Sentence comprehension							
Teixidor et al.	2007	- Object naming							
		- BDAE							
Baseline	*T1*	All subtest BDAE							In %
Follow-up	*T1-T2*	- Auditory comprehension				x			
		- Repetition (phrase)							
		- Sentence dictation							
	T2-T3								
	T1-T3	- Auditory comprehension						x	
		- Repetition (phrase)							
		- Sentence dictation							
Yoshii et al.	2008	- Naming body parts	- Mental reversal (forwards and backwards)	- Spatial cueing					
		- 4-legged animals							
		- Repetition							
		- Read and obey "close your eyes"							
		- Writing							
		- 3 stage command							

Table 2 (Continued)

Study		Neuropsychological test battery: Language	Memory (verbal and nonverbal)	Attention / executive functions	Visuospatial	Outcome: -	+	=	Remarks
Baseline	*T1*	Composite cognitive score	Composite cognitive score	Composite cognitive score					
Follow-up	*T1-T2*								
	T2-T3								
	T1-T3	Composite cognitive score	Composite cognitive score	Composite cognitive score					Subnormal cognitive performance (not clear which task)
Campanella et al.	2009	Word to picture matching: - Presentation rate (slow-fast) - Semantic distance (distant-close) - Word frequency	- Digit span						
Baseline	*T1*	Word to picture matching				x			
Follow-up	*T1-T2*	None	None						
	T2-T3								
	T1-T3								
Chainay Hanna et al.	2009	- Object naming - Category Fluency - Letter Fluency - Image description - Repetition (word and sentence) - Word-picture matching task	- Digit Span - Corsi span						
Baseline	*T1*								
Follow-up	*T1-T2*	- Object naming - Category Fluency - Letter Fluency - Image description - Repetition - Gesture imitation				x			Within 7 days after surgery

Table 2 (Continued)

Study		Neuropsychological test battery: Language	Memory (verbal and nonverbal)	Attention / executive functions	Visuospatial	Outcome: -	+	=	Remarks
	T2-T3	- Object naming - Image description - Category Fluency - Letter Fluency - Repetition					x		
	T1-T3	- Object naming - Category Fluency - Letter Fluency - Image description - Repetition				x			
		- Gesture imitation					x		
Papagno et al.	2011	- Object naming - Naming (famous faces) - Naming by description - Pointing to picture - Category Fluency - Letter Fluency - Token Test - Picture to sentence matching - Repetition (nonword, word, sentence)	- Corsi span - Verbal word learning - Supraspan learning - Nonverbal memory (figure reproduction)	- Attentional matrices - TMTA, B					
	T1	None	None	None					
Follow-up	*T1-T2*	- Famous face naming - Category Fluency - Letter Fluency	- Verbal word learning	- TMTA, B		x			
	T2-T3	- Category Fluency - Letter Fluency	- Verbal word learning	- TMTA, B			x		
	T1-T3	- Category Fluency - Letter Fluency	- Verbal word learning	- TMTA, B				x	
		- Famous face naming				x			

Table 2 (Continued)

Study		Language	Memory (verbal and nonverbal)	Attention / executive functions	Visuospatial	-	+	=	Remarks
		Neuropsychological test battery				**Outcome**			
Sarubbo et al.	2011	- Object naming - Token test							
Baseline	*T1*								
Follow-up	*T1-T2*								
	T2-T3								
	T1-T3	- Object naming - Token test							
Talacchi et al.	2011	- Object naming - Category Fluency* - Letter Fluency*	- Digit Span - Verbal word learning - Spatial Supraspan Learning - Non-verbal memory (figure reproduction)	- TMTA, B	- Copy design				
Baseline	*T1*	- Letter Fluency	- Verbal word learning	None	- Copy design	x			In %
Follow-up	*T1-T2*			- TMTB		x			
	T2-T3								
	T1-T3								
Wu et al.	2011	- Object naming - Letter Fluency	- Digit span - Verbal word learning	- Digit symbol - Digit Similarities - TMTA, B	- Block Design (WAIS-III)				
Baseline	*T1*	- Letter Fluency	- Verbal word learning	- TMTA, B	None	x			In %
Follow-up	*T1-T2*								
	T2-T3								
	T1-T3	- Letter Fluency	- Verbal word learning		None	x			

Table 2 (Continued)

		Neuropsychological test battery				Outcome			
Study		**Language**	**Memory (verbal and nonverbal)**	**Attention / executive functions**	**Visuospatial**	**-**	**+**	**=**	**Remarks**
Matavalli et al.	2012	- Token Test	- Digit span backwards	- Weigl - WCST					Prognostic
Baseline	*T1*	None	None	None					
Follow-up	*T1-T2* *T2-T3* *T1-T3*								
Moritz-Gasser et al. Sub-study 2	2012	- BDAE - Object naming - Naming time (latency) - Category Fluency* - Letter Fluency*	- Letter-Number sequencing	- TMTA, B - Stroop Test					
Baseline	*T1*	None	None	None					
Follow-up	*T1-T2* *T2-T3*								
	T1-T3	- Naming time - Category Fluency	None	None		x			
Papagno et al.	2012	- Naming (people, actions, objects) - Category Fluency - Letter Fluency - Word-picture matching task - Naming by description - Sentence picture matching - Token Test - Repetition (nonword, word sentence)	- Digit span - Corsi span - Verbal word learning - Supraspan learning - Nonverbal memory (figure reproduction)	- Raven colored progressive matrices - Weigl - WCST - Attentional matrices - TMTA, B - Stroop Test	- Letter cancellation - Reading sentences - Drawing (copy and mental)				Prognostic
Baseline	*T1*	- Naming (people, objects) - Verbal fluency	- Verbal word learning (recall)	None	None				
Follow-up	*T1-T2* *T2-T3* *T1-T3*								

Table 2 (Continued)

		Neuropsychological test battery				Outcome			
Study		**Language**	**Memory (verbal and nonverbal)**	**Attention / executive functions**	**Visuospatial**	**-**	**+**	**=**	**Remarks**
Santini et al.	2012	BADA subtests (7): - phonemic discrimination - word repetition - Naming (nouns and verbs) - auditory and visual word-to- picture matching (nouns and verbs) - auditory and visual sentence-to- picture matching (nouns and verbs) - writing to dictation - reading aloud Object naming Letter Fluency*	- Verbal digit span - Verbal word learning - Nonverbal memory (figure reproduction)	- TMTA, B	- Copy design				
	T1	- Letter Fluency	- Verbal word learning		- Copy design	x			In %
Follow-up	*T1-T2*	- Object naming - Letter Fluency	- Verbal word learning - Verbal span	- TMTB		x			
	T2-T3	- Object naming					x		
	T1-T3	- Object naming	- Verbal word learning - verbal span	- TMTB				x	
Satoer et al.	2012	AAT-subtests - Repetition - Reading - Writing to dictation - Token Test Object naming Category Fluency Letter Fluency	- Verbal word learning	- TMTA, B - Stroop Test					

Table 2 (Continued)

Study		Neuropsychological test battery: Language	Memory (verbal and nonverbal)	Attention / executive functions	Visuospatial	Outcome: -	+	=	Remarks
Baseline	*T1*	- Category Fluency - Letter Fluency	- Verbal word learning	- TMTA - Stroop Test		x			
Follow-up	*T1-T2*								
	T2-T3								
	T1-T3	- Category Fluency - Letter Fluency	Verbal word learning (recall)	- TMTB		x			
Zhao et al.	2012	WAB - aphasia rating AQ							
Baseline	*T1*	- AQ				x			
Follow-up	*T1-T2*	- AQ					x		
	T2-T3	- AQ					x		
	T1-T3								
Moritz-Gasser et al. Sub-study 2	2013	- Object naming - Naming time - Non-verbal semantic matching (Pyramid and Palm Trees Test) - Category Fluency - Letter Fluency							
Baseline	*T1*	None							
Follow-up	*T1-T2*	- Object naming - Category Fluency				x			
	T2-T3								
	T1-T3	- Object naming - Category Fluency						x	

Table 2 (Continued)

Study		Neuropsychological test battery: Language	Memory (verbal and nonverbal)	Attention / executive functions	Visuospatial	Outcome: -	+	=	Remarks
Satoer et al.	2013	Spontaneous speech variables - MLUw - TTR - Repetitions - Self-corrections - Incomplete sentences Object naming Category Fluency							
Baseline	*T1*	- Object naming - Category Fluency - Incomplete sentences				x			
Follow-up	*T1-T2* *T2-T3*								
	T1-T3	- Object naming - Category Fluency - Incomplete sentences - Utterance length				x			In comparison to normals

T1=baseline, T2=direct postoperatively, T3=follow-up measurement (see Table 1 for specific follow-up period), *=authors categorized fluency task in executive functions. For practical reasons, we classified all fluency tasks in the language domain. -: impairment/decline, +: recovery,=: no difference between test-moments (T3-T1).

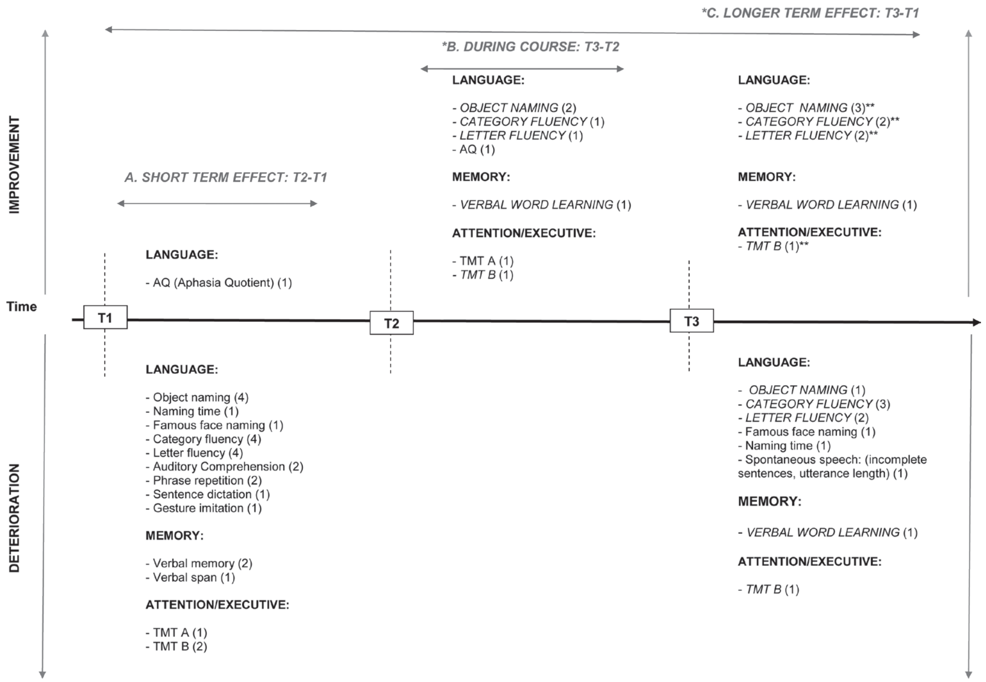
(light grey)	No comparison conducted
(dark grey)	No data available

Abbreviations: AQ=Aphasia Quotient, BDAE=Boston Diagnostic Aphasia Examination, BADA=Batteria per l'analisi dei deficit afasici, TMT=Trail Making Test, WAB= Western Aphasia Battery, WCST=Wisconsin Card Sorting Task. Verbal word learning involves: (encoding, recall, recognition)

Tumor characteristics and adjuvant therapy

Eight studies investigated the effect of tumor grade on cognition of which 3 pointed out an association between cognitive improvement and HGG[41, 45, 53], whereas 1 study showed the

Figure 2. Summary of sensitive neuropsychological tasks for deterioration or improvement short and longer term after glioma surgery.



T1=before surgery, T2=directly after surgery, T3=follow-up after surgery. Below the timeline, a summary is provided of tasks which deteriorated between test moment in the different cognitive domains, whereas improvements are shown above the timeline. Comparisons between 3 different test moments are illustrated: A=T2-T1, short-term effect of surgery; B=T2-T1, during course; and C=T3=T1, longer term effect of surgery. Tasks in italics and capital letters are tasks that show mixed outcome at short-term and/or longer term (3-6 months) after surgery, i.e. both deterioration and recovery. The number of studies finding a specific task sensitive for change are presented between brackets.

*The sensitive tasks revealed by Chainay et al. (2009) were not considered in this figure as they were all administered within 7 days after surgery.

**Some studies reported no significant difference between follow-up phase (T3) and preoperative baseline level (T1) suggesting recovery at T3 after a decline in the immediate postoperative phase (T2):

Object naming: (2) Bello et al. (2006), Moritz-Gasser et al. (2013)
Category fluency: (2) Moritz-Gasser et al., (2012, 2013)
Letter fluency: (2) Bello et al. (2006), Papagno et al. (2011)
Verbal memory: (1) Papagno et al. (2011)
TMTB: (1) Santini et al. (2012)

opposite effect[43].

Nine studies examined the relation between tumor localization and cognitive outcome. One study showed the importance of identifying a subcortical language tract that is associated with postoperative language deficits[42], another study revealed the relation between a relapse in naming and temporal and frontal tumors, and a decrease in attentional matrices in patients harbouring frontal tumors[39]. Removal of a glioma in the uncunate fasciculus related to deterioration in famous face naming[44] and glioma resection in language areas was associated with a decline in language and the executive functions[52]. Insular tumor patients performed worse on a naming test than other tumor patients[50].

Seven studies looked at tumor volume/extent of resection and cognitive outcome. Most studies did not find a relation, apart from 2 who found that a larger volume was associated with worsening of language and executive functioning[39, 41]. The effect of adjuvant therapy has been studied in 2 papers, but they did not find a relation[52, 53]. See Table 3 for specifics on cognitive outcome and tumor- and/or treatment related factors.

DISCUSSION

This systematic review provides an overview of the short and longer term effects of glioma surgery on cognition assessed with standardized neuropsychological tests. If available, tumor and/or treatment related risk factors were described as well. We identified 17 articles in which the short and/or longer term effect of neurosurgery on cognitive functioning was discussed. Generally, direct postoperative deterioration was reported followed by either recovery or remaining deterioration in one or more domains in a further follow-up (at 3-6 months), indicating the relevance of extensive neuropsychological testing. However, not all studies were representative regarding the conclusive effects of glioma surgery on cognitive functioning. For instance, test batteries did not always cover all cognitive domains, statistical comparisons between available test-moments were not consistently conducted, follow-up range across patients was too wide, or follow-up time was not precisely described.

Test protocol and procedure

In order to investigate the effect of neurosurgery on cognition, it is crucial to select a set of sensitive tests for cognitive change, as LGG patients are not heavily disturbed in cognition. The prognostic property of a subnormal naming performance for immediate postoperative aphasia was already demonstrated in primary brain tumor patients[32]. This test was the most frequently used language task and appeared, as expected, to be sensitive, although both improvement and deterioration were observed. Only 6 out of 17 studies, investigated cognition thoroughly, i.e with an extensive neuropsychological test protocol for all domains[39, 41, 44, 45, 50, 52].

Table 3. Tumor characteristics, adjuvant therapy and cognitive functions

Study		Tumor grade	Localization	Volume/EOR	Adjuvant therapy
Bello et al.	2006	No effect	Subcortical language tract associated with postoperative language deficits	n/a	n/a
Teixidor et al.	2007	n/a	n/a	n/a	n/a
Yoshii et al.	2008	No effect	n/a	No effect	
Chainay Hanna et al.	2009	n/a	n/a	n/a	n/a
Campanella et al.	2009	Preop: LH HGG worse than HC and LGG (Word to picture matching, presentation rate + semantic distance) Postop: RH HGG deteriorates compared to HC	Postop: RH HGG deteriorates compared to HC	n/a	n/a
Talacchi et al.	2011	HGG associated with improvement (word fluency, verbal memory, visuospatial memory, memory domain)		Larger tumor associated with worsening (executive functions, word fluency and TMTB)	n/a
Papagno et al.	2011	No effect	Uncinate removal in frontal or temporal lobe associated with deterioration in famous face naming	n/a	n/a
Sarubbo et al.	2011	n/a	n/a	n/a	n/a
Wu et al.	2011	n/a	No effect (but trend more decline postop learning and memory in insular gliomas)	n/a	n/a
Matavalli et al.	2012		No effect	No effect volume	
Papagno et al.	2012		- Temporal (LH) glioma associated with relapse in naming (face + object), verbal fluency - frontal (LH) glioma associated with relapse in attentional matrices - frontal and temporal (LH) associated with relapse in object naming	- Temporal (LH) glioma + volume (covariate) associated with relapse in verbal fluency - Temporal and frontal (LH) + volume (site and grade as covariates) glioma associated with object naming	
Zhao et al.	2012	n/a	n/a	n/a	n/a

Table 3. (Continued)

Study		Tumor grade	Localization	Volume/EOR	Adjuvant therapy
Santini et al.	2012	HGG associated with improvement	No effect	No effect	n/a
Satoer et al.	2012	No effect	Localization in language areas associated with decrease	No effect	No effect
Moritz-Gasser et al.	2012	n/a	n/a	n/a	n/a
Moritz-Gasser et al.	2013	n/a	n/a	n/a	n/a
Satoer et al.	2013	LGG worse than HGG and controls in Incomplete sentences	No effect	No effect	No effect

Abbreviations: LH=left hemisphere, RH=right hemisphere, LGG=low grade glioma, HGG=high grade glioma, HC=healthy controls, n/a=not administered.

Half of the studies only focused on 1-2 cognitive domains, which is obviously too limited to interpret the effect of surgery on overall cognition.

A comparison between all available time measurements is necessary to obtain a complete understanding of the course of recovery. Not all studies conducted comparisons with the available data between test-moments postoperatively, e.g. between the immediate postoperative phase (T2) and follow-up moment (T3)[42, 46, 55]. Two studies did not clearly report on follow-up moments[49, 51]. Also, the follow-up range of some studies may have been too wide; i.e. 3-6 months and 6-12 months[45, 54]. Deficits at 3-4 months postoperatively are considered 'transient', compared to 'persistent' at 6 months and 'permanent' at 12 months[36], hence, one should aim for a minimal time range as possible between test-moments across patients, not exceeding these aforementioned different recovery phases. In summary, the assessment of all cognitive domains combined with a comparison between all available test-moments with a minimal time range is necessary to obtain a valuable cognitive profile of patients.

Effects of surgery on cognition

First, the identification of impairments at baseline-level is important, as these deficits are assumed to be caused by the tumor itself. Given this information, the effects of surgery can be better clarified. Not all articles performed a statistical group comparison to a normative group on cognition before surgery. Some provided percentages of impaired tests, whereas others only used preoperative baseline scores for comparison to postoperative scores.

The general finding is that cognitive status deteriorated directly after surgery followed by improvements or a decline several months after surgery[40, 42, 46, 48, 49, 51]. In particular, in the immediate postoperative phase most studies found a deterioration in the language domain. Zhao et al.[47] was the only study reporting on a significant language improvement in the immediate postoperative phase, followed by a consecutive improvement at 3-6 months postoperatively, with a general Aphasia Quotient. It is possible that a general evaluation surpasses (subtle) language deficits at separate linguistic abilities, such as naming or verbal fluency. Language, as examined by standardized tasks and also spontaneous speech, appeared to be a dynamic domain, indicating the relevance of linguistic monitoring pre- and postoperatively. On the other hand, all studies examined language, which may have biased the results.

One study concluded no cognitive change in a follow-up, suggesting a minimal negative effect of surgery[51]. The statistics (or definition of the threshold), however were not well documented, resulting in a more descriptive status of cognition in glioma patients. A subnormal cognitive performance was also mentioned both before and after operation, suggesting no effect of surgery[49]. Yet, it remained unclear whether different cognitive domains were taken together and if so, in what manner.

Between the immediate postoperative phase and follow-up, 3 studies found a significant improvement in the domains of language, memory and attention and executive functioning.

Some studies reported no difference between postoperative follow-up and preoperative performance after deterioration in the immediate postoperative phase suggesting recovery to preoperative baseline level[42, 44, 45, 48, 54] and 1 study found an improvement in memory[52]. In particular with the following tests: naming, verbal fluency, verbal recall and TMTA, B.

Despite these positive outcome results, a large number of studies still found remaining deterioration in the follow-up phase in the before mentioned tasks that also showed improvements and also in famous face naming, naming time and spontaneous speech[44, 45, 50, 52-54]. Therefore a definite conclusion of the effects of surgery on cognition cannot be drawn yet, as the aforementioned tests showed mixed results on outcome. More studies with larger patient groups assessing at least naming, verbal fluency (language) verbal word learning (memory) and TMTB (executive functions) are necessary to better understand the effects of surgery.

The sensitive tests for change took part of larger test batteries. Longer protocols may have caused fatigue in patients resulting in worse task performance. To minimize a potential intervening factor as such, it may be helpful to eliminate insensitive tasks revealed by this review, such as nonverbal memory and visuospatial tests. The insensitivity of these tests could be explained by their specificity for right-hemisphere functioning, whereas most patients harboured left-hemipheric tumors. Also some subtests from the Aachener Aphasia Test (AAT) [56], Boston Diagnostic Aphasia Examination (BDAE)[57] or Batteria per l'analisi dei deficit afasici (BADA)[58] (e.g. phonemic discrimination, writing to dictation and reading) were not sensitive, possibly because these tasks are designed to measure more severe language disturbances, as in stroke patients. Finally, intraoperative studies indicated the relevance of calculation abilities in the left parietal lobe[59]. The use of calculation tasks was not identified by this review but should also be considered in the neuropsychological protocol.

Limitations

Although we homogeneously selected the included studies based on pre- and postoperative neuropsychological testing, this review underlines the need for more consistent neuropsychological research in glioma patients as a number of heterogeneous factors may have interfered with our results: 1) Bias to language domain. Not all studies conducted tests covering all cognitive domains; some studies found no differences between pre- and long-term postoperative neuropsychological assessment. These studies focused on the language domain. However, it is possible that deterioration occurred in a different domain for those patients which language improved. 2) Test-interval. Test-intervals following resection varied across studies and eloquent areas were not always in a similar way defined. 3) Tumor location. Some included mixed eloquent areas, whereas others included patients with specific tumor location.

On the other hand, if we would have used the above mentioned reasons as exclusion criteria, only few studies would be selected for inclusion in this literature study. The main goal of this review concerned providing an overview of the current state of affairs on cognitive examination in consecutive glioma patients. For the design of a neuropsychological outcome study for glioma patients one should avoid the inconsistencies across studies as described above.

Tumor-related factors, adjuvant therapy and cognition

As for tumor-related factors, 6 studies analyzed cognitive performance of solely grade II LGG patients. From clinical practice, we know that it is quite typical that a part of supposed LGG on MRI appears to be HGG after pathological examination. It is therefore important to consecutively analyze the entire clinical group treated for glioma surgery without excluding those with grade III or IV in retrospect and thus eliminating a bias towards cognitive outcome.

Localization in temporal or frontal areas appeared to be important for mostly language functioning, in accordance with the known neural organization of linguistic functions[60]. More specifically, patients with tumors located in the proximity of subcortical language tracts, such as the uncinate fasciculus, were more at risk for postoperative disturbances[42, 44], in contrast to patients with tumors nearby the arcuate fasciculus (AF)[47]. It is possible that preservation of AF with direct electrocortical stimulation results in better prognosis, as the AF was found to be predictive for overall efficiency of speech and naming in stroke patients[61].

Adverse effects on cognition by adjuvant therapy (radio/chemo) were not found in this review, mainly because the goal concerned investigating the effects of neurosurgery. It is known that radio- and/or chemotherapy can affect cognitive functioning[62, 63], articles discussing this matter however, were excluded due to the absence of a preoperative test-moment.

CONCLUSION

This review article provided an important overview of the sensitivity of cognitive tasks as well as the course of recovery in cognition after glioma surgery. Although many studies reported recovery of cognitive function(s) after glioma surgery to the preoperative level, the more extensive neuropsychological protocols still found deterioration in some cognitive domains in a follow-up, indicating the necessity of the administration of tasks in all domains. From these results, we can derive that one should be cautious with the general assumption of fully recovery. Distinct results on outcome in the follow-up phase demand for more research with larger patient groups to better understand the consequences of surgery on cognition. The standard neuropsychological test protocol should at least consist of the revealed sensitive tasks, i.e. object naming, verbal fluency, verbal word learning and Trail Making Test B. The language domain appeared to be the most dynamic with standardized tasks, latency effects (naming time) and spontaneous speech. This suggests that intraoperative language testing at different levels should be carefully conducted, which may lead to less severe postoperative language disturbances. In conclusion, we demonstrated that cognitive recovery to preoperative baseline level is possible to a certain extent, but that the results are still arbitrary to draw definite conclusions. Most outcome results were based on a follow-up of 3-6 months. Prospective follow-up studies exceeding this period investigating all cognitive domains with the sensitive tasks for change are crucial to elucidate the long-term effects of glioma surgery.

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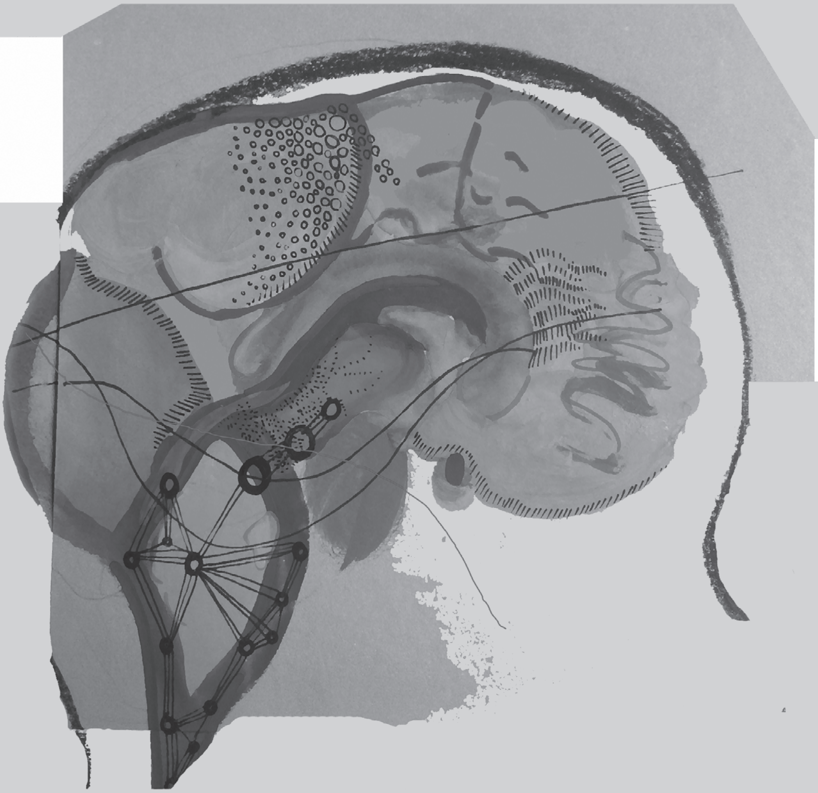

Chapter 3

Cognitive functioning early after surgery of gliomas in eloquent areas

ABSTRACT

Background. Patients with gliomas frequently have cognitive deficits. Surgery can further exacerbate these deficits. Preoperative assessment is therefore crucial in patients undergoing surgery for glioma in eloquent areas, because the proximity of functional areas increases the risk of permanent postoperative cognitive disturbances. Although pre- and postoperative language and motor function in patients with gliomas have been investigated frequently, data on good cognition studies are scarce. Most studies have focused on clinical neurological functioning or have only used brief neurological instruments.

Objective. To investigate whether surgery of glioma in eloquent areas influences cognition early after surgery, by using an elaborate test protocol.

Methods. Twenty-eight patients with gliomas in the left hemisphere in language and non-language areas were assessed before and 3 months after surgery with a comprehensive neuropsychological test protocol. A correlation analysis was performed between change in cognitive performance and tumor characteristics (that is, location, volume, pathological features and histological grade) and between cognitive change and treatment-related factors (that is, the extent of the resection and postoperative treatment with chemo- and radiotherapy).

Results. Both pre- and postoperatively, the mean performance of the patients was worse than the performance of the normal population in the language domain, the memory domain and the executive functions ($p<0.05$). Postoperatively, a decline was found in the language domain ($t=2.34$, $p=0.027$) and in the executive functions ($t=2.45$, $p=0.022$). However, cognitive change postsurgery was influenced by the location of the tumor; the decrease of cognitive score in the language domain was only observed in patients with tumors in or close to language areas ($t=2.33$, $p=0.029$). No effect on cognitive change was found for the other tumor characteristics and treatment related factors.

Conclusion. This study underlines the importance of the use of a neuropsychological test protocol before and after surgery in patients with gliomas, because several tasks in the domains of language, memory and executive functions appeared to deteriorate after surgery. Tumor resection in language areas increases the risk of cognitive deficits in the language domain postoperatively.

INTRODUCTION

The relevance of neuropsychological assessment in patients with gliomas is increasingly recognized[1-5]. Most untreated patients have deficits in 1 or more cognitive domains[2, 4-6]. Because cognitive status is crucial for the quality of life and is associated with overall survival [7], neurocognitive performance is currently considered to be one of the central outcome measures of brain tumor treatment[1, 4].

Cognitive assessment is particularly crucial in patients undergoing surgery for gliomas in functional areas because the proximity of functional tissue increases the risk of permanent postoperative neuropsychological dysfunction. Gliomas are infiltrating tumors that lack a clear interface between normally functioning brain tissue and pathological tumor tissue[8]. Using functional mapping under awake conditions, the localization of functions can be determined during surgery and the resection can be performed according to the individual functional boundaries. The goal is to maximize the extent of resection, resulting in a longer survival time with minimal cognitive deficits[9]. Cognitive deficits occurring during or directly after this surgical procedure are reported to be mostly transient[5, 6, 10-12]. However, most evaluation studies focused on clinical neurological functioning or used brief neuropsychological instruments[6, 10, 11] such as the Mini Mental State Examination[13]. These global diagnostic tools might be not sensitive enough to measure the cognitive deficits of patients with gliomas[4].

