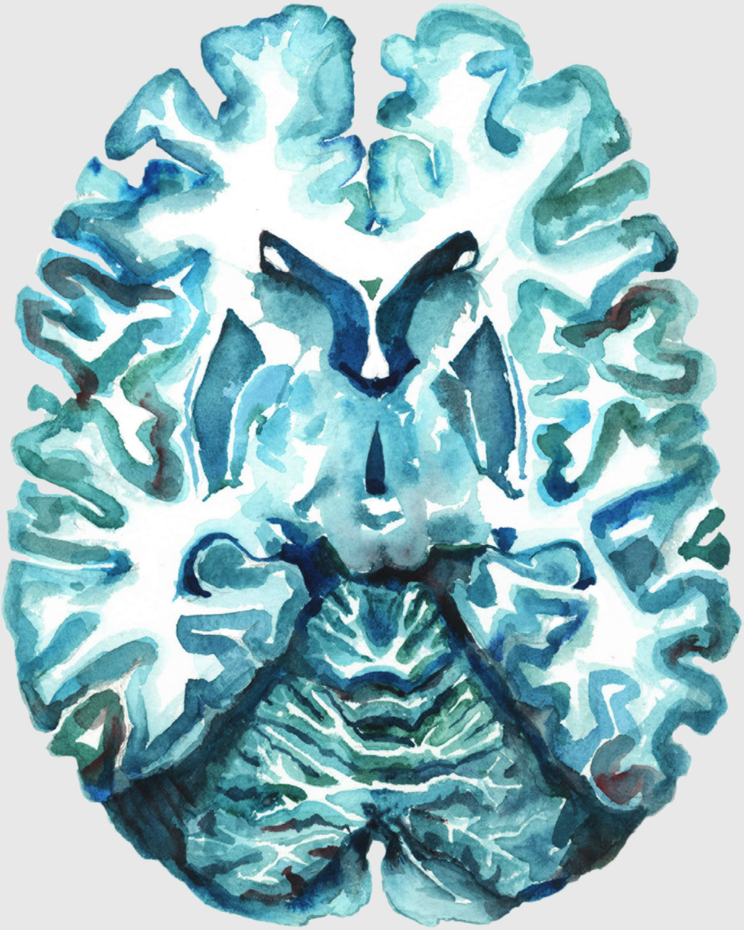
WRITTEN LANGUAGE IN AWAKE SURGERY

MONITORING OF READING AND SPELLING IN GLIOMA PATIENTS UNDERGOING AWAKE SURGERY



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We don’t read things as they are, we read them as we are

Voor mijn familie

Table of Contents

List of Figures

List of Tables

1

General introduction

Gliomas

Glioma patients are affected by a progressive primary brain tumor, which causes fatal intracranial pressure when left untreated [1,2]. Accounting for a diagnosis of 5-7 per 100.000 adults per year in high-developed countries, gliomas are the most common primary brain tumors (70% of cases [3,4]). Based on their pathology, a distinction is made between low-grade gliomas (LGG; astrocytomas, oligodendrogliomas or oligoastrocytomas), which due to their slow-growing nature diffusely infiltrate in cerebral tissue, and high-grade gliomas (HGG; anaplastic astrocytomas or glioblastomas) that grow more rapidly and may cause intracranial pressure [1]. LGGs typically affect young adults, which show few symptoms at presentation [5] and have a relatively long prognosis after diagnosis (from 5 to over 15 years [6]). However, the majority of LGGs will, even after long periods of stable state, eventually transform into more malignant HGGs [7], characterized by rapid deterioration and a poorer life expectancy (between 1 to 2 years [6]).

Given the progressive nature of gliomas, treatment is often initiated early after diagnosis, although 'wait-and-see' policies have also been advocated for [6]. Interventions are aimed at prolonging life expectancy, reducing deficits induced by intracranial pressure, and preserving quality of life as much as possible [8,9]. Cognitive dysfunction may however not only arise from pressure caused by the glioma, but also by glioma treatment [10,11]. In particular, a substantial risk of side effects has been identified for radiotherapy and chemotherapy, which may interfere with cognitive functioning at the whole-brain level [12]. These therapies are often delivered as concomitant adjuvant therapies, in addition to primary surgical treatment.

Classical surgical resection, under general anesthesia, also induces a risk of cognitive dysfunction. The infiltrative character of gliomas complicates to establish functional boundaries of the tumor, which are required to define which areas can be resected without inducing permanent impairments. Non-invasive neuroimaging techniques, such as fMRI, DTI, PET and CT, may been used to localize neurofunctional activity around the tumor, yet those techniques cannot distinguish between areas that mediate in the execution of a function and areas that are crucial for the execution of that specific function [13]. Hence, during surgery under general anesthesia it cannot be established whether crucial (sub)cortical brain areas are resected. Surgery under local anesthesia (awake surgery), on the other hand, allows determining those boundaries intra-operatively. This procedure may be less suitable for certain patients (e.g., for psychological reasons), yet as improved outcome has been reported for awake surgery as compared to surgery under general anesthesia [14-16], it is widely advocated for. In order to preserve quality of life, awake surgery is therefore regarded as the gold standard for treatment in glioma practice [14,17,18].

Awake surgery

Awake surgery provides the unique opportunity to monitor cognitive functioning during tumor mass removal. During awake brain surgery, Direct Electrical Stimulation (DES) is applied to temporarily inactivate (sub)cortical regions, while a neuropsychologist assesses a cognitive function. Inability to perform the task under evaluation is taken to mean that the stimulated area is crucial to carry out that function [19,20]. Localization using DES has been shown to be more accurate and precise (at 5mm) in the localization of essential structures for cognitive functions relative to non-invasive methods [21]. As a comparison, fMRI could identify only 66% of functional sites that were revealed intra-operatively by DES [17]. Awake surgery using DES thereby serves as the most accurate tool to detect functional boundaries and to control for preservation of cognitive functioning during surgery in each individual glioma patient.

Language monitoring

As gliomas often infiltrate in areas that are essential for language, cognitive assessments in glioma patients have mainly focused on linguistic tasks [18,22,23]. Classically, peri-operative assessments have relied on counting (as a measure of "automatic" speech) and spoken object naming (as a measure of vocabulary skills) tasks [23]. Language deficits in glioma patients are typically not as opaque as a complete inability to express themselves. Instead, patients often complain about difficulties in executing complex tasks or show word-finding difficulties [11,24]. Therefore, increasing attention has been appointed to the development of more sensitive tasks that were standardized for glioma practice [25,26]. Over the last decade, batteries have expanded to include a wider variety of tasks (e.g., comprehension or verb generation tasks [18,27,28]).

Even though assessment protocols have expanded vastly, glioma batteries include almost exclusively spoken language tasks. While spoken and written language tasks are often impaired simultaneously, research has shown that the neural substrates that implement written language are at least partly distinct from those critical for spoken language, which may result in selective deficits following brain damage [29,30]. Hence, when spoken language is assessed in absence of written language monitoring in glioma patients, it remains largely unknown how written language processes are affected by glioma and glioma surgery. In this thesis, we aim to evaluate if and how written language assessment could complement current glioma practice.

Written language

Written language, comprising of reading and spelling [i], is indispensable for human communication. The ability to use written language is essential for personal and professional life and is exploited on a daily basis from note taking to understanding instructions. Reliance on the complex linguistic processes of reading and spelling has further increased in modern society, as a large part of communication is now text-based (e.g., through messaging, e-mailing and Internet surfing on smartphones, tablets and computers). Written language skills are therefore crucial to obtain high quality of life, and preservation of written language in glioma patients undergoing awake surgery is thus of vital importance.

Reading and spelling rely on multiple cognitive components. Although different cognitive models of language processing at the word level have been proposed, there is general consensus on certain central (cognitive) and peripheral (output/motor) processes that are deemed essential for written language processing. In the model we consider (Figure 1.1; as used throughout this thesis), a systematic distinction is made between orthographic, phonological and semantic representations, as well as between lexical and sub-lexical processing in reading and spelling [31-33].

Classical lesion and neuroimaging studies have proposed detailed hypotheses on the functional architecture of these components. Each component processes information in a specific way, and may therefore result in a specific error pattern when damaged in isolation. Patients with selective deficits in either reading or spelling have contributed to the notion of functional autonomy of reading and spelling [34-40]. Yet, recent studies have also proposed that reading and spelling rely on shared neural networks for phonological, orthographical and semantic representations, regardless of input or output modalities [41-47]. Converging evidence seem to indicate that reading and spelling may rely on partially shared and independent processes.

This knowledge may be of particular interest in awake surgery practice, as it can be applied to personalize treatment. When all components are evaluated, understanding of the functional characteristics of each component can aid identification of the cognitive locus of impairments in glioma patients. Performance profiles that converge with an error pattern specifically reported for a component may indicate damage to that component. Intra-operative assessments may subsequently be tailored

[i] In the literature, different terminology is used with respect to written language processes. Throughout this thesis we use *written language* to refer to the processes of reading and spelling combined. *Reading* refers to reading a visually presented stimulus aloud. *Spelling* is used as an umbrella term for the output modalities of handwriting, typing and oral spelling. *Handwriting* refers to the process of spelling with a pen/pencil on a (paper) sheet. *Oral spelling* refers to the process of spelling each letter of a word out loud. *Typing* refers to spelling using the keyboard on a computer, tablet or smartphone.

to target the damaged component(s). In addition, neuroanatomical theories may guide neurosurgical practice, if these can identify which components may be at risk of damage given tumor location.

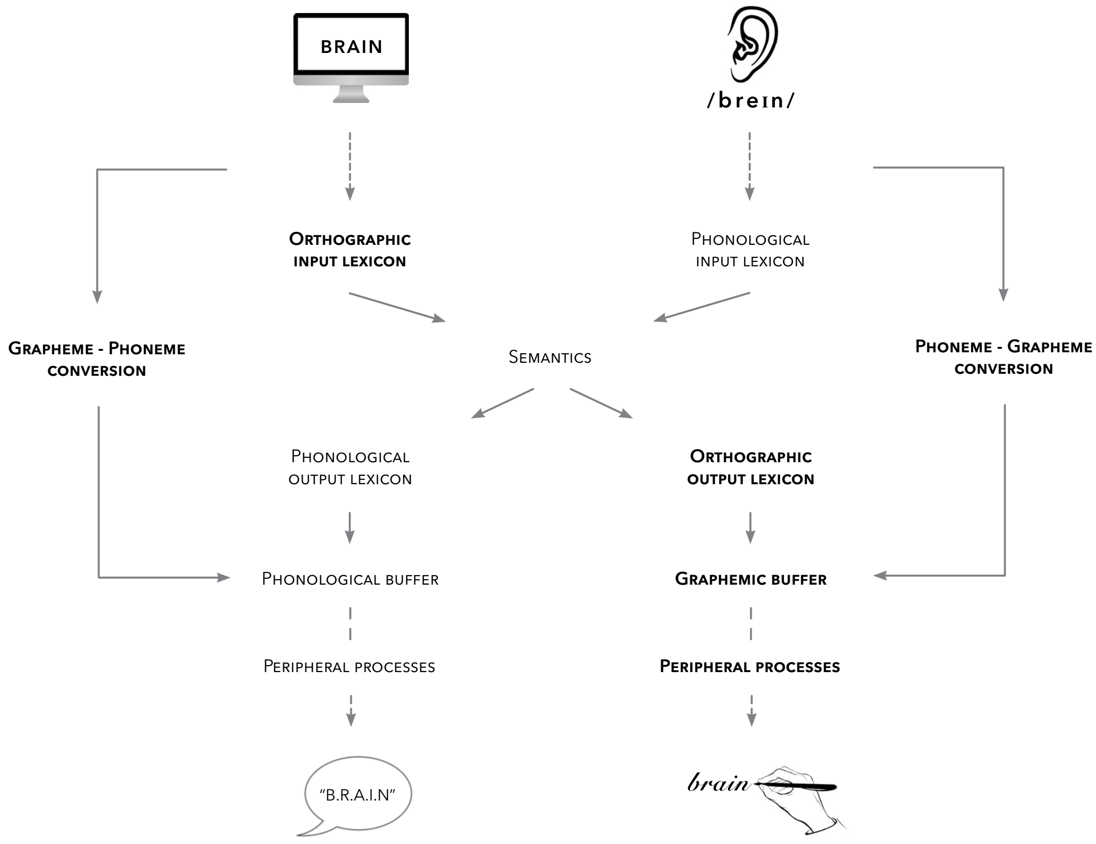

Figure 1.1 Cognitive architecture of reading and spelling processes. Components represent repositories (containing information) and processors of information (guiding towards information). Arrows represent channels of communication between the different processes. Cognitive processes printed in bold represent reading- and spelling- specific components. The model is an adaptation from Ellis and Young [48].

Reading

For the cognitive processes underlying reading, relative circumscribed neural regions have been identified by lesion and neuroimaging studies (Figure 1.2; For a review – see [30]). This anatomo-functional knowledge may indicate for which glioma locations it is advisable to focus on reading evaluations.

When a familiar word is read, the orthographic representation (i.e., strings of abstract letter identities; graphemes) that is stored in the *orthographic input lexicon* is recognized. Impaired access or functioning of the orthographic input lexicon results in the loss of stored word representations. When orthographic input lexicon is damaged in the presence of spared grapheme-phoneme conversion, words will be read via that sublexical pathway. Regular words will be read correctly (e.g., *miss* > /mɪs/ [ii]), while words with irregular or unpredictable orthography will be read incorrectly (e.g., *bear* > /bɪr/). Errors are typically "phonological plausible", as the pronunciation of the orthographic sequence is legitimate in the language, but not for the specific word. As sublexical processing of words (via grapheme-phoneme conversion rules) is typically slower than lexical processing, damage to the orthographic input lexicon may result in slowed reading. Moreover, since word representations in the mental lexicon are coded for grammatical class, and are sensitive to frequency of usage, damage to this level may affect low-frequency words more severely than high-frequency words, and selectively disrupt performance on a grammatical class. In the lesion and neuroimaging literature, processing of orthographic input lexicon has consistently been reported in the posterior part of the inferior temporal gyrus [49] (Figure 1.2).

The meaning corresponding to the orthographic string is subsequently activated in the *semantics* component. Semantic damage prevents access to the meaning of the word. When this component is selectively damaged, in the presence of spared sublexical processing, words will be read via grapheme-phoneme conversion rules, possibly yielding stress assignment errors in reading. This particular component is also targeted in widely used spoken language tasks (e.g. in object naming), and has been the focus of many previous awake surgery studies. With the aim to evaluate how written language assessment could complement current glioma practice, we therefore do not concentrate on semantics in this thesis.

To pronounce the identified word correctly, the stored pronunciation, or phonological representation, must be accessed in the *phonological output lexicon*. Damage to phonological output lexicon impairs access to the target phonological word form. In the case of preserved grapheme-phoneme conversion, words will be read through the sublexical pathway. Irregular, low-frequency words and words from

[ii] Stimuli are denoted in *italics*, and reading output is written in /International Phonetic Alphabet/

certain grammatical classes are then more error-prone than regular or high-frequency words. Errors typically result from applying grapheme-phoneme correspondences that are acceptable in the language, but unacceptable for that word (*comb* > /komb/). Processing of this component has been related to the posterior part of the middle temporal gyrus [50-52] and the inferior frontal gyrus [53-55] in lesion and neuroimaging studies (Figure 1.2).

The phonological representation is temporarily placed in a working memory component (the *phonological output buffer*), which maintains the representation accessible for the time needed to activate subsequent peripheral processes. Selective damage to phonological buffer results in the inability to maintain information on the identity, number and order or phonemes active while programming and executing motor output. Phonemic level errors will occur (e.g., *celebration* > /ˌsɛbəˈbreɪʃən/ / ˌsɛlbreɪʃən/ /ˌsɛləˈbreɪʃɔɪn/), more frequently in response to long than to short stimuli, but with comparable frequency across spoken tasks and in both words and non-words. Anatomo-functional correlates of the phonological output buffer have been most consistently reported in supramarginal gyrus processing [35,56,57], as well as the posterior part of the inferior frontal gyrus / the inferior part of the precentral gyrus [58-60] (Figure 1.2).

Lastly, word reading relies on *peripheral processes*, which convert abstract information into speech output (i.e., specific motor programs for articulation). Impaired peripheral processing prevents access to motor programming and articulation, which may result in dysarthria or apraxia of speech in reading as well as across all spoken tasks. Similar to the semantic component, we therefore do not concentrate on peripheral processing in this thesis.

In parallel to words, we can also read unfamiliar or non-existing words (i.e., non-words). As these sequences are not part of the subject's vocabulary, they have no stored meaning and are not represented in the orthographic or phonological lexicons. As a result, these non-words cannot be processed by the lexical-semantic route. Instead, they are read via sublexical *grapheme-phoneme conversion* processes, by applying language-specific rules that convert graphemes (or short graphemic sequences) into phonemes (or short phonemic sequences). The subsequent processing of phonological representation is effected via the same phonological buffer and peripheral processes as words. Selective damage to grapheme-phoneme conversion processing yields errors on non-words (*bluck* > /talf/), while leaving words unaffected. Errors result from incorrect print-to-sound mapping and usually are not orthographically or phonologically related to the target non-word. In the anatomo-functional literature of reading, critical nodes for grapheme-conversion processing are tied to the superior temporal gyrus [51,58] and the supramarginal gyrus [61-64], or posterior perisylvian regions in more general terms [46,65-68] (Figure 1.2).

Moreover, increasing attention is appointed to the neural substrates of sublexical processing with regards to the underlying subcortical tracts, within a dual-stream model of reading. In this model, lexical processing is considered to rely on a ventral stream, which connects posterior parts of the middle temporal gyrus with fronto-insular-temporal regions [62,69-71], and sublexical processing on a dorsal stream that connects posterior parts of the superior temporal gyrus with posterior parts of the inferior frontal gyrus via the supramarginal gyrus and fronto-parietal regions [62,66,71,72]. Subcortical tracts that modulate the information processing are in particular the arcuate fasciculus and the superficial layer of the inferior fronto-occipital fasciculus for dorsal processing, and the deep layer of the inferior fronto-occipital fasciculus for the ventral stream [62,71,72].

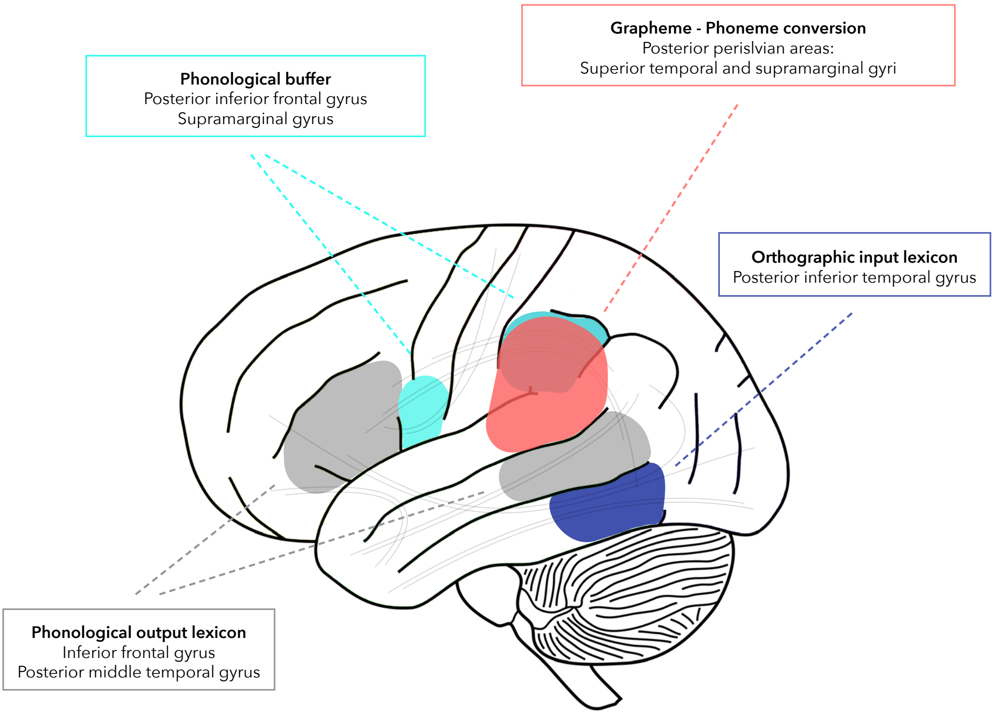

Figure 1.2 Schematic overview of neural regions identified in central reading processes. Cortical regions that are most consistently reported in lesion and neuroanatomical studies are depicted. For the orthographic input lexicon, the posterior part of the inferior temporal gyrus is frequently reported. For phonological buffer processing, involvement of the posterior part of the inferior frontal gyrus (inferior precentral gyrus) and supramarginal gyrus are mentioned. For the phonological output lexicon, the inferior frontal gyrus and the posterior part of the middle temporal gyrus are mentioned. Grapheme – phoneme conversion processing is thought to rely on posterior perisylvian areas, including the posterior part of the superior temporal gyrus and the supramarginal gyrus.

Reading in awake surgery

It was evaluated if this knowledge from lesion and neuroimaging studies can be applied to glioma patients in neurosurgical practice. Assessments of reading in awake surgery studies have provided possible support for dual-stream processing, by reporting disruption of non-word reading during stimulation of the posterior part of the arcuate fasciculus [73]. Moreover, induced alexia was reported during stimulation of the posterior part of the superior temporal gyrus [74], the supramarginal gyrus [74], and the posterior part of the middle/inferior frontal gyrus [75], which were all identified as neurofunctional correlates of reading, as depicted in Figure 1.2.

Although these results confirm that the identified neural regions are crucial for reading processes, data do not provide information about the involvement of individual underlying components. Moreover, a large discrepancy in reading tasks and error definitions used across studies further complicate interpretations [27]. Hence, reading monitoring in neurosurgical practice should be exploited further to focus on the independent components.

Spelling

Compared to reading, spelling processes have received even less attention in the literature. Although lesion and neuroimaging studies have identified neural regions that may be involved in the execution of certain components, there remains an ongoing debate concerning certain specific anatomo-functional correlates of spelling. Furthermore, reports of spelling monitoring in awake surgery studies are particularly scarce, and it is largely unknown if and how knowledge from other populations applies to glioma patients. We will therefore address the functional neuroanatomy of spelling and exploit available data of spelling in glioma practice in a separate chapter (Chapter 2).

Outline of the thesis

As an understudied but crucial aspect of quality of life, written language remains often neglected in glioma practice. The aim of this thesis is to contribute to the improvement of written language monitoring in glioma patients, by evaluating current assessments and providing alternatives for clinical practice.

Chapter 2 is a systematic literature review of the assessment of spelling in glioma patients undergoing awake surgery. This review examines how current neuroanatomical theories may guide neurosurgical practice, and provides a first overview of the frequency of dysgraphia in awake surgery.

In Chapter 3, a retrospective study is described, which evaluates the use of short clinical subtests in glioma practice. Quantitative and qualitative analyses are conducted before and after awake surgery to examine how evaluations of written language in glioma patients may be improved.

Chapter 4 provides an overview of the development of the written language battery for glioma patients, which was standardized in a neurologically healthy Italian and Dutch population.

In Chapter 5, the efficacy of the written language battery for glioma patients is assessed. Two cases studies are described to validate that the cognitive examination tool is more sensitive than a current clinical battery, and demonstrate its clinical application in neurosurgical practice.

Chapter 6 is a clinical group study, in which the influence of intra-operative assessment on written language outcome after glioma surgery is inspected. This study provides insight in how reading and spelling may be affected in glioma patients, and gives considerations for intra-operative task selection.

In Chapter 7, the influence of lesion site, cognitive profiles and timing of post-operative assessments is discussed. These are considered with regard to interpretations of written language in glioma patients undergoing awake surgery.

Finally, Chapter 8 provides a general discussion of the main findings and gives directions for future studies.

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2

Assessing spelling in glioma patients undergoing awake surgery: A systematic review [i]

[i] This chapter was submitted as: Van Ierschot, F.C., Bastiaanse, R., & Miceli, G. Assessing written spelling in glioma patients undergoing awake surgery: A systematic review. *Submitted to Neuropsychology Review*

Abstract

Written spelling has become crucial in daily life with an increasing reliance on text-based communication. Awake surgery for glioma treatment has devoted scarce attention to spelling, even though one of its main goals is the preservation of language to facilitate return to work and to maintain quality of life. We review assessments of written spelling carried out in awake surgery studies, to inspect how current neuroanatomical theories may guide neurosurgical practice. A systematic database search in Embase, Medline, PubMed and Web of Science identified studies reporting on spelling assessment in glioma patients undergoing awake surgery. Twenty-three studies were included, 9 of which report details on spelling assessments. We evaluate the incidence of dysgraphia in glioma patients, the type of spelling errors in light of tumor location, and the specificity of spelling sites with respect to other language functions. Post-operative dysgraphia arose in 26.9% of the patients with preserved pre-operative spelling, and persisted in 45.0% of them at follow-up. Intra-operative stimulation elicited isolated spelling interferences in 37.7% of the patients. A network of frontal, parietal and temporal regions was found to underlie central and peripheral spelling processes. Glioma data converged with anatomo-functional knowledge of spelling can aid neurosurgical practice, yet more controlled examinations of written spelling are needed to draw reliable probabilistic (sub)cortical resection maps. Clinical guidelines are proposed for a detailed examination of spelling, to predict and ultimately prevent spelling disorders in glioma patients, as to preserve quality of life after awake surgery.

Introduction

Awake surgery aims at resecting tumor tissue while preserving linguistic and sensorimotor functions. Given the relatively long survival of patients with low-grade gliomas (i.e., from 5 to over 15 years after diagnosis [1]), preservation of language is crucial to facilitate return to work and to maintain quality of life. As a result, interest in language assessment has increased over the last decades [2-6]. Studies on awake surgery have mostly focused on spoken language, while paying less attention to written language [7]. Given the increasing amount of text-based communication (e.g., Internet surfing, e-mailing and instant messaging), intact reading and written spelling (handwriting and typing) have risen from the status of luxury skills to that of basic needs in personal and professional life. Written language monitoring in glioma patients undergoing awake surgery is thus of critical relevance. An increasing number of reports on the assessment of reading has been published recently [8-11]. However, tasks evaluating written spelling are still largely neglected.

This state of affairs in awake surgery contrasts with the development of detailed hypotheses on the neurofunctional architecture of written spelling by lesion and neuroimaging studies. Based on these investigations, it is possible to predict the pattern of impairments that is most likely to follow damage to each functional and anatomical component of the spelling system. The possibility to associate distinct error types to the impairment of specific spelling processes and to predict that a given error type should follow damage to specific brain regions, provides the neuroscientist with powerful testing tools for the diagnosis of functional damage. In the context of awake surgery, this opportunity can be exploited before, during and after surgery, and can provide helpful constraints and opportunities for neurosurgical practice. Following a brief outline of the current hypotheses on the functional and neuroanatomical organization of spelling processes, we review the evidence reported in neurosurgical studies, and assess its strengths and weaknesses *vis à vis* the practice of awake surgery and the investigations on the neural underpinnings of the spelling system.

The functional architecture of spelling

The processes involved in spelling-to-dictation tasks are schematically reproduced in Figure 2.1. The model (adaptation from Ellis & Young [12]) shows both spelling-specific components, which are engaged only in spelling tasks, and components that are recruited during spelling tasks, but are shared by other language tasks. For example, spelling-to-dictation starts with the auditory analysis of a spoken string (phonological input). When the stimulus is a word, the stimulus string activates a phonological representation stored in a long-term memory component (the *phonological input lexicon*), which in turn activates the corresponding meaning representation in the *semantics* component.

From this stage on, spelling-specific representations are activated. The meaning of the target word activates the corresponding orthographic string in a long-term memory system – the *orthographic output lexicon* [i]. The string is placed in a working memory component (the *graphemic buffer* [ii]), that maintains the orthographic sequence active for the time needed by downstream processes to sequentially convert graphemes into task-specific output formats (i.e., *grapheme-letter name conversion* for oral spelling, *grapheme-allograph conversion* and *allograph-graphomotor planning* for handwriting, and *grapheme-graphomotor planning* for typing).

Non-words (e.g., sequences that are not part of the subject's vocabulary, such as *pretil*) cannot be processed by the lexical-semantic route, as they have no meaning and are not represented in the phonological or orthographic lexicons. They are spelled via sublexical *phoneme-grapheme conversion* [ii] processes, i.e., by language-specific rules that convert phonemes (or short phonemic sequences) into graphemes (or short graphemic sequences). The stages of processing that follow phoneme-grapheme procedures are identical to those involved in word handwriting, typing and oral spelling.

Evidence for the functional architecture sketched in Figure 2.1 has been provided by cognitive neuropsychological studies in subjects with acquired spelling disorders (dysgraphia; mostly following cerebrovascular accidents). These investigations have shown that each component of the spelling processes may be damaged selectively, and have elucidated the error patterns expected in each case.

Damage to the orthographic output lexicon results in the loss of stored word representations. Since word representations in the mental lexicon represent grammatical categories and are sensitive to frequency of usage, damage to this level may selectively impair a specific class of words (disproportionate impairments of nouns as opposed to verbs, or *vice versa*), and will typically affect low-frequency words more severely than high-frequency words. When the orthographic output lexicon is damaged selectively in the presence of spared phoneme-grapheme conversion (as in the so-called 'surface dysgraphia' [13]), spelling relies on such sublexical procedures. As a consequence, the patient can still spell words with transparent orthography (e.g., *miss* > MISS[ii]) and non-words (e.g., *nabe* > NABE) correctly, but produces "phonologically plausible" responses to words with irregular or unpredictable orthography (e.g., *subtle* > SUTTEL and *yacht* > YOT in English, or *saint* > CEIN in French). The defining feature of these errors is the presence of orthographic sequences that are permissible in the language, but do not correspond to entries in that language's vocabulary (for a review, see [14]).

[i] In the literature, the terms orthographic output lexicon/orthographic long-term memory, phoneme-grapheme conversion/phonology-orthography conversion, graphemic buffer/orthographic buffer/orthographic working memory are used interchangeably.
The terminology as presented in Figure 2.1 is used in this chapter.

[ii] Throughout this chapter, we denote dictated stimuli in italics, and written strings in CAPITALS.

A different error pattern is observed following selective damage to phoneme-grapheme conversion procedures (also referred to as 'phonological agraphia'). In this case, spared orthographic lexical knowledge ensures correct responses to words (regardless of regularity and grammatical class), but damage to sublexical conversion yields errors on non-words [15]. Selective damage to the graphemic buffer results in the inability to maintain information on the identity, number and order of graphemes active while spelling the target string. Consequently, errors affect long stimuli more than short stimuli and result in letter substitutions, insertions, omissions and transpositions (e.g., *table* > TARLE, TABOLE, TABE, TALBE). Words and non-words are comparably affected [16], and word spelling accuracy is not constrained by regularity, grammatical class or frequency of usage.

Damage to any of these levels will affect all spelling tasks to a comparable extent. This is because handwriting, typing and oral spelling share the task-independent, spelling-specific central mechanisms needed to process orthographic information (irrespective of whether it is retrieved in the orthographic lexicon, or assembled by phoneme-grapheme procedures; Figure 2.1). However, they differ in the peripheral mechanisms needed to convert orthographic knowledge in a task-specific format [12]. Selective damage to one of these mechanisms can affect just one spelling task. Thus, selective damage to grapheme-letter name conversion will disrupt only oral spelling; damage to grapheme-allograph conversion or allograph-graphomotor planning will affect only handwriting; and, damage to grapheme-graphomotor planning will disrupt only typing. Such cases are rare [14]. The error types that follow selective damage to the various components of the spelling system are depicted in Figure 2.1.

The neural correlates of spelling

Converging evidence from lesion data in brain-damaged patients with acquired dysgraphia and from neuroimaging investigations in healthy individuals has tied spelling-specific processes to increasingly detailed anatomical loci in the left, language-dominant hemisphere (Figure 2.2).

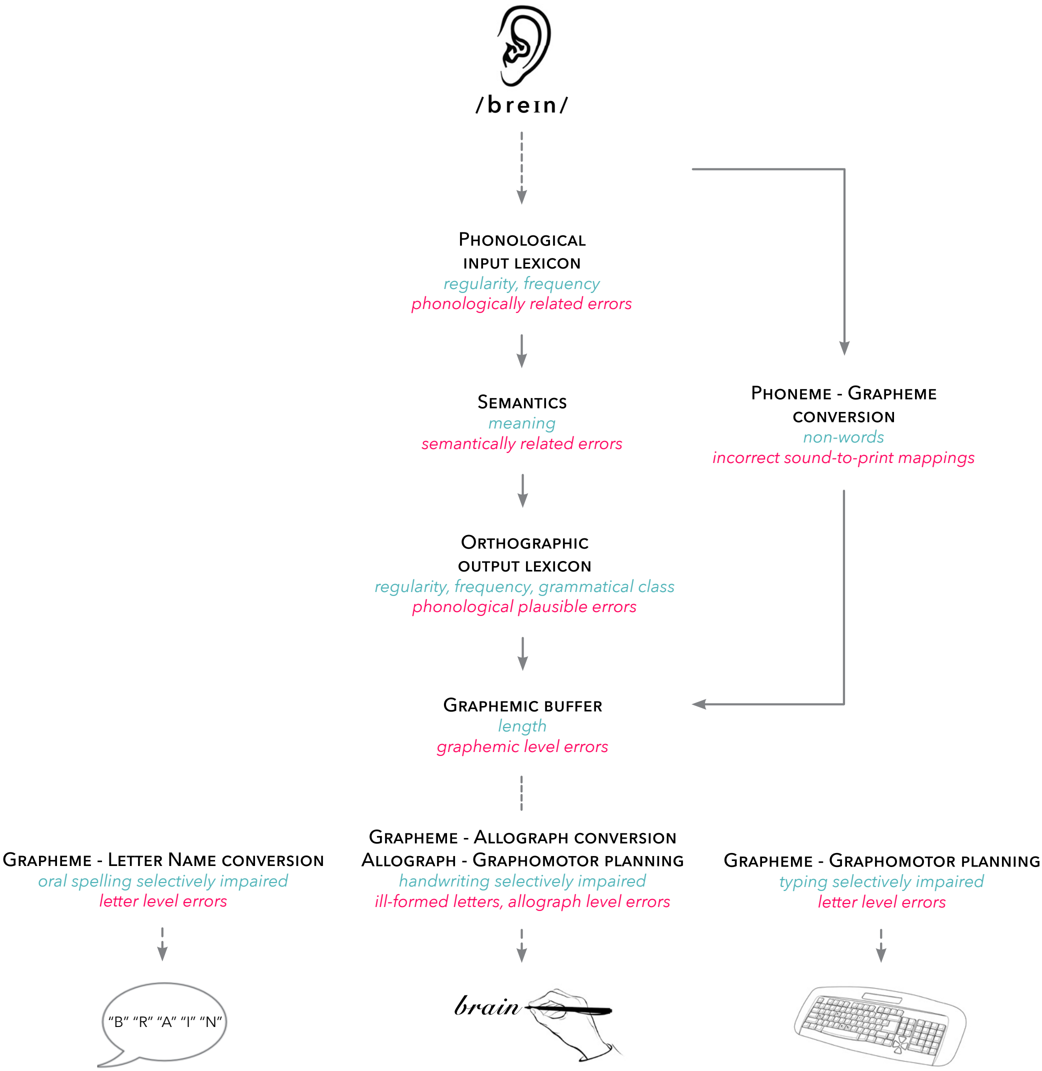

Figure 2.1 Cognitive architecture of the spelling process at the single item level, with frequent error profiles after selective component damage. Psycholinguistic variables sensitive for damage to specific components are printed in green. Frequent error types observed following damage to specific components are printed in red. Components represent repositories (containing information) and processors of information (guiding towards information). Arrows represent channels of communication between the different processes. The model is an adaptation from Ellis and Young [12].

Orthographic output lexicon

Early lesion studies documented damage to the orthographic lexical following lesions of the superior temporal lobe [17], and of the parieto-occipital junction [13,18,19] including the angular gyrus [20,21]. However, subsequent studies with more precise localization techniques report sparing of the superior temporal gyrus, the parietal lobe [22], and of the angular gyrus [23,24], and identified other regions for orthographic lexical processing. The typical signs of orthographic output lexicon damage (misspellings influenced by regularity and frequency) were observed in patients with damage to the inferior temporal and posterior occipito-temporal (fusiform) gyri [23-25] and to posterior inferior frontal regions [26,27]. In a recent lesion study, loss of orthographic lexical information was associated with damage to two distinct loci, in the ventral temporal lobe and in the posterior inferior frontal gyrus [22]. Neuroimaging studies in healthy populations provide converging evidence for the relation between inferior frontal and inferior temporal gyri and lexical spelling processes [28,29]. fMRI studies showed increased BOLD activity in these areas in response to low-frequency compared to high-frequency words in an alphabetic language [30]. In non-alphabetic languages, analogous results were noted in the left fusiform [31,32], but not the inferior frontal gyrus [31].

Phoneme – grapheme conversion

Damage to sublexical phoneme-grapheme conversion processes has been associated with perisylvian lesions. In early studies, phoneme-grapheme damage (phonological agraphia) was reported following posterior perisylvian lesions [15,21,33,34]. More recent studies show impaired phoneme-grapheme processing following both damage to posterior (including superior temporal gyrus and supramarginal gyrus [35]) and to anterior perisylvian regions (including inferior frontal gyrus, precentral gyrus and insula [35,36]). Failure to identify cases with solely anterior or posterior perisylvian damage led Rapcsak [37] to conclude that a distributed perisylvian network, rather than a specific perisylvian region, underlies phoneme-grapheme conversion. Neuroimaging studies in healthy volunteers showed increased BOLD activity in the posterior superior temporal gyrus during non-word spelling [38].

Graphemic buffer

Early studies associated graphemic buffer damage to small superior angular gyrus [39] or frontal lesions [40,41], or to more extensive damage including the fronto-parietal junction [16]. Studies using finer spatial resolution confirmed the association between graphemic buffer damage and parietal [42] and fronto-parietal lesions [43]. In 10 cases with selective buffer damage, lesions overlapped in the intraparietal sulcus [22]. In these subjects, additional damage to frontal regions was documented, but failed to reach significance [22]. Lesions in subcortical prefrontal areas and in pre- and postcentral gyri correlated with graphemic buffer damage profiles [44]. Two fMRI studies examining graphemic buffer-related activity in healthy subjects found increased neural activity in the posterior portion of the left superior and middle frontal gyri [31,45], the left superior parietal lobe around the intraparietal sulcus [45], and in the inferior parietal lobe including the angular gyrus [31]. Interestingly, the angular gyrus was not independently identified in two large meta-analyses focusing on central spelling processes [28,29].

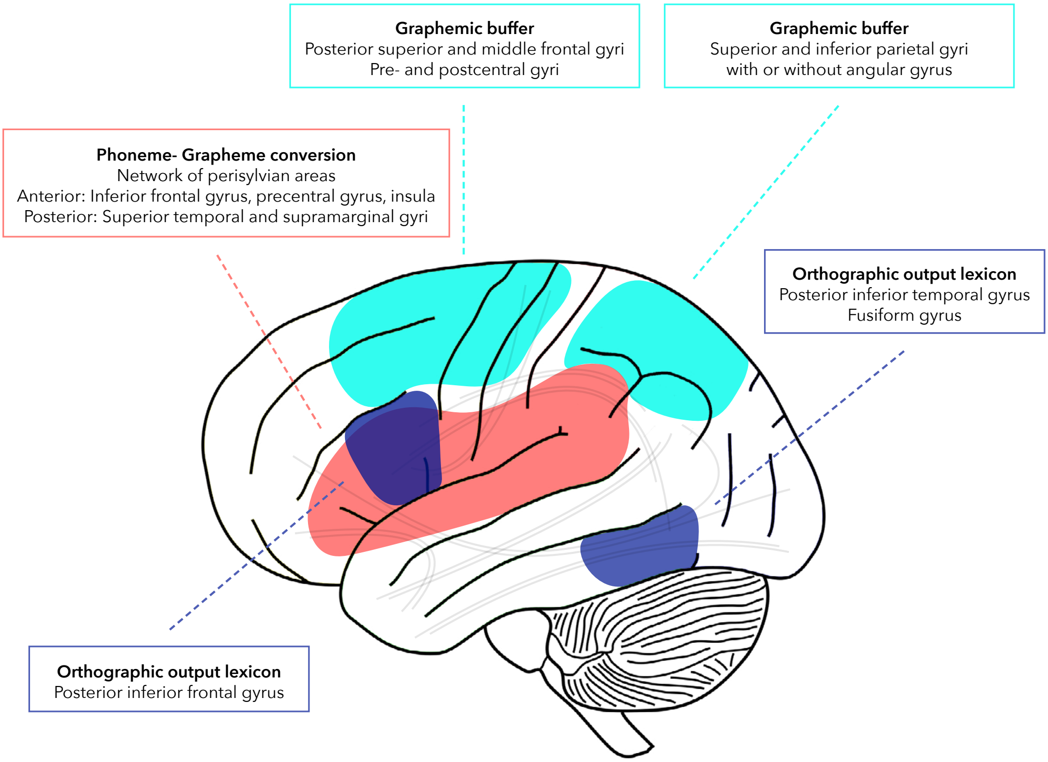

Figure 2.2 Schematic overview of neural regions identified in spelling-specific central processes. Cortical regions that are most consistently reported in lesion and neuroanatomical studies are depicted. For the orthographic output lexicon, posterior IFG and the posterior ITG (fusiform gyrus) are frequently reported. Phoneme – grapheme conversion processing is thought to rely on a distributed network of perisylvian regions, including anterior (IFG, PreCG, Insula) and posterior (SMG, STG) areas. For graphemic buffer processing, involvement of posterior frontal regions (SFG, MFG, PreCG), parietal regions (PoCG, SPL, IPL, with or without the AG) and subcortical prefrontal regions are mentioned.

Task-specific components of spelling

Lesion and neuroimaging studies of task-specific spelling processes are rare. The posterior aspects of the middle and superior frontal gyrus and the superior parietal lobe are thought to be relevant for allograph conversion and letter name conversion. Posterior frontal regions include the dorsal premotor areas that were associated with graphomotor skills [46]. Supplementary motor areas have been involved in motor planning and initiation [26,47]. Motor impairments of handwriting have been frequently described also following superior parietal lobe lesions [33,48,49]. Similarly, motor areas in the cerebellum, caudate, putamen and thalamus may be involved in peripheral handwriting processes [28], but whether their role in handwriting is specific remains to be established. The neural correlates of peripheral processes of typing and oral spelling are still largely unexplored.

The current study

This review examines the studies on awake brain surgery that assessed written spelling abilities before, during and after surgery. It aims at understanding how the practice of awake surgery can benefit from current hypotheses on the functional neuroanatomy of spelling processes. To this end, the reported incidence of dysgraphia associated with awake surgery for gliomas in various regions of the dominant hemisphere is evaluated, and error types are correlated to lesion sites. Given that awake surgery provides an unique opportunity to directly inspect the neural correlates of language functions using Direct Electrical Stimulation (or DES) of specific brain areas during surgery, the effects of intra-operative stimulation on spelling skills are identified, in combination with those on other language and cognitive skills, to distinguish sites yielding pure interference with written spelling from those resulting in combined interference with other language tasks. Current anatomo-functional knowledge and available evidence from neurosurgery studies may provide constraints to awake surgery practice, for example by identifying the patients for whom an assessment of written spelling should be strongly advised or less advisable. Some clinical guidelines for the peri-operative and follow-up monitoring of spelling tasks in glioma patients undergoing awake surgery are proposed. We also discuss how evidence from neurosurgical cases can contribute to a fine-grained understanding of the neural underpinnings of spelling processes.

Methods

To identify all studies that address written spelling tasks in glioma patients undergoing awake surgery, publications until 1 February 2016 were systematically searched in electronic databases (Embase, Medline, PubMed and Web of Science). An example of the search string used is reported in Appendix A. All search results were screened and irrelevant studies targeting different patient groups were excluded. All remaining full-text articles were assessed for eligibility based on the description of written spelling assessment in glioma patients undergoing awake surgery. Studies describing glioma patients who did not undergo awake surgery or pediatric glioma patients, and publications different from primary studies (i.e., editorials, errata, letters, notes, reviews, conference abstracts, or conference papers) were excluded. The level of detail in reporting assessment results was not considered at this stage. For each study, the types of stimuli used for assessment task design, timing of assessment(s), error classification, error analyses, associated errors, patient characteristics, tumor characteristics, and identified (sub)cortical areas were considered.

Results

The electronic database search identified 621 articles. Three additional publications were added manually. In the screening stage, 192 duplicates and 148 irrelevant studies were excluded. Another 203 studies were excluded because they reported on different patient groups, or focused on neuroimaging, neurology or oncology rather than on neurocognitive issues. The remaining 78 full-text articles were assessed for eligibility. Fifty-five studies that did not report written spelling assessment, did not consider awake surgery, or described pediatric patients were excluded. The remaining 23 studies, which considered written spelling performance in patients undergoing awake surgery for gliomas, were included in this review (Figure 2.3).

In 14 papers, the assessment of written spelling is described very superficially. In 10 of these, results are provided without details on testing tools and error analyses. Post-operative difficulties are reported in most studies [51-57], but not in all [58-60]. Two papers report performing assessments of written spelling, of which they do not provide results [61,62]. In two other studies, results on written spelling tasks are conflated with those of other written language tasks in the context of elaborate batteries [63,64].

The remaining 9 studies provide more detailed information and are retained for analysis (Table 2.1). Of these, 7 include pre- and post-operative testing, and 7 (from 4 research groups) monitored spelling intra-operatively. Some are single-case studies [10,65-68], others are group studies [7,69-71]. These studies include patients with low-grade gliomas (5/9 studies), high-grade gliomas (5/9 studies), and/or other brain tumor types (3/9 studies). All studies recruited patients with gliomas in the language-dominant hemisphere, except for Roux and colleagues, who also examined 9 right-handed patients with right-hemisphere gliomas [7,66,71]. In this latter group, intra-operative stimulation affected spelling in one patient only [66]. Most studies do not report the extent of resection, nor whether patients were receiving adjuvant therapy at the time of testing.

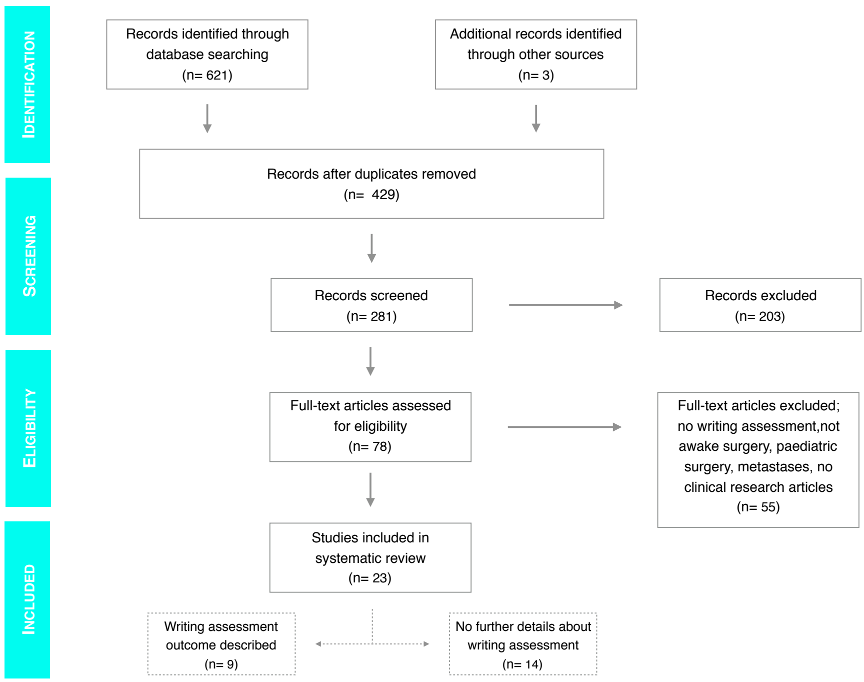

Figure 2.3 Flow-chart of Systematic Review search following PRISMA guidelines [50]. A total of 624 records were identified using the search string (Appendix A) and through other sources. From these, 23 studies that mentioned written spelling assessment in glioma patients undergoing awake surgery were included. Of these, 14 are reported briefly due to lack of assessment specifications, and 9 are described in detail, as they provide details on assessments and its outcomes.

Table 2.1 Overview of studies describing detailed assessment of spelling in glioma patients undergoing awake surgery

Study, year	Pre spelling, timing	Intra spelling	Post spelling, timing	Follow-up spelling, timing	Patient(s) characteristics					Tumor characteristics			Cortical stimulation	Subcortical stimulation	Extent of resection	Adjuvant therapy
					n	Gender	Age	Hand	Language	Tumor Type (grade)	Tumor site	Tumor Location				
Scarone et al., 2009	Yes, NS	No	Yes, within 48h	Yes, 3 & 24 months	15	9F, 6M	μ = 38	13 rh 2 lh	French	LGG (NS)	13 LHe, 2 RHe	- Frontal: SMA, anterior IFG/MFG - Parietal: SPL, SMG - Insular			5 total, 8 subtotal, 2 partial	NR
Tomasino et al., 2015b	Yes, NS	No	Yes, 1 week	Yes, 1 year	1	M	42	rh	Italian	LGG (NS)	LHe	- Temporal: STG, posterior perisylvian regions			NR	NR
Lesser et al., 1984	Yes, NS	Yes (grids)	No	No	3	1F, 2M	30, 34, 36	rh	NR	1 LGG (NS), 2 Other	LHe	- Frontal: IFG	Yes	No	NR	NR
Roux et al., 2003	Yes, days	Yes	Yes, 1-12 weeks	No	6	4F, 2M	μ = 52	rh[a]	French	2 HGG (III), 4 Other	5 LHe, 1 RHe	- Parietal: AG	Yes	No	NR	NR
Lubrano et al., 2004	Yes, NS	Yes	Yes, within 1 week	Yes, 2 months	14	8F, 6M	μ = 47	12 rh 2 lh	French	6 HGG (III, IV), 1 LGG (NS), 7 Other	11 LHe, 3 RHe	- Frontal: posterior, SFG, MFG, IFG	Yes	No	NR	RT for some
Roux et al., 2009	Yes, NS	Yes	Yes, 18 days (1/12), NS (11/12)	Yes (1/12), 103 days; NR (11/12)	12	5F, 7M	μ = 37	10 rh 2 lh	French	NR	11 LHe, 1 RHe	- Frontal: posterior SFG, MFG, IFG	Yes	No	NR	NR
Magrassi et al., 2010	Yes, 1 week, NS	Yes	Yes, NS	No	2	1F, 1M	82, 38	rh	Italian	2 HGG (III, IV)	LHe	- Parietal: anterior SPL	Yes	No	NR	NR
Roux et al., 2014	Yes, NS	Yes	Yes, 1 month	No	30	9F, 21M	μ = 48	27 rh 3 lh	French	15 HGG (NS), 9 LGG (NS)	23 LHe, 7 RHe	- Temporo-parietal	Yes	No	NR	NR
Motomura et al., 2014	NR	Yes	NR	NR	1	M	48	rh	Japanese	HGG (IV)	LHe	- Parietal: IPL	Yes	Yes	90%	NR

NR = Not Reported, NS = Not Specified; F = female, M = male; μ = mean; rh = right hander, lh = left hander; LGG = Low-Grade Glioma, HGG = High-Grade Glioma, Other = Metastases, Cavernoma, Meningioma, Arteriovenous Malformation, Clonic Seizure, Cortical Dysplasia; LHe = Left Hemisphere, RHe = Right Hemisphere; SFG = Superior Frontal Gyrus, MFG = Middle Frontal Gyrus, IFG = Inferior Frontal Gyrus, SMA = Supplementary Motor Area, SPL = Superior Parietal Lobe, IPL = Inferior Parietal Lobe, SMG = Supramarginal Gyrus, AG = Angular Gyrus, STG = Superior Temporal Gyrus; RT = Radiotherapy. [a] 1 patient EHI +60 but handwriting LH

Our analyses focus on pre-, intra- and post-operative assessments, and on follow-up evaluations. Reports vary along many dimensions, of which the most critical are timing of assessments, testing tools, patient selection criteria (Section 3.1) and scoring criteria (Section 3.2). Pre-operative assessments were generally conducted within a week before surgery. Post-operative assessments took place at intervals ranging from 48 hours to a month after surgery. Follow-up evaluations took place 2 to 24 months after surgery (four studies [7,10,69,70]). Although written spelling comprises of handwriting and typing, only 1/9 studies discussed typing in addition to handwriting [68]. Therefore, we restrict analyses of written spelling performance in this study to handwriting.

Pre- and post-operative handwriting performance was always assessed via *handwriting to dictation* [words, non-words, sentences, single letters/numbers, or unspecified], and less systematically by means of *copying* [words, sentences, single letters/numbers], *written naming*, *spontaneous handwriting*, and *serial handwriting* tasks. Details on test structure are provided in only one study [69]. In 3/7 studies with pre- and post-operative spelling testing, the assessment was part of language batteries for the clinical evaluation of aphasia [72-74]. Intra-operatively, most patients were asked to *write sentences to dictation*, but also to *write words to dictation*, to *write spontaneously*, to *write words in response to an on-screen cue* (Table 2.2). In most cases, spelling was part of broader intra-operative protocols, including object naming and/or reading tasks. Except for the earliest study [65], all intra-operative investigations used Direct Electrical Stimulation [75,76].

We inspect the incidence of dysgraphia at pre-operative, post-operative and follow-up evaluations (Section *The incidence of spelling disorders in glioma surgery*); the types of errors observed during peri-operative and follow-up assessments (Section *Error types observed*); and whether intra-operative interference with spelling occurs in isolation or combined with disruption of other linguistic processes (Section 3.3). Owing to the substantial variability and lack of detail in the available data, reviewed studies did not allow performing a meta-analysis. Performance evaluations will be conducted on different patient samples. In each case, performance will be discussed in relation to intra-hemispheric lesion site in the language dominant hemisphere.

