# Language ability in patients with low-grade glioma

– detecting signs of subtle dysfunction

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‘It is the brain, the little grey cells on which one must rely.’

~ Hercule Poirot

# Abstract

*Background:* Low-grade glioma (LGG) is a slow-growing brain tumour often situated in or near areas involved in language and/or cognitive functions. Consequently, there is a risk that patients develop language impairments due to tumour growth or surgical resection.

*Purposes:* The main aim of this thesis was to investigate language ability in patients with LGG in relation to surgical treatment. Language ability was investigated using various sensitive methods such as a test of high-level language. To acquire norms for the test used to investigate high-level language, normative values were obtained in a methodological study (Study I).

*Methods:* In Study I, 100 adults were assessed using a Swedish test of high-level language (BeSS) and a test of verbal working memory. Relationships between these tests and demographic variables were investigated. In Study II, the language ability of 23 newly diagnosed LGG patients was assessed and compared with that of a reference group. The patients were also asked about self-perceived changes in language. In Study III, the language ability of 32 LGG patients was assessed before surgery, early after surgery and at three-months follow-up. The patients' language ability was compared across these assessment points and with a reference group. Finally, in Study IV, 20 LGG patients wrote a short narrative before and after surgery. The aim was to explore whether the lexical-retrieval difficulties previously seen in oral language could be seen in writing as well. Keystroke logging was used to explore writing fluency and word-level pauses. Here, too, comparisons were made between the assessment points and with a reference group.

*Results and conclusions:* Study I showed that demographic variables had a limited impact on performance on the BeSS whereas verbal working memory influenced performance. Hence verbal working memory was found to influence performance on a test of high-level language. In Study II, the LGG group performed worse than the reference group on tests of lexical retrieval. However, the majority of the newly diagnosed patients with presumed LGG had normal or nearly normal language ability prior to surgery. Only a few patients reported a change in their language ability. In Study III, most patients with a tumour in the left hemisphere manifested language impairment shortly after surgery, but the majority of them had returned to their preoperative level of performance three months after surgery. Language impairment in patients with a tumour in the right hemisphere was rare at all assessment points. In Study IV, LGG patients had a higher proportion of pauses within words before surgery than the reference group did. After surgery, the patients' production rate decreased and the proportion of pauses before words increased. Measures of lexical retrieval showed moderate to strong relationships with writing fluency both before and after surgery. The higher frequency of word-level pauses could indicate a lexical deficit. Overall, lexical-retrieval deficits were the most common type of impairment found both before and after surgery in patients with presumed LGG.

*Keywords*
Low-grade glioma, language ability, high-level language, tumour surgery, brain tumour, writing, keystroke logging

# Sammanfattning på svenska

Låggradiga gliom är en typ av hjärntumör som växer långsamt och infiltrerar frisk vävnad i hjärnan. En språklig nedsättning drabbar framför allt dem som har en tumör i den del av hjärnan som styr språket. Personer som har en hjärntumör i eller nära en del av hjärnan som är involverad i språk kan få svårt att hitta orden eller förstå vad andra säger. Denna typ av språklig påverkan kan bero på tumörens tillväxt, men det är framförallt efter kirurgisk behandling som det finns en stor risk att de med tumörer i hjärnans språkområden drabbas av en språkstörning, s.k. afasi.

Avhandlingens övergripande syfte var att undersöka den språkliga förmågan hos personer med låggradiga gliom, vilket undersöktes i tre av avhandlingens fyra studier. Studie I rörde däremot hur personer utan någon neurologisk sjukdom presterade på ett test som mäter högre språkliga förmågor, ett test som sedan användes i två av de andra studierna. I studie I deltog 100 vuxna mellan 20 och 80 år som gjorde ett test som mäter olika högre språkliga förmågor, dvs. förmågor som kräver flera komplexa språkliga och kognitiva processer.

Avhandlingens övergripande syfte sönderfaller i tre delsyften. Det första av dem, som utforskades i studie II, var att undersöka språkförmågan hos nydiagnostiserade patienter med förmodat låggradigt gliom. I denna studie testades 23 patienter med förmodat låggradigt gliom före kirurgi med ett omfattande batteri av språktester. Det andra delsyftet var att undersöka hur den kirurgiska behandlingen påverkade språkförmågan. Detta utforskades huvudsakligen i studie III, men delvis också i studie IV. I studie III undersöktes 32 patienters språkliga förmåga med samma test som i studie II före, direkt efter och tre månader efter kirurgisk behandling. Det tredje delsyftet var slutligen att utreda om olika aspekter av skrivflyt påverkas hos patienter med förmodat låggradigt gliom. Tjugo patienter skrev en berättelse på dator före och efter kirurgi, och deras skrivprocess undersöktes med ett program för tangentbordsloggning, som registrerar allt som en skribent gör på tangentbordet eller med musen, så att dessa olika handlingar sedan kan analyseras för att ta reda på vad som händer under skrivprocessen.

Avhandlingens studier visade att de flesta av de nydiagnostiserade patienterna hade en normal språklig förmåga eller endast en mindre språklig nedsättning innan de genomgått någon behandling av tumören. Många av patienterna med tumör i vänster hjärnhalva fick afasi direkt efter operationen, men majoriteten av dem återgick sedan till den språkliga nivå de befunnit sig på före operationen. Generellt var afasi eller annan språklig påverkan vanligare hos de med en tumör i vänster hjärnhalva. Några av de med tumör i höger hjärnhalva fick ett lågt resultat på ett ordflödestest – ett test som mäter en persons förmåga att komma på så många ord som möjligt i en viss kategori på en minut. Detta kunde även ses hos de med tumör i vänster hjärnhalva, men de hade även andra svårigheter såsom att mobilisera ord genom att benämna bilder.

Studien som undersökte patienternas skrivprocess visade att deras skrivflyt var lägre än referensgruppens både före och efter kirurgi. Vissa skillnader som observerades före operationen kunde förklaras av att patienterna skrev långsammare. Efter kirurgin hade patienterna lägre produktivitet i skrift, dvs. de skrev färre ord per minut. De gjorde även fler pauser före ord, vilket kan vara relaterat till ett lexikalt problem.

Studie 1 tog fram svenska normer för vuxna på testet av högre språklig förmåga. Den studien visade också att arbetsminnet hade en relation till hur man presterar på testet. Även patienterna med låggradiga gliom undersöktes med testet av högre språklig förmåga. Resultaten av dessa undersökningar var tvetydiga och det är oklart både om patienter med låggradigt gliom har problem med komplexa språkliga förmågor och om det test som användes för att bedöma dessa är lämpligt.

Då studierna i den här avhandlingen av språket hos personer med låggradigt gliom innefattade få patienter, behövs det fler studier med större grupper för att bekräfta och utveckla de slutsatser som avhandlingen kommit fram till.

# List of papers

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Antonsson, M., Longoni, F., Einald, C., Hallberg, L., Kurt, G., Larsson, K., Nilsson, T., & Hartelius, L. High-level language ability in healthy individuals and its relationship with verbal working memory. *Clinical Linguistics & Phonetics* 2016; 30: 944–958.

II. Antonsson, M., Longoni, F., Jakola, A., Thordstein, M., Tisell, M., & Hartelius, L. (2017). Pre-operative language ability in patients with presumed low-grade glioma. *Submitted for publication.*

III. Antonsson, M., Jakola, A., Longoni, F., Carstam, L., Hartelius, L., Thordstein, M., & Tisell, M. (2017). Post-surgical effects on language in patients with presumed low-grade glioma. *Submitted for publication.*

IV. Antonsson, M.[1], Johansson[1], C., Hartelius, L., Henriksson, I., Longoni, F., & Wengelin, Å. (2017). Writing fluency in patients with low-grade glioma before and after surgery. *Submitted for publication.*

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# Abbreviations

The following abbreviations are used in the thesis and in the four studies:

| | |
|---|---|
| BeSS | Bedömning av subtila språkstörningar<br>[‘Assessment of subtle language disorders’] |
| BNT | Boston naming test |
| CELF | Clinical Evaluation of Language Fundamentals |
| DDK | diadochokinesis |
| DES | direct electrical stimulation |
| DSB | digit span backward |
| DSF | digit span forward |
| FAS | a letter-fluency task (words beginning with ‘F’, ‘A’ and ‘S’) |
| fMRI | functional magnetic resonance imaging |
| HGG | high-grade glioma |
| HLL | high-level language |
| IQR | interquartile range |
| LGG | low-grade glioma |
| LH | left hemisphere |
| MRI | magnetic resonance imaging |
| OR | odds ratio |
| RG | reference group |
| RH | right hemisphere |
| SD | standard deviation |
| VAS | visual analogue scale |
| VWM | verbal working memory |

# Introduction

## Language function

Language is a unique human ability to use a complex system of conventional symbols. Any human language is a system consisting of arbitrary symbols referring to different objects, actions, emotions, concepts, etc. This system encompasses many different sub-systems, such as a system for language sounds (phonology), a system consisting of rules for how you can form words (morphology), a system of rules for how you can combine words with each other (syntax), a system for organising the words and their meaning (lexicon, semantics), and a system for how context affects the use of the language (pragmatics). Language disorders may affect some or all of these language systems, wholly or in part, and may have effects that cause communicative problems, such as difficulties finding the right word (anomia), pronunciation difficulties or difficulties understanding what other people say or mean.

Language is a higher cognitive function. As such, its neural basis is located in the brain. Although theories about language and its origin in the brain date back many centuries, the idea that specific brain areas are related to language and speech emerged in the 19th century (Code, 2016), when many discoveries were made with regard to how specific brain regions were connected with speech and language. For instance, Paul Broca's famous cases involving patients with left frontal brain damage who had no speech contributed knowledge about the involvement of the left frontal lobe in language production.

Current views on the cerebral organisation of language, which are more holistic than the earlier models, describe large-scale cortical-subcortical networks encompassing areas in both hemispheres. These networks are assumed to be task-dependent, meaning that networks involving different regions are activated depending on the linguistic task (Indefrey & Levelt 2004; Hickok & Poeppel, 2004). The left hemisphere of the brain is usually the language-dominant one. Figure 1 presents an overview of its anatomical areas. In a meta-analysis, Vigneau et al. (2006) summarises the language-related areas of the left hemisphere by stating that phonological processing involves a perceptual processing component in the temporal lobe (Heschl's gyrus and the planum temporale) and a motor component in the frontal lobe (mouth motor area). Another part of the phonological network is the fronto-parietal loop for phonological working memory, connecting frontal areas to areas in the parietal lobe (supra marginal gyrus and angular gyrus). Semantic processing involves areas in the frontal lobe (the frontal part of the inferior frontal gyrus) as well as dorsal and ventral parts of the temporal lobe. Syntactic processing involves a part of the inferior frontal gyrus (pars opercularis) but also temporal areas, which are important for sentence comprehension. Another part of the inferior frontal gyrus (pars triangularis) is linked to sentence comprehension and language production. The comprehension of sentences and texts involves the posterior part of the superior temporal gyrus.

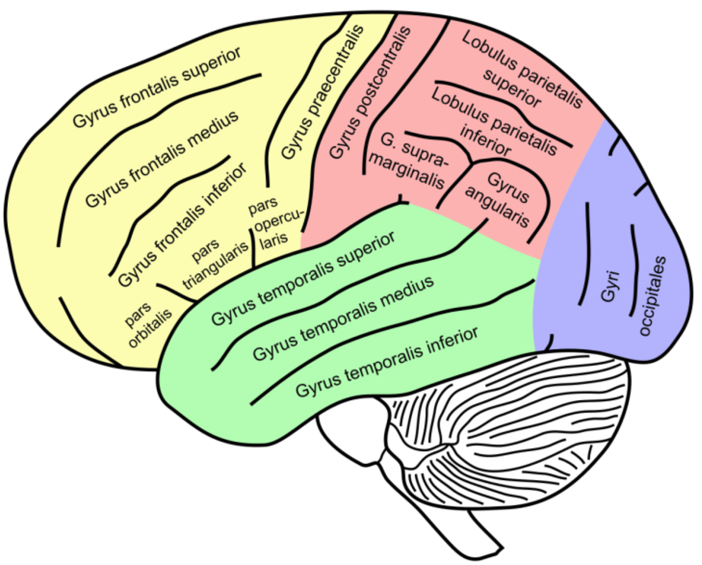


Figure 1. Overview of the left hemisphere of the brain. The different lobes of the brain are presented in different colours: yellow = frontal lobe, red = parietal lobe, green = temporal lobe and purple = occipital lobe. Source: Wikimedia Commons, the free media repository. 'Lateral view of a human brain, main gyri labelled' by NEUROtiker (downloaded on 4 October 2017).

The right hemisphere is believed to contribute to the processing of language in context. This is based on observations of unilateral activation in temporal regions during sentence- and text-processing tasks. In the context of language networks, right-hemisphere activation is often seen as co-activation with homologue areas in the left hemisphere (Vigneau et al., 2011). Lesions in the right hemisphere can result in difficulties understanding language as used in context, such as problems interpreting and using speech prosody (Lalande, Braun, Charlebois & Whitaker, 1992) and problems understanding figurative speech such as idioms (i.e. 'She's got him eating out of her hand') (Van Lancker & Kempler, 1987; Kempler, Van Lancker, Marchman & Bates, 1999).

## Acquired language impairments

Neurological conditions such as stroke, progressive neurological diseases, traumatic brain injury and brain tumours can affect the neural basis of communication and result in aphasia or cognitive-communication disorders. These conditions can also affect neural control of motor functions required for speech, causing dysarthria or apraxia of speech; these are speech impairments rather than language impairments.