Postoperative cognitive change may be due to several tumor-inherent factors such as the location, size and grade[1, 3]. Candidates for awake surgery have gliomas that are located in or near language or motor areas. Neural networks subserving language often contribute to other cognitive functions as well[14, 15]. A larger tumor volume has been associated with increased risk of postoperative cognitive decline. Surgical removal of high grade gliomas (HGGs) has been reported to induce cognitive improvement, in contrast with the resection of low grade gliomas (LGGs)[1]. Other factors that are potentially associated with cognitive deficits are as follows: the histological type of the tumor (astrocytoma, oligodendroglioma or oligoastrocytoma), the extent of the resection and postoperative treatment with chemotherapy, radiotherapy or both[1, 16].

In this study, we investigated the effect of glioma resection on cognitive functioning. Patients were assessed with a comprehensive neuropsychological test protocol before and within 4 months after surgery. We analyzed the effect of tumor characteristics (that is, the location, volume, pathological findings and histological grade of the tumor) and treatment related factors (that is, the extent of the resection and postoperative treatment with chemo- and radiotherapy) on cognitive performance after surgery. Results of this study can be used to better inform patients prior to the operation about possible treatment plans (aggressive or less aggressive glioma resection) and about the prognosis in the short-term postoperatively in terms of cognition, which is an essential aspect of patients' quality of life.

METHODS

Patient population

Cognitive functioning was assessed of 28 native Dutch speakers (mean age 41.52, range 19-74) with untreated or recurrent gliomas in the left hemisphere close to language or motor areas. Exclusion criteria were as follows: history of a medical or psychiatric condition known to affect cognitive functioning, permanent motor or language deficits as a result of prior treatment, pre-existing language deficits, deafness or severe visual disorder, and mental retardation.

Study procedures

The localization of the tumor was determined by a neuroradiologist using 3D T1-weighted magnetic resonance images (MRI) and 2D T2-weighted MRI, and categorized as follows: 1) involving frontal or parietotemporal language areas (inferior frontal gyrus, subcentral gyrus, supramarginal gyrus, angular gyrus, or inferior, middle and superior temporal gyrus); and 2) involving non-language areas (precentral, middle or superior frontal gyrus, with no involvement of the inferior frontal gyrus) based on the classic model of language[17]. The pre- and postoperative tumor volume was calculated by manual delineation of 3D deviant signal intensity on T2-weighted MRI studies using Osirix version 3.7.1. (http://homepage.mac.com/rossetantoine/osirix). Postoperative MRI scans were obtained within 72 hours of resection. The extent of the resection was calculated by subtracting the postoperative from the preoperative volume. The histological type of the tumor (astrocytoma, oligodendroglioma, oligoastrocytoma) and the pathological World Health Organization (WHO) grade were determined by a neuropathologist, from tissue obtained during the tumor resection. The study was approved by the Ethical Committee of Erasmus MC and patients gave their informed consent.

Neuropsychological assessment

Patients were assessed between 1 and 2 months preoperatively (mean=1.4 months; standard deviation (sd)=1.06) and between 3 and 4 months postoperatively (mean=3.4 months; sd=0.72) with a comprehensive neuropsychological protocol (see Table 1). We chose a short follow-up, because glioma patients have a poor prognosis. Hence, short-term information about cognition is necessary in order to improve quality of life.

The quality of verbal communication (based on a 10 minute sample of spontaneous speech) is rated on with the Aphasia Severity Rating Scale (ASRS)[26], a 6 point scale varying from 0 'no usable speech or auditory comprehension' to 5 'minimal discernable speech handicap'.

Based on the normative data, the test scores of the patients were transformed into z-values to compare the performance of patients to that of healthy adults. Domain scores were calculated by computing the mean z-score of all tests belonging to a particular cognitive domain. Impairment was defined as a z-score below -2. For each patient, the pre- and postop-

Table 1. Neuropsychological test protocol

Test	N*	Cognitive Abilities	Description
Language			
Subtests of Akense Afasie Test (AAT)[18]			
- Token Test (TT)	26	Language comprehension; severity of language disorder	Pointing to and manipulating geometric forms on verbal commands
- Repetition	28	Repetition	Repeating phonemes, words and sentences
- Reading aloud	24	Reading	Reading aloud words and sentences
- Writing to dictation	21	Writing	Writing words and sentences on dictation
Boston Naming Test (BNT)[19]	27	Naming (word-finding)	Naming 60 pictures, presented in order of word frequency and word difficulty
Category Fluency[20]	28	Flexibility of verbal semantic thought processing; working memory	Producing words of a given category (animals and professions) within a limited time span
Letter Fluency[21] (parallel versions)	28	Flexibility of verbal phonological thought processing; working memory	Producing words beginning with a given letter (D,A,T, or K,O,M) within a limited time span
Memory			
15 Words Test (15WT), Encoding, Recall, Recognition[22] (parallel versions)	27	Verbal learning; immediate and delayed recall and recognition	Learning a list of 15 words, with 6 recall trials; 5 immediate and 1 delayed, and a recognition trial
Attention and executive functions			
Trail Making Test (TMT) A, B, BA[23]	26	TMTA: visuomotor speed, attention; TMTB: + mental flexibility, divided attention	Connecting numbers placed randomly in ascending order as rapidly as possible (TMTA) and connecting alternating numbers and letters as rapidly as possible (TMTB)
Stroop Color-Word Test (Stroop) I, II, III, Interference[23]	24	Mental speed; selective attention, inhibition and switching	Reading color words, naming colors and naming colors of printed words, denoting another color
Visuoconstruction			
Clock Drawing Test [24, 25]	18	Visuoconstructive skills; symbolic and graphomotor presentation	Drawing the face of a clock, putting the numbers in the correct position and indicate a given time

* N=Number of patients assessed both before and after surgery. For several reasons, the full protocol could not be applied to all patients. Priority was given to tests that were most relevant to the preparation and evaluation of the operative procedure.

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erative percentages of tests with a z-score lower than -2 were calculated. Improvement was defined as a decreased percentage of tests showing impairment.

Statistical analyses

Neuropsychological test data were checked for normal distribution, using the Shapiro-Wilk test. Parametric statistical tests were used for normally distributed test scores; otherwise a non-parametric alternative was applied.

First, it was determined whether pre- and postoperative mean scores of the patients by cognitive domain and by test differed from the average performance in the normative group, using either a one-sample t-test with 0 (the mean score of the normal group) as test value or the Wilcoxon Signed-Rank Test. Subsequently, the pre- and postoperative average scores were compared with either paired-samples t-tests or the Wilcoxon Signed-Rank Test. To minimize the number of statistical comparisons, only tests and domains in which the pre- or postoperative mean performance deviated from normal performance were selected.

The influence of tumor and treatment related variables on change in cognitive performance was analyzed for the scores in the selected domains and the scores on the selected tests; the postoperative scores were subtracted from the preoperative scores. The resulting scores represent the individual changes between the pre- and postoperative assessments. The effect of the location and tumor grade on these scores was assessed using either a paired-samples t-test or the Mann-Whitney Test. The different histological tumor types were compared using a one-way ANOVA or the Kruskal-Wallis Test. The influence of postoperative treatment with chemo- and radiotherapy was analyzed with the same statistical tests. The influence of the preoperative volume of the tumor was determined by calculating Spearman rank correlations between the tumor volume and the 'change' scores. The same statistical method was used to examine the relationship between the extent of resection and change of cognitive performance.

RESULTS

Demographic and clinical characteristics

Patients' demographic characteristics and data on tumor and treatment related variables are presented in Table 2.

No relationship was found between demographic characteristics and tumor variables. In the majority of the tumors (60%), language areas were involved. Tissue obtained during the tumor resection showed that 52% of the gliomas were high grade (WHO grade III or IV). The majority (64%) of the tumors were astrocytomas, 12% were oligodendrogliomas and 24% were mixed oligoastrocytomas. The mean extent of resection was 70.7%. In 24% of the patients a resection of >90% was obtained. In one patient no residual tumor was visible on

Table 2. Demographic characteristics (n=28) and tumor- and treatment related variables (n=25)

Characteristic	Value
Patients	
Male gender	19 (67.9%)
Mean age (years); range	41.52; 19-74
Education[*27]; range	5 (4-7)
Handedness (right)	26 (92.9%)
Localization tumor	
Frontal	12 (48.0%)
Temporal	4 (16.0%)
Parietal	1 (4.0%)
Insular	3 (12.0%)
Frontoparietal	1 (4.0%)
Frontoinsular	2 (8.0%)
Temporoinsular	2 (8.0%)
Language area	15 (60.0%)
Non-language area	10 (40.0%)
Tumor histology	
Astrocytoma	16 (64.0%)
Oligodendroglioma	3 (12.0%)
Oligoastrocytoma	6 (24.0%)
Tumor grade	
WHO grade I or II	1 (4.0%)
WHO grade II	11 (44.0%)
Total low grade	12 (48.0%)
WHO grade III or IV	4 (16.0%)
WHO grade III	7 (28.0%)
WHO grade IV	2 (8.0%)
Total high grade	13 (52.0%)
Mean tumor volume (cm3); range	64.54; 6-156
Mean residual volume (cm3); range	20.71; 0-96
Mean extent of resection (%); range	70.72; 3.28-100
Postoperative treatment	
None	9 (36.0%)
Radiotherapy	10 (40.0%)
Chemotherapy	1 (4.0%)
Both	5 (20.0%)
Treatment with anti-convulsants	
Yes	20 (80.0%)
No	5 (20.0%)

* Education was classified ranging from 1 (only primary school) to 7 (university).

MRI scans postoperatively. Sixty-four percent of the patients were treated with chemo- and/or radiotherapy after surgery; 20% of this group received a combination treatment of radio- and chemotherapy. Patients received postoperative treatment with focal radiation in total doses ≤ 60 Gy. Eighty percent of patients were treated with anti-convulsants preoperatively. The type and dose of anti-convulsants remained equal postsurgery.

Neuropsychological preoperative results

At domain level, patients' mean scores deviated from normal scores in the language domain ($t=-5.15$, $p<0.001$), the memory domain ($t=-4.35$, $p<0.001$) and the executive domain ($t=-3.55$, $p=0.001$).

At test level, preoperative mean performance deviated from normal performance in the language domain on BNT ($t=-4.21$, $p<0.001$), category fluency ($t=-7.90$, $p<0.001$) and letter fluency ($t=-5.97$, $p<0.001$), in the memory domain on 15WT encoding ($t=-6.29$, $p<0.001$) and 15WT recall ($t=-4.16$, $p<0.001$) and in the domain of attention and the executive functions on TMTA ($t=-3.18$, $p=0.004$), Stroop I ($t=-7.11$, $p<0.001$), Stroop II ($t=-5.03$, $p<0.001$) and Stroop III ($t=-2.65$, $p=0.014$). However, the mean preoperative performance results did not deviate from normal in the language domain on the AAT subtests (Token Test, repetition, reading aloud, writing to dictation) or in the domain of attention and executive functions on TMTB, TMTBA, Stroop Interference and clock drawing (see Figure 1).

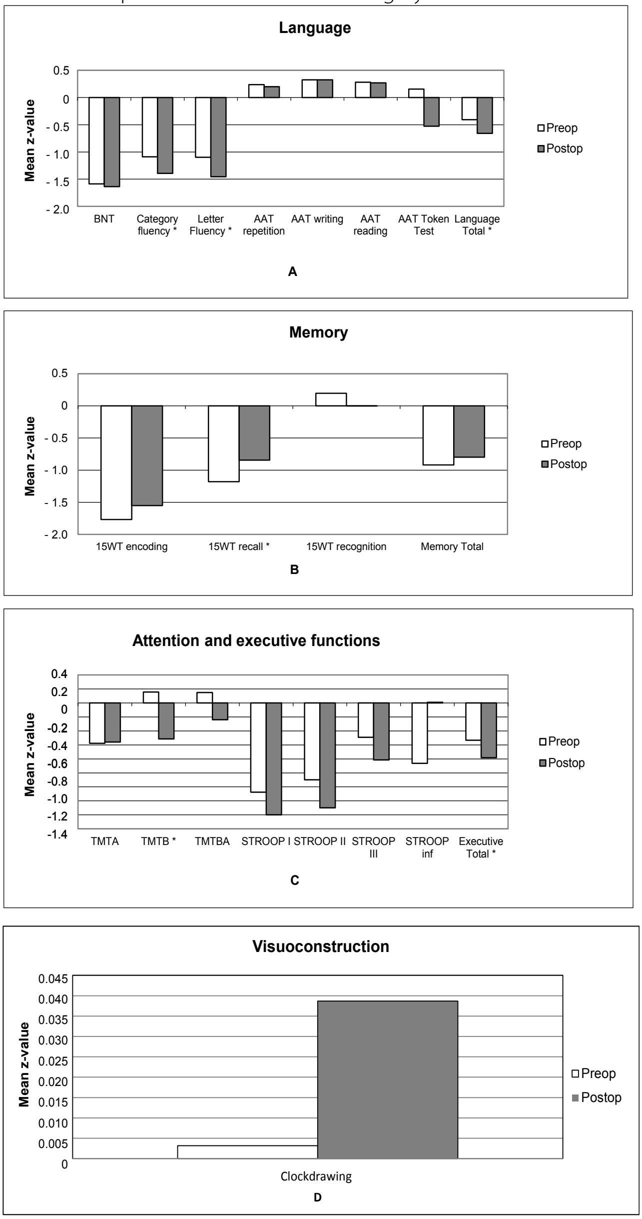
Neuropsychological postoperative results

At domain level, patients' mean scores remain deviant from normal scores in the language domain ($t=-4.35$, $p<0.001$, the memory domain ($z=-2.36$, $p=0.19$) and in the executive domain ($t=-3.44$, $p<0.001$). There was a significant postoperative decline in the language domain (mean difference -0.25, $p=0.027$) and in the executive domain (mean difference -0.29, $p=0.022$).

At test level, the mean performance was impaired on the same tests as before surgery (Language: BNT: $z=-3.27$, $p=0.001$; category fluency: $t=-9.28$, $p<0.001$; letter fluency: $z=-4.17$, $p<0.001$, Memory: 15WT encoding: $t=-5.36$, $p<0.001$; 15WT recall: $z=-3.37$, $p<0.001$, Attention and executive functions: TMTA: $t=-3.06$, $p=0.005$; Stroop I: $t=-7.05$, $p<0.001$; Stroop II: $t=-5.65$, $p<0.001$ and Stroop III : $t=-3.07$, $p=0.005$), with the addition of TMTB ($z=-1.91$, $p=0.028$).

When comparing cognitive scores pre- versus postoperatively, a significant decline was found in the language domain ($t=2.34$, $p=0.027$) and in the executive functions ($t=2.45$, $p=0.022$). Within the language domain there was a significant decline (pre- versus postoperatively) in performance on category fluency (mean difference -0.30; $p=0.031$) and letter fluency (mean difference -0.36; $p=0.02$). Within the domain of executive functioning, there was a significant decline in performance on TMTB (mean difference -0.43; $p=0.013$). Improvement was observed on a memory task 15WT recall (mean difference=0.39; $p=0.041$) (see Figure 1).

Figure 1. Mean z-scores of the patients before and after surgery on the tests in the 4 cognitive domains.



A: Pre- and postoperative mean z-score of the patients in the language domain. **B:** Pre- and postoperative mean z-score of the patients in the memory domain. **C:** Pre- and postoperative mean z-score of the patients in the domain of attention and executive functions. **D:** Pre- and postoperative mean z-score of the patients in the visuoconstructive domain. * Significant difference between pre- and postoperative performance (p<.05). A mean z-value of 0 equals mean performance in the healthy population. Negative z-values indicate that patients performed worse than the healthy population.

After surgery, the patients failed on a larger percentage of tests (18.22%) than before surgery (12.32%) (t=2.09, p=0.046). Based on the percentage of tests showing impairment, 6 patients improved postoperatively, 11 deteriorated and 11 remained stable.

Both before and after surgery, defective communication according to the ASRS (Scores 3 and 4) was found in 9 of 23 and 11 of 21 patients, respectively. However, during anamnesis more patients reported problems in daily conversational speech; before operation in 13 of 23 and after operation in 13 of 21 patients (Table 3).

Table 3. A. Patients' verbal communication according to the ASRS (0-5) and B. Number of patients with self-reported word-finding problems within the indicated ASRS scale (to the left).

Preop*			Postop**		
A		**B**	**A**		**B**
ASRS scale	*N*	*Self-reported word-finding problems*	*ASRS scale*	*N*	*Self-reported word-finding problems*
0	0	0	0	0	0
1	0	0	1	0	0
2	0	0	2	0	0
3	1	1	3	2	2
4	8	5	4	9	8
5	14	7	5	10	3
Total	23	13/23 (56.5%)	Total	21	13/21 (61.9%)

* Five recordings are missing in the analysis.

** Seven recordings 3 months post surgery are missing in the analysis.

Table 4. Mean (sd) difference between pre- and postoperative z-scores, based on localization of the tumor.

Tests	Language area	Non-language area
Language domain	-0.44 (0.64)*	-0.07 (0.29)
BNT	-0.62 (1.25)*	0.59 (0.86)
Category Fluency	-0.51 (0.74)*	0.04 (0.63)
Letter Fluency	-0.47 (0.49)	-0.12 (1.12)
Memory domain	0.06 (1.18)	0.30 (0.47)
15WT Encoding	0.01 (1.08)	0.57 (0.74)
15WT Recall	0.45 (1.14)	0.20 (0.62)
Attention and executive domain	-0.47 (0.68)	-0.14 (0.49)
TMTA	-0.26 (0.85)	-0.08 (1.13)
TMTB	-0.67 (0.86)	-0.14 (0.74)
Stroop I	-0.56 (0.96)	-0.08 (1.42)
Stroop II	-0.45 (1.00)	-0.13 (1.11)
Stroop III	-0.45 (1.19)	-0.21 (0.64)

* Significant difference; p<0.05

Tumor and treatment related variables
The change of cognitive performance was influenced by the localization of the tumor (Table 4).

The cognitive score of patients with tumors in language areas decreased postoperatively in the language domain ($t=2.33$, $p=0.029$), at test level on BNT ($t=2.57$, $p=0.018$) and category fluency ($z=-2.05$, $p=0.041$), whereas the cognitive scores of patients with gliomas not involving language areas did not significantly decrease. There was no effect on the difference scores from the other tumor-related variables, from the treatment related factors or from the extent of the lesion.

DISCUSSION

This is one of the few studies that assesses the influence of resection of glioma in eloquent areas on cognition. In accordance with earlier studies, patients had preoperative deficits in several cognitive domains: language, memory, attention and executive functions[3-6]. Resection of the tumor caused a slight deterioration within the domains of language and executive functions, but not in the memory domain. Changes in cognitive functioning were predominantly dependent on tumor localization; surgery in the proximity of language areas increased the risk of postoperative cognitive decline, especially in the language domain. No relation was found between cognitive change and extent of the resection, indicating that more aggressive resections (>90% tumor volume) did not lead to further cognitive deterioration. Tumor related factors such as pathological findings, histological grade, volume of the tumor and treatment with radio- and/or chemotherapy did not influence the postoperative status of cognitive functioning either.

Effect of glioma surgery on cognitive tests
At test level, after surgery there was a slight decline on the domains of language (category and letter fluency,) and executive functions (TMTB). In addition, a small improvement on a memory subtest (delayed recall) was found without influence on the total score of the memory domain.

The fluency tasks are described as sensitive for this group of patients; in addition to linguistic processing, they require a search strategy mediated by the prefrontal cortex[28]. The decline of concept shifting and the improvement of delayed recall agree with the results of Talacchi et al.[29]. This finding underlines the importance of tasks that assess memory and executive functions, because they showed to be sensitive in our patient group. Before the operation we can better prepare patients for short-term postoperative language difficulties and problems with the executive functions, which could negatively affect their quality of life. A longer follow-up with a larger patient group at 1 year is necessary to investigate whether these problems are transient or more permanent. Currently, we are collecting data at longer follow-up durations with more patients.

Tumor location

We made a distinction between language and non-language areas in the left hemisphere. Patients with tumors in language areas had a worse prognosis with respect to 3 months post-operative language functioning than did patients with tumors in non-language areas. The fact that resection in a language area induced a slight decrease in tasks assessing attention and executive functions, might be explained by the dependence of cognitive functions on integrated activity of several specialized brain areas[30], i.e. neural networks subserving language, which are also necessary for other cognitive functions.

At test level patients performed worse in naming and category fluency (a semantic task) both pre- and postoperatively. The importance of a naming task was already indicated by Ilmberger et al.[6]: a preoperative submaximal naming performance is a robust predictor of an early postoperative aphasic disturbance. Predominantly, patients with word-finding problems with a semantic background might be vulnerable in awake operations in the language areas. More than half of the patients had word-finding complaints in everyday communication pre- and postoperatively. A remarkable finding is that there was a number of patients with self-reported words-finding complaints whereas their communication was well-rated according to the ASRS. This finding suggests that word-finding problems cannot always be objectified by existing standard language examination tools and thus need more attention in the future, especially when surgical procedures have to be performed near speech areas.

The distinction between language and non-language areas was based on anatomical knowledge of classic language areas[17]. However, some debate exists about categorization of the precentral, middle, and superior frontal gyri in non-language areas. It is known that the language network is not limited to a single brain region and spreads out through at least large parts of the temporal and frontal lobes[31]. Several studies have shown variable specificity and sensitivity to language activation in the aforementioned gyri[32]. In our study, there was no significant decrease in performance of language tasks in patients with tumors in non-language areas. We can thus conclude that the influence of language function in these areas is minimal.

Histological type, pathological grade and volume of the tumor

The absence of an influence of tumor-related characteristics does not preclude the possibility that these factors affect cognitive performance. Due to the small sample size of this exploratory study, it had only limited power. Previous studies have shown mixed results. It was found that larger tumor size was associated with postoperative cognitive deterioration[29], whereas other studies did not detect such findings[3]. Patients with HGGs are reported to have generally more cognitive deficits than patients with LGGs[1]. After surgery, this difference tends to disappear, because in patients with HGGs cognition may improve due to release of the mass effect, while cognition of LGG patients may not show this improvement, or may even deteriorate[29, 33]. A larger data set with a longer follow-up will shed more light on these factors. It could be the case that a more aggressive glioma resection in HGG patients would result in a better quality of life than in those with LGG.

Postoperative treatment with radiotherapy, chemotherapy and anti-convulsants

The absence of an effect of postoperative treatment with radiotherapy and/or chemotherapy must be interpreted with caution also, due to the limited power of this study and the short-term follow-up (3 months postoperatively). Several studies however, showed that radiotherapy of doses <2 Gy does not affect cognitive performance until several years after treatment[16, 34-36]. In our study, the patients received focal radiation therapy in 'safe' total doses of ≤ 60 Gy, the upper limit of the 'safe dose'[37]. Nevertheless, total doses of 59.4 Gy have shown to have a negative effect on the quality of life by causing fatigue and insomnia[38]. Both fatigue and insomnia may have a negative influence on cognitive performance. Combination therapy may induce cognitive side-effects[33, 36] and could lead to lower scores in several cognitive domains. Klein et al.[34], however, suggest that deficits should not be attributed to treatment but to the tumor itself, because only a few tasks in various cognitive domains were impaired in a follow-up study that lasted 6 years. Long-term cognitive follow-up is therefore necessary to study these effects.

The use of anti-epileptic drugs could affect cognition, such as impairment in attention and cognitive slowing[39]. In our study, however, the majority of the patients in the group already used anti-convulsants at baseline, suggesting an exclusion of a negative effect of medication on cognition postoperatively.

Importance of the test protocol

The results from this study imply that it is important to test different cognitive domains in patients with glioma: that is language, memory and executive functions. Both pre- and postoperatively, patients deviated from normal in all domains, with the exception of visuoconstruction. Sensitive tests for cognitive change in our study in the domain of language were naming and the verbal fluency tasks; in memory 15WT encoding and recall; and in executive functions TMTA, TMTB and Stroop I-III. Results on these tasks will be analyzed in a consecutive follow-up study 1 year after surgery to evaluate whether cognitive performance improved, stabilized, or deteriorated.

Limitations of the test protocol

Cognitive disabilities of glioma patients are often not detected during neurological examination. Therefore, a test protocol should be created that consists of neuropsychological tests, as well as a refined spontaneous speech assessment tool that are sensitive to the deficits in this patient group and to the effect of surgery[4]. The requirements of a neuropsychological test protocol for the assessment of glioma patients are described by Taphoorn and Klein[1]. Our test protocol had some limitations which may restrain the interpretability of the results. Firstly, the test for visuoconstructive skills (Clock Drawing Test) was originally developed for the assessment of elderly patients with possible dementia[40]. Studies using other visuoconstructive tests (for example, the Block Design of the Wechsler Adult Intelligence Scale - Revised)[2] detected visuoconstructive deficits in approximately half of glioma patients[41]. Secondly, most of the tests we applied had a verbal component. Therefore, language impairment may have interfered with performance on tests meant to measure other cognitive functions. However, no significant deterioration was found in patients with gliomas in language areas when other cognitive tasks were performed. This finding suggests minimal possible language impairment interference in these tasks.

CONCLUSION

This exploratory study is a first step towards the identification of factors predicting cognitive change after glioma resection in eloquent areas. The results suggest that it is possible to perform an extended glioma resection in non-language areas without inducing major cognitive decline, whereas resection in language areas increases the risk of subtle cognitive deficits in the longer term after surgery. This study result can help to inform patients preoperatively and to optimize the treatment plan. A biopsy or less aggressive surgery could be proposed for gliomas in or near language areas if patients choose to have a maximal quality of life. In addition, our results underline the importance of neurocognitive assessment before and after surgery with word-finding as an essential ability to assess. Because the prognosis of this group of patients is dependent on the extent of surgery, it is important to know the effect on cognition with implications for cognitive rehabilitation[42]. Furthermore, this factor is also important for the detection of tumor recurrence; cognitive deterioration may be a first sign of tumor growth, even before this is visible on MRI studies[1].

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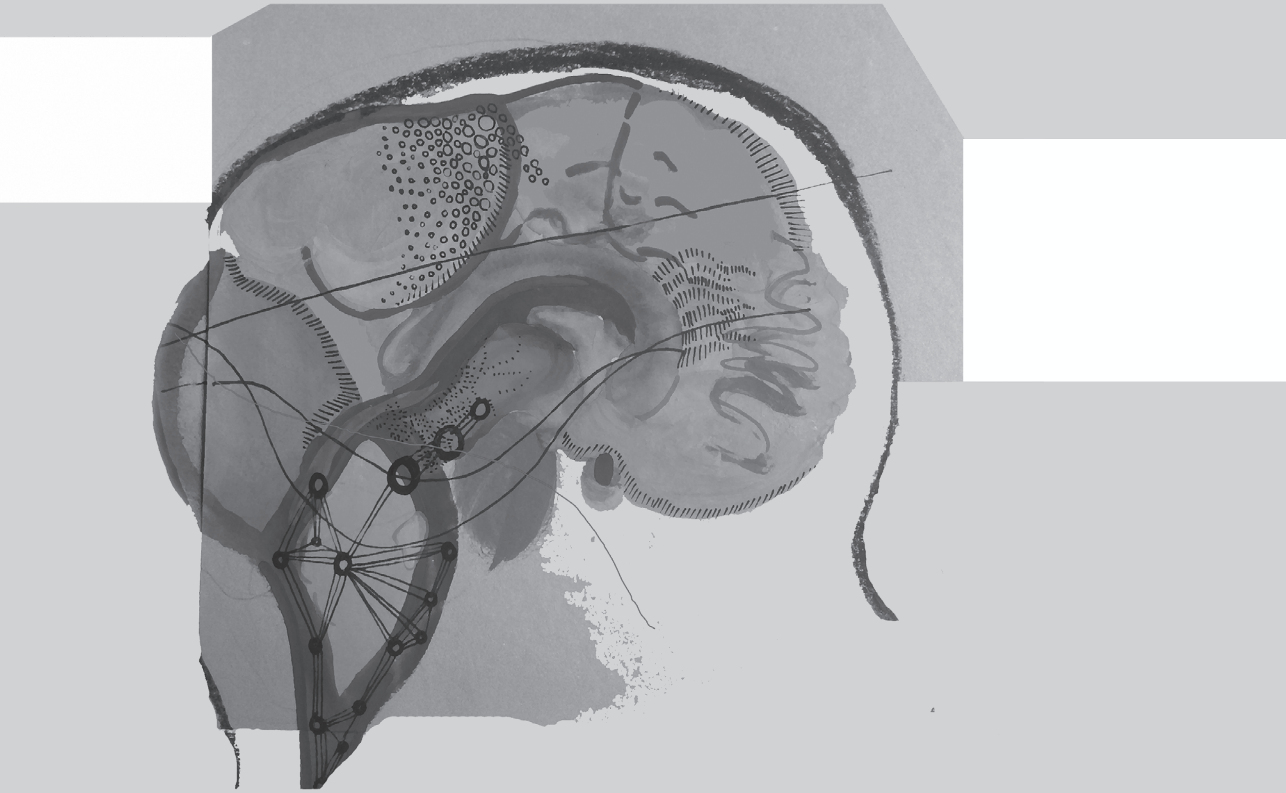

Chapter 4

Spontaneous speech of patients with gliomas before and early after surgery

ABSTRACT

Background. Glioma patients often complain about problems in daily conversation. A detailed spontaneous speech analysis could provide more insight in these communicative problems; no previous studies are reported.

Objective. To select sensitive parameters in spontaneous speech pre- and postoperatively in patients with gliomas in eloquent areas.

Methods. We included 27 patients and 21 healthy controls. In addition to a naming and a category fluency test, spontaneous speech was collected 1 month preoperatively and 3 months postoperatively and analyzed with the variables Self-corrections, Repetitions, Lexical Diversity, Incomplete Sentences and Mean Length of Utterance of words (MLUw). A correlation analysis was performed between the linguistic variables and tumor characteristics (grade, localization, and volume), treatment related factors, and between the linguistic variables and the language tasks.