Table 2.2 Current assessments of spelling in awake surgery: Pre-, intra-, and post-operative testing and follow-up

Study (author, year)	Testing	Spelling assessment (as handwriting)	Test variables	Nb of items	Spelling errors reported (number of patients / total number of patients)	Interpretation (number of patients / total number of patients)
Scarone et al., 2009	**Pre**	BDAE: - To dictation: words, sentences, letters, numbers - Written naming - Serial handwriting	Length, Complexity	62	No errors (15/15)	Unimpaired, *as inclusion criterion* (15/15)
	Post	BDAE: - To dictation: words, sentences, letters, numbers - Written naming - Serial handwriting	Length, Complexity	61	- IFG / MFG: Spelling errors; *letter level and word level* (2/2) - SMA: Altered handwriting; *ill-formed, non-fluent* (4/4) - SMG: Altered handwriting & Spelling errors; *slow & letter level* (4/4) - SPL: Altered handwriting & Spelling errors; *spatial disorganization, ill-formed, non-fluent & letter level* (2/4), Altered handwriting (1/4), Spelling arrest (1/4) - Insula: Altered handwriting & Spelling errors; *ill-formed & letter level* (1/1)	Impaired, *as inclusion criterion* (15/15): - IFG / MFG: Central impairment (2/2) - SMA: Peripheral impairment (4/4); - SMG: Peripheral & Central impairment (4/4); - SPL: Peripheral & Central & Uninterpretable impairment (4/4); - Insula: Peripheral & Central impairment (1/1);
	Follow-up	BDAE: - To dictation: words, sentences, letters, numbers - Written naming - Serial handwriting	Length, Complexity	61	- IFG / MFG: No errors (1/2), NR (1/2) - SMA: No errors (1/4), Altered handwriting; *ill-formed, non-fluent* (2/4), Altered handwriting & Spelling errors; *ill-formed, non-fluent & letter level* (1/4) - SMG: No errors (1/4), NR (3/4) - SPL: Altered handwriting; *non-fluent* (2/4), NR (2/4) - Insula: Altered handwriting & Spelling errors; *ill-formed* & *letter level* (1/1 – 6 months), No errors (1/1 – 9 months)	- IFG / MFG: Unimpaired (1/2 – 3 months), NR (1/2) - SMA: Unimpaired (1/4 – 1year), Peripheral & Central impairment (1/4 – 3 months), Peripheral impairment (2/4 – 2 year) - SMG: Unimpaired (1/4 – 3 months), NR (3/4) - SPL: Peripheral impairment (2/4 – 6 months), NR (2/4) - Insula: Peripheral & Central impairment (1/1 – 6 months), Unimpaired (1/1 – 9 months)
Tomasino et al., 2015b	**Pre**	BADA: - To dictation: words, non-words	NR	50	No errors (1/1)	Unimpaired (1/1)
	Post	BADA: - To dictation: words, non-words	NR	50	Spelling errors; *letter level, equally in words and non-words* (1/1)	Central impairment, *as inclusion criterion* (1/1)
	Follow-up	BADA: - To dictation: words, non-words	NR	50	Spelling errors; *letter level, more in non-words than in words* (1/1)	Central impairment; *worsened compared to post* (1/1)
Lesser et al., 1984	**Pre**	- To dictation: sentences - Written picture description	NR	NR	No errors (1/3), Spelling errors; *letter level* (1/3), Spelling errors; *NS* (1/3)	Unimpaired (1/3), Peripheral impairment (1/3), Uninterpretable impairment (1/3)
	Intra	- Written naming: objects - Spontaneous: sentences	NR	NR	Cortical Stimulation - IFG: Spelling arrest & Spelling errors; *word level* (2/3), No errors (1/3)	Cortical Stimulation - IFG: **Combined:** Central & Uninterpretable interference (2/3), No interference (1/3)
Roux et al., 2003	**Pre**	- To dictation: NS - Copying: text	NR	NR	Altered handwriting & NS; *ill-formed* (3/6), No errors (3/6)	Peripheral & Uninterpretable impairment; *compared to pre-morbid sample* (3/6), Unimpaired (3/6)
	Intra	- To dictation: sentences	NR	NR	Cortical Stimulation - AG: Spelling errors; *word and letter level* (at least 1/6), Spelling arrest (at least 1/6), Altered handwriting; *ill-formed* (6/6)	Cortical Stimulation - AG: **Pure:** Peripheral & Central interference (1/6), **Pure:** Peripheral & Uninterpretable interference (1/6), **Combined:** Peripheral interference (4/6)
	Post	- To dictation: NS - Copying: text	NR	NR	NR; *stable compared to pre*	Peripheral & Uninterpretable impairment (3/6), Unimpaired (3/6)
Lubrano et al., 2004	**Pre**	- To dictation: sentences - Copying: words, letters, numbers	NR	NR	NR	Unimpaired, *as inclusion criterion* (12/12)
	Intra	- To dictation: sentences	NR	NR	Cortical Stimulation - Language dominant hemisphere - post SFG: No errors (5/5) - post MFG: Spelling errors & Altered handwriting; *letter level & ill-formed* (2/10), Spelling errors & Spelling arrest; *word and letter level* (3/10), Altered handwriting; *ill-formed* (1/10), No errors (4/10) - post IFG: Spelling errors & Spelling arrest; *word and letter level* (2/6), Altered handwriting; *ill-formed* (2/6), No errors (2/6) - ant STG: Spelling errors; *letter level* (1/1)	Cortical Stimulation - Language dominant hemisphere - post SFG: No interference (5/5) - post MFG: **Pure:** Central & Peripheral interference (2/10), **Combined:** Central & Peripheral & Uninterpretable interference (3/10), **Combined:** Uninterpretable interference (1/10), No interference (4/10) - post IFG: **Combined:** Central & Peripheral & Uninterpretable interference (2/7), **Combined:** Peripheral interference (2/7), No interference (3/7) - ant STG: **Combined:** Central interference (1/1)
	Post	- To dictation: sentences - Copying: words, letters, numbers	NR	NR	Altered handwriting; *ill-formed* (1/12), Spelling errors; *letter level* (1/12), No errors (10/14)	Peripheral & Central impairment (1/12), Central impairment (1/12), Unimpaired (10/12)
	Follow-up	NR	NR	NR	Altered handwriting & Spelling errors; *ill-formed & letter level* (1/12), No errors (2/12), NR (9/12)	Peripheral & Central impairment; *worsened compared to post* (1/12), Unimpaired (11/12)

Roux et al., 2009	**Pre**	MT-86: - To dictation: sentences - Copying: words, letters, numbers	NR	NR	NR	Unimpaired, as inclusion criterion (12/12)
	Intra	- To dictation: sentences	NR	NR	<u>Cortical Stimulation</u> - post SFG: Spelling arrest and/or Altered handwriting; *non-fluent, ill-formed* (1/8), Spelling arrest (2/8), No errors (5/8) - post MFG: Spelling arrest and/or Altered handwriting; *non-fluent, ill-formed* (4/12), Spelling arrest (1/12), No errors (7/12) - post IFG: Spelling arrest (2/4), Spelling errors; *NS* (1/4), No errors (1/4)	<u>Cortical Stimulation</u> - post SFG: **Pure:** Peripheral & Uninterpretable interference (1/8), **Pure:** Uninterpretable interference (1/8), **Combined:** Uninterpretable interference (1/8), No interference (5/8) - post MFG: **Pure:** Peripheral & Uninterpretable interference (4/12), **Combined:** Uninterpretable interference (1/12), No interference (7/12) - post IFG: **Combined:** Uninterpretable interference (2/4), **Combined:** Central interference (1/4), No interference (1/4)
	Post	MT-86: - To dictation: sentences - Copying: words, letters, numbers	NR	NR	Altered handwriting; *non-fluent, ill-formed* (1/12), NR (11/12)	Peripheral impairment (2/12), NR (10/12)
	Follow-up	MT-86: - To dictation: sentences - Copying: words, letters, numbers	NR	NR	Altered handwriting; *non-fluent, ill-formed* (1/12), NR (11/12)	Peripheral impairment (1/12), NR (11/12)
Magrassi et al., 2010	**Pre**	Handwriting and typing (1/2) - To dictation & spontaneous: NS - Copying: words, text, letters Handwriting: NS (1/2)	NR	NR	Spelling errors in handwriting and typing; *NS* (1/2 – 1 week), No errors (1/2 – 1 day), No errors (1/2)	Central impairment (1/2 – 1 week), Unimpaired (1/2 – 1 day), Self-reported peripheral difficulties; (1/2)
	Intra	Handwriting, typing & oral spelling (1/2) - To dictation & spontaneous: sentences Handwriting (1/2) - To dictation & spontaneous: words	NR	16 (1/2) NR (1/2)	<u>Cortical Stimulation</u> - ant SPL: Spelling errors in handwriting and typing & Spelling arrest & Altered handwriting; *word and letter level* & *ill-formed* (1/2), Spelling errors & Spelling arrest & Altered handwriting; *letter level* & *ill-formed*(1/2)	<u>Cortical Stimulation</u> - ant SPL: **Pure:** Central, Peripheral & Uninterpretable interference (2/2)
	Post	Handwriting and typing (1/2) - To dictation & spontaneous: NS Handwriting: NS (1/2)	NR	NR	NR	Unimpaired (2/2)
Roux et al., 2014	**Pre**	- To dictation: sentences - Copying: words, letters, numbers	NR	NR	NR	Unimpaired, as inclusion criterion (24/24)
	Intra	- To dictation: sentences	NR	NR	<u>Cortical Stimulation - Language dominant hemisphere</u> - PoCG: Spelling errors; *letter level* (3/5), Spelling errors; *word level* (1/5), Spelling arrest (1/5) - SMG: Spelling errors; *letter level* (6/8), Spelling errors; *word level* (1/8), Spelling arrest (1/8) - AG: Spelling errors; *letter level* (2/2) - STG: Spelling errors; *letter level* (6/17), Spelling errors; *word level* (8/17), Spelling arrest (3/17) - MTG: Spelling errors; *letter level* (3/3) - ITG: Spelling errors; *letter level* (1/1)	<u>Cortical Stimulation - Language dominant hemisphere</u> [a] - PoCG: **Pure:** Central interference (1/5), **Combined:** Central interference (4/5) - SMG: **Pure:** Central interference (2/8), **Combined:** Central interference (6/8) - AG: **Combined:** Central interference (2/2) - STG: **Pure:** Central interference (4/17), **Combined:** Central interference (13/17) - MTG: **Pure:** Central interference (2/3), **Combined:** Central interference (1/3) - ITG: **Combined:** Central interference (1/1)
	Post	- To dictation: sentences - Copying: words, letters, numbers	NR	NR	NR	Uninterpretable impairment (10/24), NR (14/24)
Motomura et al., 2014	**Intra**	Cortical: NR Subcortical: - To a cue on screen: words (kanji)	NR	NR	<u>Cortical Stimulation</u> - IPL: No errors (1/1) <u>Subcortical Stimulation</u> - dorsal IFOF: Spelling arrest (1/1)	<u>Cortical Stimulation</u> - IPL: No interference (1/1) <u>Subcortical Stimulation</u> - dorsal IFOF: **Combined:** Uninterpretable interference (1/1)
	Post	NR	NR	NR	NR	Unimpaired, *"no remarkable deteriorations"* (1/1)

Spelling performances is only displayed from patients with a glioma in the dominant hemisphere, as reported in the reviewed studies.
Pre = pre-operative assessment, Intra = intra-operative assessment, Post = post-operative assessment, Follow-up = long-term post-operative assessment; NR = not reported, NS = Not specified; BADA = Batteria per l'Analisi dei Deficit Afasici, BDAE = Boston Diagnostic Aphasia Examination, MT-86 = Montréal-Toulouse Aphasia Battery; SFG = Superior Frontal Gyrus, MFG = Middle Frontal Gyrus, IFG = Inferior Frontal Gyrus, SMA = Supplementary Motor Area, PoCG = Postcentral gyrus, SPL = Superior Parietal Lobe, IPL = Inferior Parietal Lobe, SMG = Supramarginal Gyrus, AG = Angular Gyrus, STG = Superior Temporal Gyrus, MTG = Middle Temporal Gyrus, IFOF = Inferior Fronto-Occipital Fasciculus | ant = anterior part, post = posterior part; Pure = Selective interference of spelling, Combined = Spelling interference in combination with interferences on other language tasks [a] Results of stimulated sites were only reported when stimulation interfered with spelling

The incidence of spelling disorders in glioma surgery

In the 7 studies in which spelling was assessed before and after surgery, dysgraphia was documented post-operatively for 33/72 patients (45.8%), and at follow-up for 9/40 (22.5%). However, 5/7 studies recruited only patients without pre-operative spelling problems [7,69-71] and/or with post-operative spelling problems [10,69] (see Table 2.2). Therefore, the just-reported figures are not entirely reliable as by disregarding patients with pre-operative dysgraphia or with post-operatively intact spelling, dysgraphia maybe under- or over-represented, respectively. Ideally, only studies that adopted unrestricted inclusion criteria (i.e., that enrolled participants regardless of whether pre- or post-operative spelling performance was normal) should be considered. Unfortunately, only 9 case reports are available to calculate pre-operative incidence [10,66,68], and only 8 to calculate post-operative incidence [66,68]. Dysgraphia was observed pre-operatively in 4/9 cases (44.4%), and post-operatively in 3/8 (37.5%). More reliable figures, based on a larger number of observations, are obtained if subgroups of published cases are considered. When subjects with preserved pre-operative spelling and information on post-operative performance are considered, deficits appeared after surgery in 14/52 patients (26.9%, Table 2.3a [7,66,68,70,71]). When follow-up data are considered in patients with post-operative dysgraphia, persistent difficulties were documented at follow-up in 9/20 cases, or 45.0% (Table 2.4a [7,10,69,70]). Pre-operative, post-operative and follow-up dysgraphia in the latter samples were inspected in the light of lesion site.

a. Incidence of pre-operative dysgraphia. The incidence of pre-operative dysgraphia was evaluated in 8 patients with parietal glioma and in 1 with glioma in the superior temporal gyrus (STG). Spelling impairments were observed in 4/8 cases with parietal glioma (50.0%); of which 3/6 with angular gyrus lesions (AG; 50.0%), and 1/2 with anterior superior parietal lobe lesions (SPL; 50.0% [66,68]). No dysgraphia was reported for glioma in superior temporal gyrus (0/1 case [10]).

b. Post-operative spelling performance in patients with preserved pre-operative spelling. Dysgraphia was reported after surgery in 4/24 cases with frontal gliomas with intact pre-operative spelling, or 16.7% [7,70]. Of these, 3/13 had gliomas in the posterior superior and middle frontal gyri (SFG/MFG; 23.1%), and 1/11 in the posterior middle and inferior frontal gyri (MFG/IFG; 9.1%). Of 4 parietal gliomas with preserved pre-operative spelling, none showed dysgraphia after surgery to AG (0/3 cases) or anterior SPL (0/1 case [66,68]). Finally, Roux reported post-operative dysgraphia in 10/24 cases (41.7%) with temporo-parietal glioma and preserved pre-operative spelling [71]. The incidence of post-operative dysgraphia in patients with frontal, parietal and temporo-parietal gliomas is statistically indistinguishable ($p = .09$, two-tailed Fisher's Exact Test).

c. Performance at follow-up in patients with post-operative dysgraphia. Dysgraphia persisted at follow-up in 5/10 cases with frontal gliomas (50.0% [7,69,70]). It was observed in 2/3 patients with posterior SFG/MFG glioma (66.7%), and in 3/4 with supplementary motor area (SMA) glioma (75.0%); but post-operative dysgraphia did not persist in 3 patients with a posterior MFG/IFG glioma. Long-term spelling impairments were documented in 2/8 cases (25.0%) with parietal glioma who had post-operative dysgraphia [69]. They persisted in 2/4 subjects treated for SPL glioma (50.0%), but was no longer observed in 4 subjects operated for a glioma in the supramarginal gyrus (SMG). As regards other sites, one patient with insular glioma was described, who showed persistent spelling impairments 6 months after surgery [69]. Lastly, in a patient with STG glioma, post-operative dysgraphia persisted (and worsened) at follow-up [10]. Incidence of persistent dysgraphia at follow-up in frontal, parietal, temporal or insular lesion sites is statistically indistinguishable (p= .290, two-tailed Fisher's Exact Test).

Table 2.3a Incidence of post-operative dysgraphia in patients with preserved pre-operative spelling, grouped by lesion site, N (%)

	Patients	Dysgraphic patients
Frontal	24	4 (16.7)
Post SFG/MFG	13	3 (23.1)
Post MFG/IFG	11	1 (9.1)
Parietal	4	0 (0.0)
Ant SPL	1	0 (0.0)
AG	3	0 (0.0)
Temporo-parietal	24	10 (41.7)

Incidence of post-operative dysgraphia, calculated for all reported patients with preserved pre-operative spelling (n= 52). Percentages correspond to the number of post-operatively dysgraphic patients / total number of patients with preserved pre-operative spelling. Patients are grouped by lesion site. Only patients with gliomas in the dominant hemisphere are reported.
Post = posterior, Ant = anterior; SFG = Superior Frontal Gyrus, MFG = Middle Frontal Gyrus, IFG = Inferior Frontal Gyrus, SMA = Supplementary Motor Area, SPL = Superior Parietal Lobe, SMG = Supramarginal Gyrus, AG = Angular Gyrus, STG = Superior Temporal Gyrus

Table 2.4a Incidence of persistent dysgraphia at follow-up, grouped by lesion site, N (%)

	Patients	Dysgraphic patients
Frontal	**10**	**5 (50.0)**
Post SFG/MFG	3	2 (66.7)
Post MFG/IFG	3	0 (0.0)
SMA	4	3 (75.0)
Parietal	**8**	**2 (25.0)**
SPL	4	2 (50.0)
SMG	4	0 (0.0)
Temporal	**1**	**1 (100.0)**
STG	1	1 (100.0)
Insular	**1**	**1 (100.0)**

Incidence of dysgraphia at >3 months follow-up, calculated for all reported patients with post-operative dysgraphia who were assessed at follow-up (n= 20). Percentages correspond to the number of dysgraphic patients at follow-up / total number of patients with post-operative dysgraphia who were assessed at follow-up. Patients are grouped by lesion site. Only patients with gliomas in the dominant hemisphere are reported.
Post = posterior; SFG = Superior Frontal Gyrus, MFG = Middle Frontal Gyrus, IFG = Inferior Frontal Gyrus, SMA = Supplementary Motor Area, SPL = Superior Parietal Lobe, SMG = Supramarginal Gyrus, STG = Superior Temporal Gyrus

Error types observed

As a next step, we focused on a qualitative analysis of the errors observed in glioma patients undergoing awake surgery, as error types may shed light on the relationships between the neural substrate and the spelling system, thereby helping to identify in detail pre-operatively the components of the system that are at risk during surgery to various brain structures.

Qualitative analyses vary greatly across studies, and reports do not permit to unambiguously adjudicate errors at a specific cognitive level. Some investigations list the items that elicited errors [10,69], others classify error types [7,65-68,70,71] and/or interpret performance without specifying error types [66,68,70,71]. Different criteria and terminologies are used in defining, scoring and interpreting errors. In some cases, errors resulting from disparate causes are classified under the same heading. For example, *j'aime* (I love) > J'EN VAIS (I'm leaving), resulting in incorrect words with verb and tense alteration; and *italienne* (Italian) > ATTILIE, resulting in a non-word with letter substitutions and shifts, were both scored as phonemic paragraphia [71]. In other cases, potentially similar errors are scored differently. For example, two very similar errors like *cadeva* (he was falling) > CADEIA [68], and *tendre* (tender) > TENDRDE [7] were classified as a graphemic error and as letter perseveration, respectively.

As a consequence, only broad distinctions are possible for the purposes of this review. We distinguish between *Central*, *Peripheral* and *Unclassifiable* errors. We consider as *Central* errors those that arise at spelling-specific, but task-independent levels (orthographic lexicon; phoneme/grapheme conversion; graphemic buffer), and therefore occur in all spelling tasks (handwriting, typing, oral spelling). Whenever the information provided in the manuscript allows it, a further distinction is made within *Central* errors, between misspellings at the letter level (letter substitutions, insertions, omissions, and transpositions; e.g., *table* > TALBE) and at the word level (word substitutions, irrespective of whether they are semantically related to the target; e.g., *table* > CHAIR). We include among *Peripheral* errors those that originate at spelling-specific and task-specific levels, and affect handwriting, typing and oral spelling independently. Peripheral errors in handwriting include ill-formed letters, non-fluent handwriting (i.e., long pauses between letters), spatial disorganization, and non-specified alterations in handwriting. *Unclassifiable* errors include spelling arrests or spelling interferences that cannot be disambiguated. These include errors that indisputably show disruption of spelling (e.g., *ran* > RAM), but cannot clearly be attributed to a central disorder (phonological, as the phonemes /n/ and /m/ are phonologically related; or graphemic, as *n* is incorrectly selected instead of *m*) as opposed to a Peripheral impairment (graphomotor; the letters N and M are motorically similar).

Error types observed during pre-operative, post-operative and follow-up assessments

All spelling impairments and disruptions reported in eligible studies were considered, irrespective of participant selection biases. Pre-operative error analyses were feasible in 6 patients, post-operative analyses in 33 and follow-up analyses in 9. Different types of dysgraphias were observed, characterized by Central errors only, by Peripheral errors only, or by a combination of various error types (Tables 2.4b, 2.5b).

Isolated Central dysgraphia was observed post-operatively in MFG/IFG (3/3 patients [7,69]), and STG glioma patients (1/1 patient [10]). After STG resection letter-level errors persisted and worsened. Detailed error analysis showed that words and non-words were equally affected post-operatively, but that non-word spelling was more impaired at follow-up, when Diffusion Tensor Imaging (DTI) revealed damage to the arcuate fasciculus that terminates in STG [10]. Post-operative Central (letter-level) errors were also consistently reported following surgery in SMG (4/4 patients), SPL (4/4 patients) and in the insula (1/1 case), but always in combination with Peripheral errors [69]. At follow-up, both Central and Peripheral errors were reported for insular patients, but only Peripheral errors persisted in SPL patients (SMG patients were unimpaired [69]). Pre-operatively, SPL patients showed Central errors, which resolved after anti-edema therapy [68]. Resection of SFG/MFG yielded Central errors in 1/3 patients (33.3% [7,70]).

Isolated Peripheral dysgraphia was consistently reported before and shortly after AG surgery (3/3 cases [66]) and SMA surgery (4/4 cases [69]). At follow-up, Peripheral dysgraphia persisted in 3/4 cases with SMG gliomas (75.0%). Isolated Peripheral dysgraphia was also observed in a patient with IFG glioma before surgery [65]. Peripheral errors were always observed after SFG/MFG, SPL, SMG and insular surgery, at times associated with Central errors. At follow-up, dysgraphia in patients with SFG/MFG, SPL and insular gliomas was always Peripheral. A patient with glioma in SMA showed at follow-up Central (letter-level) errors (previously absent) in addition to Peripheral errors [69].

Table 2.3b Types of post-operative spelling errors reported, grouped by lesion site, N (%)

	Total N of impairments	**Central errors**	**Peripheral errors**	**Unclassifiable errors**
Frontal	10	4 (40.0)	7 (70.0)	-
Post SFG/MFG	3	1 (33.3)	3 (100.0)	-
Post MFG/IFG	3	3 (100.0)	-	-
SMA	4	-	4 (100.0)	-
Parietal	11	8 (72.7)	11 (100.0)	7 (63.6)
SPL	4	4 (100.0)	4 (100.0)	4 (100.0)
AG	3	-	3 (100.0)	3 (100.0)
SMG	4	4 (100.0)	4 (100.0)	-
Temporo-parietal	10	-	-	10 (100.0)
Temporal	1	1 (100.0)	-	-
STG	1	1 (100.0)	-	-
Insular	1	1 (100.0)	1 (100.0)	-

Types of errors observed in all reported patients with post-operative dysgraphia. Numbers deviate from those in Table 2.3a, as Table 2.3b also includes patients with selection bias and with pre-operative impairments (n= 72). Percentages refer to the number of subjects who produce Central, Peripheral or Unclassifiable errors / total number of reported dysgraphic subjects. Since each subject may produce more than one error type, the sum total of participants with damage to each lesion site who produced Central, Peripheral and Unclassifiable errors is higher than the number of subjects with damage to that site.

Table 2.4b Types of spelling errors at follow-up reported, grouped by lesion site, N (%)

	Total N of impairments	Central errors	Peripheral errors	Unclassifiable errors
Frontal	5	2 (40.0)	5 (100.0)	-
Post SFG/MFG	2	1 (50.0)	2 (100.0)	-
SMA	3	1 (33.3)	3 (100.0)	-
Parietal	2	-	2 (100.0)	-
SPL	2	-	2 (100.0)	-
SMG	0	-	-	-
Temporal	1	1 (100.0)	-	-
STG	1	1 (100.0)	-	-
Insular	1	1 (100.0)	1 (100.0)	-

Types of errors observed in all patients with dysgraphia at follow-up. Percentages refer to the number of subjects who produced Central, Peripheral or Unclassifiable errors / total number of patients with dysgraphia at follow-up. Since each subject may produce more than one error type, the sum total of participants with damage to each lesion site who produced Central, Peripheral and Unclassifiable errors is higher than the number of subjects with damage to that site. Only patients with gliomas in the dominant hemisphere are reported.
Post = posterior; SFG = Superior Frontal Gyrus, MFG = Middle Frontal Gyrus, IFG = Inferior Frontal Gyrus, SMA = Supplementary Motor Area, SPL = Superior Parietal Lobe, SMG = Supramarginal Gyrus, STG = Superior Temporal Gyrus

Intra-operative spelling performance

Direct Electrical Stimulation disrupted intra-operative spelling in 88.3% of the cases (53/60 patients, Table 2.5a [7,65-68,70,71]). Spelling interference was reported during surgery for gliomas in the posterior frontal lobe (in 22/27 patients, or 75.9% [7,65,70]), and in temporo-parietal areas (in 31/33 patients, or 93.9% [66-68,71]). Stimulation yielded Central, Peripheral and/or Unclassifiable errors (for a summary, see Figure 2.4).

Stimulation of postcentral gyrus (PoCG [71]), SMG [66,71] and superior, middle and inferior temporal gyri (STG, MTG, ITG) yielded only Central errors (Table 2.5b [71]). Among STG glioma patients, a double dissociation was observed between stimulation of dorsal STG (including perisylvian sulcus), which caused errors at the letter-level, and of ventral STG, which resulted in word-level errors [71]. Interference with central spelling processes was also reported during stimulation of posterior MFG [7], IFG [7,70,77], AG [66], and anterior SPL [68], yet not exclusively. In all these sites, as well as in SFG [70], also Peripheral errors were reported. Even though both Central and Peripheral errors were observed, in most cases one error type occurred more consistently. During IFG stimulation Central errors prevailed, whereas mostly Peripheral errors were reported during MFG and AG stimulation. Stimulation of anterior SPL always resulted in combined error types [68]. Lastly, except for Roux et al. (2014), all studies report Unclassifiable errors; during cortical stimulation of SFG, MFG, IFG, anterior SPL, AG and during subcortical stimulation of the dorsal inferior fronto-occipital fasciculus (IFOF) in the cavity of the AG.

Table 2.5a Incidence of intra-operative spelling interference, grouped by stimulated site, N (%). Each patient was stimulated on multiple sites in different gyri

	Patients	Patients with spelling interference
Frontal	27	22 (75.9)
Post SFG	13	3 (23.1)
Post MFG	22	11 (50.0)
Post IFG	14	9 (64.3)
Temporo-parietal	33	31 (93.9)
Parietal		
PoCG	5	5 (100.0)
Ant SPL	2	2 (100.0)
AG	9	8 (88.9)
SMG	8	8 (100.0)
Temporal		
STG	17	17 (100.0)
MTG	3	3 (100.0)
ITG	1	1 (100.0)

Incidence of intra-operative spelling interference, calculated for all patients who underwent awake surgery with monitoring of spelling skills (n= 60). For each site, percentages refer to the number of patients showing intra-operative spelling interference / total number of patients stimulated. Numbers and percentages from different stimulated gyri do not add up per lobe, as patients were stimulated in multiple sites.
Pure interference = Direct Electrical Stimulation selectively interfered with spelling. Combined interference = Direct Electrical Stimulation interfered with spelling and with other language skills (typically, speech).
Post = posterior, Ant = anterior; SFG = Superior Frontal Gyrus, MFG = Middle Frontal Gyrus, IFG = Inferior Frontal Gyrus, PoCG = Postcentral Gyrus, SPL = Superior Parietal Lobe, SMG = Supramarginal Gyrus, AG = Angular Gyrus, STG = Superior Temporal Gyrus, MTG = Middle Temporal Gyrus, ITG = Inferior Temporal Gyrus

Table 2.5b Types of intra-operative spelling errors reported grouped by stimulated site, N (%)

	Total N of interferences	Central errors	Peripheral errors	Unclassifiable errors	Pure interference	Combined interference
Frontal						
Post SFG	3	-	1 (33.3)	2 (66.7)	2 (66.7)	1 (33.3)
Post MFG	11	5 (45.5)	9 (81.8)	2 (18.2)	6 (54.5)	5 (45.5)
Post IFG	9	5 (45.5)	2 (18.2)	2 (18.2)	0 (0.0)	9 (100.0)
Temporo-parietal						
Parietal						
PoCG	5	5 (100.0)	-	-	1 (20.0)	4 (80.0)
Ant SPL	2	2 (100.0)	2 (100.0)	2 (100.0)	2 (100.0)	0 (0.0)
AG	8	3 (37.5)	6 (75.0)	1 (12.5)	2 (25.0)	6 (75.0)
SMG	8	8 (100.0)	-	-	2 (25.0)	6 (75.0)
Temporal						
STG	17	17 (100.0)	-	-	4 (23.5)	13 (76.5)
MTG	3	3 (100.0)	-	-	2 (66.7)	1 (33.3)
ITG	1	1 (100.0)	-	-	0 (0.0)	1 (100.0)

Types of errors are given for all reported intra-operative spelling disruptions. Percentages refer to the number of patients who produced Central, Peripheral or Unclassifiable errors / total number of patients in whom interference was reported. Since each patient may produce more than one error type, the sum total of participants who produced Central, Peripheral and Unclassifiable errors during intra-operative mapping of a given site is higher than the number of subjects with damage to that site.
Pure interference = Direct Electrical Stimulation selectively interfered with spelling. Combined interference = Direct Electrical Stimulation interfered with spelling and with other language skills (typically, speech).
Post = posterior, Ant = anterior; SFG = Superior Frontal Gyrus, MFG = Middle Frontal Gyrus, IFG = Inferior Frontal Gyrus, PoCG = Postcentral Gyrus, SPL = Superior Parietal Lobe, SMG = Supramarginal Gyrus, AG = Angular Gyrus, STG = Superior Temporal Gyrus, MTG = Middle Temporal Gyrus, ITG = Inferior Temporal Gyrus

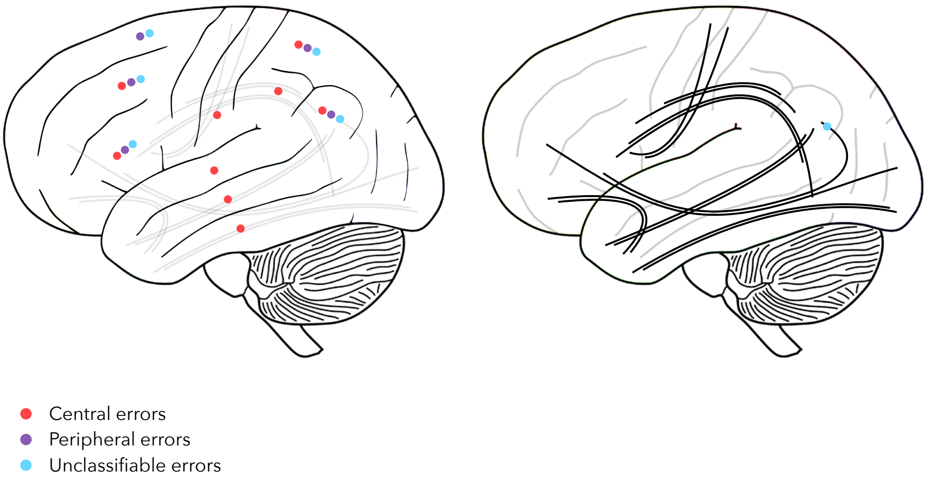

Figure 2.4 Types of errors identified during intra-operative assessment of spelling. In the seven reviewed papers, Direct Electrical Stimulation of cortical (Fig. 2.4a) and subcortical (Fig. 2.4b) regions resulted in different types of interference with spelling. Colored dots indicate the types of errors (from above to below: Central errors in red, Peripheral errors in purple, and Unclassifiable errors in blue). Dots are placed in the middle of functional sites as reported in the reviewed studies, and do not indicate specific coordinates. Central errors were reported while stimulating the posterior MFG [7], IFG [7,70,77], PoCG [66,71], SMG [66,71], AG [66,68], anterior SPL [68], STG [71], MTG [71] and ITG [71]. Peripheral errors were reported during stimulation of the posterior SFG [70], posterior MFG [7,70], IFG [7], AG [66] and anterior SPL [68]. Unclassifiable errors were reported during cortical stimulation of the posterior SFG [70], posterior MFG [7,70], IFG [7,70,77], AG [66], and anterior SPL [68], and after subcortical stimulation of the dorsal IFOF in the cavity of the AG [67].

Selective disruption of spelling vs. combined damage to spelling and speech

Spelling assessments were in most cases part of broader testing protocols, tapping also other language skills and cognitive abilities. In principle, analyses of these protocols could shed light on the association between dysgraphia and other (language) impairments, and therefore help identify the neural substrates selectively engaged by spelling and those shared with other language functions. However, these correlations cannot be reliably inferred from the results of pre- and post-operative assessments, because the outcome of neuropsychological testing at these stages is largely omitted from the reviewed reports. On the other hand, intra-operative data on language mapping allow relevant analyses, as they establish whether stimulation to specific regions disrupts spelling selectively, or in association with other language skills. In the studies reviewed here, all stimulated sites were assessed with multiple tasks (mainly object naming and/or reading tasks), and details of interferences were reported.

We considered the instances in which intra-operative stimulation affected spelling only (pure interference) and those in which it also disrupted other language skills (combined interference). An overview is provided in Figure 2.5.

Data on intra-operative spelling disruptions were available on 53 cases. When intra-operative stimulation disrupted spelling processes, stimulation interfered in 20/53 patients (37.7%) with spelling but not with object naming or reading. This was reported for all stimulated sites, except for posterior IFG and ITG (Table 2.5b). Pure interference was observed in 8/22 cases with frontal gliomas, or 36.4% [7,70,77]. It occurred during stimulation of posterior SFG (2/3 times, or 66.7% [70]) and posterior MFG (6/11 times, or 54.5% [7,70]). Spelling disruption was selective in 12/31 cases with temporo-parietal gliomas (38.7% [66,68,71]). Pure interferences in these patients were always associated with Central errors. Substantial individual variations were observed during stimulation of PoCG, SMG, AG, STG and MTG, which resulted more often in combined or no interference (Table 2.5b). Noticeably, stimulation of anterior SPL yielded only pure spelling disruptions [68].

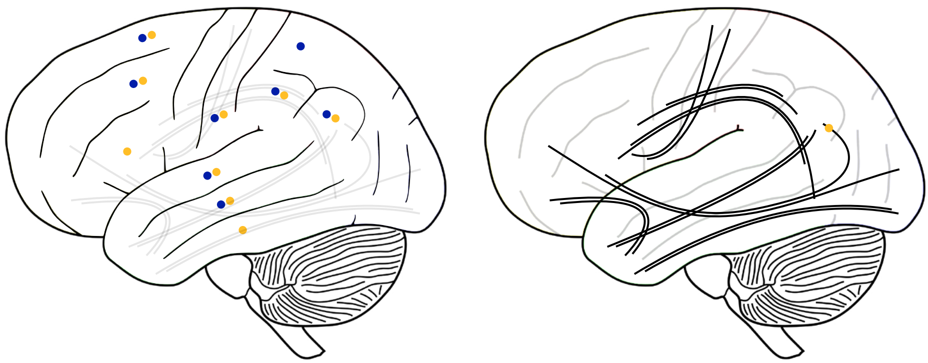

Figure 2.5 Selective involvement of neural regions in spelling, as identified during intra-operative assessment. In the seven reviewed papers, Direct Electrical Stimulation of cortical (Fig. 2.5a) and subcortical (Fig. 2.5b) regions either interfered only with spelling (pure interference; dark blue dots) or with both spelling and other language tasks (combined interference; light yellow dots). Dots are placed in the middle of functional sites as reported in reviewed studies, and do not refer to specific coordinates. Pure spelling interferences were reported while stimulating the posterior SFG [70], posterior MFG [7,70], PoCG [71], anterior SPL [68], SMG [71], AG [66], STG [71] and MTG [71]. Spelling interferences in combination with other language impairments were reported when stimulation was applied to posterior SFG [70], posterior MFG [7,70], IFG [7,70,77], PoCG [71], SMG [71], AG [66,71], STG [71], MTG [71], ITG [71] and after subcortical stimulation of the dorsal IFOF in the cavity of the AG [67].

Combined interference with spelling and with other language functions was reported in 33/53 cases (62.3%), during intra-operative stimulation to posterior SFG, posterior MFG, IFG, PoCG, SMG, AG, STG, MTG, ITG, and during subcortical stimulation of the dorsal IFOF in the cavity of the AG (Figure 2.5). Stimulation of IFG yielded always combined disorders of spelling, reading, naming, and motor functions (9/9 cases [7,70,77]). Similarly, stimulation of ITG (as reported in 1 patient [71]) resulted in the combined disruption of spelling and reading, and subcortical stimulation of the dorsal IFOF resulted in combined interference with reading and naming tasks (as reported in 1 patient [67]). Spelling, reading and naming were affected during stimulation of PoCG (4/5 cases, 80.0%), SMG (6/8 cases, 75.0%), and STG (13/17 cases, 76.5% [71]). Combined disruptions were also frequent following AG stimulation (6/8 cases, or 75.0%), yet mainly in association with errors on non-language skills such as finger recognition and calculation tasks [66,71]. Combined interferences were less frequent during intra-operative stimulation to posterior MFG, posterior SFG and MTG. When it did occur, spelling was affected in association with reading, and sometimes also with naming [7,70,71].

Discussion

We systematically reviewed published reports on written spelling in patients undergoing awake surgery. Assessments of written spelling are often neglected in neurosurgical practice, although language preservation is one of the main outcome goals of surgery. At this stage, several factors make a critical analysis of available data very difficult (Section *Future Directions*). Notwithstanding current limitations, published reports allow interesting conclusions.

Data show that post-operative dysgraphia is frequent and that, congruent with stroke and neuroimaging studies, the integrity of a network of frontal, parietal and temporal regions is critical for spelling. In subjects with intact pre-operative performance, post-operative dysgraphia was reported in 14/52 cases (26.9%). Even though differences were not statistically significant (possibly due to the low number of observations), it occurred more frequently following surgery to temporo-parietal regions (10/24 cases, or 41.7%) than to frontal (4/24 cases, or 16.7%) or purely parietal damage (0/4 cases, 0%). At follow-up, dysgraphia persisted in almost half of the cases (9/20, or 45.0%) with post-operative dysgraphia. It was documented in 5/10 (50.0%) subjects with frontal, 2/8 (25.0%) with parietal, 1/1 with insular, and 1/1 with temporal damage. Damage to different portions of each lobe affected spelling skills in different ways.

In line with the functional neuroanatomy based on current lesion and neuroimaging literature, Central errors were observed in specific regions (Figure 2.2).

During intra-operative, post-operative and follow-up assessments, spelling impairments in gliomas of PoCG, SMG, STG, MTG, ITG and insula always involved central processes. This is congruent with literature reports that specifically tie PoCG, SMG, STG and insula to central spelling processes (i.e., PoCG and SMG to graphemic buffer processes [31,42,78]; STG and insula [iii] to phoneme-grapheme conversion [35,36,38]; and ITG to orthographic output lexicon [23-25]). MTG may be consistently involved in central spelling processes, but not exclusively. In fact, Central dysgraphia in patients with MTG (as well as STG and ITG) gliomas co-occurred with other language impairments, consistent with the observations suggesting that these regions are also involved in reading and speech [24,25,79,80]. Central errors were also reported, albeit less systematically, in patients with gliomas in posterior IFG, posterior MFG, SPL and AG, which are also implied in spelling-specific central processes (i.e., IFG for phoneme-grapheme conversion [35,36]; IFG and AG for orthographic output lexical processes [20,21,26,30,39,81]; and MFG, SPL and AG for graphemic buffer processes [31,39,41-43]). In line with the ongoing debate on the role of AG in central processes, Central errors were reported in only a few AG glioma cases. Spelling interferences in MFG/IFG were systematically accompanied by disruption of other language tasks, congruent with earlier demonstrations of the combined role of MFG/IFG (including Broca's area) in reading and naming (e.g., [82,83]).

Peripheral errors were reported in neural regions that were also identified in the extant stroke literature. SPL lesions always affected peripheral processes, as in stroke cases (e.g., [33,48,49]). Patients with gliomas in SFG/MFG, AG and insula also showed Peripheral errors, albeit less consistently. SFG/MFG has been repeatedly involved in peripheral processes (i.e., motor planning, initiation and graphomotor skills [26,46,47]). Such an involvement was not stated for AG and insula. Since the AG is connected with posterior MFG regions via the superior longitudinal fasciculus, Peripheral errors could have been caused by intra-operative stimulation unintendedly reaching the superior longitudinal fasciculus. Insular involvement in peripheral processes of handwriting remains to be investigated.

Clinical Implications

It is well known that written spelling and speech, while often impaired simultaneously, can be disrupted selectively by brain damage (for a review, see [14]). In the reviewed papers, intra-operative stimulation interfered with spelling in 20/53 cases (37.7%), and with both spelling and other language tasks in 33/53 cases (62.3%). The knowledge that intra-operative stimulation (or tissue removal) at a specific brain site is likely to damage spelling selectively rather than in combination with speech, will help decide if

[iii] Since only word spelling was assessed in the patient with insular glioma [69], Central errors may also be due to lexical damage in this case.

an intra-operative assessment of written spelling is strongly recommended or simply advisable in a patient with a glioma in that site. Such an assessment should be strongly recommended in gliomas involving areas in which intra-operative stimulation is known to selectively affect spelling processes, as in these cases only spelling tasks will indicate whether tissue can be safely removed without inducing post-operative dysgraphia. An evaluation of spelling is also advisable, but not indispensable, when intra-operative stimulation is applied to an area that is assumed to process spelling and speaking, as in these cases assessments of speech and of spelling are both likely to identify crucial language sites (even though dissociated impairments cannot be ruled out *a priori*). Based on our review, an intra-operative assessment of spelling is strongly recommended for gliomas in posterior SPL, AG, SMG, STG and MTG, as in these regions stimulation mainly induced pure Central interferences. It is also desirable for gliomas in MFG and PoCG, although pure Central disruptions were observed less consistently. An assessment of spelling seems less critical for gliomas in posterior MFG/IFG and ITG, as in these cases intra-operative stimulation always interfered also with other language functions. Assessment of handwriting is advisable for patients with gliomas in SFG and anterior SPL, as in these cases intra-operative stimulation resulted in pure Peripheral errors.

Future Directions

Reviewed neurosurgical reports largely converge with available lesion and neuroimaging data, and provide useful suggestions for the assessment of spelling in glioma patients. Limitations stemming from different clinical procedures across different neurosurgical centers are probably inevitable. However, one should be aware that they might prevent the correct interpretation of results in clinical studies. For example, the outcome of a cognitive assessment may depend on concomitant adjuvant therapy (e.g., radiotherapy and chemotherapy [84-86]) and on individual tumor characteristics (e.g., size, pathology, extent of resection [87,88]). The schedule of post-operative and follow-up evaluations also varies across and within centers. In reviewed papers, post-operative assessments took place between 48 hours and 1 month from surgery; and follow-up assessments between 2 and 24 months from surgery. Failure to control these variables may lead to inaccurately estimate post-operative sparing of language skills, especially if patients are taken as a group. Solving these problems requires reaching a consensus in the awake surgery/neuro-oncology community, for which the first attempts have recently been reported in Europe [89].

Improving the assessment of written spelling before, during and after awake surgery

In reviewed papers, spelling skills were often assessed cursorily, or by means of tools originally designed for stroke patients, whose linguistic deficits are typically more severe than those observed in glioma cases [56,58]. As a consequence, and with only few exceptions, the spelling performance reported in glioma cases allowed diagnosing dysgraphia, but not locating the functional damage.

An adequate testing battery should tap all the components of the spelling system (Figure 2.1). It should evaluate at least the ability to write words, non-words and sentences. Performance on sublists of words (controlled for grammatical category, orthographic regularity, frequency of usage and length) and non-words (controlled for similarity to words and length) can reveal the status of spelling-specific components. Performance at the sentence level can inform on (morpho)syntactic and working memory skills. Written picture naming tasks may also be included to evaluate spelling, but need not be administered systematically, as spoken picture naming is routinely used during awake surgery, and the skills differentially engaged by spoken vs written naming are fully covered by spelling-to-dictation. Therefore, a handwriting-to-dictation or a typing-to dictation task (paired with oral spelling-to-dictation in selected cases) may suffice to evaluate spelling skills.

Detailed analysis of performance on carefully constructed test batteries can accurately diagnose damage to one or more spelling processes. In each patient, errors must be considered in the context of performance on various language tasks, to establish whether damage affects mechanisms shared by spoken and written output, or spelling-specific mechanisms. Error analysis should include not only quantitative (i.e., error rates), but also qualitative measures (i.e., error types), as a combination of the two allows a more sensitive "cognitive staging" of the disease.

To interpret a patient's performance accurately, spelling should be monitored longitudinally (Table 2.6). The *pre-operative* assessment has two main goals: assessing the status of each component of the system, and guiding stimulus selection for intra-operative testing. It should be reasonably exhaustive, so that quantitative and qualitative performance on word/non-word sublists allows identifying spared/impaired processes (Figure 2.1). Preparation of the individually tailored, intra-operative battery should be guided by current knowledge of the functional neuroanatomy of spelling (Figure 2.2). As customary in awake surgery, stimuli for intra-operative mapping should be selected among those responded to correctly before surgery, and putatively processed by the components at risk. For example, since the ITG is critical for correct spelling of irregular words [22], intra-operative mapping in a subject with ITG glioma will include irregular words spelled correctly during the pre-operative assessment.

The *intra-operative* assessments must be quick and efficient, and ensure that crucial functional areas are not resected [90]. Given that intra-operative stimulation can be applied for 4 seconds at the most [91,92], and that the stimulus/response cycle for a sentence may not be completed in such a short time, it should focus on words and non-words rather than on sentences. The intra-operative assessment of handwriting or typing may cause greater discomfort compared to that of speech, especially if the patient is positioned lying on his/her right side to facilitate exposure of the surgical field. However, this should not discourage an evaluation in patients at risk for dysgraphia, as even this surgical position is compatible with sufficiently free hand movement [7,66-68,70,71]. Alternatively, central processes may also be assessed by oral spelling-to-dictation tasks.

Post-operative and *follow-up* assessments should be detailed, like pre-operative assessments, as they must establish if spelling processes were spared during surgery, and contribute to monitoring disease progression. Post-operative assessments can also be used to target rehabilitation if necessary. As patients are assessed multiple times after surgery, ideally parallel versions of the battery should be available to avoid practice effects.

Table 2.6 Phases of written spelling evaluations

Testing phase	Materials to be administered	Goals
Pre-operative	Written spelling battery *(words, non-words, sentences)*	- Diagnose deficits (if any) - Establish status of components at risk based on tumor location - Select stimuli for intra-operative tasks
Intra-operative	Tailored tasks *(words, non-words)*	- Monitor status of components at risk during surgery
Post-operative	Written spelling battery *(words, non-words, sentences)* *Parallel version, if possible*	- Monitor status of spelling system and disease progression - Target rehabilitation (if necessary)
Follow-up	Written spelling battery *(words, non-words, sentences)* *Parallel version, if possible*	- Monitor status of spelling system and disease progression - Verify long-term outcome

Contribution of neurosurgical studies to the understanding of the relationships between spelling processes and the brain

Systematic assessments and accurate error analyses have led to a better understanding of the functional architecture of spelling processes and of their relationships with the brain. Most studies of dysgraphia focused on stroke cases, but reports of glioma patients prove that also neurosurgical cases can inform hypotheses on the functional neuroanatomy of spelling (e.g., [10,24]). In the first place, glioma cases may contribute complementary information to that provided by vascular lesions, due to some features of tumor growth – for example, the fact that the regularities in the territory of brain arteries constrain the distribution of tissue damage in stroke, but not in tumors. As a case in point, a dual stream model of language processing received support from the double dissociation observed in STG gliomas between letter-level errors during dorsal stimulation (possibly disrupting the termination parts of arcuate fasciculus, connecting STG with posterior frontal regions via SMG), and word-level errors during ventral stimulation (possibly disrupting the termination parts of IFOF, connecting STG with prefrontal regions via the external capsule [93-95]). Similarly, awake surgery studies could provide critical data for differentiating the role of various portions of the perisylvian cortex in phoneme-grapheme conversion procedures, or for clarifying whether or not the ITG plays a fully parallel role in the lexical orthographic processes recruited by reading and spelling.

Awake surgery also affords intra-operative investigations of subcortical pathways [28,92,96]. On a current view of brain functioning, cognitive skills are subsumed by a network of areas connected by subcortical pathways [97-99]. Damage to the latter can permanently impair cognitive skills [100,101]. In a neurosurgical report [67] spelling interference was caused by intra-operative stimulation of the dorsal IFOF. Systematic subcortical stimulation of the fiber tracts critical for the functional neuroanatomy of language (arcuate fasciculus; superior, middle and inferior longitudinal fasciculus; uncinate fasciculus; frontal aslant tract [11,102]) will shed further light on the functional neuroanatomy of spelling.

Finally, awake surgery investigations can provide critical information on the peripheral processes involved in output-specific spelling tasks. These processes have received relatively little attention in the stroke literature, at least in part because vascular lesions are usually large and cause complex deficits, which prevent reliable comparisons of handwriting, typing and oral spelling. Neurosurgical studies have shown that gliomas in posterior SFG and SMA may selectively interfere with peripheral handwriting processes, and that a combination of Peripheral and Central errors may emerge in gliomas of posterior MFG, posterior IFG, anterior SPL, AG, SMG, and insula. Which peripheral processes are affected by lesions in each of these regions, and how they specifically affect handwriting, typing and oral spelling remains to be investigated. Assessing across-modality performance on the same stimuli can provide critical information on task-specific neural substrates.

Conclusions

In current awake surgery practice, written spelling is often evaluated cursorily, or altogether neglected. This article reviews studies that assessed spelling skills before, during and after awake surgery, and discusses to what extent available knowledge on the functional neuroanatomy of spelling has been exploited in glioma surgery. Incidence rates point to the relevance of assessments of spelling in glioma patients undergoing awake surgery. Dysgraphia occurred post-operatively in 26.9% of the cases, and persisted at follow-up in approximately half of the cases. In over a third of the patients, crucial functional sites were identified intra-operatively only by spelling tasks.

In conjunction with current hypotheses on the functional neuroanatomy of spelling, data from glioma patients can inform surgical practice. Pre-operatively, they can guide error analyses leading to accurate diagnoses of spelling-specific deficits, and establish in each patient the components of the system at risk during surgery. Intra-operatively, they can assist the neurosurgeon in removing as much tumor tissue as possible, while at the same time preserving spelling skills. After surgery, they can constrain remediation programs (if needed) and monitor disease progress. In the context of more homogeneous testing schedules and stricter patient selection criteria, detailed quantitative and qualitative analyses of finer-grained spelling assessments can refine the theoretical knowledge of the underlying neurofunctional processes, and improve the clinical care for the individual glioma patient.

Abbreviations used in Chapter 2

AG	Angular gyrus
IFG	Inferior frontal gyrus
IFOF	Inferior fronto-occipital fasciculus
IPL	Inferior parietal lobe
ITG	Inferior temporal gyrus
MFG	Middle frontal gyrus
MTG	Middle temporal gyrus
PoCG	Postcentral gyrus
PreCG	Precentral gyrus
SFG	Superior frontal gyrus
SMA	Supplementary motor area
SMG	Supramarginal gyrus
SPL	Superior parietal lobe
STG	Superior temporal gyrus

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3

The need for detailed written language assessment in glioma patients undergoing awake surgery

Abstract

Although written language is important for the preservation of quality of life, reading and spelling processes are rarely monitored in glioma patients undergoing awake surgery. When this happens, typically short subtests from post-stroke practice are administered. We examine the sensitivity of a reading and spelling subtests from a commonly used clinical language battery to assess written language deficits in neurosurgical practice. Fourteen left-hemisphere glioma patients were retrospectively included. Written language was assessed pre-operatively, post-operatively and at follow-up. At the group level, reading and spelling impairments were observed before and after surgery. At the individual level, large variability in error patterns and error types was observed. Qualitative analyses of performance on the short clinical test provided better insight in individual performances, but did not allow to identify which underlying processes were damaged using the short clinical test. Results show that current clinical evaluations are not always suitable to detect subtle deficits in glioma patients. It is argued that development of detailed, theory-driven assessment of written language is crucial to target patient-tailored treatment and to preserve language after awake surgery.

Introduction

Classical neuropsychological and neuroanatomical models identified that written and spoken language rely at least partly on distinct neural substrates [1]. Nevertheless, the focus of language assessment in awake surgery practice remains almost exclusively on spoken language [2], whilst data on written language are scarce. The complex processes of reading and spelling are comprised of multiple cognitive components, which may result in different error profiles when damaged in isolation [3-5] (see Chapter 1 for reading, and Chapter 2 for spelling). Certain components of written language processing are shared with spoken language, such as the access to meaning (semantics). These may be equally adequately evaluated by either spoken or written language tasks. Yet, the distinct functional components in written language (such as orthographic representations) imply that spoken language may not be informative on all facets of reading and spelling. Hence, specific processes of written language remain uncontrolled for when a spoken language task is administered. To that extent, it seems crucial to not only concentrate on spoken language, but to also evaluate written language in neurosurgical practice. More specifically, to target specific testing for individual patients, identification of the underlying components of reading and spelling may be especially critical for glioma patients. As specific components are known to be sensitive to different psycholinguistic variables, damage to independent processes can be identified in sensitive assessments that evaluate these variables.

Studies that have reported on written language assessments in glioma patients typically used short subtests from batteries originally developed for the assessment of post-stroke aphasia (Chapter 2). Yet, for other cognitive and spoken language functions, it has been reported that these may not be sensitive enough for glioma patients [6,7]. Stroke patients typically present more severe impairments than glioma patients [8,9], hence assessment tools may not be aimed at identifying subtle underlying deficits. Moreover, when reported, results on these tests are often restricted to quantitative error analyses (i.e., error percentage), whereas insight in the underlying cognitive components requires careful evaluation of performance using additional qualitative analyses of performance (i.e., inspecting which items elicited errors and which error types occurred). Lastly, results in neurosurgical studies on written language are typically limited to group level evaluations. Although group data may inform on the viability of the approach, these do not apply to each individual patient. As awake surgery takes a highly personalized approach, group analyses may therefore be of limited use in glioma practice to aid the preservation of quality of life.

Thus, the question arises of whether current clinical assessments suffice to reliably assess written language in awake surgery practice. We retrospectively evaluate the applicability of commonly used subtests to the monitoring of reading and spelling in glioma patients. First, we inspect whether error rates (quantitative analyses) at the group level inform on written language performance. Secondly, error rates of individual cases are evaluated, to weigh the significance of personalized evaluations. Lastly, we evaluate if an in-depth data scrutiny of the same materials (qualitative analyses) provides insight in damage to underlying components of written language.

Methods

Patients

Between January 2007 and March 2016, 47 patients received written language assessments before and/or after glioma surgery in the university hospitals of Brescia (Spedali Civili di Brescia) and Verona (Azienda Ospedaliera Universitaria Integrata Verona, Borgo Trento), Italy. Patients were selected for retrospective analyses when they were right-handed, had more than 8 years of formal education, underwent awake surgery for left hemispheric gliomas with intra-operative mapping of object naming only, and completed spelling assessment at least pre- and post-operatively. These criteria resulted in the inclusion of 14 patients, all native Italian speakers (8 males, M_{age} = 50.7 years; Table 3.1). Pre-operative testing took place at 1-15 days before surgery, and post-operative testing within 6 weeks after surgery. A follow-up evaluation (3-9 months post-surgery) was available for 9/14 patients.

Materials

Language was assessed with subtests from the Batteria per l'Analisi dei Deficit Afasici (BADA [10]), and with two tests developed for the evaluation of spoken naming of objects (ECCO [11]) and actions in glioma patients (VISC; Verb production In Sentence Context [11]). Given the retrospective character of the study, evaluations focus on tasks that were part of the clinical routine in the hospitals of Verona and Brescia. These differed across patients and assessment times (pre-operative, post-operative, follow-up). All patients completed non-word spelling (BADA; 12-13 items), non-word repetition (BADA; 18 items), spoken object naming (ECCO; 57 items), and spoken action naming (VISC; 70 items) tasks before and after surgery. Moreover, 8/14 patients completed sentence spelling (BADA; 5 items) and 7/14 patients a non-word reading task (BADA; 22-23 items).

Non-word spelling items were dictated by the task administrator, while sentence spelling was administered as a written picture description task. In both tasks, spelling was assesses as handwriting. As sentences were written as a picture description, patients were unrestricted in the words they chose for their descriptions. Sentence length could therefore vary among patients. For non-word reading, the patient was asked to read aloud single items presented on a computer screen. For these written language tasks, psycholinguistic variables were post-hoc defined for each item (non-word length and similarity to words for non-words; grammatical class, word length and sentence length for sentences). In addition, all patients received general neuropsychological assessments, as well as apraxia tests.

Table 3.1 Demographic data of patients included in the retrospective analysis (n= 14)

	N (%)	Mean (SD)	Range
Age		50.7 (11.7)	33 - 69
Years of education		13.7 (3.3)	8 - 17
Gender			
Male	8 (57.1)		
Female	6 (42.9)		
Assessment (days from surgery)			
Pre-operative		4.6 (4.8)	1 - 15
Post-operative		9.8 (9.9)	3 - 39
Follow - up		163.9 (71.2)	92 - 266
Handedness rh	14 (100)		
Lesion site LH	14 (100)		
Tumor location			
Frontal	4 (28.6)		
Fronto - Insular	1 (7.1)		
Parietal	2 (14.3)		
Temporal	6 (42.9)		
Temporo - Occipital	1 (7.1)		
Tumor grade			
II	4 (28.6)		
III	6 (42.9)		
IV	4 (28.6)		
Tumor histology			
Astrocytoma	4 (28.6)		
Anaplastic Astrocytoma	3 (21.4)		
Oligodendroglioma	2 (14.3)		
Anaplastic Oligodendroglioma	1 (7.1)		
Glioblastoma	4 (28.6)		
Extent of resection			
Total	9 (64.3)		
Subtotal	4 (28.6)		
Partial	1 (7.1)		

rh = right handed, LH = Left Hemisphere

Analyses

All 14 patients were included for quantitative performance analyses. Error rates on each test were calculated and descriptive statistics were used to establish whether scores on language tasks fell above or below cut-off. Normative data from healthy controls indicated a cut-off of two items per subtest for BADA, and for ECCO & VISC age-corrected norms were used [11]. Group performance on the six language tests was compared by means of ANOVA. Changes between pre-operative, post-operative and follow-up assessments on specific tests were analyzed by Wilcoxon Rank Sum test. For these analyses, only scores from patients who completed the same test at the assessment stages that were being compared were considered. Due to the retrospective character of the study, it was unclear whether missing data at specific assessments times resulted from the neuropsychologist's decision not to assess the task or from the patients' inability to perform it. To avoid under- or over-representation of impairments, incomplete test results were disregarded when comparing assessments.

To analyze the errors of individual patients, original handwriting samples and reading recordings were required. These were available in a subset of 4/14 patients, who were included in finer-grained analyses. Sentences were divided in grammatical constituents (i.e., nouns with articles, verbs, function words and adjectives), which were scored separately. Each item was scored using an error classification system that was based on the cognitive model of written language processing (Chapter 1, Figure 1.1). We differentiate between *Central errors,* which result from damage to central processes, and errors that did not result from damage to central processes (reading: *Other errors*; handwriting: *Peripheral* & *Unclassifiable errors*). *Central errors* are characterized by incorrect letter choices, word level errors, no responses or misplaced stress (e.g., the dictated word *brain* written as BRANE, BRIN, BRAINS, or MIND). *Other errors* in reading represent changes in more qualitative features (e.g., slowed or hesitant responses). *Peripheral errors* consist of qualitative changes in handwriting as a result of damage to peripheral processes (e.g., ill-formed letters or case mixing). Moreover, for certain errors in handwriting it cannot be distinguished whether they result from central or from peripheral damage (e.g., a dictated *m* written as N could be an incorrect letter choice or an ill-formed M). These were scored as *Unclassifiable errors*. An overview of all distinctive error types within Central, Peripheral, and Other errors is provided in Appendix C.2. In addition, performance is evaluated considering all error types together, by means of *Overall errors*. *Overall errors* refer to the number of responses that contained an error of any type (i.e., Central, Other, Peripheral and/or Unclassifiable). For this count, each response is considered only once (e.g., if a response string contained a Central and a Peripheral error, it was counted as 1 incorrect response in the Overall errors count).

In all error analyses only first responses were considered. All items were scored independently by the author and a trained student, and inter-rater reliability was calculated to assess consistency between the two raters using two-way, agreement, average-measures Inter-Class Correlations (-1 to +1). For Central errors, inter-rater reliability was in the excellent range (non-word reading: ICC= 0.99; non-word spelling: ICC= 0.97; sentence spelling: ICC= 0.99 [12]), hence independent raters agreed on almost all Central errors classifications. Non-central error types proved to be more difficult to score objectively. Inter-rater reliability for Other errors in non-word reading was in the poor range (ICC= 0.22). For spelling, agreement between raters for non-word scoring was in the fair range (Peripheral errors: ICC= 0.52; Unclassifiable errors: ICC= 0.42), while inter-rater reliability for scoring sentence varied (excellent range for Peripheral errors: ICC= 0.92; poor range for Unclassifiable errors: ICC= 0.37). As non-central error types mainly rely on interpretations of qualitative changes, individual differences between scorers may influence evaluations (e.g., someone with poor handwriting may judge ill-formed letters of others differently than a scorer with clear handwriting). To assure that evaluations of Other, Peripheral and Unclassifiable errors were also suitable to use in the current study (and be as objective as possible), a third independent and experienced scorer decided on incongruent scorings.

Effects of psycholinguistic variables were analyzed using Fisher's Exact Tests (for non-continuous variables, e.g., grammatical class) and Generalized Linear Models (for continuous variables e.g., word length). Individual changes between pre-, post-operative and follow-up assessments were analyzed using Fisher's Exact Test as well. All statistical analyses were conducted in R using *stats*, *gmodels* and *irr* packages [13-15], at a $p < 0.05$ level of significance.

Results

Performance analyses

Pre-operative impairments (i.e., scores below cut-off) were most frequently observed in object naming, non-word repetition and non-word spelling tasks (on each task, in 5/14 or 35.7% of patients; Table 3.2a). Post-operatively, on each task except sentence spelling, more than 40.0% of the patients scored below cut-off. At follow-up, long-term impairments were most frequently observed in non-word reading (5/8 cases or 62.5%) and non-word repetition (4/8 cases or 50.0%), as compared to only 1 case who showed a persistent impairment on action naming (12.5%; Table 3.2b). Yet, at all assessment times, performance on the different language tasks was significantly indistinguishable (pre-operatively: $F(5,75)=0.15$, $p= .979$; post-operatively: $F(5,67)=0.80$, $p= .553$; follow-up: $F(5,43)=0.40$, $p= .849$).

Analyzing the test results over time, performance changed significantly after surgery. Post-operatively, error rates on the six language tasks together were significantly higher (M = 22.45, SD = 28.03) than pre-operatively (M = 9.7, SD = 13.54;

t(152)=3.66, *p*< .001). When each task is considered separately, a significant decline from pre- to post-operative performance was observed for action naming only (Z = 2.20, *p*= .028; Table 3.2a), but not for written language tasks. At follow-up, combined error rates (on all tasks together) were significantly lower as compared to the post-operative assessment (M = 11.44, SD = 16.99; t(120)=2.46, *p*= .015). Yet, on individual tests, performance improvement from post-operative to follow-up assessment was only significant for object naming (Z = 2.12, *p*= .034) and action naming (Z = 2.03, *p*= .043). Performance on written language tasks did not significantly improve on the long-term after surgery. Compared to pre-operative scores, performance at follow-up was statistically indistinguishable (t(128)=0.66, *p*= .513; Table 3.2b).