Aphasia has been defined in many different ways, often with a view to either narrowing or broadening existing definitions. One usefully general definition is that aphasia is an 'impaired ability to comprehend or express linguistic symbols, or both', resulting from an acquired neurological damage (Vinson, 1999, p. 226). Symptoms of aphasia are often grouped into syndromes based on the language modalities and functions affected. For instance, aphasia types can be roughly divided into 'fluent' and 'non-fluent' aphasias. Fluent aphasias affect receptive language and can cause an impaired ability to comprehend language as well as problems with naming and with reading and writing. By contrast, persons with non-fluent aphasias have problems expressing themselves: they may have problems finding the right words and producing correct speech, owing to motor-planning deficits.

Aphasia is caused by damage to the language-dominant left hemisphere; the most common etiologic factor is stroke. Quite a few definitions, such as that of Papathanasiou and Coppens (2012), specify that aphasia is a *selective* impairment of language, but there is considerable research supporting the claim that persons with aphasia can also have other cognitive impairments such as deficits in attention, working memory or executive functions (e.g. Murray, 2012; Martin & Allen, 2008; Kalbe, Reinhold, Brand, Markowitsch & Kessler, 2005; Leśniak, Bak, Czepiel, Seniów & Członkowska, 2008). Aphasia can have a negative impact on quality of life (Cruice, Worrall & Hickson, 2010), both as regards daily activities and as regards working life. People with aphasia report a higher-than-average frequency of negative emotions such as anxiety, nervousness and depression, and previous studies have indeed shown that persons with aphasia have significantly fewer social contacts and activities than persons without aphasia (Cruice, Worrall & Hickson, 2006).

Language impairments that are associated with dementia or traumatic brain injuries are generally not called ‘aphasia’. Instead they are sometimes referred to as ‘subtle language disorders’ or ‘cognitive-communication disorders’. Traumatic brain injuries can result in cognitive problems due to reduced executive control, goal direction, attention, initiation ability and concentration (Ahlsén, 2006; Constantinidou & Kennedy, 2016). Impaired language or communication includes problems such as anomia, pragmatic difficulties, discourse problems, difficulties understanding and using abstract language, and difficulties making inferences. Language problems in dementia are also strongly linked to cognitive impairments, particularly memory problems. Depending on the type of dementia, different language symptoms can be observed. The most common type of dementia is Alzheimer’s disease, in which problems vary depending on the stage of the disease: anomia is seen early on, followed by semantic and pragmatic problems affecting discourse, while persons with late-stage dementia have global aphasia (Ahlsén, 2006). Cognitive-communication deficits can also be caused by damage to the right hemisphere (Tompkins, Klepousniotou & Scott, 2016); then they tend to include problems with prosody, discourse, pragmatics and lexical-semantic processing as well as reading and writing. Further, right-hemisphere damage can also cause cognitive impairments such as neglect, impaired attention, impaired visuo-perceptual processing, memory deficits, impaired executive functioning and an impaired self-awareness of disabilities. Unlike in the case of aphasia, the cognitive impairments found in patients with right-hemisphere damage, traumatic brain injuries and dementia are suggested to be responsible for some or all of the difficulties seen in communication.

An assessment of an acquired language impairment usually involves an investigation to identify the aspects of the language system that are affected and the functional impact of the deficits on the person’s communicative ability (Ahlsén, 2008). The symptoms observed should be linked to a possible underlying disorder, and the issue of differential diagnosis should be addressed. To assess language and communication, different types of tests are used. Psychometric tests assess different aspects of language, such as naming, word fluency, repetition or dictation tasks. These tests are standardised: they use norms to assess whether an ability level is within the normal range or deviates from it, indicating a language impairment. Other types of tests include neuro-psychological and psycho-linguistic ones, which are based on different language and cognitive theories and aim to identify the underlying dysfunction causing an impairment. There are also more functional approaches such as questionnaires aiming to assess the presence and frequency of different symptoms (e.g. word-finding difficulties) as well as methods for analysing video-recorded interactions.

Patients with such language deficits of a more subtle nature as can be seen in patients with mild traumatic brain injury (Blyth, Scott, Bond & Paul, 2012), mild aphasia and early dementia (Ahlsén, Hartelius, Laakso & Brunnegård, 2001) often perform within the normal range on language test batteries. To detect mild language difficulties, assessments of complex language are used, including tests of 'high-level language', which refers to the ability to use several complex linguistic and cognitive processes at the same time (Lethlean & Murdoch, 1997). Examples include the ability to understand *metaphors* (e.g. 'the boy does not know which leg to stand on' or 'she has taken them under her wing') and *ambiguous sentences* (sentences with several possible interpretations) and to *draw conclusions* (make inferences) about something that is not stated explicitly (e.g. 'it is really chilly in here', which, in particular circumstances, can mean 'would you please close the window?'). Cognitive abilities that are crucial for higher-level language production and processing are attention, working memory and executive functions such as the ability to plan and to solve problems (Lewis, LaPointe, Murdoch & Chenery, 1998). Difficulties with high-level language have previously been found in patients with different neurological diseases and types of right-hemisphere damage (Laakso, Brunnegård, Hartelius & Ahlsén, 2000; Berg, Björnram, Hartelius, Laakso & Johnels, 2003; Bryan & Hale, 2001). The main usefulness of high-level language tests resides in their sensitivity to subtle language/cognitive disabilities that are not captured by traditional language tests.

One Swedish test used to assess high-level language is the BeSS test (BeSS stands for 'Bedömning av subtila språkstörningar', meaning 'Assessment of subtle language disorders') (Laakso et al., 2000). In part, the BeSS is an adaptation of the Test of Language Competence (TLC) (Wiig & Secord, 1989), a test of pragmatic language which aims to assess abilities needed in conversation. The BeSS test has previously been used to assess high-level language deficits in patients with multiple sclerosis (Laakso et al., 2000) and Parkinson's disease (Berg et al., 2003). Some studies have also investigated healthy individuals' performance on the BeSS (Ahlsén et al., 2001), but there is a shortage of normative studies for certain age groups. To the best of our knowledge, no study has investigated high-level language pre- and post-surgery in patients with LGG.

Another linguistically and cognitively taxing process is *writing*. The symptoms of aphasia, such as difficulties finding the right words and combining them into syntactically and semantically acceptable phrases, may manifest themselves both in speaking and in writing. The analysis of a (final) written text can provide information about deficits in various aspects of the language system such as phonology, lexicon and syntax. Studying the writing *process* also enables the temporal patterns of language production to be investigated. Previous research into the writing process has used methods such as thinking-aloud protocols, video-recording and text analysis (Janssen et al., 1996). One problem with some of these methods, however, is that they may interfere with the writing process. Another method is to use the output of keystroke-logging software, which make it possible to study the writing process as it unfolds in real time (Flinn, 1987; Strömqvist & Karlsson, 2002; Leijten & Van Waes, 2005). For example, this enables analyses of where and how often pauses occur, which reflects a writer's level of fluency. Writing fluency and pause patterns have been found to be sensitive measures for distinguishing elderly people with cognitive impairments from elderly people without them (Leijten et al., 2014).

In a fluent writer, low-level processes such as spelling, lexical retrieval and typing are automatised, meaning that he or she may devote more cognitive effort to high-level processes related to features such as text structure and evaluation. If the automatisation of low-level processes is impaired, this may make the writing process disfluent and may also exert a negative impact on the quality of the final text (Chenoweth & Hayes, 2001; Wengelin, 2007). Disfluencies occur to some extent in all text production, but they are more frequent in persons with reading and writing disabilities (Wengelin, 2007), in persons writing in a second language (Lindgren, Spelman Miller & Sullivan, 2008) and in persons with post-stroke aphasia (Behrns, Ahlsen & Wengelin, 2008).

One possible reason why a person's writing may be disfluent is that his or her lexical retrieval is impaired. Lexical retrieval, or the ability to find the right word, is an important aspect of the 'translating part' of the writing process ('translate' as in translating ideas into texts) according to Flower and Hayes (1981; Hayes 2012). In Flower and Hayes' early model of the writing process, which has subsequently been expanded to include more aspects, three sub-processes are outlined: planning, translating and reviewing. Since the writing process is dynamic, all these sub-processes are interactive. The expanded version (Hayes, 2012) stresses the importance of cognitive functions acting as resources for the writing process, and it includes a task-schema level governing all interactions to ensure that the task goals are met.

# Low-grade glioma: classification and treatment

Low-grade glioma (LGG) is a diffusive and infiltrative type of brain tumour (Duffau & Capelle, 2004). Owing to the tumour's frequent proximity to 'eloquent' areas in the brain (i.e. areas essential for language, sensory or motor functions) (Duffau & Capelle, 2004), both tumour growth and tumour treatment may cause language deficits.

## Tumour classification and symptoms

LGGs are a type of glioma. Although some researchers believe that gliomas derive from glial cells (Kumthekar, Raizer & Singh, 2015), the origin of gliomas is still a subject of controversy in cancer research (Alcantara Llaguno & Parada, 2016). Gliomas are graded from I to IV based on histology as defined by the World Health Organization (WHO). A higher grade corresponds to a more malignant tumour. Grades I and II are categorised as LGGs whereas grades III and IV are categorised as high-grade gliomas (HGG). Gliomas account for 81% of all malignant tumours in the brain and central nervous system (Ostrom et al., 2013), and LGGs make up 15% of all primary brain tumours in adults (Sanai, Chang & Berger, 2011). While HGGs typically affect persons in their 60s, LGGs most often affect young adults (in their 40s).

An LGG is a slow-growing tumour. If not treated, it will expand by an average of 4 mm per year (Pallud et al., 2012). A first, preliminary, diagnosis is made on the basis of an MRI (magnetic resonance imaging) scan. Even if the radiographic findings suggest an LGG, the diagnosis needs to be confirmed by a histopathological examination (Forst, Nahed, Loeffler & Batchelor, 2014) – actually, up to one-third of all tumours that first appear to be LGGs are in fact HGGs (Whittle, 2004). The most common presenting symptom is seizures, occurring in 65–95% of individuals with LGG (DeAngelis, 2001). Further, headaches are typically experienced by about 27–40%, weakness/numbness/hemiparesis by 3–15% and abnormal mental status, including aphasia, confusion, impaired memory and personality change, by 10–12% (DeAngelis, 2001; Inskip et al., 2003).

Although patients with LGG have a better prognosis than those with HGG, there is a risk that an LGG may undergo anaplastic transformation: that is, malignify into an HGG (Turkoglu et al., 2013; Kumthekar et al., 2015). The reported incidence and timing of such histological upgrading varies greatly between studies: a review of clinical studies ranging back 15 years found rates of transformation between 17% and 73% and times of transformation between 2.1 and 10.1 years (Sanai et al., 2011). Factors identified as associated with an early transformation are greater pre-operative tumour volume and fast growth rate, whereas a greater resection is associated with a longer time before malignant progression. Median survival time has been estimated at 5–10 years; approximately 50–75% die of their disease (Sanai & Berger, 2012).

## Treatment of LGG

Treatments of LGGs include surgical resection, chemotherapy and radiation. In most cases of newly diagnosed LGG, surgical treatment is the primary treatment option (Tate, 2015). The benefits of surgical resection have been the subject of debate, but recent studies have associated early resection with a better outcome (Jakola et al., 2017). There is also increasing evidence that extensive resection has a positive effect on survival (Sanai et al., 2011).

Radiation is often used as post-operative treatment for patients at risk of early malignant transformation (Kumthekar et al., 2015); early post-operative radiation is associated with prolonged survival. Chemotherapy can be given at different times: at the same time as radiation, after radiation, or in case of tumour progression. Several studies have shown that the combination of radiation and chemotherapy is useful. There is no consensus as regards when to start post-operative treatments, but an increasing number of patients receive some kind of post-operative tumour treatment during the first six months (Buckner et al., 2016).

For patients with a tumour located in a language-eloquent region, awake surgery using direct electrical stimulation is generally considered as the gold standard (De Witt Hamer, Robles, Zwinderman, Duffau & Berger, 2012; De Witte & Mariën, 2013). As its name suggests, awake surgery means that the patient is kept awake during part of the surgical procedure. This enables language functions to be mapped and monitored during surgery (intra-operatively). The purpose of this mapping is to identify eloquent areas and hence guide the resection. The gold standard for intra-operative functional mapping of language is direct electrical stimulation (DES) (Penfield & Rasmussen, 1950; De Witte & Mariën, 2013). With DES, the mapping of functions is performed using a weak electric current which, when applied to the cortex, creates an abrupt, transient activation (motor activity) or inactivation (language and other higher cortical functions) that disappears with the cessation of stimulation (Whitaker & Ojemann, 1977). During functional mapping, task disruption is deemed to indicate that the cortical region stimulated is necessary for the task performed (Talacchi et al., 2013). Nowadays, stimulation of both cortical and sub-cortical sites is used in awake surgery to identify eloquent cortical areas as well as their tracts. This makes it possible to maximise the extent of resection while minimising the risk of inducing deficits (Szelenyi et al., 2010). It is also possible to map other functions than language function intra-operatively, including short-term memory, calculation and visual and visuo-spatial functions (Talacchi et al., 2013).

## Clinical outcome after surgical treatment

Most patients present with mild or no symptoms, except for seizures, before surgery. For this reason, patients with LGG usually lead a normal social and working life before tumour treatment (Moritz-Gasser, Herbet, Maldonado & Duffau, 2012), and they are expected to go back to work after surgery. In a study by Campanella et al. (2017), all fifty patients returned to their occupation or previous activity; they did so, on average, 3.8 months after surgery (standard deviation: 3.7). About 30% of the patients had experienced a change in their working duties, but only 14% of them considered this to be a consequence of their illness (specifically, cognitive limitations).