Results. Preoperatively, patients produced more Incomplete Sentences than the controls ($p<0.001$). Postoperatively, patients' utterance length (MLUw) was also deviant ($p<0.05$). The quality of the spontaneous speech was influenced by tumor grade and localization. There was no influence of tumor volume or treatment related factors. Pre- and postoperatively, patients' performance on the naming and the fluency task deviated from normal ($p<0.001$). The majority of the linguistic variables did not correlate with the language tasks, pointing to a measurement of distinct linguistic aspects.

Conclusion. Pre- and postoperatively there was a disorder in naming, category fluency and spontaneous speech, partly influenced by tumor characteristics. A spontaneous speech analysis appeared to be a valuable addition to standardized language tasks. Both measurements are important tools to obtain a complete linguistic profile.

INTRODUCTION

Spontaneous conversation is the most natural form of speech and crucial in daily life to convey a message. Patients with gliomas often report problems in daily conversation. Although the quality of communication is a core hallmark of quality of life[1], no data about the characteristics of spontaneous speech in glioma patients are available. Partly, the conversational problems might be caused by a word-finding deficit; naming problems are observed in glioma patients before and after surgery[2-4]. For instance, a sub-maximal naming performance was a robust predictor for an early postoperative aphasic disturbance[5]. However, word-finding is an important but not comprehensive element of everyday conversation. Adequate communicative language behavior requires a flawless performance on phonemic, word, syntactic and discourse level. With a quantitative analysis of aphasic symptoms in spontaneous speech, the mutual influence of the different layers of speech, normally assessed in isolation (with standardized tasks), could be identified and as such be sensitive to capture language difficulties in a naturalistic language activity[6].

Several tumor related factors, such as localization, tumor size, and histological grade might be responsible for cognitive change in general in this group of patients[7]. Our goal is to select sensitive parameters in the spontaneous speech of glioma patients pre- and postoperatively and to examine the relation with usual standardized language tasks and tumor-specific characteristics.

METHODS

Design

This is a longitudinal observational study. The effect of glioma surgery on language was examined. Inclusion criteria: 1) untreated glioma in or near eloquent brain areas, 2) at preoperative diagnosis a presumed LGG (no contrast enhancement on preoperative MRI-scans), 3) native (or fluent) in speaking and understanding Dutch. Exclusion criteria: 1) history of a medical, neurological or psychiatric condition known to affect cognition, 2) (history) of substance abuse, 3) suffering from permanent cognitive or motor problems.

Subjects

The spontaneous speech of 27 patients (mean age 41.52, range 19-74) with gliomas in the left hemisphere was examined before and after surgery. Tumor localization was determined by a neuroradiologist using 3D T1-weighted magnetic resonance imaging (MRI) and 2D T2-weighted MRI. The pre- and postoperative tumor volume was calculated by manual delineation of 3D deviant signal intensity on T2-weighted MRI using Osirix version 3.7.1. (http://homepage.mac.com/rossetantoine/osirix). Postoperative MRI scans were performed within

72 hours of resection. The pathological WHO (World Health Organization) grade was determined by a neuropathologist, from tissue obtained during the tumor resection. The study was approved by the Ethical Committee of Erasmus MC and patients gave their informed consent. Twenty-one controls (non-brain-damaged speakers) matched for gender, age, education and handedness with no history of neurological disease were selected.

Pre- and postoperative language testing

The spontaneous speech of the glioma patients was collected and recorded for analysis in an interview setting about 1 month pre- and 3 months postoperatively. The spontaneous speech of controls was collected in private settings (at home or in another quiet environment). To elicit speech, 3 different topics were discussed with minimal intervention of the interviewer: medical status (glioma patients), most recent doctor's visit (controls) work, and hobbies. A sample of 300 words from contiguous speech, the number required for a reliable linguistic analysis, was selected per subject[8]. The first 50 words were not transcribed to control for possible intervening factors, such as unresponsiveness and/or emotional reactions. Fillers such as "erm", "ah", and "well" were not included. Subsequently, each sample was analyzed to ascertain Self-corrections, Repetitions, Lexical Diversity, Incomplete Sentences and Mean Length of Utterance of words (MLUw) using the linguistic computerized program CLAN[9] (see Table 1).

Furthermore, the Boston Naming Test (BNT)[10], a standardized test to assess word-finding problems (60 items of high and low frequency) and a category fluency test[11] (generation of words of the category animals within one minute), were administered.

Intraoperative language testing

All patients were operated on in an awake setting after administration of local anesthesia. Direct electrocortical and subcortical stimulation was performed to identify individual functional boundaries. A bipolar electrode *(*biphasic pulse, 50 Hz frequency, 1msec duration, 6-12 mA*)* was applied.

During cortical and subcortical stimulation, repetition of 3-syllabic words and a naming task were used to identify positive language sites. During the resection, besides repetition and naming, also the spontaneous speech of patients was monitored by the linguist. Topics of discussion were mainly autobiographic (as agreed on with the patient preoperatively). The linguist checked whether the patient was still able to speak fluently and whether he/she was able to start a conversation. In case of change of the quality of the spontaneous speech (word-finding problems, paraphasias), more specific language production or comprehension tasks focussing on individual language levels (e.g. phonology, semantics, syntax) were selected to control more adequately for language disturbances.

Table 1. Classification of linguistic variables

Linguistic variable	Examples	Glossary
Lexical Diversity	Measures Type Token Ratio Number of words divided by number of tokens times 100	
Mean Length of Utterance (words) (MLUw)	Measures linguistic productivity: Number utterances divided by number of words	
Repetition	de [/] de [/] de winkels zijn al gesloten	the [/] the [/] the shops are already closed
Self-correction	ik heb [//] moet naar huis	I have[//] must go home.
Incomplete sentence:	Incomplete Sentences were calculated in percentages: number of Incomplete Sentences per patient divided by the mean number of complete utterances	
a) content word	ik droeg de […]	I carried the […]
b) verb	gisteren heb ik die tas […]	yesterday I did […] the bag
c) obligatory parts of speech	toen ik op vakantie was toen dacht ik van eh nou […] ik vind het ook heel leuk werk want je hebt toch best wel met eh […]	when I was on holiday I thought erm […] I also really like the work because there's quite a lot of erm […]
e) content word or obligatory parts of speech	ik had al ehm nou sowieso voor mijn gevoel al eh nou 3 jaar […]	for 3 years I already had erm the feeling erm well […]
f) other (e.g. incorrect syntax)	aan het gaat het weer eh ja mindset […]	to it is again erm yes mindset […]

Statistical analyses

Parametric or non-parametric (normal distribution checked with Shapiro-Wilk test) statistical tests were performed to compare the performance on the linguistic variables: 1) of the patients pre- and postoperatively and the controls, 2) of the patients pre- and postoperatively. A univariate analysis of variance (ANOVA) was performed to examine differences between the patients' pre- and postoperative spontaneous speech and that of the controls in terms of Self-corrections, Repetitions, Lexical Diversity, Incomplete Sentences and Mean Length of Utterance of words (MLUw). A paired samples t-test was applied to compare the difference on the linguistic variables within the patient group pre- and postoperatively. To investigate differences in the spontaneous speech in patients according to tumor grade and tumor localization, an ANOVA or the Kruskal-Wallis test was performed with the control group as baseline. With the same statistical tests, the influence of postoperative treatment with chemo- and radiotherapy was analyzed. The influence of the preoperative volume of the tumor was determined by calculating Pearson rank correlations between the tumor volume and the preoperative deviating linguistic values.

To determine whether pre- and postoperative mean scores of the patients on the BNT and the category fluency test differed from the average performance in the normative group, a one-sample t-test with 0 (the mean score of the normal group) was used. To investigate whether the quality of spontaneous speech was correlated with the performance on formal language tests, Pearson rank correlations were calculated between the deviating linguistic variables and the raw scores from the BNT and category fluency pre- and postoperatively.

Table 2. Demographic characteristics of patients and controls and tumor-related variables

Demographics	**Patients (=27)**		**Controls (N=21)**
Male gender	18 (66.7%)		8 (38.1%)
Mean age; range	41.52; 19-74		39.44; 19-62
Education[1]; range	5; 4-7 (2x)		5; 4-7 (2x)
Handedness (left)	2 (7.4%)		2 (9.5%)
Tumor localization			
Frontal	13 (48.2%)		
Temporal	4 (14.8%)		
Parietal	1 (3.7%)		
Insular	3 (11.1%)		
Frontoparietal	2 (7.4%)		
Frontoinsular	2 (7.4%)		
Temporoinsular	2 (7.4%)		
Functional area[2]			
Language area	15 (55.6%)		
Non-language area	10 (37.0%)		
Unknown	2 (7.4%)		
Tumor grade			
Low grade glioma (LGG)	15 (55.6%)		
High grade glioma (HGG)	12 (44.4%)		
Distribution tumor grade	LGG	HGG	
Language area	10	8	
Non-language area	3	3	
Unknown	2	1	
Postoperative treatment			
None	10 (36.0%)		
Radiotherapy	10 (40.0%)		
Chemotherapy	2 (4.0%)		
Both	5 (20.0%)		

1 Education was classified according to the coding system of Verhage [29], ranging from 1 (only primary school) to 7 (university).

2 Two patients were treated in a different hospital. Data about language or motor area were not available.

RESULTS

Patient Information

Demographic characteristics of the patients and the controls, matched for gender, age, education and handedness, are presented in Table 2.

Tumor location

The gliomas were located in the left frontal or parietotemporal language areas (inferior frontal gyrus, subcentral gyrus, supramarginal gyrus, angular gyrus, inferior, middle and superior temporal gyrus), or in non-language areas (precentral, middle or superior frontal gyrus, with no involvement of the inferior frontal gyrus) based on the classic neuro-anatomical model of language[12].

Preoperative results

Preoperatively, the patients produced more Incomplete Sentences (p=0.001) than the controls. A more refined analysis of the Incomplete Sentences, showed that only the omission of content words was responsible for this deviation (p=0.010) (see Table 3). There was a trend to significance for the variable Repetitions (p=0.055).

Table 3. Mean values for linguistic variables patients versus controls pre- and postoperatively (standard deviation).

	Preoperatively		Postoperatively		
Linguistic variable	**Patients (N=27)**	**p-value**	**Patients (N=24[3])**	**p-value**	**Controls (N=21)**
Lexical Diversity	0.46 (0.04)	0.184	0.46 (0.03)	0.204	0.48 (0.30)
MLUw	8.74 (1.67)	0.0168	8.12 (1.18)	0.011	9.5 (2.05)
Repetitions	10.70 (9.63)	0.055	9.79 (7.45)	0.064	6.05 (5.44)
Self-corrections	5.65 (4.83)	0.122	5.04 (6.52)	0.432	3.86 (2.17)
% Incomplete Sentences	7.80 (6.79)	0.001	7.80 (6.79)	0.001	2.0 (2.34)

3 Postoperative recordings of 3 patients were missing.

LGG patients made more Incomplete Sentences (p=0.001) in comparison to controls and HGG patients (p=0.046), also with localization as covariate (p=0.001) (see Table 4). In comparison with the controls, both patients with tumors in language and non-language areas had more Incomplete Sentences in their spontaneous speech (p=0.003) than controls (see Table 5). There was no influence of tumor volume on the linguistic variables.

The mean performance of the patients deviated from normal performance on the BNT and the category fluency task (p<0.001). A positive correlation was found between the BNT and Incomplete Sentences (r=0.430, p=0.028), indicating that patients with higher BNT scores

Table 4. Mean values for linguistic variables patients according to tumor characteristics versus controls pre- and postoperatively (standard deviation)

	Preoperatively					Postoperatively					
Linguistic variable	**LGG (N=15)**	**HGG (N=12)**	**p-value (LGG - HGG)**	**p-value (LGG-controls)**	**p-value (HGG-controls)**	**LGG (N=14)**	**HGG (N=10)**	**p-value (LGG - HGG)**	**p-value (LGG-controls)**	**p-value (HGG-controls)**	**Controls (N=21)**
MLUw	8.79 (2.06)	8.54 (1.01)	1.0	1.0	0.571	7.94 (1.26)	8.33 (1.11)	0.851	0.036	0.177	9.50 (2.05)
Incomplete Sentences (%)	7.47 (4.26)	3.86 (4.51)	0.046	0.001	0.505	8.64 (7.03)	8.95 (6.23)	0.989	0.001	0.003	2.0 (2.34)

Table 5. Mean values for linguistic variables patients according to tumor localization[4] versus controls pre- and postoperatively (standard deviation)

	Preoperatively					Postoperatively					
Linguistic variable	**Lang. (N=18)**	**Non-lang. (N=6)**	**p-value (lang-non-lang)**	**p-value (lang-controls)**	**p-value (non.lang-controls)**	**Lang. (N=17)**	**Non-lang. (N=5)**	**p-value (lang-non-lang)**	**p-value (lang-controls)**	**p-value (non-lang-controls)**	**Controls (N=21)**
Incomplete Sentences	6.59 (4.82)	6.67 (4.49)	0.999	0.003	0.037	8.97 (6.45)	9.47 (8.65)	0.981	0.001	0.016	2.0 (2.33)
MLUw[5]						8.14 (1.2)	8.60 (0.91)	1.0	0.076	0.082	9.5 (2.05)

4 Two localizations were unknown pre- and postoperatively, and 3 postoperative recordings were missing.

5 Only post-operative MLUw was investigated by localization, since MLUw did not deviate preoperatively.

produce more Incomplete Sentences. No significant correlation was found between Incomplete Sentences and category fluency.

Postoperative results

Apart from Incomplete Sentences, the patients deviated also on MLUw compared with the controls (*p*<0.001, *p*=0.011 respectively) (see Table 3). The deviant omissions in Incomplete Sentences concerned more different categories than preoperatively: in addition to content words (*p*=0.024), obligatory parts of speech (*p*=0.026) and a mixed category with content words and obligatory parts of speech (*p*=0.003) were observed. However, the linguistic variables did not deteriorate within the patient group.

Regarding tumor characteristics, patients with LGGs had a shorter MLUw (*p*=0.036) than the controls and both LGGs and HGGs produced more Incomplete Sentences (*p*=0.001, p=0.003) (see Table 4). Both patients with tumors in language areas and non-language areas had more Incomplete Sentences than the controls (language: *p*=0.001, non-language: *p*=0.016) (see Table 5). There was no effect on the linguistic variables from the treatment related factors. There was no change in the spontaneous speech of the patients pre- versus postoperatively according to tumor related characteristics.

Mean performance of patients on BNT and category fluency was impaired compared to normal performance (BNT: *p*=0.001; category fluency: *p*<0.001). There was a positive correlation between the BNT and MLUw (r=0.449, *p*=0.041), indicating that patients with higher BNT scores produce longer utterances. There were no other significant correlations between standardized tasks and deviating linguistic variables.

At individual level, there were 10 patients with deviant spontaneous speech (Incomplete sentences) preoperatively. Of this group, 5 patients remained to have less fluent speech postoperatively (Incomplete sentences: 3 patients, MLUw: 2 patients, Both: 1 patient), and 5 patients recovered. The gliomas of the recovered patients were all located in language areas, with 4 LGGs and 1 HGG. There were 7 patients who developed problems in their spontaneous speech postoperatively. These gliomas were located in language areas (2 unknown), and most were LGG (5 out of 7). It is unclear if/which patients received language rehabilitation, since the aftercare program is not similar in each center. It is therefore difficult to track down exactly the application of language treatment, and if so, the intensity and content thereof. Moreover, the language rehabilitation program used in the Netherlands is mainly focused on stroke patients. These treatment methods might not be sensitive enough for glioma patients, since the communicative problems of this patient group are in general less severely disturbed and more disease-specific.

DISCUSSION

We conducted an exploratory spontaneous speech analysis in patients harbouring eloquent-area gliomas. Deviating linguistic parameters in the spontaneous speech of glioma patients before and after surgery were observed: Incomplete Sentences and MLUw. Tumor resection did not induce substantial linguistic change, apart from a slight decrease of MLUw. Tumor grade partly influenced patients' spontaneous speech. Also the patients' performance on the BNT and the category fluency task deviated pre- and postoperatively. The majority of the linguistic variables however, did not correlate with the performance on those usually administered tasks in LGG patients. A spontaneous speech analysis seems to be a valuable additional task in the domain of language.

Effect of gliomas on spontaneous speech

The selected spontaneous speech variables have been widely used in language pathology (and language acquisition) in individual patients and in group studies[13-15]. These variables play an important role in spontaneous speech analysis because they can shed light on impairments on different linguistic levels such as the lexical level (word choice) and/or the syntactic level (sentence construction)[6].

The lack of content words in Incomplete Sentences, as observed pre- and postoperatively, might be due to a word-finding deficit: a lexical problem. However, after surgery there was also a positive correlation between the BNT and the Incomplete Sentences, indicating that the higher the score on the naming test the more Incomplete Sentences came up. A disability to build a right syntactic frame with correctly activated lexical items might be the background of this at first sight strange correlation. Consequently, the omissions of content words in sentences may arise both from impairments at the syntactic or/and the lexical level, just as a shorter MLUw. The omission of obligatory parts of speech in the Incomplete Sentences, as observed postoperatively might be also a marker of a syntactic deficit.

Patients' performance on the BNT and the category fluency task was worse than that of healthy controls pre- and postoperatively. Postoperatively there was a positive correlation between the BNT scores and MLUw. Other spontaneous speech variables, however, did not correlate with BNT or with category fluency. A spontaneous speech analysis seems to be an essential addition to standardized tasks to capture language difficulties in LGG patients and should be used in order to obtain a complete linguistic profile during course.

When we compared linguistic performance pre- and postoperatively, no significant linguistic decline was found, apart from a slight decrease in MLUw (although we did find a difference between the patient group and the controls). This finding supports the results from other studies that report maximal tumor resection accompanied by minimal or at least transient deterioration of linguistic or other cognitive impairments[5, 16-18]. At individual level, improvement or deterioration in the spontaneous speech was variable. Five patients recovered from preoperative language deviations in their spontaneous speech, whereas 7 patients developed speech problems. Most of all these gliomas were located in language areas and were low grade. It could be plausible that surgery of gliomas in language areas in patients with preoperative language disturbances induces recovery due to the release of mass effect. On the other hand, patients with gliomas in language areas without preoperative language disturbances could be more at risk for (transient) postoperative language problems due to the surgery itself.

Tumor characteristics

Linguistic deviations were found in patients with tumors in both language areas and non-language areas. Patients with gliomas in language areas are at risk for linguistic problems, which is consistent with the known relative functional specialization of brain areas[12]. The fact that the non-language group also produced more Incomplete Sentences than controls is consistent with the emerging notion that language is functionally much more distributed than the classic language model accounts for[19] and might also be the result of a reorganization process due to the tumor growth.

A sub-analysis of the patients according to tumor grade revealed that pre- and postoperatively, the spontaneous speech of LGG patients deviated more than that of the HGG patients, This might be due to the fact that grade II gliomas migrate more frequently along white matter tracts (e.g. the arcuate fasciculus or the inferior fronto-occipital fasciculus) compared to HGGs [20]; these neural structures mostly involve language pathways. Another explanation for the disparity in postoperative linguistic deviations in these patient groups could be attributable to the release of mass effect by surgical removal of the faster growing HGGs which induces cognitive improvement[18, 21, 22]. In another recent study, where standardized tests were used, a difference in language performance between tumor grades was not found[3]. An additional spontaneous speech analysis seems to be necessary to point out these subtle differences.

The absence of a relation between initial tumor volume and linguistic performance in our group is in line with the findings of other studies[3, 22] and might be explained by the small sample size and its limited statistical power.

We found no effect of postoperative treatment with radiotherapy and/or chemotherapy on the linguistic variables. Short follow-up studies could be limited in showing an effect on cognition[7]. Klein et al.[23] however, have shown in a 6 year follow-up study that the use of radiotherapy was associated with poor cognition on only a few tasks (in various domains), suggesting that deficits should not be attributed to treatment but to the tumor itself. Long-term linguistic follow-up is therefore necessary to study these effects.

Limitations of a spontaneous speech analysis

A spontaneous speech analysis is time-consuming and therefore not easily applicable in clinical settings. The most time-consuming aspect is the transcription of the expressive speech. For the analysis of the deviancies according to basic linguistic parameters, we used the quantitative computer-assisted method CLAN, also used by others (but designed for child language)[24, 25]. Our future goal is to develop a more refined language test protocol based on our findings, which is able to capture conversational problems in glioma patients more effectively and efficiently, such as a sentence completion task (as Incomplete Sentences was the most sensitive variable). A restriction of our study is the small sample size and a relatively short follow-up. A more elaborate study is in progress.

CONCLUSION

This spontaneous speech analysis is the first study investigating daily conversation of glioma patients. It is a naturalistic method to measure language improvement or deterioration after glioma resection. The results can be used in the future to develop a more structured language rehabilitation program. Currently, the rehabilitation program is too various and might not be sensitive enough for the specific language problems of this group of patients. The results suggest that a spontaneous speech analysis provides additional information to the linguistic profile of glioma patients besides standardized languages tasks. Tumor grade partly influenced patients' language performance. Both patients groups with tumors in language or non-language areas were at risk for language disturbances, pointing to the necessity of language testing in general. These study results can help to inform patients preoperatively and to optimize the neurosurgical treatment plan. The judgment about the quality of spontaneous speech is a necessary element of awake operations; insight in the preoperative status of this speech modality is mandatory to be able to detect deviances during the awake interval.

Spontaneous speech is the most important language modality in daily life. It is therefore important to know the effect of infiltrating tumors on language in glioma patients.

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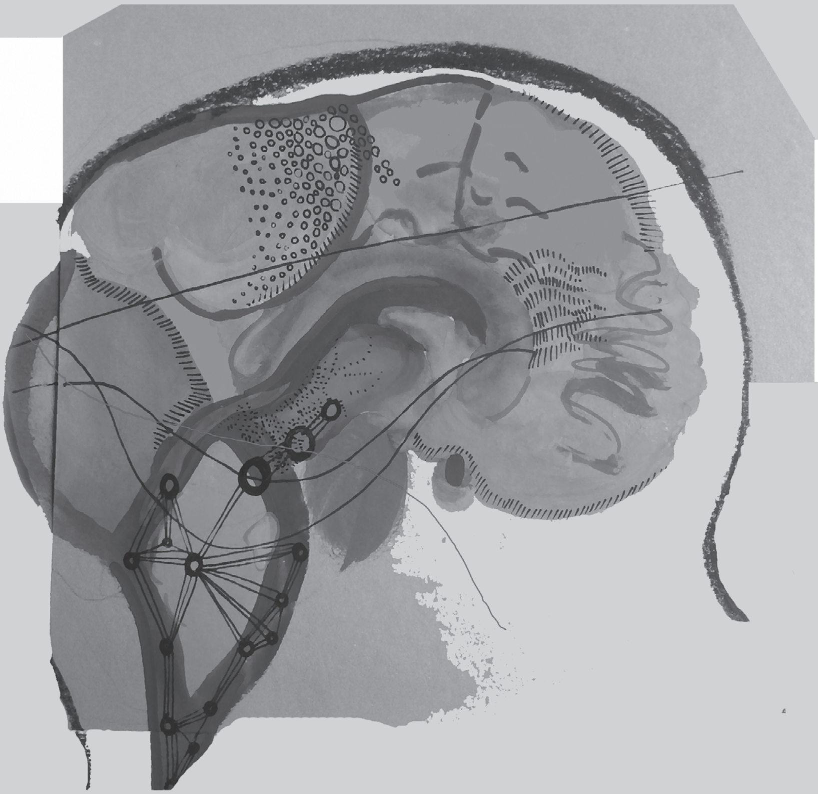


Chapter 5

Cognition, anxiety, depression and quality of life early after surgery for glioma in eloquent areas

ABSTRACT

Background. Maintenance of Quality of Life (QoL) is an essential outcome measure for patients undergoing glioma surgery. Several factors are claimed to have influence on QoL of this patient group, such as disturbed cognition, physical and psychological functions.

Object. To investigate the short-term effect of eloquent area glioma surgery on QoL, cognitive status, symptoms of anxiety and depression and subsequently to examine the predictive value of these factors on QoL.

Methods. Thirty-four consecutive patients with presumed low grade glioma in eloquent areas were assessed preoperatively and 3 months postoperatively with an extensive neuropsychological test-protocol, a global QoL rating (QLQ-C30) and with questionnaires for anxiety and depression (CES-D, STAI-DY).

Results. The level of QoL was moderate to good both pre- and postoperatively in most patients (76.4% versus 67.7%). Overall cognitive functioning was disturbed in 35.3% of the patients preoperatively, and in 32.4% postoperatively. Signs of anxiety and depression were also found and remained relatively stable pre- and postoperatively: 37.5% versus 31.3%, 44.1% versus 41.2% respectively. Depression was the only predictor for change in QoL ($F_{(1,30)}=18.733$, $p<0.001$, Adjusted $R^2=.364$).

Conclusion. Our findings show that QoL is preserved after glioma surgery as showed by patients' stable rating. Despite deviating cognitive status and symptoms of anxiety, no relation to QoL was found. Depression was most strongly related to change in QoL rating. We suggest that psychological monitoring is of utmost importance in glioma patients in order to optimize and maintain QoL.

INTRODUCTION

Glioma surgery may transiently enhance or deteriorate cognitive functioning[1, 2]. In patients with gliomas in eloquent areas direct electrical stimulation (DES) is often applied during neurosurgical intervention for functional mapping. The goal of DES is to maximize tumor resection with preservation of neurological and cognitive functions and Quality of Life (QoL), and inducing longer survival time[3]. Cognitive impairments, such as language disturbances, can negatively influence QoL[4, 5], which is an important outcome measure in treatment of primary brain tumors[6]. Although radio- and/or chemotherapy have received considerable attention in playing a role in QoL of brain tumor patients[7-10], the consequences of neurosurgery on QoL still remain uncertain.

A crucial factor associated with QoL is epilepsy burden, as the occurrence of seizures was ascribed to a decline in QoL[11]. In addition, cognition, depression, fatigue and emotional distress are also relevant aspects associated with QoL. Karnofsky Performance Scale (KPS) or Mini Mental State Examination (MMSE) have frequently been used to investigate neurological outcome cognition and QoL. These global diagnostic tools, however, are not aimed to detect cognitive disturbances in LGG patients[12, 13]. MMSE is known as an effective screening instrument to detect symptoms of cognitive deterioration specifically in Alzheimer's disease[14], but not as an adequate instrument to diagnose disorders and varying performances in the different cognitive domains. KPS was designed to measure the level of general patient independence; this scale may be insensitive to neurological or cognitive change as already indicated by Grant et al.[15]. There is only 1 study in which the authors used a comprehensive neuropsychological test battery[16] and showed a relation between QoL and cognition. However, the subjects in this study were patients with recurrent high grade glioma (HGG), who generally suffer from more neurological problems than LGG patients. Moreover, patients with tumor recurrence are expected to have a different degree of QoL from newly diagnosed patients[17]. A fine-grained study investigating QoL in patients with presumed LGGs by means of an extensive objective cognitive test-battery has not been conducted yet. Apart from cognitive impairments, psychological factors such as depression and anxiety have also been found to affect QoL in brain tumor patients[3, 18, 19]. Possible influences are the disease itself, the treatment, the awareness of the diagnosis or a combination of factors[20]. The influence of surgery on QoL is investigated by Jakola et al.[21] with the use of a questionnaire (EQ-5D). In a relatively early follow-up, 6 weeks postoperatively, they found no change in QoL. However, the recovery process is reported to take more time[1, 22]. We therefore suggest that a follow-up at 3 months provides a more stable QoL profile of glioma patients.

In this study, we will investigate global QoL rating, cognition, symptoms of anxiety and depression of glioma patients pre- and postoperatively. Subsequently, we will analyze the predictive value of cognition and the above-mentioned psychological factors for change in QoL. As a result, possible factors influencing QoL could be identified earlier in glioma patients in order to preserve the quality of their daily living. Also the short-term effect of glioma surgery on QoL can be better understood. Finally, a primary understanding of global QoL rating after glioma surgery will subsequently lead us to more detailed research issues that may be involved in this delicate topic of neuro-oncological research.

METHODS

Procedure

This is a longitudinal observational study of 34 consecutive Dutch (native speaking) patients who were operated for untreated gliomas in eloquent areas (language or motor area) without contrast enhancement at diagnosis on MRI-scans in the left or right hemisphere. Patients were excluded if they had a history of a medical, neurological or psychiatric condition known to affect cognition, substance abuse, or if they were suffering from permanent cognitive or motor problems, concomitant with the brain tumor. After pathological examination, 32% of

Table 1. Demographic and clinical characteristics of the patient group

Characteristic	Patients (N=34) (%)
Male gender	18 (52.9%)
Mean age (years); range	38.8; 20-72
Education[23]; range	5; 3-7
Handedness (right)	29 (85.3%)
Tumor grade	
Low grade (grade II)	18 (53%)
High grade (grade III + IV)	11 (32%)
Unclear	5 (15%)
Tumor localization	
Left (total)	27 (79.4%)
Frontal	11 (32.4%)
Parietal	4 (11.8%)
Occipital	1 (2.9%)
Temporal	2 (5.9%)
Frontoparietal	5 (14.7%)
Temporoparietal	1 (2.9%)
Insular	2 (5.9%)
Fronto-insular	1 (2.9%)
Right (total)	7 (20.6%)
Frontal	3 (8.8%)
Parietal	4 (11.8%)

all gliomas appeared to be high grade. Cognitive and psychological functioning was assessed before and 3 months after glioma surgery (see Table 1 for demographics).
Tumor localization was determined by a neuroradiologist by using 3D T1-weighted MRI studies and 2D T2-weighted MRI studies. The histological type of the tumor and the pathological WHO grade were determined by a neuropathologist, from tissue obtained during surgery. The study was approved by the ethics committee of the Erasmus Medical Center and all patients gave their informed consent.

Quality of life
The EORTC QLQ-C30 (European Organization for Research and Treatment of Cancer – Core Quality of Life Questionnaire) is administered to measure overall quality of life[24]. We chose to evaluate the response to a global QoL question *"How would you rate your quality of life with a number between 0-7? (referring to the last 7 days)"* (0 least positive – 7 most positive rating, transformed into a scale from 1-100 to facilitate comparisons).