Table 3.2a Short-term changes in language performance

	N	Below cut-off N (%)		Error rate (%) Mean ± SD		*p* value
		Pre	**Post**	**Pre**	**Post**	
Object naming	14	5 (35.7)	7 (50.0)	8.8 ± 8.8	28.7 ± 34.2	ns
Action naming	14	3 (21.4)	7 (50.0)	11.3 ± 12.4	31.1 ± 28.1	.028 *
Non-word repetition	14	5 (35.7)	6 (42.9)	7.9 ± 7.5	12.3 ± 16.5	ns
Non-word reading	7	2 (28.6)	5 (71.4)	8.7 ± 13.7	24.7 ± 33.1	ns
Non-word spelling	14	5 (35.7)	6 (42.9)	9.5 ± 11.7	19.8 ± 26.8	ns
Sentence spelling	8	1 (12.5)	1 (12.5)	7.5 ± 14.9	20.0 ± 31.6	ns

Time course of number of impaired language tasks and error percentages at the group level.
Pre = pre-operative, Post = post-operative; ns = *p*> .05

Table 3.2b Long-term changes in language performance

	N	Below cut-off N (%)		Error rate (%) Mean ± SD		*p* value
		Pre	**Follow-up**	**Pre**	**Follow-up**	
Object naming	8	3 (37.5)	2 (25.0)	7.9 ± 7.0	9.6 ± 11.9	ns
Action naming	8	2 (25.0)	1 (12.5)	11.6 ± 7.5	10.0 ± 7.4	ns
Non-word repetition	8	1 (12.5)	4 (50.0)	4.9 ± 7.5	6.9 ± 4.9	ns
Non-word reading	8	2 (25.0)	5 (62.5)	8.2 ± 12.8	18.5 ± 31.9	ns
Non-word spelling	9	2 (22.2)	2 (22.2)	5.6 ± 7.2	11.1 ± 16.7	ns
Sentence spelling	8	1 (12.5)	2 (25.0)	7.5 ± 14.9	12.5 ± 18.3	ns

Time course of number of impaired language tasks and error percentages at the group level
Pre = pre-operative, Follow-up = follow-up assessment; ns = *p*> .05

Finer-grained analyses

Individual analyses of the same materials were conducted in 4/14 cases for which original handwriting samples and reading recordings were available (Table 3.3). Considering all types of errors together (*Overall errors;* including Central, Peripheral, and Unclassifiable errors for handwriting; and Central and Other errors for reading), large individual variability was observed (Figure 3.1).

In 3/4 patients, grammatical constituents in sentences elicited the highest Overall errors rate. Errors contributing to the Overall count originated from different sources in individual patients. In patient GM, they reflected both Central and Peripheral errors, whereas in patients RP and DR they resulted from Peripheral errors only. In all cases, Central vs. Other and Peripheral errors behaved independently. For example, across assessments patient DR presented with comparable numbers of Central errors, but showed significantly more Other errors on non-word reading in pre- to post-operative assessment (p= .009) and from post-operative to follow-up assessment (p= .047). Moreover, patterns differed across cases. In the same subject, the occurrence of an error type could be similar at two assessment times, and that of another error type very different. For example, when pre-operative and post-operative sentence spelling performance was compared, patients RP and IR showed comparable Central error rates (0% for RP; 0 – 5.6% for IR), but substantially different Peripheral error rates (>38.9% for RP; <5.6% for IR). If Central and Other/Peripheral errors are considered separately, distinct patterns are shown in each task, which changed differently over time in the same individual (Figure 3.1).

In addition to calculating error rates, the possible influence of psycholinguistic variables on Central errors was examined by means of qualitative analyses. Also in this case large individual variability in error profiles and error types was observed. In patient GM, Central errors in non-word reading after surgery were significantly influenced by similarity to words (post-operative p= .032) and length (post-operative p= .013; follow-up p= .034). In addition, a significant effect of word (p< .001) and sentence length (p= .009) and was found in sentence spelling for GM. For patient DR, similarity to words significantly influenced post-operative non-word reading (p= .018) and a length effect was found in sentence spelling (pre-operative: word length, p< .001; post-operative & follow-up: sentence length, p= .009 & p= .009). For patients RP and IR, no significant effects of error patterns were detected. With regard to error types, Central errors were most frequently unrelated segmental errors (Table 3.4). Non-word reading often resulted in phonologically-related segmental errors. Non-fluent reading was most frequently observed in the context of Other errors in reading (Table 3.5). Peripheral errors in spelling were predominantly ill-formed letters; only one patient (RP) showed case mixing (Table 3.5).

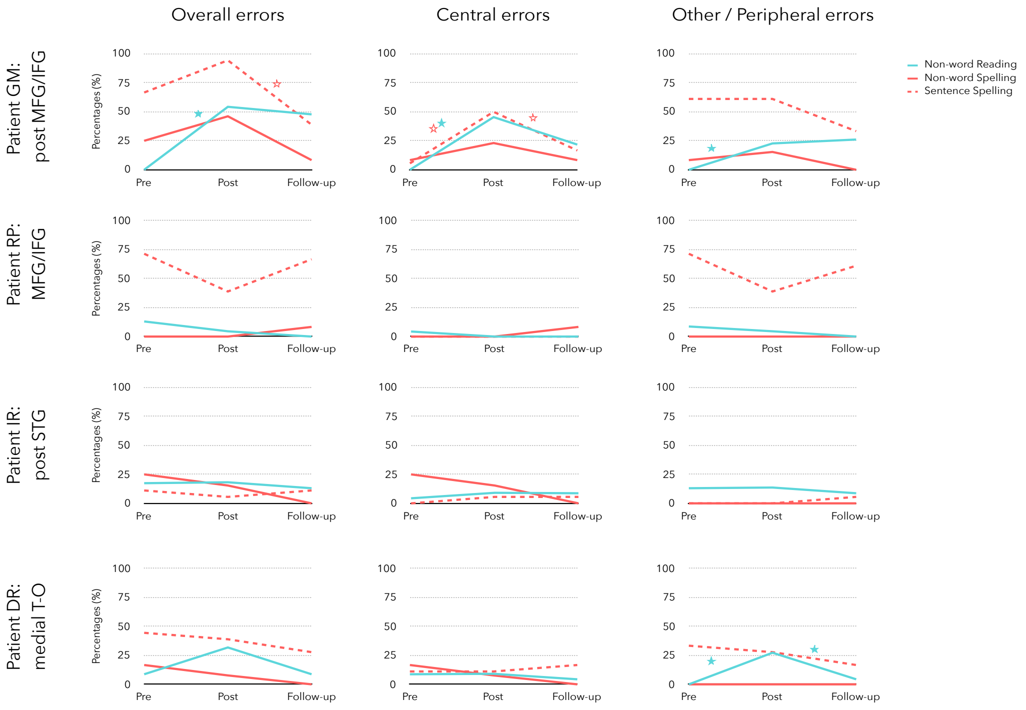

Figure 3.1 Individual error patterns on BADA written language subtests. Overall, Central and Other/Peripheral error rates are shown for four glioma patients. Graphs in each row represent the errors produced by each patient. In each graph, lines correspond the errors produced in the three written language subtest of BADA. Reading is displayed in blue, and spelling in red. Overall errors refer to the number of responses that contained an error of any type (i.e., Central, Other, Peripheral and/or Unclassifiable) – for this count, each response is considered only once (e.g., if a response string contained a Central and a Peripheral error, it was counted as 1 incorrect response in the Overall errors count). Central and Other/Peripheral errors were scored according to a structured error classification system (see Methods). Non-word reading consisted of 22 (post-operative) or 23 items (pre-operative & follow-up); non-word spelling of 12 (post-operative) or 13 items (pre-operative & follow-up); sentence spelling of 5 picture descriptions with 14 or 18 sentence constituents.
* Significant difference in error rates between assessment moments ($p < .05$).
Overall error rates ranged between 0.0 and 54.3% in non-word reading (in 0/22 – 12/22 items), between 0.0 and 46.2% in non-word spelling (in 0/13 – 6/13 items), and between 11.1 and 94.0% in sentence spelling (in 2/18 – 17/18 grammatical constituents). Central errors ranged from 0.0 and 45.5% in non-word reading (in 0/22 – 10/22 items), from 0.0 to 23.8% in non-word spelling (in 0/13 – 3/13 items), and from 0.0 to 55.6% in sentence spelling (in 0/18 – 10/18 grammatical constituents). Other errors ranged from 0.0 to 27.3% in non-word reading (in 0/22 – 6/22 items). Peripheral errors ranged between 0.0 and 15.4% in non-word spelling (in 0/13 – 2/13 items), and between 0.0 and 71.4% in sentence spelling (in 0/14 – 10/14 grammatical constituents).

Table 3.3 Demographic data of the subgroup of patients included for finer-grained analyses

Patient	Age	Gender	Education (years)	Lesion site	Tumor histology (WHO grade)	Extent of resection	Timing of assessment (days from surgery) Pre	Post	Follow-up
GM	63	M	17	Left post MFG/IFG, PreCG	Astrocytoma (II)	Partial	6	8	106
RP	41	M	13	Left MFG/IFG	Astrocytoma (II)	Total	4	8	115
IR	43	M	11	Left post STG	Glioblastoma (IV)	Subtotal	2	17	92
DR	33	M	13	Left medial T-O, parahippocampal gyrus	Astrocytoma (II)	Total	1	39	92

Four right-handed patients included for finer-grained analyses, who underwent awake surgery with object naming for left-hemispheric glioma resection. Pre = pre-operative, Post = post-operative, Follow-up = follow-up assessment; MFG = Middle Frontal Gyrus, IFG = Inferior Frontal Gyrus, PreCG = PreCentral Gyrus, STG = Superior Temporal Gyrus, T-O = temporo-occipital

Discussion

We evaluated the applicability of subtests from a commonly used battery to the monitoring of reading and spelling in glioma patients. Results of quantitative performance analyses, and of finer-grained quantitative and qualitative analyses at the single-subject level indicate that short subtests may not suffice for the evaluation of written language in glioma patients.

The significance of written language assessment

Evaluations of written language in glioma practice are scare, and generally restricted to group level analyses [2,16-18]. When we followed this approach to data analysis, quantitative analyses of performance in each of the subtests taken into consideration provided a reasonable overview of performance accuracy in written language tasks in glioma patients. Only considering error rate (i.e., the number of correct/incorrect items), group level analyses showed that reading and spelling impairments were frequent before (in up to 35.7% of cases) and after surgery (in up to 71.4% of cases). With persistent impairments in 62.5% of cases, non-word reading was the most frequently impaired of all tasks. At the group level, performance on reading and spelling tasks followed the same longitudinal pattern as that on spoken language and on other cognitive tasks (i.e., performance decline from pre- to post-operative assessment, performance increase from post-operative to follow-up assessment [19-21]). Interestingly, the long-term improvement from post-operative to follow-up assessment was significant for spoken language tasks (which were assessed intra-operatively), but not for written language tasks. This may indicate that return to baseline after surgery is more likely for intra-operatively monitored tasks than for non-monitored tasks, and/or that written language processes are more sensitive to damage than spoken language processes.

Table 3.4 Types of Central errors observed in written language assessments before and after surgery

	Total number of central errors	Phonological related segmental error	Segmental error resulting in a word	Unrelated segmental error	Word omission	Fragment	Phonological plausible error	Word substitution	Diacritic	Other central error
Patient GM										
Non-word reading	**15**	0 (0.0%)	2 (13.3%)	13 (86.7%)	0 (0.0%)	0 (0.0%)	*na*	*na*	*na*	0 (0.0%)
Non-word spelling	**5**	2 (40.0%)	0 (0.0%)	3 (60.0%)	0 (0.0%)	0 (0.0%)	*na*	*na*	*na*	0 (0.0%)
Sentence spelling	**13**	0 (0.0%)	0 (0.0%)	10 (76.9%)	0 (0.0%)	1 (7.7%)	0 (0.0%)	1 (7.7%)	1 (7.7%)	0 (0.0%)
Patient RP										
Non-word reading	**1**	0 (0.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	*na*	*na*	*na*	0 (0.0%)
Non-word spelling	**1**	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	*na*	*na*	*na*	0 (0.0%)
Sentence spelling	**0**	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Patient IR										
Non-word reading	**5**	0 (0.0%)	1 (20.0%)	4 (80.0%)	0 (0.0%)	0 (0.0%)	*na*	*na*	*na*	0 (0.0%)
Non-word spelling	**4**	3 (75.0%)	0 (0.0%)	1 (25.0%)	0 (0.0%)	0 (0.0%)	*na*	*na*	*na*	0 (0.0%)
Sentence spelling	**2**	0 (0.0%)	0 (0.0%)	1 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)
Patient DR										
Non-word reading	**5**	0 (0.0%)	1 (20.0%)	3 (60.0%)	0 (0.0%)	1 (20.0%)	*na*	*na*	*na*	0 (0.0%)
Non-word spelling	**2**	1 (50.0%)	0 (0.0%)	1 (50.0%)	0 (0.0%)	0 (0.0%)	*na*	*na*	*na*	0 (0.0%)
Sentence spelling	**7**	2 (28.6%)	1 (14.3%)	3 (42.9%)	0 (0.0%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

This Table shows Central errors produced on the subtests of the BADA Each row shows the total number of Central errors, and the number of each subtype of Central errors in each subtest. Each row also shows the percentage of each subtype of Central error / Total number of Central errors. Errors from pre-operative, post-operative and follow-up assessments are collapsed. *na* = not applicable

Table 3.5 Types of Other/Peripheral errors observed in written language assessments before and after surgery

Patient GM						
Non-word reading	**11**	5 (45.5%)	5 (45.5%)	1 (9.1%)	*na*	*na*
Non-word spelling	**3**	*na*	*na*	*na*	3 (100.0%)	0 (0.0%)
Sentence spelling	**27**	*na*	*na*	*na*	27 (100.0%)	0 (0.0%)
Patient RP						
Non-word reading	**3**	3 (100.0%)	0 (0.0%)	0 (0.0%)	*na*	*na*
Non-word spelling	**0**	*na*	*na*	*na*	0 (0.0%)	0 (0.0%)
Sentence spelling	**28**	*na*	*na*	*na*	15 (53.6%)	16 (57.1%)
Patient IR						
Non-word reading	**6**	2 (33.3%)	1 (16.7%)	3 (50.0%)	*na*	*na*
Non-word spelling	**1**	*na*	*na*	*na*	1 (100.0%)	0 (0.0%)
Sentence spelling	**2**	*na*	*na*	*na*	2 (100.0%)	0 (0.0%)
Patient DR						
Non-word reading	**7**	3 (42.9%)	1 (14.3%)	3 (42.9%)	*na*	*na*
Non-word spelling	**1**	*na*	*na*	*na*	0 (0.0%)	0 (0.0%)
Sentence spelling	**13**	*na*	*na*	*na*	13 (100.0%)	0 (0.0%)

This Table shows Other and Peripheral errors produced on the subtests of the BADA Each row shows the total number of Other/Peripheral errors, and the number of each subtype of Other/Peripheral errors in each subtest. Each row also shows the percentage of each subtype of Other/Peripheral error / Total number of Other/Peripheral errors. Errors from pre-operative, post-operative and follow-up assessments are collapsed. *na* = not applicable.

Written language encompasses reading and spelling processes that may be assessed in a variety of tasks. In the current retrospective study, materials selected for assessment were restricted to non-words in reading and spelling, and to written picture description in spelling. It is easily acknowledged that, since reading and spelling rely on complex processes, a comprehensive assessment should also target lexical processes by testing words. However, it may be understandable why the neurosurgical teams chose to assess written language in glioma patients undergoing awake surgery by administering non-words. Non-word reading/spelling may be more complex (hence, more sensitive to brain damage) than word reading/spelling. Moreover, while the neural correlates of lexical (word) processing are relatively well described, sublexical (non-word) processing seems to involve larger perisylvian regions [5,22,23]. Therefore, non-word reading/spelling may be more vulnerable than word reading/spelling to damage in a larger variety of left hemisphere regions. Irrespective of these methodological limitations, results stress the need for written language monitoring in glioma patients undergoing awake surgery.

The significance of individual evaluations

Group level analyses provided a first insight in written language performance in glioma patients, but large standard deviations in error rates indicated the need for further individual analyses. Patient-specific analyses are particularly fundamental for glioma patients selected for awake surgery, as surgery takes a highly personalized approach. Since each tumor differs in location, histology and growth rate, and each patient differs in premorbid cognitive functioning, educational level and age, individual differences in cognitive performance are inevitable. Finer-grained analyses confirmed these large differences in patient's performances on written language tasks.

Quantitative evaluations of Central and Other/Peripheral errors showed that the patterns observed in performance analyses generally do not hold for individual cases. As an example, when the 4 subjects whose data could be analyzed in greater detail were considered as a group, error rate for each task increased from pre-operative to post-operative testing, and decreased from post-operative to follow-up testing. At the individual level, only 1/4 patients (GM) showed an increase in Central errors from pre- to post-operative assessment and a decrease from post-operative to follow-up assessment on all tasks. Error rates differed, and changes in error rates over time followed distinct individual patterns. For example, patients with similar performance profiles in Central errors (such as RP and IR on sentence spelling) showed substantially different Peripheral errors on the same task. In the literature and in clinical practice, performance is often evaluated in terms of Overall errors (i.e., collapsing across Central, Other, Peripheral and Unclassifiable errors) or of Central errors only. As presented in Figure 3.1, the difference between Central and Peripheral/Other errors is easily overlooked when only Overall or only Central errors are considered. Peripheral and Other errors inform on additional aspects of reading and spelling processes that could influence performance beyond Central processes. Correct strings of graphemes/phonemes (i.e., preserved Central processing) cannot be communicated properly when post-central processes such as graphomotor skills in spelling or fluency in reading are impaired. The specific influence of these written language components, albeit obvious, remains to be systematically examined. On an object naming tasks, speed was found to correlate significantly with return to work [24]. In order to accurately evaluate reading and spelling in glioma patients, and to comply as much as reasonable with each patient's functional needs and wishes, qualitative error analyses are necessary.

The significance of qualitative evaluations

One of the main goals of qualitative analyses of performance in brain-damaged individuals is the identification of the cognitive locus of damage. For written language, damage to specific cognitive components can be identified by evaluating error types. Each component is associated with particular psycholinguistic variables, which are typically affected when the component is damaged (e.g., a length effect for buffer processes; see Chapter 1 and 2 for a detailed description). Analyses of the influence of psycholinguistic variables on errors can therefore provide clues as to which underlying process is disrupted. The effects of psycholinguistic characteristics on performance accuracy and the occurrence of specific error types were evaluated in a subgroup of cases, to find out to what extent performance on a short clinical battery provides insight in the functioning of the various components of the reading and spelling systems.

Qualitative analyses provided additional evidence for individual differences among glioma patients, above and beyond quantitative evaluations. For example, even though post-operatively Central error rates in non-word reading were equal for patients IR and DR, DR's Central errors were significantly influenced by non-words' similarity to words, whereas IR's errors were not influenced by any psycholinguistic variable. Distinct psycholinguistic variables accounted for errors in individual patients, which sometimes varied over different assessment moments.

Yet, neither the number nor the distribution of incorrect responses in the subjects evaluated sufficed to identify underlying functional impairments. Even when the qualitative aspects of performance on the BADA subtests were thoroughly analyzed, results failed to provide the range of information that would be necessary to evaluate the status of the components of reading and spelling in each patient.

Some observed patterns were congruent with expectations based on the functional and anatomical theories, but not all findings were consistent. As an example of consistent evidence, consider patient GM. This patient has a glioma in the posterior middle and inferior frontal gyrus. In agreement with observations involving these regions in short-term memory processes (graphemic and phonological buffer [25-28]), GM showed a length effect in both reading and spelling. As another example of consistent evidence, high Peripheral error rates were observed in sentence spelling in two patients with gliomas in (posterior) middle and inferior frontal gyri (≥33.3% or ≥6/18 items), coherent with lesion and neuroimaging studies point to the role of these regions in peripheral spelling processes [29-33]. Yet, against expectations, in the same patients this pattern was not found in non-word spelling (≤15.6% Peripheral errors or ≤2/13 items). Moreover, in 2/4 patients, qualitative analyses failed to identify influences of psycholinguistic variables, or specific error patterns, thus giving no clues to the impairments underlying dysgraphia in these subjects.

In other cases, too few errors were observed to allow sophisticated interpretations of performance. For example, phonologically plausible errors in spelling have been described in the presence of damage to posterior inferior frontal and posterior inferior temporal damage as a consequence of orthographic lexicon deficits (see Chapter 2). Only one such error was observed in the current study, made by DR. The patient had a glioma in medial temporo-occipital regions, which could indeed influence orthographic lexical processing via posterior inferior temporal gyrus. Yet, conclusions cannot rely on a single error.

The lack of significant effects of psycholinguistic dimensions on our patients' performance probably results from limitations of the assessment tool. The battery used in this retrospective study was part of a much larger screening tool for post-stroke aphasia, which included also tasks that evaluate word comprehension, picture naming, word reading, spelling and repetition. The non-word subtests, if administered as a standalone battery, are probably too short and easy to detect the subtle deficits usually found in glioma patients. In order to carefully assess the status of the components of reading and spelling processes in glioma patients, more detailed testing tools are required.

Conclusions

The current study underlines that assessment batteries for glioma patients should be extended to include written language, as written language deficits are frequent before and persistently after surgery. The large individual variability emphasizes that performance should be thoroughly evaluated in each patient. Yet, this study has also shown that current clinical evaluations of written language (i.e., short subtests usually taken from post-stroke aphasia batteries) are not sufficiently sensitive to disclose deficits of underlying components in glioma patients. More sensitive assessments are needed for the detailed and customized evaluation of reading and spelling in glioma patients undergoing awake surgery.

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3

4

Detailed cognitive assessment of written language in awake surgery: A new examination tool

Abstract

This study describes the development of a theory-driven written language assessment tool for glioma patients undergoing awake surgery. We aimed to design a sensitive and specific written language battery based on current cognitive neuropsychological theories of language processing. A cognitive model that distinguishes multiple underlying components of reading and spelling served as the foundation for new written language battery. The battery includes word, non-word and sentence tasks for reading and spelling, and was standardized in a population of Italian and Dutch neurologically healthy adults. Norms, imageability ratings, mean reaction times and inter-rater reliability from healthy participant data provide guidelines for the use of the battery in neurosurgical practice. The clinical applicability of the comprehensive battery for pre-, intra- and post-operative use in glioma practice is discussed.

Introduction

Although reading and spelling are indispensable for communication, and an important issue in awake surgery for glioma patients is to preserve quality of life, assessments of written language in neurosurgical practice are scarce (Chapter 1, 2) and insufficient to identify the cognitive locus of impairments (Chapter 3). However, this is a necessary goal if one is to target personalized intra-operative assessment and post-operative treatment for glioma patients effectively and efficiently. We aimed to design a sensitive and specific written language battery, based on current cognitive neuropsychological theories of language. The test battery includes different reading and spelling tasks, and was standardized in a population of neurologically healthy adults.

Cognitive framework

Classical lesion and neuroimaging literature has identified multiply cognitive components to underlie the processes of reading and spelling. In order to accurately assess the underlying cause of impairments, an examination tool is required that allows disentangling these components. Cognitive neuropsychology has provided insight in the signs resulting from damage to separate underlying components. When injured in isolation, each component results in a typical error pattern, characterized by specific types of errors and constrained by psycholinguistic and/or cognitive variables (e.g., grammatical class, frequency, word length, etc.). Detailed descriptions of error patterns related to each component are provided in Chapter 1 section 'Reading', and in Chapter 2 section 'The functional architecture of spelling'. Based on these studies, it is possible to predict the pattern of impairments that is most likely to follow damage to each component. Figure 4.1 schematically represents the components involved in reading and spelling, and shows the corresponding sensitivity to psycholinguistic variables and frequent error types.

Reading- and spelling-specific processes may be evaluated by assessing psycholinguistic variables that are known to be sensitive to damage of distinct components. Error profiles on different psycholinguistic variables may provide insight in possible damage to the associated underlying process, yet dysfunction does not directly indicate that there is damage to the associated component. When performance on separate variables converges with the profile of a specific component (e.g., impaired non-word spelling for phoneme-grapheme conversion), the impairment may also have arisen from damage to other components (e.g., a phonological input or graphemic buffer deficit). Diagnosis can therefore not be based on performance on one task only. Careful evaluation of written language requires considerations of performance on several tasks, other variables and all error types to diagnose functional damage.

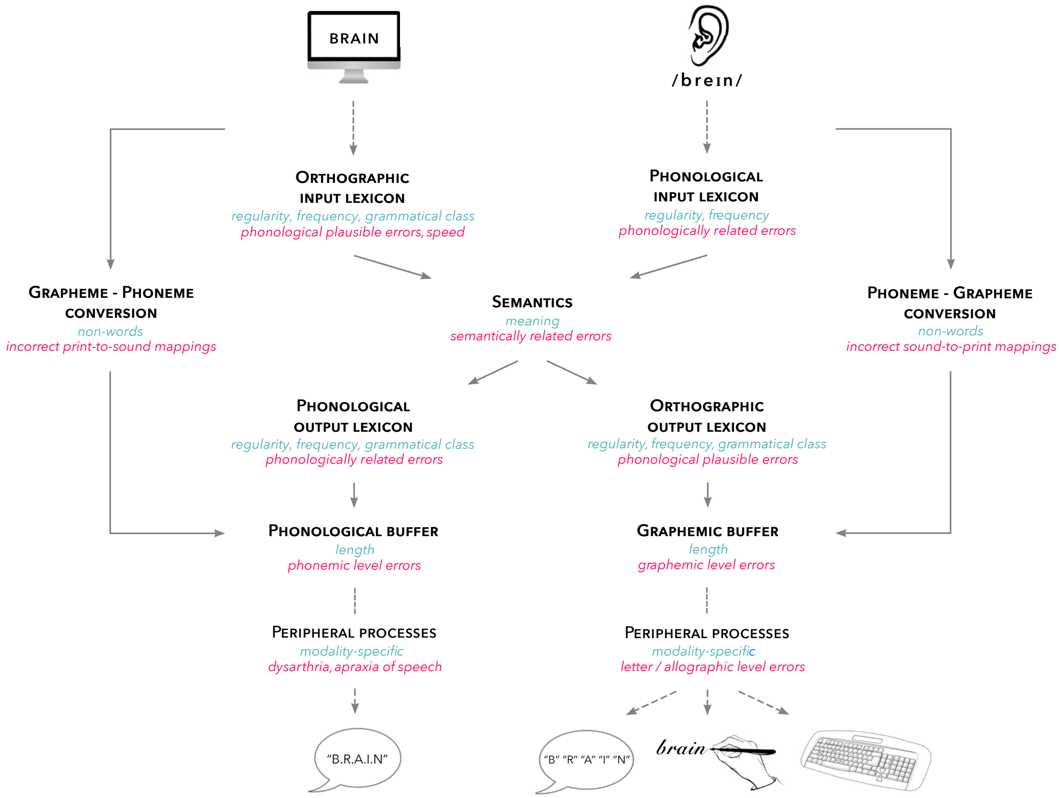


Figure 4.1 Schematic representation of the cognitive components involved in reading and spelling, with frequent error profiles after selective component damage. Starting from written or spoken input, single words are processed by distinct components. Damage to each component may result in incorrect performance, which qualitative features are constrained by the dimensions reported in *italics* under each component. Psycholinguistic variables sensitive for damage to specific components are printed in blue. Frequent error types observed following damage to specific components are printed in red.

Spelling modalities

Spelling can be assessed by different tasks; including handwriting, typing and oral spelling tasks. As depicted in Figure 4.1, all modalities depend on shared central processes (i.e., from phonological input lexicon up until the graphemic buffer). Hence, their status can be assessed with comparable effectiveness by different tasks. In contrast, peripheral processes are modality-specific and tap handwriting, typing and oral spelling to different extents, and must therefore be assessed by separate tasks.

With regards to the written language test development, we aimed to design the battery so that spelling may be assessed in different modalities, depending on the goal of testing. In general, the output modalities of handwriting and typing would add most information to the existing assessment of spoken naming tasks (Table 4.1). Within written spelling, handwriting tasks may be most informative, as the grapheme – graphomotor conversion in handwriting relies on multiple levels of peripheral processing. Graphemes are first converted into allographics (specific letter shapes such as upper- or lowercase) and then into graphomotor sequences for handwriting, while the conversion occurs directly for typing. Yet, although little research has been conducted on these peripheral processes, conversion processes of handwriting and typing have been suggested to rely on the same neural substrates [1,2]. In that case, assessment of handwriting may also be indicative of peripheral processes of typing and vice versa.

Increasing reliance on typing in contemporary society (texting, e-mailing, etc.), may lead one to push for the assessment of typing in addition to (or, even instead of) handwriting. Certainly, evaluations of typing will be increasingly relevant before and after surgery. For the time being, however, typing does not lend itself to intra-operative evaluation in glioma cases. Since the patient cannot place both hands on the keyboard during surgery, intra-operative typing heavily relies on visual search, more than on spelling. Handwriting normally involves only the dominant hand and is, despite some discomfort due to positioning of the patient during surgery, feasible during surgery (e.g., [1,3-5]). Therefore, handwriting should be given preference over other spelling tasks when assessing written language in glioma patients undergoing awake surgery. Oral spelling and typing may be considered in specific cases. The materials of the battery can be used for that purpose. With regards to the description of the written language battery, we consider spelling assessment in the modality of handwriting.

Table 4.1 Peripheral processes assessed by each spelling task, in comparison to a spoken naming task

	Handwriting	Typing	Oral spelling	Spoken naming
Grapheme - letter name conversion			✓	
Grapheme – graphomotor planning		✓		
Grapheme – allograph conversion	✓			
Allograph – graphomotor planning	✓			
Motor output: Speech			✓	✓
Motor output: Hand	✓	✓		

Motor output = combined representation of all motor processing stages

Cognitive assessment of written language

A comprehensive test battery was designed for the assessment of written language in glioma patients. The battery includes reading and spelling tasks, designed in such a way as to tap each reading and spelling-specific component of the cognitive model (Figure 4.1). Tests were developed in Italian and Dutch. In both languages, the battery includes the same kind of stimuli; words, non-words and sentences. Items for the Italian battery were based on lists from Miceli and Capasso (unpublished) and on the battery for the evaluation of developmental Dyslexia and Dysgraphia (DDE-2 [6]). Dutch stimuli were based on the Dutch Psycholinguistic Assessments of Language Processing in Aphasia (PALPA [7]). In addition, for both languages, additional non-words were generated specifically. Each task was controlled for various psycholinguistic variables, including word frequency, grammatical class, length, morphological structure, orthographic regularity, and similarity to words (for non-words). Absolute frequency counts and grammatical class information are taken from the written language databases CoLFIS for Italian [8] and SUBTLEX-NL for Dutch [9]. When multiple grammatical classes could be attributed to one word (e.g. *work* can be a noun and a verb; *last* can be a verb, an adjective and an adverb), the ratio dominant/non-dominant usage of frequency was calculated. Only words with a dominant ratio >4.0 were included. For each non-word, similarity to words was calculated using N-count, which refers to the number of words that can be generated by changing a single letter of the non-word. High N-count non-words are more similar to words than low N-count non-words. The aim of each list and task, the psycholinguistic variables controlled for each list and task, and general instructions for administration are described separately for reading and spelling. Psycholinguistic variables are discussed with references to the cognitive component that they are related to, when components are damaged in isolation (Figure 4.1). Administration of the complete battery is needed to diagnose the exact impairments. Considerations for pre-, intra- and post-operative assessments are described in the section on *Test administration*. Full stimulus lists with all parameters considered are reported in Appendix B.

Reading tasks

Reading words

The patient is asked to read aloud single words presented on a computer screen. This task provides insight in the functioning of the orthographic input lexicon, phonological output lexicon and phonological buffer. The Italian and Dutch word reading subtasks consist of three assessment lists, which were controlled for different psycholinguistic variables. In each list, items were balanced for letter and syllable length and for frequency. For each item, imageability ratings are included as a parameter.

Italian

List 1 assesses the effect of frequency, length and grammatical class (Table 4.2). Damage to the orthographic input and/or phonological output lexicon may cause incorrect reading of low-frequency words and a selective dysfunction of different grammatical classes. Incorrect reading of longer words (compared to shorter words) may result from damage to phonological buffer processing. List 2 assesses the effect of morphological regularity and (root and inflection) length (Table 4.3). Damage to the phonological output lexicon may lead to incorrect reading of verbs with irregular morphology. Different performance on longer and shorter inflected verbs may be caused by damage to phonological buffer processing. List 3 assesses the effect of orthographic regularity (Table 4.4). As words with irregular orthography rely on lexical processing, damage to the orthographic input and/or phonological output lexicon may result in incorrect reading of these words. Words with irregular orthography in Italian that are assessed in this list include words with geminate consonants (i.e., double letters), with a specific pronunciation of the letters c and g. In addition, words with irregular stress (i.e., not on the penultimate syllable) are included. Incorrect stress assignments may result from damage to the phonological output lexicon.

Table 4.2 Italian word reading: List 1 (frequency, length and grammatical class)

96 words	48 High frequency	24 Long	6 Nouns	*famiglia* (family)
			6 Verbs	*afferma* (says)
			6 Adjectives	*piccola* (small)
			6 Function words	*qualcuno* (someone)
		24 Short	6 Nouns	*fiori* (flowers)
			6 Verbs	*penso* (think)
			6 Adjectives	*vera* (real)
			6 Function words	*circa* (about)
	48 Low frequency	24 Long	6 Nouns	*progressi* (progress)
			6 Verbs	*segnava* (marked)
			6 Adjectives	*medesimo* (same)
			6 Function words	*appieno* (fully)
		24 Short	6 Nouns	*guanti* (gloves)
			6 Verbs	*udire* (to hear)
			6 Adjectives	*medi* (average)
			6 Function words	*ossia* (namely)

High frequency words occurred more than 45 times per 1.000.000 words. Low frequency words occurred less than 30 times per 1.000.000 words in the database. Verbs were included in infinitive and inflected forms, and in present and past tense. Short words: 4-6 letters (3-6 phonemes); long words: 7-9 letters (5-8 phonemes).

Table 4.3 Italian word reading: List 2 (morphological regularity and length)

32 words	24 Regular morphology	12 Long root	6 Long inflection 6 Short inflection	*prendiamo (take)* *spingo (push)*
		12 Short root	6 Long inflection 6 Short inflection	*sedette (sat)* *alzi (lift)*
	8 Irregular morphology	4 Long root		*potresti (could)*
		4 Short root		*rise (laughed)*

Verbs were included with long (4-6 letters) and short (0-3 letters) roots. For regular verbs, long and short inflections were distinguished, of respectively 4-5 and 1-2 letters.

Table 4.4 Italian word reading: List 3 (orthographic regularity)

30 words	9 Geminate consonants	*penna (pen)*
	9 Specific pronunciation of c/g	*gusti (taste)*
	12 Irregular stress	*portici (arcades)*

Irregular stress = stress not on the penultimate syllable. Only nouns were included.

Table 4.5 Dutch word reading: List 1 (frequency, length and grammatical class)

44 words	22 High frequency	11 Long	3 Nouns 3 Verbs 3 Adjectives 2 Function words	*opdracht (assignment)* *nadenken (to think)* *hetzelfde (the same)* *nergens (nowhere)*
		11 Short	3 Nouns 3 Verbs 3 Adjectives 2 Function words	*mens (human)* *valt (falls)* *groot (big)* *meteen (immediately)*
	22 Low frequency	11 Long	3 Nouns 3 Verbs 2 Adjectives 3 Function words	*wijsheid (wisdom)* *uitkijken (to look out)* *inclusief (inclusive)* *derhalve (therefore)*
		11 Short	3 Nouns 3 Verbs 2 Adjectives 3 Function words	*strik (bow)* *weven (to weave)* *scheef (skew)* *zelden (rarely)*

High frequency words occurred more than 45 times per 1.000.000 words in the database, while low frequency words occurred less than 30 times per 1.000.000 words. Verbs were included in infinitive and inflected forms, and in present and past tense. Short words: 4-6 letters (3-6 phonemes); long words: 7-9 letters (6-9 phonemes).

Dutch

List 1 assesses effects of frequency, length and grammatical class (Table 4.5). Incorrect reading of low-frequency words and disproportionate impairments of different grammatical categories may result from damage to the orthographic input and/or phonological output lexicon. Damage to the phonological buffer may cause difficulty in reading longer words (as compared to shorter words). List 2 assesses the effect of morphological regularity (Table 4.6). Incorrect reading of morphologically complex verbs may result from damage to the phonological output lexicon. List 3 assesses the effect of orthographic regularity (Table 4.7). Nouns with irregular orthography may be read poorly following damage to the orthographic input and/or phonological output lexicon. For each word, age of acquisition is included as a parameter.

Table 4.6 Dutch word reading: List 2 (morphological regularity)

16 words	8 Regular morphology	*zwemt* (*swims*)
	8 Irregular morphology	*kocht* (*bought*)

Inflected verbs were included in present and past tense.

Table 4.7 Dutch word reading: List 3 (orthographic regularity)

14 words	7 Regular orthography	*houding* (*posture*)
	7 Irregular orthography	*ceintuur* (*belt*)

Regular orthography = following grapheme-phoneme conversion rules; Irregular orthography = not following grapheme-phoneme conversion rules.

Reading non-words

The patient is asked to read aloud orthographically plausible letter strings that do not correspond to words. Stimuli are presented on a computer screen. Performance on this task provides insight in grapheme-phoneme conversion and phonological buffer functioning.

Italian

The Italian non-word reading task consists of three lists, controlled for several psycholinguistic variables. In each list, items were balanced for letter and syllable length, and for similarity to words. List 1 assesses effects of similarity to words and of length (Table 4.8). Incorrect reading of non-words may be caused by damage to grapheme-phoneme conversion rules. A length effect may result from damage to the phonological buffer. List 2 assesses the effect of morphological structure (Table 4.9). Non-words that are morphological decomposable (in which it is possible to parse the stimulus into a plausible yet non-existing combination of a root and affix) and non-words that are morphological not decomposable were included. List 3 assesses the effect of orthographic structure (Table 4.10). This list includes non-words with simple-CV (consonant-vowel) structure, which is the most common syllable structure in Italian, and non-words with at least one syllable that is not of the simple-CV type. Errors on list 2 and 3 may be related to disruption of phonological and/or early orthographic processing.

Table 4.8 Italian non-word reading: List 1 (similarity to existing words and length)

24 non-words	12 High similarity	6 Long	*lotare*
		6 Short	*pata*
	12 Low similarity	6 Long	*imieto*
		6 Short	*deie*

High similarity non-words = more than 5 words can be derived from non-words when changing one letter; Low similarity = less than 3 words can be derived from non-words when changing one letter. Short non-words: 4 letters/phonemes; long non-words: 6 letters/phonemes.

Table 4.9 Italian non-word reading: List 2 (morphological structure)

30 non-words	15 Morphological decomposable	*moreva*
	15 Morphological not decomposable	*strivule*

Table 4.10 Italian non-word reading: List 3 (orthographic structure)

24 non-words	8 Consonant-vowel order orthography	*pacilo*
	16 No consonant-vowel order orthography	*flitori*

Dutch

The Dutch non-word reading subtask consists of one assessment list, controlled for similarity to words and length (Table 4.11). Similarity clusters were balanced for letter and syllable length. Non-words will be read incorrectly when grapheme-phoneme conversion processing is damaged. Incorrect reading of longer items may result from damage to the phonological buffer.

Table 4.11 Dutch non-word reading: List 1 (similarity to existing words and length)

32 non-words	16 High similarity	8 Long	*boesten*
		8 Short	*nak*
	16 Low similarity	8 Long	*verkoerd*
		8 Short	*beum*

High similarity non-words = more than 5 words can be derived from non-words when changing one letter; Low similarity = less than 3 words can be derived from non-words when changing one letter. Short non-words: 3-5 letters (3-4 phonemes); long non-words: 6-8 letters (5-7 phonemes).

Reading sentences

The patient is asked to read aloud a short sentence shown on a computer screen. In addition to all other lexical processes targeted during sentence reading, the variables controlled for in this task provide additional insight in phonological output lexicon functioning. In addition, insight is provided in processes not included in the model of Figure 4.1, such as grammar. For each word in the sentences, word frequency, length, and grammatical class, and sentence length are included as parameters.

Italian

The Italian sentence reading task includes two assessment lists. List 1 assesses the pronunciation of homographs (Table 4.12). These words have identical spelling but are pronounced differently depending on the meaning of the word (e.g., scrivàno[i]; *writer,* and scrìvano[i]; *they write*). Each homograph typically carries stress on the penultimate syllable (the most common stress pattern in Italian) or on the ante-penultimate syllable (a less frequent stress pattern). List 2 assesses clitic pronouns (Table 4.13). Italian clitics are attached to a verb and have a syntactic function (they can be personal pronouns or adverbs). They are written as a part of a word, but do not modify stress assignment (consequently they may result in uncommon stress patterns). These words can only be pronounced correctly when the word is stored in the phonological output lexicon. Damage to this component will result in incorrect stress assignments on both lists.

Table 4.12 Italian sentence reading: List 1 (sentences with homographs)

22 sentences	11 Homographs with stress on the penultimate syllable	*Queste stoffe sono leggère come piume.* [i] *(These fabrics are light as a feather.)*
	11 Homographs with stress on a non-penultimate syllable	*Lèggere rende colti.* [i] *(Reading makes you educated.)*

Table 4.13 Italian sentence reading: List 2 (clitic pronouns)

2 sentences	2 Clitic pronouns	*Pòrtamelo quando hai tempo.* [i] *(Bring it to me when you have time.)*

[i] Stress is generally not marked with diacritics in Italian and Dutch, written marks (`) indicate stress position for clarification purposes

Dutch

The Dutch sentence reading task consists of a list that assesses the pronunciation of homographs (i.e., word pairs with identical spelling but different meaning; Table 4.14). Homographs with stress on the initial syllable and with stress on the non-initial syllable were included (e.g., vòòrkomt[i]; *appear* and voorkòmt[i]; *prevent*). Stress assignment in Dutch is not fixed to a specific position in a word, but is stored with the word in the lexicon. In Dutch, additional homographs exist, of which pronunciation changes depending on whether it is an original Dutch or a loan word (e.g., band; *band* and band; *tire*). Homographs can only be read aloud faultlessly when the correct phonological string of the word is stored in the phonological output lexicon. Damage to this component may therefore result in reading with incorrect stress assignments and in incorrect pronunciation of Dutch/loan words.

Table 4.14 Dutch sentence reading: List 1 (sentences with homographs)

16 sentences	7 Homographs with stress on the initial syllable	*De atleet verbrak het record vèrspringen.* [i] *(The athlete broke the long jump record.)*
	7 Homographs with stress on a non-initial syllable	*De regels op de computer verspr̀ingen.* [i] *(The lines on the computer jump in.)*
	2 Homographs with pronunciation depending on the origin of the word	*De fiets heeft een lekke band.* *(The bicycle has a flat tire.)* *Jan vindt de Beatles de beste band.* *(Jan thinks the Beatles are the best band.)*

Spelling tasks

Spelling words

When spelling is assessed in the modality of handwriting, the patient is asked to write down single words on a sheet of paper, which are dictated by the examiner. This task provides insight in the functioning of the phonological input lexicon, orthographic output lexicon, and graphemic buffer, as well as the peripheral processes of handwriting. The Italian and Dutch word spelling subtasks consist of respectively four and three assessment lists, which were controlled for different psycholinguistic variables. In each list, items were balanced for letter and syllable length, frequency and for grammatical class. For each item, imageability ratings are included as a parameter.

Italian

List 1 assesses the effect of frequency, length and grammatical class (Table 4.15). Damage to the phonological input and/or orthographic output lexicon may cause incorrect spelling of low-frequency words. In addition, damage to the orthographic output lexicon may cause a selective dysfunction of different grammatical categories. Incorrect spelling of longer words (compared to shorter words) may result from damage to graphemic buffer processing. List 2 assesses morphology (Table 4.15). Long verbs (7-10 letters) with complex and non-complex inflections were considered. For each item, root length (3-8 letters) and length of inflection (3-4 letters) were included as parameters. Incorrect spelling of morphologically complex verbs may result from damage to the phonological input lexicon. List 3 assesses orthographic structure (Table 4.17), and list 4 assesses orthographic regularity by administering words with opaque segments (Table 4.18). List 3 includes words with the most commonly used simple-CV (consonant-vowel) structure, and words with at least one syllable that is not of the simple-CV type. Moreover, words with geminate consonants are included, which, in Italian, mark that stress is placed on the preceding syllable. Words with complex or irregular orthography can only be written correctly when the corresponding string of sequences is stored in the orthographic output lexicon. Hence, these words will be written incorrectly when access to the orthographic output lexicon is restricted.

Table 4.15 Italian word spelling: List 1 (frequency, length and grammatical class)

48 words	24 High frequency	12 Long	3 Nouns	*progetto* (project)
			3 Verbs	*comincia* (begins)
			3 Adjectives	*semplice* (simple)
			3 Function words	*neppure* (not even)
		12 Short	3 Nouns	*paesi* (countries)
			3 Verbs	*finito* (finished)
			3 Adjectives	*bella* (beautiful)
			3 Function words	*ecco* (here)
	24 Low frequency	12 Long	3 Nouns	*contagio* (contagion)
			3 Verbs	*chiarire* (to clarify)
			3 Adjectives	*discreto* (discreet)
			3 Function words	*innanzi* (before)
		12 Short	3 Nouns	*orlo* (edge)
			3 Verbs	*stacca* (detaches)
			3 Adjectives	*vile* (cowardly)
			3 Function words	*donde* (whence)

High frequency words occurred more than 45 times per 1.000.000 words in the database, while low frequency words occurred less than 30 times per 1.000.000 words. Verbs were included in infinitive and inflected forms, and in present and past tense. Short words: 4-6 letters (3-6 graphemes); long words: 7-8 letters (6-8 graphemes).

Table 4.16 Italian word spelling: List 2 (morphology)

12 words	12 Long inflected verbs	*ridendo (laughing)*

Table 4.17 Italian word spelling: List 3 (orthographic structure)

36 words	12 Consonant-vowel order orthography	4 Nouns 4 Verbs 4 Adjectives	*miracolo (miracle)* *lavora (works)* *numerose (numerous)*
	12 No consonant-vowel order orthography	4 Nouns 4 Verbs 4 Adjectives	*stazione (station)* *concluse (concluded)* *fresca (fresh)*
	12 No consonant-vowel order orthography with geminate consonants	4 Nouns 4 Verbs 4 Adjectives	*castello (castle)* *assicura (ensures)* *perfetto (perfect)*

Table 4.18 Italian word spelling: List 4 (orthographic regularity)

54 words	15 Words with c- (ce/ci-a-o-u/che-i/cie/cuo)	*piacere (pleasure)* *baciare (to kiss)*
	17 Words with g- (ghe-i/ge/gi-a-o-u/gna-e-i-o-u)	*funghi (mushrooms)* *agnello (lamb)*
	8 Words with q- (qua-e-i/quo)	*quercia (oak)* *equo (fair)*
	14 Words with sc- (sce/sche-i/sci-a-o-u/scie)	*maschi (males)* *fascino (charm)*

Dutch

List 1 assesses the effect of frequency, length and grammatical class (Table 4.19). Incorrect reading of low-frequency words may result from damage to the orthographic input and/or phonological output lexicon. Damage to the orthographic output lexicon may also result in disproportionate impairments of different grammatical categories. Incorrect spelling of longer words (compared to shorter words) may be caused by damage to graphemic buffer processing. List 2 assesses the effect of morphological regularity (Table 4.20). Verbs (4-5 letters) with regular and irregular inflections were included. Incorrect spelling of morphologically complex verbs may result from damage to the phonological input lexicon. List 3 assesses the effect of orthographic regularity (Table 4.21). Incorrect spelling of these words may be caused by damage to the orthographic output lexicon. As words with irregular orthography rely on lexical processing, damage to the orthographic output lexicon may result in incorrect spelling of these words. For each word, age of acquisition is included as a parameter.

Table 4.19 Dutch word spelling: List 1 (frequency, length and grammatical class)

30 words	14 High frequency	8 Long	3 Nouns 2 Verbs 1 Adjective 2 Function words	*onderzoek* (research) *luisteren* (to listen) *duidelijk* (clear) *inderdaad* (indeed)
		6 Short	3 Nouns 1 Verb 1 Adjective 1 Function word	*koffie* (coffee) *vieren* (to celebrate) *raar* (weird) *tussen* (between)
	16 Low frequency	8 Long	1 Noun 3 Verbs 1 Adjective 3 Function words	*schouder* (shoulder) *regenen* (to rain) *waardevol* (valuable) *aangaande* (regarding)
		8 Short	2 Nouns 1 Verb 2 Adjectives 3 Function words	*gezag* (authority) *hakte* (chopped) *blut* (broke) *tevens* (in addition)

High frequency words occurred more than 45 times per 1.000.000 words. Low frequency words occurred less than 30 times per 1.000.000 words in the database. Verbs were included in infinitive and inflected forms, and in present and past tense. Short words: 4-6 letters (3-6 graphemes); long words: 7-8 letters (6-9 graphemes).

Table 4.20 Dutch word spelling: List 2 (morphological regularity)

8 words	4 Regular morphology	*denkt* (thinks)
	4 Irregular morphology	*hing* (hang)

Table 4.21 Dutch word spelling: List 3 (orthographic regularity)

14 words	7 Regular orthography	*toga* (gown)
	7 Irregular orthography	*douche* (shower)

Spelling non-words

The patient is asked to write down phonologically plausible letter strings that are no words. Stimuli are dictated by the task administrator. Performance on this task provides mainly insight in phoneme-grapheme conversion and graphemic buffer functioning.

Italian
The Italian non-word spelling task consists of two lists, controlled for different psycholinguistic variables. In each lists, items were balanced for letter and syllable length and for similarity to words. List 1 assesses the effects of orthographic structure and of length (Table 4.22). Incorrect spelling of non-words may be caused by damage to phoneme-grapheme conversion rules. A length effect may result from graphemic buffer damage. Common orthography includes simple-CV (consonant-vowel) and plausible CV structures, whereas CV structures of uncommon orthography are less plausible for Italian words. List 2 assesses the effect of morphological structure, contrasting morphological decomposable (i.e., possible to parse the stimulus into a plausible yet non-existing combination of a root and affix) and not decomposable non-words (Table 4.23). In addition to phoneme-grapheme conversion damage, non-words with uncommon orthography and morphology may be written incorrectly after disruption of early phonological and/or orthographic processing.

Table 4.22 Italian non-word spelling: List 1 (orthographic structure and length)

28 non-words	14 Common orthography	7 Long	*nortedi*
		7 Short	*spivo*
	14 Uncommon orthography	7 Long	*raschelo*
		7 Short	*rogli*

Short non-words: 4-6 letters (3-6 graphemes); long non-words: 7-8 letters (6-8 graphemes).

Table 4.23 Italian non-word spelling: List 2 (morphological structure)

30 non-words	15 Morphological decomposable	*sedono*
	15 Morphological not decomposable	*pedovi*

Dutch
The Dutch non-word spelling task consists of one list, which assesses the effect of similarity to existing words and length (Table 4.24). Similarity clusters are balanced for letter and syllable length. Damage to phoneme-grapheme conversion rules may result in incorrect non-word spelling. Incorrect spelling of longer words (compared to shorter words) may be caused by damage to the graphemic buffer.

Table 4.24 Dutch non-word spelling: List 1 (similarity to existing words and length)

16 non-words	8 High similarity	3 Long	*wussen*
		5 Short	*mer*
	8 Low similarity	3 Long	*kruiter*
		5 Short	*slun*

High similarity non-words = more than 5 words can be derived from non-words when changing one letter; Low similarity = less than 3 words can be derived from non-words when changing one letter. Short non-words: 3-5 letters (3-5 graphemes); long non-words: 6-8 letters (5-7 graphemes).

Spelling sentences

The patient is asked to write down a short sentence, which was dictated by the examiner. In addition to all other lexical processes targeted during sentence spelling, this subtask was controlled for several variables to provide additional insight in orthographic output lexicon functioning. For each word in the sentences, word frequency, length, and grammatical class, and sentence length are included as parameters. The Italian and Dutch sentence spelling tasks consist of one list, assessing different spellings of homophones (Tables 4.25 and 4.26). These words have identical pronunciations but are spelled differently depending on the meaning of the word (e.g., /tʃera/ as "c'era"; *it was* or "cera"; *wax* in Italian, and / ɛ is/ as "ijs"; *ice* or "eis"; *claim* in Dutch). In Dutch, homophones were split over sentences based on homophone dominance. Dominance of homophones was determined based on frequency of usage. These words can only be written correctly when the correct spelling sequence of the word is accessed in the orthographic output lexicon. Damage to this component will cause incorrect spelling of homophone words in the sentences.

Table 4.25 Italian sentence spelling: List 1 (sentences with homophones)

11 sentences	11 Homophones	*Venezia l'hanno visitata una sola volta.* *(They have visited Venic only once.)* *Ci vediamo l'anno prossimo.* *(We will see each other next year.)*

Table 4.26 Dutch sentence spelling: List 1 (sentences with homophones)

8 sentences	4 Dominant homophones	*Zij heeft een gebroken hart.* *(She has a broken hart.)*
	4 Non-dominant homophones	*De auto reed te hard.* *(The car drove too fast.)*

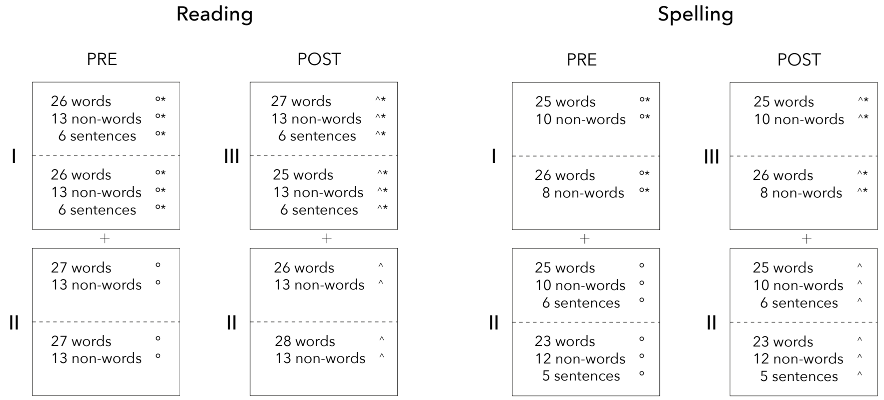
Test administration

Parallel versions for pre- and post-operative assessment

Given the short interval between pre- and post-operative assessments in glioma patients (often less than 2 weeks), parallel versions of the test batteries were developed to control for repetition and retest effects. The stimulus list set up for each task was split into three sublists (I, II, III). Items in each sublist were fully matched for each relevant dimension. The items from sublists I + II were used for pre-operative assessment, and those from sublists II + III for the post-operative assessment (Figure 4.2). Hence, in the post-operative assessment half of the stimuli were familiar to the patient, and half were new. The overlap of stimuli between the two versions allows inspecting changes at the item-specific level, whereas, performance on the "new" stimuli allows an evaluation of changes in the absence of retest effects. Both versions were designed in such a way that they could be stopped halfway, without losing reliability. The two halves were matched for all relevant psycholinguistic variables (Figure 4.2). In this way, both the pre-operative and the post-operative sessions could be shortened if necessary (e.g., when testing was too time consuming or the patient was too fatigued).

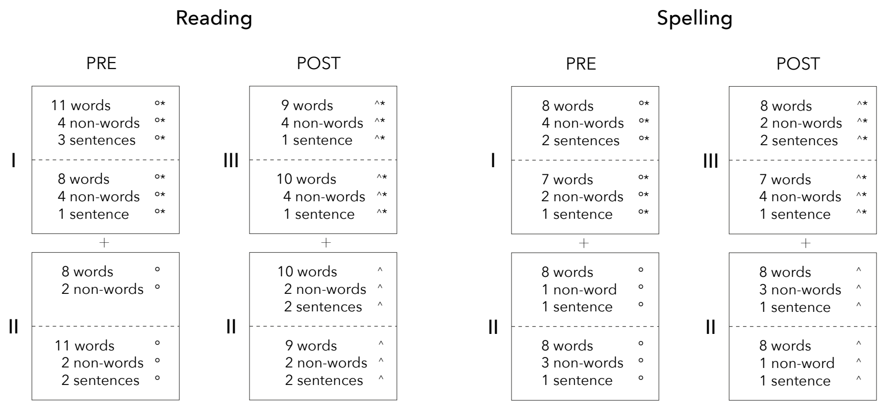
Pre- and post-operative stimuli were administered in pseudorandomized order. To avoid priming effects, stimuli of the same category in an assessment list (e.g., non-words with high similarity) and of the same grammatical class were never in successive order. When a word had more than one grammatical class, it was made sure that the non-dominant grammatical class was not the same as the preceding stimulus to avoid priming. Phonological, orthographic and semantic cueing (e.g., administering consecutively words starting with the same graphemes, or belonging to the same semantic category [10,11]) was limited as much as possible.

The length of the Italian and Dutch test is different. The collaborating Dutch hospital had limited time resources for pre- and post-operative neuropsychological evaluations. Due to clinical feasibility, the Dutch battery for pre- and post-operative assessment was shortened. For the final pre- and post-operative versions, a selection of original stimuli, as described in *Reading tasks* and *Spelling tasks,* was based on data from the standardization phase. Items were selected when healthy participants completed them without difficulties (> 90% correct per item). Final pre- and post-operative Italian versions contain 106 words, 52 non-words and 12 sentences for reading, and 99 words, 40 non-words and 11 sentences for spelling. The Dutch versions contain 38 words, 12 non-words and 6 sentences for reading, and 31 words, 10 non-words and 5 sentences for spelling. A full overview of stimulus lists, sublists and parameters is presented in Appendix B.



°^* balanced

Figure 4.2a Design of Italian pre- and post-operative stimuli lists. In both reading and spelling, the pre-operative version (PRE) comprised of sublists I + II, and the post-operative version (POST) of sublists II + III. Stimuli in sublists I and III are fully balanced on relevant psycholinguistic variables. In addition, each version provides the possibility to stop halfway through if the patient is too tired. First and second halves in all sublists are matched on all parameters.
°^* indicate which items were balanced.



°^* balanced

Figure 4.2b Design of Dutch pre- and post-operative stimuli lists. In both reading and spelling, the pre-operative version (PRE) comprised of sublists I + II, and the post-operative version (POST) of sublists II + III. Stimuli in sublists I and III are fully balanced on relevant psycholinguistic variables. In addition, each version provides the possibility to stop halfway through if the patient is too tired. First and second halves in all sublists are matched on all parameters.
°^* indicate which items were balanced.

Intra-operative assessment

The written language test battery may also be used intra-operatively. Certain practical constrains should be taken into account for intra-operative assessment of reading and spelling. Classically, the temporal limit to safely apply Direct Electrical Stimulation (DES) for functional mapping during surgery is set at 4 seconds [12,13]. Hence, according to these guidelines, a complete stimulus-response cycle (i.e., stimulus presentation and response to the stimulus) during mapping should be conducted within 4 seconds. Yet, there is a debate in awake surgery practice concerning this time constrain, wherein longer stimulation times are proposed when no afterdischarges on electrocorticography are detected [14]. Moreover, it should be taken into consideration that a patient's reaction to DES may not always occur immediately. It may therefore be argued that some functional areas remain undetected when a time-restricted stimulus-response cycle is adopted. However, delayed interferences, in which the patient continues to perform normal for a few second after DES before making errors, are likely to reflect indirect effects of stimulation (e.g., spreading of inactivation through networks). These types of interference provide information about involvement of the stimulated area in the function under scrutiny, but cannot disclose if that area is crucial for the execution of the function. Hence, it remains uncertain what one is measuring, and what approach should be taken with regard to resection of these areas. During resection, no time constraint to administer a stimulus-response cycle applies. Tasks are at this stage not used to determine functional boundaries (as in mapping), but may be administered to inspect if language functions deteriorate during tumor removal.