Surgery with maximum tumour resection can have a positive impact on both survival (Sanai & Berger, 2008) and seizure control (Englot, Han, Berger, Barbaro & Chang, 2012). However, surgical treatment may also affect several neurological functions and consequently exert a negative impact on quality of life. Since it is nowadays possible to tailor resections in areas relevant to motor, sensory or language functions – for example by means of intra-operative stimulation mapping – permanent deficits can be minimised (Pouratian & Schiff, 2010). Some studies have found only mild cognitive deficits in patients after surgery for brain tumours, but these findings have been attributed in part to the poor sensitivity of the screening instruments used (Robinson, Biggs & Walker, 2015). More detailed investigations of cognitive outcome following glioma surgery have shown that several cognitive abilities deteriorate after surgery, such as memory (Papagno et al., 2012; Santini et al., 2012), verbal working memory (Teixidor et al., 2007) and executive functions (Santini et al., 2012). Still, the cognitive deterioration that may be seen immediately after surgery will usually be followed by an improvement in the next few months (Satoer, Visch-Brink, Dirven & Vincent, 2016).

Further, the possible causes of impaired neuro-cognitive abilities include not only the tumour treatment as such but also the tumour itself, psychological distress and tumour-related epilepsy (including the effects of anti-epileptic medication) (Soffietti et al., 2010). The burden of epilepsy has been found to have a negative influence on well-being (Aaronson et al., 2011; Campanella et al., 2017), but when Campanella et al. (2017) explored whether various cognitive, affective and clinical factors, including the burden of epilepsy, predicted well-being in patients with LGG a few years after surgery (when they were in a stable state), only the level of depression was found to predict their well-being.

The impact of surgery on quality of life is considered to be linked to the extent of the cognitive impairments. Hence it is recommended only to remove as much of a tumour as can be done without causing a permanent impairment (Duffau & Mandonnet, 2013). Aaronson et al. (2011) investigated health-related quality of life in patients with LGG and found them to have lower ratings on six out of eight scales as well as on the mental-health component score of the SF-36 Health Survey compared with healthy people, but not compared with other cancer patients (with hematologic lymphoma or chronic lymphatic leukemia). Further, about 25% of the patients with LGG reported problems with memory and concentration. It should be noted that the patients studied had undergone various treatments, including surgery and radiotherapy, and had been diagnosed an average of 5.6 years ago. By contrast, in a study by Jakola, Unsgård & Solheim (2011), quality of life was investigated six weeks after surgery in patients with glioma. These patients had a lower quality of life than healthy individuals both before and after surgery. Although some of them experienced a decline in quality of life after surgery, this change was not statistically significant. Factors predicting a deterioration of quality of life included a worsening of motor function and language, unsteadiness and/or ataxia as well as occipital lesions.

## Language impairment in LGG patients

Depending on its localisation and characteristics, the tumour creates risks of language impairments as it grows because of the successive displacement or infiltration of language areas. However, tumour presence in such an area does not always result in a language impairment. It is noteworthy that even where a tumour is large and situated in a language area, it is common for there to be minimal or no language disturbance (Miceli, Capasso, Monti, Santini & Talacchi, 2012). Miceli et al. (2012) notes that we have learned much of what we know about the relationship between language and the brain from the stroke population. This is not very surprising, given that stroke is the most frequent cause of brain damage. However, there are several important differences between a lesion due to a stroke and a brain tumour, including in terms of onset, time course, growth mechanism and location. This may influence the prevalence of a language impairment and can also be expected to affect its character. One of the characteristics of an LGG is that it is a slow-growing tumour. This slow growth allows the brain to undertake a neural reorganisation which will vary between individuals but which has been suggested to have several functional consequences (Desmurget, Bonnetblanc & Duffau, 2007). There is extensive research about the neural plasticity and neural reorganisation of language after stroke, but little is known about such mechanisms following tumour surgery (Desmurget et al., 2007; Finch & Copland, 2014).

The language symptoms associated with LGG surgery are suggested to differ from the classic symptoms of post-stroke aphasia (Bello et al., 2007).

Even so, many studies of LGG patients use test batteries designed to assess aphasia due to stroke (e.g. Ilmberger et al., 2008; Duffau, Peggy Gatignol, Mandonnet, Capelle & Taillandier, 2008; Yordanova, Moritz-Gasser & Duffau, 2011; Bizzi et al., 2012). This has been criticised on the ground that the level of difficulty of such test batteries is often too low to enable the detection of mild or subtle disorders (Papagno et al., 2012; Finch & Copland, 2014). Instead, it has been suggested that sensitive and in-depth tasks should be used, with additional tasks depending on tumour location (Papagno et al., 2012). Miceli et al. (2012) suggests the use of test batteries focusing on the assessment of specific language abilities rather than on the detection of specific neuro-psychological profiles.

Attempts have indeed been made to design specific test batteries for this group. The Milano-Bicocca Battery (MIBIB) (Papagno et al., 2012) is a neuro-psychological evaluation designed to assess clinical outcomes in neuro-oncology. It includes tasks measuring language, apraxia, memory, visuo-constructional abilities and executive functions. Other types of test batteries, such as the Right Hemisphere Language Battery (RHLB) (Bryan, 1989), have also been evaluated for their utility and sensitivity in (right-hemisphere) brain-tumour patients (Thomson, Taylor & Whittle, 1997). However, despite the criticism levelled at the use of insensitive measures and the attempts made to design new test batteries, there is no consensus about what a language assessment for brain-tumour patients should consist of nor how and when it should be performed.

## Tumour effects on language

Language outcome after tumour treatment in LGG patients, as well as in patients with HGG or other types of brain tumours, has predominantly been investigated in patients with a tumour in or near language-eloquent areas of the brain selected for awake surgery. In studies including LGG patients as well as other brain-tumour patients, language impairment is reported to occur in 10.4–36.4% of patients before surgery (Bello et al., 2007; Sanai, Mirzadeh & Berger, 2008; Ilmberger et al., 2008; Duffau et al., 2008). The differences in prevalence may be attributed to a number of reasons. The most important one is the inclusion of heterogeneous patient groups, but the use of different assessment tools is probably also an important part of the explanation.

The effect on language has been explored in a few studies investigating language impairment in newly diagnosed brain-tumour patients who had not yet undergone treatment. Several studies have shown that poor performance on word-fluency and/or naming tests is a common impairment (e.g. Ek, Almkvist, Wiberg, Stragliotto & Smits, 2010; Satoer et al., 2012; Racine, Li, Molinaro, Butowski & Berger, 2015; Satoer, Vincent, Smits, Dirven & Visch-Brink, 2013). Satoer et al. (2013), investigating the spontaneous speech of patients with glioma, found that, before surgery, patients with LGG had a higher frequency of incomplete sentences than a matched control group. Additional analyses revealed that the sentences were incomplete mainly because of the exclusion of content words – a finding which also suggests the existence of early lexical-retrieval difficulties in patients with glioma.

Studies investigating surgical outcome in patients with gliomas in a language-eloquent area of the brain have found a worsening in their language ability immediately after surgery but also a high degree of recovery in the first few months following surgery (Bello et al., 2007; Ilmberger et al., 2008; Duffau et al., 2003; Duffau, Moritz-Gasser & Gatignol, 2009; Duffau et al., 2008; Santini et al., 2012; Sanai et al., 2008). There are few studies investigating the long-term effects on language more than six months after surgery. Satoer et al. (2014) found a permanent deterioration of semantic fluency but an improvement of letter fluency and naming at a long-term follow-up, twelve months after surgery. Sarubbo et al. (2011) followed twelve patients with an LGG in an eloquent area for three years after surgery, finding that no patient's language ability was worse at the last follow-up than it had been before surgery.

As mentioned, many studies investigating language in glioma patients include patients with tumours of various grades, patients with recurrent tumours and/or patients who have already undergone treatment. All of these factors may cause language impairment. How, and to what extent, tumour characteristics such as size, grade and location affect language is not entirely known.

Whether or not tumour size or volume influences language performance is not clear. In a few studies, tumour volume has been found not to influence language performance (Satoer et al., 2013; Satoer et al., 2012), but Talacchi, Santini & Gerosa (2011) found a relationship between cognitive impairment (including impaired word fluency) and tumour volume when investigating cognition in glioma patients. However, one limitation of all of these studies was the small sample sizes, which may have influenced the results.

The effect of tumour location has been investigated in terms of location in language-eloquent versus non-language-eloquent areas. It has also been examined with respect to more specific brain regions, for example in studies investigating language function following a tumour in the temporal lobe (Campanella et al., 2009), mesial frontal lobe (Chainay et al., 2009), uncinate fasciculus (Papagno et al., 2011) and insula (Duffau et al., 2009). Still, studies investigating language in patients with tumours outside language areas are scarce. One reason for this might be that such patients are generally not selected for awake surgery, which is what most studies focus on. However, Satoer et al. (2014) found that patients with a tumour in a language-eloquent area and patients with a tumour in a non-language-eloquent area had comparable results both before and after surgery. Yordanova et al. (2011) found an early post-operative worsening of language function in patients with tumours in non-eloquent areas in the left hemisphere, paralleling findings from patients with tumours in language areas. A few studies have also investigated language deficits in patients with a tumour in the right hemisphere, finding poor word fluency (Papagno et al., 2012) and an impaired naming ability (Thomson et al., 1998).

Finally, when it comes to tumour grade, many studies include both LGG and HGG (e.g. Bello et al., 2007; Santini et al., 2012; Ilmberger et al., 2008) but only a few make comparisons between them. Bello et al. (2007) found no relationship between tumour grade and post-operative language deficit when investigating 88 patients with LGG or HGG undergoing awake surgery for resection of a tumour in a language area. Nor did Satoer et al. (2014) find any effect of tumour grade when comparing deviant performance on naming and word-fluency tests in glioma patients, even though a previous study (Satoer et al., 2013) had found that tumour grade partly influenced the spontaneous speech of glioma patients

## Language assessment of LGG patients in a Swedish context

In Sweden, language assessment before and after surgery for brain-tumour patients has been carried out only in the past few years, and not at all hospitals treating such patients. Such assessments have been introduced at a few Swedish hospitals following the elevation of awake surgery to the status of the primary treatment option for patients with a glioma in an eloquent area. Interviews with representatives of Swedish university hospitals reported in an unpublished master's thesis from 2014 (Andersson & Sandström, 2014) showed that six out of seven of these hospitals carried out surgery on brain-tumour patients and that four of them performed awake surgery while one was planning to start (and has since done so). In 2016, examinations of language before and after surgery were carried out on a regular basis at three of Sweden's university hospitals. At two of them, this constituted clinical routine, but only for patients selected for awake surgery with intra-operative language monitoring.

At the Sahlgrenska University Hospital in Gothenburg, where data collection for this thesis was carried out, language assessments of patients with LGG were not normally performed before 2014. Language assessment of LGG patients was initiated there because the Department of Neurosurgery had started performing awake surgery on patients with tumours close to language or motor areas. The Sahlgrenska University Hospital commissioned a health-technology assessment (HTA) report in 2012 (Nilsson et al., 2012) to assess the quality of the current evidence for performing intra-operative cortical stimulation in brain-tumour surgery. Following the HTA report, this procedure was implemented in 2013. According to the report, the new routine might increase the cost of surgery, mainly owing to an increase in the duration of the surgical intervention and the involvement of other professions. However, given that several studies had found increased survival and decreased morbidity, it might reduce the overall costs owing to a reduction of the requisite sick-leave period and of the need to care for disabled patients. From a socio-economic perspective, a further beneficial aspect would be the increase in expected working years. Language assessment before and after surgery in patients with LGG at the Sahlgrenska University Hospital began concurrently with the initiation of this thesis project in late 2014, but it has not yet been implemented as a clinical routine.

## Summary of the introduction

Previous studies investigating language ability in patients with LGG in relation to surgery have focused on tumours in language areas in the left hemisphere. These studies have found predominantly mild language impairments before surgery; a few of them report permanent deficits. Studies investigating language ability in patients with tumours in non-language-eloquent areas are scarce. Further, recent studies have questioned the sensitivity of the test instruments currently used to detect language impairment. Other methods, such as tests of high-level language and investigation of the writing process, could perhaps provide additional, more sensitive measures of language impairment and shed light on how a language impairment could affect a functional task such as writing.

# Aims

The main aim of this thesis was to investigate language ability in patients with low-grade glioma (LGG) in relation to surgical treatment. Language ability was investigated using various sensitive measures such as a test of high-level language. One additional aim was to obtain norms for the test used to investigate high-level language; this was explored in Study I.

The specific aims of each of the four studies included in the thesis were:

I. To investigate how adults without any known neurological disease perform on a test of high-level language and how demographic variables and verbal working memory are related to their performance.

II. To investigate language ability in newly diagnosed patients with presumed LGG.

III. To investigate language outcome following surgery in patients with presumed LGG, using a comprehensive and sensitive language assessment.

IV. To explore whether writing fluency is affected in LGG patients before and after surgery and whether it is related to performance on tasks of oral lexical retrieval.