Table 2. Neuropsychological tasks

Test	N[1]	Cognitive abilities	Description
Language			
Boston Naming Test (BNT)[25]	34	Naming (word-finding)	Naming 60 pictures, presented in order of word frequency and word difficulty
Category Fluency[26]	34	Flexibility of verbal semantic thought processing; semantic memory	Producing words of a given category (animals and professions) within a limited time span
Letter Fluency[27]	34	Flexibility of verbal phonological thought processing	Producing words beginning with a given letter (D,A,T, or K,O,M) within a limited time span
Memory			
15 Word Test (15WT)[28]	30	Verbal learning; immediate recall and delayed recall, recognition	Learning a list of 15 words, with 6 recall trials; 5 immediate and 1 delayed, and a recognition trial
Rey Figure Test[29]	32	Visual learning; delayed recall	Copying a complex figure and delayed reproduction
Attention and executive functions			
Trail Making Test (TMT) A + B[30]	32	TMTA: visuomotor speed, attention; TMTB: + mental flexibility, divided attention	Connecting numbers placed randomly in ascending order as rapidly as possible (TMTA) and connecting alternating numbers and letters as rapidly as possible (TMTB)
Wisconsin Card Sorting Test (WCST)[31]	25	Mental flexibility	

[1] N=number of patients examined pre- and postoperatively.

Neuropsychological assessment

Patients were assessed around 1 month pre- and 3 to 4 months postoperatively with a comprehensive neuropsychological test-protocol (see Table 2). Based on the normative data, the test scores of the patients were transformed into z-values to compare the performance of patients to that of healthy adults. Domain scores were calculated by computing the mean z-score of all tests belonging to a particular cognitive domain. Change scores were computed by subtracting the preoperative z-scores from the postoperative z-scores. The threshold of (mild) cognitive impairment was defined as a z-score below -1.

Anxiety and depression

The STAI-DY (Dutch version of State Anxiety Inventory for Adults)[32] measures symptoms of anxiety consisting of 20 items assigned 1 value 1-4 (0 least anxious symptoms – 80 most anxious symptoms (threshold>44). The CES-D (Center for Epidemiologic Studies Depression scale)[33] is a questionnaire consisting of 20 items assigned one value of 0-3 to measure depressive symptoms (0 least depressive symptoms – 60 most depressive symptoms (threshold>16). Both rating scales were transformed into a scale from 0-100.

Statistical analyses

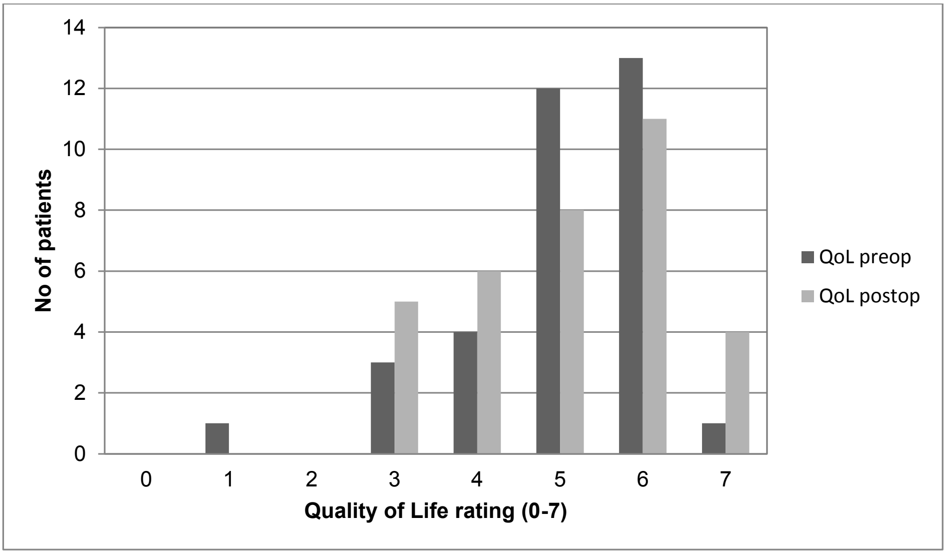
We investigated whether patients' pre- and postoperative mean test-scores differed from the normal population, using either a one-sample t-test with 0 (the mean score of the normative group) as test value or the Wilcoxon Signed-Rank Test. A linear regression analysis was conducted between preoperative QoL and cognition, anxiety and depression. Subsequently, we wanted to examine whether we could predict the change of QoL postoperatively based on cognition and symptoms of anxiety or depression. A linear regression analysis was used to investigate the relation between change in QoL and change in cognition, judgment of anxiety and depression. In our model, QoL rating was our outcome measure, with change scores of cognition, anxiety and depression as predictors. The relation between change of QoL and the performance on individual cognitive tasks was also investigated by means of the same statistical procedure. Finally, we checked whether tumor grade and adjuvant therapy (radio and/or chemo) had influence on QoL rating with a one-way-ANOVA.

RESULTS

EORTC QLQ-C30; Quality of Life

Twenty-six patients (76.4%) rated their QoL at or above 5 (out of 10) preoperatively. Postoperatively, 23 patients (67.7%) rated their QoL at or above 5 (see Figure 1). Ten patients out of 34 (29.4%) rated their QoL postoperatively better than preoperatively. Eleven patients (32.4%)

Figure 1. Rating QoL (scale 0-7) pre- and postoperatively



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deteriorated in their QoL rating, 13 patients (38.2%) remained stable. No effect of tumor grade on QoL was found ($x^2(2)=2.474$, p=.290), nor of adjuvant therapy ($x^2(1)=.026$, p=.872).

Neuropsychological assessment

Preoperatively, 35.3% of the patients were (mildly) impaired compared to normals based on the mean composite z-score of all cognitive tests (t=-6.21, p<0.0001). Each cognitive domain was disturbed compared to normal population (Language: t=-6.50; p<0.0001, Memory: -6.54, p<0.0001; Attention and executive: t=-2.78, p=.009). At test level, apart from Wisconsin Card Sorting, performance on all tasks were disturbed (BNT: t=-5.07, p<0.0001; Cat.fl.: t=-5.40, p<0.0001; Let.fl: t=-2.88, p=.007; 15WT enc: t=-6.20, p<0.0001; 15WT recall: t=-4.50, p<0.0001; Rey recall: t=-4.24, p<0.0001; TMTA: t=-2.15, p=.039) There was a trend for significance on TMTB (t=-2.02, p=.051). Postoperatively, 32.4% of the patients remained within the impaired range on the mean composite z-score of all cognitive tasks (t=-5.04, p<0.0001). Each cognitive domain remained disturbed (Language: t=-6.57; p<0.0001, Memory: -3.85, p=.001; Attention and executive: t=-2.68, p=.011). Based on the composite z-score at individual level, 3 patients recovered from preoperative impairments, 2 patients developed new impairments, and 29 patients remained stable (of which 9 patients with cognitive disturbances). In addition to tests that were impaired, TMTB also deteriorated (TMTB: t=-2.76, p=.010, BNT: t=-4.74, p=.000; Cat. fl.: t=-6.28, p<0.0001; Let.fl: t=-3.31, p=.002; 15WT enc: t=-3.43, p=.002; 15WT recall: t=-2.75, p.010; Rey recall: t=-3.91, p<0.0001). Performance on TMTA recovered (t=-1.87, p=.071) and

Table 3. Difference in cognitive performance between patients pre- and postoperatively compared with healthy population (z=0).

Task	Preop			Postop		
	Mean z-score (sd)	95% CI		Mean z-score (sd)	95% CI	
		Lower	Upper		Lower	Upper
BNT	-1.26 (1.44)[c]	-1.76	-.75	-1.28 (1.58)[c]	-1.83	-.73
Category Fluency	-.71 (.77)[c]	-.98	-.44	-1.03 (.95)[c]	-1.36	-.69
	-.59 (1.20)[b]	-1.01	-.17	-.80 (1.41)[c]	-1.36	-.69
Language domain	-.82 (.73)[c]	-1.07	-.56	-1.03 (.92)[c]	-1.35	-.71
15WT encoding	-1.26 (1.17)[c]	-1.26	-1.67	-92 (1.48)[b]	-1.46	-.37
15WT recall	-.98 (1.26)[c]	-.98	-1.43	-.58 (1.18)[b]	-1.01	-.15
Rey recall	-.98 (1.30)[c]	-.98	-1.44	-.91 (1.35[c]	-1.38	-.43
Memory domain	-1.09 (.94)[c]	-1.09	-1.43	-.78 (1.14)[b]	-1.19	-.37
TMTA	-.40 (1.09)[a]	-.78	-.02	-.42 (1.29)	-.87	.03
TMTB	-.50 (1.45)	-1.01	.00	-.72 (1.47)[b]	-1.25	-.19
Wisconsin Card Sorting	-.20 (.76)	-.48	.09	-.06 (.51)	-.25	.14
Attention and executive domain	-.43 (.89)[b]	-.75	-.12	-.46 (.98)[a]	-.46	-.81
Mean z-score cognition	-.69 (.65)[c]	-.92	-.47	-.73 (.84)[c]	-1.02	-.43

[a]=p<0.05, [b]=p<0.01, [c]=p<0.0001

Wisconsin Card Sorting remained unimpaired (t=-.59, p=.563). See Table 3 for all mean scores and standard deviations. There was a main effect of tumor grade on the difference score on cognition ($F(2,31)=.563$, p=0.046). However, when comparing cognition between LGG and HGG patients, there was only a tendency of worse performance of the LGG group (mean difference LGG: -.201, HGG: .197, 95% CI [-.803, .008], p=.056). No effect of radio- and/or chemotherapy on change in cognition was found ($F(1,32)=945$, p=.338).

STAI-I: Anxiety

Thirteen out of 32 patients (2 questionnaires were missing) (37.5 %) reported to have symptoms of anxiety preoperatively. After surgery, 11 patients (31.3%) had signs of anxiety. Comparing pre- and postoperative anxiety ratings, 6 patients developed new symptoms (below the threshold before operation), 19 patients remained stable. Four out of these 19 patients remained to have symptoms, whereas 15 patients did not have anxiety symptoms at all. Tumor grade had no influence on anxiety (F (2,29)=.294, p=.748, η^2=.020). There was an effect of radio- and/or chemotherapy on anxiety ($F(1,30)=6.065$, p=.020, η^2=.168).

CES-D: Depression

Before surgery, 15 patients (44.1%) reported to have symptoms of depression. 3 months postoperatively, 14 patients (41.2%) had signs of depression. At individual level postoperatively, the symptoms of depression disappeared in 6 patients, 5 patients developed new symptoms of depression (below the threshold before operation) and 23 patients remained stable. Nine out of these 23 patients still had symptoms of depression, whereas 14 patients had no signs of depression at all. There was no effect of tumor grade or postoperative treatment on change in depression ($F(2,31)=.504$, $p=.609$, $\eta^2=.031$; $F(1,32)=1.046$, $p=.314$, $\eta^2=.032$ respectively)

Linear regression analysis: QoL , cognition, symptoms of anxiety and depression

Preoperatively, we did not find an effect of our model with cognition, depression and anxiety as predictors ($p>0.05$). Performance on individual cognitive tasks was also not a predictor for QoL.

When investigating postoperative change of QoL using the Enter method, a significant model emerged ($F(3,28)=8.443$, $p<0.001$). The model explained 31.7% of the variance (Adjusted $R^2=.317$). Table 4 provides information for the predictor variables entered into the model. Depression was the only significant predictor. The stepwise method also revealed a significant model ($F(1,30)=18.733$, $p<0.001$). The model explained 36.4% of the variance (Adjusted $R^2=.364$). Table 5 provides information for the predictor variable depression entered into the model.

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When analyzing each factor separately, both change in anxiety and depression were correlated with change in QoL ($F(4, 29)=4.741$, $p<0.05$, $F(4, 27)=3.570$, $p<0.05$ respectively), but not with cognition. Also, no effect was found for change on individual cognitive tasks and change in QoL. At individual test moments (pre- and postoperatively), we only found a postoperative effect of our model with the Enter method ($F(3,30)=14.872$, $p<0.001$). It was able to explain 55.8% of the variance (Adjusted $R^2=.558$) caused by postoperative depressive symptoms. Cognition and anxiety were not significant predictors in our model. Performance on individual cognitive tasks was not a predictor for postoperative QoL.

Table 4. Predictors on pre- and postoperative change QoL Enter method linear regression.

Variable	B	95% CI	
		Lower	Upper
Change cognition	7.35	-9.37	24.07
Change anxiety	-.844	-1.81	.12
Change depression	-1.20*	-2.14	.25

*=$p<0.05$

Table 5. Predictor depression on pre- and postoperative change in QoL Stepwise method linear regression.

Variable	B	95% CI	
		Lower	Upper
Change depression	-1.687**	-2.48	-.89

**=$p<0.01$

DISCUSSION

We investigated QoL, cognitive performance, symptoms of anxiety and depression of glioma patients with gliomas in eloquent areas before and early after surgery. Subsequently, the predictive value of cognition, symptoms of anxiety and depression in relation with QoL were examined. The results showed impairment in all cognitive domains as compared to normal population and remained relatively stable after surgery. A similar pattern was observed for symptoms of anxiety and depression. Anxiety was correlated to postoperative QoL rating. Depression was most strongly related to change in QoL rating; postoperative QoL could be explained (about 50%) by symptoms of depression. Cognition and anxiety were not associated with change in QoL. An important finding is that glioma surgery in eloquent areas did not induce major deterioration on QoL, as most patients reported to have moderate to good QoL before and after surgery.

The majority of our patient group rated their QoL above 50% both pre- and postoperatively suggesting that QoL is relatively preserved at short-term after surgery, as ultimately pursued in awake glioma surgery. However, a large individual variance, was found, in accordance with another study[21]. The subjective nature of QoL could be responsible for this individual variance; some patients considered the fact that they had resumed their job as good QoL whereas others consider physical health as an important outcome measure. Another explanation for a stable QoL early after surgery could be that QoL significantly declines not only until the end of life phase[34]. The fact that postoperative symptoms of anxiety were correlated to QoL, may be due to future uncertainty and/or fear for tumor recurrence.

Contrasting to our expectations and to what most studies have claimed so far, cognition did not affect QoL in glioma patients. This finding, also described for meningioma patients[35], implies that, at least at short-term after surgery, extensive neuropsychological performance is not a sensitive predictor for QoL in our patient group. However, this is no ground to deny the importance of cognitive performance for QoL. Objective neuropsychological tasks may not reflect QoL as experienced in daily life. QoL is a subjective phenomenon; a subjective rating of cognition could be therefore more sensitive as a predictor[36], such as judgment of problem solving, short-term memory, attention, and the ability to convey and understand spoken/ written messages. On the other hand, stable QoL rating in the year after surgery or adjuvant therapy despite cognitive deterioration measured with questionnaires, was also found in glioblastoma multiforme (GBM) patients[37]. This might indicate that GBM patients, consider other aspects important for QoL experience, such as physical functioning and self-care.

Already in the preoperative stage, the cognitive disturbances in LGG patients were not correlated to QoL. As cognition did not deteriorate severely postoperatively, an absence of a relation between change and QoL is a logical consequence. Ruge et al.[38] demonstrated a correlation between divided attention and general health perception and pain, which are aspects of QoL, but different from our QoL rating question. Aaronson et al.[39] found a relation between objective neurocognitive performance and QoL in LGG patients (without surgery). QoL, however was referred to a mental component score relating to psychological distress, which could have induced bias towards emotional factors. Our group also showed a correlation between emotional factors and QoL: the most important predictor associated with QoL in our study was a subjective measurement of depressive symptoms, as found by others[3, 18, 40, 41]. The knowledge of a high chance of tumor recurrence could impose a heavy psychological burden. However, in contrast to Raysi et al.[42] QoL was not affected by tumor grade both pre- and postoperatively, even though all patients were aware of their tumor pathology in the latter stage. An absence of an effect of tumor grade may be explained by our small sample size.

Furthermore it remains unclear, whether emotional disturbances are caused by the diagnosis itself or by illness-related issues (nausea, headache). The decrease of occupational activity and social functioning may play a role as well. Yavas et al.[43] did not find change in depression long-term after treatment. The relation between depression and QoL however, was not examined; absence of significant change in depression does not exclude a relation between depression and QoL, as our study showed.

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There are some limitations; we used a global QoL question from the QLQ-C30 in order to capture a rating of daily life in a broad sense. Other subparts of the QLQ-C30, such as fatigue or physical functioning could also have (independent) influence on QoL[40]. We should be careful generalizing these results to all glioma patients, as this group consisted of only 34 patients and follow-up assessment was solely conducted on one moment. Due to small subgroups, we did not investigate the effect of tumor localization. Jakola et al.[44] however, demonstrated that eloquence (versus non-eloquence) in general did not affect long-term QoL at all. On the other hand, their study was retrospective and no pre-treatment results were available; the neurosurgical effect remained unclear on QoL.

Finally, anti-epileptic drugs are reported to have an important effect on QoL[11]. We did not examine the influence of medication on QOL, because the majority of our patients used both pre- and postoperatively anti-epileptic drugs, excluding to a certain extent an intervening effect on QoL. Only postoperative radio- or chemotherapy negatively affected anxiety, but not QoL, cognition or depression. It is possible that side effects which could have influence on QoL or cognition, could arise at longer term after treatment[45, 46], also confirmed by our earlier short-term follow-up study[47]. A longer follow-up might reveal more of the effect of adjuvant therapy on QoL. Other factors we did not check, may have additional predictive value to QoL apart from the occurrence of depressive feelings, such as epilepsy burden[11], age or social networks[48], marital and employment status[49] but also extent of resection[50].

We showed that glioma surgery did not induce major deterioration in patients' global QoL experience as evidenced by patients' stable rating. This is valuable information, since low grade glioma patients have relatively long survival time and maximal preservation of

QoL is an essential outcome measure[51]. Despite disturbed cognitive performance, extensive neuropsychological results were not directly associated with QoL. Important components for QoL rating were judgments of emotional factors, in particular symptoms of depression. Hence, the relation of possible other predictors closer to daily life should be investigated in glioma patients treated with surgery. We suggest that a multidisciplinary team is necessary for the care of glioma patients, with special attention to coping strategies in order to decrease depressive and anxiety symptoms and to optimize QoL. Preservation of QoL could improve survival function and is therefore of utmost importance.

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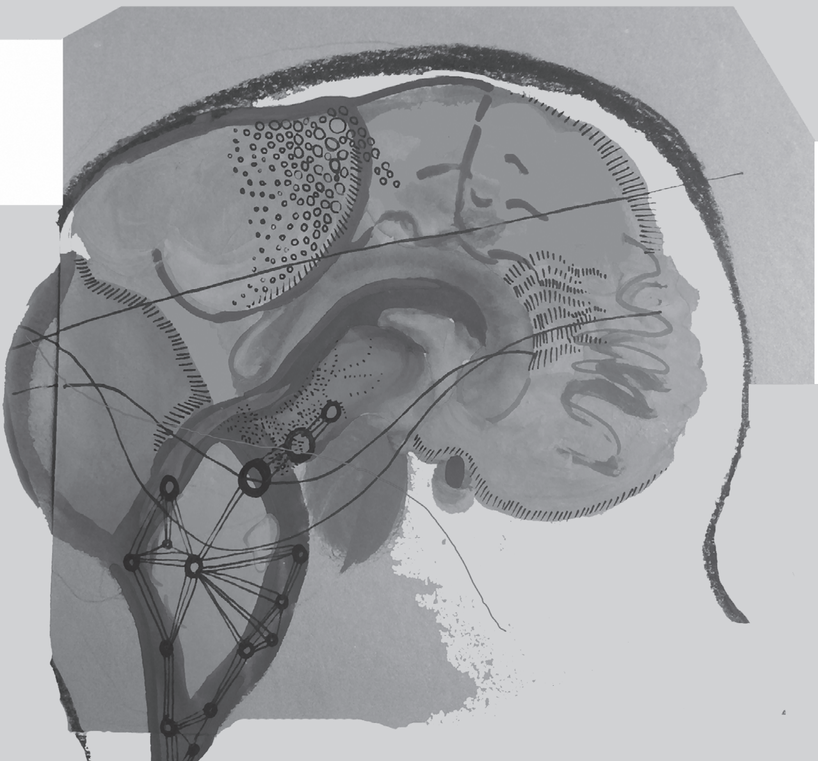


Chapter 6

Dynamic aphasia following low grade glioma surgery near the supplementary motor area: a selective spontaneous speech deficit

ABSTRACT

We describe a patient (KO) with reduced spontaneous speech, resembling dynamic aphasia, after awake glioma surgery in the proximity of the Supplementary Motor Area. Naming, repetition and comprehension were intact. He was tested with an extensive neuropsychological test battery and a protocol for dynamic aphasia at 1 year postoperatively. He presented with postoperative reduced spontaneous speech and selective executive function deficits. Most language recovery took place at 3 months postoperatively, whereas the executive functions improved between 3 months and 1 year. Results suggest that resection near the Supplementary Motor Area could increase the risk of cognitive disturbances at long-term, especially language.

INTRODUCTION

Awake surgery using direct electrocortical stimulation, as opposed to classical surgery, is a generally accepted treatment method for tumor resection in functional areas in order to avoid permanent postoperative disorders[1]. Resection in or close to the fronto-medial lobe, however, may result in immediate postoperative language (and/or motor) disturbances, often without the identification of positive stimulation sites[2-4]. Language impairment after tumor resection in this brain area is usually characterized by problems in propositional speech with (relatively) intact naming, repetition and comprehension. The severity of the disorder may vary, but spontaneous recovery within a few days or weeks is common[5]. These transient postoperative speech disorders are associated with the (selective) resection of the Supplementary Motor Area in the hemisphere dominant for language, also known as the SMA syndrome[3,4]. The SMA is involved in preparation, initiation and monitoring of complex movements as well as the initiation of a speech plan[6]. Other (transient) cognitive impairments after resection of frontal lobe are also found, such as deficits of (verbal) working memory, attention and executive functioning[7,8]. Linguistic disturbances resembling the SMA syndrome, have been described earlier in the context of frontal neurodegenerative diseases and focal lesions, known as *Dynamic Aphasia*[9-12]. The underlying mechanism of dynamic aphasia has been associated with a language specific impairment or with a more general impairment of the executive functions[13-15].

Although it is generally accepted that relative complete recovery spontaneously occurs, there are some patients with speech difficulties at long(er) term[16-18]. Moreover, different time courses of recovery are reported in the literature (varying from 1 week to 6 months) and different measurement tools have been used. The course of recovery remains uncertain.

The goal of this study is to assess the course of recovery in a patient with a one-year follow-up and to investigate which cognitive functions are affected. With this case study we aim to gain more insight about the prognosis and possible postoperative risks of surgical treatment in the SMA area.

CASE REPORT

KO is a 32-year-old, right-handed male, who works as a construction advisor. In March 2011, following a history of a low grade glioma resection (classical surgery), KO entered Erasmus University Medical Center Rotterdam without cognitive complaints (besides mild concentration problems) for preoperative neuropsychological testing before awake craniotomy in the Medical Center Haaglanden. An MRI scan in 2011 revealed recurrent left-hemispheric glioma, anterior and lateral to the Supplementary Motor Area in the left frontal lobe (see Figures 1A-C). A large part of recurrent tumor was currently removed (58%) but the resection cavity is filled with residual tumor or edema (note the retraction of the lateral ventricle, see figures 1D-F). The patient reported epileptic seizures and he reported taking anticonvulsants.

During awake craniotomy, no positive stimulation sites were found in the region of resection, i.e. the fronto-medial lobe. At the end of the resection (see postoperative scans in figures 1D-F), KO however, developed a strong reduction of the spontaneous speech in the context of intact naming and repetition. Comprehension was also intact.

METHOD

Subjects

KO's language and cognitive functions were compared to healthy participants (HC) and glioma patients (GP) (see Table 1 for demographics).

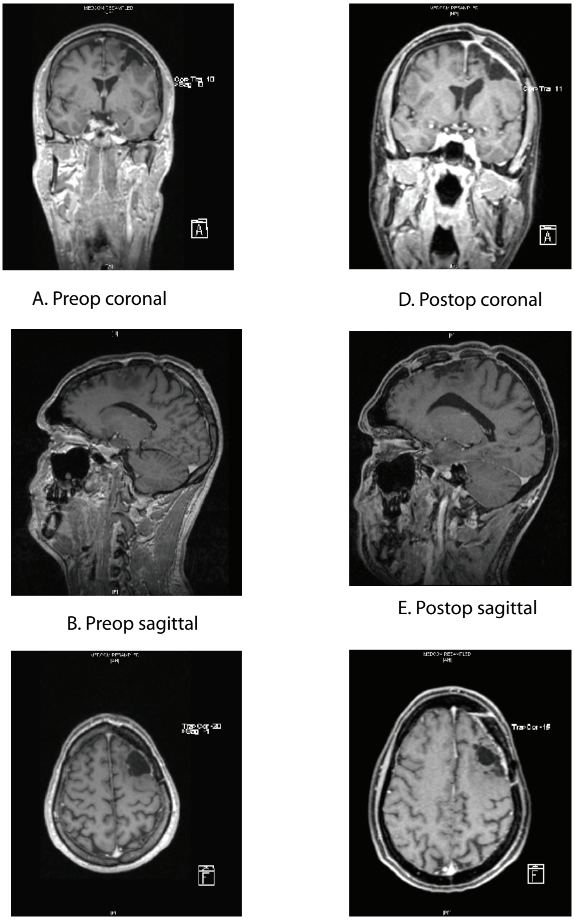
Table 1. Demographic characteristics control groups

Demographics	**A. Spontaneous speech analysis**			**B. Dynamic Aphasia Test**		
	HC1 (N=21)	**GP1 (N=27)**	**GP2 (N=27)**	**HC2 (N=18)**	**GP3 (N=7)**	**GP4 (N=4)**
Male gender	8 (38.1%)	18 (66.7%)	18 (66.7%)	9 (50%)	4 (57%)	3 (75%)
Mean age; range	39.44; 19-62	41.52; 19-74	41.52; 19-74	33.6; 20-60	36.71; 16-57	35.75; 33-41
Mean education[19]; range	5; 4-7	5; 4-7	5; 4-7	6; 4-7	5.71; 5-7	4.75; 3-7
Handedness (left)	2 (9.5%)	2 (7.4%)	2 (7.4%)	0 (0%)	0 (0%)	0 (0%)
Tumor localization						
Left frontal		13 (48.2%)	13 (48.2%)		2 (28.6%)	1 (14.3%)
Left temporal		4 (14.8%)	4 (14.8%)		1 (14.3%)	
Left parietal		1 (3.7%)	1 (3.7%)		3 (42.8%)	3 (85.7%)
Left insular		3 (11.1%)	3 (11.1%)			
Left frontoparietal		2 (7.4%)	2 (7.4%)			
Left frontoinsular		2 (7.4%)				
Left temporoinsular		2 (7.4%)	2 (7.4%)			
Right parietal			2 (7.4%)		1 (14.3%)	
SMA involvement[1]		6 (22.2%)	6 (22.2%)		0 (0%)	0 (0%)
Tumor grade						
Low grade glioma		15 (55.6.0%)	15 (55.6.0%)		1 (85.7)	2 (50%)
High grade glioma		12 (44.4%)	12 (44.4%)		6 (14.3)	2 (50%)

HC1=healthy controls (analyzed with spontaneous speech), HC2=healthy controls (assessed with dynamic aphasia test), GP1=glioma patients (preop analyzed with spontaneous speech), GP2=glioma patients (3 months postop analyzed with spontaneous speech), GP3=glioma patients (2-5 days postop assessed with dynamic aphasia test), GP4=glioma patients (3 months postop assessed with dynamic aphasia test).

[1] SMA involvement in the language dominant hemisphere.

Figure 1. Pre- (a-c) and postoperative (d-f) MRI scans KO



A. Preop coronal

D. Postop coronal

B. Preop sagittal

E. Postop sagittal

C. Preop transversal

F. Postop transversal

Procedure

KO was tested preoperatively (KO1), and 4 times postoperatively until 1 year (see Figure 2 overview test procedure and timetable)

1) Spontaneous Speech Analysis

Spontaneous speech of KO was collected and recorded for analysis in an interview setting 1 month pre- (KO1), 3 months (KO4) and 1 year postoperatively (KO5). Twenty-seven other glioma patients were also recorded pre- (GP1) and 3 months postoperatively (GP2). Twenty-one healthy controls (HC1) were included, matched for gender, age, education and handedness with no history of neurological disease.

2) Dynamic Aphasia Test

This test was only administered postoperatively on KO at 2 weeks (KO2), 7 weeks (KO3) 3 months (KO4) and 1 year (KO5) and compared to performance of healthy controls (HC2) and other glioma patients at 2-5 days (GP3) and 3 months postoperatively (GP4).

3) Standardized neuropsychological test-protocol

KO was assessed with a neuropsychological test-protocol (NTP) preoperatively, 3 months and 1 year postoperatively and was compared to other glioma patients pre- (GP1) and 3 months postoperatively (GP2) (see Figure 2 for overview). We used a short neuropsychological screening-test at 2 weeks and 7 weeks postoperatively.

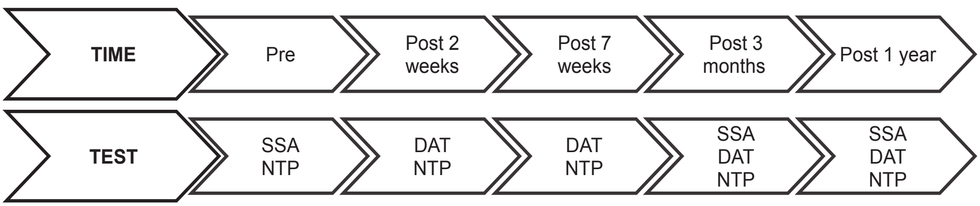
The study was approved by the Ethical Committee of Erasmus MC. All patients gave their informed consent.