Given the restricted time for neuropsychological assessment in the operating room, testing should be as targeted and customized as possible. During surgery, it is therefore advised to use a selection of items, based on tumor location, pre-operative performance and patient's characteristics (such as age, education, profession, and cognitive profile) [15-17]. To select stimuli for intra-operative assessment, items can be chosen from those presented in sections *Reading tasks* and *Spelling tasks*. A total of 158 words, 78 non-words and 24 sentences are available for reading in Italian and 150 words, 58 non-words and 11 sentences for spelling. In Dutch, 74 words, 32 non-words and 16 sentences are available for reading, and 46 words, 16 non-words and 8 sentences for spelling.

Scoring

Damage to underlying processes of reading and spelling may cause a variety of error types. Yet, in order separate two main error types, we first aimed to distinguish between errors that result from disruption of central and peripheral processes. In reading, a distinction is made between *Central errors,* which result from damage to central processes (such as incorrect letter choices, word level errors, no responses, or misplaced stress), and *Other errors* (responses that do not result from damage to central processes; i.e., changes in more qualitative features such as slowed or hesitant reading). In spelling, errors may be classified as *Central errors* (incorrect letter choices, word level errors, or no responses), *Peripheral errors* (qualitative changes in handwriting, resulting from peripheral damage), and *Unclassifiable errors* (responses that could be either a Central or Peripheral error). Furthermore, distinctive error types within Central and Peripheral / Other errors could be monitored with structured scoring forms (Appendix C).

Sentences were divided in grammatical constituents (i.e., nouns with articles, verbs, function words and adjectives), to be scored separately. For intra-operative use, an additional, less detailed, scoring form is available that allows immediate observation and offline scoring. Reading recordings and handwriting samples should be collected for post-hoc analyses and fine-grained comparisons.

Scoring is in all cases based on the first answer given after stimulus presentation. For spelling, patients are explicitly instructed to spell the whole stimulus at once, to prevent partial processing of the stimulus (i.e., writing the first syllable down after the first presentation of the stimulus, the second syllable after stimulus repetition, etc.). Whole word spelling requires the patient to keep the orthographic string active for the duration of handwriting, typing or oral spelling. Hence, it recruits all the components normally engaged in spelling, including the graphemic buffer, which would not be taxed in the event of a letter-by-letter or syllable-by-syllable spelling. When repetition is asked, the letters written to that point are covered and the entire string musty be re-written. The same applies to reading. Second (and following) responses are noted down for post-hoc qualitative analyses and to inspect self-corrections.

Standardization

The Italian and Dutch batteries were standardized in 101 healthy participants (50 Italian and 51 Dutch) to obtain imageability ratings and mean reaction times per item, and to obtain normative data, and inspect inter-rater reliability for scoring. As a first step, imageability ratings and mean reaction times per item were collected in 39 Italian and 29 Dutch participants, via computerized assessments. Secondly, to acquire reliable normative data, the sample of healthy participants was enlarged after collection of imageability ratings and of reaction times was completed. To mimic clinical setting, where spelling items are dictated via live speech and not via audio recordings, the remaining participants in the normative study were assessed via live speech. All participants were native speakers of Italian or Dutch (for the Italian and Dutch batteries respectively), were between 20 – 75 years old and had received >8 years of formal education. Volunteers were all right-handed, had no auditory or visual problems, were not diagnosed with dyslexia or dysgraphia, and had no history of psychiatric or neurological diseases. Participants were from a variety of geographical and cultural backgrounds. Dutch participants received a €15 gift card; Italian participants received €25 for participation. Written informed consent was obtained from all participants before testing. Demographic data are summarized in Table 4.27.

Tests were administered in the same order for each participant, starting with the cognitive screening, followed by the spelling and reading tasks. Cognitive screening included the Montreal Cognitive Assessment (MoCA [18]) for all participants, and the Edinburgh Handedness Inventory was administered to determine handedness [19]. The Italian standardization battery also included a more comprehensive neuropsychological assessment, including Raven Coloured Progressive Matrices [20], 15-Word Test [21], Digit span [22], Corsi Block-Tapping Task [23], Trail Making Test [24], Letter Fluency test [21] and Boston Naming Test [25]. A group of students in psychology, cognitive neuroscience and clinical linguistics were trained to administer the written language test battery.

In the standardization stage, sublists I, II, and III of the written language battery were assessed conjointly (see Figure 4.2). Stimuli were administered in pseudorandomized order, following the same procedure as applied for the pre- and post-operative versions. Hence, stimuli of the same assessment list and grammatical class were never in successive order, and phonological, orthographic and semantic cueing was limited as much as possible. Participants were offered three breaks in the reading and spelling tests to warrant concentration. Scoring was completed post-hoc using structured scoring forms (Appendix C). Uncertain or ambiguous scorings were discussed with the test developers until consensus was reached. The total duration was 2,5 hours for the Italian version, and approximately 1,5 hours for the Dutch version. Data from all participants were analyzed at an item-specific level, as well as per task and test version.

Computerized assessments were conducted using MatLab with the Psychophysics Toolbox extensions [26,27]. For reading, stimulus presentation was similar to the original setup; each stimulus was presented separately on a computer screen and the participant was asked to read it aloud. The stimulus was preceded by a 300ms fixation cross. A microphone recorded the response. For spelling, a native speaker of Italian and Dutch recorded all the stimuli so that these could be presented via computer. Auditory stimuli were preceded by a 500ms beep, after which the recording was played and the participant was presented a blank screen. The participant was asked to write the stimulus down on a lined sheet of paper in front of the computer (Figure 4.3). Assessments using live speech were administered according to the guidelines described in section *Test administration*.

Table 4.27 Demographic data of participants in the normative study

	Italian			Dutch		
	N (%)	Mean (SD)	Range	N (%)	Mean (SD)	Range
Age		48.8 (14.6)	26 - 73		45.8 (13.2)	24 - 68
< 50 years-old	27 (54.0)			26 (51.0)		
≥ 50 years-old	23 (46.0)			25 (49.0)		
Years of education		14.8 (3.5)	8 - 21		14.5 (2.8)	9 - 22
< 13 years of education	6 (12.0)			12 (23.5)		
≥ 13 years of education	44 (88.0)			39 (76.5)		
Gender						
Male	25 (50.0)			28 (54.9)		
Female	25 (50.0)			23 (45.1)		
Right handedness	50 (100)			51 (100)		
EHI (%)		88.3 (20.5)	-30 - 100		92.5 (25.1)	-70 - 100
MoCA (score)		26.9 (2.3)	21 - 30		27.9 (1.6)	23 - 30
Raven Matrices (raw score)		33.3 (2.6)	23 - 36			
15 Word Test immediate (score)		46.7 (9.2)	25 - 68			
15 Word Test delayed (score)		9.9 (3.1)	3 - 15			
Digit Span forward (span)		6.1 (0.9)	4 - 9			
Digit Span backward (span)		4.8 (0.9)	3 - 7			
Corsi Block-Tapping Task (span)		5.9 (0.9)	4 - 8			
Trail Making Test A (sec)		34.7 (11.2)	17 - 69			
Trail Making Test B (sec)		63.1 (23.5)	21 - 139			
Trail Making Test B/A		1.9 (0.8)	0.5 - 5.0			
Letter Fluency (raw score)		44.5 (10.2)	47 - 71			
Boston Naming Test (raw score)		55.1 (2.9)	48 - 60			

EHI = Edinburgh Handedness Inventory, MoCA = Montreal Cognitive Assessment

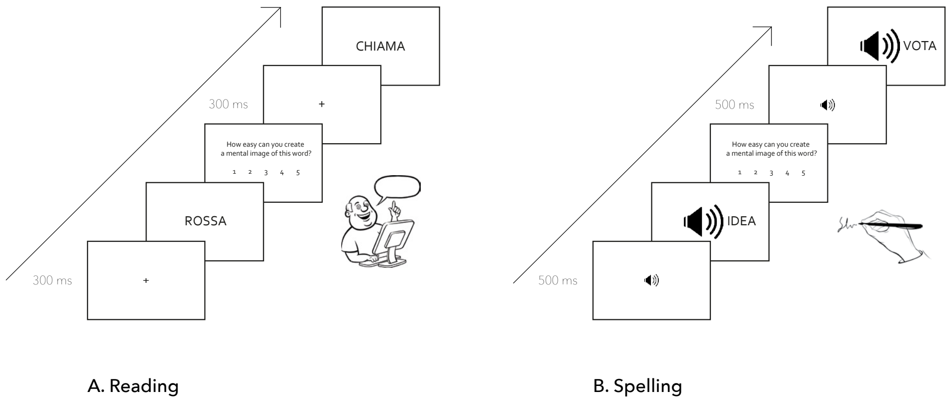


Figure 4.3 Stimuli presentation in computerized assessment. In the standardization phase, computerized testing was conducted using MatLab to obtain imageability rating and to acquire mean reaction times per stimulus. A. Reading assessment started with a fixation cross (300ms), followed by stimulus presentation centered on the screen. When the participant finished reading aloud, he/she was instructed to press space bar. Reaction time was measured from onset of stimulus until space bar was pressed. Following word reading, a screen with the imageability-rating question was presented. The participant was asked to press a number between 1 and 5 to indicate the degree of imageability. B. Spelling assessment started with a beep (500ms), followed by an auditory-presented stimulus while the screen remained blank. When the participant finished writing the stimulus down on a lined sheet of paper, he/she was instructed to press space bar. Reaction time was measured from onset of stimulus until space bar was pressed. Following word spelling, a screen with the imageability-rating question was shown. The participant was asked to press a number between 1 and 5 to indicate the degree of imageability.

Imageability

Imageability of a word has been found to influence word retrieval, in which highly imageable words (i.e., concrete words such as *chair*, of which a mental image is easily formed) are retrieved more easily than low-imageability words (i.e., abstract words such as *love*, of which it is more difficult to form a mental image [28,29]). To account for this possible influence, imageability ratings of each word had to be collected, in order to include imageability as a parameter in the tests for written language for glioma patients. Since for both Italian and Dutch databases with imageability ratings are unavailable, an imageability questionnaire was added to the standardization battery.

In computerized assessment, healthy participants were asked to indicate how easy it was to create a mental image of the word on a 5-point Likert scale (1 for difficult / low imageability vs. 5 for easy / high imageability). The imageability question was shown directly after each word, as soon as participants completed their response (Figure 4.3). In addition to imageability ratings obtained via computerized testing with "recorded" speech, imageability of Italian words was also inspected using a questionnaire after assessment with "live" speech, in which the test administrator dictated a stimulus in person. Although data from the 39 participants who completed computerized testing could provide sufficient insight in imageability of Italian words, a questionnaire was administered to compare the two test modalities (recorded vs. live speech). This comparison was conducted because preliminary analyses revealed that poor audio quality of some stimuli had influenced spelling performance of healthy participants in computerized assessments – therefore, it could not be ruled out that poor auditory input had also influenced imageability ratings. Imageability ratings during assessments with recorded or live speech did not differ. Imageability ratings of each item from Italian (n= 50) and Dutch participants (n= 29) are included in Appendix B.

Reaction times

Mean reaction times per item were acquired via computerized assessment to inspect the applicability of test items for intra-operative use, in case time restrictions of DES are adopted (see Section *Intra-operative assessment*). In the collaborating hospitals of this study, neurosurgical teams practice in accordance with the 4 seconds limitation [12,13], wherein the complete stimulus-response cycle should be completed. Hence, we evaluated the applicability of test items pursuant to their methods.

Reaction times were registered from the moment of stimulus presentation (after the fixation cross / beep) until the participant finished the stimulus response. The end of stimulus response was determined by the participant, who was instructed to press the spacebar directly after reading the stimulus from the computer screen. For handwriting, participants were asked to move their hand from the answer sheet to the space bar to stop the recording of the reaction time. Mean reaction time for a complete stimulus-response cycle of each item was collected.

The stimulus-response cycle was always completed in <4 seconds in word and non-word reading (Table 4.28). For these items, a length effect was observed, as longer (non-)words resulted in longer reaction times (Italian: $F(1,8474)= 48.8$, $p< .001$; Dutch: $F(1,3420)= 154.2$, $p< .001$). Reaction times were longer for sentences, and often exceeded the 4-second limit. In handwriting, recorded reaction times were on average over 4 seconds. Words and non-words exceeded the temporal limit only marginally. In contrast, the average time needed to write a sentence to dictation ranged between 15,0 and 19,3 seconds. Similar to reading, word and non-word length correlated significantly with reaction times (Italian: $F(1,7278)= 102.7$, $p< .001$; Dutch: $F(1,3246)= 57.9$, $p< .001$). Mean reaction times from Italian (n= 39) and Dutch participants (n= 29) are included for each stimulus in Appendix B.

Table 4.28 Mean reaction times per subtask of the written language battery

	Italian				Dutch			
	Pre **version**		*Post* **version**		*Pre* **version**		*Post* **version**	
	Mean RT (SD)	Range	Mean RT (SD)	Range	Mean RT (SD)	Range	Mean RT (SD)	Range
Reading								
Words	2,27 (0,29)	1,69 – 3,07	2,29 (0,31)	1,69 – 3,29	1,99 (0,22)	1,47 – 2,50	1,97 (0,21)	1,47 – 2,50
Non-words	2,15 (0,25)	1,62 – 2,58	2,14 (0,24)	1,62 – 2,58	1,70 (0,20)	1,42 – 2,02	1,69 (0,22)	1,32 – 2,01
Sentences	4,18 (0,51)	3,22 – 5,02	3,94 (0,58)	3,21 – 5,23	3,46 (0,33)	3,03 – 3,91	3,64 (0,60)	2,93 – 4,58
Spelling								
Words	5,95 (1,21)	3,58 – 13,3	6,08 (2,17)	3,58 – 20,5	6,25 (1,19)	4,53 – 10,6	6,19 (1,02)	4,43 – 8,57
Non-words	6,36 (1,08)	4,37 – 8,55	6,20 (1,19)	4,26 – 10,1	4,98 (0,65)	3,86 – 6,35	5,18 (0,98)	3,84 – 7,11
Sentences	19,3 (4,31)^	13,1 – 30,5	19,3 (4,31)^	13,1 – 30,5	15,9 (2,75)	12,2 – 19,0	15,0 (3,37)	11,1 – 19,0

Pre version = stimulus list for pre-operative assessments, *Post* version = stimulus list for post-operative assessments; RT = Reaction Time; SD = Standard Deviation. All values are given in seconds. Based on responses from 39 healthy Italian participants and 29 Dutch controls.
^ Pre- and post-operative versions contain the same items.

Inter-rater reliability

Inter-rater reliability refers to the degree of agreement that two independent scorers reach in their evaluations. We assessed inter-rated reliability in a subset of healthy participants who received natural assessments via live speech (20 Dutch participants), using structured score forms (Appendix 4.3). All items were scored twice, once by the test developer and once by a bachelor student. The student had been instructed on the use of scoring forms and on the test in general. Cohen's kappa (-1 to +1) was computed for each task as well and for each type of error separately, with R using *stats* and *irr* packages [30,31]. Kappa indicated almost perfect and substantial inter-rater agreement for Central errors in both reading (words: κ= 0.71; non-words: κ= 0.77; sentences: κ= 0.86) and in spelling (words: κ= 0.80; non-words: κ= 0.67; sentences: κ= 0.86). Other errors reached moderate and fair agreement in reading (words: κ= 0.33; non-words: κ= 0.23; sentences: κ= 0.42). In spelling, both Peripheral errors (words: κ= 0.09; non-words: κ= 0.24; sentences: κ= 0.29) and Unclassifiable errors (words: κ= 0.08; non-words: κ= 0.00; sentences: κ= -0.24) reached fair and slight agreement [32].

Normative data

In order to establish which scores on the written language battery should be regarded as pathological, and which fall within normal ranges, normative data was collected. Numbers of Central, Peripheral, Other and Unclassifiable errors from all healthy participants in the standardization study were evaluated.

Given possible effects of age and education in neuropsychological testing [33], as a first step the influence of these parameters was inspected on overall reading and spelling performance (i.e., word, non-word and sentence tasks combined). Performance was compared for younger and elder adults (18-49 vs. ≥50 years-old), and for lower and higher educational level (8-12 vs. ≥13 years). Age groups were defined according to the median, and according to possible onset of age-related cognitive decline [34,35]. As for education, placing the dividing line at 12 or more years of formal education is common in normative studies (e.g., [33,36]), as receiving >12 years of education usually implies continuation of education after the age of 18. Using R with *stats* and *gmodels* packages [30,37], Wilcoxon Rank Sum test was conducted to compare performance in the age and education groups (Table 4.29). Overall error rates of younger and older (≥50 years-old) adults were not significantly different. Significant differences were found for education, in which participants with fewer than 13 years of formal education produced more errors in reading (Central errors) and spelling (all error types). However, the lower education groups were underrepresented (6/50 Italian participants and 12/51 Dutch participants). To set reliable norms for educational groups, a larger group of healthy participants with low education is required. In light of this limitation, only whole-group normative data can be produced at this time.

Normative data are based on responses of assessments with both recorded (computerized testing) and live speech (natural testing). However, the audio quality of some stimuli recorded for the computerized spelling assessment turned out to be poor; participants frequently commented on it, asked for multiple repetitions, or even made phonologically related errors that were not in line with performance on the rest of the stimuli. For those obscure items, performance was compared between participants who completed the recorded vs. live speech version of the spelling tasks. It showed that no errors occurred in the live condition, which indicates that errors on the recorded items were most likely because of misperception of the stimulus (due to the quality of the recordings). Hence, these items can still be used if administered naturally. With regards to the configuration of normative data, for these items, only responses from assessments with live speech were considered, while responses from assessments with recorded speech were disregarded. As a result, normative data is exclusively based on reliable performances, including all responses from the naturalistic live speech version and responses with good audio quality from the recorded speech version.

Each subtask was analyzed separately for the pre- and post-operative versions, resulting in task- and version-specific norms. Mean number of incorrect responses, ranges and cut-off scores were calculated for each task (Table 4.30). Cut-off values were set at the 5th percentile; i.e., at 95.0% of the healthy participants' performance. As data in the standardization phase were collected simultaneously for all sublists included in the pre- and post-operative versions (sublists I, II, and III), post-hoc analyses were conducted to split up responses in their respective stimulus lists (I & II for pre-operative, II & III for post-operative versions).

Table 4.29 Influence of age and education on error production in healthy controls

	Age <50 vs ≥50	**Education** <13 vs ≥13
Italian		
Reading		
Central errors	W = 269.5, *p*= .426	W = 226.0, *p*= .005 *
Other errors	W = 287.0, *p*= .620	W = 166.0, *p*= .268
Spelling		
Central errors	W = 242.5, *p*= .187	W = 169.5, *p*= .268
Peripheral errors	W = 320.5, *p*= .845	W = 140.5, *p*= .801
Unclassifiable errors	W = 299.0, *p*= .795	W = 216.5, *p*= .002 *
Dutch		
Reading		
Central errors	W = 254.0, *p*= .175	W = 321.0, *p*= .050
Other errors	W = 232.5, *p*= .071	W = 288.0, *p*= .216
Spelling		
Central errors	W = 294.0, *p*= .564	W = 327.5, *p*= .038 *
Peripheral errors	W = 271.5, *p*= .283	W = 329.0, *p*= .024 *
Unclassifiable errors	W = 267.0, *p*= .145	W = 318.0, *p*= .013 *

Reading and spelling performance is considered combined for words, non-words and sentences. Stimuli lists in the normative study included all items from *pre* and *post* versions (plus additional items for Dutch). * *p*= < .05 on Wilcoxon rank-sum test

Table 4.30 Normative data for each task and version of the written language battery for glioma patients

	Italian				Dutch			
	Pre **version**		*Post* **version**		*Pre* **version**		*Post* **version**	
	Mean (Range)	Cut-off / stimuli	Mean (Range)	Cut-off / stimuli	Mean (Range)	Cut-off / stimuli	Mean (Range)	Cut-off / stimuli
Reading								
Words								
Central errors	0,38 (0 - 3)	1/106	0,48 (0 - 3)	1/106	0,10 (0 - 1)	1/38	0,24 (0 - 2)	1/38
Other errors	0,10 (0 - 1)	1/106	0,14 (0 - 2)	1/106	0,14 (0 - 1)	1/38	0,20 (0 - 2)	1/38
Non-words								
Central errors	0,80 (0 - 3)	2/52	0,82 (0 - 5)	2/52	0,28 (0 - 3)	1/12	0,16 (0 - 2)	1/12
Other errors	1,04 (0 - 32)	3/52	1,02 (0 - 30)	2/52	0,14 (0 - 2)	1/12	0,12 (0 - 2)	1/12
Sentences ^								
Central errors	0,74 (0 - 4)	2/65	1,24 (0 - 6)	3/47	0,10 (0 - 2)	1/27	0,49 (0 - 3)	2/28
Other errors	0,06 (0 - 1)	1/65	0,26 (0 - 6)	1/47	0,08 (0 - 1)	1/27	0,10 (0 - 1)	1/28
Spelling								
Words								
Central errors	2,85 (0 - 8)	6/99	2,17 (0 - 7)	5/99	1,00 (0 - 8)	3/31	1,10 (0 - 5)	4/31
Peripheral errors	0,65 (0 - 5)	2/99	0,50 (0 - 4)	2/99	0,73 (0 - 8)	3/31	0,61 (0 - 11)	3/31
Unclassifiable errors	0,21 (0 - 2)	1/99	0,29 (0 - 2)	1/99	0,18 (0 - 2)	1/31	0,24 (0 - 3)	2/31
Non-words								
Central errors	3,10 (0 - 9)	7/40	2,92 (0 - 10)	7/40	0,14 (0 - 3)	1/10	0,47 (0 - 3)	2/10
Peripheral errors	0,23 (0 - 3)	1/40	0,10 (0 - 2)	1/40	0,67 (0 - 4)	2/10	0,18 (0 - 3)	1/10
Unclassifiable errors	0,08 (0 - 1)	1/40	0,07 (0 - 1)	1/40	0,04 (0 - 1)	1/10	0,08 (0 - 1)	1/10
Sentences ^								
Central errors	1,74 (0 - 5)	4/55	1,74 (0 - 5)	4/55	0,41 (0 - 3)	2/24	0,45 (0 - 3)	2/22
Peripheral errors	0,26 (0 - 3)	1/55	0,26 (0 - 3)	1/55	0,20 (0 - 4)	1/24	0,18 (0 - 3)	1/22
Unclassifiable errors	0,18 (0 - 3)	1/55	0,18 (0 - 3)	1/55	0,00 (0 - 0)	0/24	0,02 (0 - 1)	1/22

Pre version = stimulus list for pre-operative assessments, *Post* version = stimulus list for post-operative assessments. Error rates and cut-offs are based on responses from 25 healthy Italian and 29 Dutch controls. Cut-off scores are presented as number of errors / total number of stimuli per task. Error rates above cut-off indicate impaired performance. ^ Sentences are scored separately for grammatical constituents as defined on the stimulus lists and scoring forms (Appendices B and C). Numbers reported for sentences in this table refer to the constituents and not to the number of sentences.

Discussion

This study describes the rationale, development, and standardization of a theory-driven written language assessment battery for glioma patients. The Italian and Dutch tests consist of multiple tasks, which allow detailed inspection of cognitive components underlying reading and spelling. The normative data and clinical applicability of the battery in pre-, intra- and post-operative settings are discussed.

Normative data

We aimed to develop a sensitive written language battery for glioma practice, based on current cognitive models. To ensure sensitivity (i.e., the probability to detect a true error), the cut-off for normative data was set at 95% of the healthy participants' performances. Particularly in awake surgery, it is crucial to know if a patient's performance deviates from the norm. During surgery, it must be ascertained that an observed error during DES is a result of the stimulation, rather than an error that arises independent of stimulation. The risk of producing these false positives can be minimized, by selecting only items for intra-operative assessment that did not elicit errors pre-operatively, on a test with high sensitivity.

Established normative values have shown to be equally applicable for the interpretation of written language performance in different age groups, but not in each education group. Patients with lower education (<13 years) may produce more errors than patients who received more years of formal education. Although the normative study should be expanded to include a larger group of lower-educated participants, the limitations of the current norms do not restrain the use of the battery with less educated patients. The written language battery for glioma patients is primarily developed to allow longitudinal monitoring of reading and spelling performance. Cut-off values may provide valuable insight in performance accuracy, yet it is the overall performance profile that is most important in the personalized practice of awake surgery. Patients' pre-operative assessment should be considered to evaluate individual post-operative performance, and to establish the basis for intra-operative testing. Rather than absolute performance levels, it is crucial to inspect the quantitative and qualitative changes in performance during and after surgery, as compared to the pre-operative baseline. Therefore, also performance of less educated patients can be evaluated longitudinally in clinical practice of awake surgery using this written language battery.

Clinical practice

The written language battery was specifically developed to assess glioma patients undergoing awake surgery during pre-, intra- and post-operative assessments. The goals of testing differ at each assessment stage, and may depend on the goals set by the neurosurgical team. The battery provides a flexible tool that can be used for different purposes in clinical practice. Extensive testing before and after surgery allows obtaining information for tumor removal while preserving quality of life (clinical goal), as well as obtaining finer-grained knowledge of functional neuroanatomy of written language (theoretical goal). Moreover, the battery can be used for short intra-operative assessments from both a clinical or neuro-scientific perspective. Different applications in clinical practice are discussed.

Pre-operative, post-operative and follow-up assessment

The pre-operative assessment sets a baseline for the patient's performance, and allows one to establish the pre-operative status of the components that may be at risk during surgery. Analyses of extensive pre-operative assessments provide the possibility to set up intra-operative tasks as short and selective as possible, by focusing on components at risk for the individual case. In addition to its clinical relevance, comprehensive assessments before surgery provide insight in brain behavior relationships. Although knowledge about the functional neuroanatomy of reading and spelling is considerably advanced (see Chapters 1 and 2), awake surgery dispenses the unique opportunity to examine the functional neuroanatomy or reading and spelling further. Subsequently, post-operative assessments inform on the components that may have been affected by surgery and allow for a comparison with pre-operative assessment. Clinically, identification of specific impairments can facilitate faster and more targeted rehabilitation. Follow-up assessment demonstrates the long-term effects of glioma treatment on specific components.

For pre- and post-operative assessment, two versions of the battery were developed to optimize performance comparisons in a short time window, and to inspect qualitative changes over time. Comparisons between pre- and post-operative lists in healthy participants showed similar performance profiles, indicating very good balancing of stimuli between the two versions. The pre-operative version can be used again at follow-up, as the time between pre-operative and follow-up is usually long enough to avoid retest effect. Scoring the patient's performance, the objectivity of one's evaluation should be considered. Inter-rater reliability was high for Central error identification, whereas scoring of other (Peripheral, Unclassifiable and Other) errors were less reliable. Although structured scoring forms facilitate more homogeneous evaluations as compared to unconstrained scoring, this observation underlines that the evaluation of non-central errors is at least in part subjective. Furthermore, one of the scorers in the reliability study was a bachelor student who received instructions and some training, but had no previous experience with neuropsychological assessments. It is plausible that more experience may have resulted in higher inter-rater reliability. Results stress the need for experienced neuropsychologists or neurolinguists to administer the battery.

Intra-operative assessment

Assessments during surgery need to be administered in a very limited time frame, hence often as quickly as possible. Nevertheless, this by no means implies that items should be chosen haphazardly or intuitively based. On the contrary, particularly during surgery, each item presented to the patient should be relevant for the individual case. The written language battery allows selecting stimuli with clearly specified properties (i.e., the different stimuli lists), based on extensive pre-operative assessment. If the patient or clinical setting does not permit full pre-operative assessments, MR based lesion localization allows predicting which functions are at risk and which stimuli should thus be selected. Applying this approach, intra-operative testing can be as short or comprehensive as preferred. Administration of selected stimuli only will suffice to detect deficits intra-operatively, yet will not improve our understanding of brain - language relationships.

Contrary to fixed stimulus lists for pre- and post-operative testing, the written language battery can thus be tailored for each patient for intra-operative use. Considerations for stimuli selection may differ for neurosurgical teams. The temporal restriction to safely apply DES is under debate, which may facilitate interesting possibilities for extended intra-operative testing. Classically, a stimulus-response cycle should be conducted within 4 seconds [12,13]. Data of healthy individuals indicated that all words and non-words of the reading test could be responded to within this time window, hence intra-operative use should be unproblematic. However, for all other tasks, longer stimulation time may be required to assess complete stimuli. In these cases, it should be questioned whether it is safe to apply longer stimulation (e.g., no afterdischarges should emerge), and whether it can be established what is being measured (e.g., is it result of inactivation of the stimulated area, or of spreading of inactivation through a network?).

These considerations are required when assessing sentence reading, as well as spelling. As for sentences, healthy participants could not complete all items within 4 seconds. In spelling, even short sentences largely exceeded the 4 seconds limit (on average >18 seconds). Although sometimes reported in the literature [4], interpretations of errors during intra-operative sentence tasks are problematic. If DES is applied from the moment of stimulus presentation, stimulation will most probably only influence the first word(s) of the sentence. Yet, as sentence processing relies on a variety of components, interpretation during surgery is complicated regardless of stimulation times. In addition to cognitive processes underlying single word processing, sentence reading and spelling also requires syntactic processing. Although the sentence tasks included in the battery targets specific elements (homographs or homophones) that may be informative of underlying components (phonological/orthographic output lexicon), evaluations of other tasks are required to verify where errors arose. Intra-operative settings are therefore not considered suitable to assess sentences.

With regards to word and non-word spelling, healthy participants also completed a stimulus-response cycle in more than 4 seconds. Yet, interpretations of these results require more inspection, as these values may not be informative of the actual times needed for a stimulus/response cycle in a spelling task. First, reaction times were recorded in the same session as the word imageability ratings. Hence, in anticipation of the judgments required by the questionnaire, participants may have delayed pressing the spacebar while preparing their answer on the Likert scale. However, data showed that word spelling did not take longer than non-word spelling, which was not followed by an imageability question. This may indicate that anticipation influence is negligible, or that the influence is not detected due to a general increased time needed for non-word spelling. In absence of the anticipation influence, words may have been written faster than non-words. Second, the reaction times recorded for spelling are imprecise approximations. Although participants were encouraged to press the spacebar as soon as possible after giving a response, observation during testing showed that this was not always the case. This may be due to the fact that participants were not under time pressure. As average reaction times exceed the time limit only marginally, responses on both words and non-words may be feasible within 4 seconds when there is pressure of time, and when reaction times are recorded more precisely. Finally, the experimental setting does not resemble the clinical setting as reaction times were measured during computerized testing. Participants were required to put their pen down and to move their hand to the space bar to stop the recording of the reaction time. As a result, recorded reaction times are a composite measure that includes not just the time needed to write the response, but also the interval between stimulus presentation and the beginning of the response, and time needed to drop the pen and press the spacebar. In short, reaction times of word and non-word spelling are likely to be shorter than represented here. This would implicate that actual stimulus-response cycles could be administered within 4 seconds, which suggests that (non-)word spelling is suitable to be used intra-operatively to monitor spelling skills.

However, these data are collected from healthy participants, while patients in the operation room (who are sedated and in a less comfortable position) are usually less quickly than healthy controls and than patients in pre-operative assessments. In addition to a more general debate on the maximum time for stimulus-response cycles during DES, decisions on whether to include spelling tasks in intra-operative assessments therefore rely on evaluations of individual cases. In case of handwriting, pre-operative testing can inform on the 'idiosyncratic' handwriting speed for each patient. Individual reaction time data could be used to establish possible upper limits on the length of the stimuli to be administered to the subject (e.g., a subject could be able to write stimuli of up to 7 letters in 4 seconds, but not stimuli consisting of 8 or more letters).

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4

5

Validation and clinical application of a new written language battery for glioma patients

Abstract

This study describes the validation and clinical application of the newly developed Written language battery for glioma patients, as presented in Chapter 4. The new battery was compared to short subtests from a commonly used clinical battery in two glioma patients, to evaluate if better accounts can be provided by evaluating reading and spelling performance using the Written language battery. Results indicated that the new battery disclosed more subtle deficits and more comprehensive error profiles. In order to evaluate the clinical applicability of the Written language battery was developed based on a cognitive model of reading and spelling, we evaluated whether damaged components underlying written language could be disentangled. Two case studies were described, in which damaged components could be identified, and patient-tailored treatment could be planned in line with expectations based on the literature. It was feasible to use the battery in all peri-operative phases of clinical practice, including intra-operative handwriting. The Written language battery for glioma patients is a valid test to evaluate reading and spelling, and may be applied in neurosurgical practice to target patient-specific intra-operative testing.

Introduction

A comprehensive battery was specifically developed to evaluate reading and spelling in neurosurgical practice (Chapter 4). As glioma patients often present subtle language impairments before and after surgery [1,2], the goal in neurosurgical practice is not simply to verify sparing vs. impairment of a function, but also to identify impairment loci [1,4-7]. Particularly in awake surgery, it is important to thoroughly evaluate the status language functions under scrutiny, to preserve quality of life. As described in Chapter 4, the Written language battery was therefore developed with the aim to disentangle specific components of reading and spelling processes at all peri-operative stages. Pre-operative assessments can provide insight in damaged components, so that patient-tailored surgical planning may be targeted. During surgery, specific components at risk may be assessed to guide resection and preserve function. Post-operatively, detailed evaluation of reading and spelling processes may inform on the effects of surgery in specific regions and facilitate individualized treatment.

To validate if the newly developed battery provides a sensitive approach to the evaluation of reading and spelling performance in glioma patients, the battery was compared to commonly used clinical subtests. Previous research has established that these clinical tasks may not always suffice to disentangle specific deficits in glioma patients (Chapter 3). To contrast the merits of the new battery and those of sublists from clinical batteries, the performance of two glioma patients was considered. The Written language battery is moreover evaluated to establish if it is feasible to use in neurosurgical practice at all peri-operative stages (before, during and after surgery), and if it can disentangle damaged components to aid identification of underlying disorders of reading and spelling.

Methods

Patients

Two Italian patients who underwent surgery for glioma resection in Spedali Civili di Brescia were studied. Both were assessed in their native language. Ethical approval was granted by the Brescia Ethical Committee of Spedali Civili. Patient FO, a 56-year-old right-handed male with 17 years of education, was operated under general anesthesia for a glioblastoma (WHO grade IV) in the posterior part of the left inferior temporal gyrus (Figure 5.1). Surgery resulted in subtotal resection (75%). Patient LZ was a 74-year-old, right-handed female with 8 years of education, who underwent awake surgery for glioma resection. Magnetic Resonance Imaging (MRI) revealed a glioblastoma (WHO grade IV) in the posterior part of the left middle temporal gyrus, with restricted subcortical infiltration in short-range white matter fibers (Figure 5.2). Total resection (100%) was attained.

In both cases, anti-epileptic treatment (levetiracetam) was given pre- and post-operatively, and surgery was followed by the Stupp protocol of combined radio- and chemotherapy for 6 weeks, plus 4 weeks of only chemotherapy (temozolomide). At the last post-operative MRI (around 1,5 year after surgery), both patients presented full autonomy without apparent language deficits.

Pre- and post-operative assessments

Before and after surgery, the Written language battery for glioma patients (Chapter 4) was administered in full. Two parallel versions, in which half of the items overlap between each version and all the items are matched for the relevant psycholinguistic variables, were used for pre-operative and post-operative assessment. At follow-up, the pre-operative version was administered. Both versions consist of 106 words, 52 non-words and 12 sentences for reading and 99 words, 40 non-words and 11 sentences for spelling. A detailed description of the subtests and test administration can be found in Chapter 4.

To compare the battery with a clinical tool, reading and spelling were also assessed with two subtests from the Batteria per l'Analisi dei Deficit Afasici (BADA [10]). In clinical practice of Spedali Civili di Brescia, non-word reading and non-word handwriting were evaluated with half of the available items (henceforth the *Clinical battery*). Parallel versions consisted of 23 items for reading and 13 for spelling (pre-operative), and of 22 items for reading and 12 for spelling (post-operative). In both batteries, spelling was administered in the modality of handwriting.

Spoken language assessments included object and action naming for glioma patients (ECCO & VISC [11]). In addition, non-word repetition, oral and written picture description, auditory and visual lexical decision, and auditory and visual comprehension of object names from the BADA [10] were administered. A general neuropsychological assessment included Raven's Coloured Progressive Matrices [12], Trail Making Test [13], Stroop Test [14], Letter Fluency test [15], Digit Span forward and backward [16,17], 15-Word Test [15], and ideomotor limb and oral praxis tests [18].

Language testing for FO was conducted 1 and 2 days before surgery, and 16 days after surgery. Patient LZ was assessed 9 and 6 days before surgery, and 9 days after surgery. In addition, a long-term post-operative assessment (follow-up) was administered for LZ after 27-34 weeks (27 weeks for Clinical battery subtests, 28 weeks for handwriting from the Written language battery, and 34 weeks for reading from the Written language battery).

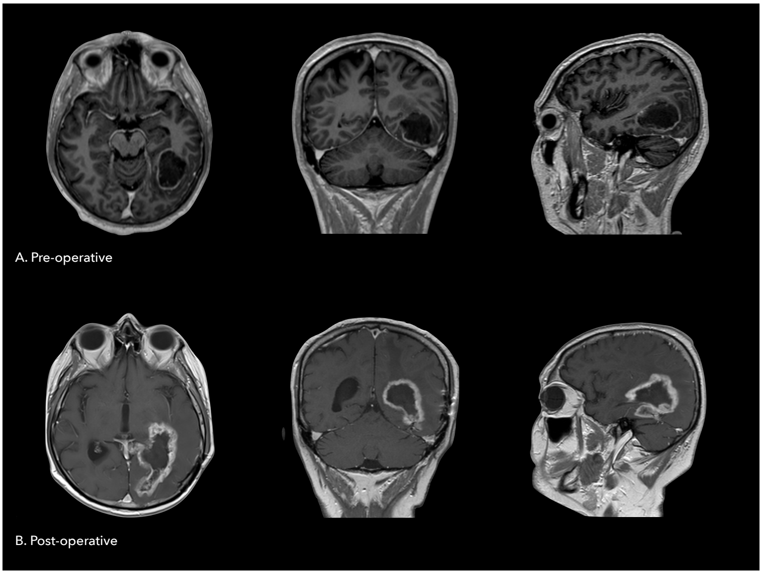

Figure 5.1 Pre- and post-operative MRI scans for patient FO. Patient FO underwent surgery under general anesthesia for a glioblastoma (IV) in posterior part of the inferior temporal gyrus. **A.** MRI T1 axial, coronal and sagittal sections obtained 26 days before surgery. **B.** MRI T1 axial, coronal and sagittal sections obtained 1 year, 3 months after surgery (469 days) with subtotal resection.

Figure 5.2 Pre- and post-operative MRI scans for patient LZ. Patient LZ underwent awake surgery for a glioblastoma (IV) in posterior part of the middle temporal gyrus. **A.** MRI T2-weighted axial, coronal and sagittal sections obtained 13 days before surgery. **B.** MRI T2-weighted axial and coronal sections obtained 1 year, 6 months after surgery (566 days) with total resection.

Intra-operative assessment

Awake surgery for glioma resection is a patient-specific and tailored approach. Pre-operative performance, tumor location and suitability for the procedure (e.g. level of emotional stability and anxiety) are considered to decide on eligibility for awake craniotomy. Patient FO presented too severe deficits on pre-operative neuropsychological assessment that interpretation of intra-operative stimulation would become problematic. Glioma resection for FO was performed under general anesthesia. For patient LZ, individualized assessments for cortical and subcortical mapping were prepared. Based on tumor location and pre-operative performance, the components at risk during surgery were identified. LZ was selected for awake surgery with intra-operative monitoring of reading and spelling in addition to spoken naming tasks (ECCO & VISC [11]). The Written language battery served to build individualized intra-operative assessment, targeting only components at risk. Separate sublists assessing the psycholinguistic variables associated with these components were selected (see Chapter 4 for an overview). The tailored stimulus lists for reading and spelling included frequency-matched items of varying orthographic regularity (regular vs. opaque spelling and infrequent stress positions) and length (short vs. long stimuli). The assessment of reading consisted of 64 words and 30 non-words, that of spelling of 28 words and 13 non-words.

Reading stimuli were presented separately on a 13-inch laptop screen, positioned on the right side of the patient. Practice items were displayed to ensure that the patient could see the stimulus. Each stimulus was preceded by a beep, to indicate stimulus onset for the neurosurgeon. The patient was asked to read each stimulus aloud. Spelling stimuli were dictated by a native speaker of Italian. The patient was asked to write each stimulus down with a pencil on a blank sheet of paper. Her dominant (right) hand was free to move. For support and for flexible positioning of the paper sheet relative to the patient, a neuropsychologist held a hardboard sheet on the right side of the patient in such a way that patient could see her own handwriting (Figure 5.5b). After each written word, the neuropsychologist provided feedback about the spelling of the word to the neurosurgeon. Qualitative features about the patient's handwriting (i.e., ill-formed letters or case mixing; Peripheral errors) were not considered intra-operatively. A new sheet of paper was placed every few words to ensure the patient's visual feedback of her handwriting and to avoid discomfort in her hand positioning.

The intra-operative procedure was recorded both from the neurosurgeon's (in the microscope; Figure 5.5a) and the neuropsychologist's perspective (with a mobile camera; Figure 5.5b). We aimed to identify errors post-hoc, and to establish if errors emerged during stimulation. Due to technical problems with the microscope video recording, this goal could however not be obtained. During surgery, the neurosurgeon indicated positive mapping sites with numbered tags (Figure 5.5a), when Direct Electrical Stimulation of the same region resulted in 3 consecutive errors. All produced errors, including single and non-reproducible ones, were marked by the neuropsychologists and kept for post-hoc evaluations.

Analyses

Structured scoring procedures from the Written language battery for glioma patients were used to classify error types (Chapter 4 section *Scoring*). The same error classification system was applied to the reading and spelling subtests from the Clinical battery. A broad distinction was made between incorrect responses resulting from damage to central processes (Central errors) and errors that did not result from damage to central processes (reading: Other errors, resulting in qualitative changes such as slowed or hesitant responses; spelling: Peripheral errors, consisting of qualitative changes in handwriting, such as ill-formed letters or case mixing). In handwriting, incorrect responses that could result either from central or from peripheral damage (e.g., a dictated /m/ written as *n* instead of *m*) were scored as Unclassifiable. A glossary of all Central, Other, and Peripheral error types may be found in Appendix C.2.

Error rates on all tests were calculated and descriptive statistics were used to establish if scores fell above or below cut-off, compared to a neurologically healthy population. Effects of psycholinguistic variables were analyzed by Fisher's Exact Test (for non-continuous factors e.g., grammatical class) and Generalized Linear Models (for continuous variables e.g., word length). Changes between pre-, post-operative and follow-up assessments were analyzed by Fisher's Exact Test. All statistical analyses were conducted in R using *stats* and *gmodels* packages [19-21]. A significance level of $p < 0.05$ was used for all analyses.

5

Results

Comparisons with a clinical battery

To inspect if the Written language battery is more sensitive to evaluate reading and spelling performance in glioma patients as compared to commonly used clinical tasks, two patients were evaluated with the new battery and the Clinical battery. Non-word reading and non-word spelling tasks, that are part of both batteries, were included for comparison.

Table 5.1 Central and Other/Peripheral errors observed using of the Clinical battery and the Written language battery

		Central errors						Other / Peripheral errors					
			Patient FO		Patient LZ				Patient FO		Patient LZ		
	Number of items	Cut-off	T_{-1}	T_1	T_{-1}	T_1	T_2	Cut-off	T_{-1}	T_1	T_{-1}	T_1	T_2
Clinical battery													
Non-word reading	22 / 23 ±	1	0 (0.0)	**6 (27.7)**	0 (0.0)	1 (4.6)	1 (4.4)	1	0 (0.0)	**4 (18.2)**	0 (0.0)	0 (0.0)	**2 (8.7)**
Non-word spelling	12 / 13 ±	1	0 (0.0)	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	1	0 (0.0)	**2 (15.4)**	1 (8.3)	**2 (15.4)**	0 (0.0)
Written language battery													
Non-word reading	52	2	**8 (15.4)**	**13 (25.0)**	**3 (5.8)**	2 (3.9)	**7 (13.5)**	3	3 (5.8)	**7 (13.5)**	1 (1.9)	**9 (17.3)**	**6 (11.5)**
Non-word spelling	40	7	**10 (25.0)**	**8 (20.0)**	4 (10.0)	2 (5.0)	**7 (17.5)**	1	**7 (17.5)**	**12 (30.0)**	**3 (7.5)**	0 (0.0)	1 (2.5)

This table shows individual results on pre-operative, post-operative and follow-up assessment on the Clinical battery and the Written language battery for glioma patients, by numbers of errors / number of items on the subtask (%); **Bold** = number of errors indicating pathological performance (> cut-off). Cut-offs per error type and per subtask are based on performance of 50 Italian healthy controls (see Chapter 4); T_{-1} = pre-operative assessment, T_1 = post-operative assessment, T_2 = follow-up assessment. ± = Number of items depends on pre- or post-operative version.

Quantitative analyses

Batteries were first evaluated quantitatively, by inspecting error rates and impaired performances before and after surgery. Individual error rates are displayed in Table 5.1 and Figure 5.3.

Patient FO

Before surgery, performance on the Written language battery indicated impaired non-word reading (Central errors) and non-word handwriting (Central and Peripheral errors; Table 5.1). The Clinical battery did not reveal any errors pre-operatively. Post-operatively, performance on the Written language battery indicated impaired non-word reading (Central and Other errors) and non-word handwriting (Central and Peripheral errors). The Clinical battery also indicated impaired non-word reading (Central and Other errors), yet non-word handwriting was only impaired for Peripheral errors on the Clinical battery.

Between the pre- and the post-operative assessment, errors of non-word reading increased significantly on the Clinical battery (Central errors: p= .009; Other errors: p= .049), but not on the glioma battery (Central errors: p= .329; Other errors: p= .319). Non-word handwriting performance remained significantly unchanged on both batteries (Figure 5.3).

Patient LZ

Pre-operatively, performance on the Written language battery indicated impaired non-word reading (Central errors) and non-word handwriting (Peripheral errors; Table 5.1). The Clinical battery did not reveal any pathological scores compared to cut-off rates before surgery, and disclosed no errors in 3/4 instances. Early after surgery, the Written language battery revealed pathological scores on non-word reading (Other errors). The Clinical battery showed impaired non-word handwriting (Peripheral errors) post-operatively. At follow-up assessment, performance on the Written language battery indicated impaired non-word reading (Central and Other errors) and non-word handwriting (Central errors). The Clinical battery revealed impaired non-word reading (Other errors).

Comparisons of pre- and post-operative assessments showed significantly increased Other errors on non-word reading in the Written language test only (Written language battery: p= .016; Clinical battery: p= 1.000).

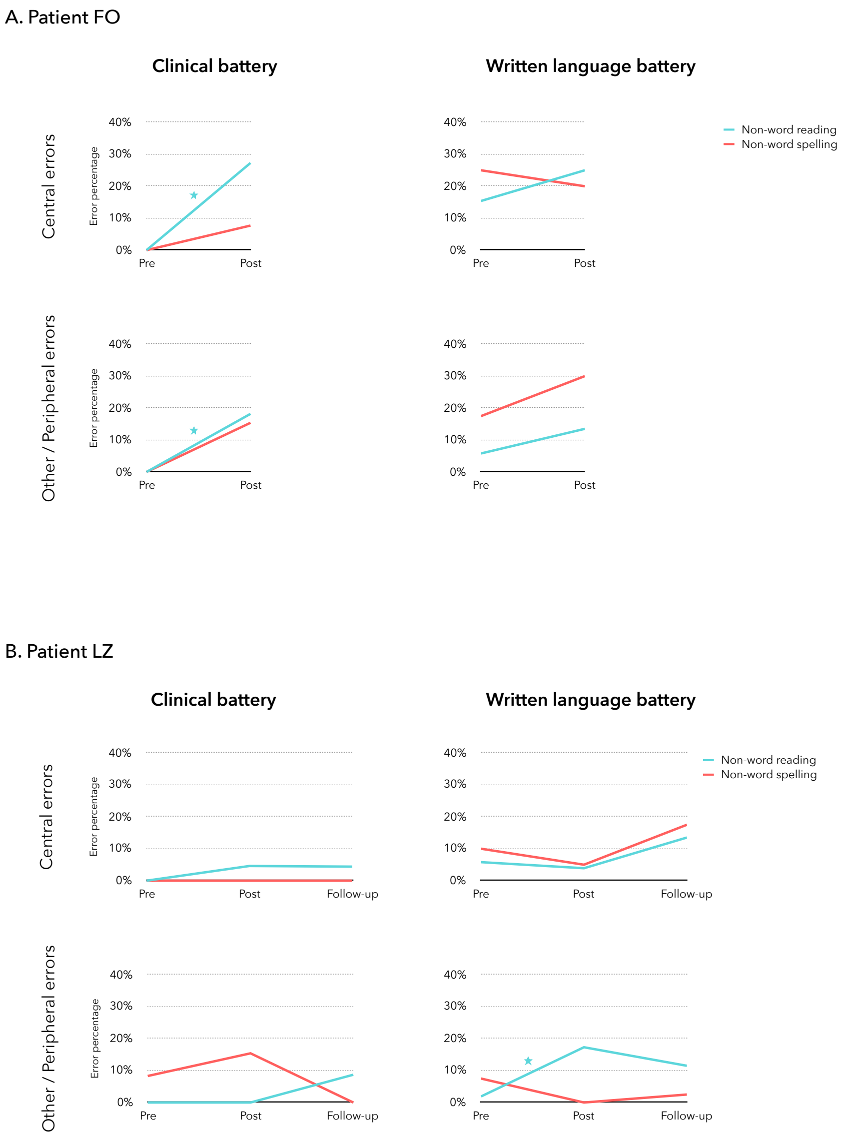

Figure 5.3 Assessment comparisons of Central and Other/Peripheral errors on the Clinical battery and the Written language battery for glioma patients. Quantitative analyses of Central and Other/Peripheral errors are shown for patients FO (Figure 5.3A) and LZ (Figure 5.3B). Performance on non-word reading is presented in blue; non-word spelling is displayed in red. Non-word reading subtasks comprised of 23 (pre-operative & follow-up assessment) or 22 items (post-operative assessment) on the Clinical battery; and of 52 items on the Written language battery for glioma patients. Non-word spelling comprised of 13 (pre-operative & follow-up assessment) or 12 items (post-operative assessment) on the Clinical battery; and of 40 items on the Written language battery for glioma patients. * Significant change between assessments on separate subtests (Fisher's Exact Test $p < .05$)

Qualitative analyses

Quantitative analyses of performance on the Written language battery disclosed more Central, Other, and Peripheral errors than using the Clinical battery. However, they did not inform on the status of individual components of the reading and spelling processes. These components can solely be inspected by reviewing the influence of corresponding psycholinguistic variables, as outlined in Chapters 1 (for reading) and 2 (for spelling). To evaluate the role of psycholinguistic variables on Central errors, responses produced by FO and LZ were analyzed qualitatively. Based on structured scoring forms, 7 types of Central errors were identified in non-word handwriting and 6 in non-word reading (Table 5.2).

Table 5.2 Types of Central errors observed using the Clinical battery and the Written language battery for glioma patients, by number of specific error types / number of Central errors produced on the subtask (%)

	Clinical battery		**Written language battery**	
	Non-word reading	Non-word spelling	Non-word reading	Non-word spelling
Patient FO				
Total number of Central errors	6	1	21	18
Phonological related segmental error	0 (0.0%)	0 (0.0%)	9 (42.9%)	12 (66.7%)
Unrelated segmental error resulting in a word	0 (0.0%)	1 (100%)	1 (4.8%)	1 (5.6%)
Unrelated segmental error resulting in a non-word	5 (83.3%)	0 (0.0%)	10 (47.6%)	5 (27.8%)
Fragment	1 (16.7%)	0 (0.0%)	1 (4.8%)	0 (0.0%)
Diacritic error	*na*	0 (0.0%)	*na*	0 (0.0%)
No response	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Patient LZ				
Total number of Central errors	2	0	12	13
Phonological related segmental error	2 (100%)	0 (0.0%)	10 (83.3%)	9 (69.2%)
Unrelated segmental error resulting in a word	0 (0.0%)	0 (0.0%)	1 (8.3%)	0 (0.0%)
Unrelated segmental error resulting in a non-word	0 (0.0%)	0 (0.0%)	1 (8.3%)	3 (23.1%)
Fragment	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Diacritic error	*na*	0 (0.0%)	*na*	0 (0.0%)
No response	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.7%)

Overall error rates are reported, representing pre- and post-operative assessments for patients FO, and pre-operative, post-operative and follow-up assessments LZ. Incidence of types of errors is reported relative to the total number of Central errors produced per subtask, per patient.
na = not applicable for reading assessments

Patient FO

Before surgery, the Written language battery revealed a significant length effect in non-word reading ($p = .010$). The Clinical battery subtests did not reveal any effects pre-operatively (Table 5.3). Post-operatively, no effects were observed on the Written language battery, whereas effects of non-word similarity ($p = .005$) and letter length (more errors on longer non-words, $p = .012$) were observed in the Clinical battery. As regards error types, patient FO showed 4 types of Central errors on non-word reading and 3 on non-word handwriting on the Written language battery, compared to respectively 2 and 1 error types using the Clinical battery.

Patient LZ

Pre-operatively, the Written language battery revealed effects of similarity to word in non-word reading (more errors on non-words dissimilar to words, $p < .001$) and handwriting ($p = .003$). Post-operatively, a reverse length effect was observed in the Written language battery (more errors on short non-words, $p < .001$). The Clinical battery subtests did not reveal any effects before or after surgery (Table 5.3). The Written language battery yielded 3 error types on both non-word reading and handwriting, whereas 1 error type was observed on non-word reading on the Clinical battery.

Table 5.3 Significant effects of psycholinguistic variables on Central errors observed using the Clinical battery and the Written language battery for glioma patients

	Clinical battery									**Written language battery for glioma patients**								
	Non-word similarity to word			Letter length			Syllable length			Non-word similarity to word			Letter length			Syllable length		
	T_{-1}	T_1	T_2	T_{-1}	T_1	T_2	T_{-1}	T_1	T_2	T_{-1}	T_1	T_2	T_{-1}	T_1	T_2	T_{-1}	T_1	T_2
Patient FO																		
Non-word reading	–	✓		–	✓		–	–		–	–		✓	–		–	–	
Non-word spelling	–	–		–	–		–	–		–	–		–	–		–	–	
Patient LZ																		
Non-word reading	–	–	–	–	–	–	–	–	–	✓	–	–	–	–	–	–	–	–
Non-word spelling	–	–	–	–	–	–	–	–	–	✓	–	–	–	✓	–	–	–	–

Non-word similarity to word = number of words that can be generated by changing a single letter of the non-word; T_{-1} = pre-operative assessment, T_1 = post-operative assessment, T_2 = follow-up assessment; Each symbol represents the results of the tested effect in one assessment.
✓ significant effect ($p < .05$) – no significant effect ($p > .05$)

Application of the Written language battery

To evaluate in finer detail the clinical applicability of the Written language battery in glioma patients, the full battery was administered before and after surgery to patients FO and LZ. In addition, reading and handwriting were assessed intra-operatively with a tailored stimulus list for LZ. Results of pre-, intra- and post-operative assessments of reading and spelling are discussed separately.

Pre- and post-operative reading

Patient FO

Patient FO produced pathological numbers of Central errors on words, non-words, and sentences before and after surgery. Central errors occurred more frequently in responses to non-words than to words and sentences (pre-operatively: p= .018, post-operatively: p= .002; Figure 5.4).

Pre-operatively, Central errors on words were influenced by frequency (more errors on low-frequency words, p< .001), and Central errors on non-words were influenced by length (p= .010). After surgery, Central errors were no longer significantly influenced by these or other psycholinguistic variables (Table 5.4a). Yet, post-operatively a length effect was found on longer words in sentences (p= .038).

In List 3, which consists of words with opaque segments, Central errors occurred before and after surgery only on stimuli with less frequent stress patterns (e.g., *pòrtici* > /portìtʃi/ [i]). In all other sublists, FO produced predominantly segmental errors (pre-operatively such errors accounted for 9/15, or 60.0%, of Central errors, and post-operatively in 18/23, or 78.3%). Most errors on words were phonologically related letter substitutions (e.g., *parso* > /barso/, *vicolo* > /vigolo/, *godo* > /gode/). In sentences, morphosyntactic errors were observed (*il concorrente* > /i koŋkorrenti/, *trovava* > /trovavo/, and *un grado* > /una grado/).

Other errors typically presented as reduced reading speed. After surgery, Other errors increased significantly as compared to the pre-operative assessment (p< .001), and indicated pathological performance at all tasks.

Patient LZ

Patient LZ produced a pathological number of Central errors on all tasks (words, non-words and sentences) before surgery. Post-operatively, impairments were only observed on words, and at follow-up on words and non-words. At follow-up, non-words were significantly more impaired than words and sentences (p= .040; Figure 5.4).

[i] Presented stimuli are denoted in *italics*, responses are provided in /International Phonetic Alphabet/ for reading and in CAPITALS for handwriting. Written marks ` indicate stress placements. Self-corrections are indicated with – in the response.

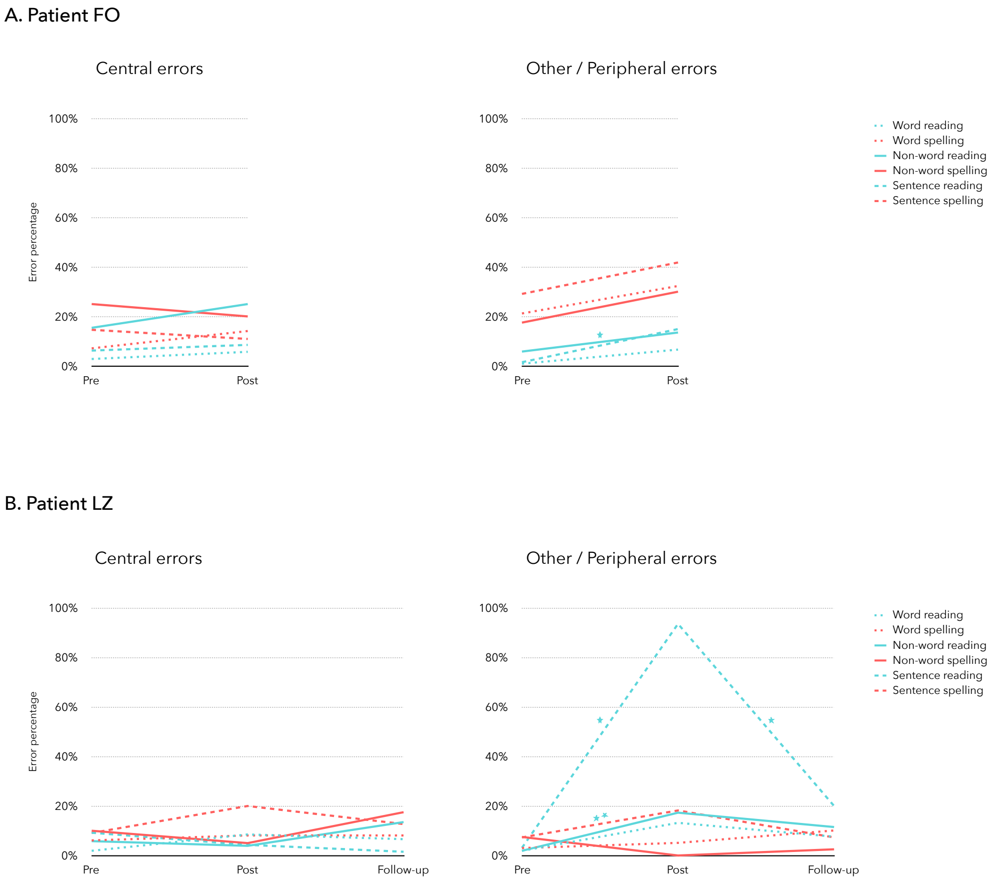

Figure 5.4 Error rates on all subtasks of the Written language battery for glioma patients. Quantitative analyses of Central and Other/Peripheral errors are shown for patients FO (Figure 5.3A) and LZ (Figure 5.3B). Performances on reading tasks are presented in blue; spelling is displayed in red. Each line represents a separate subtask. * Significant change between assessments on separate subtests (Fisher's Exact Test p< .05)

As for psycholinguistic variables, Central errors on words were influenced by frequency (*p*= .002) and grammatical class (Verbs 27.8%, Nouns 5.3%, Adjectives and Function words 0.0% errors; *p*= .019). At follow-up, they were still influenced by frequency (*p*< .001) but no longer by grammatical class. An additional length effect was observed across lists (*p*= .029). Central errors on non-words were pre-operatively influenced by similarity to words (more errors on dissimilar non-words; *p*< .001).