# Materials and Methods

## Participants

Table 1 presents an overview of the characteristics of the participants in the four studies. In brief, the participants in the main project (Studies II–IV) were 32 patients with presumed low-grade glioma (LGG) scheduled to undergo surgery or biopsy at the Sahlgrenska University Hospital, Gothenburg, Sweden. In addition, 100 adults without any known neurological disease participated in Study I, which investigated how adults perform on a test of high-level language. These 100 adults also constituted the basis for the selection of a group-matched reference group used in Studies II and III. Further, there was a second reference group, consisting of 31 healthy adults with no self-reported neurological disease, who participated in Study IV.

Table 1

Overview of study design and participants in Studies I–IV

| *Study* | *Participants* | | | |
|---|---|---|---|---|
| | *Study group and reference group* | *Sex* | *Age in years (mean)* | *Educational level in years (mean)* |
| I | 100 participants | 47♂ 53♀ | 20–79 (50.2) | 7–24 (14.8) |
| II | 23 patients with presumed LGG | 15♂ 8♀ | 24–67 (44.7) | 11–22 (14.8) |
| | 80 participants (reference group) | 42♂ 38♀ | 24–67 (46.0) | 10–24 (15.1) |
| III | 32 patients with presumed LGG | 20♂ 12♀ | 24–67 (45.6) | 9–22 (14.5) |
| | 80 participants (reference group) | 42♂ 38♀ | 24–67 (46.0) | 10–24 (15.1) |
| IV | 20 patients with presumed LGG | 12♂ 8♀ | 25–62 (45.8) | 9–22 15.0 |
| | 31 participants (reference group) | 14♂ 17♀ | 26–62 (45.5) | 11–21 (16.1) |

## Study I

A total of 104 participants were initially recruited to the study. Four of them were later excluded (one owing to neurological disease and three owing to current reading and writing difficulties), yielding a total of 100 participants in Study I. The participants were mainly recruited from various workplaces and organisations. One explicit aim was to achieve a high level of diversity in terms of socio-economic status, level of education, age and sex. The inclusion criteria were: age 20–80 years, no known neurological disease, no current reading or writing difficulties, adequate hearing and vision, and Swedish as first language (or one of several first languages).

## Studies II–IV

The patients with LGG recruited to the project were consecutive patients with presumed LGG who presented at the Department of Neurosurgery of the Sahlgrenska University Hospital in Gothenburg, Sweden, between November 2014 and September 2016. Their diagnosis was based on MRI scans, physical examination and medical history. Demographic variables for the participants are presented in Table 1.

The inclusion criteria for participants in Studies II–IV – besides a diagnosis of presumed LGG – were age over 18 years and absence of moderate or severe developmental language or cognitive disorders. The participants in Study II were 23 patients with presumed LGG and 80 adults without any known neurological disease serving as a reference group. The participants in Study III were 32 patients with presumed LGG and the same reference group as in Study II. In Study IV, the participants were 20 patients with presumed LGG. Additional inclusion criteria in Study IV were Swedish as native language and no developmental reading or writing difficulties. Study IV also included a different reference group from Studies II and III; this group consisted of 31 healthy adults with no self-reported neurological disease.

Histological examination after surgery revealed that some of the patients (five in Study II, nine in Study III and eight in Study IV) had a tumour of a higher grade (i.e. > 2, meaning that their correct diagnosis was HGG rather than LGG). Since the criterion for inclusion was *presumed* LGG, all patients were included in the analyses. However, additional analyses excluding the patients with HGG were added to Study II.

# Materials

An overview of the tests and methods included in Studies I–IV is provided in Table 2. The materials consisted of results on individual tests measuring specific abilities such as lexical retrieval and language comprehension as well as two test batteries, one designed to assess aphasia and one designed to assess high-level language.

Table 2

Language tests included in Studies I–IV

| TESTS/METHODS | | STUDY | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | I | II | | III | | | | IV | | |
| | | Healthy adults | LGG | RG | LGG | | | RG | LGG | | RG |
| | | | pre | | pre | post | 3 m | | pre | 3 m | |
| Aphasia: | A-ning | - | x | - | x | - | x | - | x | x | - |
| HLL: | BeSS | x | x | x | x | - | x | x | - | - | - |
| Morphological ability: | Sentence analysis | - | x | x | x | - | x | x | - | - | - |
| | Morphological completion | - | x | x | x | - | x | x | - | - | - |
| Word finding: | BNT | - | x | x | x | x | x | x | x | x | - |
| Word fluency: | FAS | - | x | x | x | x | x | x | x | x | - |
| | Animals | - | x | x | x | x | x | x | x | x | - |
| | Verbs | - | x | x | x | x | x | x | x | x | - |
| Language comprehension: | Token test | - | x | - | x | x | x | - | - | - | - |
| Verbal working memory: | Digit span | x | - | - | - | - | - | - | - | - | - |
| Writing Process: | Keystroke-logged writing tasks | - | - | - | - | - | - | - | x | x | x |

Further, the materials consisted of the output from a writing task carried out using special software designed to explore the writing process. In addition, the patients were asked whether they had experienced any changes in their language, speech or communication before and after surgery.

In Studies II–III, most tests were administered both to the patients with presumed LGG and to the patients in the reference group. The reference group in Studies II and III did not undergo the A-ning or Token tests because of their shorter testing session. In Study IV, the participants in the reference group were not tested using any language tests besides the keystroke-logged writing tasks used to investigate the writing process.

## Language tests

*A-ning* (Werner & Lindström, 1995)
A-ning is a Swedish standardised test battery designed to diagnose aphasia. The test provides both a profile of the aphasia symptoms and an indication of the degree of severity. It consists of seven sub-tests addressing the following: informative speech, repetition, auditory comprehension, reading comprehension, reading aloud, dictation and informative writing. In this thesis, A-ning was primarily used as a global measure of aphasia.

*BeSS* (Laakso et al., 2000; version from Berg et al., 2003)
The BeSS test (BeSS stands for 'Bedömning av subtila språkstörningar', i.e. 'Assessment of subtle language disorders') is designed to detect difficulties in different high-level language abilities, including the ability to understand abstract language such as metaphors and the ability to make inferences, i.e. to draw conclusions from information not explicitly stated.

The BeSS is in part an adaptation of the Test of Language Competence (TLC) (Wiig & Secord, 1989), which was developed for children and adolescents and is used as a test of pragmatic language aiming to assess abilities needed in conversation. The TLC includes tests of comprehension of ambiguous sentences and of the ability to make inferences, explain figurative language and recreate sentences. The BeSS includes similar tasks, but it also tests the ability to repeat long sentences, to define words and to understand metaphors and complex sentences. The main usefulness of tests of high-level language such as the BeSS resides in their sensitivity to subtle language/cognitive disabilities that are not captured by traditional language tests. The BeSS has been used to assess difficulties with high-level language in patients with other neurological diseases such as multiple sclerosis and Parkinson's disease (Laakso et al., 2000; Berg et al., 2003).

The BeSS comprises seven sub-tests measuring different complex language abilities:

1. Repetition of long sentences
The subject is asked to repeat sentences between 9 and 16 words in length verbatim. The sentences consist of main clauses and subordinate clauses. The complexity of the sentences is such that they could be found in a daily newspaper or a contemporary novel.

2. Recreating sentences
The subject is asked to create an utterance using three words and a context presented to him or her. To receive the maximum score, a sentence has to be deemed syntactically, semantically and pragmatically correct.

3. Making inferences
The subject is presented with texts both in writing and verbally. He or she is then asked to answer questions about information that is not explicitly stated in the text.

4. Comprehension of logico-grammatical sentences
The subject is asked to answer questions or to follow verbal instructions. The questions or instructions consist of sentences with complex logical or grammatical features such as double negation, inverted word order or multi-step instructions.

5. Comprehension of (lexically and syntactically) ambiguous sentences
The subject is presented with sentences containing lexical or syntactic ambiguities. The sentences are presented both visually and verbally. The task is to give two different explanations for each sentence.

6. Comprehension of metaphors
The subject is presented with sentences containing metaphorical expressions and asked to explain their meaning. The sentences are presented both visually and verbally.

7. Word definitions
The subject is presented with ten words and asked to give a definition of (or a synonym for) each of them. The words are presented both visually and verbally.

*Morphological completion* and *Sentence analysis* (Elbro, 1990)
Both the test of morphological completion and that of sentence analysis measure morphological ability. In the morphological-completion test, the subject is asked to complete a word with one morpheme missing either at the end or at the beginning. The sentence-analysis test consists of eighteen sentences, between two and nine words long. The sentences are presented orally. The subject is asked to repeat each sentence and then count the number of words in it.

*Boston naming test* (Kaplan & Goodglass, 1983)
The Boston naming test (BNT) consists of 60 pictures representing different objects to be named. In the present study, the BNT was presented digitally on a laptop computer (digitalisation of picture material with the permission of the copyright owner, picture material from: Kaplan, Goodglass & Weintraub, 2001). The test was administered and scored in accordance with Tallberg (2005).

*Word fluency* (Spreen & Benton, 1969)
Tests of verbal word fluency measure a person's ability to generate words within a certain category during a limited time. This is regarded as a test of both language and executive processing. In this case, letter-based and semantic fluency tasks were used. The letter-fluency task used the categories 'F', 'A' and 'S' (meaning that the subjects were asked to produce words beginning with those letters) (Spreen & Benton, 1969) and the semantic-fluency task used the categories of animals and verbs. Administration and scoring were performed in accordance with Tallberg, Ivachova, Jones Tinghag and Östberg (2008).

## Subjective language ability

At the pre-operative assessment (and post-operatively), all patients were asked whether they themselves had experienced any change in their language, speech or communication. The question was worded as follows (my translation from Swedish): 'Have you experienced any change in your communication, language or speech?' All answers were written down. If a patient was uncertain, he or she was asked to elaborate. The pre-operative answers to this question were included only in Study II, which investigated language ability in newly diagnosed patients with presumed LGG. The post-operative answers were not analysed in any of the studies.

## Writing tasks

To investigate writing fluency in Study IV, written narratives produced using the keystroke-logging software ScriptLog were collected. ScriptLog records the nature and timing of all actions taken on the keyboard and using the mouse.

The patients performed two writing tasks, a copy task and a narrative task. The copy task consisted of a well-known Swedish proverb, 'Bättre sent än aldrig' (English: 'Better late than never'), which the participants were asked to repeat in writing twelve times. The narrative task was picture-elicited. Two different sets of elicitation pictures were used before and after surgery, to avoid a learning effect. Each picture set consisted of six pictures obtained from two picture books for children called *Frog, where are you?* (Mayer, 1969) and *One frog too many* (Mayer & Mayer, 1975). These short versions of the book have been tested and found to elicit comparable Swedish-language narratives with regard to text length, holistic text quality and typing speed in children (Lindström, 2009; Egevad, 2009).

## Tests of verbal working memory

A digit-span task from the Clinical Evaluation of Language Fundamentals: Version 4 (CELF 4) (Swedish version: Semel, Wiig & Secord, 2013) consisting of both digit span forward tasks and digit span backward tasks was used to assess verbal working memory. In both types of tasks, digit spans between two and eight or nine digits in length are read out to the subjects, who are then asked to repeat them back, either in the same order or backwards. Digit span forward tasks test the storage capacity of the verbal working memory, i.e. the capacity of the phonological loop (Baddeley, 2000). Digit span backward tasks require both storage and manipulation; this is therefore often referred to as a measure of complex working memory. In Study I, both digit span forward and digit span backward were considered measures of verbal working memory.

# Procedures and data analysis

## Data collection

### Study I

The participants in Study I (a selection of whom also made up the reference group in Studies II and III) were tested by five final-year students on the Speech and Language Pathology Programme of the University of Gothenburg. The students conducted the testing in pairs, with one student administering the test and the other one observing; however, both students scored the answers.

### Studies II–IV

Data collection was carried out collectively for Studies II–IV between November 2014 and December 2016. The patients were tested at four time points: before surgery, soon after surgery, at three-months follow up and at twelve-months follow-up. All tests were performed by the author. When data collection ended, all patients had been offered a three-months follow-up. Since only approximately half of the patients had been offered a twelve-months follow-up, data from the twelve-months follow-up were not included in any of the studies (but a summary of these data is given at the end of the Results section).

The testing before surgery and at follow-up after three (and twelve) months consisted of two sessions lasting two or three hours each, with a lengthy break between them. The patients were assessed using the language tests presented in Table 2 and a narrative-writing task in which their writing process was recorded using keystroke logging. The early post-operative assessment was shorter and included only the BNT, word-fluency tasks and the Token test. All tests were video-recorded to make it possible to assess some of them at a later time and to double-check cases of uncertain scoring.

At the pre-operative assessment, all patients were asked questions about their background, working life and reading habits, and they were asked whether they had experienced any changes in their language, speech or communication. Not all of this background information was included in the studies, but the answers to the question on subjective experiences of change were analysed in Study II. This question was also asked at the follow-up assessments, but the related data were not included in any of the studies. Besides performing language tests as set out in Table 2, the patients (both before surgery and at the three months follow-up) also completed a spontaneous-speech task and a test of speech-motor performance and filled in a VAS questionnaire with questions about their communication. This was not included in any of the studies but collected in order to be analysed in future research.

Data concerning tumour characteristics were derived from patient records. Tumour localisation was determined by a neurosurgeon using T2-weighted/FLAIR (Fluid-Attenuated Inversion Recovery) images, a type of magnetic resonance imaging. The neurosurgeon was blind to the language-test results of the individual patients. Language-eloquent regions were defined according to Chang et al. (2008) as superior temporal, inferior frontal, insula and inferior parietal areas in the left hemisphere. Based on this definition, the patients' tumour locations were divided into three groups for the purpose of this thesis. The first group were patients with a tumour in language-eloquent areas in the left and presumed dominant (left) hemisphere. The second group consisted of patients with a tumour in non-language-eloquent areas in the presumed dominant (left) hemisphere. The third and final group were patients with a tumour in the presumed non-dominant (right) hemisphere. Two patients were left-handed; fMRI examination of them showed that they both had their language function lateralised to the left hemisphere.