LANGUAGE MEASURES

Spontaneous speech

To elicit speech, medical status (patients), most recent doctor's visit (controls), work, and hobbies were discussed with minimal intervention of the interviewer. We selected a speech sample of 300 words, the number required for a reliable linguistic analysis in Dutch, per subject[20]. The first 50 words were not transcribed to control for possible intervening factors, such as unresponsiveness and/or emotional reactions. Meaningless utterances, such as "erm",

Figure 2. Overview test procedure (SSA: Spontaneous Speech Analysis, DAT: Dynamic Aphasia Test, NTP: Neuropsychological Test Protocol)



"ah", and "well", were not included. Subsequently, the quantity of Self-corrections, Repetitions, Lexical Diversity, Incomplete Sentences and Mean Length of Utterance of words (MLUw) was measured using the linguistic computerized program CLAN[21].

In addition, the quality of verbal communication from the AAT part I 'communicative behavior' (based on a ±10-minute sample of spontaneous speech) is judged using a 6-point scale ranging from 0 ("no usable speech or auditory comprehension") to 5 ("minimal discernable speech handicap").

Dynamic Aphasia Test

We developed a test for dynamic aphasia based on earlier research and existing English and Dutch tests for language[13, 22, 23]. It consists of 6 parts, increasing in difficulty (high to low constraint), in which the participant is indirectly requested to produce spontaneous speech (see Table 2 and Appendix II). Percentages of correct responses were calculated and Reaction Time (RT) was measured from the end of the spoken stimulus until the onset of the subjects' response.

Standardized neuropsychological test-protocol

We administered a comprehensive neuropsychological protocol which consisted of well-established tests for each main cognitive domain; language, memory, attention and executive functions (see Table 3).

Statistics

To assess whether KO's spontaneous speech deviated from controls (HCs and GPs), mean scores and standard deviations were calculated. Two standard deviations below or above the controls' mean was considered deviant. The same procedure was used to evaluate RT of the Dynamic Aphasia Test. See Satoer et al.[33] for a detailed statistical method of the other glioma patients on the Spontaneous speech variables.

The test scores on standardized tasks of KO were transformed into z-values for comparison to normal performance. Domain scores were calculated by computing the mean z-score of all tests belonging to a particular cognitive domain. Impairment was defined as a z-score below -2. As for the glioma patients, pre- and postoperative mean scores by domain and by test were compared to the normative group using either a one-sample t-test or the Wilcoxon Signed-Rank Test with 0 (the mean score of the normal group) as test-value.

RESULTS

Language baseline

KO's preoperative spontaneous speech appeared fluent at first sight. A more detailed analysis revealed deviations on Incomplete Sentences, Self-corrections, Repetitions compared to

Table 2. Dynamic Aphasia Test

Sub-tests	Example	Description
A. Sentence completion: generation of a single word.		Based on Bloom & Fisher[22]
1. High constraint	The captain stayed at the sinking…	The number of alternative completion words is divided according to high to low probability for being the dominant response
2. Middle constraint	Nothing beats a cup of hot…	
3. Low constraint	They were startled by…	
B. Sentence completion: generation of a constituent.		Based on Bloom & Fisher[22]
1. High constraint	The sun disappeared…	The number of alternative completion constituents is divided according to high to low probability for being the dominant response
2. Middle constraint	Anne walked into the house…	
3. Low constraint	Unfortunately I can't…	
C. Sentence generation: word cue		Based on Robinson et al.[13]
1. Proper nouns	Paris	The alternative words were derived from CELEX[24] with different frequencies (from 5245 times for 'glass' until 100142 times for 'has') in 930 fiction and non-fiction books published between 1970 and 1988.
2. Common nouns	glass	
3. Verbs	to come	
D. Sentence generation: sentence cue		Based on Robinson et al.[13]
No levels of constraints	Sophie went to her friend's birthday.	The participant was requested to generate a second sentence which fits in the context of the given sentence.
E. Picture description		Based on Robinson et al.[13]
1. Baseline description	Can you tell me what you see in this picture?	The participant was presented with two pictorial scenes and was asked to describe what he sees on the picture and what he thinks the person on the picture will do next.
2. 'What might happen next?'	What do you think the man will do next?	
F. Daily situations		Based on the Amsterdam-Nijmegen Test voor Alledaagse Taalvaardigheden. In English: Amsterdam-Nijmegen Everyday Language Test[23]
	You have just moved into my street and you want to meet me. You ring at my door and you say…	The participant was asked to imagine himself being placed in a situation of daily life

Table 3. Neuropsychological test-protocol

Tests normal protocol	Cognitive Abilities	Description
Language		
Subtests of Akense Afasie Test (AAT)[25]		
- Spontaneous Speech	Communicative behavior (part I)	Six point scale ranging from 0 ("no usable speech or auditory comprehension") to 5 ("minimal discernable speech handicap")
- Token Test (TT)	Language comprehension	Pointing to and manipulating geometric forms on verbal commands
- Repetition	Repetition	Repeating phonemes, words and sentences
- Reading aloud	Reading	Reading aloud words and sentences
- Writing to dictation	Writing	Writing words and sentences on dictation
Boston Naming Test (BNT)[26]	Word-finding	Naming 60 pictures, presented in order of word frequency and word difficulty
Category Fluency[27]	Flexibility of verbal semantic thought processing; working memory	Producing words of a given category (animals and professions) within a limited time span)
Letter Fluency (parallel versions)[28]	Flexibility of verbal phonological thought processing; working memory	Producing words beginning with a given letter (D,A,T or K, O, M) within a limited time span
Memory		
15 Words Test (15WT), Encoding, Recall, Recognition (parallel versions)[29]	Verbal learning; immediate and delayed recall and recognition	Learning a list of 15 words, with 6 recall trials; 5 immediate and 1 delayed, and a recognition trial
Attention and executive functions		
Trail Making Test (TMT) A, B, BA[30]	TMTA: visuomotor speed, attention; TMTB: + mental flexibility, divided attention	Connecting numbers placed randomly in ascending order as rapidly as possible (TMTA) and connecting alternating numbers and letters as rapidly as possible (TMTB)
Stroop Color-Word Test (Stroop) I, II, III, Interference[30]	Mental speed; selective attention	Reading color words, naming colors and naming colors of printed words, denoting another color
Design Fluency: Five point task[31]	Non verbal fluency	Producing different designs by connecting at least 2 dots (out of 5) within a limited time span
Wisconsin Card Sorting Task (WCST)[32]	Mental flexibility, strategic planning	Sorting and altering cards according to different principles (4 stimulus cards are divided into color, shape, number).

healthy controls (>2sd) (see Table 4). Other glioma patients only deviated on Incomplete sentences.

His performance on tests was intact at domain level of language (i.e. the mean of all language tests, z=-0.21) and also on individual test-level (BNT: z=-0.21; category fluency: z=-1.42; letter fluency: z=-1.35; AAT-repetition: z=0.06; AAT-reading: z=0.54; AAT-writing: z=0.27; Token Test: z=1.91). On part I 'communicative behavior' from the AAT, KO was rated 4 out of 5, which indicates a sign of loss of fluency in the spontaneous speech (but still able to bring a message across). Preoperative mean scores of glioma patients deviated from normal scores in the language domain (t=-5.15, p<.001), and on test-level on BNT (t=-4.21, p<.001), category fluency

Table 4. KO's Spontaneous speech in comparison with healthy controls and glioma patients.

Spontaneous speech variables	HC1 (N=21)	GP1 (N=27)	GP2 (N=27)	KO1	KO2	KO3	KO4	KO5
MLUw	9.5	8.7	8.1[a]	6.1	3.9[a,b,c,d]	5.6[b]	6.8	7.2
TTR	0.500	0.500	0.500	0.447	0.353	0.387	0.387	0.353
Repetitions	6	10.7	9.8	22[a]	61[a,b,c,d]	32[a,b,c,d]	36[a,b,c,d]	39[a,b,c,d]
Self-corrections	3.9	5.7	5	11[a]	9[a]	10[a]	4	7
Incomplete sentences (%)	2.3	6.2[a]	7.8[a]	12.1[a]	9.1[a]	12.1[a]	9.1[a]	9.1[a]

HC1=healthy controls, GP1=glioma patients (preop), GP2=glioma patients (3 months postop), KO1=KO preop, KO2=KO2 weeks postop, KO3=KO 7 weeks postop, KO4=KO 3 months postop, KO5=KO 1 year postop. [a>]2 sd HC1, [b>]2sd GP1, [c]>2 sd GP2, [d>]2 sd GP1 and GP2.

(t=-7.90, p<.001) and letter fluency (t=-5.97, p<.001). The mean of AAT spontaneous speech rating of the other glioma patients was 4.48 out of 5. In general, however, KO's language performance was better than that of other glioma patients.

Language follow-up

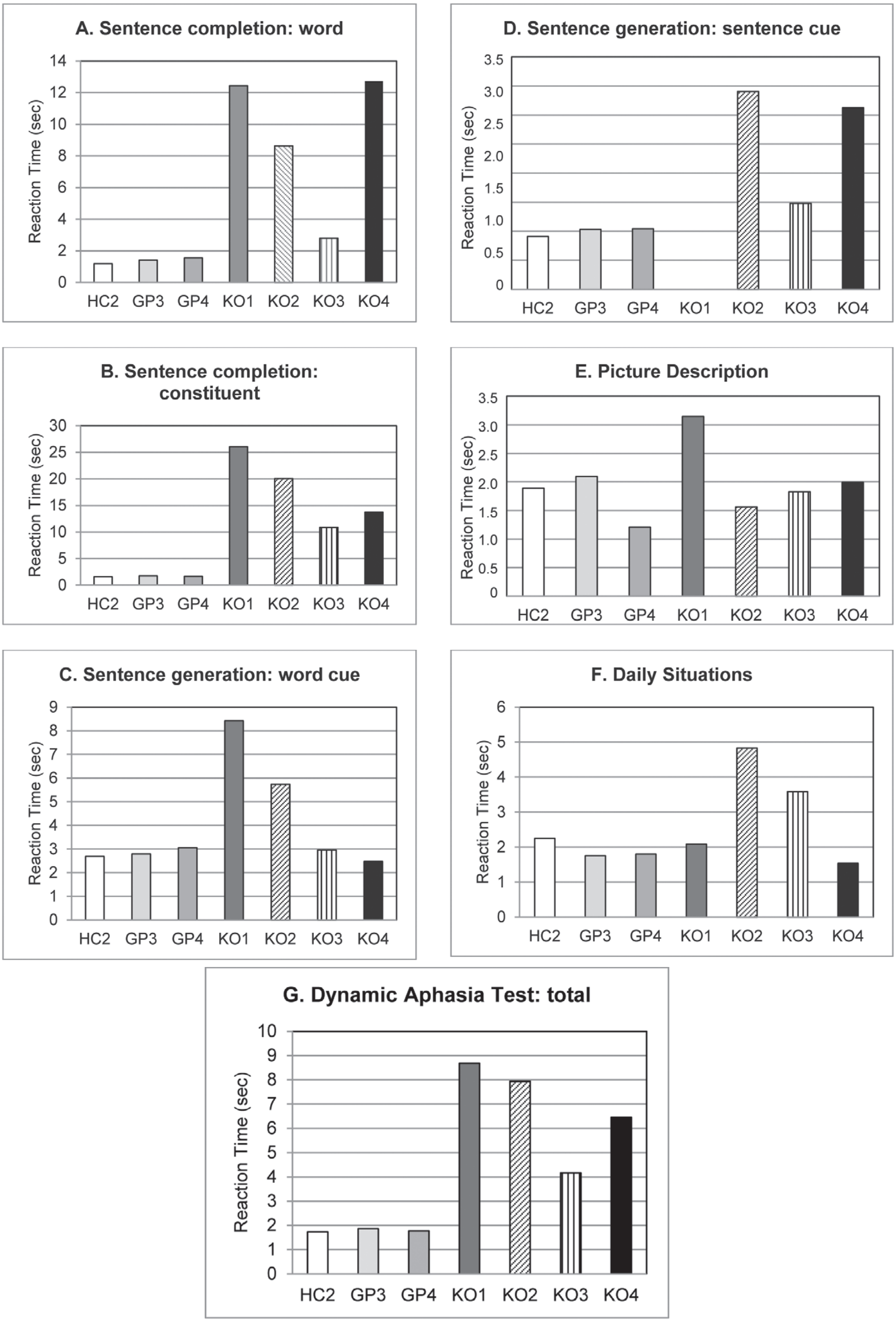
During awake surgery KO developed a severe reduction in his spontaneous speech. KO was not able to start a conversation or to correctly perform a sentence completion task, whereas naming, repetition and comprehension stayed intact. At the end of the operation, KO was only able to respond to yes/no questions. At 2 weeks postoperatively the reduction in his spontaneous speech somewhat improved in comparison to the intraoperative interval. KO described his language problems as a difficulty to express his thoughts. A spontaneous speech analysis revealed an increase of Repetitions and shorter Utterance Length (MLUw) compared to all control groups (>2sd HC1 and GP2). At 7 weeks postoperatively, KO reported slight improvement, although the ability to react rapidly in daily conversations remained difficult. Our analysis showed a slight improvement on MLUw (>2sd GP2). At 3 months postoperatively KO reported more improvement, although his speech was still not as fluent as before surgery. Based on our analysis, he completely recovered in comparison to the control groups on MLUw and Self-corrections whereas Repetitions, and Incomplete Sentences remained impaired. At

Table 5. KO's post-operative performance on the Dynamic Aphasia test in comparison with mean (sd) RT's from healthy controls and glioma patients.

Sub-test	HC2 (N=18)		GP3 (N=7)		GP4 (N=4)		KO2		KO3		KO4		KO5	
	RT	%	RT	%	RT	%	RT	%	RT	%	RT	%	RT	%
A. Sentence completion: word	1.19 (0.57)	98	1.40 (0.82)	95	1.55 (0.90)	100	12.45[a, b, c]	83	8.64[a, b, c]	100	2.80[a]	100	12.72[a, b, c]	100
High constraint	0.62 (0.30)		0.49 (0.21)		0.69(0.79)		8.58[a, b,c]		1.13		1.16		2.55[a]	
Middle constraint	0.82 (0.45)		1.56 (1.12)		1.42(1.17)		6.81[a,b,c]		8.76[a,b,c]		2.64[a]		2.93[a]	
Low constraint	2.13 (1.19)		2.17 (1.19)		2.54 (1.91)		21.95[a,b,c]		16.02[a,b,c]		4.61[a]		32.67[a, b, c]	
B. Sentence completion: constituent	1.56 (0.49)	94	1.75 (0.66)	83	1.93 (0.76)	95	26.07[a, b, c]	100	20.08[a, b, c]	100	10.89[a, b, c]	100	13.74[a, b, c]	100
High constraint	1.10 (0.39)		1.23 (0.38)		1.51(0.68)		16.78[a, b, c]		8.86[a, b,c]		4.65[a,b,c]		4.97[a,b,c]	
Middle constraint	1.87 (0.83)		2.21 (1.07)		1.82 (0.56)		32.98[a,b,c]		33.66[a,b,c]		13.22[a,b,c]		24.36[a,b,c]	
Low constraint	1.69 (0.73)		1.79 (0.84)		2.44 (1.17)		28.45[a, b, c]		17.73[a, b]		14.81[a, b, c]		11.87[87a,b,c]	
C. Sentence generation: word cue	2.69 (0.90)	94.7	2.79 (1.28)	71.5	3.05 (1.69)	95.8	8.42[a, b, c]	100	5.74[a, b]	100	2.96	100	2.47	100
Proper nouns	2.31 (1.04)		2.14 (2.07)		2.87 (1.77)		1.18		2.20		1.84		2.34	
Common nouns	3.20 (1.83)		2.14 (2.07)		2.87 (1.77)		14.97[a, b, c]		10.46[a, b, c]		5.28[a]		3.18	
Verbs	2.55 (1.08)		2.45 (1.40)		3.20(2.33)		9.11[a, b, c]		4.57		1.76		1.89	
D. Sentence generation: sentence cue	1.82(0.94)	100	2.06 (1.46)	86.7	2.08(1.13)	95.8	n.r.[a, b, c]	0	6.80[a, b, c]	100	2.96	100	6.25[a, b, c]	100
E. Picture description	1.89 (0.46)	100	2.09 (1.56)	93	1.21(0.50)	93.8	3.15[a]	100	1.56	100	1.83	100	1.99	100
F. Daily situations	2.25 (1.27)	98	1.76 (1.56)	81	1.80(0.56)	83.3	2.08	100	4.83[a,c]	100	3.59[c]	100	1.54	100
Mean RT per item (A,B,C,D, F)	1.73 (0.49)	97.5	1.87 (0.66)	85	1.78(0.92)	94	8.69[a, b, c]	85	7.94[a, b, c]	100	4.17[a, b, c]	100	6.45[a, b, c]	100

RT: Reaction Time; %: correct responses; HC2: Healthy Controls, GP3: glioma patients 2-5 days postoperatively, GP4: glioma patients 3 months postoperatively, RT KO1: 2 weeks postoperatively, KO2: 7 weeks postoperatively, KO3: 3 months postoperatively, KO4: 1 year postoperatively, n.r.=no reponse. [a]>2 sd HC2, [b]>2 sd GP3, [c]>2 sd GP4.

Figure 3. KO's postoperative performance (KO1-KO4) on the Dynamic Aphasia test in comparison with healthy controls and glioma patients (HC2, GP3, GP4).



1 year postoperatively, there were no further improvements. Other glioma patients were also impaired on MLUw besides Incomplete sentences.

As for the Dynamic Aphasia Test compared to all control groups, KO deviated (>2sd) in terms of RT; 2 weeks postoperatively on 83.3% (5 out of 6 parts) of the task (with no response on the sub-part "sentence generation with sentence cue"), as well as 7 weeks postoperatively (without no responses), 3 months postoperatively on 33.3 % (2 out of 6 parts) and 1 year postoperatively on 50% (3 out of 6 parts) of the test. Progress was made predominantly on picture description and on a sentence generation task with a word cue (see Table 5), whereas deterioration took place at 1 year on a sentence completion task (word) and a sentence generation task with sentence cue. In terms of high to low constraints, there were no consistent differences on part A sentence generation (word). In part B, sentence generation (constituent) at 3 months postoperatively, there was influence on total RT by lower performance on high constraints in which not many competing responses were possible. On part C, sentence generation (word cue), there was a lower performance in generation of sentences with a common word cue until 3 months postoperatively. Proper nouns were not deviant, whereas verbs already recovered after 2 weeks postoperatively. The glioma groups (GP3 and GP4) did not deviate from healthy controls (HC2). In terms of correct responses on the entire test, KO was only worse than healthy controls and glioma patients 2 weeks postoperatively. See figure 3 for RT on all parts of the Dynamic Aphasia Test from KO, HC and GPs and Table 5 for mean RT's with standard deviations

Repetition, reading aloud and comprehension (with a shortened protocol) were at ceiling performance both at 2 weeks (repetition: 6/6; reading: 6/6; comprehension: 11.5/12) and 7 weeks postoperatively (repetition: 6/6; reading: 6/6; comprehension: 12/12).

Three months postoperatively, performance at domain level (mean z-score of all language tasks) remained intact (Language: z=-1.02). At test-level, however, letter fluency deteriorated compared to preoperatively (z=-2.25) and AAT Token Test (z=2.18), other language tasks remained intact (BNT: z=0.05; AAT-repetition: z=0.51; AAT-reading: missing; AAT-writing: z=0.54; category fluency: z=-1.99). On part I 'communicative behavior' from the AAT, KO was rated 3 out of 5, indicating obvious communicative difficulties in the spontaneous speech. KO performed worse than baseline, but in general better than glioma patients on standardized tasks (GP2), their mean scores remained deviant from normals in the language domain (t=-4.35, p<.001) and also on test-level (BNT: t=-3.27, p=.001; category fluency: t=-9.28, p<.001; letter fluency: t=-4.17, p<.001).The mean of AAT spontaneous speech rating of the other glioma patients was 4.5 out of 5.

At 1 year postoperatively, KO's performance on the language domain was still intact (z=-0.09), at test-level, however, category fluency became impaired (z=-2.07), letter fluency and Token Test improved (z=-1.25; z=1.91, respectively) and other tasks remained unimpaired

Cognitive baseline

Preoperatively, there were no impairments at domain level (i.e. mean scores of all tests per domain, Memory: z=1.00; Attention and Executive: z=-0.26) or at test-level (imprinting: z=0.80; recall: z=1.20; TMTA: z=-0.70; TMTB: z=-0.30; TMTBA: z=0.10; STROOPI: z=-0.40; STROOPII: z=-0.70; STROOPIII: z=-1.00; STROOPinf: z=-0.70; WCST: z=-0.20; Design Fluency, productivity: z=-0.76; flexibility: z=0.11; strategy: z=0.81). KO performed better than glioma patients (GP1), their mean scores were impaired in the memory domain (t=-4.35, p<.001) and the executive domain (t=-3.55, p=.001).

Cognitive follow-up

Both 2 weeks and 7 weeks postoperatively, performance on a short memory task and a test for executive functions were (relatively) intact (memory: 3/5; executive: 4/4).

Three months postoperatively, KO's performance remained intact at domain level (Memory: z=0.25; Attention and executive: z=-0.39). At test-level, KO became selectively impaired compared to baseline in executive functioning (TMTB: z=-2.60; TMTBA: z=-2.90; STROOPII: z=-2.60; STROOPIII: z=-2.00; STROOPint: z=-2.00, but not on TMTA, STROOPI, WCST (z=-0.30; z=-1.50; -.20 respectively). Memory tests remained intact (imprinting: z=-0.20; recall: z=0.70). Glioma patients' (GP2) mean scores remained impaired in the memory domain (t=-2.36, p=0.19) and in the executive domain (t=-3.44, p<.001), and also at test-level (15WT imprinting: t=-5.36, p<.001; 15WT recall: t=-3.37, p<.001, TMTA: t=-3.06, p=.005; Stroop I: t=-7.05, p<.001; Stroop II: t=-5.65, p<.001 and Stroop III : t=-3.07, p=.005), in the addition of TMTB (t=-1.91, p=.028). KO's cognitive performance was better than that of other glioma patients.

One year postoperatively, KO's performance was still unimpaired at domain level (Memory: z=0.30; Attention and executive: z=0.40). At test-level, performance on TMTB, TMTBA and STROOPint recovered (z=0.50; z=0.70, z=-1.40 respectively), performance on STROOP II, STROOPIII remained impaired (z=-2.50, z=-2.50 respectively). TMTA, STROOPI, WCST and memory tasks remained unimpaired (z=-0.20; z=0; z=-.20; imprinting: z=-0.20; recall: z=0.40 respectively).

In sum, KO's performance on cognitive tasks is better than other glioma patients, but was worse than his baseline performance at 1 year postoperatively.

DISCUSSION

Summary

The current study investigated the course of recovery in a patient with postoperative speech disorder, resembling dynamic aphasia and/or the SMA syndrome, after glioma resection in the fronto-medial lobe with an extensive test protocol.

The results demonstrate that KO shows a different cognitive profile than other glioma patients, which is mainly characterized by a deviant quality of the spontaneous speech. At cognitive domain level (i.e. the mean of all tests belonging to a specific cognitive domain) KO was not impaired both pre- and postoperatively, whereas glioma patients (GP1 and GP2) did deviate from normals. Selective impairments at test-level in executive functioning, however, were found in KO at 3 months and at 1 year postoperatively. KO became impaired in several language tasks; his postoperative speech deficit consisted of a reduced spontaneous speech, slower RT on the Dynamic Aphasia Test and impaired verbal fluency in the context of intact naming, repetition and relatively intact comprehension. Most recovery in KO's spontaneous speech took place between 7 weeks and 3 months postoperatively, but failed to reach baseline level within 1 year. The same recovery course holds for RT in the Dynamic Aphasia Test, with deterioration at 1 year. The production of new sentences with a word cue and picture description was most prone to progress. Performance on most executive functions tasks improved between 3 months and 1 year postoperatively, apart from one task measuring selective attention (STROOPIII).

SMA syndrome and recovery

Our study showed that the SMA area is involved in language production and partially in the executive functions. These results help to clarify the roles of the SMA region in cognition. It is known that spontaneous recovery of motor deficits is common in this area, due to brain plasticity (reshaping of functional networks) but can vary[16-18, 34]. Our case study reports that cognition can partially recover within 1 year with a more restricted recovery course for the spontaneous speech than for other cognitive functions, i.e. the executive functions. It must be taken into account that KO already demonstrated slight reduced spontaneous speech pre-morbidly, which may have interfered with his language recovery process. Some studies reported cases (after tumor resection in SMA area) in which patients experienced (long-term) speech disturbances[17, 18]. These speech disturbances were often described as speech hesitancies and speech initiation problems. It was raised that discrimination can be difficult between initiation problems and slight speech disturbances[35]. In general, it is not clearly documented in what way speech is evaluated. Our spontaneous speech analysis appears to be a sensitive method to capture speech deficits in glioma patients. Progress can be adequately documented; specific speech parameters can be quantified.

Several factors are reported to correlate with the immediate speech disturbances: patients with severe paresis postoperatively had more pronounced speech deficits and vice versa[35]. KO however, did not suffer from paresis. On the other hand, it has been claimed that motor output and speech output are functionally distinct between the SMA proper and pre-SMA[36]. The extent of resection (>90%) and the area of the SMA involved in language might have a relation with postoperative speech disturbance, as demonstrated by other researchers[16, 18].

In our patient, 58% of the tumor was resected; interference of the extent of resection can be ruled out. Also, it has been raised that anti-epileptic drugs can have an effect on cognition[37]. In our study KO used anti-epileptic drugs both pre- and postoperatively. We therefore suggest that an effect of anti-epileptic drugs on cognition is excluded. The observation of incomplete cognitive recovery until 1 year can be explained by tumor recurrence. On the other hand, low grade gliomas grow slowly and linearly at rates about 4 mm/year[38]. We therefore assume that an effect of tumor growth on cognitive performance is minimal.

Our study showed that KO did not completely reach cognitive baseline level in the long-term (1 year). Extensive cognitive testing appears to be necessary during course. These results can be used to inform patients about postoperative risks. Recovery could be a long process and might not be favorable for all patients taken into account survival period and maintaining patients' quality of life.

Dynamic aphasia: language specific or not?

The underlying mechanism that explains postoperative speech disorders after frontal lobe lesions is still unclear. Costello and Warrington[11] suggested that this speech impairment resulted from a (selective) defect at the early stage of verbal planning. If we assume a deficit in forming a linear scheme of sentence, KO would be impaired in any task requiring the generation of sentences, which was not the case. In addition, errors in word order, which remained absent, would be expected in case of a disturbance as such. We therefore assume that there was no general deficit in initial planning of language.

Dynamic aphasia can be divided into a pure and a mixed form[12] with both forms characterized by impaired propositional speech. Pure forms of dynamic aphasia are presented with intact naming, repetition and comprehension, mixed forms might also have syntactic and/or articulatory problems. KO did not present clear syntactic or dysarthric problems in his (spontaneous) speech; a mixed form cannot account for KO's deficit. In the context of a relatively pure form, Cox and Heilman[39] raised the possibility of a failure to spontaneously or intentionally activate the semantic and lexical network. Their patient showed reduced spontaneous speech in the context of intact naming, repetition and comprehension. He also suffered from impaired verbal fluency and some impairment in verbal memory, partially resembling the profile of KO. Tasks assessing executive functions however, such as WCTS or TMT, were not conducted in their study. The possibility of intervening executive disorders can therefore not be eliminated. Our patient also showed problems in selective attention/executive functioning. However, a pure executive account, in which deficits are mostly observed after frontal lobe lesions[15], cannot hold for KO's profile. KO was only impaired in TMTB (3 months) and Stroop (3 months and 1 year), but not in Design Fluency or WCST. The background of dynamic aphasia could be a combined deficit of a prominent language deficit with probable selective executive dysfunctioning, which fits with our patient KO[40-42]. Bormann et al.[42] explained this phenomenon by a deficit in the selection of speech act intentions. He argued that activated elements may interfere with verbal planning (e.g. resembling verbal interference in the Stroop task). Borrmann also ruled out the possibility of a selection/competition account[12, 40] since it does not provide an explanation to why a dynamic aphasic patient, like KO, is able to generate words in a fluency task at all. KO did not consistently show an effect of word frequency (high to low constraints) on the sentence completion task, which is typical for the selection/ competition account. This finding is in line with other case descriptions[13, 43]. They explained the deficit by an impairment at discourse generation/fluent sequence of novel thought. Their patients produced many perseverations in both a verbal and non-verbal fluency task which could point to fluency of novel thought disturbances. KO however, showed no tendency for perseverations in verbal or non-verbal tasks.

We argue that difficulties in selecting speech act intentions with interference of the inability to search the lexicon with a semantic strategy (word-finding) can account for KO's, since KO's semantic fluency remained impaired. Also a slower reaction time may be caused by difficulties in selecting a correct speech plan. Moreover, Repetitions and Incomplete Sentences in his spontaneous speech can point to a lexical problem; Repetitions could be a strategy of time-gaining before the next content word and Incomplete sentences could be a sign of word-finding problems. We therefore assume that KO's underlying deficit is mainly linguistic, with a possible influence of the (minimal) deficit in the executive functions.

Limitations

These are results of a single case study and may therefore not be representative for a general group. Furthermore, KO had a recurrent tumor. Deviations in his preoperative spontaneous speech could be caused by earlier tumor resection. The Dynamic Aphasia Test was not conducted preoperatively, so we cannot rule out the possibility of premorbid slower RT.

KO's spontaneous speech and his performance on formal tests was not compared to glioma patients 1 year postoperatively. To obtain a more complete recovery profile, we should compare his spontaneous speech to other glioma patients 1 year postoperatively in the future.

CONCLUSION

This is the first case study at long-term investigating postoperative speech disturbances after glioma resection in the fronto-medial lobe. The results suggest that resection in this area in conjunction with slight pre-morbid difficulties in the spontaneous speech could increase the risk of cognitive disturbances at longer term, especially language. This is valuable information, since mostly positive language sites are absent intraoperatively. These results can be used to inform patients preoperatively and to optimize or adapt the neurosurgical treatment plan.

Language is crucial in daily life. It is important to assess the impact of glioma resection on cognition as this may influence patients' quality of life.