Central errors before and after surgery were mainly of the segmental type. These errors accounted for 7/11 incorrect responses (63.6%) pre-operatively; for 8/13 (61.5%) post-operatively; and for 12/15 (80.0%) at follow-up. All errors were orthographically and/or phonologically related letter substitutions (e.g., *unirono* > /urirono/, *piuttosto* > / bju - pjuttˈɔsto/, and *denuncio* > /demun - denuntʃo/). Patient LZ corrected spontaneously 13/18 errors (72.2%). In sentences, morphological-syntactic errors resulting in incorrect words occurred (e.g., *musica* > /muzike/, *portamelo* > /portameli/, *chiese* > /kjede/). These were self-corrected less frequently (in 2/5 cases, or 40.0%).

At all assessments, LZ read at a reduced speed, which caused pathological scores on Other errors. In the post-acute phase, they were significantly more frequent than in the pre-operative assessment ($p < .001$), but performance improved significantly between post-operative and follow-up assessments ($p < .001$; Figure 5.4).

Pre- and post-operative spelling

Patient FO

Pre-operatively, FO produced a pathological number of Central errors on all tasks (words, non-words and sentences), although significantly more errors occurred on non-words than on other stimulus types ($p = .017$). After surgery, error rates increased and impairments persisted on all tasks (Figure 5.4).

As regards psycholinguistic variables, Central errors were pre-operatively constrained by word frequency ($p < .001$), and length ($p < .001$; Table 5.4b). After surgery, a paradoxical length effect was observed (more errors on shorter words; letter length, $p = .033$; syllable length, $p = .039$). Central errors on non-words were not influenced by known psycholinguistic variables.

Central errors occurred most frequently in responses to words with opaque orthography (in 11/21 cases; or 52.4%). Out of 21 Central errors, 14 (66.7%) were segmental, often yielding phonologically plausible (*usciere* > USCERE; *cero* > CIERO). Six of the 14 segmental errors were of these types (42.9%). In sentences, 6/14 errors (42.9%) occurred on homophones, yielding errors such as l'etto > LETTO, *c'era* > CERA, and *l'ama* > LA – L'AMA.

Peripheral errors, suggesting post-graphemic damage, indicated impairments before and after surgery on all tasks, yet were significantly more frequent after surgery ($p = .013$; Figure 5.4). They consisted mainly of ill-formed letters, which occurred significantly more often in longer stimuli (pre-operatively: $p = .017$ and post-operatively: $p = .031$). After surgery, they were significantly more frequent on verbs (in 10/14 items, or 71.4%) than on nouns, function words, or adjectives ($p = .007$).

Table 5.4a Central reading errors on all subtasks of the Written language battery for glioma patients, per assessment list and per psycholinguistic variable

	Patient FO		Patient LZ		
	Pre-operative	Post-operative	Pre-operative	Post-operative	Follow-up
Reading					
Words					
List 1: Frequency (low – high)	0/32 – 0/32	1/32 – 1/32	1/32 – 0/32	3/32 – 1/32	3/32 – 0/32
List 1: Length (long – short)	0/32 – 0/32	0/32 – 2/32	0/32 – 1/32	2/32 – 2/32	1/32 – 2/32
List 1: Grammatical class [1]	2/38 – 0/16	3/36 – 0/16	1/16 – 0/36	4/38 – 0/16	5/38 – 0/16
List 2: Morphology (irreg – reg)	1/6 – 1/16	1/6 – 1/6	0/6 – 1/16	0/6 – 3/16	0/6 - 4/12
List 3: Orthography [1]	1/8 – 0/6	2/8 – 0/6	0/6 – 0/8	2/8 – 0/6	0/6 – 0/8
Imageability (error – no error)	3.03 – 3.24	3.04 – 3.16	3.08 – 3.23	2.83 – 3.18	2.97 – 3.25
Frequency (error – no error)	4.00 – 52.53 **	37.17 – 50.93	6.58 – 52.03 **	23.46 – 52.63	5.53 – 54.39 **
Letter length (error – no error)	6.33 – 6.20	5.33 – 6.24	6.00 – 6.21	6.78 – 6.13	7.00 – 6.15
Syllable length (error – no error)	3.00 – 2.60	2.67 – 2.63	3.00 – 2.61	2.78 – 2.62	3.29 – 2.57 **
Non-words					
List 1: Similarity (low – high)	0/8 – 1/8	0/8 – 2/8	0/8 - 0/8	0/8 – 1/8	0/8 – 1/8
List 2: Morphology (not deco – deco)	1/10 – 3/10	4/10 – 2/10	1/10 – 0/10	0/10 – 0/10	0/10 – 1/10
List 3: Orthography (no cv – cv)	3/11 – 0/5	4/11 – 1/5	2/11 – 0/5	0/11 – 1/5	3/11 – 2/5
N-count (error – no error)	1.38 – 2.52	1.92 – 2.56	0.00 – 2.49 **	6.50 – 2.24	2.14 – 2.38
Letter length (error – no error)	7.00 – 5.84 **	6.38 – 5.90	6.67 – 5.98	5.00 – 6.06	6.14 – 6.00
Syllable length (error – no error)	3.13 – 2.84	2.92 – 2.90	3.00 – 2.88	2.50 – 2.92	2.86 – 2.89
Sentences					
List 1: Homographs (non-pen – pen)	0/5 – 0/6	0/6 – 0/5	0/5 – 0/6	0/5 – 0/6	0/5 – 1/6
List 2: Clitic pronoun [2]	0/1	0/1	1/1	0/1	0/1
Grammatical class [1]	2/14 – 0/14	2/16 – 0/10	5/18 – 0/14 *	1/5 – 0/16	1/14 – 0/14
Letter length (error – no error)	6.50 – 5.80	8.00 – 5.72 *	6.50 – 5.78	8.50 – 5.80	6.00 – 5.85
Syllable length (error – no error)	2.25 – 2.38	3.00 – 2.56	2.67 – 2.34	3.00 – 2.58	2.00 – 2.37
Overall					
Letter length (error – no error)	6.73 – 6.01	6.39 – 6.04	6.45 – 6.04	6.77 – 6.04	6.53 – 6.02
Syllable length (error – no error)	2.87 – 2.59	2.90 – 2.67	2.82 – 2.59	2.77 – 2.69	3.00 – 2.69 *

For each assessment list, error rates on contrasted items are reported. In addition, effects of psycholinguistic variables on Central errors are reported, contrasting items that did result in Central errors vs. items that did not result in Central errors. [1] More than 2 items are contrasted; these show comparisons of the items with the highest error rate vs. items with the lowest error rate. [2] One type of items included, of which error rates are provided. N-count = the number of words that can be generated by changing a single letter of the non-word; Reg = regular, Irreg = irregular; Deco = decomposable, Not deco = not decomposable; Cv = consonant-vowel order, No cv = no consonant-vowel order; Pen = stress on the penultimate syllable, Non-pen = stress on a non-penultimate syllable; Com = common, Uncom = uncommon. * Significant differences in error rates between the contrasted items; ^ .05≤ *p*≤ .07, * *p*< .05, ** *p*< .01

Table 5.4b Central spelling errors on all subtasks of the Written language battery for glioma patients, per assessment list and per psycholinguistic variable

	Patient FO		Patient LZ		
	Pre-operative	Post-operative	Pre-operative	Post-operative	Follow-up
Spelling					
Words					
List 1: Frequency (low – high)	1/16 – 0/16	1/16 – 3/16	1/16 – 1/16	0/16 – 0/16	1/16 – 1/16
List 1: Length (long – short)	0/16 – 1/16	2/16 – 2/16	1/16 – 1/16	0/16 – 0/16	0/16 – 2/16
List 1: Grammatical class [1]	3/28 – 0/20	9/44 – 1/20	2/20 – 0/9	4/26 – 9/19	5/42 – 0/20
List 2: Morphology [2]	3/8	0/8	0/8	1/8	0/8
List 3: Orthographic structure (no cv – cv)	0/16 - 0/8	1/16 - 1/8	1/16 - 1/8	2/16 - 1/8	0/16 - 0/8
List 4: Orthographic regularity [2]	3/35	8/35	2/35	4/35	6/35
Imageability (error – no error)	3.02 – 3.38	3.94 – 3.36 ^	3.65 – 3.33	3.08 – 3.46	3.72 – 3.32
Frequency (error – no error)	10.20 – 43.39 **	39.86 – 39.79	27.43 – 41.79	15.66 – 42.04 *	34.53 – 41.48
Letter length (error – no error)	7.14 – 6.64	5.93 – 6.74 *	6.50 – 6.69	6.43 – 6.66	5.75 – 6.76 **
Syllable length (error – no error)	3.00 – 2.73	2.36 – 2.78 *	2.83 – 2.74	2.71 – 2.73	2.38 – 2.78 ^
Non-words					
List 1: Orthography (uncom – com)	4/10 – 3/10	4/10 – 3/10	1/10 – 1/10	1/10 – 1/10	1/10 – 2/10
List 1: Length (long – short)	5/10 – 2/10	3/10 – 4/10	1/10 – 1/10	0/10 – 2/10	2/10 – 1/10
List 2: Morphology (not deco – deco)	2/10 – 1/10	1/10 – 0/10	1/10 – 1/10	0/10 – 0/10	1/10 – 3/10
N-count (error – no error)	0.80 – 1.77	1.75 – 1.38	0.25 – 1.67 **	1.50 – 1.45	1.00 – 1.64
Letter length (error – no error)	6.90 – 6.43	6.25 – 6.59	6.50 – 6.56	5.00 – 6.61 **	7.29 – 6.39 ^
Syllable length (error – no error)	3.30 – 2.87	2.88 – 2.91	3.25 – 2.94	2.50 – 2.92	3.29 – 2.91
Sentences					
List 1: Homophones [2]	3/12	3/12	1/12	4/12	4/12
Grammatical class [1]	4/10 - 0/8	3/14 – 0/13	3/14 – 0/20 ^	4/13 - 0/8	5/14 - 0/8 *
Letter length (error – no error)	5.88 – 5.04	6.00 – 5.06	4.40 – 5.24	6.73 – 4.77 *	5.00 – 5.19
Syllable length (error – no error)	2.75 – 2.17	2.67 – 2.20	2.00 – 2.28	3.09 – 2.05 **	2.43 – 2.23
Overall					
Letter length (error – no error)	6.64 – 6.16	6.04 – 6.22	5.80 – 6.26	6.45 – 6.17	6.00 – 6.25
Syllable length (error – no error)	3.04 – 2.60 **	2.57 – 2.63	2.67 – 2.65	2.90 – 2.59	2.68 – 2.65

Spelling was assessed in the modality of handwriting. For each assessment list, error rates on contrasted items are reported. In addition, effects of psycholinguistic variables on overall Central errors are reported (contrasting items that did result in Central errors vs. items that did not result in Central errors). [1] Comparisons between the contrasts items with the highest error rate – class with the lowest error rate. [2] One type of items included, of which error rates are provided. N-count = the number of words that can be generated by changing a single letter of the non-word; Cv = consonant-vowel order, No cv = no consonant-vowel order; Com = common, Uncom = uncommon; Deco = decomposable, Not deco = not decomposable. * Significant differences in error rates between the contrasted items; ^ .05≤ *p*≤ .07, * *p*< .05, ** *p*< .01

Patient LZ

Before surgery, patient LZ produced a pathological number of Central errors in sentence reading. After surgery, Central errors rose above cut-off on words and sentences. Sentences were significantly more affected than words (*p*= .043; Figure 5.4).

Effects of psycholinguistic variables differed across assessments. Pre-operatively, Central errors were more frequent on non-words that were less similar to words (*p*= .003). A non-significant trend toward a grammatical class effect was also observed (Verbs 21.4%, Adjectives 15.4%, Nouns and Function words 0.0% errors; *p*= .065). Post-operatively, Central errors were influenced by frequency (*p*= .005), and a paradoxical length effect was observed, affecting shorter non-words (*p*< .001), but longer words in sentences (*p*= .013). In contrast, at follow-up, marginal length effects were observed that affected longer non-words (*p*= .055), but shorter words (*p*= .004). In addition, Central errors were influenced by grammatical class at follow-up (Verbs 35.7%, Nouns 10.0%, Adjectives and Function words 0.0% errors; *p*= .031).

Across assessments, most Central errors (11/21, or 52.4%) occurred on words with 'opaque' orthography (on shorter words with orthographic irregularity). At follow-up, 6/8 Central errors (75.0%) were produced on this list. Segmental errors were the most frequent error type (16/21, 76.2%). Of these, 7/16 (43.8%) were phonologically plausible (*scienza* > SCENZA; *cuoco* > QUOCO), and 2/16 (12.5%) phonologically related (*finito* > VI – FINOTO). Similarly, in sentences 6/15 segmental errors (40%) were phonologically plausible misspellings of homophones (*l'hanno* > L'ANNO; *v'era* > VERA), and 4/15 (26.7%) were phonologically related errors (*Valeria* > FALERIA; *inizio* > UNIZO). At follow-up, errors in sentences affected verbs in 5/7 cases (71.4%). Peripheral errors indicating post-graphemic impairment occurred before and after surgery.
Peripheral errors presented mainly as ill-formed letters, which affected long stimuli significantly more often than short items (pre-operatively: *p*< .001 and post-operatively: *p*= .024). Scores were pathological on all tasks before surgery, and impairments persisted on words and sentences after surgery.

Intra-operative assessment

In addition to object naming and action naming, patient LZ was assessed intra-operatively for reading and spelling (Figure 5.5). Since the glioma was in the posterior part of the middle temporal gyrus, intra-operative testing took account of the potential consequences of tumor removal in that region. Knowledge of the neural correlates of reading invited to consider possible post-surgical damage to the phonological output lexicon. Since no specific spelling processes have been linked to the middle temporal gyrus (Chapter 2), in this subject pre-operative performance was considered when selecting spelling stimuli for surgery. The pre-operative error profile was consistent with orthographic output damage (i.e., effects of frequency, orthographic regularity and grammatical class). Consequently, stimuli tapping this component were selected for the intra-operative assessment of spelling (sublists assessing frequency, length and grammatical class, and orthographic regularity), while phonological output lexicon processing was targeted for reading. Words and non-words were assessed, focusing on orthographic regularity and length.

Figure 5.5 Demonstration of intra-operative assessment of handwriting. A. Surgical area during surgery of patient LZ. The glioblastoma was located in the posterior part of middle temporal gyrus. Posterior perisylvian regions were revealed for resection. Tags represent positive mapping sites, where DES applied to a region resulted in three consecutive errors. Tags 1 and 2 (upper right) indicate sensory motor area of the mouth. Stimulation of areas indicated by tags 4 and 8 (middle left) resulted in anomia on spoken naming tasks. **B.** Set-up for monitoring of handwriting to dictation during awake surgery. The right (dominant) hand is free to write. The hardboard sheet is placed in such a way that the patient could see her own handwriting. A new paper was placed every few words when needed to ascertain good visual feedback for the patient. **C.** Examples of non-reproducible errors in handwriting produced during surgery by LZ. Two Central errors (left), and two Unclassifiable errors (right) are displayed.

Positive mapping sites were identified by spoken naming tasks (Figure 5.5a). Although positive sites were not explicitly found during reading or handwriting, non-reproducible errors were detected when LZ was asked to read or write. In word reading, 12/64 stimuli (18.8%) resulted in Central errors, predominantly on words with infrequent stress placement (6/12; 50.0%) and on long, low-frequency words (4/12; 33.3%). Non-word reading resulted in 4/30 errors (13.3%), all on longer items. In handwriting, 8/28 words (28.6%) were written incorrectly. Of these errors, 4 were Unclassifiable (see Figure 5.5c for examples), and the others were Central (segmental) errors. In non-word handwriting, 1/13 items (7.7%) resulted in a Central error during stimulation of the supramarginal gyrus. Subcortical stimulation in the cavity of the resected area did not elicit errors. Surgery led to a total resection (100%), and all the functional sites that resulted in errors during stimulation were preserved. Patient LZ showed no significant deterioration in reading or handwriting performance 9 days and 4 months after surgery.

Discussion

In absence of a detailed examination tool to evaluate reading and spelling in neurosurgical practice (Chapter 3), a comprehensive written language battery was developed, specifically for glioma patients (Chapter 4). In this study, the newly developed battery was validated to establish: if it provides more information than short subtests of clinical batteries; if its use in clinical practice is feasible; and if it aids identification of underlying disorders of reading and spelling.

The additive value of detailed written language assessment in glioma patients

In clinical neurosurgical practice, short subtests of post-stroke aphasia batteries are often used to evaluate written language in glioma patients. The Written language battery was compared to such a Clinical battery (items taken from BADA [10]) to see if it would enhance the detection of written language deficits and error patterns in glioma patients. Comparisons of results on non-word reading and handwriting obtained by two patients, who completed both the short subtests and the new battery, showed that the new battery is more sensitive.

Quantitative analyses identified more Central and Other / Peripheral errors using the Written language battery than the Clinical battery (Figure 5.3). Contrasting the two tasks directly per assessment moment in individual cases, the Written language battery disclosed more Central errors in 9/10 instances (90.0%), and more Other / Peripheral errors in 7/10 cases (70.0%). Particularly pre-operatively, the new test revealed errors while the Clinical battery elicited barely any errors in reading and spelling. The Written language tests identified the same impairments as the Clinical battery in terms of scores deviating from the cut-off point, but revealed more subtle impairments on other reading and spelling subtasks, which were not picked up by the Clinical battery. Significant increases in error rates were shown in the Clinical battery only, but this is probably due to the absence of pre-operative errors on this battery, as post-operative error rates were comparable to those in the Written language battery (Figure 5.3).

Qualitative analyses showed that performance profiles could be explained in more detail by the Written language test, by isolating significant effects of psycholinguistic variables more often than possible with the Clinical test (Table 5.3), indicating functional impairments to corresponding components. This difference was especially apparent pre-operatively, when only the Written language battery demonstrated effects. Moreover, the new battery elicited a larger variety of Central error types (Table 5.2).

These results show that the Written language battery is a sensitive tool for the evaluation of subtle deficits in glioma patients. Results clarify that the lack of sensitivity of the Clinical tests does not simply result from the possibly arbitrary choice of tasks (see Chapter 3), as the theory-driven test shows greater sensitivity even when the analysis is restricted to non-word tasks.

Data also demonstrate the need for detailed evaluations. A longer battery yields more errors, which allow a reliable measure of the integrity of underlying components. Incidental errors on a short battery may occur for many reasons (e.g., following damage to different underlying components or by chance), which complicates interpretations. On longer batteries, it is more plausible to observe error patterns, which may identify the functional locus of damage to the reading or spelling system. Moreover, exhaustive testing facilitates qualitative error analyses, which are instrumental in identifying spared or damaged underlying processes.

Application in neurosurgical practice

Two patients were examined in the pre-, intra- and post-operative phase. In both, the complete battery was administered before and after surgery without problems – on debriefing, patients did not report fatigue or discomfort, nor complaints. In addition, a tailored battery was successfully administered intra-operatively to patient LZ.

Assessing the integrity of cognitive components

In the perspective of pre-surgical planning, we were particularly interested in inspecting to what extent pre-operative assessments provide an insight on the preparation of intra-operative testing. Before surgery, patient FO showed frequency and length effects in word reading, and produced Central errors (phonologically plausible responses and incorrect stress assignments). Moreover, responses were characterized by reduced reading speed. This pattern of performance is consistent with damage to the orthographic input lexicon and the phonological buffer. Frequency and length effects were observed also in word handwriting. They resulted mainly in phonologically plausible and phonologically related Central errors. This dysgraphic profile is consistent with damage to the orthographic output lexicon and the graphemic buffer. Moreover, patient FO was both in reading and in handwriting more impaired on non-words than on words and sentences, consistent with damage to sublexical processing (grapheme-phoneme conversion in reading and phoneme-grapheme conversion in spelling).

Patient LZ showed pre-operatively effects of frequency and grammatical class (greater damage to verbs) in reading, with orthographically and/or phonologically related errors on words, and morphological errors in sentences. These results suggest damage to the phonological output lexicon. In handwriting, only performance on sentences was impaired before surgery. As errors mostly occurred on words with opaque orthographies and on homophones, and resulted in phonologically plausible/ related misspellings, this patient is likely to have orthographic output lexical damage. This hypothesis receives some indirect support from the observation that after surgery patient LZ showed a frequency and a grammatical class effect.

For both cases, results are broadly in line with current theories of the neurofunctional correlates of reading and spelling. The posterior part of the inferior temporal gyrus (patient FO) has been related to processing of orthographic input/ output lexical processing [22-27], and damage to this region has been described to result in similar effects of frequency, regularity and grammatical class in reading and spelling [22]. As for LZ, whose glioma was located in the posterior portion of the middle temporal gyrus, results showed an error profile compatible with phonological output lexicon damage in reading. This is in line with the literature, associating damage to this region with effects of regularity, frequency, grammatical class, morphology [27].

The performance profile of patient FO is also compatible with damage to the graphemic and phonological buffers, and to sublexical processes (phoneme-grapheme / grapheme-phoneme conversion). While these components have not been classically related to posterior ventral temporal regions, impaired processing may be expected when subcortical tracts underlying the inferior temporal gyrus (arcuate fasciculus and inferior fronto-occipital fasciculus) are damaged. Unfortunately, Diffusion Tensor Imaging was not available to evaluate subcortical infiltration, but damage to these tracts may have disrupted processing in connected functional areas. For graphemic and phonological buffer processing, the relevant areas include the supramarginal gyrus and posterior frontal regions [28-34]. Sublexical impairments, on the other hand, are typically related to dorsal stream processing, via posterior perisylvian regions [35-37]. Since the arcuate fasciculus and the superficial layer of the inferior fronto-occipital fasciculus are components of the dorsal stream processing system, damage to these tracts may also cause deficits in sublexical processing.

An unexpected error pattern was observed in both patients. Central errors in word handwriting (after surgery for FO, and before surgery for LZ) were influenced by a reverse length effect, in which shorter items elicited more errors than longer ones. However, further qualitative error analyses revealed that most errors occurred on words with orthographically opaque segments (on the sublist assessing orthographic regularity; Chapter 4). Although variables in all assessment lists were balanced during test development, words with opaque orthography were non-significantly shorter than other words of the word spelling task. As a result, when errors are almost exclusively made on these items, errors mainly arise on shorter words. The reverse length effects observed in the two cases discussed here are likely to reflect this list bias. These results stress that it is crucial to not just inspect effects, but complete performance profiles should be considered to evaluate the integrity of underlying components of written language before and after surgery.

Pre- intra- and post-operative assessments

Results showed that many features of the patients' performance could be interpreted based on pre-operative assessments using the Written language battery. When evaluating performance in these two patients, effects of psycholinguistic variables were thoroughly documented when data on individual sublists (e.g., the sublist of frequency, length and grammatical class, of orthographic regularity, or of morphology; Chapter 4) were complemented by finer-grained analyses (i.e., by taking absolute number such as frequency count, number of letters/syllables). Similar analyses on the Clinical battery, on the other hand, failed to identify subtle impairments pre-operatively, and may thus not be sufficiently sensitive. Given the key role of pre-operative assessment in surgical planning for glioma patients, it is therefore advisable to administer the Written language battery in full and to evaluate all variables in depth. This may provide insight in the patient's difficulties, and reliably identify components at risk to guide stimulus selection for intra-operative assessment.

This rationale was applied in patient LZ, in whom intra-operative stimulus selection was based on glioma location and pre-operative assessment. Consideration of these two issues directed to evaluate the status of the phonological output lexicon in reading, and the orthographic output lexicon in spelling. During surgery, all selected items from the written language battery (94 items for reading and 41 for handwriting) were successfully and without complaints of discomfort administered. The intra-operative monitoring of reading and spelling, in addition to that of spoken naming, resulted in total resection (100%). Absence of decline in written language subtasks following surgery suggests that the approach described here successfully ensured extensive tumor removal and protection of functional sites. The presence of the same type of spelling errors pre- and intra-operatively confirms that the pre-operative spelling evaluation accurately predicted the functional profile for this patient.

Post-operative evaluations were less consistent in identifying impairments. However, both patients were receiving chemo- and radiotherapy in the post-acute phase of testing. In line with studies that established an influence of adjuvant therapies on cognition [41-43], post-operative assessments during additional treatment may be less informative. The influence of several nuisance factors (e.g., timing of assessment, concomitant therapy, emotional status, possibility of further tumor growth/transformation) should be explored further and in detail (Chapter 7). The comparison between the evaluated batteries showed that short subtasks from the Clinical battery may suffice to assess post-operative performance when written language deficits are profound. To also evaluate more subtle impairments, and to inspect whether functional preservation is separate components was successful, assessment using the Written language battery is advisable after surgery.

Although these examples shows promising results for the clinical application of the Written language battery in all peri-operative phases, more patients should be evaluated using the same paradigm. Moreover, the influence of specific intra-operative assessment (i.e., using both reading and spelling tasks, or one task during surgery) on written language preservation should be explored further (Chapter 6). In addition, as both patients discussed here were operated for a high-grade glioma, it should be investigated whether the same considerations apply to low-grade gliomas with slower but more infiltrative growth [38-40] (Chapter 7).

Conclusions

In this study, a newly developed battery for the evaluation of reading and spelling in glioma patients was administered to two patients with high-grade gliomas. The battery aided understanding of reading and spelling performance as compared to short clinical subtests. It was administered successfully and without problems at all peri-operative stages (including the intra-operative administration of handwriting tasks). The battery allowed identifying damage to components of written language, which were in line with expectations based on the lesion and neuroimaging literature. Results hold promise for the application of the Written language battery in clinical practice, to target patient-specific intra-operative testing aimed at predicting and preventing written language disorders after glioma surgery. Its usefulness in the design of patient-tailored treatment should be explored further in glioma patients.

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6

Written language preservation in glioma patients undergoing awake surgery: The value of intra-operative assessment

Abstract

Attention to reading and spelling in neurosurgical practice has been scarce, and it remains unknown how written language is affected by surgery and what may guide preservation of reading and spelling. We aimed to evaluate how preservation of written language may be obtained in glioma patients. Reading and spelling were inspected before and after glioma surgery, and we weighted the value of intra-operative assessments at an individual level. Using a detailed cognitive written language battery, it showed that substantial written language impairments arose in glioma patients. Awake surgery with intra-operative written language assessment resulted in more positive reading and spelling outcome, compared to surgery without written language assessment. Moreover, task-specific preservation of written language via intra-operative assessment was successful in all cases, yet non-monitored written language tasks were not always preserved. Results showed that intra-operative assessment may aid preservation of reading and spelling.

Introduction

The outcome of our effort to evaluate written language in glioma patients emphasizes the need to assess reading and spelling in neurosurgical practice in addition to more routinely monitored spoken language tasks, as these skills may also be impaired by the glioma surgery or by the glioma itself (Chapter 2 and 3). So far, evaluations have relied typically on short subtests used in clinical practice, that do not suffice to reveal subtle deficits, such as those most frequently observed in glioma patients (Chapter 3 and 5). To large extent, how written language functions are affected remains largely unknown. To tackle this issue, detailed evaluations with tools targeted for glioma practice are required (Chapter 5).

In current glioma practice, awake surgery with intra-operative monitoring of cognitive functions serves as the gold standard for treatment [1-5] (see Chapter 1 for a description of the awake surgery procedure). Compared to surgery under general anesthesia, longer survival time and higher quality of life have been reported following awake surgery [3,6,7]. In addition, intra-operative monitoring of spoken language tasks has been shown to improve outcome on those tasks [8,9]. However, since written language is unsatisfactorily assessed in awake surgery, the influence of intra-operative monitoring on the outcome of reading and spelling remains unknown.

Spoken and written language tasks have been shown to rely at least partly on distinct functional and anatomical neural substrates [10]. Hence, when intra-operative testing is restricted to spoken language, the mechanisms underlying written language remain unexplored, and may be inadvertently damaged during surgery. Retrospective analyses show significant post-operative improvement only for the spoken language tasks monitored during surgery (Chapter 3), supporting the hypothesis that preservation through intra-operative assessment may not generalize across spoken and written language tasks.

Within written language, a further distinction can be made between the neural substrates involved in reading and in spelling. Classical neuropsychological studies have shown that these two skills rely on at least partially distinct cognitive components (see Chapter 1 and 2 for a detailed description of each component). As represented in Figure 1.1 (Chapter 1; p. 19), reading and spelling share a semantic component, but also require distinct components. Lesion and neuroimaging studies confirmed these distinctions and identified the partly independent brain regions underlying them [11-13]. In agreement with this view, in individual cases Direct Electrical Stimulation (DES) during awake surgery led to identify neural sites independently linked to reading or handwriting [14-21]. Nonetheless, based on the premise that both tasks process the same type of information, it has also been argued that components underlying reading and spelling may not be completely independent [22-24]. In reading aloud, orthographic (input) information must be converted into phonological (output) information, while spelling-to-dictation starts with phonological (input) information that needs to be converted into orthographic (output) information. Hence, both skills rely on stored orthographic and phonological knowledge (input/output lexicons in Figure 1.1). Particularly for orthographic word forms, there is an ongoing debate regarding whether these are represented by a shared component or rely on two distinct components for input and output processing [22-28]. In the former case, the orthographic representations involved in reading and in writing would be implemented in a shared neural substrate; and, brain damage should affect both tasks similarly. In the latter case, the two sets of representations might be implemented in distinct neural substrates; and, brain damage should affect reading and spelling to a different extent.

The two views make distinct predictions as regards possible functional outcomes in glioma patients. In the case of independent components, intra-operative assessment of reading would not ensure preservation of spelling, and the reverse should also apply – in other words, assessing only one written language skill would not protect the non-assessed skill. On the other hand, if the neurofunctional representations of orthographic forms are shared, intra-operative monitoring of one skill may ensure preservation of the other. To our knowledge, intra-operative handwriting has been reported only by four research groups [14,15,17,29]. Reading has been evaluated more frequently [20,21,30-32]. In both cases, post-operative functional outcome of reading or of written language in general (reading and spelling) has not been considered carefully. Insight in how the functional preservation of written language may be attained through intra-operative assessment could aid clinical practice (a topic to which we return in the discussion).

In this study, we aim to evaluate how written language may be preserved in glioma patients. Firstly, we inspect to what extent reading and spelling are affected by glioma surgery. Secondly, we inspect the influence of specific intra-operative assessment on the preservation of written language, by comparing reading and spelling outcome in glioma patients who completed different language tasks during surgery.

Methods

Patients

Written language was administered to 18 glioma patients before and after surgery. Patients were included when they: a. had at least 8 years of education; b. were scheduled for surgical resection of a glioma in the language-dominant hemisphere; and c. completed reading and spelling assessments both before and after surgery. To prevent biased evaluations of the incidence of written language deficits after surgery, pre- and post-operative written language performance was not considered as an inclusion criterion in this study. Participants were included regardless of tumor location. Language lateralization was identified by fMRI when possible. Detailed lesion topography was determined by pre-operative T1-weigthed MRI. Histological diagnosis was established by intra-operative biopsies.

Patients were assessed in Dutch or Italian, in the university hospitals of Groningen (the Netherlands), or Brescia or Verona (Italy), respectively. One patient's native language was Albanian, but this patient had lived in Italy for over 15 years, was fluent in Italian and preferred to be tested in Italian. In our participants, pre-operative testing was conducted at 1-83 days before surgery, and post-operative testing within 2 months after surgery. A follow-up evaluation (between 3-8 months post-surgery) was available for 6/18 patients (Table 6.1).

Ethical approval was granted to the study "ClinicoGLIOWRITE" (identification number 2903) by Ethical Committee of Spedali Civili, Brescia. All procedures were in accordance with the ethical standards of the institutional and/or national research committees of the country of each participating member and with the 1964 Helsinki declaration and its later amendments or comparable standards.

Pre- and post-operative assessments

Reading and spelling were evaluated with comprehensive written language batteries (one for Italian, one for Dutch), specifically designed for the assessment of written language in glioma patients. Both batteries are comprised of subtasks that assess words, non-words and sentences, for reading and for spelling. Each task is controlled for psycholinguistic variables (e.g., length, frequency, grammatical class, morphology, orthography and similarity to words) in order to target underlying components of reading and spelling (Figure 4.1, p. 96). Spelling was assessed via handwriting. For both languages, two parallel versions of each battery were administered before and after surgery, to control for repetition and practice effects in the short interval between pre- and post-operative assessments. The Italian test contains 106 words, 52 non-words and 12 sentences for reading, and 99 words, 40 non-words and 11 sentences for spelling. The Dutch test contains 38 words, 12 non-words and 6 sentences for reading, and 31 words, 10 non-words and 5 sentences for spelling. The Written language batteries for glioma patients are described in detail in Chapter 4.

Language assessment also included spoken language tasks developed for glioma patients; an object naming test (ECCO) and action naming test (VISC; Verb production In Sentence Context) [33]. In each patient, the neuropsychological assessment evaluated executive functions, attention, and memory using the Trail Making Test [34], Letter Fluency test [35], Digit Span forward and backward [36,37], 15-Word Test [35]. In addition, 14/18 patients completed the Stroop Test [38], 11/18 patients the Raven Coloured Progressive Matrices [39], 10/18 a Semantic Fluency task [40], and 10/18 the Hospital Anxiety and

Depression Scale to monitor mood [41]. Apraxia was assessed with ideomotor limb and oral praxis tests in 8/18 cases [42]. The Edinburgh Inventory was administered to determine handedness in all patients [43].

Intra-operative assessment

15/18 Patients were selected for awake surgery based on clinical evaluations by the neurosurgical team. To decide on eligibility for awake surgery, suitability for the procedure (e.g., level of emotional stability and anxiety) was considered in each individual. Intra-operative functional mapping was carried out in all patients undergoing awake surgery. DES was applied with a bipolar electrode delivering a biphasic current, with pulse amplitude from 2 to 8 mA. Each procedure started with determination of current intensity, starting from 2 mA until after-discharge was obtained. Cortical mapping initiated with positive functional mapping in combination with electrocorticography to identify sensorimotor areas in each case. Intra-operative language tasks for subsequent (sub)cortical mapping were prepared individually. In all cases, language monitoring included a spoken object naming task (ECCO in Italian [33], and from the Dutch Linguistic Intra-operative Protocol; DuLIP in Dutch [44]).

In selected cases (10/15), subtasks from the written language batteries were monitored intra-operatively. These patients were selected based on pre-operative performance and on tumor location, when gliomas were located in regions known to underlie reading or spelling processes. From the written language battery, words and non-words were used for intra-operative mapping. The participating hospitals followed the temporal limit of 4 seconds to safely apply DES [45,46], hence time for a stimulus-response cycle was constrained during surgery. Sentences were not assessed during stimulation, as data from healthy controls showed that sentences could not be reliably assessed within this time limit (Chapter 4). Since the time constraint does not apply when functions are monitored during resection, sentences and longer spelling stimuli were occasionally administered when intra-operative monitoring continued during surgical removal of the tumor.

For Italian patients, tailored lists of words and non-words from the written language battery were set up for intra-operative use, targeting components at risk in each individual case. An average of 59 Italian words and 41 non-words for reading and 28 Italian words and 12 non-words for handwriting were administered intra-operatively. For Dutch patients, a fixed intra-operative reading battery (55 words and 24 non-words) was used, since the pre-operative task did not include enough items to allow a personalized selection. Handwriting was not assessed intra-operatively in Dutch. A detailed description of intra-operative administration of written language subtasks is provided in Chapter 5 (Methods section *Intra-operative assessment*; Figure 5.5).

Analyses

Incorrect responses were classified using structured scoring forms from the Written language battery for glioma patients (Chapter 4 section *Scoring*; Appendix D). A distinction was made between incorrect responses that result from damage to central processes (*Central* errors) and errors that do not result from damage to central processes (*Other* errors in reading: changes in more qualitative features such as slowed or hesitant reading; *Peripheral* errors in handwriting: qualitative changes in handwriting). In handwriting, responses that could result either from central or peripheral damage (e.g., a dictated *m* written as N) were reported as *Unclassifiable* errors. Only the first response produced by the patient was scored. Reading responses were recorded and original handwriting samples were kept for post-hoc analyses and for qualitative comparisons between assessment times. The neurosurgeon indicated positive mapping sites with numbered tags when Direct Electrical Stimulation of that site yielded 3 consecutive errors. Intra-operatively, all errors, including single and non-reproducible ones (when stimulation did not result in a positive mapping site), were marked by the neuropsychologists and kept for post-hoc evaluations. A camera in the microscope recorded a picture of the tags when (sub)cortical mapping was completed.

On all subtasks, error rates were calculated and descriptive statistics were used to establish if error rates fell above (impaired) or below (preserved) cut-off according to normative data. At a group level, changes between assessments before and after surgery on specific tests were analyzed by Wilcoxon Rank Sum test. Individual changes between assessments were analyzed by Fisher's Exact Test. To inspect differences between surgical groups, demographics, tumor characteristics and cognitive profiles were compared using Generalized Linear Models (for continuous variables; e.g., age) and Fisher's Exact Test (for non-continuous variables; e.g., tumor type). Performance on language tasks in different surgical groups was analyzed by Wilcoxon Rank Sum test. All statistical analyses were conducted in R using *stats*, *gmodels* and *nnet* packages [47-49]. A significance level of $p< 0.05$ was used throughout the study.

6

Results

Demographic, tumor and surgical characteristics of 18 glioma patients (11 males, M_{age} = 41.4 years) are presented in Table 6.1. Of the 18 patients, 15 underwent surgery with local anesthesia and 3 were operated under general anesthesia.

As a first step, written language outcome after glioma surgery was evaluated. For these analyses, only assessments carried out one week after surgery were considered, as in the first week aspecific effects of surgery (e.g., edema, fatigue, medical therapy, seizures) may interfere with a reliable evaluation of outcome [50,51]. In case of multiple

Table 6.1 Demographic, tumor and surgical characteristics of glioma patients who underwent pre- and post-operative written language assessment (n=18)

Patient	Age	Gender	Education (years)	Hand preference	Tumor type (WHO grade)	Lesion site	Extent of resection	Timing of assessment (days from surgery) Pre	Post	Follow-up	Intra-operative assessment	Language assessed
1	44	M	13	Right	Anaplastic astrocytoma (III)	Left posterior MFG	Supratotal	1	21	-	ON + Reading + Spelling	Italian
2	74	F	8	Right	Glioblastoma (IV)	Left posterior MTG/ITG	Total	9	9	124	ON + Reading + Spelling	Italian
3	38	M	16	Right	Glioblastoma (IV)	Left MFG / SFG	Total	1	46	-	ON + Reading	Italian
4	29	F	14	Left	Astrocytoma (II)	Left F-I-T	Partial	14	-	97	ON + Reading	Dutch
5	63	F	16	Right	Astrocytoma (II)	Left SMG (- anterior perisylvian)	Subtotal	38	1, 17	77, 172	ON + Reading	Dutch
6	41	F	15	Left	Glioblastoma (IV)	Left STG	Total	4	3	-	ON + Reading	Dutch
7	43	F	20	Right	Astrocytoma (II)	Left STG, T pole, I	Subtotal	1	-	189	ON + Reading	Dutch
8	58	M	16	Right	Oligodendroglioma (II)	Left T pole, I	Partial	83	36	-	ON + Reading	Dutch
9	26	F	13	Right	Oligodendroglioma (II)	Left post ITG	Subtotal	11	-	139	ON + Reading	Dutch
10	34	F	8	Right	Astrocytoma (II)	Left PreCG / posterior MFG	Total	4	3	-	ON + Spelling	Italian
11	28	M	12	Left	Astrocytoma (II)	Right Frontobasal	Total	26	51	-	ON	Dutch
12	29	M	15	Right	Astrocytoma (II)	Left PreCG / posterior MFG	Total	40	58	-	ON	Dutch
13	32	M	12	Right	Astrocytoma (II)	Left F-P (SMG)	Subtotal	11	41	-	ON	Dutch
14	44	M	15	Right	Astrocytoma (II)	Left SMG	Subtotal	2	19	-	ON	Italian
15	27	M	16	Right	Oligoastrocytoma (II)	Left T-I	Subtotal	20	-	225	ON	Dutch
16	56	M	17	Right	Glioblastoma (IV)	Left posterior ITG	Subtotal	2	16	-	*Asleep*	Italian
17	47	M	13	Right	Glioblastoma (IV)	Left MTG	Total	3	30	-	*Asleep*	Italian
18	32	M	8	Right	Anaplastic astrocytoma (III)	Left T-I	Total	4	27	-	*Asleep*	Italian

Pre = pre-operative assessment, Post = post-operative assessment, Follow-up = follow-up assessments; M = male, F = female; RH = right-handed, LH = left-handed; F = Frontal, SFG = Superior Frontal Gyrus, MFG = Middle Frontal Gyrus, PreCG = Precentral Gyrus, P = Parietal, SPL = Superior Parietal Lobe, SMG = Supramarginal Gyrus, T = Temporal, STG = Superior Temporal Gyrus, MTG = Middle Temporal Gyrus, ITG = Inferior Temporal Gyrus, I = Insula; ON = object naming assessments after surgery (post-operative and follow-up), the longest available follow-up was considered. Such assessments were available for 16/18 patients (Table 6.1; Cases 6 and 10 were excluded from these analyses). Written language outcome was inspected for all patients conjointly.

Secondly, the influence of intra-operative assessment on written language performance was evaluated. For these analyses, only the 15 patients who underwent awake surgery were considered (Table 6.1). To inspect the direct influence of intra-operative assessment of language skills (or the lack thereof), we focused on the earliest post-operative assessments (including those carried out during the first week). The patients included in the analyses of early post-operative performance were assessed with different intra-operative tasks; spoken language only (n=5), or both spoken and written language (including reading and/or spelling tasks; n=10).

Written language before and after glioma surgery

Reading and spelling outcome (>1 week post-operatively) was contrasted with pre-operative performance. At the group level (n=16), error rates increased for all error types on all written language subtasks, except for Unclassifiable errors on sentence spelling (Figure 6.1). Pre- to post-operative error increases in spelling words were (marginally) significant for Central (M_{pre}= 4.9%, M_{post}= 9.2%, p= .050) and Peripheral errors (M_{pre}= 3.1%, M_{post}= 6.7%, p= .007). None of the differences between pre- and post-operative reading error rates were significant (p> .05). Error percentages also increased in spoken language tasks; both in object naming (M_{pre}= 5.2%, M_{post}= 8.7%) and action naming (M_{pre}= 6.3%, M_{post}= 9.2%). Yet, these changes were not significant (p> .05).

Error rates indicated written language impairments before and after glioma surgery (Table 6.2). When compared to cut-off values, pathological performance in spelling was mainly observed pre- and post-operatively on words and sentences (in up to 7/16 cases, or 43.8%), and less frequently on non-words (in up to 3/16 cases, or 18.8%). Central error rates were most frequently pathological. In reading, Central errors were also most frequently above cut-off. More varied error patterns were observed across subtasks. Before surgery, pathological performance was mainly observed on non-words and sentences (both in 5/16 cases, or 31.3%), while post-operatively words and sentences were impaired in 5/16 cases (31.3%). As a comparison, pre-operative object naming was impaired in 1/16 cases (6.3%) and action naming was normal in all 16 patients. Post-operative impairments were observed in 5/16 cases on object naming (31.3%) and in 4/16 cases on action naming (25.0%).

Comparisons between pre- and post-operative performance, both based on error rates and on number of impaired patients, disclosed deterioration in reading and spelling performance on all subtasks at the group level. Yet, not all patients went from normal to pathological scores, as also improved performances (i.e., pathological pre-operative score, but normal post-operative performance) were observed at the individual level. Improvements in Central errors were more frequently observed in reading tasks (in 4/16 patients, or 25.0%), than in spelling (in 2/16 patients, or 12.5%). Other / Peripheral impairments mainly improved in spelling (in 3/16 patients, or 18.8%; compared to 1/16, or 6.3%, in reading).

Table 6.2 Incidence of pathological scores on reading and spelling tasks, before and >1 week after surgery

		Impaired number of patients (%)	
Language task	**Type of errors**	**Before surgery**	**> 1 week After surgery**
Spelling			
Words	Central errors	5 (31.3)	7 (43.8)
	Peripheral errors	4 (25.0)	7 (43.8)
	Unclassified errors	3 (18.8)	4 (25.0)
Non-words	Central errors	3 (18.8)	3 (12.5)
	Peripheral errors	3 (18.8)	3 (18.8)
	Unclassified errors	2 (12.5)	2 (12.5)
Sentences	Central errors	7 (43.8)	7 (43.8)
	Peripheral errors	5 (31.3)	6 (37.5)
	Unclassified errors	4 (25.0)	4 (25.0)
Reading			
Words	Central errors	3 (18.8)	5 (31.3)
	Other errors	2 (12.5)	2 (12.5)
Non-words	Central errors	5 (31.3)	4 (25.0)
	Other errors	1 (6.3)	4 (25.0)
Sentences	Central errors	5 (31.3)	5 (31.3)
	Other errors	1 (6.3)	2 (12.5)
Spoken naming			
Object naming		1 (6.3)	5 (31.3)
Action naming		0 (0.0)	4 (25.0)

All patients in Table 6.2 completed the Written language battery before and at least 1 week after surgery for glioma resection. Patients who underwent awake (n= 13) and asleep (n= 3) surgery are presented conjointly. Pathological performance was identified on the basis of cut-off scores obtained by matched controls. Performance obtained on the pre-operative assessment and on the last available post-operative assessment is presented.

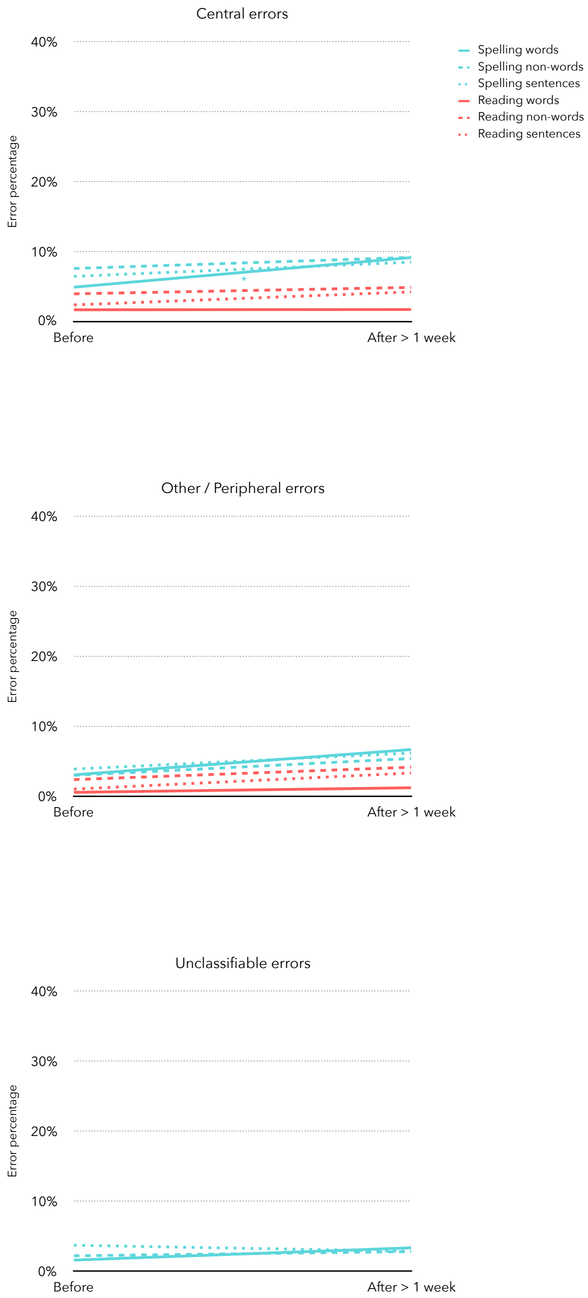

Figure 6.1 Written language performance before and after glioma surgery (n=16). All patients included completed all reading and spelling subtests pre-operatively and at least one week post-operatively. Mean percentage values are reported. * Significant difference between pre- and post-operative assessments on separate subtests (Wilcoxon Rank Sum test, $p < .05$) level.

Influence of intra-operative assessment

To establish the role of intra-operative assessment in the preservation of written language skills, the performance in reading and spelling during the intra-operative assessment was evaluated in the 15 glioma patients who underwent awake surgery. All patients were assessed intra-operatively for spoken language skills. Ten (*ASws*) were assessed intra-operatively with written and spoken language tasks and 5 (*ASs*) only with spoken language tasks. In the *ASws* group, assessment was limited to reading in 7/10 subjects; the remaining participants were tested with both reading and spelling tasks (2/10), or only with the spelling task (1/10). In total, during surgery 9 patients were assessed with reading and 3 with spelling (Table 6.1).

Written vs. spoken language tasks

Data from the 10 *ASws* patients and from the 5 *ASs* patients were compared. Before surgery, performance of the two groups on reading and spelling tasks was statistically indistinguishable ($p > .05$). After surgery, the patients who had not received an intra-operative assessment of written language (*ASs)* had higher Central, Peripheral and Unclassifiable error rates on most reading and spelling tasks than those tested with written language tasks during surgery (*ASws*), but differences failed to reach significance ($p > .05$). Insignificantly higher error rates in the *ASws* than in the *ASs* group were observed in non-word spelling and sentence reading (Central errors), and in word and sentence reading (Other errors).

Yet, differences and distinct patterns across tasks were observed as concerns the incidence of pathological scores (Tables 6.3a & 6.3b). Compared to *ASws*, patients in the *ASs* group showed more pathological numbers of Central errors on all reading subtasks after surgery (Table 6.3b). Other errors were uncommon in both groups. In spelling, Central errors in sentences were more frequently pathological in the *ASs* group, but impairments on word and non-word spelling were more common in the *ASws* group (Table 6.3a). High numbers of Peripheral and Unclassifiable errors in spelling were most frequently observed across subtasks in patients of the *ASs* group.

Spoken language tasks were affected to the same extent in *ASws* and *ASs* patients ($p > .05$). In both groups, spoken language was intact in all cases pre-operatively, and impaired in one participant post-operatively (*ASws*: 1/10, or 10.0%; *ASs*: 1/5, or 20.0%).

To evaluate the influence of intra-operative assessment in more depth, written language performance was inspected over time in the 6 cases (out of 15) who did not receive specific intra-operative assessments of reading or spelling. A significant post-operative decline in Central error rates (combined for words, non-words and sentences) was observed for 1/6 subjects (16.7%; Figure 6.2). Of the 12 subjects who did not receive an intra-operative assessment of spelling, 3 (25.0%, Figure 6.2) showed a significant decline. We describe Patient 14 as an illustrative case.

Patient 14 is an Italian, 44-year-old right-handed male with an astrocytoma (WHO grade II) in the left supramarginal gyrus. Before surgery, difficulties were observed in handwriting and reading, but not in spoken language tasks. Awake surgery was performed with intra-operative monitoring of spoken object naming, but not of written language. Post-operative assessment at 19 days after surgery revealed significantly declined performance in handwriting (Central errors pre: 14.7%, post: 29.1%, p= .001) and reading (Central errors pre: 3.1%, post: 8.8%, p= .014), whereas spoken object naming performance remained stable (errors pre: 1.8%, post: 10.7%, p= .113). Hence, in this case, intra-operative testing of oral picture naming allowed preserving spoken language, but not written language tasks.

Reading vs. spelling tasks

The influence of specific written language assessment was further evaluated in 10 patients in whom written language was assessed during awake surgery. These patients were assessed for reading only, for spelling only, or for both reading and spelling. We inspected the performance of patients who were assessed with reading during surgery (n= 9), and of those assessed with spelling (n= 3). Two patterns of written language preservation after intra-operative assessment were considered. Illustrative cases are described for both types.

First, *task-specific preservation* was considered. For each written language task, we evaluated changes of performance accuracy after surgery. Pre-operative scores served as baselines for individual comparisons. When pre- and post-operative Central error rates (collapsed across words, non-words and sentences) were considered, reading accuracy did not decrease post-operatively in 9/9 patients whose reading had been assessed pre-operatively, and the same was true for spelling in 3/3 patients whose handwriting skills had been monitored during surgery (Figure 4). The case of Patient 1 is presented as an example.

Patient 1 is an Italian, 44-year-old right-handed male with an anaplastic astrocytoma (III) in the left posterior middle frontal gyrus. Intra-operative cortical mapping at 3mA identified positive sites in the posterior superior frontal gyrus (interfering with object naming), and in the posterior middle frontal gyrus (interfering with spelling words). No errors in word and non-word reading were elicited during stimulation. Positive sites were spared during supratotal resection of the tumor. Three weeks after surgery, pre-operative performance accuracy had not changed for spelling (Central errors pre: 10.3%,

Table 6.3a Incidence of pre-operatively and post-operatively pathological scores on reading and spelling tasks in patients whose written language was monitored during surgery (*ASws* group; n=10)

		Impaired number of patients (%)	
Written language task	**Type of errors**	**Pre-operative**	**Post-operative**
Spelling			
Words	Central errors	3 (30.0)	5 (50.0)
	Peripheral errors	2 (20.0)	2 (20.0)
	Unclassified errors	1 (10.0)	0 (0.0)
Non-words	Central errors	2 (20.0)	3 (30.0)
	Peripheral errors	1 (10.0)	0 (0.0)
	Unclassified errors	1 (10.0)	1 (10.0)
Sentences	Central errors	4 (40.0)	4 (40.0)
	Peripheral errors	5 (50.0)	2 (20.0)
	Unclassified errors	1 (10.0)	1 (10.0)
Reading			
Words	Central errors	3 (30.0)	3 (30.0)
	Other errors	3 (30.0)	1 (10.0)
Non-words	Central errors	2 (20.0)	1 (10.0)
	Other errors	0 (0.0)	2 (20.0)
Sentences	Central errors	2 (20.0)	2 (20.0)
	Other errors	1 (10.0)	1 (10.0)

Table 6.3b Incidence of pre-operatively and post-operatively pathological scores on reading and spelling tasks in patients whose written language was not monitored during surgery (*ASs* group; n=5)

		Impaired number of patients (%)	
Written language task	**Type of errors**	**Pre-operative**	**Post-operative**
Spelling			
Words	Central errors	1 (20.0)	2 (40.0)
	Peripheral errors	1 (20.0)	2 (40.0)
	Unclassified errors	2 (40.0)	1 (20.0)
Non-words	Central errors	1 (20.0)	1 (20.0)
	Peripheral errors	1 (20.0)	2 (40.0)
	Unclassified errors	1 (20.0)	1 (20.0)
Sentences	Central errors	2 (40.0)	3 (60.0)
	Peripheral errors	1 (20.0)	2 (40.0)
	Unclassified errors	2 (40.0)	1 (20.0)
Reading			
Words	Central errors	0 (0.0)	2 (40.0)
	Other errors	0 (0.0)	0 (0.0)
Non-words	Central errors	2 (40.0)	1 (20.0)
	Other errors	1 (20.0)	1 (20.0)
Sentences	Central errors	2 (40.0)	2 (40.0)
	Other errors	0 (0.0)	0 (0.0)

All patients in Table 6.3a received intra-operative assessment of reading and/or spelling subtasks, in addition to spoken language assessment. Patients in Table 6.3b completed intra-operatively only spoken language tasks. Pathological performance was identified on the basis of cut-off scores obtained by matched controls. Performance obtained on the pre-operative assessment and on the first available post-operative assessment is presented.

post: 7.7%, p= .479), reading (Central errors pre: 3.6%, post: 5.9%, p= .360) and action naming (errors pre: 0.0%, post: 4.3%, p= .245), while spoken object naming accuracy had decreased (errors pre: 0.0%, post: 8.8%, p= .057). Hence, task-specific preservation was successful for the intra-operatively administered written language tasks, yet just marginally for the intra-operatively assessed spoken language tasks.

Secondly, *generalization of preservation* through intra-operative assessment was considered. We wished to evaluate whether intra-operative monitoring of one language skill sufficed to ensure preservation of the other – e.g., if intra-operative testing of reading only ensured post-operative sparing of *both* reading and spelling. Of 10 patients tested with written language tasks during surgery, 7 were assessed only with reading. While reading was preserved in all cases, 2/7 patients (28.6%) showed a significant decline in spelling (see the illustrative case of patient 10). The only patient who was tested intra-operatively only with handwriting showed no significant post-operative decline in either spelling or reading.

Patient 10 is a Dutch, 41-year-old left-handed female who underwent awake surgery for a glioblastoma (IV) in the left superior temporal gyrus with gliosis in fronto-temporal regions towards the insula. fMRI indicated left hemispheric lateralization of language. Pre-operative assessment showed preserved reading and spelling. Intra-operatively, reading was monitored during subcortical resection, after mapping with spoken naming tasks. No errors were observed during word and non-word reading. During sentence reading, stress placement errors and word-level errors emerged, which suggested terminating tissue removal. Post-operative MRI showed total tumor resection. Three days after surgery, reading was preserved (Central errors pre: 2.6%, post: 2.6%, p= 1.000), whereas spelling accuracy declined significantly as compared to the pre-operative assessment (Central errors pre: 0.0%, post: 14.3%, p= .001). In this subject, intra-operative monitoring of reading successfully preserved reading accuracy, but did not suffice to preserve spelling.