## Data analysis

In Study I, the final-year students who collected the data also scored the tests according to the scoring criteria provided for each sub-test. These students were supervised by the author and had been trained to administer and score the test. They also took part in a pilot study carried out prior to data collection, following which the scoring criteria were revised and a few minor changes were made to the test. Two students were present during each testing session and each of them scored the subject's performance individually; after the test, a consensus assessment was performed. All steps of data collection and data analysis were supervised by the author.

In Studies II–IV, all language tests were scored and analysed by the author. Test scoring was in all cases based on the respective test manuals. The answers to the question of whether the patients had experienced any change in their communication, language or speech (which were examined in Study II) were categorised into three categories: 'yes' (patients who clearly had experienced a change), 'uncertain' (patients who were not sure but believed they had experienced some subtle changes, such as difficulties finding words) and 'no' (patients who clearly had not experienced any change).

In Studies II and III, to provide an overview of the individual patients' performance on the tests, scores on the BeSS, the BNT and the word-fluency tasks were transformed into z-scores using Swedish clinical norms. For the z-transformed tests, a cut-off of –2 SD was chosen as an indication of impairment. For the A-ning and Token tests, it was not possible to carry out a z-transformation. Instead, different degrees of severity were defined. The aphasia index derived from A-ning was analysed according to the manual, and the following interpretative categories were used: a mean of 4.5 was taken to correspond to mild aphasia, a mean of 3.2/3.4 to moderate or moderately severe aphasia, a mean of 1.8 to severe aphasia and a mean of 0.5 to very severe aphasia. As for the Token test, its standardisation provides a cut-off, meaning that scores below that cut-off indicate difficulties in language comprehension. Since the manual provides no categorisation of the level of difficulty, a severity grading based on scores on the test, which consists of five sections with increasing difficulty, was used. The various severity levels were defined as corresponding to scores in the following manner: normal: ≥ 33 points; mild deficit: 20–32 points; moderate deficit: 7–20 points; and severe deficit: < 7 points.

The analyses of ScriptLog data in Study IV were performed by the other joint first author of that study. The primary measure used to investigate writing fluency was burst length, i.e. the mean number of characters produced between pauses. Other measures were also compared, including median inter-key interval, production rate, word-level errors and word-level pauses.

Measures analysed in the writing process:

*Burst length*
Burst length was the primary measure of writing fluency. It was defined as the mean number of characters produced in 'linear' text (i.e. all text produced, not the final text after editing) between pauses longer than 2 seconds.

*Production rate*
The production rate measures overall productivity and is defined as the total number of words in the final text divided by the total time spent on the task.

*Median inter-key interval*
The median inter-key interval is a measure of typing speed, defined as the median time between two characters within a word.

*Word-level pauses*
Word-level pauses are pauses before, within and after words. The measure was defined as the number of inter-key intervals (pauses) longer than 2 seconds before/within/after words divided by the total number of inter-key intervals before/within/after words.

*Word-level errors*
Word-level errors was defined as the number of misspelled words divided by the total number of words in the final text. No distinctions were made between different types of spelling errors.

*Typing speed (median inter-key interval in the copy task)*
Typing speed in the copy task was defined as the median time between two characters.

## Statistical analysis

A variety of statistical methods were used in the different studies. Because the groups studied were generally small and because the data tended to be skewed, the tests used to explore differences between groups and relationships between variables were predominantly non-parametric in nature. To investigate differences between the LGG group and the reference group, the Mann–Whitney U test for independent samples or the independent *t*-test was used. Comparisons before and after surgery were made using the Wilcoxon rank-sum test.

In Studies I and III, Bonferroni corrections were used given the existence of multiple comparisons and correlations. Because of the more explorative nature of Studies II and IV, no corrections were made in those studies. In Study I, multiple-regression analysis was used to explore the relationships between BeSS performance, the demographic variables and the digit-span task. In Study IV, logistic-regression models were used to analyse the difference between the patient group and the reference group in terms of the proportion of word-level pauses, controlled for typing speed.

IBM SPSS Statistics version 20 was used as a computational tool for most analyses. In Study IV, the SAS statistical software version 9.3 (SAS Institute Inc., Cary, N.C., USA) was used to perform logistic regressions.

## Reliability

In Study I, both inter- and intra-rater reliability was calculated. This was done using the intra-class correlation coefficient (ICC), adapted to the two-way mixed model with absolute agreement. Average measures (AM) were used for inter-rater reliability and single measures (SM) for intra-rater reliability. This was calculated on five randomly selected recordings (5%) for inter-rater reliability and on 20 randomly selected recordings (two from each test-leader constellation) (20%) for intra-rater reliability. The results from these calculations are presented in Study I.

Neither intra- nor inter-rater reliability was calculated in Studies II–IV. This was because the tests used were standardised and had previously been investigated for both reliability and validity. However, to ensure that all scoring and testing was performed in accordance with the manual, all video-recorded tests were viewed by the author afterwards. Whenever uncertainties arose in the scoring, this was noted to ensure that all cases involving the same kind of uncertainties could be viewed together or compared with other patients' answers and then consistently scored. To ensure that the author was consistent in her early assessments compared with later ones, the first testing sessions were re-assessed to check for assessor's drift.

Whenever uncertainties arose that could not be resolved by reference to the manuals, the author discussed the issue with her supervisors. For the BeSS test, which does not have a manual except for the instructions for each subtest, the students who scored the test wrote down instructions for how they should interpret the scoring in case of uncertainties. These additional instructions were followed when testing the patients. The author also looked at samples from the reference group (i.e. the subjects in Study I) in order to check that the scoring had been performed consistently.

# Results

## Study I

*High-level language ability in healthy individuals and its relationship with verbal working memory*

The specific research questions in Study I were:

– How do healthy adults aged 20–80 years perform on the BeSS test and how is their performance related to demographic factors such as sex, age and level of education?
– How is performance on the BeSS related to verbal working memory?

The results of Study I represent norms for the BeSS test for adults between 20 and 80 years old. The mean score on the BeSS for all participants was 178.1 (SD = 17.4, range = 128–200). However, since the correlation analyses revealed that level of education had a positive relationship with total scores on the BeSS which almost reached the Bonferroni corrected-significance level, it was decided to present separate norms for three different educational groups. Analysis of scores broken down by educational group showed that the group with elementary/upper-secondary school ($N$ = 29) had a mean of 173.7 ($SD$ = 15.1), that with a post-secondary education ($N$ = 27) had a mean of 175.4 ($SD$ = 18.6) and that with higher education ($N$ = 44) had a mean of 182.8 ($SD$ = 17.3). Further, age was found to exert a negative influence on the sub-test relating to comprehension of logico-grammatical sentences; hence, norms were also presented for three different age groups: 20–39, 40–59 and 60–79 years. In all, however, the demographic variables had little influence on test performance, whereas the measures of verbal working memory were moderately correlated to five of the seven subtests (repetition of long sentences, recreating sentences, comprehension of logico-grammatical sentences, comprehension of ambiguous sentences and word definition).

To further explore the relationships between the demographic variables, verbal working memory and BeSS scores, explorative forward stepwise regression analyses were performed. The procedure for the regression model is described in detail in Study I. The regression model for the BeSS had digit span forward, digit span backward and years of education as unique predictors (adjusted R2 = 0.35, F = 18.84, $p < .001$), meaning that better performance on digit span forward and digit span backward and more years of education were associated with a higher (better) score on the BeSS. Sex, age, education and/or verbal working memory all contributed to models for the different sub-tests, except the sub-test of making inferences. Sex was as a unique contributor to the model for repetition of long sentences in that female sex was associated with better performance on that sub-test. Age was a unique contributor to two models (comprehension of logico-grammatical sentences and comprehension of metaphors). Digit span forward was a unique contributor to four models (repetition of long sentences, recreating sentences, comprehension of metaphors and word definitions) and digit span backward was a unique contributor to three models (repetition of long sentences, comprehension of logico-grammatical sentences and comprehension of ambiguous sentences). Education was a candidate for three of the regression models, but it did not contribute as a unique contributor to any of them.

# Study II

*Pre-operative language ability in patients with presumed low-grade glioma*

The specific research questions in Study II were:

– Do patients with presumed low-grade glioma (LGG) differ in performance on a set of language tests compared with a matched reference group?
– Does the occurrence of language impairment differ depending on whether the tumour is located in a language-eloquent area?
– Have the patients experienced any change in language, speech or communicative ability?

In Study II, the patients with presumed LGG (*N* = 23) differed significantly from the reference group (*N* = 80) on three tests. On two of them, the BNT and the word-fluency test relating to Animals, the patients performed worse than the reference group. There was also a significant difference between the presumed-LGG group and the reference group on the BeSS sub-test relating to Comprehension of metaphors, but in this case the patients performed better than the participants in the reference group.

In an additional analysis excluding patients with high-grade glioma, similar results were found for the BNT and the Comprehension of metaphors sub-test, but the difference in the Animals word-fluency measure was no longer significant.

The patients' scores on each test were compared with the Swedish norms that are used in clinical practice. Patients who performed below the cut-off level for impairment on at least one test or sub-test were found in all three tumour-localisation groups. A total of seven of the 23 patients (30.4%) performed below the cut-off level on at least one test or sub-test. The corresponding percentage for the reference group was similar: 27.5%. Table 3 presents an overview of the numbers of patients who performed below the cut-off level and their responses to the question as to whether they had experienced a change in their language or communication.

Table 3

Summary of the results of Study II as regards research questions 2 and 3

| Tumour location | Number of patients with impaired test performance (tests with impaired scores) | Subjective change |
|---|---|---|
| Language-eloquent area (*N* = 7) | 2 (BeSS, BNT, word fluency) | 2 Uncertain<br>5 No |
| Non-language-eloquent area (*N* = 9) | 2 (BeSS, Token test) | 1 Yes<br>2 Uncertain<br>6 No |
| Right hemisphere (*N* = 7) | 3 (BeSS, Token test) | 1 Yes<br>6 No |
| All patients (*N* = 23) | 7 (30.4%)<br>(BeSS, BNT, word fluency, Token test) | 2 Yes<br>7 Uncertain<br>17 No |
| Reference group (*N* = 80) | 22 (27.5%)<br>(BeSS, BNT, word fluency, Morphological completion, Sentence analysis) | - |

# Study III

*Post-surgical effects on language in patients with presumed low-grade glioma*

The specific research questions in Study III were:
– How do patients with presumed low-grade glioma (LGG) in either the left hemisphere (LH) or the right hemisphere (RH) of the brain perform on a set of language tests before surgery, compared with a reference group?
– How do patients with presumed LGG in either LH or RH perform on a set of language tests early after surgery and at three-months follow-up compared with their pre-operative test results?
– How does tumour location influence language impairment in individual patients before and after surgery?

The pre-operative performance of the patients with LGG was worse than that of the reference group on three tests: the BNT, Animals and Verbs. When the patients with a tumour in LH or RH, respectively, were analysed separately, the same differences were seen for the patients with a tumour in LH whereas no significant differences were found between the patients with a tumour in RH and the reference group.

After surgery, at the early post-operative assessment, the patients with a tumour in LH performed worse on all language tests than they had done before surgery, whereas no significant changes were seen in the patients with a tumour in RH. Three months after surgery, the patients with a tumour in LH had improved and performed worse than before only on the FAS word-fluency measure. For the patients with a tumour in RH, no significant change was seen between the baseline and three months after surgery.

The patients' scores before and after surgery on tests measuring aphasia, lexical retrieval, language comprehension and high-level language were compared with norms (see overview in Table 4). Before surgery, four patients had mild aphasia; all of them had a tumour in a language-eloquent area. Eight patients had a deficit in lexical retrieval; they also all had a tumour in a language-eloquent area. Four patients had a mild language-comprehension deficit; their tumours were in different locations. Finally, three patients, all with a tumour in a language-eloquent area, had a high-level language deficit (one mild and two severe).

Immediately after surgery, at the early post-operative assessment, 68.8% (22 out of 32) of the patients had a lexical-retrieval deficit and/or a language-comprehension deficit. The degree of severity ranged from mild to severe. The majority of the deficits were found in the group with a tumour in a language-eloquent area, but five of the nine patients with a tumour outside language-eloquent areas in LH also had a language impairment. Three patients with a tumour in RH had a mild lexical-retrieval deficit.

Table 4

Overview of the patients' language status before and after surgery

| | Pre-op | | | | Early post-op | | 3 months post-op | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Tumour location | A | LR | LC | HLL | LR | LC | A | LR | LC | HLL |
| Language-eloquent area in LH: | 4 mi | 8 mi | 2 mi | 1 mi, 2 se | 6 mi, 2 mo, 5 se | 4 mi, 4 mo, 5 se | 3 mi | 9 mi, 1 mo | 5 mi | 1 mi, 1 se |
| Non-language-eloquent area in LH | | | 1 mi | | 3 mi, 2 mo | 1 mi, 2 mo | 1 mi | 1 mi, 2 mo | 2 mi | |
| RH: | | | 1 mi | | 3 mi | | | 2 mi | | |
| Total: | A: 4 mild<br>LR: 8 mild<br>LC: 4 mild<br>HLL:1 mild/ 2 severe | | | | LR: 12 mild/ 2 moderate/ 7 severe<br>LC: 5 mild/ 6 moderate/ 5 severe | | A: 4 mild<br>LR: 12 mild/3 moderate<br>LC: 7 mild<br>HLL: 1 mild/1 severe | | | |

Abbreviations: A = aphasia; LR = lexical retrieval; LC = language comprehension; HLL= high-level language; mi = mild; mo = moderate; se = severe.