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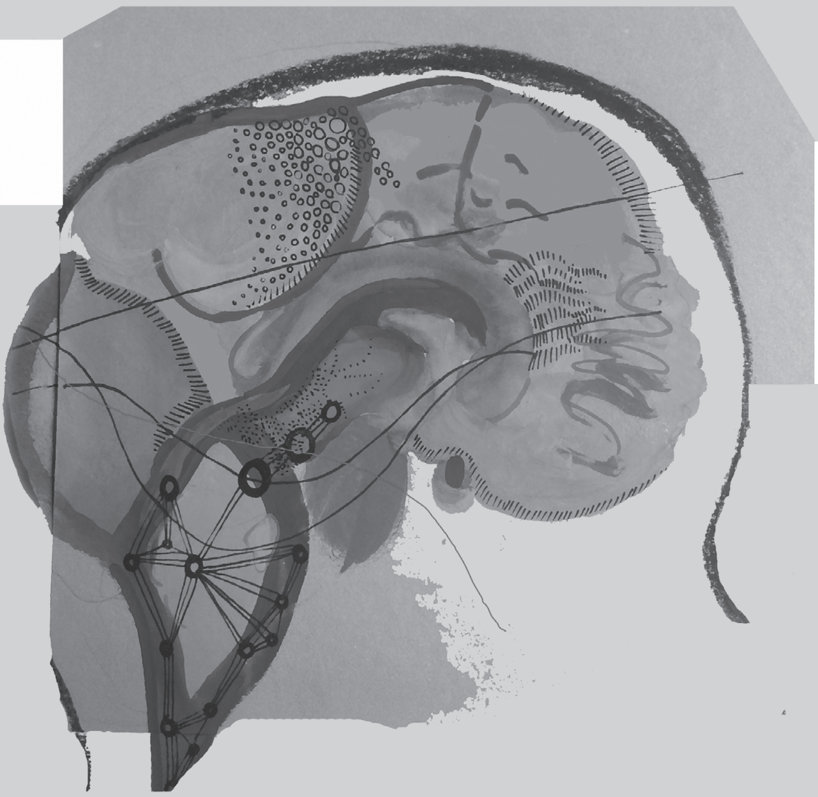

Chapter 7

Long-term evaluation of cognition after glioma surgery in eloquent areas

ABSTRACT

Background. Preservation of cognition is an important outcome measure in eloquent area glioma surgery. Glioma patients may have preoperative deficits in 1 or more cognitive domains which could deteriorate postoperatively. It is assumed that these impairments recover within 3 months; some studies however, still detected cognitive deterioration at this stage. Longer follow-up is necessary to gain more insight into the course of recovery.

Objective. To investigate the long-term effects on cognition after glioma surgery in eloquent areas.

Methods. Forty-five patients with gliomas (low- and high grade, but without contrast enhancement at diagnosis) in eloquent areas were assessed preoperatively, 3 months and 1 year postoperatively with a neuropsychological test protocol. Patients' performance was compared to normal population. Univariate analyses were performed between cognitive change and tumor-characteristics (localization, grade, volume, extent of resection) and treatment-related factors (radio-/chemotherapy).

Results. Pre- and postoperatively, impairments were found in all cognitive domains; language, memory, attention and executive functions ($p<.05$). Postoperatively, permanent improvement was observed on a memory test (verbal recall: t=-1.931, p=0.034), whereas deterioration was found on a language test (category fluency: t=2.517; p=0.030). Between 3 months and 1 year, the patients improved on 2 language tests (naming: t=-2.781, p=0.026 and letter fluency: t=-1.975, p=0.047). There was no influence of tumor- or treatment-related factors on cognitive change.

Conclusion. The findings underline the importance of cognitive testing at longer term postoperatively, as cognitive recovery took longer than 3 months, especially within the language domain. However, this longitudinal follow-up study showed that glioma surgery is possible without major long-term damage of cognitive functions. Tumor characteristics and extent of resection are no additional risk factors for cognitive outcome.

INTRODUCTION

Low grade gliomas are slow growing brain tumors infiltrating the central nervous system often in the proximity of eloquent areas. During brain surgery, direct electrocortical stimulation is used to identify individual functional boundaries to prevent permanent neurological and/or cognitive deterioration[1, 2]. Maintenance of cognitive functioning is an important outcome measure in treatment of glioma surgery, and essential for quality of life.

Glioma patients often complain about word-finding problems, memorizing facts at short-term or carrying out complex tasks. The occurrence of preoperative deficits in 1 or more cognitive domains such as language, memory and executive functions is well-known[3-6] and restricts daily life activities. Brain surgery may aggravate (or induce) cognitive disorders, but most studies claim that postoperative cognitive deterioration is transient and recovers within 3 months[7-10]. However, testing was usually restricted to 1 domain[11, 12] or performed with global measures, such as Karnofsky Performance score or Mini Mental State Examination which are thought to be not sensitive to cognitive change[13]. Our recent study still showed a decrease in several domains at 3 months postoperatively, indicating that the effect of surgery on cognition is still present. Cognitive change can take place until 1 year after surgery due to brain plasticity[14]. A longer follow-up than 3 months with an elaborate neuropsychological examination is necessary to detect the conclusive cognitive effects of brain surgery. Tumor-related factors such as localization, histopathology and tumor volume and extent of resection (EOR) have also been reported to affect cognition[3, 4, 6, 15.]

We investigated the long-term effects of surgery and potential tumor-related risk factors on different cognitive domains in patients with gliomas in eloquent areas. Since (low grade) glioma patients have relatively long survival time, this study could lead to important clinical information.

METHODS

Subjects

Cognitive functioning of a consecutive series of 45 Dutch native speakers (mean age 39.09, range 19-62) with gliomas in eloquent areas without enhancement after contrast administration) was assessed pre- and postoperatively. All tumors were well demarcated (focal). Most gliomas were left-hemispheric (93.3%) , most tumors were low grade (60%) and about one-third (37.8%) appeared to be high grade after pathological examination.

Procedures

Patients were treated with surgery at the Erasmus MC University Medical Center Rotterdam (N=44) and at the Medical Center Haaglanden the Hague (N=1) in the Netherlands. Localization of the tumor was determined by a neuroradiologist using 3D T1-weighted magnetic resonance imaging (MRI) and 2D T2-weighted images, and categorized as (i) involving frontal or parietotemporal language areas (inferior frontal gyrus, subcentral gyrus, supramarginal gyrus, angular gyrus, inferior, middle and superior temporal gyrus), or (ii) non-language areas (precentral, middle or superior frontal gyrus, with no involvement of the inferior frontal gyrus) based on the classic model of language[16]. The pre- and postoperative tumor volume was calculated by manual delineation of 3D deviant signal intensity on T2-weighted MR images using Osirix version 4.1.2. (http://homepage.mac.com/rossetantoine/osirix). Postoperative MRI scans were performed around 3 months and 1 year after resection. The extent of the resection (EOR) was calculated in percentages and subsequently divided into the following categories: biopsy (<20%), partial resection (20-89%), subtotal resection (90-99%) and total resection (100%). The histological type of the tumor (astrocytoma, oligodendroglioma, oligoastrocytoma) and the pathological WHO (World Health Organization) grade were determined by a neuropathologist, from tissue obtained during the tumor resection. The study was approved by the Ethical Committee of Erasmus MC, patients gave their informed consent.

Neuropsychological assessment

Patients were assessed between 1 and 2 months preoperatively (mean=1.4 months; sd=1.06) and 3 months (mean=3.4 months; sd=0.72) and 1 year (mean=1.01 years – sd=0.16) postoperatively with a comprehensive neuropsychological protocol (see Table 1). Based on the normative data, the test scores of the patients were transformed into z-values to compare the performance of patients to that of healthy adults.

Statistical analyses

We investigated whether patients' pre- and postoperative mean scores differed from the normal population on each test, using a one-sample t-test with 0 (the mean score of the normative group) as test value. Subsequently, the pre- (T1) and postoperative (T2 and T3) scores were compared with paired t-tests. To limit the number of statistical comparisons, only tests of which the pre- or postoperative mean performance deviated from normal population were selected. The influence of tumor and treatment related variables on cognitive "change scores" in the selected tasks was analyzed with a univariate analysis of variance. For non-normal distributions, an additional bootstrapping method was applied based on 1000 samples with a CI of 95%. "Change scores" were calculated by subtracting postoperative scores from preoperative scores ('T2-T1', 'T3-T2', and 'T3-T1'). Pearson rank correlations were conducted between the selected "change scores" and tumor volume and extent of resection. Since most patients used anticonvulsants both pre- and postoperatively, the effect of anti-epileptics drugs was not investigated.

Table 1. Neuropsychological test protocol

Test	N[1]	Cognitive Abilities	Description
Language			
Subtests of Akense Afasie Test (AAT)[17]			
- Token Test (TT)	42	Language comprehension; severity of language disorder	Pointing to and manipulating geometric forms on verbal commands
- Repetition	42	Repetition	Repeating phonemes, words and sentences
- Reading aloud	41	Reading	Reading aloud words and sentences
- Writing to dictation	40	Writing	Writing words and sentences on dictation
Boston Naming Test (BNT)[18]	44	Naming (word-finding)	Naming 60 pictures, presented in order of word frequency
Category Fluency[19]	45	Flexibility of verbal semantic thought processing; working memory	Producing words of a given category (animals and professions) within a limited time span
Letter Fluency[20] (parallel versions)	45	Flexibility of verbal phonological thought processing; working memory	Producing words beginning with a given letter (D,A,T or K,O,M) within a limited time span
Memory			
15 Words Test (15WT), Encoding, Recall, Recognition (parallel versions)[21]	45	Verbal learning; immediate and delayed recall and recognition	Learning a list of 15 words, with 6 recall trials; 5 immediate and 1 delayed, and a recognition trial
Attention and executive functions			
Trail Making Test (TMT) A, B, BA[22]	43	TMTA: visuomotor speed, attention; TMTB: + mental flexibility, divided attention	Connecting numbers placed randomly in ascending order as rapidly as possible (TMTA) and connecting alternating numbers and letters as rapidly as possible (TMTB)
Stroop Color-Word Test (Stroop) I, II, III, Interference[22]	38	Mental speed; selective attention, inhibition and switching	Reading color words, naming colors and naming colors of printed words, denoting another color

[1] N=Number of patients assessed both before and after surgery. For several reasons, the full protocol could not be applied to all patients. Priority was given to tests that were most relevant to the preparation and evaluation of the operative procedure.

RESULTS

Demographic and clinical characteristic

Table 2 shows patients' demographic and clinical characteristics of glioma patients.

Table 2. Demograpic and clinical characteristics

Characteristic	Value
Patients	
Male gender	28 (62.2%)
Mean age; range	39.09; 19-62
Education[23]; range	6; 4-7
Handedness (right)	39 (86.7%)
Localization tumor	
Hemisphere:	
Left	42 (93.3%)
Dominant	34 (75.6%)
Non-dominant	1 (2.2%)
Unclear	10 (22.2)
Lobe:	
Frontal	19 (42.3%)
Temporal	1 (2.2%)
Parietal	2 (4.4%)
Frontoparietal	5 (11.2%)
Frontoinsular	1 (2.2%)
Temporoinsular	1 (2.2%)
Temporoparietal	3 (6.7%)
Parietotemporal	2 (4.4%)
Insula/frontal	1 (2.2%)
Frontal, temporoinsular	1 (2.2%)
Frontal, insular, parietal	1 (2.2%)
Insula, frontoparietal	2 (4.4%)
Insula, frontotemporal	3 (6.7%)
Functional area:	
Language area	21 (46,7%)
Non language area	21 (46.7%)
Unclear	3 (6.6%)
Tumor histology	
Astrocytoma	9 (20.0%)
Oligodendroglioma	13 (28.9%)
Oligoastrocytoma	2 (4.4%)
Mixed oligoastrocytoma	3 (6.7%)
Anaplastic astrocytoma	6 (13.3%)
Anaplastic oligodendroglioma	5 (11.1%)
Glioblastoma	3 (6.7%)
Anaplastic mixed oligoastrocytoma/ oligodendroglioma	2 (4.4%)
Undefinable	1 (2.2%)

Table 2 (Continued)

Characteristic	Value
Tumor grade	
Low grade	27 (60.0%)
High grade	17 (37.8%)
Unclear	1 (2.2%)
Tumor volume in cm3 mean (range)	62.61 (11-156)
Extent of resection in % at T2: mean (range):	69.37% (3.12-100)
Biopsy[2]: <20	4 (8.9%)
Partial: 20-89	26 57.8%)
Subtotal: 90-99	7 (15.6%)
Total: 100	2 (4.4%)
(Postop MRI not available)	6 (13.3%)
Postoperative treatment	
None	16 (34.8%)
Radiotherapy	19 (41.3%)
Chemotherapy	4 (8.7%)
Both	6 (13.0%)

[2] In 4 patients only a small part of the tumor could be resected due to adherence to eloquent areas.

No relation was found between demographic characteristics and tumor variables.

Preoperative cognitive functioning

In the language domain, preoperative mean scores were worse than those of normals on BNT (t=-4.867, p<0.001), category fluency (t=6.259, p<0.001), letter fluency (t=-3.983, p<0.001), but not on the AAT-subtests (Token Test, repetition, reading aloud, writing to dictation). In the memory domain, patients were worse on 15WT encoding (t=-7, p<0.001) and on 15WT recall (z=-4.282, p<0.001). In the domains of attention and the executive functions, patients deviated on TMTA (t=-3.095, p=0.003), Stroop I (t=-6.349, p<0.001), Stroop II (t=-4.761, p<0.001) and Stroop III (t=-2.590, p=0.014), but they were not impaired on TMTB, TMTBA and Stroop Interference (see Figure 1).

Postoperative cognitive functioning

At 3 months postoperatively, mean performance was impaired on the same tests as preoperatively compared to normals (Language: BNT: z=-4.031, p<0.001; category fluency: t=-7.455, p<0.001; letter fluency: t=-3.816, p<0.001, Memory: 15WT encoding: t=-5.222, p<0.001; 15WT recall: t=-3.454, p=0.001, Attention and executive functions: TMTA: t=-2.942, p=0.005; Stroop I:t=-7.259, p<0.001; Stroop II: t=-5,166, p<0.001 and Stroop III : t=-3.753, p=0.001). In contrast with the preoperative assessment, TMTB was disturbed (t=-2.301, p=0.026).

At 1 year postoperatively, mean performance remained impaired on the same tests (Language: BNT: t=-4.230, p<0.001; category fluency: t=-6.764, p<0.001; letter fluency:z=-2.837,

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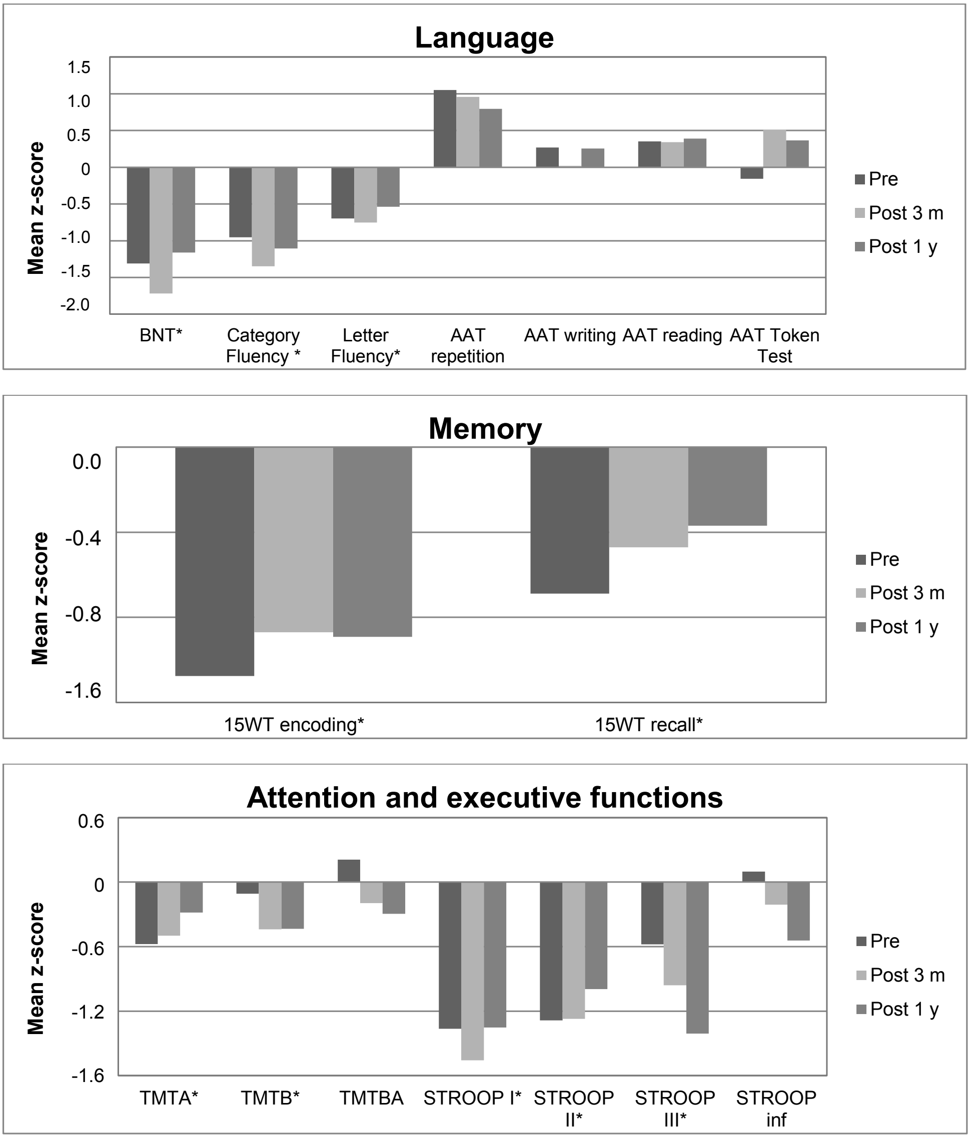
Figure 1. Z-scores on cognitive tasks before and after surgery (3 months and 1 year).



A mean z-value of 0 equals mean performance in the healthy population. Negative z-values indicate that patients performed worse than the healthy population. *Significant difference between patients and healthy population ($p<0.05$). Note that TMTA was impaired at T1 and T2, and TMTB at T2.

p=0.007, Memory: 15WT encoding: t=-5.20, p<0.001; 15WT recall: t=-2.551, p=0.015, Attention and executive functions: Stroop I:t=-5.330, p<0.001; Stroop II: t=-3.676, p=0.001 and Stroop III : t=-5.501, p<0.001). In contrast with the assessment of 3 months postoperatively, Stroop interference was disturbed (t=-2.045, p=0.047) and the performance on TMTA and TMTB recovered to the normal range (t=-1.839, p=0.073, t=-1.306, p=0.199 respectively) (see Figure 1).

Short-term effect of glioma surgery on cognition

In the language domain at 3 months postoperatively compared to preoperative level, there was a significant decline on category fluency (mean difference: -3.47, t=2.517; p=0.030). We only found a slight decrease on BNT and letter fluency compared to normals (p>0.05). In the memory domain, 15WT recall improved (mean difference: 0.744, t=-1.931, p=0.034). There were no improvements or declines in the domain of attention and executive functions (p>0.05).

Cognitive follow-up and long-term effect of glioma surgery

Between 3 months and 1 year postoperatively, positive change scores were observed in the language domain on BNT (mean difference: 0.93, t=-2.781, p=0.026) and on letter fluency (mean difference: -2.163 t=-1.975, p=0.047). The positive change scores on BNT and letter fluency were not correlated (Pearson r=-0.71, p=0.656). There were no changes on category fluency, in the memory domain or in the domain of attention and executive functions.

Tumor and treatment related factors

No effect of tumor related factors were observed on the deviating cognitive tasks both pre- and postoperatively, such as tumor grade (low / high) and tumor localization (language / non-language) (p>0.05).

EOR (biopsy-total resection) did not affect cognitive change scores (p>0.05). Only moderate negative correlations were found between preoperative tumor volume and preoperative scores on all memory tests (15WT encoding: Pearson r=-0.387, p=0.012; 15WT recall: Pearson r=-0.455, p=0.003; 15WT recognition: Pearson r=-0.371, p=0.020). Postoperative treatment, i.e. radio-, chemotherapy or a combination did not have an effect on cognitive performance at domain level (p>.05).

DISCUSSION

This is the first study examining the effects of glioma surgery on several cognitive domains in patients with eloquent area gliomas with a one-year follow-up. In accordance to other studies, we found cognitive impairments pre- and postoperatively[3, 4, 6, 25]. These deficits were observed in all cognitive domains: language, memory, attention and the executive functions.

Apart from deterioration in category fluency and improvement in verbal recall, surgery did not induce major cognitive changes at short and long-term. During course, naming and letter fluency were sensitive tasks for improvement. Slight improvement was observed in the attention and executive domain. Preoperative performance on all verbal memory tasks were related to tumor volume. Tumor or treatment-related characteristics and EOR were no risk factors for cognitive change.

Short and long-term effect of glioma surgery on cognition

With respect to language, both verbal fluency tasks were sensitive for change in glioma patients. Permanent deterioration postoperatively was found on category fluency. On letter fluency a slight decrease was observed at short-term postoperatively with an improvement at 1 year. The slight decrease of letter fluency at short-term contrasted with the significant decline we observed in our earlier examination of 28 patients. Large individual variance could be an explanation to this difference. The validity and sensitivity of a category fluency task has already been demonstrated in aphasic patients[26].

Apart from letter fluency, naming also improved at longer term, which was marginally observed earlier[12]. These change scores were not correlated, which suggests that both tasks assess distinct functions within the language domain. Santini et al.[6] showed that naming was not related to other cognitive tasks, pointing to the more language specific nature of this task.

In accordance to our short follow-up, memory in our patients improved in verbal recall (retaining verbal information after interference) and remained stable at long-term. Short-term improvement on verbal memory may be accounted for by the release of mass effect which remains stable due to the slow growth rate of (low grade) gliomas (4 mm p/y)[27]. Santini et al.[28], however, found a decline in memory and attention at 3 to 6 months postoperatively whereas Correa and colleagues[29] reported a decline at 1 year in non-verbal memory prior to improvement at 6 months post-treatment (RT/chemo). Differences in sample size, treatment (adjuvant therapy versus surgery), or a dissociation between a verbal and a non-verbal memory network could explain the variance in results[30]. However, the simultaneous decline in language tasks at short-term and improvement in verbal memory contradicts the latter assumption.

No changes in executive functions were observed between test-moments contrasting our short follow-up. However, compared to normals TMTB was impaired at 3 months as found earlier, and recovered at 1 year postoperatively, as well as TMTA. The long-term improvement in executive functions could be mediated by a close connection between verbal working memory neural networks (which improved) and processes of selective attention[31]. Long-term brain reorganization mediated by both hemispheres or perilesional areas, is not uncommon, as observed earlier in chronic post-stroke patients[32, 33].

In sum, short-term improvement in cognition might be explained by the release of mass effect, whereas brain plasticity is responsible for a positive long-term effect, resulting in a potential unmasking of latent cognitive networks[8, 12]. The latter explanation, however, does not hold for category fluency, which permanently remained on a lower level. It may be that compensation is not possible because of the multidimensional background of this task, i.e. it depends on language (lexical retrieval), semantic memory, and (partly) attention and executive functioning.

Tumor related factors; pathological grade, localization, volume.

The absence of tumor-related effects on cognitive change was already mentioned in our earlier study. A larger sample size and longer follow-up did not reveal differences between cognitive change and tumor pathology, localization and volume/EOR. Other studies also showed that both LGGs and HGGs performed subnormal or within an impaired range on several neuropsychological tasks[34, 35]. The absence of an effect of tumor grade, in contrast to some other studies[3, 28, 36] might be due to a small inclusion of glioblastomas patients (WHO grade IV) who are typically more neurologically impaired[37]. Our spontaneous speech analysis did differentiate between tumor grades[38]; LGG patients had poorer verbal communication than HGG patients. Standard neuropsychological tasks could be too global to detect strong differences between tumor grades.

A preoperative negative correlation was found between tumor volume and memory performance; i.e. the larger the tumor volume, the lower performance scores. A relation between tumor volume, extent of resection and postoperative cognitive decline was absent, in accordance with Santini et al.[28], and in contrast to another study who found who found a relation with a decline in the executive functions[39]. Extent of resection is possibly not associated to cognition, but 1:1 related to tumor progression free survival[40]. Longer follow-up is needed to confirm this statement.

No localization effect was found on cognitive performance contrasting our earlier results [24]. A dependency of cognitive functions on an integrated activity of several specialized brain areas could explain a comparable performance between patients with tumors in language areas versus non-language areas[41]. Another explanation is that only lesion side might be responsible for crucial differences[42].

Effect of postoperative adjuvant treatment

Postoperative treatment with radio- and/or chemotherapy did not affect cognitive change. Patients received the same "safe" dose of 2 Gy of focal radiation therapy as in our short follow-up, to avoid a negative effect on cognitive performance until several years after treatment[43, 44]. A follow-up of 1 year is possibly too early to detect cognitive side effects. At this stage, deficits should not be attributed to treatment but to the tumor itself[45, 46].

Importance of a longitudinal cognitive follow-up study

The occurrence of cognitive changes until 1 year postoperatively illustrates the relevance of conducting neurocognitive examination at longer term. The language domain was found to be the most dynamic, as category fluency deteriorated permanently and letter fluency and naming improved during course. In addition, verbal recall was sensitive for improvement. Several tasks in the domain of attention and executive functions were also sensitive for impairment; TMTA, TMTB, StroopI-III and Stroop interference. Our next step is to investigate the relation between objective and subjective cognitive measurement as well as the opinion of their proxies. The main question is whether patients and their partners notice differences in cognitive functioning relating to daily life activities. In addition, deterioration on the sensitive language tasks (naming and letter fluency) for improvement could be indicative for tumor recurrence. The results of these tasks at 1 year could serve as a baseline before a second surgery.

Limitations

A limitation of our study might be the existence of a selection bias; patients with more clinical symptoms would have been less likely to finish all tasks. Furthermore, additional test-moments could have been included, e.g. at 6 or 9 months postoperatively. Although we observed cognitive change during course, it remains unclear when improvement took place. To obtain more information about the memory domain, a non-verbal memory task should be conducted in addition to our verbal memory task. An effect of tumor grade on cognition was absent. Larger subgroups divided by tumor grades should be included to make more detailed comparisons. Anti-epileptic drugs could negatively affect cognition[29, 47]. The majority of the patients, however, took anticonvulsants both pre- and postoperatively, excluding to a certain extent an influence of medication on cognition. Possible pre-operative effects of AED on cognition could not be examined. A control group without medication should therefore be included for future analyses.

Language intervention could have influenced the results. Unfortunately, we did not have information about patients' postoperative rehabilitation. Until recently, some positive intervention effects have been observed in (working) memory and the executive functions after a specific rehabilitation program[35]. No effect of language rehabilitation has been reported yet. Nonetheless, evidence for the benefit of language therapy is not overwhelming in stroke patients[48]. We therefore assume that possible language intervention did not affect language performance, as glioma patients are less impaired than stroke patients.

Conclusion

Our longitudinal follow-up study showed that glioma surgery is possible without major long-term damage of cognitive functions. The language domain appeared to be the most dynamic line, since both deterioration and improvements were observed. Language recovery takes longer than 3 months, in contrast to what most studies have documented so far[3, 9, 10]. This finding underlines the importance of language testing at longer term, with in particular category fluency as a crucial ability to assess during operation, in order to limit postoperative decline. We can conclude that specific tumor characteristics, such as grade, localization, volume and EOR, are no additional risk factors for cognitive outcome. Patients can be preoperatively informed on their long-term prognosis with regard to their cognition, an essential aspect of quality of life.

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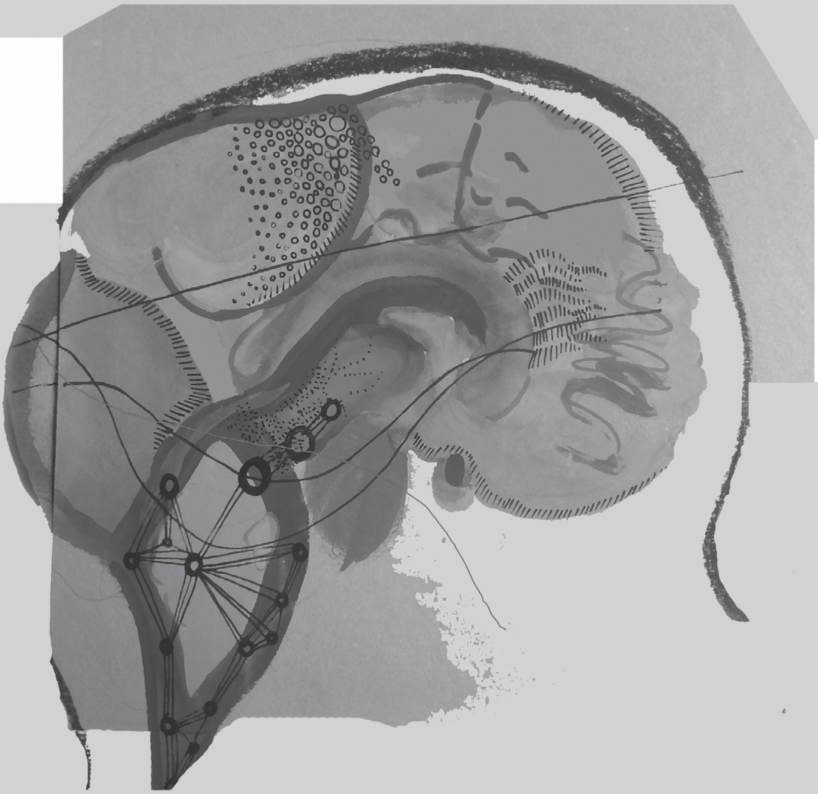

Chapter 8

General discussion

In this final chapter I discuss the main findings of this thesis. First, the effects of surgery in eloquent areas on cognition, global QoL rating and emotional behavior in glioma patients are addressed. Then the effect of surgery on spontaneous speech is discussed followed by an illustration of its clinical value in a case study. Finally, I explain the clinical relevance of this longitudinal study, its limitations and directions for future research.