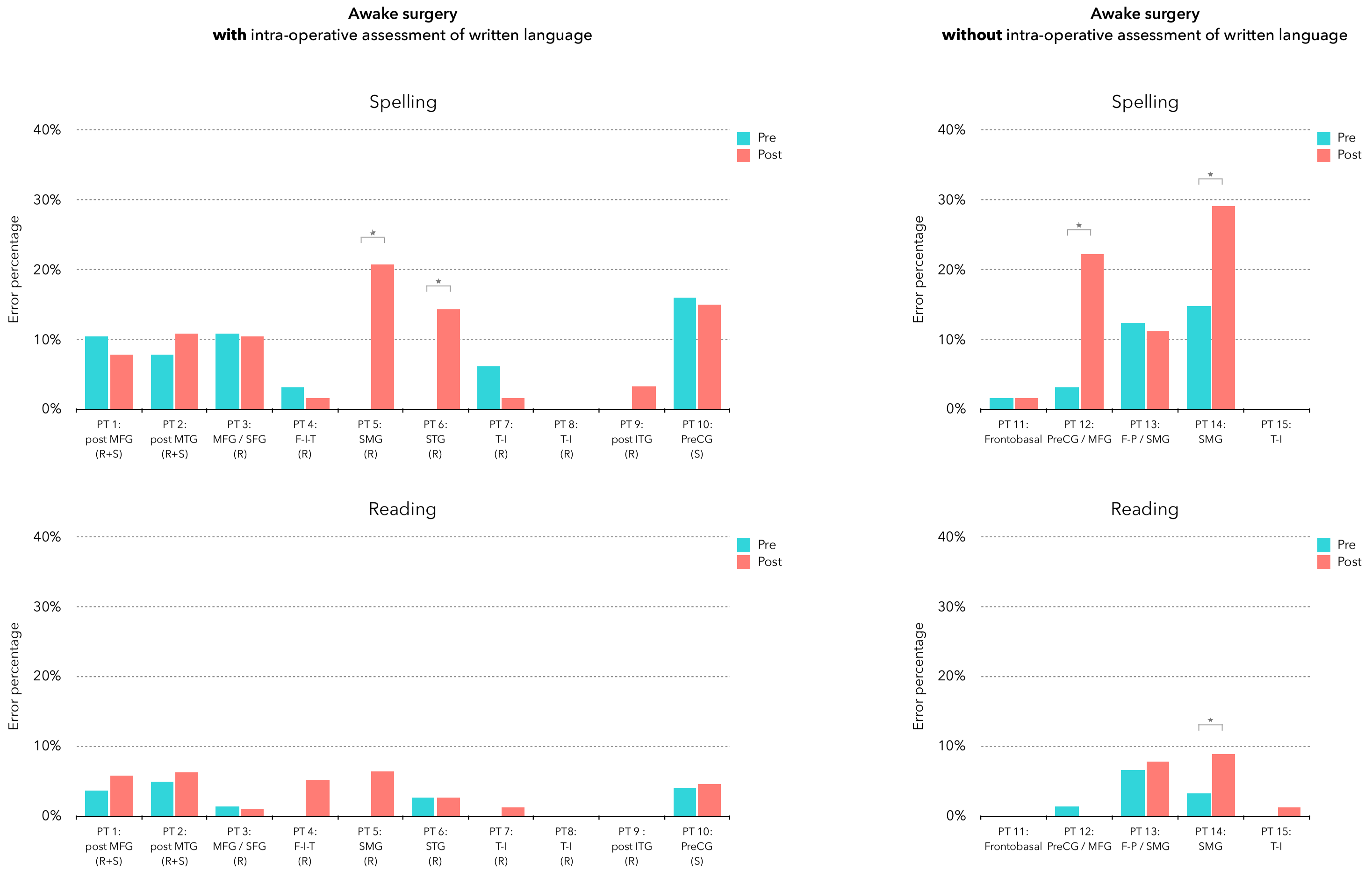

Figure 6.2 Individual performance on written language tasks before and immediately after awake surgery, in patients assessed intra-operatively. Fifteen patients underwent awake surgery for glioma resection. All 15 patients completed the intra-operative assessment of spoken language tasks. Of these 15 patients, 10 were assessed intra-operatively with written language tasks. Two completed both reading and spelling (R+S), seven only reading (R), and one only spelling (S). In the remaining 5/15, written tasks were not assessed intra-operatively. Central overall error rates (collapsed across words, non-words and sentences) before and after surgery (first post-operative assessment available) are presented for each patient. Absence of a visible bar represents an error rate of 0.0%. * Significant difference between individual error rates on pre- and post-operative assessments (Fisher's Exact Test, $p < .05$)

Discussion

Attention to reading and spelling in neurosurgical practice has been scarce. It is still largely unclear how these functions are affected by glioma surgery and how preservation of written language may be achieved in awake surgery practice. To evaluate the role of intra-operative assessments in this endeavor, tools specifically constructed for the assessment of cognitive skills in glioma were administered to 18 patients. All participants completed reading and spelling tasks as well as spoken picture naming tasks, pre- and post-operatively.

Written language outcome was investigated in 16/18 patients, whose post-operative assessment took place at least one week after surgery. Of these 16, 13 were operated awake and 3 during general anesthesia. We evaluated performance on reading and spelling tasks relative to spoken naming tasks.

Secondly, the influence of specific intra-operatively assessed tasks on written language performance was investigated. These analyses were conducted among in all 15 patients who underwent awake surgery, including the 13 subjects considered in the previous analyses, plus 2 patients for whom only early post-operative evaluations were available (Patients 6 & 10; Table 6.1). Written language was assessed intra-operatively in 10 cases. Of these, 7 were assessed only for reading, 1 only for spelling, and 2 for both reading and spelling. We evaluated whether the intra-operative assessment of a written language task aids the preservation of the skill assessed during surgery (*task-specific preservation*). Moreover, we evaluated whether intra-operative monitoring of one written language skill (i.e., only reading or only spelling) sufficed to ensure preservation of the other, untested task (*generalization of preservation*). In particular, we examined if sparing of both reading and spelling could be achieved by testing only reading.

Written language in glioma surgery practice

Assessments of written language by means of short clinical tasks showed that reading and spelling are often affected before and after surgery for glioma treatment (Chapter 2 and 3). Detailed evaluations with a more extensive battery confirm these findings. Substantial pre- and post-operative impairments in reading and spelling were found in glioma patients undergoing awake and asleep surgery. Pre-operatively, pathological numbers of Central errors were observed in 8/16 patients (50.0%) in at least one spelling subtask, and in 6/16 (37.5%) patients in at least one reading subtask. Spoken language tasks, on the other hand, were impaired in only 1/16 patients (6.3%) before surgery. Post-operatively (>1 week after surgery), impairments were more frequent in written than in spoken language tasks. Pathological numbers of Central errors on spelling and reading subtasks were present after surgery in 8/16 (50.0%) and 7/16 patients (43.8%) respectively. By contrast, post-operative damage to spoken language was observed in only 3/16 cases (18.8%).

Although the number of impaired participants did not increase substantially from pre- to post-operative assessment, performance accuracy did deteriorate after surgery on all language tasks, congruent with the literature on post-operative performance on other cognitive functions in glioma patients [52-54]. In our sample, the decline was significant only for word spelling (Central & Peripheral errors). The incidence of written language impairments as shown by our test battery (specifically developed for glioma patients) supports the notion that reading and spelling are frequently affected after glioma surgery. Differences between written and spoken tasks moreover confirm that written and spoken language may be affected independently, as they rely on at least partly distinct neurofunctional substrates [10].

Within written language, differences were observed between reading and spelling outcome. After surgery, Central errors indicated combined pathological performance on both a reading and a spelling subtask in 5/16 patients (31.3%), while 3/16 (18.8%) had isolated spelling impairment and 2/16 (12.5%) cases were only impaired in reading. Pathological numbers of Peripheral/Other errors on both a reading and a spelling task were observed in 3/16 (18.8%), compared to isolated pathological scores on Peripheral spelling errors in 5/16 (31.3%) and on Other reading errors in 2/16 (12.5%). Differences between reading and spelling tasks converge with theories on independent neural substrates of reading and spelling [11-13].

Preservation of written language through specific intra-operative assessment

Although improved quality of life has been reported after awake surgery [1-3], and only small numbers of errors were found due to careful neurosurgical procedures, language impairments were nevertheless observed after awake surgery, even with intra-operative assessment. Yet, data showed that an expected increase in difficulties could be either fully controlled or effectively restricted after intra-operative monitoring. To better understand how written language may be more efficiently spared, the value of intra-operative assessment was evaluated in greater detail by contrasting different types of testing during surgery.

Given the difference in neural and functional substrates of spoken and written language, it was first inspected if reading and spelling performance differed between patients who received intra-operative assessment of spoken and written language or of spoken language only. Pre-operatively, performance on all language tasks was statistically indistinguishable in the two groups. Shortly after surgery, error rates on spoken language tasks (monitored intra-operatively in all cases) were also indistinguishable between groups. Thus, patients who underwent awake surgery with or without written language testing had comparable performance on these parameters. On written language tasks, however, clear (albeit insignificant) differences were observed. Patients in whom written language (reading and/or spelling) was monitored intra-operatively showed better outcome than patients in whom it was not monitored. Written language impairments were more common after surgery without intra-operative written language monitoring. Yet, word and non-word spelling were marginally more often impaired in the group with intra-operative written language monitoring. At the group level, the outcome of reading and spelling skills would seem to improve when written language is added to the intra-operative assessment, even though this study provides only partial evidence in support of this.

Data inspection revealed large across-subject variations (Figure 6.2), which may possibly account for the lack of significant differences across the groups with and without written language assessment during surgery. Written language preservation was therefore further inspected in individual cases. In addition to comparing spoken and written language assessments, we contrasted the outcome of the intra-operative assessment of reading, of spelling, and of both. Improved written language outcome following awake surgery with written language monitoring may suggest that preservation of reading and spelling functions may be combined. In that case, assessment of a written language task (for example reading) would aid preservation of both written language tasks (reading and spelling). Such a generalization of preservation would be consistent with theories that posit shared neural substrates of reading and spelling, which predict that monitoring one task would allow simultaneous monitoring of two skills (reading and writing) [22,24,55]. We were particularly interested to see if generalization of preservation could be obtained by assessing reading only. Reading is a less demanding task to assess intra-operatively than handwriting. Hence if it were possible to preserve both reading and spelling by assessing just reading, an intra-operative assessment restricted to reading alone would be welcome. This was not the case. Almost one-third of the patients tested with intra-operative reading (28.6%) showed preserved reading after surgery, but a significant decline in spelling. Converging with research demonstrating independent components underlying reading and spelling [11-13], and illustrating selective deficits in only reading or only spelling following damage to certain brain regions [12,22,56-59], the failure to generalize preservation to spelling after monitoring reading provides indirect evidence for (partly) independent processing of reading and spelling. In patients in whom spelling impairments were observed after intra-operative reading, resected areas were critical for a spelling-specific component. In these cases, spelling could have been spared if specifically assessed intra-operatively. Although data do not yet allow comparisons of patients with same lesions but different intra-operative written language assessments, investigations into task-specific preservation shed light on this hypothesis.

To inspect the influence of specific intra-operative assessment on the preservation of a specific written task, reading and spelling performance was evaluated over time for each patient. We examined whether tasks monitored intra-operatively changed significantly from pre- to post-operative assessment. In all cases, task-specific preservation was successful; converging with the literature [32,60], reading was preserved in 8/8 patients, and handwriting in 3/3 patients. Yet, in line with the lack of generalization of preservation, significant declines after awake surgery were observed in 16.7% of the cases not tested for reading, and in 25.0% of the cases not tested for writing. When a certain skill needs to be preserved, intra-operative assessment of that skill is strongly advised.

Implications for intra-operative assessment

Results demonstrate that assessing spoken language does not always suffice to preserve all communicative abilities in individuals with gliomas in language areas, but also that task-specific preservation is successful. This may imply that many tasks must be administered intra-operatively, including reading and spelling, in order to spare functional outcome. However, since awake procedures are subjected to time restrictions [45,46], intra-operative assessment must be limited to a small number of short tasks. Therefore, to preserve quality of life in the individual patient, the intra-operative assessment must be tailored and targeted to the needs of each case.

For each patient, functions at risks should be identified before surgery. Detailed pre-operative evaluations with sensitive test batteries for glioma patients can be used to diagnose damage to components of reading and spelling (Chapter 5). As each component is known to be sensitive to certain psycholinguistic variables (Chapter 1 and 2; Figure 4.1), these processes can be pinpointed separately by appropriate testing. Identifying components at risk may guide the selection of tasks and stimuli for intra-operative assessment, to facilitate short and targeted testing aimed at task-specific preservation. In addition, knowledge about the neurofunctional correlates of written language may be used to identify the components at risk in the specific patient, given the location of the glioma (Chapter 7). Intra-operative mapping should probe those components.

The distinction between reading and spelling outcome has clear implications for intra-operative testing. Since results show that an assessment of reading may not suffice to preserve spelling, both skills should be assessed. Therefore, the intra-operative assessment of spelling is strongly advisable in order to preserve quality of life in patients at risk of dysgraphia. This and previous studies have demonstrated that intra-operative handwriting is feasible [14-16,18,19,29,61] (see also Chapter 5).

Conclusions

The current study inspected the value of intra-operative assessments in the preservation of written language. Use of a detailed cognitive assessment battery showed that substantial reading and spelling impairments may arise before and after glioma surgery, and that written language may be differently affected as compared to spoken language. More positive outcomes after awake surgery procedures that included the assessment of written language, as compared to awake surgery without written language assessment, support the notion that intra-operative assessment helps preserve reading and spelling. Post-operative evaluations after awake surgery with intra-operative monitoring showed that written language can be preserved via task-specific intra-operative assessment. Yet, non-monitored written language tasks may not be preserved. Targeted intra-operative assessments are strongly advised for each task at risk, to preserve quality of life in the individual patient.

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7

On interpreting performance on written language tasks in glioma patients undergoing awake surgery: Lesion site, cognitive profiles, and timing of assessments

Abstract

Reading and spelling may be affected in glioma patients undergoing awake surgery. Yet, interpretations of patient's written language performance may be influenced by specific parameters in glioma practice. Glioma patients represent a heterogeneous group, in which demographic, tumor and treatment characteristics may vary for each individual patient. We inspected to what extent tumor locations, cognitive profiles, and timing of assessments may be associated with written language outcome in glioma patients undergoing awake surgery. Knowledge from lesion and neuroimaging studies succeeded in most cases to predict error profiles in reading and spelling given the specific glioma location. In line with reports of other cognitive functions, pre- and post-operative written language performance was related to timing of assessments, yet the relation with impairments on other cognitive domains could not be established. These results connote that knowledge about the neural correlates of reading and spelling can be exploited to guide intra-operative assessment. Subsequent interpretations of written language performance require careful considerations of individual parameters. For accurate interpretations of written language performance in glioma patients undergoing awake surgery, it is therefore central to evaluate each patient individually and longitudinally.

Introduction

The gold standard in treatment for glioma patients is awake surgery, which allows resection of tumor tissue while preserving cognitive functioning and quality of life [1-4]. Nonetheless, cognitive and linguistic impairments are still commonly reported following glioma surgery [5-8]. While relatively little attention has been paid to written language in the literature on awake surgery, available data show that written language may also be affected in glioma patients (Chapters 3 and 6). Vast individual differences have been observed across patients. As glioma patients form a heterogeneous group, with variable demographic, tumor, and treatment characteristics, these parameters may influence cognitive functioning to a different extent in individual patients. In this study, we aim to establish to which extent specific parameters may influence written language in glioma practice.

A profound difference among glioma patients undergoing awake surgery is tumor location, and thus the neural regions affected by the glioma or by glioma resection. Lesion and neuroimaging studies have provided insight in the cognitive/linguistic architecture of reading and spelling, and have identified relatively circumscribed brain areas for each component (see Chapter 1 for reading, and Chapter 2 for spelling). Such knowledge can be applied to identify functions at risk given the lesion site. Predictions on which functional component(s) are likely to be damaged by a glioma in a specific brain region could be employed in neurosurgical practice, to make intra-operative assessments be more time-effective, informative, and tailored for the individual patient. This would assist intra-operative testing and bring into focus the variables that should be assessed intra-operatively to ensure sparing of the component at risk (Chapter 6). Current knowledge on the neural correlates of reading and spelling is mostly based on stroke patients and functional neuroimaging studies with healthy controls, but has not been systematically studied in glioma patients. Gliomas differ from cerebrovascular accidents with regards to onset (sudden for stroke vs. slow for glioma) and distribution of damage (constrained by vascular territories and typically destroying gray and white matter in stroke vs. infiltrating white matter pathways in glioma). Moreover, glioma patients differ from individuals with other neurological conditions and from healthy populations under specific respects. Pre-operative plasticity may have been induced more effectively in slow-growing, low-grade gliomas than in fast-growing, high-grade tumors, thus yielding changes in the neural implementation of the cognitive skill at hand. Given these differences, it may be unclear whether knowledge from neurofunctional studies can be applied to glioma practice. Retrospective studies (Chapter 2) and a pilot study in two high-grade glioma patients (Chapter 5) suggest that knowledge from extant literature may be consistent with observed written language performance. Yet, it remains unknown whether this applies to glioma cases at large, including low-grade gliomas.

Apart from lesion location, gliomas differ in grade and histology. These characteristics may also influence individual performance, as more aggressive (high-grade) gliomas have been associated with worse functional outcome than low-grade gliomas [7], yet not across all studies [6]. Regardless of grade, glioma patients often receive adjuvant therapies after surgery, including radiotherapy and chemotherapy. These affect the brain (directly or indirectly), and may influence cognitive functioning [7,9-12]. Patient's performance may also be influenced by demographics, as previously established for age, gender and education [13-16]. For example, older age and lower education have been associated with poor cognitive outcome. Hence, demographic, tumor and treatment characteristics should be considered when evaluating cognitive performance in neurosurgical practice. Correspondingly, most studies reporting on cognitive or linguistic performance in glioma patients take account of these parameters. Yet, additional variables considered less consistently, may be particularly important for the evaluation of written language.

Performance on written language tasks may be influenced by non-linguistic, cognitive processes. Although some components are specific to reading or spelling, others are shared by different cognitive functions. For example, aphasia research has shown that other domains, like attention, working memory and executive functions, are critical for many language tasks [17,18]. Language deficits in stroke patients have often been shown to co-occur with non-linguistic impairments [17-19], just as, in turn, linguistic deficits can influence performance on other neuropsychological tasks that require an implicit or explicit verbal component [17]. Congruent with observations in other neurological populations, glioma patients frequently present impairments of executive functioning, attention and memory, both before [20] and after surgery [5,6,21-23], in addition to more commonly described language impairments [8,24-26]. Specific correlations between performance in language tasks and in other cognitive tasks have been rarely investigated in this patient population. Direct electrical stimulation of cortical regions during glioma surgery has revealed neural substrates shared by linguistic and non-linguistic functions [27-29]. For example, stimulation of the inferior frontal gyrus disrupted performance on both object naming and digit span (i.e., working memory) tasks [30].

With regard to reading and spelling, some specific components are expected to be influenced by other cognitive functions. As described in Chapters 1 and 2, accurate reading and spelling require the integrity of graphemic and phonological short-term (buffer) systems. These temporarily keep active strings of graphemes and phonemes, while subsequent stages of reading and spelling are completed. Buffer systems operate as working memory systems, which are also needed for other (non-linguistic) tasks. Yet, it is still unclear if the same working memory systems are used for different tasks. Working memory impairments frequently co-occur with linguistic deficits [6,31,32], yet selective damage to the graphemic buffer has been documented in presence of spared performance on phonological working memory tasks [33-37]. In patients with damage to other working memory tasks, the possibility that deficits affect multi-purpose buffers should be considered. Accurate written language output requires also intact orthographic and phonological long-term memory systems (lexicons), storing orthographic and phonological knowledge about familiar words [33-35]. However, also for long-term memory it remains largely unclear how systems that play a role in other cognitive functions are related to those of reading and spelling.

In addition to demographic, tumor and treatment variables, the timing of post-operative assessments is a possible confounding dimension in the evaluation of written language in glioma patients. The schedule of post-operative and follow-up evaluations varies greatly across and within centers (Chapters 2, 3, 6). In the first week to ten days after surgery, surgical effects (e.g., edema, fatigue, medical therapy, seizures) may influence cognitive functioning to such extents that reliable evaluations of outcome may become problematic [38,39]. Assessments conducted in such subacute stage can be difficult to interpret when trying to accurately estimate post-operative performance. However, this variable has not been considered systematically. With regard to post-operative evaluations after the subacute phase, the role played by assessment timelines remains unclear. Cognitive impairments have been observed to persist up until 3 months [6,40], but not after a year [21]. Performance returning to pre-operative baseline has been more frequently reported in long-term assessments, yet definitions of "long-term" vary from 3 months [23,40,41] to 3 years [42].

In short, interpretations of written language performance in glioma patients undergoing awake surgery may be complicated by many variables. In this study, we aim to establish to which extent evaluations of reading and spelling are influenced by tumor, neuropsychological and treatment characteristics. First, we examine reading and spelling performance given different glioma locations, to explore if knowledge from neurofunctional studies may be applied to glioma practice to guide and tailor individual assessments. Second, we evaluate associations between written language performance and patients' cognitive profiles, to constrain accurate interpretations of test results. Finally, we contrast written language performance in three different phases after surgery, to inspect the influence of timing of assessments and to establish directions for post-operative evaluations.

Methods

Patients

To answer the research questions of this study, we consider a subgroup of patients described in Chapter 6. Fifteen glioma patients (10 Dutch, 5 Italian) who underwent awake surgery were included in the analyses. Demographic, tumor and surgical characteristics are described in Table 7.1.

Table 7.1 Demographic, tumor and surgical characteristics of glioma patients who underwent pre- and post-operative written language assessment (n=15)

Patient initials	Age	Gender	Education (years)	Hand preference	Language	Tumor type (WHO grade)	Lesion site	Extent of resection	Adjuvant therapy	Timing of assessment (days from surgery)		Impaired scores on other cognitive domains	
										Before	After	Before	After
RB	38	M	16	Right	Italian	Glioblastoma (IV)	Left MFG / SFG	Total	RT + CT	1	46	Memory, Executive F	Executive F
RP	44	M	13	Right	Italian	Anaplastic astrocytoma (III)	Left posterior MFG	Supratotal	RT + CT	1	21	Memory, Executive F	Memory, Executive F
BJ	29	M	15	Right	Dutch	Astrocytoma (II)	Left PreCG / posterior MFG	Total	RT + CT	40	58	Attention, Executive F	Attention, Executive F
HT	32	M	12	Right	Dutch	Astrocytoma (II)	Left F-P (SMG)	Subtotal	RT + CT	11	41	Attention, Executive F	Executive F
HJ	63	F	16	Right	Dutch	Astrocytoma (II)	Left SMG (- anterior perisylvian)	Subtotal	RT + CT	38	1, 17, 77, 172	None	Attention, Executive F
MF	44	M	15	Right	Italian	Astrocytoma (II)	Left SMG	Subtotal	None	2	19	Executive F	Executive F
LZ	74	F	8	Right	Italian	Glioblastoma (IV)	Left posterior MTG/ITG	Total	RT + CT	9	9, 124	Memory, Executive F	Memory, Attention, Executive F
HC	26	F	13	Right	Dutch	Oligodendroglioma (II)	Left posterior ITG	Subtotal	RT + CT	11	139	Executive F	Attention, Executive F
PS	43	F	20	Right	Dutch	Astrocytoma (II)	Left STG, T pole, I	Subtotal	RT + CT	1	189	Executive F	Attention, Executive F
JB	58	M	16	Right	Dutch	Oligodendroglioma (II)	Left T pole, I	Partial	RT + CT	83	36	None	None
MJ	27	M	16	Right	Dutch	Oligoastrocytoma (II)	Left T-I	Subtotal	RT + CT	20	225	None	Executive F
AH	29	F	14	Left	Dutch	Astrocytoma (II)	Left F-I-T	Partial	RT + CT	14	97	Executive F	Attention, Executive F
MK	28	M	12	Left	Dutch	Astrocytoma (II)	Right Frontobasal	Total	None	26	51	Executive F	None
FG	34	F	8	Right	Italian	Astrocytoma (II)	Left PreCG / posterior MFG	Total	None	4	3	Attention, Executive F	*na*
MdJ	41	F	15	Left	Dutch	Glioblastoma (IV)	Left STG	Total	RT + CT	4	3	None	*na*

M = male, F = female; F = Frontal, SFG = Superior Frontal Gyrus, MFG = Middle Frontal Gyrus, PreCG = Precentral Gyrus, P = Parietal, SMG = Supramarginal Gyrus, T = Temporal, STG = Superior Temporal Gyrus, MTG = Middle Temporal Gyrus, ITG = Inferior Temporal Gyrus, I = Insula; RT = radiotherapy, CT = chemotherapy; Executive F = Executive Functioning; *na* = not assessed

Materials

All patients completed the Written language battery for glioma patients before and after surgery (Chapter 4). Spelling assessment consisted of 31 words, 10 non-words and 5 sentences in Dutch, and of 99 words, 40 non-words and 11 sentences in Italian. Reading was assessed with 38 words, 12 non-words and 6 sentences in Dutch, and with 106 words, 52 non-words and 12 sentences in Italian. In addition to the written language battery, a comprehensive neuropsychological assessment was also administered, before and after surgery. To evaluate executive functions, the Trail Making Test (B/A) [43], Letter Fluency test [44], Digit Span backward [45,46] and the Stroop Test (III) [47] were assessed. To investigate memory and attention, the 15-Word Test [44], and the Digit Span forward [45,46] were administered. Handedness was determined in all participants via the Edinburgh Inventory [48].

Analyses

For the Written language test, structured scoring forms as described in Chapter 4 were used to distinguish specific error types (Appendix C.2). Error rates were calculated and descriptive statistics were generated to establish if performance was in the normal or pathological range compared to normative data (Chapter 4; Table 4.30). As regards other neuropsychological tests, a score below the 10th percentile was considered as an indication of impaired functioning.

Linear regression analyses were conducted to inspect how demographic (age, education, and gender), tumor (site, histology, and grade), treatment characteristics (extent of resection, and adjuvant therapy) and cognitive status related to error rates. Effects of psycholinguistic variables were analyzed using Fisher's Exact Test (for factors e.g., grammatical class) and Generalized Linear Models (for continuous variables e.g., word length). Pearson's correlation coefficients were computed to evaluate the relationship between changes in performance accuracy (post-operative error rate – pre-operative error rate) and time of assessment (days after surgery). All statistical analyses were conducted in R using *stats*, *gmodels* and *nnet* packages [49-51]. A significance level of $p < 0.05$ was used, or Bonferroni adjusted alpha levels in case of multiple comparisons.

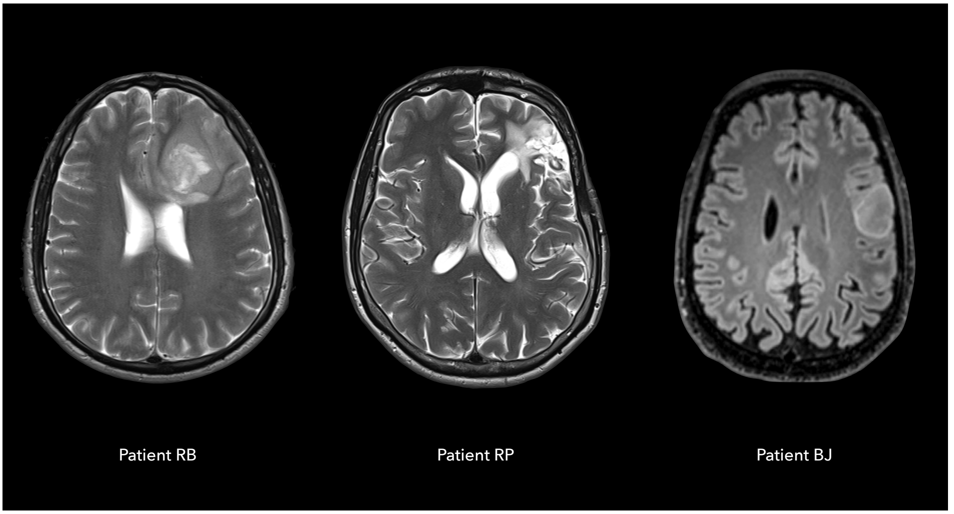


Figure 7.1 Magnetic Resonance Imaging of patients with gliomas in the frontal lobe.
Pre-operative MRI scans are presented for three patients with frontal lesions. Patient RB: high-grade glioma in the middle and superior frontal gyrus. Patient RP: high-grade glioma in the posterior part of middle frontal gyrus. Patient BJ: low-grade glioma in the posterior part of the middle frontal and precentral gyrus.

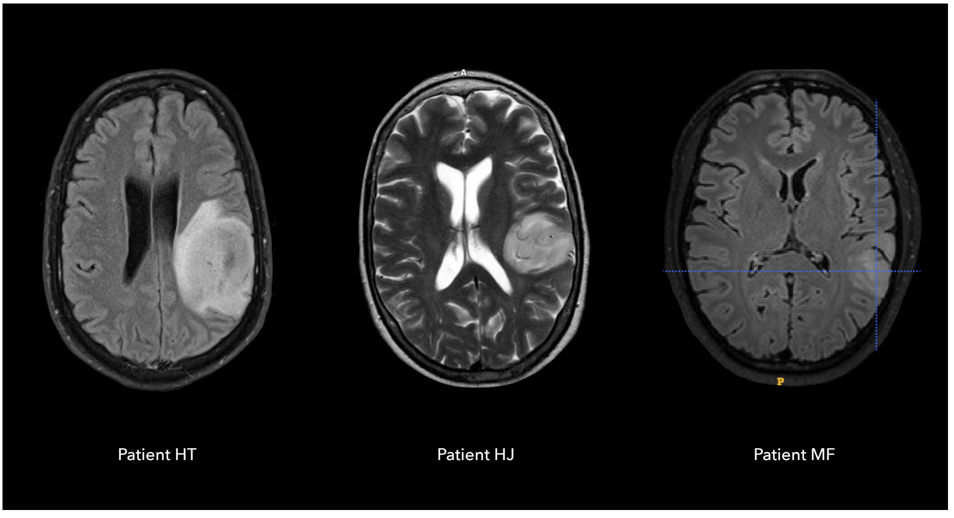


Figure 7.2 Magnetic Resonance Imaging of patients with gliomas in the parietal lobe.
Pre-operative MRI scans are presented for three patients with parietal lesions. Patient HT: low-grade glioma in the fronto-parietal lobe, including the supramarginal gyrus. Patient HJ: low-grade glioma in the supramarginal gyrus, which extended towards the central sulcus. Patient MF: low-grade glioma in the supramarginal gyrus.

Results

Reading and spelling performance (for each subtask separately, and for words, non-words and sentences combined) was not significantly associated with demographic (age, education, and gender), tumor (histology, grade, and affected lobe) or treatment characteristics (extent of resection, and adjuvant therapy) before or after surgery ($p > .05$).

We discuss the influence of tumor location, cognitive profiles, and timing of assessments on written language performance separately. For the first two evaluations, written language outcome was considered as a dependent variable. Given the possible influence of surgical effects on cognitive functioning in the first week [35,36], evaluations of written language outcome in relation to tumor location and cognitive profiles are based on post-operative evaluations carried out more than one week after surgery only. Post-operative assessments after one week were available for 13/15 patients (Table 7.1). With respect to analyses of timing of assessments, we were particularly interested to establish the influence of early post-operative assessment. Hence for these analyses, each assessment moment of all 15 patients (including those in the first week) was considered.

Tumor location

Data from 13 patients who completed the written language assessments before and at least one week after surgery were considered. In case of multiple post-operative assessments, the longest available follow-up was considered. Inspecting the relation between lesion site and reading and spelling performance, we focused on Central errors; as these can inform on the status of underlying central components, and on Peripheral errors (for spelling only) to evaluate the neural correlates of peripheral processes. Patients with frontal, parietal, temporal and fronto-insular-temporal lesions are discussed separately. Examples of misspellings (Central errors) and alterations in handwriting (Peripheral errors) in Table 7.2, and individual error rates are presented in Table 7.3.

Frontal lesions

In three patients, gliomas involved the posterior middle frontal gyrus (Figure 7.1). In spelling, pathological numbers of Central errors were observed in 2/3 cases pre-operatively, and in all cases post-operatively. Pre-operatively, all patients showed a length effect on Central errors. Case RP also showed a grammatical class effect in sentence spelling (he only produced errors on verbs) and had poor non-word spelling before surgery. Patients with frontal lesions produced mostly segmental errors (> 45.0% of errors were letter omissions, substitutions and transpositions resulting in non-words) before and after surgery. Pathological numbers of peripheral errors were observed in 1/3 cases before surgery (Case RP), and after surgery in the other 2 cases (Table 7.2).

Reading was less impaired in these patients. Before surgery, Central error rates were lower in reading than in spelling, though performance on reading subtasks was impaired in 2/3 cases (Table 7.3). Post-operatively, impairments were revealed in 1/3 cases only. Central errors before surgery were in patients RB and RP characterized by a length effect. Case RP produced significantly more errors on non-words than on words before surgery (so-called "phonological agraphia"). Segmental errors were the predominant error type in all cases (> 50.0% of total errors). In the pre-operative assessment, they were self-corrected in more than 75% of cases.

Parietal lesions

Three patients had gliomas in the parietal lobe, affecting in all cases the supramarginal gyrus (Figure 7.2). In spelling, pathological numbers of Central errors were observed pre- and post-operatively in 2/3 cases. All subtasks were affected in one patient, only sentences in another (Table 7.3). The third patient (Case HJ) produced significantly more Central errors post-operatively on non-words than on words. Post-operatively, a length effect was observed for Central errors in 2/3 cases (Cases HJ & MF). A grammatical class effect was also observed after surgery in MF, who made more errors on function words (62.5%) than on nouns, verbs or adjectives (respectively 29.3%, 17.4%, 10.5%). Incorrect responses consisted of segmental errors resulting in non-words. Patient HT made predominantly phonologically plausible errors after surgery (57.1% of Central errors). Cases HT & MF often corrected themselves (in > 23.0% Central errors), while Case HJ never did. Peripheral errors were observed in 1/3 cases, before and after surgery (Case MF; Table 7.2).

Central impairments in reading were found pre-operatively in 2/3 cases, and post-operatively in 3/3. In all cases, non-word reading was more impaired than word reading. Before surgery, 2/3 patients showed impaired non-word but preserved word reading (Cases HT & MF). After surgery, 2/3 patients made significantly more errors on non-words than on words (Cases HJ & MF). In addition, both subjects showed a length effect. Central errors were mainly of the segmental type, and often resulted in an existing word (30.0% to 50.0% of segmental errors).

Temporal lesions

In two patients, gliomas involved the inferior temporal gyrus (Figure 7.3). In case LZ, the tumor affected the posterior parts of the middle and inferior temporal gyri. Post-operatively, both Central and Peripheral error rates were abnormal in all tasks except non-word spelling (Table 7.3). Central errors resulted mainly in phonologically plausible or phonologically related segmental errors, and occurred mainly on verbs.

Patient HC was operated for a glioma in the posterior part of the inferior temporal gyrus. He only produced 2 Central errors, both phonologically plausible (Table 7.2).

In reading, patient LZ also showed high Central error rates, both before and after surgery. His reading was slow. Pre-operatively, reading errors occurred mostly on verbs. After surgery, effects of frequency and length were observed, but not of grammatical class, and Central errors were significantly more frequent on non-words than on words. Errors were mainly segmental, and typically resulted in non-words with orthographically related letter substitutions, such as *trovava* > /travava/ (pre-operatively: 25.0%; post-operatively: 30.8%), or transpositions, such as *erulche* > /elruke/ (pre-operative: 62.5%; post-operative: 53.8%). Case HC made no errors in reading.

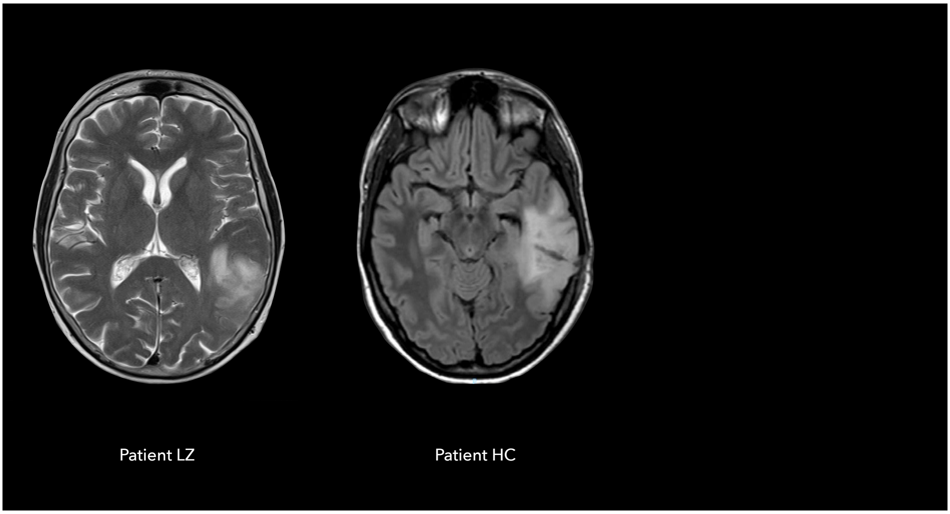


Figure 7.3 Magnetic Resonance Imaging of patients with gliomas in the temporal lobe. Pre-operative MRI scans are presented for two patients with temporal lesions. Patient LZ: high-grade glioma in the posterior part of the middle and inferior temporal gyrus. Patient HC: low-grade glioma in the posterior part of the inferior temporal gyrus.

Temporo-insular, fronto-insular-temporal and frontobasal lesions

Our experimental sample included 5 patients with gliomas affecting two or more lobes. Tumors were temporo-insular in 3 cases (Cases PS, JB, & MJ), fronto-temporo-insular in 1 (Case AH), and fronto-basal in 1 (Case MK; Figure 7.4). In spelling, a pathological number of Central errors (mainly morphological errors; Table 7.3) was observed in 1/5 patients before surgery, restricted to sentences (Case PS; Table 7.3). Two patients (2/5) produced segmental, phonologically plausible and related errors, often followed by self-corrections, but no distinct error patterns were detected (Cases AH & MK; Table

7.2). The remaining two patients completed all spelling tasks without Central errors (Cases JB & MK). Post-operatively, performance was normal in all patients.

Reading was impaired in 1/5 patient – but, not in the subject who produced spelling errors pre-operatively. This patient (Case AH) was selectively impaired on the sentence reading subtask after surgery. He produced 4 errors (2 incorrect stress assignments, 1 segmental and 1 morphological-syntactic), and showed a word length effect. Of the other patients, two made isolated errors (PS failed to self-correct and MJ produced a segmental error), and two had errorless performance.

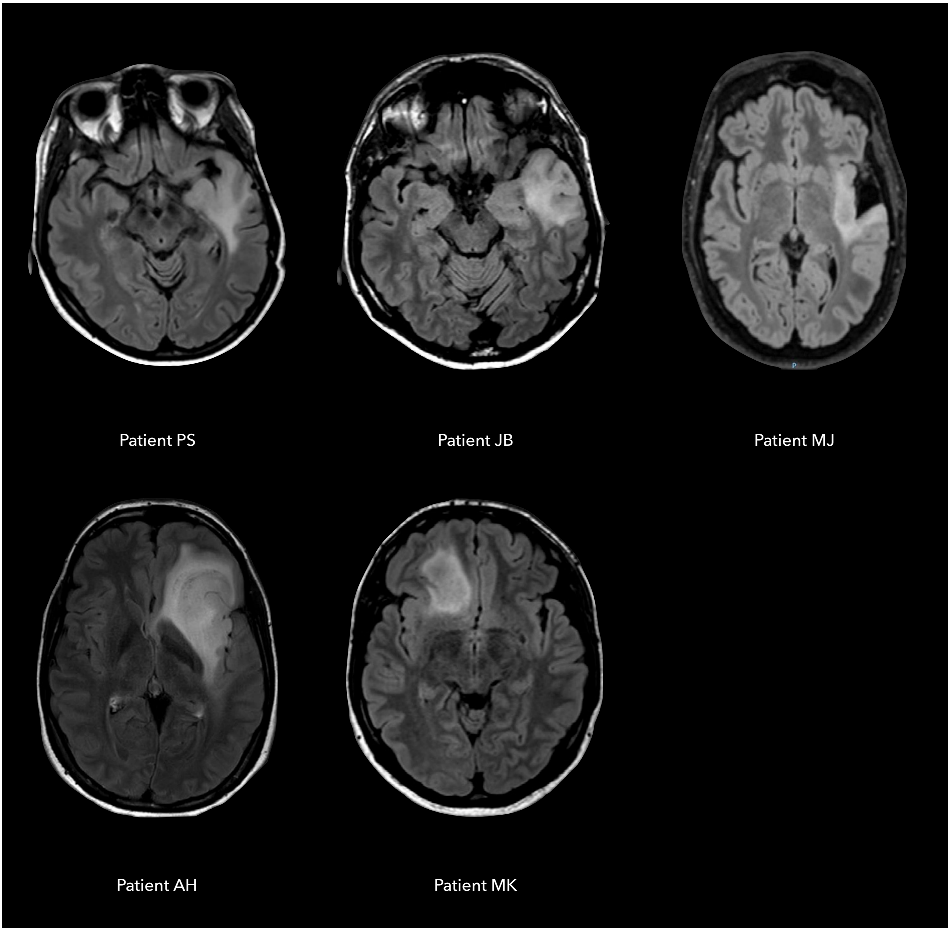
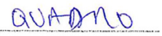
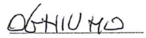
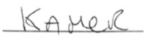
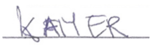
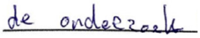
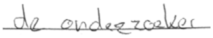
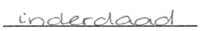
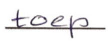
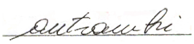
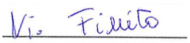
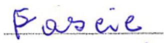
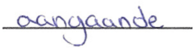
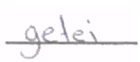
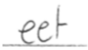
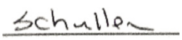
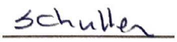
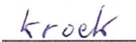
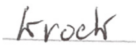
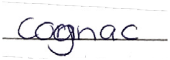
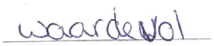
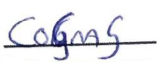
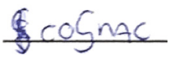


Figure 7.4 Magnetic Resonance Imaging of patients with gliomas in temporo-insular, fronto-insular-temporal and frontobasal regions. Pre-operative MRI scans are presented for five patients with fronto-insular-temporal and frontobasal lesions. Patient PS: low-grade glioma in the superior temporal gyrus, temporal pole and the insula. Patient JB: low-grade glioma in the temporal pole and the insula. Patient MJ: low-grade glioma in the temporal-insular lobe. Patient AH: low-grade glioma in the fronto-insular-temporal lobe. Patient MK: low-grade glioma in frontobasal regions.

Table 7.2 Examples of patient's handwriting before and after awake surgery

Patient initials	Lesion site	Before surgery: *Dictated stimulus* > ERROR	Before surgery: Example of handwriting	After surgery: *Dictated stimulus* > ERROR	After surgery: Example of handwriting
RB	Left MFG / SFG	*qualcosa* (something) > QUALCOCA [1] - QUALCOSA		*quadro* (picture) > QUAN [2] - QUADRO	
RP	Left post MFG	*coscienza* (consciousness) > COSCENZA [3]		*ognuno* (each) > OGNIUNO [3]	
BJ	Left PreCG / post MFG	*kamer* (room)		*kamer* (room) > KE [1] - KAMER	
HT	Left F-P (SMG)	*De onderzoeker* (the researcher) > DE ONDERZOEK [2] (the research)		*De onderzoeker* (the researcher) > DE ONDEZZOEKER [1]	
HJ	Left SMG	*inderdaad* (indeed)		*doep* (non-word) > TOEP [4]	
MF	Left SMG	*contagio* (contagion) > CANTAGIO [1]		*entrambi* (both) > ANTRAMBI [4]	
LZ	Left post MTG/ITG	*finito* (finished) > VI [4] - FINITO		*fasce* (bands) > FASCIE [3]	
HC	Left post ITG	*aangaande* (regarding)		*getij* (tide) > GETEI [3]	
PS	Left STG, T pole, I	*eet* (eats) > ETEN [5] (to eat)		*eet* (eats)	
JB	Left T pole, I	*schullen* (non-word)		*schullen* (non-word)	
MJ	Left T-I	*kroek* (non-word)		*kroek* (non-word)	
AH	Left F-I-T	*cognac* (cognac) > COCNAC [4] - COGNAC		*waardevol* (valuable) > WAARDEWOL [4] - WAARDEVOL	
MK	Right Frontobasal	*cognac* (cognac) > COCNAG [4] - COGNAG [4,6]		*cognac* (cognac) > G [7] - COGNAC	

Dictated stimuli are denoted in *italics* (English translation in brackets). Central errors in handwriting are provided in CAPITALS, and Peripheral errors are underlined. Self-corrections are indicated with – in the response. When only dictated stimuli are reported, spelling was faultlessly.
[1] Segmental error resulting in a non-word; [2] Segmental error resulting in a word; [3] Phonological plausible error; [4] Phonological related segmental error; [5] Morphological error; [6] Failed attempt to self-correct; [7] Central error not defined

Table 7.3 Pre- and post-operative error rates per patient

	Patient RB (SFG/MFG)		**Patient RP** (post MFG)		**Patient BJ** (PreCG/post MFG)		**Patient HT** (F-P; SMG)		**Patient HJ** (SMG)		**Patient MF** (SMG)	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
Reading Central errors												
Words	**1.9%**	0.0%	0.9%	**3.8%**	0.0%	0.0%	2,6%	**5.3%**	0.0%	0.0%	0.0%	**3.8%**
Non-words	1.9%	1,9%	**7.7%**	**9.6%**	8.3%	0.0%	**16.7%**	8.3%	0.0%	0.0%	**7.7%**	**9.6%**
Sentences	0.0%	2,1%	**4.6%**	6.4%	0.0%	0.0%	**7.4%**	**10.7%**	0.0%	**3.7%**	**4.6%**	**19.2%**
Spelling Central errors												
Words	**10.1%**	**11.1%**	**7.1%**	**9.1%**	3,2%	**29.0%**	6.5%	9.7%	0.0%	0.0%	**14.9%**	**25.3%**
Non-words	15.0%	10.0%	**25.0%**	**10.0%**	0.0%	10,0%	10.0%	0,0%	0.0%	20.0%	**21.4%**	**39.4%**
Sentences	**9.1%**	**9.1%**	5.5%	3.6%	4.2%	**18.2%**	**20.8%**	**18.2%**	0.0%	0.0%	**10.9%**	**29.1%**
Spelling Peripheral errors												
Words	2,0%	**7.1%**	2.0%	1.0%	6.5%	**29.0%**	0.0%	3.2%	0.0%	3.2%	**3.2%**	**5.5%**
Non-words	0.0%	0.0%	0.0%	0.0%	10.0%	**40.0%**	0.0%	0.0%	0.0%	0.0%	**10.7%**	**9.1%**
Sentences	1.8%	1.8%	**3.6%**	1.8%	4.2%	**18.2%**	0.0%	4.6%	0.0%	0.0%	**14.6%**	**12.7%**

Post = posterior; Before = pre-operative assessment, After = latest post-operative assessment, at least >1 week
Bold = error rate below cut-off compared to normative data

Table 7.3 continued Pre- and post-operative error rates per patient

	Patient LZ (post MTG/ITG)		**Patient HC** (post ITG)		**Patient PS** (STG, T pole, I)		**Patient JB** (T pole, I)		**Patient MJ** (T-I)		**Patient AH** (F-I-T)		**Patient MK** (Frontobasal)	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
Reading Central errors														
Words	**1,9%**	**6.6 %**	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	2.6%	0.0%	0.0%	0.0%	0.0%
Non-words	**5,8%**	**13.5%**	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	8.3%	0.0%	0.0%
Sentences	**9.2%**	1.5%	0.0%	0.0%	0.0%	3.6%	0.0%	0.0%	0.0%	0.0%	0.0%	**10.7%**	0.0%	0.0%
Spelling Central errors														
Words	6.1%	**8.1%**	0.0%	3,2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	6.5%	3,2%	3.2%	3.2%
Non-words	10.0%	17,5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Sentences	**9.1%**	**12.7%**	0.0%	4,6%	**16.7%**	4.6%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Spelling Peripheral errors														
Words	**3.0%**	**10.1%**	0.0%	0.0%	0.0%	3.2%	0.0%	0.0%	3.2%	3.2%	0.0%	0.0%	0.0%	0.0%
Non-words	**7.5%**	2.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Sentences	**7.3%**	**7.3%**	0.0%	0.0%	**8.3%**	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%

Before = pre-operative assessment, After = latest post-operative assessment, at least >1 week
Bold = error rate below cut-off compared to normative data

General cognitive functioning

To evaluate the relation between written language skills and cognitive profiles, reading and spelling outcome was correlated with the status of other cognitive domains. Data from the 13 patients who completed the written language assessments before and at least one week after surgery were considered.

Pathological scores on cognitive tasks were frequently observed before (in 10/13 cases, or 76.9%) and after surgery (in 11/13 cases, or 84.6%). Pre-operatively, executive tasks were most frequently impaired (in 10 cases), while scores on memory and attention tasks were below the 10^{th} percentile in 3 and 2 cases, respectively (Table 7.1). Post-operatively, pathological scores were observed in executive tasks in 11 cases, in memory tasks in 2, and in attention tasks in 6.

Regression analyses aimed at evaluating the relationships between reading and writing subtests and the various cognitive domains (attention, memory and executive functions) failed to show significant correlations before (Table 7.4a) and after surgery (Table 7.4b).

Timing of assessments

Post-operative and follow-up assessments were carried out in wide time frames, varying from 1 to 225 days after surgery. To inspect the possible influence of timing of assessment, we evaluated the data gathered in three phases: *subacute* (1-10 days after surgery), *post-operative* (11-90 days) and *long-term* (91-365 days) evaluations. The relation between interval after surgery and performance on written language tasks was analyzed at each of these post-operative intervals. Given the individual variability observed before surgery, pre-operative error rates were considered as individual baselines to evaluate post-operative changes. Changes in performance (post-operative error rate – pre-operative error rate) were evaluated given the timing of assessment in days after surgery.

Confidence intervals of the regression lines in Figures 7.5a and 7.5b demonstrated large individual variability in the subacute phase. Regression lines furthermore indicated divergence between tasks and error types. In the first ten days after surgery, on spelling and reading, and for all error types, changes in performance on separate tasks showed insignificant decreases (improvement in performance) and increases (decline in performance). After 10 days, performance on some tasks improved as compared to pre-operative assessment (as shown by a negative change on non-word spelling and Central errors on sentence reading at the end of the subacute phase), while in most cases performance declined as compared to pre-operative assessments (as demonstrated by positive change values, corresponding to more errors post-operatively than pre-operatively). A significant increase in Other errors was found in non-word reading in the subacute phase (R^2=0.988, $F(1,2)$=162.6, p= .006).

In the post-operative phase (11 days up to 3 months after surgery), less variation was observed than in the subacute phase. Positive change values indicated persistently higher error rates at three months than before surgery. Changes in Peripheral spelling errors increased in the post-operative stage, indicating further performance decline between 10-90 days after surgery. On reading tasks, changes in performance decreased and reached negative values (mainly on Other errors), due to fewer reading errors at three months compared to pre-operative performance. None of the relations were significant.

At long-term outcome (after more than 3 months), performance changes declined over time on all tasks. Although graphs showed this pattern consistently, no significant relations between timing of assessment and change in error rates were observed. In most cases, change rates reached negative values at 1 year after surgery, indicating improving performance over time as compared to pre-operative values. This pattern was clearest for reading, in which all but one tasks (Central errors on word reading) showed a negative change. On spelling tasks, negative changes were observed with sentences (Central and Peripheral errors), and in Unclassifiable errors.

Discussion

Available data show that written language may be affected in glioma patients undergoing awake surgery (Chapters 3 and 6). However, patients differ for demographic characteristics, tumor-related medical and surgical variables, and cognitive profiles. In this study, we tried to establish to which extent specific parameters may influence written language performance.

The effects of tumor location

An initial aim of the study was to identify patterns of written language impairments for different glioma locations. Lesion and neuroimaging studies have shown that reading and spelling rely on a complex cognitive architecture, whose selective impairments result in specific errors patterns. For each component, relatively circumscribed neural substrates have been identified (see Chapter 1 for reading, and Chapter 2 for spelling). In this Chapter, reading and spelling patterns associated with different glioma locations were considered, to explore if knowledge from neurofunctional studies may be applied to glioma practice. We focused on Central errors, as these can inform on the status of central processes of reading and spelling (Chapter 1, Figure 1.1), and because clearer neurofunctional correlations are assumed by current studies. Peripheral handwriting errors were also considered, to evaluate the neural correlates of post-grapheme level processes.

Table 7.4a Relation between pre-operative cognitive impairments and error rates before surgery

	Impairments per domain		
	Memory	Executive functioning	Attention
Reading overall			
Central errors	R^2= 0.19, *p*= .139	R^2= 0.17, *p*= .164	R^2= 0.21, *p*= .116
Other errors	R^2= 0.11, *p*= .279	R^2= 0.01, *p*= .746	R^2= 0.24, *p*= .089
Reading words			
Central errors	R^2= 0.37, *p*= .028	R^2= 0.12, *p*= .256	R^2= 0.12, *p*= .240
Other errors	R^2= 0.32, *p*= .042	R^2= 0.15, *p*= .190	R^2= 0.10, *p*= .285
Reading non-words			
Central errors	R^2= 0.02, *p*= .609	R^2= 0.16, *p*= .170	R^2= 0.56, *p*= .003
Other errors	R^2= 0.01, *p*= .724	R^2= 0.00, *p*= .834	R^2= 0.30, *p*= .051
Reading sentences			
Central errors	R^2= 0.20, *p*= .120	R^2= 0.12, *p*= .251	R^2= 0.05, *p*= .450
Other errors	R^2= 0.04, *p*= .540	R^2= 0.01, *p*= .816	R^2= 0.09, *p*= .309
Spelling overall			
Central errors	R^2= 0.21, *p*= .115	R^2= 0.33, *p*= .039	R^2= 0.04, *p*= .522
Peripheral errors	R^2= 0.08, *p*= .352	R^2= 0.08, *p*= .339	R^2= 0.03, *p*= .592
Unclassifiable errors	R^2= 0.00, *p*= .848	R^2= 0.08, *p*= .351	R^2= 0.03, *p*= .583
Spelling words			
Central errors	R^2= 0.17, *p*= .168	R^2= 0.29, *p*= .056	R^2= 0.00, *p*= .897
Peripheral errors	R^2= 0.15, *p*= .191	R^2= 0.03, *p*= .585	R^2= 0.08, *p*= .363
Unclassifiable errors	R^2= 0.01, *p*= .788	R^2= 0.11, *p*= .265	R^2= 0.20, *p*= .130
Spelling non-words			
Central errors	R^2= 0.42, *p*= .016	R^2= 0.15, *p*= .186	R^2= 0.00, *p*= .842
Peripheral errors	R^2= 0.00, *p*= .884	R^2= 0.09, *p*= .326	R^2= 0.09, *p*= .319
Unclassifiable errors	R^2= 0.00, *p*= .865	R^2= 0.04, *p*= .536	R^2= 0.02, *p*= .631
Spelling sentences			
Central errors	R^2= 0.03, *p*= .595	R^2= 0.22, *p*= .102	R^2= 0.17, *p*= .155
Peripheral errors	R^2= 0.06, *p*= .427	R^2= 0.10, *p*= .286	R^2= 0.00, *p*= .911
Unclassifiable errors	R^2= 0.00, *p*= .895	R^2= 0.07, *p*= .397	R^2= 0.01, *p*= .772

Overall = words, non-words and sentences combined
Impairments were defined when performance was < 10^{th} percentile
Bonferroni adjusted alpha levels of *p*< .00083 were used

Table 7.4b Relation between post-operative cognitive impairments and error rates after surgery

	Impairments per domain		
	Memory	Executive functioning	Attention
Reading overall			
Central errors	R^2= 0.19, *p*= .134	R^2= 0.16, *p*= .171	R^2= 0.03, *p*= .571
Other errors	R^2= 0.62, *p*= .001	R^2= 0.06, *p*= .423	R^2= 0.00, *p*= .989
Reading words			
Central errors	R^2= 0.42, *p*= .017	R^2= 0.10, *p*= .298	R^2= 0.06, *p*= .433
Other errors	R^2= 0.48, *p*= .009	R^2= 0.04, *p*= .527	R^2= 0.02, *p*= .626
Reading non-words			
Central errors	R^2= 0.45, *p*= .013	R^2= 0.12, *p*= .246	R^2= 0.00, *p*= .846
Other errors	R^2= 0.46, *p*= .010	R^2= 0.06, *p*= .403	R^2= 0.07, *p*= .390
Reading sentences			
Central errors	R^2= 0.00, *p*= .903	R^2= 0.11, *p*= .260	R^2= 0.04, *p*= .518
Other errors	R^2= 0.38, *p*= .026	R^2= 0.04, *p*= .496	R^2= 0.01, *p*= .778
Spelling overall			
Central errors	R^2= 0.09, *p*= .780	R^2= 0.12, *p*= .240	R^2= 0.01, *p*= .782
Peripheral errors	R^2= 0.00, *p*= .989	R^2= 0.07, *p*= .392	R^2= 0.07, *p*= .391
Unclassifiable errors	R^2= 0.00, *p*= .848	R^2= 0.08, *p*= .351	R^2= 0.03, *p*= .583
Spelling words			
Central errors	R^2= 0.00, *p*= .910	R^2= 0.09, *p*= .334	R^2= 0.00, *p*= .848
Peripheral errors	R^2= 0.00, *p*= .926	R^2= 0.08, *p*= .344	R^2= 0.10, *p*= .297
Unclassifiable errors	R^2= 0.01, *p*= .788	R^2= 0.11, *p*= .265	R^2= 0.20, *p*= .130
Spelling non-words			
Central errors	R^2= 0.04, *p*= .497	R^2= 0.10, *p*= .305	R^2= 0.00, *p*= .936
Peripheral errors	R^2= 0.01, *p*= .724	R^2= 0.03, *p*= .605	R^2= 0.07, *p*= .373
Unclassifiable errors	R^2= 0.00, *p*= .865	R^2= 0.04, *p*= .536	R^2= 0.02, *p*= .631
Spelling sentences			
Central errors	R^2= 0.00, *p*= .936	R^2= 0.13, *p*= .220	R^2= 0.01, *p*= .722
Peripheral errors	R^2= 0.01, *p*= .809	R^2= 0.07, *p*= .369	R^2= 0.01, *p*= .717
Unclassifiable errors	R^2= 0.00, *p*= .895	R^2= 0.07, *p*= .397	R^2= 0.01, *p*= .772

Overall = words, non-words and sentences combined
Impairments were defined when performance was < 10^{th} percentile
Bonferroni adjusted alpha levels of *p*< .00083 were used

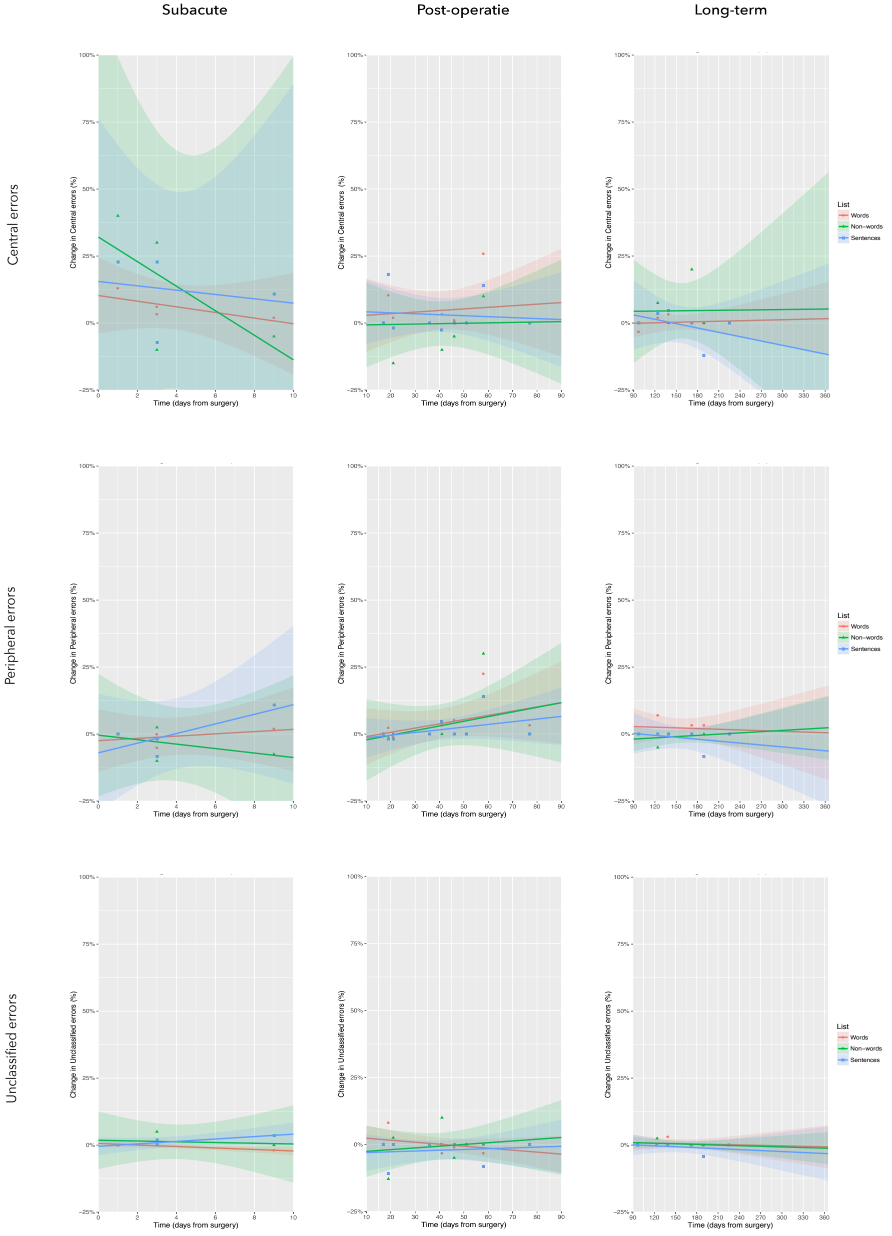


Figure 7.5a Relation between timing of post-operative assessment and changes in spelling performance accuracy. Changes in performance refer to individual differences in post-operative scores relative to pre-operative scores. As pre-operative error rates are considered as reference points for individual performance, the scores displayed here represent the difference (errors after surgery – errors before surgery). Positive values correspond to higher post-operative error rates as compared to the pre-operative assessment, and negative values to lower post-operative error rates than pre-operative error rates. Changes in performance are separately presented for subacute (0-10days after surgery), post-operative (11-90days), and long-term phases (>3months). Scatterplots present changes in Central, Peripheral and Unclassifiable spelling errors. Linear regression lines with confidence intervals are plotted.