Three months after surgery, many patients had recovered from their language impairments seen at the early post-operative assessment. Compared to before surgery, two patients had developed mild aphasia. Fifteen patients (51.7%) had deficits in lexical retrieval; twelve of them mild deficits and three of them moderate ones. Seven patients had a mild language-comprehension deficit. One patient had developed a mild high-level language deficit.

In all, similar patterns were seen both in the group analyses and in the individual analyses. Before surgery, the patients had predominantly mild language deficits. Most of those who had a language deficit had a tumour in LH. A deterioration was seen after surgery in almost all patients with a tumour in LH. Three months after surgery, the language deficits had disappeared or improved in the majority of the patients.

## Study IV

*Writing fluency in patients with presumed low-grade glioma before and after surgery*

> The specific research questions in Study IV were:
> – Are there any differences in writing fluency and word-level pauses between patients with low-grade glioma (LGG) before surgery and a reference group?
> – Do LGG patients' writing fluency and word-level pauses at follow-up three months after surgery differ from their pre-operative performance?
> – Is LGG patients' writing fluency related to their performance on tests of oral lexical retrieval before and after surgery?

Compared with the reference group, the LGG group had shorter burst lengths (meaning that they wrote fewer characters between pauses), longer median inter-key intervals (both in the copy task and in the picture-elicited task) and a lower production rate (meaning that they wrote fewer words per minute). The LGG group also had a larger proportion of pauses longer than 2 seconds both before, within and after words. No significant difference was seen for word-level errors.

Because the groups differed in typing speed (measured as the median inter-key interval in the copy task), a one-way ANCOVA test was conducted to examine whether typing speed accounted for the differences between the LGG group and the reference group in terms of burst length and production rate. These analyses found no differences between the groups on these measures after typing speed was controlled for.

Logistic regression was used to examine whether typing speed accounted for the differences between the LGG group and the reference group in terms of word-level pauses. The odds ratio (OR) between the LGG group and the reference group for pauses within words was 2.526 (95% CI: 1.336–4.775, $p = .004$), meaning that pauses *within* words were significantly more common in the LGG group after adjusting for typing speed, age and duration of education. However, the differences seen in pauses before or after words were no longer significant.

After surgery, the LGG group's production rate fell, meaning that they wrote fewer words per minute. The only other significant differences were an increase in pauses before words and an increase in the median inter-key interval in the picture-elicitation task. Since no significant change was seen in typing speed, no further analyses controlling for that were performed.

Before surgery, the LGG patients' results on the Verbs test had a moderate correlation with burst length (the measure of writing fluency). Burst length also had a strong correlation with typing speed. After surgery, at the three-months follow-up, all measures of oral lexical retrieval had a moderate or strong positive correlation with burst length. The test with the strongest such correlation was FAS.

# Additional results

## Language data from the twelve-months follow-up

Data collection included a follow-up assessment twelve months after surgery. However, since only half of the patients underwent this assessment, data from it were not included in any of the studies.

Summarised results for the 17 patients who completed a twelve-months follow-up are presented in Figure 2, together with an overview of their performance at the earlier language assessments as well as information about the surgical procedure that they underwent. Of the patients who were assessed twelve months after surgery, eight had a tumour in a language-eloquent area, five had a tumour in a non-eloquent area in the left hemisphere and four had a tumour in the right hemisphere.

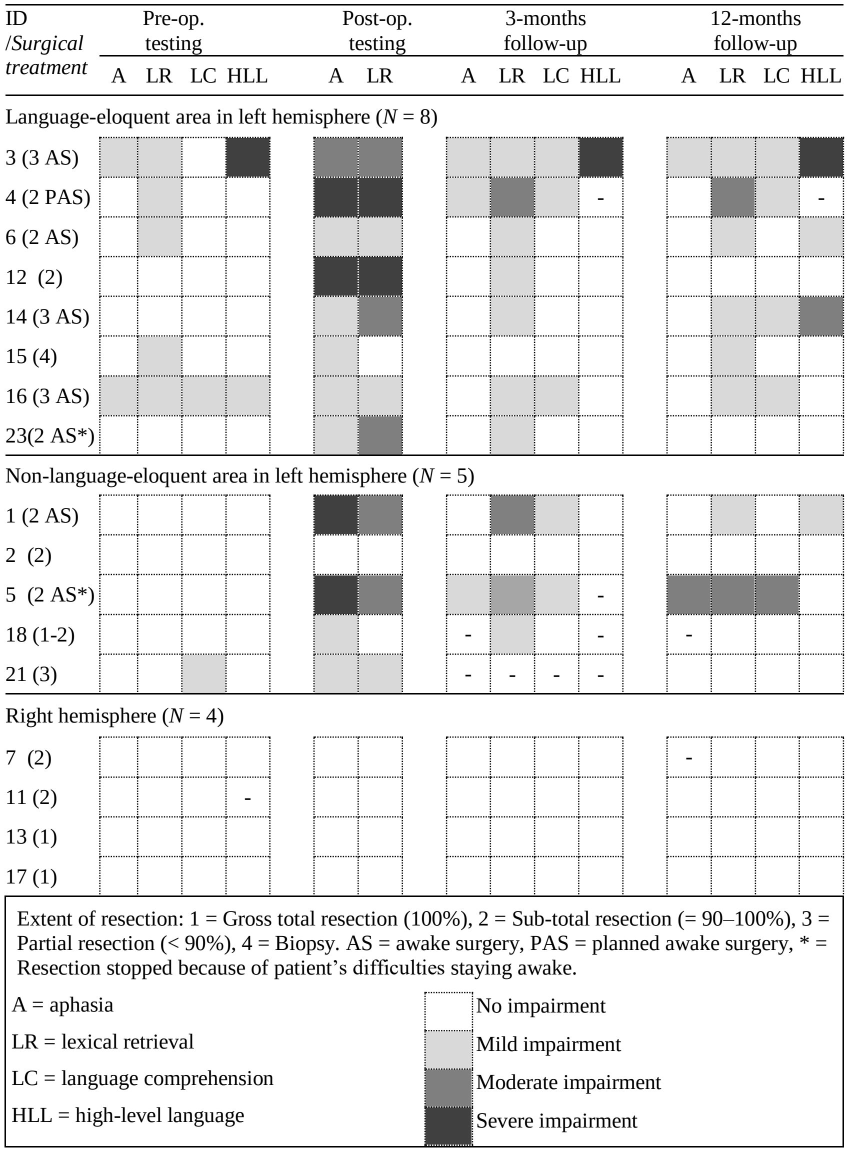


Figure 2
Language impairments in all patients who completed the twelve-months follow-up, as assessed before surgery, early after surgery and at follow-up after three and twelve months, respectively, presented by tumour location

Twelve months after surgery, two patients had aphasia (one mild, one moderate) according to the A-ning aphasia test. Both of these patients had had mild aphasia at the three-months follow-up. Eight patients had impaired lexical retrieval (six mild, two moderate). Three patients who had had a mild such impairment three months after surgery no longer had any such impairment at all. One patient had improved from a moderate impairment at the three-months follow-up to a mild one, whereas one patient who did not have an impairment three months after surgery now had a mild one. Six patients were at the same level of impairment as at the three-months follow-up.

Five patients had impaired language comprehension (four mild, one moderate). One patient who had had a mild impairment three months after surgery no longer had an impairment in this domain, one patient had a new impairment (mild), and one had deteriorated from a mild to a moderate impairment. Four patients had impaired high-level language. One of them was at the same level as at the three-months follow-up while the other three had a new deficit (two mild, one moderate).

# Discussion

## Overall aims and results

The present thesis aimed to investigate language ability in patients with low-grade glioma (LGG). Different aspects of language production and language comprehension were explored in both the oral and the written modalities. Language ability was analysed both on group level and on individual level.

Although the main focus was on patients with LGG, Study I explored how adults without any neurological disease performed on a test measuring high-level language. The results showed that sex, education and age had some, but limited, influence on how these adults performed on the high-level language test, but that verbal working memory had a relationship with test performance. Based on the conclusions from these explorations, norms for the BeSS total were presented by educational level and, as regards the Comprehension of logico-grammatical sentences sub-test, by age group; the norms for the other sub-tests are based on the entire sample.

When exploring the characteristics of a test, it is important to examine how demographic variables such as sex, age and education affect performance on it. From a clinical perspective, the influence of these factors will affect the norms. From a theoretical perspective, such an exploration can contribute knowledge about how the concept measured by the test is affected by characteristics such as educational level. One possible limitation of Study I was that the study sample contained a larger proportion of persons with higher education than the overall Swedish population. Since there was found to be a relationship between educational level and score on the BeSS, norms were presented by educational group. However, the relationships between scores on the different sub-tests and education were either weak or inexistent.

Verbal working memory influenced performance on the majority of the sub-tests included in the test of high-level language, indicating that verbal working memory is an important factor underpinning high-level language skills. It is important to identify the underlying components, such as different aspects of language and cognitive processes, that different tasks place demands on – not only from a theoretical perspective but also because poor performance on the BeSS could be a consequence of a more general cognitive impairment rather than an impaired ability to process complex language *per se*.

In Study II, 23 newly diagnosed patients with presumed LGG were tested using a comprehensive language-test battery. Compared with a reference group, the patients with presumed LGG performed worse on a naming test and a word-fluency test. When the patients whose diagnosis was subsequently changed to high-grade glioma (HGG) were excluded from the analysis, similar results were found in the group-level comparisons, except that there was no difference regarding the word-fluency test. The finding of poor performance on tests measuring lexical retrieval, such as naming and word-fluency tests, is in line with previous research (Ek et al., 2010; Tucha, Smely, Preier & Lange, 2000; Papagno et al., 2012; Santini et al., 2012; Satoer et al., 2012; Racine et al., 2015).

Study II also looked at how the patients performed compared with clinical norms. The individual analyses showed that only a few patients performed below the normal range on more than one test and that none of the patients had aphasia according to the aphasia test. One interesting finding from this study was that sub-normal performance was seen in nearly as many participants in the reference group as in the patient group. This could indicate that the patients with LGG have a fairly normal language function. Another aspect of this issue, however, is that sensitive measures often have a problem with specificity and that this yields false positive results.

The third and last research question asked in Study II concerned whether the patients themselves had experienced a change in their language, communication or speech. The vast majority answered that they had not done so or were uncertain whether they had. The two patients who had experienced a change both reported that they had problems finding words. The four patients who were uncertain also reported problems finding words, but some of them associated this with a possible age-related decline. In a study by Satoer et al. (2012), as many as 56.5% (13 of 23) of the patients with glioma reported a word-finding problem before surgery. The lower occurrence of self-reported language difficulties found here could be due to the fact that our study also included patients with tumours in the right hemisphere, who might be expected to be less at risk of developing a language impairment than patients with a tumour in the left, presumed language-dominant, hemisphere. However, one of the two patients who had experienced a change in his language – more specifically, word-finding difficulties – actually had a tumour in the right hemisphere. Another factor that may have affected the answers of the patients in our study is the wording of the question. If rather than being asked a single question, they had been given a questionnaire with questions about whether they had experienced, among other things, any word-finding difficulties, this might have yielded other results.

Study III explored how language ability was affected after tumour surgery. Unlike Study II, Study III included patients with recurrent tumours. Even so, the outcome of the pre-operative comparisons was similar to that of the group comparisons in Study II in that the patients with presumed LGG performed worse on naming and word-fluency tests than the reference group. Since the sample examined in Study III was somewhat larger, separate analyses were performed with regard to patients with tumours in the left hemisphere (LH) ($N$ = 24) or right hemisphere (RH) ($N$ = 9). These analyses revealed that the patients with a tumour in LH were the ones who differed, whereas no differences were seen between the patients with a tumour in RH and the reference group. It should be noted, however, that the patients with a tumour in LH were a larger group and that, if patients with tumours in RH have poorer language ability, larger samples are needed to attain the statistical power necessary to detect it. Even so, the data distribution in the RH group did not imply any such differences, and nor did the individual analyses where the patients' results were compared with clinical norms.

As already mentioned, Study II and Study III differed in that the latter included patients with a recurrent tumour and patients who had already undergone tumour treatment. Even though this seems to have exerted little influence on the group-level comparison between pre-operative patients and the reference group, the individual analyses of the patients' pre-operative performance did show a few differences. In Study II, none of the patients was deemed to have aphasia according to the aphasia test battery, but in Study III four patients had mild aphasia according to the same test battery. Three of these patients had a recurrent tumour and had undergone previous tumour treatment before inclusion in the study. This factor may have influenced the incidence of language impairment before surgery – but on the other hand, not all patients who had undergone previous tumour treatment had a language impairment.