MAIN FINDINGS

The effects of surgery on cognition, global Quality of life and emotional behavior

We found that patients with gliomas have impairments in several cognitive domains, but that glioma surgery does not induce major permanent cognitive deterioration at longer term. In order to be able to examine the effect of surgery on cognitive functioning, tests in several cognitive domains were selected, in particular in the domains of language, verbal memory, attention and the executive functions. Patients showed impairments in all these cognitive domains, before and after surgery. However, in the year after surgery only 1 language task (category fluency) significantly deteriorated and 1 memory task (verbal recall) improved, measured in a large group of glioma patients (N=45). These cognitive changes were already observed in a shorter time-frame postoperatively (3 months) together with slight worsening of 2 other language tasks (naming and letter fluency) which improved between 3 months and 1 year. Our smaller cohort (N=28), however, revealed a significant decline of both verbal fluency tests (category and letter fluency) and an additional executive functioning task (TMTB). The smaller sample size (with more patients with poor performance) could be responsible for these differences.

The most striking finding was that our results contradict the general assumption that spontaneous recovery of cognitive functions takes place within 3 months[1, 2]. Namely, improvement in language functioning (naming and letter fluency) occurred between 3 months and 1 year postoperatively, indicating a later onset of brain reorganization than generally assumed. We believe that the relatively mildly disturbed cognitive profile and the functional recovery in low grade glioma patients can be explained by brain plasticity. Preoperative slow tumor growth could induce brain compensation, as we observed a comparable performance on language tasks in both patients with language and non-language area gliomas. At long-term after surgery, we postulate that cognitive improvement is mediated by a compensation mechanism within the left hemisphere through a long-distance subcortical connectivity between relevant cortical regions (related to naming)[3]. The possible participation of the right hemisphere, however, should also be taken into account, as co-activation of the right hemisphere in language processing was demonstrated in healthy right handed people but also in brain tumor patients with a verb generation task and letter fluency[4-6]. Category fluency, however, might be more specific to left frontal and temporal hemispheric functioning due to strategic language behavior; such as clustering (i.e. generating words within subcategories) and switching (i.e. shifting between subcategories), and is possibly therefore less attributed to brain compensation[7]. In summary, glioma surgery in eloquent areas did not cause major permanent cognitive damage and among all cognitive domains the course of the performance in the language tasks appeared to be the most dynamic in the year after surgery. These results underline the importance of cognitive testing at long-term, especially with the focus on language functions.

Besides examining the effect of surgery on cognition, we also investigated the impact of surgery on global Quality of Life (QoL), an essential outcome measure in glioma treatment. The possible predictive value of cognition and emotional factors on QoL was also examined. We demonstrated that global QoL had not altered short-term after surgery in glioma patients (N=34), neither did symptoms for anxiety or depression increase. A prognostic model showed that the occurrence of depressive mood was the only predictor for the pre- and postoperative change in QoL, whereas anxiety was only correlated to postoperative QoL; a better global QoL can be explained by a lower occurrence of symptoms for depression in patients treated for surgery. It is possible that apart from the "regular" psychological burden patients encounter, mood disturbances could also be an additional result of specific lesion localization (e.g. more subcortical) or lesion size, which in turn affects QoL experience, as observed in stroke patients[8].

Contrary to our expectations and the assumptions in the literature so far, cognitive functioning as assessed with objective measurements was not directly associated with change in global QoL rating. However, we should be careful in translating this result to clinical practice. The artificial nature of objective cognitive testing might be responsible for the absence of a relation between cognition and QoL. Probably, the available cognitive standardized tests were not sufficiently tailored to capture daily life functioning and QoL experience, as subjective cognitive complaints have been found to be associated with QoL[9]. Only one-third of the variance of QoL rating as outcome measure in our prognostic model could be explained. This finding implies that a large part of the variance is not accounted for and that other factors should be taken into consideration, such as epilepsy burden, fatigue or pain. Left aside these considerations, in sum we showed that global QoL is relatively preserved early after glioma surgery in eloquent areas, but that symptoms for depression require a significant part of attention in the care protocol.

The relevance of spontaneous speech

From a clinical perspective, patients (and/or their proxies) often mention difficulties in daily conversation during clinical examination. We therefore examined, in addition to standardized tests, the quality of verbal communication using the Aphasia Severity Rating Scale (ASRS)[10], normally applied to aphasic stroke patients. It appeared that the word-finding complaints of LGG patients could not be always clearly captured with this classic communication rating scale. We therefore expected, that a detailed investigation of the spontaneous speech could provide more insight into the communicative abilities of this patient group. In particular, because sensitive parameters could be clinically relevant for intraoperative spontaneous speech monitoring. A spontaneous speech analysis (N=27) indeed revealed deviations before and after surgery, indicative for disturbances in linguistic productivity (correctness of speech) and linguistic fluency (effortless speech) compared to healthy speakers. In particular, the preoperative spontaneous speech of LGG patients was marked by a higher occurrence of incomplete sentences than observed in a healthy group of speakers. Surgery induced a decline in utterance length, that is the mean number of words in each spontaneous verbal expression, but did not aggravate the number of incomplete sentences. In addition, the deviating linguistic variables were not associated with other language tasks (naming and category fluency), pointing to the fact that we assessed distinct linguistic functions. These findings underline the relevance of adding the assessment of daily speech to the intraoperative language protocol, possibly in combination with sentence completion tasks. By only monitoring language functions in isolation, subtle linguistic impairments could be missed, increasing the risk for postoperative linguistic disturbances.

Spontaneous speech in a case study

A reduction of spontaneous speech, known as the Supplementary Motor Area (SMA) Syndrome[11], has been mentioned after tumor resection in the upper part of the medial frontal lobe. In the neurosurgical literature, the description of this spontaneous speech reduction is ill-defined, and mostly labeled as being "mute". Despite the absence of a more exhaustive description of the linguistic characteristics of this syndrome, most researchers reported complete recovery of the SMA syndrome within a few days or weeks. In fronto-neurodegenererative diseases and stroke patients, this loss of conversational speech is described as "dynamic aphasia". The core hallmark of dynamic aphasia concerns a reduction of daily conversation in the context of intact naming, repetition and comprehension[12, 13]. It remains a debate whether the underlying mechanism of the SMA syndrome is purely linguistic or not, as some researchers also found disturbances in the executive functions[14, 15], possibly responsible for the loss of competence to initiate speech.

From clinical practice, we know that LGG in the SMA area are not rare. In 2011, a patient (KO) was operated for LGG nearby the Supplementary Motor Area (SMA) and he developed a form of dynamic aphasia at the end of resection. We conducted a long-term follow-up in order to better understand the risks of operating in this specific brain area for speech and possibly other cognitive functions. Postoperatively KO suffered from a reduction of several spontaneous speech parameters, slowness (reaction time) on a dynamic aphasia test (sentence completion and generation), impairments on language tests (verbal fluency) and selective executive functional deficits (TMTB, BA, Stroop II, III). Recovery of most language functions took place between 7 weeks and 3 months after surgery, whereas the executive functions recovered between 3 months and 1 year postoperatively. One year after surgery, most language functions (category fluency, spontaneous speech and reaction time) and 1 task for the executive functions were still impaired. The findings of this case study suggest that resection near the SMA area could increase the risk for cognitive disturbances at longer term, in particular language. In addition, it underlines the relevance of monitoring spontaneous speech during surgery, as the testing of language functions in isolation would provide a false and incomplete idea about patients' language proficiency.

Tumor- and treatment related factors

Apart from investigating the effect of surgery, we examined the possible impact of tumor- and treatment related factors on cognitive change, such as tumor grade, localization, volume, extent of resection, radio- and/or chemotherapy. We only found a negative correlation between preoperative tumor volume with verbal memory tasks (encoding and recall); that is, the larger the volume, the lower the scores, which could be explained by mass effect. Other factors however, were not associated with the observed cognitive changes, i.e., tumor grade, localization, extent of resection and adjuvant therapy. The absence of an effect of localization suggests an equal risk for cognitive change in either a language or motor area as mentioned before. We already mentioned that we assume that brain reorganization is an important aspect with respect to recovery in the year after surgery. Perhaps it is possible to accelerate this neural process by means of noninvasive brain stimulation, such as Transcranial Magnetic Stimulation (TMS) or transcranial Direct Current Stimulation (tDCS). Some effects in language improvement have been observed in acute and chronic aphasic stroke patients[16, 17].

Patients with LGGs and higher graded gliomas (mostly grade III) in this study appeared to have more or less the same prognosis for cognitive outcome, although this could be different for glioblastoma patients (grade IV) with faster and more aggressive tumor progression. However, the spontaneous speech analysis did reveal some differences, as LGG patients produced shorter utterance and more incomplete sentences than controls, whereas HGG patients performed comparably to healthy speakers. It could be the case that patients with HGGs relatively benefit more from improvement due to the surgical release of mass effect, as compared to LGG patients.

There was also no influence of radio- and/or chemotherapy on cognitive change. The absence of an effect of adjuvant therapy on cognition suggests that adverse effects do not set off within a year after adjuvant treatment.

Clinical relevance

The results show that glioma surgery in eloquent areas can be conducted without permanent major damage to higher cognitive functions. This is essential information as patients with (presumptive) LGG have a relatively long survival time. Hence the quality of cognitive functioning is essential for adequate participation in daily life. With our findings, patients can be adequately informed before surgery about their long-term cognitive prognosis, especially if they have doubts about an operation. Moreover, the result that surgery does not induce major cognitive deterioration could prevent an additional psychological burden in patients which could subsequently affect QoL.

The observed deterioration and improvements could have some clinical implications. Deterioration at short-term on a test (verbal recall) that is supposed to improve could be a sign of a significant negative effect of surgery. A decline at long-term on tests of which performance is supposed to improve (naming, letter fluency and to some extent TMTA and B) or further aggravation (category fluency) could be indicative for tumor recurrence. On the other hand, if improvement indeed occurs, it could also point to a suitable moment to re-operate a tumor regrowth if necessary, as brain reorganization has taken place. We should continue to monitor the spontaneous speech of glioma patients during surgery, as spontaneous speech appeared to be sensitive and distinctive from standardized language tasks. It reflects daily conversation and could therefore be more in accordance with patients' anamnestic word-finding complaints than an artificial language test.

Apart from cognitive performance, QoL was also a topic of investigation in this study as a step towards a more detailed research study. Our short-term follow-up demonstrated that global QoL was relatively well preserved. An important finding was that depressive symptoms were largely responsible for change in QoL. The standardized questionnaire CES-D assessing depressive symptoms should be adopted in the standard preoperative screening moment and if possible in the aftercare as well. By doing so, depressive symptoms can be detected in an earlier stage and more suitable support can be provided in the care program.

Tumor-related characteristics were no additional risk factors for cognitive deterioration in our patient group. All patients had presumptive LGG (no contrast enhancement on MRI) in eloquent areas, but more than one-third appeared to have HGG after pathological examination. It is important to include both groups, as all patients received the same surgical indication after diagnosis. By excluding HGG patients from this group in retrospect, a bias towards grade II gliomas could have been induced.

We did not find differences in cognitive status in patients harbouring language or motor area tumors, which seems rather unexpected at first glance. The finding that patients in both language and non-language (motor) areas performed within an impaired range indicates that sometimes unpredictable brain areas are involved in specific cognitive functions (due to reorganization of slow tumor growth) and that we should continue to test language functions during awake surgery of gliomas in areas that are not classically related to language.

Limitations

When interpreting the outcomes of these studies, we should be careful in generalizing the results to all glioma patients undergoing awake surgery in eloquent areas.

The first critique is the sample size. The groups for the spontaneous speech analysis and the global QoL rating were rather small (N=27 and N=34 respectively) resulting in a limited statistical power. Moreover, a longer follow-up than 3 months was not conducted and should be performed, regarding the dynamics found in the one-year follow up with an elaborate cognitive test protocol. The inclusion of more than 45 patients for the analysis of the neuropsychological protocol is evidently desirable to increase statistical power. In addition, we currently only distinguished between language and non-language areas due to small sub-groups. Data collection should continue to investigate the relation between revealed cognitive disorders and more specific location within eloquent areas.

The second point of attention concerns inclusion bias. Some patients were only tested preoperatively for clinical purposes, they chose not to continue the follow-up testing due to several reasons. In addition, some patients with worse cognitive status did not finish all cognitive tasks. These cases of "lost to follow-up" may have resulted in a selection bias towards better cognitive outcome for the entire group, as worse patients chose not to cooperate with our study.

A possible third critique may have been the lack of intraoperative testing of other functions than language, such as memory, attention and executive functions. Language may have benefitted most from intraoperative testing, as non-verbal functions (and/or executive functions) were not structurally monitored during the awake interval. On the other hand, no cognitive differences were found in patients with tumors in language or non-language areas functions, distributed in equal groups, excluding a selective benefit of intra-operative testing for the language domain.

Unfortunately, we were not able to examine the influence of anti-epileptic drugs (AED). The administration of AED may have cast a cloud on patients' performance. However, as most patients took medication both before and after surgery, we believe that possible influence of AED on cognition is rather negligible. A control group without AED could provide more clarity on the effect of anticonvulsants on cognition.

Finally, we only administered a global QoL rating in order to obtain a preliminary idea about the effect of surgery. Analyses of the full EORTC questionnaires (European Organization for Research and Treatment of Cancer – Core Quality of Life Questionnaire) QLQ-C30 and BN20[18, 19] and possible other prognostic factors, such as symptom burden and seizure activity[20] are necessary to gain a more complete impression of the effect of surgery on QoL and its relation to cognition and emotional factors. However, administrating more and longer questionnaires could impose an emotional burden to patients.

Future research

The results of this study have initiated new topics for investigation. With the revealed sensitive cognitive tests before and until long-term after awake craniotomy, essential information is provided: 1) for evaluation of outcome results of the surgical treatment, 2) for preoperative information for the patient on the possible sequela, 3) for intraoperative testing protocols and 4) for possible detection of tumor recurrence. Testing more patients with tumors in different locations will overcome the bias and limitations of our studies.

We currently investigated the effect of glioma surgery in eloquent areas under awake conditions. The difference in detailed cognitive outcome between awake craniotomy and classic surgery, however, remains unknown, but is ethically rather impossible to resolve. The general assumption is that awake craniotomy leads to a better cognitive outcome, but only 1 study examined neurological outcome between the 2 surgical approaches[21]. Data from a meta-analysis showed that the occurrence of permanent neurologic impairment was higher in patients without functional mapping versus direct electrocortical mapping (DES)[22]. Apart from selection bias, cognitive tests and test-moments differed between studies, which could have influenced outcome. Although the findings of this study are relevant in order to understand the benefits from awake craniotomy with DES, a comparative prospective randomized study between awake and classic procedure, would reveal more details about cognitive outcome after 1 of these surgical techniques. The only possibility of including a control group as such within ethical constraints, concerns the inclusion of patients with awake indication who prefer to undergo classic surgery.

It remains unclear whether patients experience cognitive impairments as revealed by objective testing as a functional burden in daily life. Future research should focus on the relation between results obtained from objective tasks and cognitive performance in a daily setting as well as the opinion of patients' proxies. Another ethical consideration is related to this issue: is it feasible to go in dialogue with the neurosurgeon about the "sacrifice" of one or more cognitive functions? In this case, a tailored protocol can be designed according to individual patients taking into account their hobbies, work and personal preferences relating to relevant cognitive functions. Another important question concerns the extent to which patients are able to participate in social and professional life again, a tangible aspect of quality of life.

We identified cognitive impairments as well as the course of cognitive recovery in glioma patients until 1 year after surgery in eloquent areas. Prognostic factors for direct and long-term postoperative cognitive outcome are unfortunately not revealed by this study, which should be taken into account as well. Currently we collaborate with the Vrije Universiteit Brussels, AZ Sint-Lucas Gent and Rijksuniversiteit Groningen on a Dutch Linguistic Intraoperative Protocol (DuLIP) in order to identify prognostic factors (pre- and intraoperative) for language outcome. DuLIP consists of language production and language comprehension tasks at different linguistic levels, phonology, semantics, syntax and verbal motor tasks[23]. We aim to assess these tests pre- intra- and postoperatively (6 weeks, 3 months, 6 months). Consequently, the relation between anatomical neural organization and functional behavior will be examined, i.e. the combination between sensitive tasks and tumor localization. In addition, it would be interesting to ascertain the course of brain reorganization (ipsi- or contralateral) in glioma patients, possibly in combination with noninvasive brain stimulation (TMS or tDCS). The same holds true for investigating brain reorganization induced by the glioma itself before surgery. A correlation analysis should be conducted between first MRI scan on which the tumor was detected and preoperative neuropsychological performance to confirm this statement. Some patients harbour the tumor for years before undergoing surgery. Correlation analyses of time between diagnosis and operation and (subtle) cognitive impairments could lead to some important information about the decisive moment to operate.

The ultimate goal is to create a short cognitive screening test based on the sensitive tests revealed in this study in combination with a shortened linguistic test-battery from DuLIP. It is also desirable to explore the sensitive spontaneous speech variables (incomplete sentences and utterance length) in more detail in order to grasp the underlying linguistic problems in the spontaneous speech. At this point we are not certain whether these communicative difficulties arise from a lexical (word-finding) or a syntactic problem (sentence construction). Correlation analyses between both lexical (lexical diversity of nouns) and syntactic tasks (lexical diversity of verbs or syntactic fluency) with incomplete sentences could shed more light upon this issue. These results could be useful for the design of a more specific language therapy program for glioma patients.

Finally, the monitoring of other functions than language during surgery should be considered in order to limit cognitive deterioration. Currently the use of Stroop test intraoperatively has been shown to be effective during awake craniotomy, as it appeared to prohibit the occurrence of dysexecutive syndromes at 3 or between 10 and 15 months after surgery[24]. We hope to apply a variety of intra-operative cognitive functioning tasks in the future.

In summary, a tailored test protocol taking into account different relevant cognitive functions for the individual patient is a substantial aim in glioma surgery. By doing so, we wish to extend survival while maintaining patients' cognitive functions at most and to retain their ability to participate in daily life.

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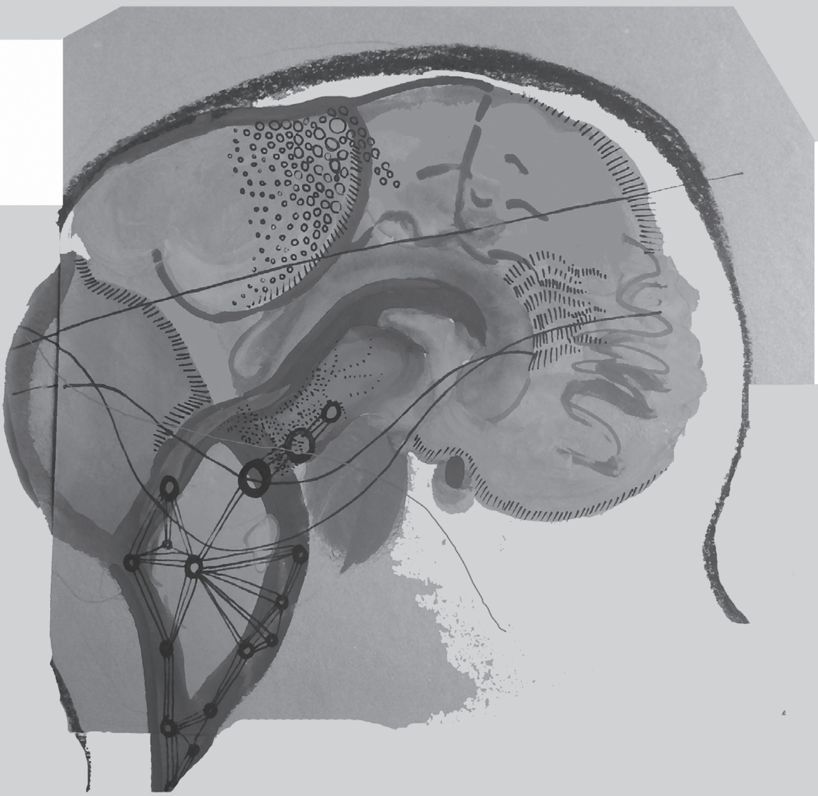


Chapter 9

Summary/ Samenvatting

List of abbreviations

SUMMARY

This thesis describes and investigates the long-term effects of glioma surgery in eloquent areas on cognition with the emphasis on language. Patients operated for glioma with an awake craniotomy were followed and tested before and after surgery with an extensive neuropsychological test-protocol. The importance of spontaneous speech was underlined by means of analyses of speech samples as elicited during anamnesis and with a case study. The relation and prognostic value of cognition, emotional factors on quality of life rating was also examined. With the results, patients can be informed about their cognitive prognosis until 1 year after surgery.

In the general introduction, **Chapter 1**, a background on cognition, language and quality of life before and after surgery in (low grade) glioma patients is provided along with a brief description of the surgical procedure. The objectives for this study are presented.

In **Chapter 2**, a systematic literature review can be found. We aimed to identify the short and long-term effects of glioma surgery on the main cognitive domains, language, memory, attention, the executive functions and visuo-construction abilities, as assessed with standardized neuropsychological tests before and after surgery. If available, secondary risk factors for cognitive change were reported, such as tumor location, volume, extent of resection and adjuvant therapy (radio or chemo). Seventeen studies were identified based on our inclusion criteria. Only 4 studies investigated cognition in all of the above mentioned domains before and after surgery. Directly after surgery, all studies except 1, found deterioration in 1 or more cognitive domains. At longer term postoperatively (3 / 6 months), both improvement and deterioration to preoperative level were found in the domains of language, memory and the executive functions. This study indicates that cognitive recovery to baseline is possible to a limited extent, but that the results are still too arbitrary to draw definite conclusions. A longer follow-up study is necessary.

Chapter 3 reports on the early effect of glioma surgery on cognition in the domains of language, memory, memory, attention, executive functions and visuoconstructive abilities. We investigated 28 patients before and 3 months after surgery with a neuropsychological test protocol. Overall we found that patients were worse than normal population in all domains apart from visuoconstructive abilities. Surgery induced a decline in the language domain and in the executive functions, partly influenced by tumor location in a language area. The following tests were sensitive for a decline: category fluency and letter fluency (language), Trail Making B (executive functioning). A test for memory improved, namely verbal recall. In addition, anamnestic word-finding complaints from patients could not always be objectified by the aphasia severity rating scale in which communicative abilities are judged.

Chapter 4 describes the verbal communication of 27 patients before and 3 months after surgery by means of a detailed spontaneous speech analysis. Several spontaneous speech

parameters were selected to measure linguistic productivity and proficiency. Both before and after surgery, patients produced more incomplete sentences than healthy controls. After surgery, also the length of a complete speech utterance of patients deteriorated compared to controls. However, between test-moments no significant decline was observed in patients' spontaneous speech. No clear relation was found between spontaneous speech parameters and standardized language tests, typically used to detect word-finding problems. These findings underline the importance of the use of both language measurements to obtain a complete linguistic profile.

Chapter 5 focuses on the early effect of glioma surgery on global Quality of Life (QoL) rating, cognition and symptoms for anxiety and depression in 34 patients. Consequently we investigated the predictive value of these components on global QoL. Global QoL rating was moderate to good and remained relatively stable 3 months after glioma surgery. Before and after surgery, we found disturbances in overall cognition as well as signs for anxiety and depression in about one-third of the patient group. Despite the observed impairments in these components, and contrary to our expectations, only symptoms of depression were a significant predictor for change in global QoL. Hence, we suggest that psychological monitoring should be systematically adopted in the (after)care program of glioma patients to maintain QoL.

In **Chapter 6**, we present a one-year follow-up case study of a patient (KO) who underwent surgery for low grade glioma nearby the Supplementary Motor Area (SMA). No positive language sites were identified with electro(sub)cortical stimulation. Nonetheless, at the end of the tumor resection he developed strong reduced spontaneous speech in the context of intact naming, repetition and comprehension, also known as the SMA syndrome or dynamic aphasia. Most language recovery took place between 2 weeks and 3 months postoperatively, but did not reach preoperative baseline level. Selective executive functions were also impaired, but recovered almost completely between 3 months and 1 year postoperatively. These results underline the monitoring of spontaneous speech during surgery, as the assessment of language functions in isolation provide an incomplete profile of patients' linguistic abilities. Surgery nearby the SMA area is possible, but it can increase the risk for (mild) postoperative language disturbances at longer term.

Chapter 7 addresses the long-term effects after glioma surgery in eloquent areas in 45 patients in the cognitive domains of language, memory, attention and executive functions. We conducted 3 assessments: before surgery, 3 months and 1 year after surgery. Impairments were present in all cognitive domains on all test-moments. One language test (category fluency) deteriorated at short-term, as already observed in our short follow-up, and remained impaired at 1 year postoperatively. Permanent improvement, however, was found in 1 memory test (verbal recall) and during course in the language domain (naming and letter fluency). Tumor- and treatment related factors, such as location, grade, extent of resection and adjuvant therapy were no additional risk factors for cognitive change. The most important conclusion of this longitudinal study is that glioma surgery is possible without inducing major cognitive damage.

Chapter 8 provides a general discussion on the main findings of the studies presented in this dissertation, followed by its clinical implications and finalized by suggestions for future research.

SAMENVATTING

Dit proefschrift is gericht op het onderzoeken van het lange termijn effect van glioom chirurgie in eloquente gebieden op de cognitie, met de nadruk op taal. Patiënten geopereerd met een wakkere craniotomie procedure werden gevolgd en getest met een uitgebreid neuropsychologisch test-protocol voor en na de operatie. Het belang van de spontane taal werd aangetoond met behulp van analyses van taalsamples die tijdens de anamnese verkregen werden en met een casus beschrijving. De relatie en prognostische waarde van cognitie, emotionele factoren op een kwaliteit van leven beoordeling werden eveneens onderzocht. Met deze resultaten kunnen patiënten beter worden geïnformeerd over hun cognitieve prognose tot een jaar na de operatie.

De inleiding, **Hoofdstuk 1**, geeft achtergrond informatie over cognitie, taal en kwaliteit van leven voor en na een operatie bij (laaggradige) glioom patiënten, evenals een korte omschrijving van de operatieve procedure. De doelstellingen voor deze studie worden gepresenteerd.

Hoofdstuk 2 geeft de resultaten weer van een systematisch literatuuronderzoek van de korte en lange termijn effecten van glioom chirurgie in eloquente gebieden op de belangrijkste cognitieve domeinen taal, geheugen, aandacht, executieve functies en visuo-constructieve vaardigheden, getest met een neuropsychologisch protocol voor en na een operatie. Indien mogelijk, werd eveneens gekeken naar secundaire risicofactoren voor cognitieve verandering, zoals tumor locatie, volume, mate van resectie en adjuvante therapie (radiotherapie of chemotherapie). Zeventien studies werden geïncludeerd, waarvan slechts vier studies de cognitie onderzochten in alle bovengenoemde cognitieve domeinen voor en na een operatie. Alle studies, behalve 1, vonden direct postoperatieve cognitieve achteruitgang in een of meer domeinen. Op de lange termijn (3 / 6 maanden) werd zowel achteruitgang als vooruitgang gevonden op het gebied van taal, geheugen en de executieve functies. Deze literatuurstudie laat zien dat cognitief herstel tot preoperatief niveau mogelijk is tot op zekere hoogte, maar dat de resultaten nog te weinig gefundeerd en onsamenhangend zijn om definitieve conclusies te trekken. Een langere follow-up periode is noodzakelijk.

In **Hoofdstuk 3** wordt het korte termijn effect van glioom chirurgie op de cognitieve domeinen taal, geheugen, aandacht, executieve functies en visuoconstructief vermogen gerapporteerd. Er werden 28 patiënten onderzocht voor en 3 maanden na de operatie met een neuropsychologisch test-protocol. In het algemeen werd gevonden dat patiënten voor de operatie slechter presteerden dan de normatieve groep in alle domeinen, behalve visuo-constructieve vaardigheden. De operatie veroorzaakte een achteruitgang op het gebied van de taal en de executieve functies, gedeeltelijk beïnvloed door tumor locatie in een taalgebied. De volgende testen waren sensitief voor een achteruitgang; category fluency en letter fluency (taal); Trail Making B (executieve functies). Verbetering werd gevonden bij een geheugentest (verbal recall). Daarnaast konden anamnestische woordvindklachten van patiënten niet altijd worden geobjectiveerd met een beoordeling van de kwaliteit van de verbale communicatie (aphasia severity rating scale).

Hoofdstuk 4 geeft een beschrijving van de verbale communicatie van 27 glioompatiënten voor en 3 maanden na een operatie via een spontane taalanalyse. Verscheidene spontane taal parameters werden geselecteerd om de linguïstische productiviteit en -bekwaamheid te onderzoeken. Zowel pre- als postoperatief produceerden patiënten meer incomplete zinnen dan gezonde sprekers. Na de operatie werd de gemiddelde uitingslengte van de patiënten korter dan die van normalen. Echter, er werd geen significante verslechtering gevonden tussen de 2 meetmomenten in de spontane taal van de patiënten. Er was geen duidelijke relatie tussen de spontane taal parameters en gestandaardiseerde taaltesten, normaliter gebruikt om woordvindproblemen te detecteren. Deze resultaten benadrukken het belang van het gebruik van beide taalmeetinstrumenten om een zo compleet mogelijk linguïstisch profiel te verkrijgen.

In **Hoofdstuk 5** wordt het korte termijn effect van glioom chirurgie bij 34 patiënten weergegeven op een beoordeling van de kwaliteit van leven, cognitie en emotionele factoren, angst en depressie. Vervolgens werd de prognostische relatie van de cognitie en emotionele factoren met de kwaliteit van leven onderzocht. De globale beoordeling van de kwaliteit van leven was gemiddeld tot goed en bleef stabiel 3 maanden na de operatie. Voor en na de operatie werden er afwijkingen gevonden in de algehele cognitie, en symptomen van angst en depressie in ongeveer een derde van de patiëntengroep. Ondanks stoornissen in deze componenten, en tegen onze verwachting in, waren alleen de symptomen voor depressie een significante voorspeller voor een verandering in de beoordeling van de globale kwaliteit van leven. Het systematisch psychologisch monitoren lijkt dus van toegevoegde waarde in de (na)zorg van glioompatiënten om de kwaliteit van leven te behouden.