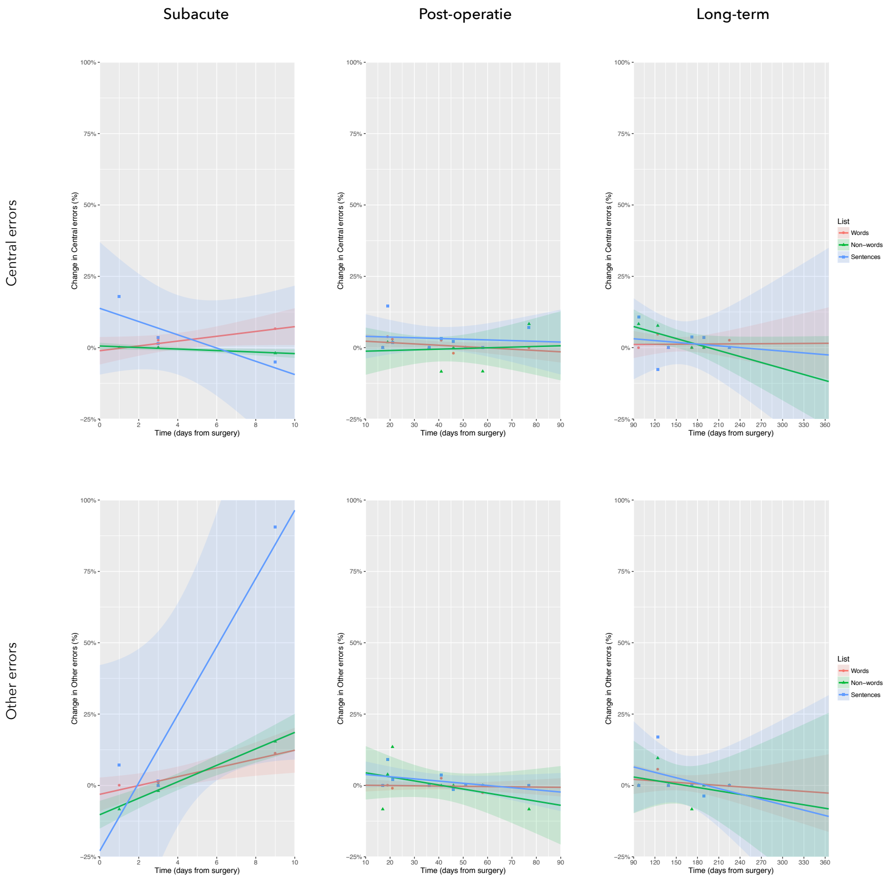


Figure 7.5b Relation between timing of post-operative assessment and changes in reading performance accuracy. Changes in performance refer to individual differences in post-operative scores relative to pre-operative scores. As pre-operative error rates are considered as reference points for individual performance, the scores displayed here represent the difference (errors after surgery – errors before surgery). Positive values correspond to higher post-operative error rates as compared to the pre-operative assessment, and negative values to lower post-operative error rates than pre-operative error rates. Changes in performance are separately presented for subacute (0-10days after surgery), post-operative (11-90days), and long-term phases (>3months). Scatterplots present changes in Central and Other reading errors. Linear regression lines with confidence intervals are plotted.

Spelling

In the 3 cases with frontal gliomas, the middle frontal gyrus was involved. In the literature, this region has been involved in graphemic buffer processing [52-56], and its posterior portions in peripheral handwriting processes [57-59]. In agreement with these observations, in all subjects Central errors were affected by length (as is the case in graphemic buffer damage), and Peripheral errors were observed, before or after surgery. Pre-operatively, one patient (Case RP), who had surgery for a recurrent glioma, presented additional effects of grammatical class and impaired non-word spelling, and made many phonologically related errors – a profile that may be due to damage to the orthographic output lexicon and to phoneme-grapheme conversion processes. However, these components are typically linked to the inferior frontal gyrus [33,35,58,60], and not to the middle frontal gyrus. Patient RP's first surgery (3 years earlier) had involved a glioma of the posterior inferior frontal gyrus. Since the observed spelling errors were present before surgery already, they are most likely to reflect damage to the inferior frontal gyrus, rather than to the middle frontal gyrus.

In three patients with parietal gliomas, the supramarginal gyrus was affected. Extant literature has involved this region in graphemic buffer [33,54] and phoneme-grapheme conversion processing [61,62]. Damage to the graphemic buffer generally results in a length effect. Damage to phoneme-grapheme processing typically results in a lexicality effect, i.e., greater impairment of non-word spelling than of word spelling. Both length and lexicality effects were observed in 2/3 cases after surgery, but not in the third patient (Case HT), who showed a frequency effect (affecting low-frequency words) instead. There is no obvious account for this pattern of performance, but some speculation can be offered. Perhaps, glioma resection damaged different underlying white matter pathways across patients. The arcuate fasciculus and superior longitudinal fasciculus (connecting posterior frontal with inferior parietal and posterior temporal regions) have both been frequently involved in language processing, in particular for phonological processing. With regard to spelling, although scarcely investigated, a distinction is proposed between damage to the arcuate fasciculus (terminating in the superior temporal gyrus), which may impair phoneme-grapheme conversion [63-65], and damage to the superior longitudinal fasciculus (terminating in the middle temporal gyrus) that disrupts phonological lexical processing (typically resulting in a frequency effect [63,65,66]). Unfortunately, Diffusion Tensor Imaging (DTI) was unavailable to confirm subcortical damage.

In addition to its involvement in central processes, the parietal lobe is also considered to be relevant for peripheral handwriting processes [67-69], which are spared in our three patients. Congruently, Peripheral error rate was within normal limits in 2/3 cases (Cases HT & HJ). Case MF, on the other hand, had poor scores before and after supramarginal gyrus resection. Although this region has not been related to peripheral processing in lesion and neuroimaging studies, Peripheral errors have been reported after supramarginal gyrus removal in glioma surgery [70]. Since little attention has been paid to the neural correlates of peripheral handwriting processes, these results stress the need to evaluate peripheral handwriting processes in gliomas of the supramarginal gyrus.

In two patients with temporal lobe gliomas, the tumor was located in the inferior temporal gyrus, whose posterior part has been associated with orthographic output lexicon [33,35,65,71-73]. Although statistically insignificant, the only two misspellings Case HC produced were phonologically plausible errors, which are expected following damage to the orthographic output lexicon. The failure to demonstrate a clearer error pattern in this patient may be due to the limited number of items in assessed the Dutch battery (the patient does suffer from orthographic output lexical damage, but the tool used for assessment is not sensitive enough). As an alternative, early plasticity mechanisms may have reallocated lexical orthographic output processes in neighboring neural regions. In line with the predictions based on the neural correlates of orthographic long-term memory patient LZ, who underwent surgery in both posterior inferior and middle temporal gyri, produced phonologically plausible and phonologically related errors, and showed a grammatical class effect (verbs were more affected than nouns). These difficulties are consistent with damage to the inferior temporal gyrus, but may also reflect additional damage to middle temporal regions. Although the (posterior) middle temporal gyrus has not been classically involved in spelling in the lesion and neuroimaging literature, intra-operative stimulation of the middle temporal cortex induced Central spelling errors in a recent study of glioma patients [74]. In addition, stimulation of the posterior dorsal inferior fronto-occipital fasciculus, underlying the middle temporal gyrus, caused spelling arrest [75] and its resection resulted in orthographic output lexicon damage [76] in two other studies. The observed performance profile may thus result from white matter damage underlying the middle temporal gliomas. Yet, the middle temporal gyrus has more frequently been associated with verb processing (e.g., [77-80]), which were also impaired in LZ. Hence, damage to inferior and middle temporal gyrus may have caused damage to orthographic and verb processing, respectively.

Lastly, five patients with temporo-insular, fronto-insular-temporal and frontobasal gliomas were discussed. The insula, as part of anterior perisylvian regions, has been associated with sublexical phoneme-grapheme conversion processes [61,81]. In contrast, anterior temporal or frontobasal regions were not specifically linked to central or peripheral spelling processes, and underlying subcortical pathways (i.e., uncinate fasciculus, anterior middle longitudinal fasciculus, and anterior inferior longitudinal fasciculus) were correlated with object naming and verbal fluency tasks, but not with spelling [82,83]. Yet, since anterior temporal or frontobasal regions could be clustered with anterior perisylvian areas, and given the involvement of the insula, one may expect damage to phoneme-grapheme conversion processing in these patients.

Nevertheless, results demonstrated spared non-word spelling in all cases. In relation to the ongoing debate on whether anterior [81] or posterior perisylvian regions [84,85] are critical for phoneme-grapheme conversion [61,62], our results show selective damage in patients with gliomas of posterior perisylvian regions. These findings suggest that the role of anterior perisylvian regions may be more indirect, possibly via subcortical connections (i.e., the arcuate fasciculus and the superficial layer of the inferior fronto-occipital fasciculus).

Reading

In the three cases with gliomas in the middle frontal gyrus, no specific impairments of reading were expected, this region has not been involved with processing at the level of the orthographic input lexicon or of grapheme-phoneme conversion. However, a patient with middle frontal gyrus lesion (Case RP) showed poor non-word reading, which results from grapheme-phoneme conversion impairments. This dyslexic profile is typically linked with damage to posterior perisylvian regions [86-89], which are connected to posterior frontal regions (anterior perisylvian regions) via the arcuate fasciculus and the superficial layer of the inferior fronto-occipital fasciculus. Hence, poor non-word reading in patients with a frontal glioma, like RP, may result from subcortical damage to this anterior-posterior perisylvian network [90-92]. Frontal regions have also been linked to central reading processes shared by other language tasks. For example, the posterior part of the inferior frontal gyrus has been associated with phonological buffer processing [93,94]. Damage to this functional component typically yields errors on longer words. Consistent with this neurofunctional correlation, a length effect was found pre-operatively in patient RP, who had been operated three years earlier for an inferior frontal gyrus glioma. The length effect observed in case RB before middle/superior frontal gyrus surgery is more difficult to account for. Phonological buffering has also been associated with the supramarginal gyrus [95-97]. In RB, white matter infiltration from a posterior middle frontal gyrus glioma may have damaged subcortical connections (e.g., the superior longitudinal fasciculus). Although the observed profile (impaired non-word reading and length effect) may denote subcortical damage, reports of the subcortical extent of the glioma were not available.

In the three patients with parietal lesions, affecting the supramarginal gyrus, we expected damage to grapheme-phoneme conversion [74,91,98,99] and phonological buffer processes [95-97]. Sublexical grapheme-phoneme conversion damage, resulting in poor non-word reading, was detected in all cases. These results were also congruent with the literature on the subcortical underpinnings of reading processes, that correlates a dorsal pathway (from posterior temporal to inferior frontal cortical regions via the inferior parietal lobe) to phonological, sublexical processing [100-103]. Phonological buffer impairments, yielding length effects, were found in 2/3 subjects.

Of the two patients with temporal lobe lesions, one had a glioma limited to the inferior temporal gyrus, and one was operated on both the inferior and middle temporal gyrus. Lesion and neuroimaging studies have associated the posterior inferior temporal gyrus with orthographic input lexicon processing [104], while the posterior part of the middle temporal gyrus has been deemed critical for phonological output lexicon processes [76]. Damage to both components typically manifests itself in effects of frequency, regularity and grammatical class, but error types vary in patients with phonological or orthographic damage. Yet, features of orthographic input lexical damage were not observed in the patient with a glioma in the inferior temporal gyrus, who showed faultless and fast reading. Possibly, the most posterior part of the inferior temporal gyrus (the visual word form area) may have been spared, or pre-surgical plasticity may have compensated for its damage. Preserved orthographic input functioning may also result from intact white matter pathways, as the posterior part of the dorsal inferior fronto-occipital fasciculus has been identified to be crucial for orthographic lexical processing [75,76]. The patient with a glioma in middle and inferior temporal gyri showed, congruent with expectations based on the likely functional correlates of both gyri and their underlying subcortical tracts, effects of frequency and grammatical class, but not of regularity. His errors (many orthographically/visually related, no phonologically plausible/related errors) are more consistent with orthographic (input) than with phonological (output) damage. The lack of a regularity effect may support the possibility that damage to inferior temporal gyrus, or to the underlying inferior fronto-occipital fasciculus, has a greater impact on reading skills than damage to the middle temporal gyrus. In addition, this patient's profile was consistent with damage to grapheme-phoneme conversion (more errors on non-words than words) and to the phonological buffer (length effect). These processes have been related to the superior temporal [93] and supramarginal gyrus [95-97], that lie superior to the resected area, but are connected to posterior parts of middle and inferior temporal gyri via subcortical tracts (i.e., the arcuate fasciculus). Subcortical damage may be responsible for grapheme-phoneme conversion and phonological buffer impairments in this subject.

Lesion and neuroimaging studies have not tied (sub)cortical anterior temporal or temporo-insular regions with specific aspects of reading. Therefore, no specific patterns of reading errors were expected for the five patients with temporo-insular, fronto-insular-temporal and frontobasal gliomas. In line with expectations, no distinctive effects were observed in the three temporal-insular patients. Reading impairments were more likely to arise in the other two patients, who were operated in fronto-basal and fronto-temporal areas. Although the literature has not explicitly linked these regions with orthographic processing in reading, damage to these areas could disrupt phonological buffer and phonological output lexicon processes, due to their close proximity to the inferior frontal gyrus, which is relevant to these components [93,94,105-107]. In fact, a length effect consistent with phonological buffer damage was reported in 1/2 fronto-temporal cases. Phonological output lexicon impairments were not observed.

Notwithstanding the possibility that pre-surgical plasticity had successfully "moved" phonological processing nodes to neighboring regions, phonological buffering and phonological output lexical processing may have been spared because they rely on more circumscribed areas in the inferior frontal gyrus, which do not include larger fronto-temporal regions. Correspondingly, in another study, resection of a white matter tract underlying these regions (i.e., the uncinate fasciculus) resulted in impaired verbal word fluency, while reading was preserved [82,83].

Considering impaired reading and spelling processes in the light of the intra-hemispheric site of lesion, error profiles in glioma patients were largely congruent with the neural correlates based on lesion and neuroimaging studies. The distinctive time course of brain tumors may complicate the interpretation of observed patterns of impairment, due to the possible effect of plasticity [26,108,109]. Notwithstanding this possibility, errors following resection of specific areas could be predicted in most cases on the basis of lesion site. Results show that current knowledge of the functional neuroanatomy of reading/spelling can be applied to the evaluation of written language in glioma practice. Functional knowledge about the cortical and subcortical structures affected by the tumor, in combination with the results of pre-operative assessments, can lead to identify the processes exposed to intra-operative damage. Stimuli targeting these processes can subsequently be selected to assess a specific patient during surgery.

Considerations for evaluating written language in neurosurgical practice

In contrast to previous studies [13-16], reading and spelling abilities were not systematically correlated with demographic (age, education), tumor (tumor site, histology, grade) or treatment characteristics (adjuvant therapy). Given the differences in tumor growth rate and in the time course of low- and high-grade gliomas [110,111], and the influence of chemo- and radio-therapy on the brain [10-12], the lack of such correlations is somewhat surprising. The patient sample described in this study may have been too small to detect influences at a group level – for example, only one patient with a WHO grade III glioma, and two patients with a grade IV glioma were included; and, only one patient included in the sample did not receive adjuvant therapy. However, the possible influence of these parameters on outcome measures of individual glioma patients should always be evaluated.

Other cognitive impairments

The relation between written language and other cognitive functions was evaluated in our sample, with special regard attention, memory and executive functions. In stroke practice, disorders of language and of other cognitive domains are often associated

[17-19]. Aphasia research has shown that non-linguistic functions are critical to carry out many language tasks [17,18], and that linguistic (dys)functions may influence performance on neuropsychological tasks, as the latter often have an implicit or explicit verbal component [17]. Although rarely investigated in glioma populations, correlations between the performance in spoken language and in other cognitive tasks have been shown by some [6], but not all studies [5]. Yet, the association between written language and neuropsychological profiles had not been specifically investigated in glioma patients. Given the reliance of written language functions on cognitive processes, a similar relation as in spoken language was expected. In principle, graphemic/phonological buffer components and working memory processes might correlate, as might be the case for orthographic/phonological lexicons and other types of long-term memory. The current study did not objectify these relations. Congruent with previous studies [5,6,20], pathological scores on cognitive tasks were frequently observed before (in 10/13 cases) and after surgery (in 11/13 cases). Moreover, linguistic impairments were observed in 7/13 cases before and in 8/13 after surgery. Yet, in our sample, these scores were not significantly correlated. Since most patients had poor scores on cognitive tasks, it is conceivable that patients without impairments were underrepresented to draw reliable comparisons between impaired and preserved patients. Clearly, this issue requires further consideration.

Nevertheless, even considering the highly personalized neurosurgical practice for glioma patients, possible associations of linguistic deficits with cognitive impairments must not limit careful written language exams. Pre-operative evaluations, including comprehensive neuropsychological and language assessments, can disclose individual performance profiles. In the presence of cognitive impairments, written language should be carefully evaluated while at the same time considering the possible reciprocal influences of linguistic and cognitive deficits. Yet, when non-linguistic functions influence pre-operative written language performance, they are likely to influence performance also at intra- and post-operative assessments. Rather than by means of across-subject comparisons, pre- and post-operative performance is therefore best compared via within-subject comparisons. To gain insight in possible associations and to customize rehabilitation programs, extensive neuropsychological assessments in combination with language assessment are strongly advisable for individual glioma patients.

Timing of assessments

Information on the relation between timing of assessment and written language performance could not be obtained by considering post-operative error rates only. Large across-subject differences in pre-operative performance may still be present post-operatively. For example, patients with high error rates before surgery are likely to present higher error rates after surgery, as compared to patients with preserved pre-operative functioning. To investigate the relation between performance after surgery and timing of assessments, changes in error rates were measured by taking the patient's pre-operative score as the reference point. Post-operative performance was evaluated at three different phases.

Compared to pre-operative assessment, post-operative performance deteriorated in the subacute phase (up to 10 days after surgery), probably reflecting surgery-related effects on cognitive functioning [38,39]. Yet, ample variability was observed. These results invite great caution when interpreting assessments conducted too early after surgery, as results may not be reliable. In the later post-operative phase (at least 2 weeks after surgery), spelling tasks still resulted in higher Central and Peripheral error rates compared to pre-operative assessment. Post-operative deterioration possibly reflects the negative influence of adjuvant therapies on brain functioning [10-12], as in most cases radio- and chemotherapy in this phase. Performance on reading tasks, on the other hand, improved over time. At the group level, at three months after surgery, error rates did not differ from pre-operative performance. Spontaneous recovery may have improved performance, possibly owing to post-operative plasticity. At long-term assessments (>3 months), performance on all tasks improved further (albeit non-significantly). The longer after surgery the post-operative assessment was conducted, the better the outcome was. For most error types and on most subtasks, error rates at the longest post-operative evaluations returned to pre-operative baseline. Compared to pre-operative performance, fewer errors were produced on the long-term in all cases.

While reading and spelling rely on partially independent processes [112], instances of differential recovery of the two skills are not on record. In our patients, reading improved more substantially than spelling, both in the post-operative and follow-up phase. Although it may be argued that spelling is a more demanding task than reading *per se*, the difference may also be due to a sample bias, as there were few subjects with gliomas in crucial reading regions, and few with selective impairments of reading.

Although data from a relatively small group of patients were discussed and large confidence intervals were observed, observed patterns indicate that timing is crucial when evaluating written language in glioma patients. Our delimitation of three time windows is unavoidably arbitrary, yet results confirmed distinct patterns at various moments in time. Congruent with previous observations in non-linguistic cognitive functioning, persistent written language impairments persisted or worsened until three months after surgery, and were followed by recovery to pre-operative baseline [5,6,21,113]. When evaluating written language skills, it may therefore be advisable to disregard (or, to interpret very cautiously) results in the subacute phase, and to monitor patients at post-operative and long-term stages. Clearly, data must be confirmed in a larger cohort, with additional focus on the difference between reading and spelling. In longitudinal assessments of glioma patients, influences of demographic, tumor and treatment characteristics should be considered while monitoring performance of individual patients.

Conclusions

This study demonstrates how specific parameters may influence the interpretation of reading and spelling assessments in neurosurgical practice. Based on lesion and neuroimaging studies, individual error profiles could be predicted in most cases given glioma location. Knowledge of the functional neuroanatomy of written language can be exploited to target processes exposed to intra-operative damage. The current study also shows that the timing of post-operative assessments may result in qualitatively and quantitatively different results, and thus influence the evaluation of treatment outcome. Although no direct relationship was established between written language and broad cognitive profiles, performance in individual cases may be influenced by damage to other cognitive domains. In the highly personalized practice of awake surgery, each patient must be evaluated individually and longitudinally. Accurate interpretation of written language performance requires careful consideration of each patient's demographic, tumor, and treatment characteristics.

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8

General discussion

The aim of this thesis was to contribute to the improvement of written language monitoring in glioma practice. By reviewing current assessments of reading and spelling in awake surgery studies, we aimed to provide a better understanding of how neuroanatomical theories may guide neurosurgical practice (Chapter 2), and to evaluate how examinations of written language in glioma patients can be improved (Chapter 3). To provide a direct clinical application for this knowledge, we developed a theory-driven written language battery specifically for glioma patients (Chapter 4). Lastly, we tested its efficacy and evaluated reading and spelling performance in neurosurgical practice (Chapters 5, 6, 7). In this final chapter, I discuss the main findings of the study, and its implications for clinical practice and future research.

Written language monitoring in glioma patients

In current awake surgery practice, written language is often evaluated cursorily or altogether neglected. Over the last decades, linguistic assessments, initially restricted to automatic speech and object naming [1,2], were extended to make up elaborate batteries for glioma patients [3-5]. Yet, these batteries almost exclusively monitor spoken language. The complex and multifaceted linguistic processes of reading and spelling are essential in modern society due to an increasing reliance on text-based communication. Hence, since one of the main goals of awake surgery for glioma treatment is the preservation of language to facilitate return to work and maintain quality of life, it has been argued in this thesis that written language monitoring in glioma patients is crucial.

Assessments before, during and after awake surgery have been more commonly described for reading than for spelling (Chapter 2). In fact, only 7 studies have described pre- and post-operative spelling assessments in reasonable detail [6-12], and intra-operative monitoring of spelling has been reported by four research groups [8,11,13,14]. In each of these studies, short clinical subtests from post-stroke aphasia batteries were used. Even though they may broadly inform on the status of a linguistic skill (impaired vs. preserved), short subtests do not suffice for monitoring cognitive/linguistic functions in glioma patients (Chapter 3). This is because, among other things, tasks adequate to evaluate stroke patients may not be sensitive enough to reveal very subtle deficits, which are common in glioma patients eligible for awake surgery [15,16]. Brain tumor patients differ from vascular cases in many respects, including lesion onset and distribution. Gliomas mostly infiltrate underlying nervous tissue, and their slow growth (on average, 4mm per year [17]) may allow pre-surgical plasticity. In contrast, strokes have a sudden onset and cause direct damage to neural tissue. Furthermore, regularities in the territory of brain arteries constrain the distribution of tissue damage in stroke, but not in tumors, which can also affect smaller regions. However, most importantly, the goal of assessments differs in the two patient populations. While both aim to evaluate patients' performance, assessments in glioma practice also serve a crucial function in surgical planning. The gold standard for glioma treatment is awake surgery, which allows monitoring of cognitive functions during surgery [2,18-21]. Particularly in pre-operative assessment, as part of surgical planning, it is therefore crucial to identify which functions are most likely to be damaged during surgery. The use of sensitive tasks that provide guidelines for resection-related decisions during surgery is widely accepted and advocated for [2,18,21-24].

In Chapter 3, we tried to establish if the limitations of short batteries could be ascribed to a limited use of the information they can provide. Therefore, we pushed the analysis of results on short subtests beyond the mere classification of impaired vs. preserved performance. Perhaps, more punctilious quantitative and qualitative analyses would yield information sufficient to pursue the goals of awake surgery. Yet, retrospective analyses in a group of glioma patients showed that even the most fine-grained analyses of available materials were not sufficiently informative on the status of reading and spelling processes. Only non-word reading, non-word spelling and written picture description tasks were available for these analyses. Therefore, the lack of detectable patterns could have resulted from the arguable choice of tasks. If this were the case, we would expect that the assessed tasks resulted in no errors. Yet, the pathological scores that were detected on the short subtests indicated that these tasks could provide some information on patients' performance, but lack sensitivity to inform on the integrity of separate components. The clinical subtests contained limited numbers of stimuli, which may not have been enough to identify distinct error types and effects. Hence, we hypothesized that the lack of sensitivity was due to the assessment tool used (Chapter 3).

To test this hypothesis, in Chapter 5, we contrasted the clinical subtests with a theory-driven written language assessment battery, which we developed specifically for glioma practice. Comparisons in two patients revealed greater sensitivity of the theory-driven test as compared to the clinical subtests, even when the contrasts were limited to non-word reading and spelling tasks. These results confirmed that the lack of sensitivity of the clinical tests did not result from an arbitrary choice of tasks. In addition, in the same patients the glioma battery identified more pathological scores than the clinical tasks (Chapter 5). Hence, even when evaluations only aim to classify performance as impaired or preserved, the written language battery is preferable in neurosurgical practice.

As an important output of this thesis, the comprehensive and standardized battery for written language monitoring in glioma patients is now available in Italian and Dutch (Chapter 4). A cognitive model that distinguishes multiple components of reading and spelling served as the foundation for the written language battery. The battery includes word, non-word and sentence reading and spelling tasks. For each task, contrasting psycholinguistic variables may inform on reading- and spelling-specific central processes. To evaluate if all tasks could be administered in each phase of glioma practice, stimuli were standardized with 101 Italian and Dutch neurologically healthy adults. Particularly for intra-operative assessment, an important temporal limitation should be considered. Direct Electrical Stimulation (DES) is used for intra-operative mapping, but can only be safely applied for a limited amount of time. Although there is a debate on the temporal limit of DES, classically the gold standard was set at 4 seconds [19,25]. The participating hospitals in our studies follow these guidelines, hence for them a complete stimulus-response cycle should take place in <4 seconds to inspect the influence of neural inhibition caused by DES. Data from healthy volunteers indicated that word and non-word reading stimuli, and probably also word and non-word spelling stimuli can be administered in this time frame. In contrast, sentence reading and, even more so, sentence spelling, are less appropriate for DES mapping, as even short sentences exceeded the 4 second limit (on average >18 seconds). Yet, stimuli selection should predominantly be guided by patient's individual characteristics (see Section *Considerations for clinical practice*).

Two features of the battery may be specifically beneficial for clinical glioma practice. First, to ensure test sensitivity (i.e., the probability to detect a true error), the cut-off for normative data was set at 95%. Particularly during awake surgery, it is crucial to know if a patient's performance deviates from the norm, as during DES the examiner must be confident that an error occurred due to the stimulation, rather arising independent of stimulation. The risk of producing false positives was minimized, by developing a test with high sensitivity. Second, we aimed to optimize the comparison of performances obtained in short time windows. To this end, we developed two fully balanced, parallel versions of the battery. They help control for incidental learning, and allow for longitudinal monitoring at short intervals, while still permitting the analysis of qualitative changes over time (Chapter 4). The battery could be administered before, during and after surgery without patients' complaints, and provided information on the status of cognitive/linguistic processes underlying reading and spelling (Chapter 5).

Written language disorders in neurosurgical practice

Although short clinical subtests proved to be of limited usefulness for an understanding of the status of reading and spelling skills in glioma patients, they nonetheless showed how vulnerable written language functions are in this patient group. The literature review of spelling in awake surgery and the retrospective study indicated that post-operative dysgraphia arose in 26.9% of patients with preserved pre-operative spelling (Chapter 2), or in 42.9% of all patients (Chapter 3). In (more than) half of these patients, dysgraphia persisted on longer-term after surgery (45.0% in the literature, and 62.5% in our retrospective analyses). Reading was affected in 71.4% after glioma surgery, which persisted at follow-up in 62.5% of the cases (Chapter 3). Retrospective analyses furthermore revealed that spelling and reading impairments were also frequent before surgery, in respectively 35.7% and 28.6% of cases (Chapter 3). Yet, as clinical subtests lack sensitivity, we hypothesized that actual frequency of written language disorders in glioma patients may be higher.

Chapter 6 provides the first available overview of written language performance in glioma patients, using a tailored assessment tool for neurosurgical practice. Before glioma surgery, central processes of spelling and reading were impaired in respectively 50.0% and 37.5% of cases. Compared to previous evaluations, these numbers indicate that the new battery revealed a higher incidence of pre-operative written language impairments. Post-operatively, similar or lower error rates were observed on the new battery compared to the clinical subtests, showing written language impairments in approximately half of the patients (50.0% on spelling and 43.8% on reading tasks). Yet, the new, longer battery is likely to provide a more reliable measure. Percentages on short subtests reflect small numbers of errors (e.g., 2/10), which may also have arisen because of a momentary lapse of attention. The same error percentage on a longer battery (e.g., 20/100) is more informative, as 20 errors do not arise by chance but reflect an error pattern.

Alternatively, differences in observed error rates may result from confounding variables that influence evaluations of performance in awake surgery (Chapter 7). For example, large variability in timing of post-operative evaluations was observed across and within studies. In the subacute post-surgery phase (the first ten days after surgery), edema and fatigue can influence performance to such different extents that reliable interpretations are not possible. Therefore, we did not consider performance in the subacute phase when describing outcome after glioma surgery. However, 'new' written language impairments (pathological post-operative scores after preserved pre-operative performance) arose up to 3 months after surgery, which recovered on the long term. Hence, when evaluating post-operative performance, a very different picture may appear when assessments are conducted at 6 weeks (when performance may still change) or 6 months after surgery (when performance is probably stable). While subacute evaluations are often disregarded in the literature [16,26-28], post-operative assessments have been reported in very disparate time frames, and are rarely considered in light of possible recovery patterns over time [26,27].

In line with reports on other cognitive functions, at the group level, written language performance returned to pre-operative baseline in the long term [16,26,27] (Chapters 3, 6). However, the observation of persistent impairments at follow-up indicated that this pattern does not apply to all individual cases (Chapters 2, 3, 6). A number or reasons may be considered. First, one may argue that written language functions are more vulnerable to damage than other tasks. Since reading and spelling rely on complex neural networks involving many (sub)cortical sites, the possibility of disrupting the network may be increased. However, although not the scope of this thesis, cognitive functions were always assessed in addition to written language, and impairments at follow-up were also observed on these tasks. Hence, other tasks are also vulnerable for persistent damage after glioma surgery. Another explanation may lie in the heterogeneity of the patient group described in our studies, which included both high- and low-grade gliomas. Even though we did not find differences in performance between these two types (Chapter 7), other studies reported more severe deficits in high-grade gliomas patients [29-31]. Lastly, although we aimed to avoid selection biases, we had no control over which patients were referred from collaborating hospitals. As a result, more patients may have been referred with gliomas in areas crucial for written language and/or with written language complaints.

These considerations recommend caution in generalizing results. Nevertheless, since persistent written language deficits were observed both on the short clinical subtests (Chapters 2, 3) and on extensive testing (Chapter 6) - and selection biases cannot have influenced retrospective analyses – it is likely that persistent reading and spelling impairments after surgery may emerge in individual patients. These results show that written language may be affected by glioma or glioma surgery, and that evaluation of written language in individual glioma patients is relevant.

Preservation of written language in awake surgery

Improved monitoring of written language in neurosurgical practice may not only facilitate more detailed insight in written language performance in glioma patients, but also contribute to predict and prevent reading and spelling impairments after surgery. Data in Chapter 6 showed that the often observed increase in difficulties after surgery can be fully controlled or effectively limited after intra-operative monitoring.

Intra-operative mapping using DES allows to identify, and spare, neural substrates of the assessed function [2]. As spoken and written language require at least partly distinct functional components and engage at least partly separate neural underpinnings [32,33], assessments of spoken language may leave specific written language processes unattained for. Hence, we expected that these functions could be affected differently by glioma surgery, depending on intra-operative assessments. Confirming our hypothesis, and congruent with other studies [2,19,22], we reported sparing of spoken language tasks after awake surgery with intra-operative spoken language (Chapter 6). Yet, the non-monitored written language tasks were not preserved (Chapters 3, 6). Correspondingly, written language impairments were more common after surgery with spoken language monitoring than when written language was monitored intra-operatively (Chapter 6).

In addition to comparing the outcome of spoken and written language as a function of the intra-operative testing of spoken language alone, or of both spoken and written language, we wished to evaluate the functional preservation of written language skills as a function of intra-operative testing of reading only, of spelling only, or of reading and spelling. Based on the cognitive model used throughout this thesis [34-36], we expected different written language tasks to be independently affected by glioma surgery. We hypothesized that intra-operative monitoring of only one written language task (e.g., reading) may not suffice to also spare the other written language task (e.g., spelling). Results provided confirmatory evidence for independent processing of reading and spelling by disclosing isolated impairments of reading (12.5%) and spelling (38.8%) after surgery, regardless of intra-operative assessment (Chapter 6). Isolated spelling interferences were similarly observed during intra-operative stimulation (in 37.7% of cases; Chapter 2). Evaluations of specific intra-operative assessments showed that task-specific preservation was successful in all cases, hence the intra-operatively assessed written language task (reading and/or spelling) was preserved after surgery. Yet, congruent with our expectations, non-monitored written language tasks were not always preserved. Almost a third of patients with intra-operative reading (28.6%) showed a significant decline in spelling after surgery (while reading was preserved; Chapter 6). These results provide additional support for theories of independent components underlying reading and spelling [35,37-43], as distinct neural substrates prevented generalization of written language functions.

In summary, our studies indicate that written language impairments may be prevented when functions are carefully assessed intra-operatively. Yet, in the absence of intra-operative testing, a relevant risk of significant decline after awake surgery was established, as reading deteriorated in 16.7% of the cases when it was not monitored intra-operatively, and spelling in 25.0% of the cases in absence of intra-operative monitoring (Chapter 6). Hence, results illustrate that task-specific intra-operative assessments are required when neurosurgical teams wish to preserve a specific written language function.

Considerations for clinical practice

Results of applications of the written language battery for glioma patients have demonstrated that the battery may be applied in all phases of clinical practice (Chapters 5, 6). The battery provides a powerful and flexible tool to monitor and ultimately prevent reading and spelling impairments. With regards to prevention of written language deficits, we further aimed to establish whether we could predict performance, based on patient's characteristics.

The large variability across subjects, documented in all studies, emphasized that assessments should be analyzed for the individual patient. In addition, the influence of assessment timing (Chapter 7) indicated that reading and spelling should ideally be monitored longitudinally to interpret a patient's performance accurately. Extensive pre-operative assessments using the complete written language battery in addition to general neuropsychological assessments provide the possibility to assess the status of each component of the reading and spelling systems, and to guide stimulus selection for intra-operative testing. In addition, pre-operative testing can inform on the 'idiosyncratic' spelling speed for each patient, to establish which items for spelling may be administered during DES. In healthy volunteers, spelling stimuli (administered as handwriting) could not be always administered within the standard time limit of 4 seconds (Chapter 4). Individual reaction time data could be used to establish the upper limits on the length of the stimuli to be administered intra-operatively (e.g., a subject could be able to write stimuli of up to 7 letters in 4 seconds, but not stimuli of 8 or more letters). In awake surgery, pre-operative performance should be regarded as the individual baseline for intra- and post-operative evaluations. Within-subject comparisons allow careful evaluation of written language, while taking possible associations with other influences into account. When non-linguistic variables (e.g., demographic variables, other cognitive impairments, or tumor characteristics) influence written language performance at pre-operative assessment, these are likely to influence performance at intra- and post-operative assessments to the same extents. Hence, performance can be reliably monitored over time when the pre-operative performance is used as an individual baseline. Post-operatively, the complete battery should ideally be administered again, to establish if written language processes were spared during surgery, and to contribute to monitoring disease progression so that early rehabilitation can be initiated if needed.

Longitudinal monitoring is the standard to be aimed at, yet certain practical considerations should be addressed. Extensive assessments provide best insight in patient's functioning, but are also time consuming. Instead, evaluations of spontaneous language production (speech, or spelling) may be quicker to assess in clinical practice. A recent comparison between formal testing and spontaneous speech showed however that formal testing should be preferred in current clinical practice, as analyses of spontaneous speech are less objective and more time consuming [44]. The written language battery provides a formal testing tool that may be used flexibly, in which also only a selection of stimuli based on individual characteristics may be assessed. Depending on the goals of the neurosurgical team, the extensive battery can pre- and post-operatively be used to obtain information on tumor removal, sparing of quality of life and on neural correlates of reading and spelling.

Intra-operative assessments on the other hand must be quick and efficient to reduce the duration of surgery while at the same time ensuring that crucial areas are not resected [45]. To preserve quality of life in the individual patient, the intra-operative assessment must be tailored and targeted to the needs of each case (Chapter 6). Task selection may be constrained by available time and ethical considerations. Although the demonstrated successful task-specific preservation may imply that all tasks of interest should be assessed intra-operatively to spare functional outcome, awake procedures are subjected to time restrictions [19,25]. Intra-operative assessment is therefore necessarily limited to a small number of short tasks. With regard to ethical considerations, it has been questioned whether intra-operative assessment of spelling in the modality of handwriting is desirable. Handwriting assessment may cause greater discomfort compared to that of reading (or other spoken language tasks), especially if the patient is positioned lying on his/her right side to facilitate exposure of the surgical field. However, our results indicated that it should not discourage an evaluation in patients at risk for dysgraphia, as even this surgical position is compatible with sufficiently free hand movement without patient's complaints (Chapters 5, 6 and [8-13]). In addition to being feasible, intra-operative spelling assessments have been shown to be necessary for some cases to spare spelling (Chapter 6). Spelling can apart from handwriting be assessed by oral spelling-to-dictation or typing tasks. The opportunity to administer these tasks depends on the patient's familiarity (Chapter 4). Moreover, task selection should aim to be as relevant for the individual patient as possible. It has been proposed to ask the patient before surgery which function he/she considers most or least important [46]. However, it could be argued that patients in these conditions (with possible anxiety, emotional instability and/or cognitive dysfunction induced by the glioma) may not be able to do so. On the other hand, it is naturally important to consider personal factors such as the patient's profession in intra-operative task selection (for example, a journalist may rely more on written language functions than a painter, for which motoric aspects may be more crucial).

These constrains could be overcome when intra-operative stimulus selection is guided by the patient's lesion location in addition to pre-operative performance. With the aim to predict functional damage based on glioma location, we evaluated whether knowledge on the neural substrates of written language from lesion and neuroimaging studies (Chapters 1, 2; Figures 1.2 and 2.2) could be applied to glioma patients. We hypothesized that performance profiles after resection of specific areas would in most cases be in conjunction with current premises on the functional neuroanatomy of written language. Data in Chapter 2 provided the first confirmative accounts of this hypothesis, by demonstrating that glioma data converged with extant literature of spelling. Yet, due to the large variability in reviewed reports, these were not yet sufficient to draw reliable probabilistic (sub)cortical maps. Subsequently, we conducted controlled examinations with the written language battery for glioma patients, which confirmed that knowledge about neural substrates of reading and spelling can be used to guide neurosurgical practice (Chapter 7). Hence, preparation of the individually tailored, intra-operative battery should be guided by current knowledge of the functional neuroanatomy of written language. For example, as a glioma in the inferior frontal gyrus may affect both written and spoken language, intra-operative assessment of spoken language may suffice. A glioma in the inferior temporal gyrus on the other hand, is likely to only affect written language, and must thus intra-operatively be tested with reading and/or spelling tasks.

Future research

Results of this thesis have proposed new considerations to address in further research. The field of awake surgery is at the cutting edge of clinical neuroscience, yet opportunities stand to improve clinical practice and research. In our studies, the written language battery for glioma patients was evaluated in light of its application in neurosurgical practice. In addition to this direct clinical value, the battery could also provides a unique opportunity to investigate the neural substrates of written language in more detail. Particularly knowledge on the subcortical tracts involved in reading and spelling, and on the neural substrates of peripheral spelling processes (of handwriting, typing and oral spelling). Given that gliomas may cause circumscribed damage to neural regions that are typically affected extensively by stroke (such as perisylvian regions), glioma data could inform on the specific function of these regions. We are currently applying this rationale by investigating the contribution of specific parts of the perisylvian cortex in sublexical processing.

In future studies, data from intra-operative stimulation could contribute complementary information to that provided by extant lesion and neuroimaging studies. DES during awake surgery is the most reliable technique to investigate the anatomo-functional correlates at both the cortical and subcortical level. Moreover, by correlating multimodal pre- and post-operative data, more insight could be gathered in the mechanisms underlying the re-organization of written language functions. Diffusion Tensor Imaging will shed further light on the infiltration of gliomas or the effect of surgery on fiber tracts critical for the processing of written language.

Relevant information could be obtained by including more patients, and by assessing them longitudinally. Yet, large variations between studies and hospitals in timing of assessments complicate comparisons across studies. Agreements on testing protocols could facilitate research collaborations. Since glioma studies almost inevitably rely on small numbers of patients, many nuisance factors may have influenced results (for example, co-occurring cognitive impairments; Chapter 7). Including more patients would allow contrasting subjects with very similar lesions and cognitive profiles, and to correlate specific intra-operative assessments with dyslexic or dysgraphic profiles. Longitudinal evaluations would provide deeper insight in changes in performances over time. Moreover, the structure of the written language battery allows adopting (not translating) the tasks into other languages, to expand data collection and clinical care.

Lastly, although patients shared complaints of written language use in daily life, which diminished after surgery, only scattered informal reports are currently available. As the aim of awake surgery is to preserve quality of life, it would be interesting to further explore the influence of written language impairments on daily life more objectively and in a larger subject sample.

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A

Appendices

Appendix A

Example of a search string

‘writing’/exp OR ‘spelling’/exp OR ‘written spelling’ OR ‘handwriting’/exp OR graphem* OR letter* OR orthography* OR ‘written language’/exp OR dysgraph* OR agraph* OR (‘writing’ OR ‘spelling’ OR ‘written language’ OR ‘written spelling’ OR orthograph* OR graphem* OR graphomotor OR allographic* OR phoneme-grapheme) NEAR/3 (disorder* OR deficit* OR difficult* OR disrupt* OR disturb* OR dysfunct* OR error* OR impair* OR trouble* OR defect) OR (writing OR spelling OR ‘written language’ OR ‘written spelling’ OR orthograph* OR graphem* OR graphomotor OR allographic* OR phoneme-grapheme) NEAR/3 (abilit* OR function* OR assessment* OR batter*) AND (‘glioma’/exp OR ‘glioblastoma’/exp OR ‘high grade glioma’ OR ‘low grade glioma’ OR ‘astrocytoma’/exp OR ‘brain tumor’/exp OR ‘brain tumour’/exp OR ‘meningioma’/exp) AND (‘awake surgery’ OR ‘awake craniotomy’ OR craniotom* OR ‘electrostimulation’/exp OR intraoperat* OR peroperat* OR preoperat* OR postoperat* OR ‘peroperative care’/exp OR ‘patient monitoring’/exp OR ‘brain mapping’/exp OR ‘brain surgery’/exp) NOT (‘child’/exp OR ‘adolescence’/exp OR ‘childhood’/exp OR ‘newborn’/exp NOT (‘adult’/exp OR ‘adulthood’/exp OR ‘aged’/exp)) AND [article]/lim AND [english]/lim

Appendix B
Stimuli lists

Appendix B.1 Italian stimuli lists

Appendix B.1a Italian reading: Pre-operative version

Italian | Word reading | Pre-operative

Presentation NR	Stimulus (IT)	Stimulus (EN)	Assessment list	Sublist	Assessment cluster	Grammatical class	Frequency count	Frequency	Letters	Phonemes	Syllables	Length	Imageability	Mean reaction time	Morphological regularity	Root	Inflection	Consonant vowel order
1	tabacco	tobacco	II	1	LFL	N	5,79	L	7	6	3	L	4,73	2,74				ccvcvcv
2	rise	he laughed	II	2	MI	V	9,21		4	4	2		3,04	2,90	I	2		cvcv
3	unico	unique	II	1	HFS	A	165,86	H	5	5	3	S	2,92	2,69				vcvcv
4	chiedere	to ask	II	1	HFL	V	78,19	H	8	7	3	L	2,92	2,79				ccvvcvcv
5	gamba	leg	I	3	Ocg	N	26,59		5	5	2		4,92	2,36				cvccv
6	parso	seemed	II	2	MI	V	8,16		5	5	2		1,76	2,44	I	2		cvccv
7	alto	high	I	1	HFS	A	164,02	H	4	4	2	S	4,16	2,50				vccv
8	spingo	I push	I	2	MR	V	0,79		6	6	2		3,54	2,47	R	4	2	ccvccv
9	medaglie	medals	I	1	LFL	N	8,95	L	8	7	3	L	4,90	2,44				cvcvccvv
10	qualcuno	someone	I	1	HFL	F	237,48	H	8	8	3	L	2,48	2,16				cvvccvcv
11	ripetendo	repeating	II	2	MR	V	2,90		9	9	4		2,38	3,07	R	5	4	cvcvcvccv
12	forte	strong	II	1	HFS	A	207,73	H	5	5	2	S	3,44	2,34				cvccv
13	progressi	progress	II	1	LFL	N	8,95	L	9	8	3	L	2,40	2,64				ccvccvGv
14	dormi	you sleep	II	2	MR	V	3,16		5	5	2		3,98	2,66	R	4	1	cvccv
15	famiglia	family	II	1	HFL	N	304,61	H	8	7	3	L	4,68	1,81				cvcvccvv
16	appieno	fully	II	1	LFL	F	2,11	L	7	6	3	L	1,76	2,06				vGvccv
17	panca	bench	I	3	Ocg	N	3,42		5	5	2		4,90	1,95				cvccv
18	vive	lives	I	1	HFS	V	90,30	H	4	4	2	S	2,88	1,89				cvcv
19	volgare	vulgar	II	1	LFL	A	6,85	L	7	7	3	L	2,92	2,22				cvccvcv
20	scrissero	they wrote	II	2	MI	V	1,84		9	8	3		2,98	2,38	I	4		cccvGvcv
21	sacro	sacred	II	1	LFS	A	18,96	L	5	5	2	S	3,18	2,47				cvccv
22	chiesa	church	I	1	HFS	N	141,38	H	6	5	2	S	4,88	1,99				ccvvcv
23	alzi	he lift	I	2	MR	V	1,84		4	5	2		2,32	2,44	R	3	1	vccv
24	piccola	small	II	1	HFL	A	135,59	H	7	6	3	L	3,71	2,18				cvcvccv
25	decoro	decorum	II	3	Ostress	N	5,00		6	6	3		3,18	2,46				cvcvcv
26	risponde	answers	I	1	HFL	V	79,77	H	8	8	3	L	2,96	2,12				cvccvccv
27	assurdo	absurd	I	1	LFL	A	17,64	L	7	6	3	L	1,80	2,47				vGvccv
28	penna	pen	I	3	Ogem	N	13,95		5	4	2		4,90	1,85				cvGv
29	segnava	marked	I	1	LFL	V	3,69	L	7	6	3	L	2,90	2,42				cvccvcv
30	scarpa	shoe	II	3	Ocg	N	7,90		6	6	2		4,90	2,14				ccvccv
31	avveniva	occurred	I	1	LFL	V	6,06	L	8	7	4	L	1,96	2,36				vGvcvcv
32	canale	channel	II	3	Ostress	N	35,02		6	6	3		4,36	2,30				cvcvcv
33	chiama	calls	I	1	HFS	V	88,20	H	6	5	2	S	3,24	2,34				ccvvcv
34	sassi	stones	II	1	LFS	N	11,58	L	5	4	2	S	4,90	2,13				cvGv
35	crea	he creates	I	2	MR	V	25,54		4	4	2		2,68	2,29	R	3	1	ccvv
36	piuttosto	rather	II	1	HFL	F	142,43	H	9	8	3	L	1,47	2,34				cvvGvccv
37	sinfonia	symphony	I	1	LFL	N	11,85	L	8	8	3	L	3,54	2,57				cvccvcvv
38	girando	turning	I	2	MR	V	10,79		7	7	3		3,06	2,44	R	3	4	cvcvccv
39	anzi	rather	I	1	HFS	F	167,2	H	4	4	2	S	1,39	2,06				vccv
40	parco	park	II	3	Ocg	N	44,49		5	5	2		4,80	2,07				cvccv
41	scatta	snaps	I	1	LFS	V	16,32	L	6	5	2	S	2,94	2,30				ccvGv
42	gusti	taste	II	3	Ocg	N	14,48		5	5	2		2,74	2,57				cvccv
43	colui	he	I	1	LFS	F	15,27	L	5	5	3	S	1,86	2,18				cvcvv
44	ragazzi	boys	II	1	HFL	N	161,9	H	7	6	3	L	4,77	1,97				cvcvGv
45	unirono	they united	II	2	MR	V	0,79		7	7	4		2,50	2,81	R	3	4	vcvcvcv
46	vecchio	old	I	1	HFL	A	164,3	H	7	5	2	L	4,31	2,06				cvGcvv
47	massa	mass	II	3	Ogem	N	49,76		5	4	2		3,37	2,62				cvGv
48	circa	about	II	1	HFS	F	244,8	H	5	5	2	S	1,56	2,02				cvccv
49	processo	process	I	1	HFL	N	126,1	H	8	7	3	L	3,56	2,39				ccvcvGv
50	spense	he turned off	I	2	MI	V	3,949		6	6	2		2,83	2,93	I	4		ccvccv
51	ossia	namely	II	1	LFS	F	27,12	L	5	4	2	S	1,43	2,08				vvcv
52	ferri	irons	I	3	Ogem	N	11,32		5	4	2		4,22	2,19				cvGv
53	oppure	or	I	1	HFS	F	175,3	H	6	5	3	S	1,65	2,05				cvccvv
54	ditta	firm	I	3	Ogem	N	24,48		5	4	2		3,98	2,17				cvGv
55	capace	capable	I	1	HFS	A	72,66	H	6	6	3	S	2,62	2,25				cvcvcv
56	albo	register	I	1	LFS	N	5,002	L	4	4	2	S	3,80	3,06				vccv
57	lavo	I wash	II	2	MR	V	0,527		4	4	2		4,08	2,38	R	3	1	cvcv
58	fiori	flowers	II	1	HFS	N	86,35	H	5	5	2	S	4,96	1,83				cvvcv
59	oramai	by now	I	1	LFS	F	5,529	L	6	6	3	S	1,54	2,18				vcvcvv
60	riga	line	I	3	Ocg	N	7,372		4	4	2		4,67	1,95				cvcv
61	circonda	surrounds	II	1	LFL	V	11,32	L	8	8	3	L	3,10	2,41				cvccvccv
62	pelli	skins	II	3	Ogem	N	6,582		5	4	2		4,49	2,18				cvGv
63	denuncio	sue	II	1	LFL	V	0,527	L	8	8	3	L	2,68	2,26				cvcvccvv
64	nemmeno	not even	I	1	HFL	F	144,8	H	7	6	3	L	1,64	2,19				cvGvcv
65	godo	I enjoy	II	2	MR	V	0,527		4	4	2		2,80	1,90	R	3	1	cvcv
66	cupo	gloomy	I	1	LFS	A	7,635	L	4	4	2	S	3,06	1,97				cvcv

67	perdere	to lose	I	1	HFL	V	101,4	H	7	7	3	L	2,90	1,99				cvccvcv
68	sedile	seat	I	3	Ostress	N	13,95		6	6	3		4,84	1,87				cvcvcv
69	rapidi	rapid	I	1	LFS	A	8,425	L	6	6	3	S	2,98	2,31				cvcvcv
70	prendiamo	we take	I	2	MR	V	11,06		9	9	3		3,04	2,59	R	5	4	vccvcvvcv
71	medesimo	same	I	1	LFL	A	11,32	L	8	8	4	L	2,06	2,22				cvcvcvcv
72	borgo	suburb	II	1	LFS	N	9,741	L	5	5	2	S	4,56	2,12				cvccv
73	sembro	I look	II	2	MR	V	1,58		6	6	2		2,22	2,23	R	5	1	cvcccv
74	portici	arcades	I	3	Ostress	N	3,949		7	7	3		4,84	2,11				cvccvcv
75	torna	returns	II	1	HFS	V	72,4	H	5	5	2	S	2,48	2,13				cvccv
76	davvero	really	II	1	HFL	F	202,5	H	7	6	3	L	1,52	2,02				cvGvcv
77	dicevo	I said	I	2	MI	V	12,64		6	6	3		2,58	2,22	I	2		cvcvcv
78	capo	chief	I	1	HFS	N	256,2	H	4	4	2	S	4,34	2,11				cvcv
79	dovunque	everywhere	II	1	LFL	F	11,06	L	8	8	3	L	2,37	2,21				cvcvccvv
80	amasse	loved	II	2	MR	V	2,369		6	5	3		2,10	3,02	R	2	4	vcvGv
81	membro	member	I	1	LFS	N	20,01	L	6	6	2	S	3,14	2,50				cvcccv
82	badi	you look after	I	1	LFS	V	2,633	L	4	4	2	S	1,66	2,01				cvcv
83	catene	chains	II	3	Ostress	N	10,53		6	6	3		4,86	1,80				cvcvcv
84	siccome	since	I	1	LFL	F	21,33	L	7	6	3	L	1,34	1,99				cvGvcv
85	maggiore	greater	I	1	HFL	A	126,9	H	8	7	3	L	3,35	2,31				cvGvvcv
86	modulo	module	I	3	Ostress	N	7,372		6	6	3		4,08	2,11				cvcvcv
87	udire	to hear	II	1	LFS	V	4,212	L	5	5	3	S	3,42	2,01				vcvcv
88	giornata	day	I	1	HFL	N	127,7	H	8	8	3	L	3,74	2,17				cvvccvcv
89	sentivano	they felt	I	2	MR	V	6,319		9	9	4		2,82	2,54	R	4	5	cvccvcvcv
90	greca	Greek	II	1	LFS	A	12,37	L	5	5	2	S	3,66	2,80				ccvcv
91	penso	I think	II	1	HFS	V	88,46	H	5	5	2	S	2,84	2,35				cvccv
92	razze	races	II	3	Ogem	N	7,635		5	4	2		3,96	2,20				cvGv
93	magnifici	magnificent	II	1	LFL	A	6,582	L	9	8	4	L	2,82	2,33				cvccvcvcv
94	gambe	legs	II	1	HFS	N	66,35	H	5	5	2	S	4,96	1,80				cvccv
95	pagando	paying	I	2	MR	V	5,266		7	7	3		3,69	2,26	R	3	4	cvcvccv
96	donde	whence	II	1	LFS	F	2,633	L	5	5	2	S	1,36	1,96				cvccv
97	colpendo	hitting	II	2	MR	V	3,949		8	8	3		3,50	2,24	R	4	4	cvccvGv
98	italiana	Italian	II	1	HFL	A	176,9	H	8	8	3	L	3,30	2,45				vcvcvvcv
99	pastore	shepherd	I	3	Ostress	N	8,425		7	7	3		4,86	1,96				cvccvcv
100	avverte	he warns	I	2	MR	V	22,38		7	6	3		2,14	2,11	R	5	2	vGvccv
101	stanotte	tonight	I	1	LFL	F	6,845	L	8	7	3	L	3,48	2,32				ccvcvGv
102	sogna	dreams	II	1	LFS	V	13,16	L	5	4	2	S	3,26	2,12				cvccv
103	tavolo	table	II	3	Ostress	N	71,35		6	6	3		4,92	1,69				cvcvcv
104	potresti	you could	II	2	MI	V	6,845		8	8	3		1,81	2,23	I	5		cvccvccv
105	tardi	late	II	1	HFS	F	90,3	H	5	5	2	S	2,72	2,14				cvccv
106	arrivato	arrived	II	1	HFL	V	97,94	H	8	7	4	L	2,98	2,46				vGvcvcv

Presentation NR	Stimulus (IT)	Assessment list	Sublist	Assessment cluster	Letters	Phonemes	Syllables	Length	N-count	Similarity to words	Mean reaction time	Consonant vowel order
1	praulo	II	3	nCV	6	6	3		0		2,16	ccvvcv
2	uteli	II	2	nMD	5	5	3		3		1,99	vcvcv
3	imieto	I	1	LS	6	6	3	L	1	L	2,11	vcvvcv
4	flitori	I	3	nCV	7	7	3		0		2,17	ccvcvcv
5	godasti	II	2	MD	7	7	3		3		2,54	cvcvccv
6	sterso	I	1	HS	6	6	2	L	6	H	2,06	ccvccv
7	roreda	I	2	nMD	6	6	3		1		2,57	cvcvcv
8	soro	I	1	HS	4	4	2	S	11	H	1,75	cvcv
9	baltovi	I	2	nMD	7	7	3		0		2,03	cvccvcv
10	midoto	I	3	CV	6	6	3		0		2,10	cvcvcv
11	chierova	I	2	nMD	8	7	3		0		2,42	ccvvcvcv
12	opruse	I	3	nCV	6	6	3		0		2,18	vccvcv
13	gomati	II	1	LS	6	6	3	L	2	L	2,01	cvcvcv
14	nemiso	II	2	nMD	6	6	3		1		2,32	cvcvcv
15	laso	I	1	HS	4	4	2	S	12	H	1,81	cvcv
16	fattida	II	2	nMD	7	6	3		1		2,36	cvGvcv
17	piaduli	I	3	nCV	7	7	3		0		2,05	cvvcvcv
18	fineva	II	2	MD	6	6	3		1		1,81	cvcvcv
19	bugeti	II	3	CV	6	6	3		0		2,48	cvcvcv
20	usevi	II	2	MD	5	5	3		1		2,11	vcvcv
21	came	II	1	HS	4	4	2	S	14	H	1,71	cvcv
22	strivate	I	2	MD	8	8	3		0		2,12	cccvcvcv
23	giruni	II	3	CV	6	6	3		2		1,97	cvcvcv
24	cirano	II	1	HS	6	6	3	L	8	H	1,89	cvcvcv
25	limbea	I	3	nCV	6	6	3		0		2,07	cvccvv
26	deie	II	1	LS	4	4	2	S	1	L	1,97	cvvv
27	gemmiva	I	2	MD	7	6	3		1		2,31	cvGvcv
28	letide	I	3	CV	6	6	3		1		1,94	cvcvcv
29	nimole	II	1	LS	6	6	3	L	0	L	2,45	cvcvcv
30	erulche	II	3	nCV	7	6	3		0		2,50	vcvcccv
31	tinema	I	2	nMD	6	6	3		1		2,57	cvcvcv
32	enotra	I	3	nCV	6	6	3		0		2,00	vcvccv
33	pata	II	1	HS	4	4	2	S	13	H	1,73	cvcv
34	neulmo	II	3	nCV	6	6	3		0		2,44	cvvcvc
35	corete	I	2	MD	6	6	3		2		2,17	cvcvcv
36	asemido	II	3	nCV	7	7	4		0		2,58	vcvcvcv
37	isco	II	1	LS	4	4	2	S	2	L	1,62	vccv
38	aprasti	I	2	MD	7	7	3		2		2,37	vccvccv
39	merota	I	1	LS	6	6	3	L	1	L	1,88	cvcvcv
40	remivo	II	2	MD	6	6	3		2		1,97	cvcvcv
41	pacilo	I	3	CV	6	6	3		0		2,31	cvcvcv
42	spalere	I	2	MD	7	7	3		1		2,48	ccvcvcv
43	recino	I	1	HS	6	6	3	L	6	H	2,04	cvcvcv
44	botilei	II	3	nCV	7	7	4		0		2,49	cvcvcvv
45	arrusti	II	2	nMD	7	6	3		3		2,19	vGvccv
46	labu	I	1	LS	4	4	2	S	0	L	1,98	cvcv
47	stalure	I	2	nMD	7	7	3		1		2,25	ccvcvcv
48	febo	I	1	LS	4	4	2	S	1	L	1,75	cvcv
49	carate	II	1	HS	6	6	3	L	14	H	2,09	cvcvcv
50	mormoti	II	2	nMD	7	7	3		2		2,23	cvccvcv
51	toarilo	II	3	nCV	7	7	4		0		2,33	cvvcvcv
52	moreva	II	2	MD	6	6	3		1		2,19	cvcvcv