A deterioration was seen on all tests administered as part of the early post-operative assessment. Again, the separate analyses showed that the patients with a tumour in LH were the ones who performed worse immediately after surgery, not the patients with a tumour in RH. Three months after surgery, most of the language impairment that had been seen, both at group level and at individual level, had resolved or improved. Transient language impairment after glioma surgery in the language-dominant left hemisphere is a common occurrence (Bello et al., 2007; Ilmberger et al., 2008; Duffau et al., 2003; Duffau, 2009; Duffau et al., 2008; Santini et al., 2012; Sanai et al., 2008). In Wilson et al.'s (2015) study of 110 patients undergoing tumour surgery (39 patients with LGG, 49 with HGG and 22 with other types of tumours), various types of transient aphasias were found in 71% of the patients in the first two to three days after surgery. However, the patients with aphasia recovered fast and almost all language deficits had resolved one month after surgery. In Study III, 83% of the patients with a tumour in LH had an impairment in either naming, word fluency or language comprehension immediately after surgery. However, a few of those patients already had a mild impairment before surgery and showed no deterioration soon after surgery. Further, there are some differences in terms of diagnoses between the patients in Study III and in Wilson et al.'s study in that the latter also included patients with epileptogenic focus and vascular malformation. Other studies have reported a lower incidence, but, as Wilson et al. (2015) note, there is probably a link between finding a high incidence of language deficits and using a comprehensive aphasia test battery.

Since only approximately half of the patients completed a follow-up assessment twelve months after surgery, data from this assessment were not included in Study III. However, an overview of the individual results for the 17 patients who did complete the twelve-months follow-up is presented in the Results section of this thesis summary. These data indicate that some of the patients continue to recover even after the three-months follow-up whereas other perform at the same level and some even show a decline.

Twelve months after surgery, many patients will have undergone post-surgical treatment. A worsening of a language impairment might be related to the side effects of such treatments. Further exploration of these data is needed to identify the factors that affect possible language impairments at this time point.

In Study IV, writing fluency was explored in 20 patients with presumed LGG before and after surgery. The reason for this choice of focus was that several studies – including Studies II and III in the present thesis – have identified word-finding problems in oral production. To explore whether such problems were apparent in written production as well, writing fluency and word-level pauses in narratives were investigated. A further issue explored was the relationship between writing fluency and patients' performance on naming and word-fluency tests.

Aspects of writing fluency such as burst length, production rate, word-level pauses and typing speed were affected both before and after surgery. However, the difference before surgery between the LGG group and the reference group in both writing fluency and production was no longer significant after a control for typing speed had been performed, and nor were the differences in pauses before or after words. Nevertheless, even after controlling for typing speed, the patients with LGG were more likely than the reference group to make pauses within words.

There are several possible reasons why the patients with LGG might have a slower typing speed than the reference group. It is hoped that future studies will be able to control for some of them. The two groups might differ in certain cognitive aspects in a way that would cause the patients with LGG to have a slower processing speed, poorer executive functions and/or poorer working memory. Other factors that might explain the patients' slower typing speed are possible fatigue – caused either by the extensive tests themselves or by the tumour – and the effect of anti-epileptic medication.

After surgery, there was a decline in production rate and an increase in before-word pauses but no change in burst length. The increase in before-word pauses and the reduced production rate could indicate a lexical problem. Nevertheless, as writing is a complex process, no clear conclusion can be drawn with regard to whether the lexical problems previously reported in the oral modality are seen in writing as well. The strong correlations found between scores on tests of oral lexical retrieval and writing fluency, respectively, might be an indication that these measures are related. However, since the scores on these tests were also related to typing speed (a measure based on a task placing low demands on lexical retrieval), this explanation seems insufficient. To fully understand the factors affecting writing fluency, there is a need to explore a model enabling the investigation of additional possible explanatory factors.

## Tumour-related factors

The extent to which a tumour's characteristics such as grade, type and size influence its functional impact on language ability is uncertain or at least not entirely known. However, one factor that has been shown to affect language is tumour location. In Studies II, III and IV, the issue of tumour location was investigated in different ways, partly depending on sample size. In Studies II and III, the patients were divided into three groups: those with tumours in language-eloquent areas in the left (presumed dominant) hemisphere, those with tumours in non-language-eloquent areas in the left (presumed dominant) hemisphere and those with tumours in the right (presumed non-dominant) hemisphere. However, these categories were not used for statistical comparisons, only in the presentation of the individual patients' results.

In Study III, which included a larger sample than Study II, separate group comparisons were made for patients with a tumour in the left or right hemisphere, respectively. This was also the original plan for Study IV, but since the sample size was too small and since the main focus was on lexical-retrieval deficits (a problem associated with tumour presence in several parts of the brain, including the right hemisphere), no separate analyses were made in Study IV.

It is noteworthy that language impairment was found in patients with tumours in both language-eloquent and non-language-eloquent areas in the left hemisphere. However, language impairments have been linked to areas previously defined as non-language-eloquent (Yordanova et al., 2011; Satoer et al., 2014), and it is probable that part of the explanation resides in the fact that the categorisation of the language-eloquent cortex was performed, in those studies as well as in our study, according to anatomical areas. Functional mapping performed using techniques such as fMRI might have provided better definitions of the language areas. It should also be noted that the organisation of language networks in the brain can vary greatly in the presence of a slow-growing mass tumour (Sanai et al., 2008; Southwell, Hervey-Jumper, Perry & Berger, 2016).

Nine patients turned out to have a tumour of a higher grade after inclusion in the studies. This was not very surprising, given that the relevant inclusion criterion was *presumed* LGG, a diagnosis based on MRI scans, physical examination and medical history. For approximately one-third (28%) of the sample to actually have a tumour of a higher grade is in line with previous knowledge to the effect that up to 30% of the patients first diagnosed with LGG in fact have a tumour of a higher grade (Whittle, 2004). A few studies have compared language ability in patients with low- and high-grade gliomas, with conflicting findings. A study analysing the spontaneous speech of glioma patients found that patients with LGG deviated more than patients with HGG both before and after surgery (Satoer et al., 2013). By contrast, Bello et al. found no relationship in post-operative deficits in patients with LGG or HGG having undergone awake surgery for resection of a tumour in a language-eloquent area. Early post-operative deficits were found in 71.4% of the patients with LGG and in 62.5% of the patients with HGG.

One factor that was discussed when the studies were being planned was the timing of the follow-up assessment. The choice made of having a follow-up after three months represents a fairly common timing for follow-up, but some studies have had their follow-up as soon as one month after surgery while some have had a follow-up after six months. One aspect of relevance when choosing the timing of follow-up assessment relates to post-operative tumour treatment (i.e. radiation or chemotherapy), but since there is no generally applicable starting point for post-operative treatment (Buckner et al., 2016), there is no single time point that will suit all patients. Other studies that examined the influence of post-operative treatment found that it did not influence cognitive performance in glioma patients (Satoer et al., 2014).

Another factor that could have influenced the results was the fact that the majority of patients had seizures. In a retrospective multi-centre study by Pallud et al. (2014), 1,509 patients with LGG were examined with a view to identifying interactions between tumour characteristics and epileptic seizures. Nearly 90% of these patients had had epileptic seizures at the time of diagnosis, and in the vast majority of cases these were well managed by anti-epileptic medication. Both epileptic seizures and anti-epileptic medication can have a negative influence of varying severity on cognitive functions and psycho-social functioning (Piotrowski & Blakeley, 2015). However, since cognitive impairments can also be caused by the tumour or by tumour treatment, it may be difficult to determine which of these factors is causing an impairment. Nevertheless, a higher epilepsy burden has been found to be associated with impaired cognitive functions such as processing speed, psycho-motor function, working-memory capacity and executive functions

(Klein et al., 2012). This was not controlled for in any of the studies, and it might have influenced patients' performance on the language tests.

## Assessing (subtle) language deficits

One explicit aim when planning this thesis project was to include sensitive measures to assess language ability. In a review of language outcomes following neurosurgery for brain tumours, Finch and Copland (2014) suggested that standard tests for post-stroke aphasia might not adequately capture more subtle language impairments found in patients with brain tumours. The same authors further stressed the need to explore whether other language tests such as tests assessing high-level language and cognitive-communication disorders used in other patient populations are sensitive in patients with brain tumours.

The present project used a comprehensive test battery including tests of naming, word fluency, language comprehension and morphological ability. Besides these tests, two test batteries were included, one assessing aphasia and one assessing high-level language. As expected, the aphasia test manifested a ceiling effect; several patients who experienced language problems and performed poorly on tests such as naming and language comprehension obtained the maximum score (low scores representing the clearest cases of aphasia) on the aphasia test or came close to it. Aphasia tests often have problems with sensitivity since they have low item difficulty and therefore cannot identify subtle language impairments (Crosson, 1996). Another potential problem when it comes to detecting mild impairments is that normative values for an aphasia test will be based on an aphasic population (most often a stroke population). However, for tumour patients representing more apparent cases of language impairment/aphasia, instruments such as A-ning or other aphasia test batteries might be useful since they screen for many different types of language abilities and can provide an aphasia profile that might be useful for the choice of further tests and for the planning of rehabilitation.

The test battery for high-level language (BeSS) was chosen since it has been suggested as a potentially appropriate type of tests for this clinical group (Finch & Copland, 2014) and has proved to be sensitive to language impairment in other neurological patient populations (Laakso et al., 2000; Berg et al., 2003). The BeSS is one of few Swedish clinical tests assessing subtle language disorders. Its use on the patients in this thesis yielded varied results. In Study II, a surprising result was found for one sub-test: the patient group was significantly better than the reference group at understanding metaphors. That study includes a discussion of possible reasons for this result: it might be a true difference, it might be due to chance or it might be due to a difficulty in measuring the comprehension of metaphors. In Study III, no significant differences were found either before or after surgery in any of the sub-tests. In that case, the lack of group-level differences is probably related to the fact that the patients with the greatest language difficulties were not tested using the BeSS. Since the BeSS aims to assess language abilities of a more complex nature, such as the ability to make inferences and to understand and explain different meanings of ambiguous sentences, it would hardly be relevant for a person to undergo this test unless his or her more low-level abilities were intact. For this reason, patients whose scores on A-ning indicated that their performance was equivalent to that of persons with aphasia were not deemed suitable for testing with the BeSS. Hence the BeSS results are based on the patients with the slightest deficits.

Another potential problem with the BeSS is the time constraint used in all but one sub-test. Sub-tests 2–7 have a time limit of 30 or 60 seconds. In some of the sub-tests, a clue is given if the 30-second mark is reached, resulting in a maximum time limit of 60 seconds. The time constraints in these tests are used to identify individuals who take a long time to answer (Laakso et al., 2000). However, since a correct answer given after the time limit is reached does not yield any points, the test cannot differentiate between complete inability to perform a task and inability to complete it within the time limit.

Further, the concept of high-level language is not that well defined or underpinned by theory. The definition used in the present thesis is in line with that of Lethlean and Murdoch (1997), which was used in a study examining high-level language dysfunction is patients with multiple sclerosis. They defined high-level language as ‘the use of varied areas of language and extensive cognitive processing’ and used the TLC (Wiig & Secord, 1989), the test that the BeSS is based on, as an assessment tool. However, there are some problems with the concept and definition of high-level language. The definition does not indicate the specific abilities needed nor the possible manifestations of the deficits, but only implies that extensive processing is needed. However, even if the concept of high-level language may be problematic in some respects, the BeSS test aims to measure language abilities of a more complex nature and as such could be a useful supplement to other tests. Each of the seven sub-tests measures a different aspect of complex language use, and a more qualitative analysis of the responses might be useful for individual patients in order to detect, for example, deficits when it comes to making inferences.

Besides more methodological aspects of language impairment in the patient population in question, the terminology used also deserves some attention. The definition of ‘aphasia’ was discussed above in the Introduction. As mentioned, some definitions of aphasia, such as that of Papathanasiou and Coppens (2012), specify that it is a *selective* language impairment, and most others include some other key aspect, for example that aphasia is an *acquired* language impairment or that it is caused by *focal* damage to the brain, most often in the language-dominant hemisphere. Even though all of these aspects are true of language impairments caused by brain tumours, it is more common in brain-tumour research to use the term ‘language impairment’ rather than ‘aphasia’. There might be several reasons for this. One is that the most common cause of aphasia is stroke and that much of what is known about aphasia, including different aphasia types/syndromes, originates from stroke-derived cases. Some researchers emphasise that language impairment following a brain tumour differs from that seen after a stroke, with the former characterised as a more subtle language disorder (Miceli et al., 2012; Papagno et al., 2012; Bello et al., 2007); this may have influenced the terminology used. Another factor relevant here is that neuro-psychological test batteries used to investigate the cognitive impact of brain tumours often include only one or two language tests (commonly word fluency and naming) and use these as a basis for determining whether the patient has a language impairment, with language seen as one among many different cognitive abilities that can be affected by the presence of a tumour. To decide conclusively whether a person has aphasia in the established sense, however, more extensive testing is needed beyond an assessment of lexical retrieval.

Another expression commonly used is ‘subtle language disorder’, a term used to emphasise that patients with brain tumours often have mild language impairments. ‘Subtle’ here refers to a minor or mild language impairment which may go undetected since patients often perform within the normal range on language tests. This term is often used to describe language deficits in patients with dementia or traumatic brain injury, along with the term ‘cognitive-communicative disorder’. However, the term ‘subtle language disorder’ has also been used to describe mild aphasia (Ahlsén, 2006). It should be noted that the term in and of itself does not imply the presence of any specific kinds of problems nor give any indications as to how assessment should be performed. In this project, tests of lexical retrieval (naming and word fluency) and tests of high-level language were included as potential sensitive measures. Both naming and word-fluency tests were sensitive to impairment whereas the test of high-level language yielded mixed results, as discussed previously. In both Study II and Study III, the terms ‘sub-normal’ language performance and ‘performance below the normal range’ are used. The reason for using these terms rather than ‘language impairment’ throughout was that many of the patients performed just below the normal range, and a small deviation might in fact not reflect a language impairment at all but instead be related to other impairments such as a cognitive impairment affecting performance. The underlying cause of an impairment may not be important for its functional consequences, and acquired language impairments often co-occur with other cognitive deficits. However, since some of the patients who performed just below the normal range did not themselves experience any language problems, this question needs to be addressed. Another reason for using the above-mentioned terms was that, in Study II, the members of the reference group were about as likely as the patients to have an impaired (or sub-normal) performance on the language tests. Since the participants in the reference group were healthy in the sense that they did not have any self-reported neurological disease, this raises the question of whether the tests used were too sensitive.