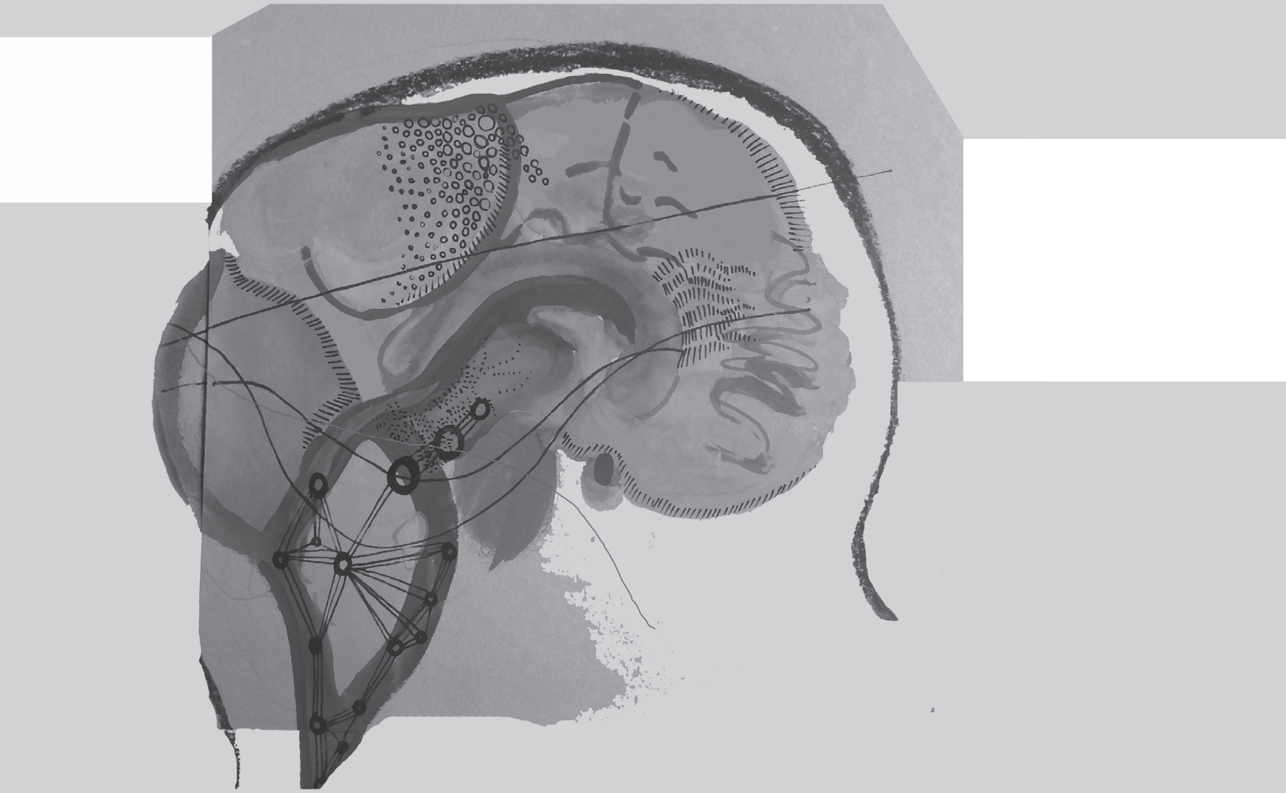
In **Hoofdstuk 6** rapporteren we over een casus beschrijving (KO) tot 1 jaar na een operatie van een laaggradig glioom nabij het Supplementair Motorisch gebied. Er werden geen positieve stimulatiepunten gevonden voor de taal middels electro(sub)corticale stimulatie. KO ontwikkelde echter aan het einde van de tumor resectie een sterke reductie in de spontane taal, in de context van een intacte prestatie op het benoemen, het nazeggen en in het taalbegrip, ook wel bekend als het SMA syndroom of dynamische afasie. Het meeste taalherstel vond plaats tussen 2 weken en 3 maanden postoperatief, maar bereikte niet het preoperatieve niveau. Selectieve executieve functiestoornissen werden ook gevonden, maar deze herstelden bijna volledig tussen 3 maanden en 1 jaar postoperatief. Deze casus benadrukt het belang van het intraoperatief monitoren van de spontane taal, aangezien het testen van gebonden taalfuncties in isolatie (zoals het nazeggen en het benoemen) een incompleet beeld geeft van het talig functioneren bij patiënten. Een operatie nabij het SMA gebied is mogelijk, maar kan het risico voor (milde) postoperatieve taaluitval op de langere termijn vergroten.

Hoofdstuk 7 omvat de lange termijn effecten na glioom chirurgie in eloquente gebieden bij 45 patiënten in de cognitieve domeinen taal, geheugen, aandacht en de executieve functies. We testten de patiënten op drie meetmomenten: preoperatief, 3 maanden en 1 jaar postoperatief. Stoornissen waren aanwezig in alle cognitieve domeinen op alle testmomenten. Een taaltest (category fluency) verslechterde op 3 maanden postoperatief in vergelijking met het preoperatieve niveau, zoals eerder geobserveerd in de korte follow-up studie, en bleef permanent slechter op 1 jaar postoperatief. We vonden echter een permanente vooruitgang op een geheugentest (verbal recall) en tussen 3 maanden en 1 jaar postoperatief was er sprake van een vooruitgang op 2 taaltesten (benoemen en letter fluency). Tumor- en behandelingseigenschappen, zoals locatie, graad, mate van resectie en adjuvante therapie, waren geen bijkomende risicofactoren voor cognitieve verandering. De belangrijkste conclusie van deze longitudinale studie is dat glioom chirurgie in eloquente gebieden mogelijk is zonder ernstige cognitieve beschadiging te veroorzaken op de langere termijn.

In **Hoofdstuk 8** worden de hoofdzakelijke bevindingen bediscussieerd van de studies die in dit proefschrift gepresenteerd zijn. Eveneens worden klinische implicaties en suggesties voor toekomstig onderzoek besproken.

LIST OF ABBREVIATIONS

15WT	15 Word Test
AAT	Akense Afasie Test
AED	Anti Epileptic Drugs
BNT	Boston Naming Test
CES-D	Center for Epidemiologic Studies Depression scale
CLAN	Corpus of Language and Nature
DES	Direct Electrocortical Stimulation
DTI	Diffusion Tensor Imaging
DuLIP	Dutch Linguistic Intraoperative Protocol
EOR	Extent of Resection
EORTC	European Organization for Research and Treatment of Cancer
GP	Glioma Patients
HC	Healthy Controls
KPS	Karnofsky Performance Score
LGG	Low Grade Glioma
HGG	High Grade Glioma
MLUw	Mean Length of Utterance (words)
MMSE	Mini Mental State Examination
MRI	Magnetic Resonance Imaging
RT	Reaction Time
SD	Standard Deviation
SMA	Supplementary Motor Area
STAI	State Anxiety Inventory for Adults
tDCS	transcranial Direct Current Stimulation
TMS	Transcranial Magnetic Stimulation
TMT	Trail Making Test
TTR	Type Token Ratio
WCST	Wisconsin Card Sorting Test
QoL	Quality of Life
WHO	World Health Organization



APPENDICES

Appendix I: Search string systematic review

Appendix II: Dynamische afasie test

Appendix III: CLAN commands

APPENDIX I: SEARCH STRING SYSTEMATIC REVIEW

(cognition/exp OR 'cognitive defect'/exp OR 'speech and language'/exp OR 'speech disorder'/exp OR 'language disability'/exp OR memory/exp OR neuropsychology/de OR 'mental function'/de OR 'intellectual impairment'/exp OR (((function* OR execut* OR psycholinguistic OR linguistic OR brain OR intellect* OR intellig* OR verbal* OR mental) NEAR/3 (control OR dysfunction* OR disabil* OR impair* OR defec* OR disturb* OR problem* OR difficult* OR disorder* OR performance* OR abilit* OR capabilit* OR capacit* OR competenc* OR outcome* OR assessment* OR evaluat* OR examin* OR monitor*)) OR ((execut* OR psycholinguistic OR linguistic OR brain OR intellect* OR intellig* OR verbal* OR mental) NEAR/3 function*) OR cognit* OR speech OR languag* OR articulat* OR aphas* OR memor* OR attention* OR alertness* OR awareness* OR concentrat* OR neurocognit* OR neuropsycholog*):ab,ti) AND (glioma/de OR oligodendroglioma/de OR astrocytoma/exp OR (astrogliom* OR oligoastrocytom* OR gliom* OR oligodendrogliom* OR astrocytom* OR (supratentorial NEXT/1 lesion*)):ab,ti) AND (surgery/exp OR surgery:lnk OR 'postoperative complication'/exp OR (surger* OR surgic* OR craniotom* OR postoperat* OR postsurg* OR preoperat* OR presurg* OR operati*):ab,ti) NOT ('child'/exp OR 'childhood'/exp OR 'childhood disease'/exp OR 'newborn'/exp OR 'adolescent'/exp OR 'adolescence'/exp NOT ('adult'/exp OR 'adulthood'/exp OR 'aged'/exp OR 'middle aged'/exp)) AND [english]/lim NOT ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [review]/lim)

A

APPENDIX II: DYNAMISCHE AFASIE TEST

1. Zin aanvullen met één woord

Ik ga een aantal zinnen voorlezen waarvan het laatste woord ontbreekt. Kunt u de zin afmaken?

*

1.De kapitein bleef op het zinkende…
2. Ze gingen zo ver als ze…
3. De meeste katten kunnen goed zien in het…
4. De auto's wachtten voor het…

**

1. De vieze modder plakte aan haar…
2. Het papier was te dik om te…
3. Er gaat niets boven een kop warme…
4. Zeehonden zijn goed in …

***

1. De vrachtwagen was beladen met …
2. Het ging goed met de…
3. Het geld werd verdeeld door de…
4. Ze waren geschrokken van …

2. Zin aanvullen met een zinsdeel

Nu ga ik een aantal zinnen voorlezen waarvan het laatste deel ontbreekt. U mag de zinnen weer afmaken.

*

1. De zon verdween…
2. De trein stopte…
3. De vrouw op het strand…
4. Ik kocht een kaartje…

**

1. Men vertelde de kinderen dat…
2. De rode kater rende…
3. Anne liep naar binnen…

4. Toen de boom omviel…

***

1. In de supermarkt…
2. Alle mensen begonnen …
3. Hij haastte zich…
4. Helaas kan ik…

3. Met een woord een zin maken

Kunt u een zin maken met het woord (…) er in?

1. Parijs
2. James Bond
3. glas
4. vriend
5. kwamen
6. heeft

4. Aan de hand van een gegeven zin een nieuwe zin maken

Ik ga nu een hele zinnen voorlezen. Kunt u er een nieuwe zin bij bedenken?

1. De televisie van de buurman is kapot.
2. Toen Hans naar buiten ging, begon het te regenen.
3. Sophie ging naar de verjaardag van haar vriendin.
4. Bob was gevallen en had zijn enkel verstuikt.
5. De auto wilde niet starten.
6. De voetbalwedstrijd was erg spannend.

5. Een zin maken aan de hand van een afbeelding

De volgende vraag gaat over een plaatje.

1. Kunt u mij vertellen wat u hier ziet?
2. Wat denkt u dat de man straks gaat doen?

6. Dagelijkse taal
Stelt u zich het volgende eens voor…

1. U bent pas bij mij in de straat komen wonen en u wilt met mij kennismaken. U belt aan en u zegt:

2. U staat bij de bakker en u ziet een sjaal op de grond liggen. Wat zegt u?

3. U heeft afgesproken met een vriend, maar er is iets tussen gekomen. U belt hem op. Wat zegt u?

APPENDIX III: CLAN COMMANDS

Type Token Ratio:
freq +t*ABC[1] +z51w-350w sample.cha

MLUw:
mlu +t*ABC +z51w-350w -t%mor sample.cha

Repetitions:
freq +t*ABC +z51w-350w +s[/] sample.cha

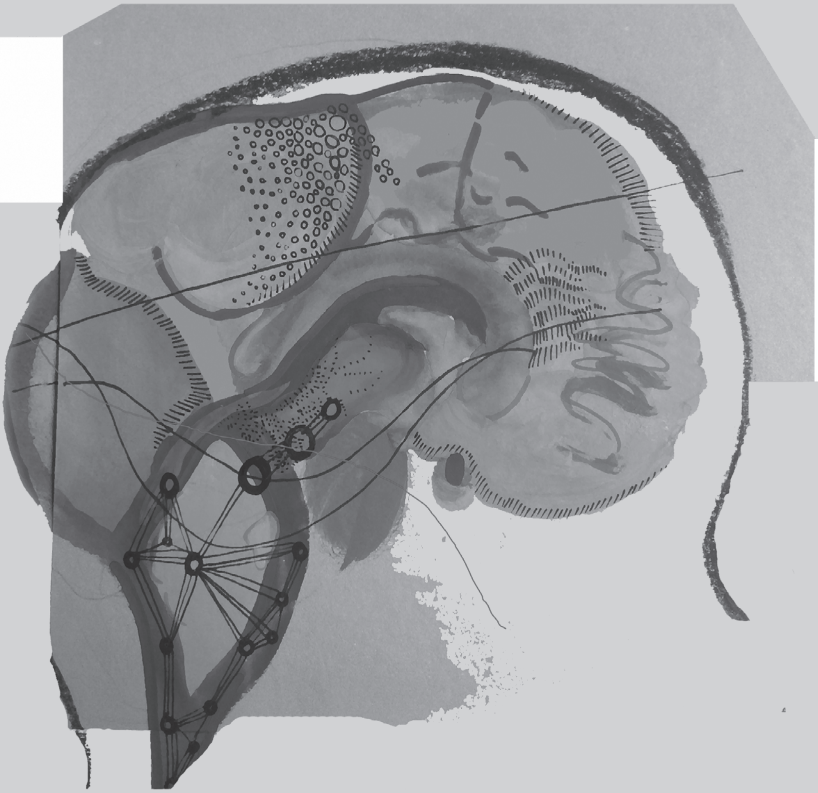
Self-corrections:
freq +t*ABC +z51w-350w +s[//] sample.cha

Incomplete sentences:
freq +t*ABC +z51w-350w +s"+…" sample.cha
freq +t*ABC +z51w-350w +s"+//." sample.cha

(Manuals CLAN programs: http://childes.psy.cmu.edu/)

A

[1] ABC denotes a letter code of the speaker in question.



Epiloque

Dankwoord

About the author

List of publications

Phd portfolio

DANKWOORD

De totstandkoming, uitvoering en voltooiing van dit proefschrift is mede te danken aan een groot aantal mensen, zowel uit mijn werk- en privéleven, die op verschillende wijze een significante bijdrage hebben geleverd.

Allereerst wil ik mijn grote dank uiten aan de patiënten en hun familieleden die hebben toegestemd mee te werken aan deze studie. Zonder hen was de realisatie van dit proefschrift onmogelijk geweest. Ik heb bewondering voor hun dapperheid, één van de onmisbare elementen om een wakkere craniotomie tot een goed einde te brengen en de motivatie om 2 keer na de operatie terug te komen naar de polikliniek voor een uitgebreid neuropsychologisch onderzoek. In het bijzonder dank aan patiënt KO, die ik intensief heb mogen volgen en thuis mocht testen voor onze casusbeschrijving.

Mijn promotor prof. dr. Clemens Dirven wil ik bedanken voor zijn begeleiding en kritische blik. Beste Clemens Dirven, voor onze besprekingen nam u altijd ruim de tijd. Ik heb vol aandacht en interesse geluisterd naar uw adviezen. In 2011 kwam ik bij u op gesprek zonder veel klinische ervaring en het waardevolste dat ik van u heb geleerd is het benaderen van de wetenschap vanuit het oogpunt van de zorg. U had vertrouwen in mij om deze vaardigheid te ontwikkelen en daar hoop ik in de toekomst veelvuldig gebruik van te blijven maken. U was ook altijd alert op de kleine details. Met uw heldere commentaar op de general introduction en de general discussion kon ik de laatste puntjes op de i zetten voor dit proefschrift!

Zonder de begeleiding van mijn co-promotoren dr. Evy Visch-Brink en dr. Arnaud Vincent had dit proefschrift nooit de vorm gekregen zoals het nu is.

Evy, je bent mijn dagelijkse begeleider geweest en bij jou kon ik altijd binnenlopen voor advies en feedback. Zelfs midden in de nacht, in de afrondingsfase van dit proefschrift, kon ik op je rekenen via e-mail! Toen ik in 2009 met jou kennismaakte, gaf je mij de kans om ervaring op te doen als taalkundig onderzoeker. Ik mocht spontane taalsamples van patiënten met een glioom transcriberen en analyseren en dat leverde tot ons groot plezier na ongeveer een jaar leuke resultaten op. Afgezien van het doen van onderzoek, keek ik mijn ogen uit als voormalig letterenstudent in zo'n groot universitair medisch centrum. Eind 2010 belde je me op om me te vragen of ik geïnteresseerd was om het onderzoek naar het effect van wakkere neurochirurgie op de cognitie voort te zetten. Dankzij jou kon ik eindelijk promotieonderzoek doen. Jij hebt me geleerd om in een klinische setting te bewegen als linguïst. Ik heb veel bewondering voor jouw passie voor het onderzoek in de kliniek en je wist mij iedere keer weer te enthousiasmeren om op nieuwe onderzoeksvragen te komen. We hebben samen ook aardig wat afgereisd, zoals naar Toulouse en San Francisco. Maar ook van onze treinreisjes naar België heb ik genoten. Het was elke keer weer opluchting als we trein op tijd hadden gehaald! Ik kijk uit naar ons aanstaande tripje naar Venetië.

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Leden van de leescommissie, prof. dr. Martin van den Bent, prof. dr. Martin Taphoorn en prof. dr. Roelien Bastiaanse, zeer veel dank voor de beoordeling van dit proefschrift.

Beste prof. van den Bent, u hebt de rol van secretaris van de kleine commissie op u genomen. Mijn dank hiervoor. De Daniël den Hoed Kliniek is een onmisbare schakel in het zorgtraject van onze hersentumorpatiënten. Om deze reden, was het dan ook evident dat u betrokken zou worden bij de beoordeling van dit proefschrift.

Beste prof. Taphoorn, ik vond het een eer dat u zo enthousiast reageerde om zitting te nemen in de kleine commissie om mijn proefschrift te beoordelen. Mijn dank hiervoor.

Beste Roelien, hartelijk dank voor het lezen van mijn proefschrift. Ik was dolblij toen je me de e-mail stuurde met je positieve beoordeling. Daarnaast voelde ik me erg vereerd toen je tegen me zei dat je me graag zou zien in Groningen. Inmiddels werken we samen en ik zie onze toekomstige projecten vol enthousiasme tegemoet. Bedankt voor je vertrouwen in mij.

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Beste Peter, we hebben de afgelopen twee jaar nauw samengewerkt aan het gestandaardiseerde linguïstische protocol DuLIP (Dutch Linguistic Intraoperative Protocol). Met veel plezier heb ik dit gedaan en ik hoop onze samenwerking succesvol voort te zetten. Van de Science of Aphasia in Brussel 2013 heb ik genoten, mede dankzij de bierproeverij die je organiseerde op de openingsavond en het diner dat we daarna hebben genuttigd. Je liet je interesse voor mijn promotieonderzoek altijd zeer duidelijk blijken, erg bedankt hiervoor.

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Lieve Elke, jij bent degene met wie ik het meeste heb gedeeld als PhD student op het gebied van wakkere craniotomie en taaltesting. Voor mijn gevoel liepen we bijna synchroon in ons onderzoeksproject en het was heel fijn om lief en leed met elkaar te delen. We hebben veel congressen samen doorgemaakt, presentaties gegeven en er staat nog wat op de agenda. Naast het harde werken tijdens de congressen, hebben we ook veel lol gehad. Vooral over ons laatste congresbezoek in Berlijn kunnen we een heel boek vol anekdotes schrijven! ;-) Bedankt voor de leerzame en gezellige tijd.

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Dr. Caspar Looman, beste Caspar, onze afspraken over de statistische analyses waren onmisbaar en door jouw adviezen was ik in staat de definitieve resultaten te interpreteren.

Wakkere craniotomie team MCH Westeinde Den Haag in het bijzonder drs. Fred Kloet, bedankt voor alle OK's die we samen hebben gedaan en voor de input bij het casus artikel.

Dr. Martine van Zandvoort, beste Martine, met jouw hulp heeft het kwaliteit van leven artikel vorm gekregen. Bedankt voor je uitgebreide feedback, kritische vragen en de telefoongesprekken die je ondanks je volle agenda met mij kon voeren.

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Judith Vork, beste Judith in 2009 kwam ik in jouw project terecht als vrijwillig onderzoeker. Ik heb veel geleerd van jou als neuropsycholoog, in het bijzonder dat je taal niet zonder de andere cognitieve domeinen kunt benaderen. Dat je de keuze hebt gemaakt om een andere richting op te gaan, vond ik heel erg dapper. Vol genoegen heb ik jouw gestarte onderzoek eigen gemaakt en ten einde gebracht.

Paranimfen, Nadia Kriek en Natasja ter Voert. Lieve Nadia, jij bent degene die mij in contact heeft gebracht met Evy. We waren toentertijd huisgenoten en je kwam thuis van een dag co-schappen bij de anesthesie. Je had een wakkere craniotomie bijgewoond en je was zo brutaal om aan de linguïst die aan het assisteren was te vragen of ik een keer bij haar langs mocht komen. Ik wist helemaal niks van dat onderwerp, laat staan was ik thuis in een klinische setting. Je stimuleerde mij om toch contact op te nemen met Evy en zonder dit initiatief had ik hier nooit gestaan. Je bent een van mijn 'oudste' vriendinnen en ik kan altijd bij je terecht of het nu werk- of privé-gerelateerd is. Het was voor mij dan ook meer dan logisch dat ik jou vroeg om naast me te komen staan bij mijn verdediging. Daarnaast weet ik natuurlijk dat jij als geen ander een feestje kan organiseren. Bedankt voor alles!

Lieve Natasja, ik ben heel blij dat jij aan de andere zijde van mij wilt staan tijdens mijn verdediging. We kennen elkaar al een aantal jaar, maar de laatste drie jaar (volop in mijn promotietraject) hebben we elkaar pas echt heel goed leren kennen. Je bent onderdeel geweest van mijn persoonlijke en zakelijke ontwikkeling, daar ben ik je erg dankbaar voor. Jij hebt het afgelopen jaar ook een aantal grote sprongen gemaakt in je leven. Zo heb je een groot hart voor onderzoek, maar heb je de keuze gemaakt om een andere richting op te gaan omdat je meer wilde leren. Daar mag je trots op zijn!

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ABOUT THE AUTHOR

Djaina Denise Satoer was born on September 19th 1983 in Dordrecht and grew up in Zwijndrecht with her parents. She attended secondary school at Develstein College (HAVO) in Zwijndrecht and graduated in 2000. She started a Bachelor study for secondary education and teaching French at Hogeschool Rotterdam. She obtained her teaching degree in 2004. She continued a master study (including a pre-master year) French Language and Culture at Utrecht University with a specialization in linguistics, language acquisition. She obtained her degree in 2006. In 2007 she decided to acquire more knowledge in the field of linguistic research and started the prestige master of Linguistics at Utrecht University with the focus on neurolinguistics. She graduated in 2009. In the same year, she met Dr. Evy Visch-Brink at Erasmus MC University Medical Center who gave her the opportunity to gain research experience in a clinical setting. For about 1 year, she performed linguistic research in glioma patients as a volunteer. In 2011 she started the job as a PhD candidate and clinical linguist at the department of Neurosurgery. At present, she continues performing research and clinical work at the same department. She also started a job at the Rijkuniversiteit Groningen as an assistant professor neurolinguistics where she coordinates the Groninger Expertisecenter for Language and Communication disorders.

LIST OF PUBLICATIONS

Satoer D, Vork J, Visch-Brink E, Smits M, Dirven C, Vincent A. Cognitive functioning early after surgery of gliomas in eloquent areas. *Journal of Neurosurgery.* 2012;117(5):831-838.

Satoer D, Vincent A, Smits M, Dirven C, Visch-Brink E. Spontaneous speech of patients with gliomas in eloquent areas before and early after surgery. *Acta Neurochirurgica*. 2013;155(4):685-692.

De Witte E, **Satoer D**, Robert E, Colle H, Visch-Brink E, P M. Essentiële taalzones detecteren tijdens wakkere neurochirurgie. In: Robert E, Visch-Brink E, A B, eds. *Het (voor)beeldig brein. Taal en interventionele geneeskunde.* Antwerpen-Apeldoorn: Garant; 2013.

Satoer D, Kloet A, Vincent A, Dirven C, Visch-Brink E. Dynamic aphasia following low grade glioma surgery near the Supplementary Motor Area: A selective spontaneous speech deficit. *Neurocase: The Neural Basis of Cognition.* 2013; http://dx.doi.org/10.1080/13554794.2013.841954.

Satoer D, Visch-Brink E, Smits M, Looman C, Dirven C, Vincent A. Long- term evaluation of cognition after glioma surgery in eloquent areas. *Journal of Neurooncology*. 2014;116(1):153-60.

Satoer D, Zandvoort v, M, Vincent A, Dirven C, Visch-Brink E. Cognition, anxiety, depression and Quality of Life early after surgery for glioma in eloquent areas. *Submitted.*

Satoer D, Visch-Brink E, Dirven C, Vincent A. Glioma surgery in eloquent areas, can we preserve cognition? A systematic review. *Submitted.*

De Witte E, **Satoer D**, Robert E, Colle H, Verheyen S, Visch-Brink E, Mariën P. The Dutch Linguistic Intraoperative Protocol (DuLIP): a standard linguistic approach to awake brain surgery, normative data and clinical use. *Submitted.*

De Witte E, **Satoer D**, Colle H, Robert E, Visch-Brink E, Mariën P. Functionele mapping binnen wakkere neurochirurgie: een review met enkele aanwijzingen voor de praktijk. *Submitted.*

Mendez Orellana C, Visch-Brink E, Vernooij M, Kalloe, S, **Satoer D**, Vincent A, van der Lugt A, Smits, M. Crossed cerebro-cerebellar language lateralization: an additional diagnostic feature for assessing atypical language representation with presurgical functional MRI. *Submitted.*

PhD PORTFOLIO

Name PhD student: Drs. D.D. Satoer	PhD period: 2011-2014
Erasmus MC Department: Neurosurgery	Promotor: Prof.dr. C.M.F. Dirven
Research School: NIHES	Supervisors: Dr. E.G. Visch-Brink and Dr. A.J.P.E. Vincent

PHD TRAINING	Year	Workload ECTS
General courses		
Presentation skills	2013	0.1
Stepping stones for grant writing and interview	2013	0.1
Effective Time management	2013	0.1
Good Clinical Practice	2012	1.0
Research Integrity	2012	0.1
PhD day – 2x	2011, 2013	0.2
Biomedical English Writing	2011	4.0
Specific courses		
Systematic literature research in Pubmed	2013	0.1
The Cognitive Neuroscience of Reading and Speech Development (Driebergen)	2012	0.7
Spatiotemporal Imaging of Normal and Abnormal Language Processing (Driebergen)	2012	0.7
Using Bayesian methods to model cognition (Driebergen)	2012	0.7
Aphasia clinics: complexity aphasia therapy	2012	0.1
Aphasia Clinics: primary progressive aphasia	2011	0.1
Seminars and workshops		
Working group language testing in awake surgery (3x, Toulouse, Gent, Heeze)	2014	0.3
Aphasia: Junior researchers days (Groningen)	2013	0.7
Education day Quality of Life (World federation of neuro-oncology)	2011	0.1
Results meeting SPEAK	2011	0.1
Presentations		
Labmeeting Neurolinguistics (Groningen)	2014	0.1
Nurses symposium neurology/neurosurgery (Erasmus MC)	2013	0.1
Staff meeting neurosurgery (Erasmus MC)	2013	0.1
Aphasia labmeeting prof. dr. C. Lapointe (Erasmus MC)	2013	0.1
Book chapter presentation (Antwerp, Belgium)	2013	0.1
(Inter)national conferences		
Aphasia conference (Zeist)	2013	0.1
Scientific day for Neuro-oncology, oral presentation (Utrecht)	2013	0.1
14th International Science of Aphasia, oral presentation (Brussels, Belgium)	2013	1.5
European Low Grade Glioma Network meeting, oral presentation (Ghent, Belgium)	2013	0.9
50th Annual Meeting Academy of Aphasia, poster presentation (San Francisco, US)	2012	1.5
3rd Joint Meeting Dutch & Belgium Society for Neurosurgery, oral presentation (Spa, Belgium)	2012	0.1
13th International Science of Aphasia, oral presentation (Groningen)	2012	1.5
European Association of Neurology, poster presentation (Marseille, France)	2012	0.9
LOT (Landelijke Onderzoeksschool Taalkunde), poster presentation (Driebergen)	2012	0.1
European Low Grade Glioma Network meeting, oral presentation (Toulouse, France)	2012	0.9
30th Workshop of Cognitive Neuropsychology, poster presentation (Bressanone, Italy)	2012	1.5
16th Meeting Society for Neuro-Oncology, poster presentation (Orange County, US)	2011	1.5

TEACHING ACTIVITIES

Lecturing

Bachelor Course: language testing in clinical linguistics (Groningen)	2014	4.0
Master and bachelor guest lectures: (Clinical) Linguistics - 3x (Groningen)	2012, 2013	0.3
Supervising Masters' Theses		
Linguistics: 1 bachelor student		0.1
Speech Therapy science: 1 master student		0.1
Clinical Neuropsychology: 4 master students		0.4
Speech and Language pathology: 1 master student		0.1
Supervising Research Internships		
Linguistics: 1 bachelor student		0.1
Neuropsychology: 1 bachelor student		0.1
Total workload		25.5