# Lexical-retrieval problems

One type of problem that occurred frequently both before and after surgery was lexical-retrieval problems, i.e. difficulties finding the right word. This was noted both in test scores and in the patients’ reports, and it was further explored in the written modality in Study IV. As previously described, this finding is not unique; several other studies have arrived at similar findings. In a study investigating cognitive impairment in patients with glioma, 56.5% of the patients reported word-finding problems before surgery, even though they had normal language or only a minimal discernible handicap according to the Aphasia Severity Rating Scale (Goodglass & Kaplan, 1983), which means that these patients had subjective difficulties that would not be apparent to a listener. This discrepancy between the patients’ subjective view of their problems and – in this case – test results is seen in Study II and was also noted by the author during data collection for Study III. In Study II, two patients reported word-finding problems; both of them performed in the normal range on both naming and word-fluency tests. During data collection for Study III, the patients were asked the same questions as in Study II about whether they had experienced any change in their communication, language or speech, both before and after surgery. Several participants in Studies II and III reported specific word-finding problems. These are not accounted for in detail in the published reports of those studies, so a few examples are given here.

*Example 1*
A 31-year-old man who had already undergone a tumour resection three years earlier said the following in his interview at the pre-operative assessment. He performed within the normal range on both naming and word-fluency tests.

> *'... but it still happens that I forget words and when I have presentations and things I need to have it kind of written down you know on paper if it's something long / I never needed that before it was very easy for me to remember everything by heart and to talk and to be very quick to answer and things if there were questions or essays or things but I'm not any more I need to read up much more on the subject ...'*
>
> (Swedish: '… men de händer ju fortfarande att jag glömmer bort ord å när ja har presentationer å sånt måste ja ha liksom nedskrivet asså ah papper om det är längre saker / de hade ja aldrig innan ja hade väldigt lätt för att komma ihåg allting utantill å kunna prata å va väldigt snabb på att ge svar å sånt om de va frågor eller uppsatser eller sånt men de e ja inte idag ja måste va mer påläst på ämnet…')

*Example 2*
A 62-year-old man explains in his interview at the three-months follow-up that his word-finding problems occur mostly when he is under pressure. He had a performance within the normal range on the BNT naming test but an impaired performance on the tests of verbal word fluency.

> *'no but I know that I have some difficulties explaining myself as I talked about before in relation to emergencies that I have to solve in [specific activity involving many people] you know ... eh ... and*

*the older people are the pushier they'll be and that's why it's a bit difficult for me to answer for myself then'*

(Swedish: 'nä men ja vet att ja har lite svårt att förklara mig som ja sagt tidigare då i samband med att det blir akuta situationer som ja ska lösa [expression withheld for reasons of anonymity] va..eh.. å ju äldre de e desto påstridigare är dom så att därför får ja lite svårt att svara för mig då')

*Example 3*
A 46-year-old woman, who experienced language problems after surgery, talks about what her greatest language problem is during testing at the three-months follow-up. She performed within the normal range on the BNT but had impaired verbal word fluency.

*'the thing is that I lose words. (Speech-language pathologist: 'and if you compare with before surgery, is it a big difference?') aah … pretty bi… well I do notice it so it's mmh it's a bit like that but then my partner is so kind and he helps me then he..s.. he.. s.. well he understands what I want to say but he doesn't say it he says "describe it" so I think that's really great'*

(Swedish: 'De e att ja tappar ord. (logoped: "och om du jämför med innan operationen är det en stor skillnad?") aah.. hyfsat st.. ja märker ju de så de e mm de e lite så men då e min sambo så snäll så han hjälper ju mig då han..s.. han..s han förstår ju vad ja vill säga men han säger de inte utan "beskriv" så de tycker ja e jättebra')

Word-finding difficulties, i.e. anomia, is the most common language deficit following brain damage. The inability to retrieve a word might be related to an impairment in one or several underlying word-retrieval processes, such as a failure to recognise the stimulus, a failure to access the semantic representation or a failure to activate the phonological word form (e.g. Goodglass, 1998; Levelt, Roelofs & Meyer, 1999). To detect this type of impairment, a valid measure of lexical retrieval is needed. The most common instruments are naming tests, but word-fluency tests (even though they test executive function as well) are also used to measure lexical retrieval.

In two of the above examples, the patient who reported a word-finding difficulty performed below the normal range on a word fluency test. Patients who present with an impaired word fluency but not an impaired naming ability could have an executive dysfunction rather than a language impairment as such (Swinburn, Porter & Howard, 2004). Although it is not clear from the quotations, both of these patients in fact had other language impairments, which indicated that they did not have an executive dysfunction only. However, a few patients who had a tumour in the right hemisphere had an impaired performance on word-fluency tests but not on naming tests. Since most of these patients also did not report any word-finding difficulties, this might indicate that they had an executive deficit.

It is noteworthy that all patients performed within the normal range on the BNT, which is a widely used naming test. Naming tests have been found to be a valid way of measuring lexical retrieval in persons with aphasia (Herbert, Hickin, Howard, Osborne & Best, 2008), but the BNT has been criticised for having poor psychometric properties and for not satisfactorily measuring the processes required for successful naming (Harry & Crowe, 2014). It has also been criticised for over-pathologising persons with poor vocabulary skills, as it does not discriminate between the failure to *retrieve* a word and the failure to *know* the word. However, since the current examples reflect the opposite problem, other explanations are needed. It might be that other tests, such as naming tests with a higher item difficulty level or naming tests administered under time constraints, for example the Swedish test 'Ordracet' (Eklund, 1996), could be better at capturing impaired lexical retrieval in these patients.

# Limitations

The main limitation of the studies including patients with LGG (Studies II–IV) is the limited sample size. In all, 43 patients with presumed LGG were asked to participate in the project. While the objective was to include all patients with presumed LGG, some patients may have been missed. The majority of the patients included had a tumour in the left hemisphere. Although Inskip et al. (2003) noted a small preference for left lateralisation in LGG (ratio L:R = 1.16), there was no significant difference in the numbers of left- and right-sided LGG. Many of the patients who declined participation had a right-hemisphere tumour. It may be that the lower risk of language impairment in patients with right-hemisphere tumours affected their motivation and willingness to participate in this project. One consequence of the rather small sample of patients with a tumour in the right hemisphere ($N = 9$) was that it reduced the power of the statistical analyses. A larger sample size would not only have provided a better basis for the statistical analyses performed to explore the effect of tumour location (i.e. hemispheric differences) but would also have enabled statistical modelling that took several of the potential sources of variation into account, such as tumour grade and previous tumour treatment, and would also have made it possible to perform more detailed analyses of the influence of tumour location.

Another limitation is that Study III did not include a twelve-months follow-up. The first 17 patients included were tested twelve months after surgery, but it was concluded that they were too few to be included in any statistical comparisons. The reason for not testing all patients at a twelve-months follow-up was that the overall data-collection exercise ended in December 2016 to ensure that there would be time for completing all manuscripts during 2017. Since there is a gap to fill and since most studies, including our own work, only has a follow-up assessment a few months after surgery, future work including additional follow-ups after more than three months is warranted.

Although this was originally intended, no cognitive tests were performed in any of the studies including patients. Word-fluency tasks were included in Studies II–IV, and these can be regarded as measuring both verbal ability and executive function. At the planning stage, the aim was for the project to include additional testing using neuro-psychological tests, but owing to a lack of resources and a gap in data collection only about two-thirds of the patients were tested by a neuro-psychologist. Since cognitive deficits are quite common in patients with LGG, and since some of the language tests are heavily reliant on other cognitive resources, having access to the results of neuro-psychological tests would have facilitated the interpretation of the language-test results. As other studies have done before, this study underscores the importance of investigating cognitive abilities in the case of mild or subtle language disorders, especially in patients with heterogeneous tumour locations.

# Ethical considerations

The studies included in this project have been approved by the Regional Ethical Review Board of Gothenburg, Sweden (Ref. No. 625-14). Study IV is actually covered by two ethical-approval decisions (Ref. Nos. 625-14 and 525-14). Written informed consent was obtained from all participants.

When the present thesis project was being planned, several ethical issues were considered. It was decided that the question of participation should be put to the patient by the neurosurgeon with whom he or she had been in contact previously. If a patient had further questions, he or she could put them to the author before deciding to participate. Some patients did indeed decide not to participate; some of those who declined said that they did not feel that they had the time for additional testing sessions. Some patients who were tired from post-surgical tumour treatment requested a shorter testing session, which they were granted. For those patients, data from the tests that they completed are included in the studies.

# Conclusions

(1) The majority of the newly diagnosed patients with presumed LGG had normal or nearly normal language ability prior to surgical treatment.

(2) Even though many patients with presumed LGG presented with a language impairment immediately after surgery, the majority had returned to their pre-operative performance three months after surgery.

(3) Language impairments after tumour surgery in patients with presumed LGG are more common in patients with a tumour in the left hemisphere, particularly in patients with a tumour in language-eloquent anatomical areas.

(4) The patients' writing process was affected both before and after surgery, but the differences seen in writing fluency and production rate before surgery might be explained by the patients' slower typing speed (compared with healthy controls).

(5) The decline in written production rate and the increase in before-word pauses seen in the patients after surgery could be related to a lexical deficit.

(6) A lexical-retrieval deficit is the most common impairment both before and after surgery in patients with presumed LGG.

(7) Verbal working memory influenced performance on a test of high-level language.

# Future Perspective

## Clinical perspectives

This project employed a comprehensive test battery, both in terms of the number of tests used and in terms of the time needed to complete a testing round. This is not always either possible or necessary as part of a clinical routine. On the other hand, in a clinical setting, the testing session can be individualised depending on whether the patient already had a language impairment before surgery. Nevertheless, since the pre-operative tests also provide a baseline for future testing, a test battery should include tests of language abilities that might be affected by tumour resection, such as language comprehension, naming and word fluency. The results from Studies II and III suggest that the A-ning aphasia test is too insensitive to be used as an assessment tool before surgery in LGG patients. However, in patients manifesting the equivalent of moderate to severe aphasia after surgery, this kind of test instrument might still be useful.

The original driving force behind the project – although it is not the focus of the present thesis – was the need for language assessment in patients undergoing awake surgery. The performance of such assessments is now a routine procedure at a few of Sweden’s university hospitals, but it should be noted that this thesis has shown that not only those patients who undergo awake surgery may present with language deficits after surgery. Given that 74% of all patients with a tumour in the left hemisphere manifested a language decline early after surgery, it seems reasonable that all patients with a tumour in the left hemisphere, regardless of the type of surgical intervention, should routinely undergo language assessment before and after surgery.

The clinical characteristics and time course of a language impairment due to a brain tumour may differ from those of a language impairment due to a stroke. It is important to ensure that clinical speech-language pathologists are aware of this. To increase our knowledge about this issue, it is also vital that patients who are at risk of developing a language impairment or already have developed one should be assessed by speech-language pathologists.

Otherwise there will be no progress in the development of clinical routines for assessment and rehabilitation in this patient group.

## Future research

The present study population is heterogeneous and consists of several subgroups. Several of the findings made in this thesis need to be verified in a larger sample, such as differences in the occurrence of language impairment depending on tumour location. Some factors need to be further explored, for instance whether there are any differences in language ability between newly diagnosed patients and patients with recurrent tumours. Other aspects which have not been taken into consideration in the analyses here but which have been discussed include the influence of post-surgical treatment and anti-epileptic medication as well as the impact of other cognitive deficits. In addition, besides having a larger sample, future studies should also include more extensive longitudinal follow-up.

Even though a comprehensive test battery was used, far from all aspects of language and communication ability were investigated. For example, apraxia or speech-motor assessments were not included in any of the studies, but there are data on the patients' performance on a verbal diadochokinesis task which it would be interesting to analyse and investigate. Other data not explored in the studies included in this thesis but available for further analyses are data on subjectively perceived changes in language, speech or communication after surgery, a VAS scale relating to communication and spontaneous-speech samples collected at each assessment.

Several of the studies used various sensitive measures, such as word-fluency tests, naming tests and tests of high-level language, and these measures have partly been proved sensitive to language impairments in this patient population. However, all of these potentially sensitive tests of language function are heavily reliant on cognitive functions such as processing speed, executive functions and working memory. Since patients with LGG, depending on their tumour location, are at risk of developing both language deficits and other cognitive deficits, it is of crucial importance to expand our insights into how the respective abilities interact and affect task performance. Hence an exploration of how different language and other cognitive abilities are related and how they affect performance on language tasks such as tests of high-level language is warranted. Above all, since the present results are somewhat inconclusive when it comes to whether the patients in question have high-level language deficits and whether the BeSS is an appropriate test for assessing such deficits, further exploration of these issues is necessary.

Lastly, there is extremely little research exploring patients' own experiences of having LGG and no studies at all focusing specifically on communication. Qualitative research is needed to explore the perception by patients with LGG experiencing an altered language ability of changes in their language function over time.

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