Presentation NR	Stimulus (IT)	Stimulus (EN)	Assessment list	Sublist	Assessment cluster	Grammatical class	Frequency count main word	Letters main word	Phonemes main word	Syllables main word	Words in sentence	Mean reaction time	Consonant vowel order
1	**Dei giorni sfortunati capitano a tutti.**	The unfortunate days happen to everyone.	I	1	nPS						6	4,46	
1	Dei	The	I	1		F	3427,61	3	3	1	6		cvv
1	giorni	days	I	1		N	524,19	6	6	2	6		cvvccv
1	sfortunati	unfortunate	I	1		A	1,58	10	10	4	6		ccvccvcvcv
1	capitano	happen	I	1	nPS	V	1,84	8	8	4	6		cvcvcvcv
1	a	to	I	1		F	13366,07	1	1	1	6		v
1	tutti	everyone	I	1		N	1183,17	5	4	2	6		cvGv
2	**Queste stoffe sono leggere come piume.**	These fabrics are light as a feather.	I	1	PS						6	4,24	
2	Queste	These	I	1		F	338,57	6	6	2	6		cvvccv
2	stoffe	fabrices	I	1		N	3,95	6	5	2	6		ccvGv
2	sono	are	I	1		V	3989,97	4	4	2	6		cvcv
2	leggere	light	I	1	PS	A	7,90	7	6	3	6		cvGvcv
2	come	as	I	1		F	3467,36	4	4	2	6		cvcv
2	piume	feather	I	1		N	5,79	5	5	2	6		cvvcv
3	**Stefano chiese perdono alla sorella.**	Stefano asked his sister for forgiveness.	I	1	PS						5	3,78	
3	Stefano	Stefano	I	1		N		7	7	3	5		ccvcvcv
3	chiese	asked	I	1		V	87,14	6	5	2	5		ccvvcv
3	perdono	forgiveness	I	1	PS	A	9,74	7	7	3	5		cvccvcv
3	al(la)	(to) his	I	1		F	2958,97	4	2	1	5		vc
3	(al)la sorella	sister	I	1		N	63,45	7	6	3	5		cv cvcvGv
4	**I carcerati pagano le conseguenze delle loro azioni.**	The prisoners pay the consequences of their actions	I	1	nPS						8	5,02	
4	I carcerati	The prisoners	I	1		N	1,32	9	9	4	8		v cvccvcvcv
4	pagano	pay	I	1	nPS	V	13,16	6	6	3	8		cvcvcv
4	le conseguenze	the consequences	I	1		N	48,71	11	11	4	8		cv cvccvcvvccv
4	delle	of	I	1		F	2346,85	5	4	2	8		cvGv
4	loro	their	I	1		F	1280,58	4	4	2	8		cvcv
4	azioni	actions	I	1		N	53,71	6	6	3	8		vcvvcv
5	**Laura non amava tenere le mani in grembo.**	Laura did not like to keep the hands in her lap.	I	1	PS						8	4,25	
5	Laura	Laura	I	1		N		5	5	2	8		cvvcv
5	non	not	I	1		A	9305,01	3	3	1	8		cvc
5	amava	did like	I	1		V	17,90	5	5	3	8		vcvcv
5	tenere	to keep	I	1	PS	V	80,30	6	6	3	8		cvcvcv
5	le mani	the hands	I	1		N	199,83	4	4	2	8		cv cvcv
5	in grembo	in (her) lap	I	1		A	5,00	6	6	2	8		vc ccvccv
6	**Dille di spedirlo subito.**	Tell her to send it immediately.	I	1	nPS						4	3,37	
6	Dille di	Tell her	I	1		V	0,26	5	4	2	4		cvGv cv
6	spedirlo	to send it	I	1		V	0,53	8	8	3	4		ccvcvccv
6	subito	immediately	I	1	nPS	A	343,84	6	6	3	4		cvcvcv
7	**Nell'ambito della musica è difficile avere successo.**	In the field of music it is difficult to have success.	I	1	nPS						8	4,60	
7	Nell'	In the	I	1		F	0,53	4	3	1	8		cvG
7	ambito	field	I	1	nPS	N	37,12	6	6	3	8		vccvcv
7	del(la)	of	I	1		F	6272,58	5	3	1	8		cvc
7	(del)la musica	music	I	1		N	142,43	6	6	3	8		cv cvcvcv
7	è	it is	I	1		V	2142,02	1	1	1	8		v
7	difficile	difficult	I	1		A	207,99	9	8	4	8		cvGvcvcv
7	avere	to have	I	1		V	362,53	5	5	3	8		vcvcv
7	successo	success	I	1		A	251,69	8	6	3	8		cvGvccv
8	**Il concorrente ha vinto l'ambito premio.**	The competitor has won the coveted prize.	I	1	PS						7	4,40	
8	Il concorrente	The competitor	I	1		N	7,90	11	10	3	7		vc cvccvGvccv
8	ha vinto	has won	I	1		V	82,41	5	5	4	7		cv cvccv
8	l'ambito	the coveted	I	1	PS	A	1,32	6	6	2	7		cvccvcv
8	premio	price	I	1		N	78,72	6	6	2	7		ccvcvv
9	**Portamelo quando hai tempo.**	Bring it to me when you have time.	I	2	CI						4	3,22	
9	Portamelo	Bring it to me	I	2	CI	V	0,00	9	9	3	4		cvccvcvcv
9	quando	when	I	2		F	1419,86	6	6	1	4		cvvccv
9	hai	you have	I	2		V	161,39	3	2	2	4		cvv
9	tempo	time	I	2		A	820,37	5	5	3	4		cvccv
10	**Il capitano fumava in silenzio sulla prua.**	The captain smoked in silence on the bow.	I	1	PS						7	4,18	
10	Il capitano	The captain	I	1	PS	N	51,87	8	8	4	7		vc cvcvcvcv
10	fumava	smoked	I	1		V	3,69	6	6	1	7		cvcvcv
10	in silenzio	in silence	I	1		A	95,83	8	8	1	7		vc cvcvcvv
10	sul(la)	on	I	1		F	893,83	5	3	2	7		cvc
10	(sul)la prua	the bow	I	1		N	3,95	4	4	1	7		cv ccvv
11	**Voglio che scrivano delle lettere di scuse.**	I want that they write the letters of apologies.	I	1	nPS						7	4,23	
11	Voglio	I want	I	1		V	138,75	6	5	2	7		cvccvv
11	che	that	I	1		F	16910,83	3	2	1	7		ccv
11	scrivano	they write	I	1	nPS	V	0,53	8	8	3	7		cccvcvcv
11	del(le)	the	I	1		F	2346,85	5	3	2	7		cvc
11	(del)le lettere	letters	I	1		N	64,77	7	6	3	7		cv cvcvcv
11	di scuse	of apologies	I	1		A	11,06	5	5	2	7		cv ccvcv
12	**Arrivò in ritardo perché non trovava un calzino.**	He arrived late because he could not find a sock.	I	1	PS						8	4,44	
12	Arrivò	He arrived	I	1		V	29,22	6	5	3	8		vGvcv
12	in ritardo	late	I	1		A	38,97	7	7	3	8		vc cvcvccv
12	perché	because	I	1		F	1587,04	6	6	2	8		cvcccv
12	non	not	I	1		A	9305,01	3	3	1	8		cvc
12	trovava	could find	I	1		V	26,33	7	7	3	8		ccvcvcv
12	un calzino	a sock	I	1	PS	N	0,26	7	7	3	8		vc cvccvcv

A

Appendix B.1b Italian reading: Post-operative version

Italian | Word reading | Post-operative

Presentation NR	Stimulus (IT)	Stimulus (EN)	Assessment list	Sublist	Assessment Cluster	Grammatical class	Frequency count	Frequency	Letters	Phonemes	Syllables	Length	Imageability	Mean reaction time	Morphological regularity	Root	Inflection	Consonant vowel order
1	colloqui	talks	III	1	LFL	N	20,80	L	8	7	3	L	3,72	2,11				cvGvcvv
2	laggiù	over there	III	1	LFS	F	13,16	L	6	5	3	S	2,96	2,65				cvGvv
3	parco	park	II	3	Ocg	N	44,49		5	5	2		4,80	2,07				cvccv
4	unico	unique	II	1	HFS	A	165,86	H	5	5	3	S	2,92	2,69				vcvcv
5	massa	mass	II	3	Ogem	N	49,76		5	4	2		3,37	2,62				cvGv
6	afferma	affirms	III	1	HFL	V	68,45	H	7	6	3	L	2,58	2,36				vGvccv
7	borgo	suburb	II	1	LFS	N	9,74	L	5	5	2	S	4,56	2,12				cvccv
8	vivendo	living	III	2	MR	V	17,38		7	7	3		2,34	2,14	R	2	5	cvcvccv
9	famiglia	family	II	1	HFL	N	304,61	H	8	7	3	L	4,68	1,81				cvcvccvv
10	limitare	to limit	III	1	LFL	V	11,58	L	8	8	4	L	2,66	2,30				cvcvcvcv
11	tasca	pocket	III	3	Ocg	N	31,07		5	5	2		4,90	1,85				vcvcv
12	avrà	he will have	III	1	HFS	V	87,41	H	4	4	2	S	1,92	2,25				cvccv
13	sassi	stones	II	1	LFS	N	11,58	L	5	4	2	S	4,90	2,13				cvGv
14	rise	he laughed	II	2	MR	V	9,21		4	4	2		3,04	2,90	I	2		cvcv
15	ossa	bones	III	1	LFS	N	17,38	L	4	3	2	S	4,84	1,97				vGv
16	lavo	I wash	II	2	MR	V	0,53		4	4	2		4,08	2,38	R	3	1	cvcv
17	greca	Greek	II	1	LFS	A	12,37	L	5	5	2	S	3,66	2,80				ccvcv
18	ragazzi	boys	II	1	HFL	N	161,92	H	7	6	3	L	4,77	1,97				cvcvGv
19	parso	seemed	II	2	MR	V	8,16		5	5	2		1,76	2,44	I	2		cvccv
20	forte	Ostressong	II	1	HFS	A	207,73	H	5	5	2	S	3,44	2,34				cvccv
21	temo	I fear	III	2	MR	V	14,48		4	4	2		2,43	1,91	R	3	1	cvcv
22	volgare	vulgar	II	1	LFL	A	6,85	L	7	7	3	L	2,92	2,22				cvccvcv
23	vicolo	alley	III	3	Ostress	N	6,85		6	6	3		4,76	2,36				cvcvcv
24	appieno	fully	II	1	LFL	F	2,11	L	7	6	3	L	1,76	2,06				vGvccv
25	muffa	mold	III	3	Ogem	N	1,58		5	4	2		4,62	2,12				cvGv
26	infinita	infinite	III	1	LFL	A	12,64	L	8	8	4	L	2,50	2,39				vccvcvcv
27	numero	number	III	1	HFS	N	244,32	H	6	6	3	S	4,44	1,86				cvcvcv
28	dormi	you sleep	II	2	MR	V	3,16		5	5	2		3,98	2,66	R	4	1	cvccv
29	finora	so far	III	1	HFS	F	83,99	H	6	6	3	S	1,68	2,10				cvcvcv
30	piccola	small	II	1	HFL	A	135,59	H	7	6	3	L	3,71	2,18				cvcvccv
31	razze	races	II	3	Ogem	N	7,64		5	4	2		3,96	2,20				cvGv
32	davvero	really	II	1	HFL	F	202,46	H	7	6	3	L	1,52	2,02				cvGvcv
33	progressi	progress	II	1	LFL	N	8,95	L	9	8	3	L	2,40	2,64				ccvccvGv
34	curo	I care	III	2	MR	V	1,58		4	4	2		3,17	2,25	R	3	1	cvcv
35	pensiero	thought	III	1	HFL	N	78,72	H	8	8	3	L	2,47	2,19				cvccvvcv
36	circa	about	II	1	HFS	F	244,85	H	5	5	2	S	1,56	2,02				cvccv
37	fico	fig	III	3	Ocg	N	2,90		4	4	2		4,76	2,22				cvcv
38	cercavano	they sought	III	2	MR	V	10,27		9	9	4		2,59	2,91	R	4	5	cvccvcvcv
39	esatto	exact	III	1	LFS	A	12,64	L	6	5	3	S	2,59	2,24				vcvGv
40	chiedere	to ask	II	1	HFL	V	78,19	H	8	7	3	L	2,92	2,79				ccvvcvcv
41	gusti	taste	II	3	Ocg	N	14,48		5	5	2		2,74	2,57				cvccv
42	dovunque	everywhere / w	II	1	LFL	F	11,06	L	8	8	3	L	2,37	2,21				cvcvccvv
43	arrivato	arrived	II	1	HFL	V	97,94	H	8	7	4	L	2,98	2,46				vGvcvcv
44	pelli	skins	II	3	Ogem	N	6,582		5	4	2		4,49	2,18				cvGv
45	tolto	removed	III	2	IL	V	17,9		5	5	2		2,61	2,20	I	4		cvccv
46	guanti	gloves	III	1	LFS	N	6,582	L	6	6	2	S	4,94	2,25				cvvccv
47	inoltre	also / moreove	III	1	HFL	F	129,3	H	7	7	3	L	1,66	2,44				vccvvcv
48	sedete	you sit	III	2	MR	V	10		6	6	3		3,24	2,68	R	1	5	cvcvGv
49	prossimo	next	III	1	HFL	A	127,7	H	8	7	3	L	2,58	2,50				vcvcvvcv
50	colpendo	hitting	II	2	MR	V	3,949		8	8	3		3,50	2,24	R	4	4	cvccvGv
51	zucchine	courgette	III	1	LFL	N	6,055	L	8	6	3	L	4,96	1,93				cvGcvcv
52	attira	he attracts	III	2	MR	V	6,055		6	5	3		2,69	2,66	R	5	1	vGvcv
53	macchina	machine / car	III	1	HFL	N	136,6	H	8	6	3	L	4,78	1,82				cvGcvcv
54	pure	too / also	III	1	HFS	F	178	H	4	4	2	S	1,46	1,81				cvcv
55	pecora	sheep	III	3	Ostress	N	8,688		6	6	3		4,92	2,03				cvcvcv
56	penso	I think	II	1	HFS	V	88,46	H	5	5	2	S	2,84	2,35				cvccv
57	tempera	tempera	III	3	Ostress	N	1,316		7	7	3		4,06	2,45				cvccvcv
58	stanno	they are	III	1	HFS	V	138,7	H	6	5	2	S	2,20	2,35				ccvGv
59	scarpa	shoe	II	3	Ocg	N	7,898		6	6	2		4,90	2,14				ccvccv
60	circonda	surrounds	II	1	LFL	V	11,32	L	8	8	3	L	3,10	2,41				cvccvccv
61	ultima	latest	III	1	HFS	A	203,8	H	6	6	2	S	3,00	1,98				ccvccv
62	tetto	roof	III	3	Ogem	N	31,33		5	4	2		4,98	1,91				cvGv
63	studiando	studying	III	2	MR	V	8,688		9	9	3		3,72	2,80	R	4	5	ccvcvvccv
64	italiana	Italian	II	1	HFL	A	176,9	H	8	8	3	L	3,30	2,45				vcvcvvcv
65	tabacco	tobacco	II	1	LFL	N	5,792	L	7	6	3	L	4,73	2,74				ccvcvcv
66	scrissero	they wrote	II	2	IL	V	1,843		9	8	3		2,98	2,38	I	4		cccvGvcv

67	**gambe**	legs	II	1	HFS	N	66,35	H	5	5	2	S	4,96	1,80				cvccv
68	**unirono**	they united	II	2	MR	V	0,79		7	7	4		2,50	2,81	R	3	4	vcvcvcv
69	**sacro**	sacred	II	1	LFS	A	18,96	L	5	5	2	S	3,18	2,47				cvccv
70	**sembrava**	seemed	III	1	HFL	V	112,9	H	8	8	3	L	1,94	2,16				cvcccvcv
71	**misteri**	mysteries	III	3	Ostress	N	15,01		7	7	3		2,06	2,40				cvccvcv
72	**piuttosto**	rather	II	1	HFL	F	142,4	H	9	8	3	L	1,47	2,34				cvvGvccv
73	**medi**	average	III	1	LFS	A	6,845	L	4	4	2	S	2,57	2,56				cvcv
74	**rango**	rank	III	3	Ocg	N	7,898		5	5	2		2,08	2,40				cvccv
75	**lassù**	up there	III	1	LFS	F	10,27	L	5	4	2	S	3,12	2,30				cvGv
76	**modesto**	modest	III	1	LFL	A	14,22	L	7	7	3	L	2,28	2,22				cvcvccv
77	**catene**	chains	II	3	Ostress	N	10,53		6	6	3		4,86	1,80				cvcvcv
78	**denuncio**	sue	II	1	LFL	V	0,527	L	8	8	3	L	2,68	2,26				cvcvccvv
79	**ossia**	namely	II	1	LFS	F	27,12	L	5	4	2	S	1,43	2,08				vvcv
80	**ripetendo**	repeating	II	2	MR	V	2,896		9	9	4		2,38	3,07	R	5	4	cvcvcvccv
81	**magnifici**	magnificent	II	1	LFL	A	6,582	L	9	8	4	L	2,82	2,33				cvccvcvcv
82	**odono**	they hear	III	2	MR	V	0,527		5	5	3		2,57	3,29	I	0		vcvcv
83	**donde**	whence	II	1	LFS	F	2,633	L	5	5	2	S	1,36	1,96				cvccv
84	**torna**	returns	II	1	HFS	V	72,4	H	5	5	2	S	2,48	2,13				cvccv
85	**ville**	villas	III	3	Ogem	N	15,27		5	4	2		4,80	2,30				cvGv
86	**odia**	hates	III	1	LFS	V	5,002	L	4	4	2	S	2,43	1,97				vcvv
87	**propria**	own	III	1	HFL	A	164,5	H	7	7	3	L	2,08	2,26				cvcvccv
88	**diventi**	you become	III	2	MR	V	12,11		7	7	3		1,90	2,62	R	6	1	cvcvccv
89	**decoro**	decorum	II	3	Ostress	N	5,002		6	6	3		3,18	2,46				cvcvcv
90	**altresì**	also	III	1	LFL	F	1,58	L	7	7	3	L	1,30	2,58				vcccvcv
91	**sogna**	dreams	II	1	LFS	V	13,16	L	5	4	2	S	3,26	2,12				cvccv
92	**sembro**	I look	II	2	MR	V	1,58		6	6	2		2,22	2,23	R	5	1	cvcccv
93	**mese**	month	III	1	HFS	N	187,5	H	4	4	2	S	3,48	2,13				cvcv
94	**posare**	to pose	III	1	LFS	V	3,949	L	6	6	3	S	3,53	2,18				cvcvcv
95	**tavolo**	table	II	3	Ostress	N	71,35		6	6	3		4,92	1,69				cvcvcv
96	**affinché**	so that	III	1	LFL	F	21,06	L	8	6	3	L	1,48	2,21				vGvcccv
97	**potresti**	you could	II	2	IL	V	6,845		8	8	3		1,81	2,23	I	5		cvccvccv
98	**fiori**	flowers	II	1	HFS	N	86,35	H	5	5	2	S	4,96	1,83				cvvcv
99	**amasse**	loved	II	2	MR	V	2,369		6	5	3		2,10	3,02	R	2	4	vcvGv
100	**tardi**	late	II	1	HFS	F	90,3	H	5	5	2	S	2,72	2,14				cvccv
101	**canale**	channel	II	3	Ostress	N	35,02		6	6	3		4,36	2,30				cvcvcv
102	**guarire**	to heal	III	1	LFL	V	9,478	L	7	7	3	L	2,96	2,38				cvvcvcv
103	**vera**	real	III	1	HFS	A	132,2	H	4	4	2	S	2,34	2,20				cvcv
104	**godo**	I enjoy	II	2	MR	V	0,527		4	4	2		2,80	1,90	R	3	1	cvcv
105	**indietro**	back	III	1	HFL	F	77,93	H	8	8	3	L	2,80	2,39				vccvvccv
106	**udire**	to hear	II	1	LFS	V		L	5	5	3	S	3,42	2,01				vcvcv

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Presentation NR	Stimulus (IT)	Assessment list	Sublist	Assessment cluster	Letters	Phonemes	Syllables	Length	N-count	Similarity to words	Mean reaction time	Consonant vowel order
1	godasti	II	2	MD	7	7	3		3		2,54	cvcvccv
2	nimole	II	1	LS	6	6	3	L	0	L	2,45	cvcvcv
3	bugeti	II	3	CV	6	6	3		0		2,48	cvcvcv
4	matica	III	1	HS	6	6	3	L	6	H	2,26	cvcvcv
5	nemiso	II	2	nMD	6	6	3		1		2,32	cvcvcv
6	botilei	II	3	nCV	7	7	4		0		2,49	cvcvcvv
7	armessi	III	2	MD	7	6	3		3		2,29	vccvGv
8	erulche	II	3	nCV	7	6	3		0		2,50	vcvcccv
9	zibo	III	1	LS	4	4	2	S	2	L	1,86	cvcv
10	fattida	II	2	nMD	7	6	3		1		2,36	cvGvcv
11	pole	III	1	HS	4	4	2	S	11	H	1,84	cvcv
12	spreago	III	3	nCV	7	7	3		0		2,52	cccvvcv
13	remivo	II	2	MD	6	6	3		2		1,97	cvcvcv
14	rudela	III	3	CV	6	6	3		0		2,07	cvcvcv
15	velive	III	1	LS	6	6	3	L	1	L	2,09	cvcvcv
16	usevi	II	2	MD	5	5	3		1		2,11	vcvcv
17	lotare	III	1	HS	6	6	3	L	7	H	2,20	cvcvcv
18	asemido	II	3	nCV	7	7	4		0		2,58	vcvcvcv
19	gosatti	III	2	nMD	7	6	3		0		2,18	cvcvGv
20	pata	II	1	HS	4	4	2	S	13	H	1,73	cvcv
21	ancure	III	2	nMD	6	6	3		0		2,14	vccvcv
22	izzi	III	1	LS	4	3	2	S	0	L	1,82	vGv
23	praulo	II	3	nCV	6	6	3		0		2,16	ccvvcv
24	uteli	II	2	nMD	5	5	3		3		1,99	vcvcv
25	enerbi	III	3	nCV	6	6	3		0		2,00	vcvccv
26	andere	III	2	MD	6	6	3		2		2,18	vccvcv
27	isco	II	1	LS	4	4	2	S	2	L	1,62	vccv
28	giruni	II	3	CV	6	6	3		2		1,97	cvcvcv
29	arrusti	II	2	nMD	7	6	3		3		2,19	vGvccv
30	gomati	II	1	LS	6	6	3	L	2	L	2,01	cvcvcv
31	imbale	III	3	nCV	6	6	3		0		2,20	vccvcv
32	moreva	II	2	MD	6	6	3		1		2,19	cvcvcv
33	cirano	II	1	HS	6	6	3	L	8	H	1,89	cvcvcv
34	dilote	III	3	CV	6	6	3		0		2,00	cvcvcv
35	urrossi	III	2	nMD	7	5	3		1		2,35	vGvGv
36	carate	II	1	HS	6	6	3	L	14	H	2,09	cvcvcv
37	tobindo	III	3	nCV	7	7	3		0		2,15	cvcvccv
38	fineva	II	2	MD	6	6	3		1		1,81	cvcvcv
39	neulmo	II	3	nCV	6	6	3		0		2,44	cvvcvc
40	cercono	III	2	MD	7	7	3		2		2,26	cvccvcv
41	came	II	1	HS	4	4	2	S	14	H	1,71	cvcv
42	strivule	III	2	nMD	8	8	3		1		2,39	cccvcvcv
43	ansola	III	1	LS	6	6	3	L	1	L	1,98	vccvcv
44	cearne	III	3	nCV	6	6	3		0		2,29	cvvccv
45	chiediva	III	2	MD	8	7	3		1		2,19	ccvvcvcv
46	vila	III	1	HS	4	4	2	S	10	H	1,70	cvcv
47	cirote	III	2	nMD	6	6	3		1		1,99	cvcvcv
48	ceresa	III	3	CV	6	6	3		1		2,02	cvcvcv
49	restuto	III	2	MD	7	7	3		1		2,05	cvccvcv
50	deie	II	1	LS	4	4	2	S	1	L	1,97	cvvv
51	toarilo	II	3	nCV	7	7	4		0		2,33	cvvcvcv
52	mormoti	II	2	nMD	7	7	3		2		2,23	cvccvcv

Presentation NR	Stimulus (IT)	Stimulus (EN)	Assessment list	Sublist	Assessment cluster	Grammatical class	Frequency count main word	Letters main word	Phonemes main word	Syllables main word	Words in sentence	Mean reaction time	Consonant vowel order
1	**Il rubino ornava la tiara.**	The ruby adorns the tiara.	III	1	PS						5	3,84	
1	Il rubino	The ruby	III	1	PS	N	2,37	6	6	3	5		vc cvcvcv
1	ornava	adorns	III	1		V	0,26	6	5	3	5		vccvcv
1	la tiara	the tiara	III	1		N	0,26	5	5	2	5		cv cvvcv
2	**Leggere rende colti.**	Reading makes you educated.	III	1	nPS						3	3,21	
2	Leggere	Reading	III	1	nPS	V	61,08	7	6	3	3		cvGvcv
2	rende	makes	III	1		V	54,76	5	5	2	3		cvccv
2	colti	educated	III	1		A	5,53	5	5	2	3		cvccv
3	**Praticavano un rito pagano.**	They practiced a pagan ritual.	III	1	PS						4	3,46	
3	Praticavano	They practiced	III	1		V	0,53	11	11	5	4		ccvcvcvcvcv
3	un rito	a ritual	III	1		N	26,59	4	4	2	4		vc cvcv
3	pagano	pagan	III	1	PS	A	5,00	6	6	3	4		cvcvcv
4	**I ritardatari perdono il treno.**	The latecomers miss the train.	III	1	nPS						5	3,51	
4	I ritardatari	The latecomers	III	1		N	1,32	11	11	5	5		v cvcvccvcvcv
4	perdono	miss	III	1	nPS	V	11,85	7	7	3	5		cvccvcv
4	il treno	the train	III	1		N	49,23	5	5	2	5		vc ccvcv
5	**La nave gettò l'ancora vicino la baia.**	The ship dropped the anchor near the bay.	III	1	nPS						8	4,19	
5	La nave	The ship	III	1		N	33,17	4	4	2	8		cv cvcv
5	gettò	dropped	III	1		V	8,95	5	4	2	8		cvGv
5	l'ancora	the anchor	III	1	nPS	N	2,11	6	6	3	8		cvccvcv
5	vicino	near	III	1		A	152,17	6	6	3	8		cvcvcv
5	la baia	the bay	III	1		N	6,85	4	4	2	8		cv cvvv
6	**Mostramelo appena vuoi.**	Show it to me whenever you want.	III	2	Cl						3	3,23	
6	Mostramelo	Show it to me	III	2	Cl	V	0,26	10	10	4	3		cvcccvcvcv
6	appena	whenever	III	2		A	265,91	6	5	3	3		vGvcv
6	vuoi	you want	III	2		V	59,24	4	4	1	3		cvvv
7	**Spero che quegli abiti le calzino a pennello.**	I hope that those clothes fit like a glove.	III	1	nPS						8	4,47	
7	Spero	I hope	III	1		V	42,65	5	5	2	8		ccvcv
7	che	that	III	1		F	16910,83	3	2	1	8		ccv
7	que(gli)	those	III	1		F	48,71	6	3	1	8		cvv
7	(que)gli abiti	clothes	III	1		N	44,76	5	5	3	8		ccv vcvcv
7	le calzino	(they) fit	III	1	nPS	V	0,26	7	7	3	8		cv cvccvcv
7	a penello	like a glove	III	1		A	5,53	7	6	3	8		v cvcvGv
8	**Chiara ha subito un terzo grado.**	Chiara has suffered a third degree (burn).	III	1	PS						6	3,69	
8	Chiara	Chiara	III	1		N		6	5	2	6		ccvvcv
8	ha subito	has suffered	III	1	PS	V	30,01	6	6	3	6		cv cvcvcv
8	un (terzo) grado	a degree	III	1		N	152,96	5	5	2	6		vc ccvcv
8	terzo	third	III	1		A	132,96	5	5	2	6		cvccv
9	**Le gattine appena nate erano tenere.**	The newborn kittens were lovely.	III	1	nPS						6	4,06	
9	Le gattine	The kittens	III	1		N	0,00	7	6	3	6		cv cvGvcv
9	appena nate	newborn	III	1		A	265,91	6	5	3	6		vGvcv cvcv
9	erano	were	III	1		V	629,23	5	5	3	6		vcvcv
9	tenere	lovely	III	1	nPS	A	2,63	6	6	3	6		cvcvcv
10	**Gli alleati non erano ancora arrivati.**	The allies had not yet arrived.	III	1	PS						6	4,28	
10	Gli alleati	The allies	III	1		N	22,12	7	6	4	6		ccv vGvvcv
10	non	not	III	1		A	9305,01	3	3	1	6		cvc
10	erano (ancora) arrivati	had arived	III	1		V	61,87	8	7	4	6		vcvcv vGvcvcv
10	ancora	yet	III	1	PS	F	1053,64	6	6	3	6		vccvcv
11	**Lo scrivano era chino sulla sua scrivania.**	The writer was leaning on his desk.	III	1	PS						7	5,22	
11	Lo scrivano	The writer	III	1	PS	N	0,53	8	8	3	7		cv cccvcvcv
11	era chino	was leaning	III	1		V	0,53	5	4	2	7		vcv ccvcv
11	sul(la)	on	III	1		F	893,83	5	3	1	7		cvc
11	(sul)la sua scrivania	his desk	III	1		N	17,64	9	9	4	7		cv cvv ccvcvcvv
12	**Spero che non mi rubino mai il portafogli.**	I hope that my wallet never gets stolen.	III	1	nPS						8	4,12	
12	Spero	I hope	III	1		V	42,65	5	5	2	8		ccvcv
12	che	that	III	1		F	16910,83	3	2	1	8		ccv
12	non (mi rubino) mai	never	III	1		A	767,19	3	3	1	8		cvc cvv
12	mi rubino	gets stolen (from me)	III	1	nPS	V	0,26	6	6	3	8		cv cvcvcv
12	il portafogli	the wallet	III	1		N	6,85	10	9	4	8		vc cvccvcvccv

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Appendix B.1c Italian spelling: Pre-operative version

Italian | Word spelling | Pre-operative

Presentation NR	Stimulus (IT)	Stimulus (EN)	Sublist	Assessment list	Assessment cluster	Grammatical class	Frequency count	Frequency	Letters	Graphemes	Syllables	Length	Imageability	Mean reaction time	Root	Inflection	Consonant vowel order
1	fascino	charm	4	II	OO	N	39,23		7	6	3		2,42	6,01			cvccvcv
2	soffre	suffers	3	II	nCVG	V	20,01		6	5	2		3,10	6,58			cvGcv
3	nera	black	1	I	HFS	A	61,61	H	4	4	2	S	4,26	5,36			cvcv
4	orlo	edge	1	I	LFS	N	16,59	L	4	4	2	S	4,32	5,50			vccv
5	equo	fair	4	I	OO	A	4,21		4	3	2		2,31	6,66			vcvv
6	piacere	pleasure	4	I	OO	N	88,20		7	7	3		3,12	6,15			cvvcvcv
7	lento	slow	1	II	LFS	A	17,90	L	5	5	2	S	3,12	5,44			cvccv
8	pesche	peaches	4	II	OO	N	2,37		6	5	2		4,94	6,20			cvcccv
9	scrivo	write	3	I	nCV	V	8,42		6	6	2		4,48	5,53			cccvcv
10	mani	hands	1	I	HFS	N	199,83	H	4	4	2	S	4,54	7,14			vcvv
11	vile	cowardly	1	I	LFS	A	3,16	L	4	4	2	S	2,02	5,99			cvcv
12	prezzi	prices	3	I	nCVG	N	73,45		6	5	2		4,02	5,58			ccvGv
13	numerose	numerous	3	II	CV	A	39,23		8	8	4		3,60	7,37			cvcvcvcv
14	modella	model	1	I	LFL	N	14,22	L	7	6	3	L	4,65	5,97			cvcvGv
15	trova	finds	1	II	HFS	V	128,22	H	5	5	2	S	2,50	3,97			ccvcv
16	intero	whole	3	II	nCV	A	63,98		6	6	3		3,24	4,58			vccvcv
17	paesi	countries	1	II	HFS	N	166,39	H	5	5	3	S	4,08	4,46			cvvcv
18	ognuno	each	4	II	OO	F	51,87		6	5	3		2,57	7,12			vccvcv
19	quota	share	4	II	OO	N	63,45		5	4	2		2,86	5,34			cvvcv
20	persero	lost	2	I	MO	V	2,37		7	7	3		2,12	8,11	4	3	cvccvcv
21	cognato	brother in law	4	I	OO	N	7,37		7	6	3		4,00	5,82			cvccvcv
22	stacca	detaches	1	I	LFS	V	3,95	L	6	5	2	S	2,02	6,62			ccvGv
23	asciutto	dry	4	I	OO	A	7,90		8	6	3		3,60	6,14			vccvvGv
24	cielo	sky	4	II	OO	N	83,20		5	5	2		4,90	4,95			cvvcv
25	chiarire	to clarify	1	I	LFL	V	18,43	L	8	7	3	L	2,33	6,09			ccvvcvcv
26	usciere	usher	4	II	OO	N	1,58		7	6	3		4,51	6,31			vccvvcv
27	saluta	greets	3	II	CV	V	6,85		6	6	3		3,88	5,64			cvcvcv
28	coniuge	spouse	4	II	OO	N	6,58		7	7	3		4,29	6,24			cvcvvcv
29	concluse	concluded	3	II	nCV	V	10,79		8	8	3		2,06	5,89			cvccccvcv
30	aquila	eagle	4	I	OO	N	7,90		6	5	3		4,98	5,57			vcvvcv
31	vieta	prohibits	1	II	LFS	V	6,85	L	5	5	2	S	2,67	8,80			cvvcv
32	cero	candle	4	II	OO	N	0,26		4	4	2		4,73	5,01			cvcv
33	lavora	works	3	II	CV	V	52,13		6	6	3		3,58	5,14			cvcvcv
34	perfetto	perfect	3	I	nCVG	A	31,59		8	7	3		2,38	6,41			cvccvGv
35	giornale	newspaper	4	II	OO	N	67,66		8	8	3		4,96	6,14			cvvccvcv
36	invano	in vain	1	II	LFS	F	13,16	L	6	6	3	S	1,54	6,34			vccvcv
37	finito	finished	1	I	HFS	V	92,67	H	6	6	3	S	2,78	5,96			cvcvcv
38	maschi	males	4	I	OO	N	28,70		6	5	2		4,46	8,69			cvcccv
39	riescono	succeed	2	II	MO	V	31,86		8	8	3		2,06	6,00	5	3	cvvccvcv
40	bestia	beast	3	I	nCV	N	12,37		6	6	2		4,20	5,40			cvccvv
41	costruirono	built	2	II	MO	V	1,84		11	11	4		3,10	7,24	8	3	cvccccvvcvcv
42	sopra	above	1	II	HFS	F	129,27	H	5	5	2	S	3,60	4,80			cvccv
43	fasce	bands	4	I	OO	N	13,16		5	4	2		4,24	5,68			cvccv
44	comincia	begins	1	I	HFL	V	76,88	H	8	8	3	L	2,52	5,71			cvcvccvv
45	naturali	natural	3	II	CV	A	36,33		8	8	4		2,51	6,15			cvcvcvcv
46	cicogna	stork	4	I	OO	N	3,42		7	6	3		4,96	5,04			cvcvccv
47	cambieremo	we will change	2	I	MO	V	0,53		10	10	4		2,13	7,80	7	3	cvccvvcvcv
48	chimera	chimera	4	II	OO	N	2,37		7	6	3		2,88	6,03			ccvcvcv
49	sincera	sincere	1	I	LFL	A	5,27	L	7	7	3	L	2,12	5,40			cvccvcv
50	calore	heat	3	I	CV	N	33,70		6	6	3		3,82	4,78			cvcvcv
51	fresca	fresh	3	II	nCV	A	15,27		6	6	2		3,42	5,31			ccvccv
52	mattina	morning	1	I	HFL	N	170,87	H	7	6	3	L	4,02	5,61			cvGvcv
53	conobbero	met	2	I	MO	V	1,05		9	8	4		2,02	6,64	6	3	cvcvGvcv
54	bella	nice	1	II	HFS	A	183,77	H	5	4	2	S	3,26	8,73			cvGv
55	progetto	project	1	II	HFL	N	121,90	H	8	7	3	L	3,06	13,29			ccvcvGv
56	sceso	descended	4	II	OO	V	20,01		5	4	2		2,57	5,49			ccvcv
57	debole	weaj	3	I	CV	A	30,01		6	6	3		3,02	5,67			cvcvcv
58	fastidio	nuisance	3	I	nCV	N	18,43		8	8	3		2,86	5,57			cvccvcvv
59	seguono	follow	2	II	MO	V	16,85		7	7	3		2,78	5,80	4	3	cvvvvcv
60	contagio	contagion	1	II	LFL	N	5,79	L	8	8	3	L	3,02	5,58			ccvcvvcv
61	spetta	be up to	3	I	nCVG	V	20,54		6	5	2		1,68	6,29			ccvGv
62	piccolo	small	1	I	HFL	A	230,89	H	7	6	3	L	3,82	4,63			cvGvcv
63	miracolo	miracle	3	I	CV	N	38,18		8	8	4		2,82	5,23			cvcvcvcv
64	mediante	through	1	II	LFL	F	16,85	L	8	8	3	L	1,51	6,24			cvcvvccv
65	pacco	pack	1	II	LFS	N	6,32	L	5	4	2	S	4,76	3,58			cvGv
66	ridendo	laughing	2	II	MO	V	6,85		7	7	3		3,92	5,28	3	4	cvcvccv

67 coscienza	consciousness	4	I	OO	N	58,71		9	8	3		2,00	6,39			cvccvvccv
68 racconta	tells	1	II	HFL	V	123,74	H	8	7	3	L	3,36	6,40			cvGvccv
69 valigia	suitcase	4	I	OO	N	14,74		7	6	3		4,94	4,67			cvcvcvv
70 eppure	and yet	1	I	HFS	F	114,79	H	6	5	3	S	1,38	5,16			vGvcv
71 prossima	next	3	II	nCVG	A	65,29		8	7	3		2,44	5,45			ccvGvcv
72 baciare	to kiss	4	I	OO	V	3,42		7	7	3		4,57	5,33			cvcvvcv
73 arcieri	archery	4	I	OO	N	0,53		7	7	3		4,64	5,80			cvcvvcv
74 telefona	phones	3	I	CV	V	5,27		8	8	4		4,12	6,76			cvcvcvcv
75 qualcosa	something	1	I	HFL	F	281,97	H	8	7	3	L	2,12	6,12			cvvccvcv
76 scuole	schools	4	II	OO	N	47,13		6	6	2		4,78	5,81			ccvvcv
77 occuperò	occupy	2	I	MO	V	0,79		8	7	4		2,24	7,67	4	3	vGvcvcv
78 brutto	bad	3	II	nCVG	A	33,17		6	5	2		3,42	4,77			ccvGv
79 sughero	cork	4	I	OO	N	1,58		7	6	3		4,76	7,83			cvccvcv
80 ballavo	danced	1	II	LFL	V	0,53	L	7	6	3	L	3,98	5,31			cvGvcv
81 profondo	deeo	3	I	nCV	A	43,18		8	8	3		3,68	5,66			ccvcvccv
82 righe	lines	4	II	OO	N	24,75		5	4	2		4,68	4,97			cvccv
83 discreto	discreet	1	II	LFL	A	9,21	L	8	8	3	L	2,00	5,74			cvcccvcv
84 pasqua	Easter	4	I	OO	N	16,06		6	5	2		3,90	5,55			cvccvv
85 assicura	ensures	3	II	nCVG	V	24,48		8	7	4		2,20	6,03			vGvcvcv
86 quadro	picture	4	II	OO	N	68,45		6	5	2		4,90	4,83			cvvccv
87 entrambi	both	1	II	HFL	F	71,61	H	8	8	3	L	2,64	7,53			cvcvccvv
88 cuoio	leather	4	I	OO	N	17,38		5	4	2		4,40	5,31			cvvvv
89 alquanto	somewhat	1	I	LFL	F	10,53	L	8	7	3	L	1,53	5,75			vccvvccv
90 lancio	throwing	4	II	OO	N	19,75		6	6	2		3,52	4,36			cvccvv
91 consiste	consists	3	II	nCV	V	21,85		8	8	3		1,62	5,81			cvccvccv
92 ascia	ax	4	I	OO	N	5,27		5	4	2		4,76	4,91			vccvv
93 bensì	but	1	I	LFS	F	25,54	L	5	5	2	S	1,52	6,00			cvccv
94 antichi	ancient	4	I	OO	A	30,28		7	6	3		3,42	5,28			vccvccv
95 sogliola	sole	4	I	OO	N	1,32		8	7	3		4,86	5,85			cvccvvcv
96 semplice	simple	1	II	HFL	A	120,58	H	8	8	3	L	2,50	6,48			cvcccvcv
97 cestello	basket	3	I	nCVG	N	1,05		8	7	3		4,68	5,25			cvccvGv
98 togliere	remove	4	I	OO	V	22,12		8	7	3		2,94	5,75			cvccvvcv
99 artigli	claws	4	II	OO	N	3,16		7	6	3		4,88	4,79			vccvccv

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Presentation NR	Stimulus (IT)	Sublist	Assessment list	Assessment cluster	Letters	Graphemes	Syllables	Length	N-count	Orthography	Morphology	Mean reaction time	Consonant vowel order
1	vivite	2	II	MD	6	6	3		3		D	6,58	cvcvcv
2	cescia	1	I	US	6	5	2	S	2	U		6,89	cvccvv
3	pedovi	2	I	nMD	6	6	3		2		nD	5,75	cvcvcv
4	ledria	1	I	CS	6	6	2	S	0	C		4,88	cvccvv
5	abitire	2	I	MD	7	7	4		1		D	6,97	vcvcvcv
6	paruntri	1	II	CL	8	8	3	L	0	C		7,40	cvcvcccv
7	abutive	2	I	nMD	7	7	4		1		nD	7,56	vcvcvcv
8	cioreli	1	I	UL	7	7	4	L	0	U		5,69	cvvcvcv
9	getruva	2	II	nMD	7	7	3		0		nD	8,00	cvccvcv
10	vallunde	1	II	UL	8	7	3	L	0	U		6,06	cvGvccv
11	cullito	2	II	MD	7	6	3		2		D	5,59	cvcGvcv
12	chebo	1	II	US	5	4	2	S	1	U		5,25	ccvcv
13	veveta	2	I	nMD	6	6	3		2		nD	8,44	cvcvcv
14	viosile	1	I	CL	7	7	4	L	0	C		7,34	cvvcvcv
15	aiupotte	2	I	nMD	8	7	4		0		nD	6,88	vvvcvGv
16	rogli	1	II	US	5	4	2	S	7	U		4,87	cvccv
17	aiutette	2	I	MD	8	7	4		0		D	6,81	vvvcvcGv
18	tenomato	1	II	CL	8	8	4	L	1	C		6,43	cvcvcvcv
19	gettiva	2	II	MD	7	6	3		2		D	6,24	cvGvcv
20	cirenghi	1	II	UL	8	7	3	L	0	U		6,73	cvcvcccv
21	sedono	2	I	MD	6	6	3		5		D	5,71	cvcvcv
22	seltunda	1	I	CL	8	8	3	L	0	C		8,35	cvccvccv
23	capei	2	II	MD	5	5	2		4		D	4,37	cvcvv
24	pefi	1	I	CS	4	4	2	S	7	C		6,26	cvcv
25	curete	2	II	MD	6	6	3		1		D	5,47	cvcvcv
26	dirto	1	II	CS	5	5	2	S	4	C		5,03	cvccv
27	femmida	2	I	nMD	7	6	3		1		nD	6,86	cvGvcv
28	erriba	1	II	US	6	5	3	S	0	U		5,30	vGvcv
29	cantevi	2	I	MD	7	7	3		1		D	6,18	cvccvcv
30	spivo	1	II	CS	5	5	2	S	4	C		8,55	ccvcv
31	ammusti	2	II	nMD	7	6	3		0		nD	5,94	vGvccv
32	sabomi	1	II	CS	6	6	3	S	2	C		6,38	cvcvcv
33	apressi	2	I	MD	7	6	3		1		D	6,43	cvcvcGv
34	egne	1	I	US	4	3	2	S	0	U		5,00	vccv
35	ammossi	2	II	nMD	7	5	3		3		nD	6,18	vGvGv
36	tasciolo	1	I	UL	8	7	3	L	0	U		6,70	cvccvvcv
37	caroi	2	II	nMD	5	5	3		3		nD	4,62	cvcvv
38	seglioto	1	II	UL	8	7	3	L	0	U		8,25	cvccvvcv
39	sintoti	2	II	nMD	7	7	3		1		nD	5,64	cvccvcv
40	alfiria	1	II	CL	7	7	4	L	0	C		6,98	vccvcvv

Presentation NR	Stimulus (IT)	Stimulus (EN)	Sublist	Assessment list	Assessment cluster	Grammatical class	Frequency count main word	Letters main word	Graphemes main word	Syllables main word	Words in sentence	Mean reaction time	Consonant vowel order
1	**La mamma cuciva i pantaloni con l'ago.**	The mom sewed the pants with the needle.	1	II	H						8	18,22	
1	La mamma	The mom	1	II		N	113,47	5	4	2	8		cv cvG
1	cuciva	sewed	1	II		V	0,53	6	6	3	8		cvcvcv
1	i pantaloni	the pants	1	II		N	29,22	9	9	4	8		v cvccvcvcv
1	con	with	1	II		F	6629,06	3	3	1	8		cvc
1	l'ago	the needle	1	II	H	N	10,79	4	4	2	8		c'vcv
2	**Era l'una di notte quando ci siamo alzati.**	It was one at night when we got up.	1	II	H						9	19,64	
2	Era	It was	1	II		V	2485,87	3	3	2	9		vcv
2	l'una	one	1	II	H	N	8076,30	4	4	2	9		c'vcv
2	di notte	at night	1	II		A	286,45	5	4	2	9		cv cvGv
2	quando	when	1	II		F	1419,86	6	6	2	9		cvvccv
2	ci siamo alzati	we got up	1	II		V	2,90	6	6	3	9		cv cvvcv vccvcv
3	**Ogni inizio d'anno si fanno delle feste.**	Every beginning of the year they have a party.	1	II	H						8	19,45	
3	Ogni	Every	1	II		A	816,69	4	3	2	8		vccv
3	inizio d'	beginning of the	1	II		A	182,98	6	6	3	8		vcvcvv c
3	(d')anno	year	1	II	H	N	638,71	4	3	2	8		vGv
3	si fanno	they have	1	II		V	227,21	5	4	2	8		cv cvGv
3	delle	a	1	II		F	2346,85	5	4	2	8		cvGv
3	feste	party	1	II		N	31,86	5	5	2	8		cvccv
4	**Quando sono passati un mucchio d'anno si dimentica facilmente.**	Whenmany years have passed you forget easily.	1	II	H						10	30,47	
4	Quando	When	1	II		F	1419,86	6	6	2	10		cvvccv
4	sono passati	have passed	1	II		V	43,70	7	6	3	10		cvcv cvGvcv
4	un mucchio d'	many	1	II		A	9,74	7	5	2	10		vc cvGcvv c
4	(d')anni	years	1	II	H	N	1793,45	4	4	2	10		vGv
4	si dimentica	you forget	1	II		V	8,95	9	9	4	10		cv cvcvccvcv
4	facilmente	easily	1	II		A	43,70	10	10	4	10		cvcvccvccv
5	**Ho nascosto io l'etto di caramelle.**	I have hidden a pound of candy.	1	II	H						7	20,33	
5	Ho nascosto	have hidden	1	II		V	33,44	8	8	3	7		cv cvccvccv
5	io	I	1	II		F	886,72	2	2	1	7		vv
5	l'etto	a pound	1	II	H	N	2,37	5	4	2	7		c'vGv
5	di	of	1	II		F	31428,48	2	2	1	7		cv
5	caramelle	candy	1	II		N	4,21	9	8	4	7		cvcvcvGv
6	**Gianni ha acquistato una pelle d'orso.**	Gianni has bought a bearskin.	1	II	H						7	18,78	
6	Gianni	Gianno	1	II		N		6	5	2	7		cvvGv
6	ha acquistato	has bought	1	II		V	23,43	10	9	4	7		cv vccvvccvcv
6	una pelle	a skin	1	II		N	109,26	5	4	2	7		vcv cvGv
6	d'orso	of a bear	1	II	H	A	13,95	5	5	2	7		c'vccv
7	**Sul pavimento non c'era la cera.**	There was no wax on the floor.	1	II	H						7	15,49	
7	Sul	On	1	II		F	1132,88	3	3	1	7		cvc
7	pavimento	(the) floor	1	II		N	22,12	9	9	4	7		cvcvcvccv
7	non	no	1	II		A	9305,01	3	3	1	7		cvc
7	c'era	was	1	II	H	V	197,98	4	4	2	7		c'vcv
7	la cera	(the) wax	1	II	H	N	6,06	4	4	2	7		cv cvcv
8	**Venezia l'hanno visitata una sola volta.**	They have visited Venice only one time.	1	II	H						7	20,53	
8	Venezia	Venice	1	II		N	65,03	7	7	3	7		cvcvcvv
8	l'hanno visitata	they have visited	1	II	H	V	1598,88	6	4	4	7		c'cvGv cvcvcvcv
8	una (sola) volta	one time	1	II		N	676,89	5	5	2	7		vcv cvccv
8	sola	only	1	II		A	168,50	4	4	2	7		cvcv
9	**Il bambino non ha preso la merenda.**	The child has not taken the snack.	1	II	H						7	18,19	
9	Il bambino	The child	1	II		N	136,38	7	7	3	7		vc cvccvcv
9	non	not	1	II		A	9305,01	3	3	1	7		cvc
9	ha preso	has taken	1	II	H	V	147,44	5	5	2	7		cv ccvcv
9	la merenda	the snack	1	II		N	1,58	7	7	3	7		cv cvcvccv
10	**Valeria sa che Carlo non l'ama più.**	Valeria knows that Carlo does not love her anymore.	1	II	H						8	17,86	
10	Valeria	Valeria	1	II		N		7	7	4	8		cvcvcvv
10	sa	knows	1	II		V	230,10	2	2	1	8		cv
10	che	that	1	II		F	6395,80	3	2	1	8		ccv
10	Carlo	Carlo	1	II		N	146,91	5	5	2	8		cvccv
10	non	not	1	II		A	9305,01	3	3	1	8		cvc
10	l'ama	love her	1	II	H	H	50,55	4	4	2	8		c'vcv
10	più	anymore	1	II		A	4140,83	3	3	1	8		cvv
11	**Non v'era traccia alcuna.**	There was not any trace.	1	II	H						5	13,05	
11	Non	Not	1	II		A	9305,01	3	3	1	5		cvc
11	v'era	there was	1	II	H	V	1,05	4	4	2	5		c'vcv
11	traccia	trace	1	II		N	32,12	7	7	2	5		ccvGvv
11	alcuna	any	1	II		A	63,71	6	6	3	5		vccvcv

Appendix B.1d Italian spelling: Post-operative version

Italian | Word spelling | Post-operative

Presentation NR	Stimulus (IT)	Stimulus (EN)	Sublist	Assessment list	Assessment Cluster	Grammatical class	Frequency count	Frequency	Letters	Graphemes	Syllables	Length	Imageability	Mean reaction time	Root	Inflection	Consonant vowel order
1	**contagio**	contagion	1	II	LFL	N	5,79	L	8	8	3	L	3,02	5,58			ccvcvvcv
2	**assicura**	ensures	3	II	nCVG	V	24,48		8	7	4		2,20	6,03			vGvcvcv
3	**gnocchi**	gnocchi	4	III	OO	N	5,79		7	4	2		4,96	4,80			ccvGcv
4	**numerose**	numerous	3	II	CV	A	39,23		8	8	4		3,60	7,37			cvcvcvcv
5	**rendere**	to make	1	III	HFL	V	61,08	H	7	7	3	L	2,38	7,31			cvccvcv
6	**quadro**	picture	4	II	OO	N	68,45		6	5	2		4,90	4,83			cvvccv
7	**rimarrebbe**	would remain	2	III	MO	V	1,05		10	8	4		1,71	8,96	6	4	cvcvGvGv
8	**paesi**	countries	1	II	HFS	N	166,39	H	5	5	3	S	4,08	4,46			cvvcv
9	**ognuno**	each	4	II	OO	F	51,87		6	5	3		2,57	7,12			vccvcv
10	**progetto**	project	1	II	HFL	N	121,90	H	8	7	3	L	3,06	13,29			ccvcvGv
11	**cieca**	blind	4	III	OO	A	5,53		5	5	2		4,16	4,86			cvvcv
12	**moneta**	currency	3	III	CV	N	27,91		6	6	3		4,86	4,90			cvcvcv
13	**trova**	finds	1	II	HFS	V	128,22	H	5	5	2	S	2,50	3,97			cvccv
14	**scienza**	science	4	III	OO	N	59,76		7	6	2		2,70	5,81			ccvvccv
15	**concluse**	concluded	3	II	nCV	V	10,79		8	8	3		2,06	5,89			cvcccvcv
16	**scuole**	schools	4	II	OO	N	47,13		6	6	2		4,78	5,81			ccvvcv
17	**saluta**	greets	3	II	CV	V	6,85		6	6	3		3,88	5,64			cvcvcv
18	**giacca**	jacket	4	III	OO	N	26,85		6	5	2		4,90	4,80			cvvGv
19	**elegante**	elegant	3	III	nCV	A	35,81		8	8	4		3,80	6,08			vcvcvccv
20	**chimera**	chimera	4	II	OO	N	2,37		7	6	3		2,88	6,03			ccvcvcv
21	**neppure**	not even	1	III	HFL	F	124,27	H	7	6	3	L	1,40	5,96			cvGvcv
22	**funghi**	mushrooms	4	III	OO	N	7,11		6	5	2		4,84	4,97			cvcccv
23	**canterà**	sing	2	III	MO	V	1,58		7	7	3		3,04	8,65	4	3	cvccvcv
24	**cielo**	sky	4	II	OO	N	83,20		5	5	2		4,90	4,95			cvvcv
25	**lisci**	smooth	4	III	OO	A	2,11		5	4	2		3,78	3,96			cvccv
26	**termina**	ends	1	III	LFL	V	3,69	L	7	7	3	L	2,51	5,46			cvccvcv
27	**coniuge**	spouse	4	II	OO	N	6,58		7	7	3		4,29	6,24			cvcvvcv
28	**educavano**	educated	2	III	MO	V	0,26		9	9	5		2,64	6,66	6	3	vcvcvcvcv
29	**occhio**	eye	1	III	HFS	N	88,20	H	6	4	2	S	4,94	4,59			vGcvv
30	**mediante**	through	1	II	LFL	F	16,85	L	8	8	3	L	1,51	6,24			cvcvvccv
31	**dramma**	drama	3	III	nCVG	N	35,81		6	5	2		3,09	5,27			ccvGv
32	**vota**	votes	1	III	LFS	V	9,21	L	4	4	2	S	3,51	4,45			cvcv
33	**squillo**	ring	4	III	OO	N	3,95		7	5	3		3,92	5,30			ccvvGv
34	**passa**	passes	1	III	HFS	V	77,93	H	5	4	2	S	2,22	6,35			vcccv
35	**pacco**	pack	1	II	LFS	N	6,32	L	5	4	2	S	4,76	3,58			cvGv
36	**soffre**	suffers	3	II	nCVG	V	20,01		6	5	2		3,10	6,58			cvGcv
37	**artigli**	claws	4	II	OO	N	3,16		7	6	3		4,88	4,79			vccvccv
38	**lavora**	works	3	II	CV	V	52,13		6	6	3		3,58	5,14			cvcvcv
39	**usciere**	usher	4	II	OO	N	1,58		7	6	3		4,51	6,31			vccvvcv
40	**pubblica**	public	1	III	HFL	A	124,00	H	8	7	3	L	2,58	5,99			cvGcvcv
41	**stazione**	station	3	III	nCV	N	44,49		8	8	3		4,92	5,53			ccvcvvcv
42	**vieta**	prohibits	1	II	LFS	V	6,85	L	5	5	2	S	2,67	8,80			cvvcv
43	**veloce**	fast	4	III	OO	A	31,59		6	6	3		3,46	6,24			cvcvcv
44	**sopra**	above	1	II	HFS	F	129,27	H	5	5	2	S	3,60	4,80			cvccv
45	**cero**	candle	4	II	OO	N	0,26		4	4	2		4,73	5,01			cvcv
46	**fresca**	fresh	3	II	nCV	A	15,27		6	6	2		3,42	5,31			ccvccv
47	**anelli**	rings	1	III	LFS	N	10,53	L	6	6	3	S	4,76	5,28			vcvGv
48	**riescono**	succeed	2	II	MO	V	31,86		8	8	3		2,06	6,00	5	3	cvvccvcv
49	**fianco**	side	3	III	nCV	N	65,56		6	6	2		3,96	13,06			cvvccv
50	**veloci**	fast	1	III	LFS	A	11,85	L	6	6	3	S	3,26	5,13			cvcvcv
51	**schermo**	screen	4	III	OO	N	35,81		7	6	2		4,84	5,36			cccvccv
52	**consiste**	consists	3	II	nCV	V	21,85		8	8	3		1,62	5,81			cvccvccv
53	**innanzi**	before	1	III	LFL	F	7,64	L	7	6	3	L	2,31	5,99			vGvccv
54	**agnello**	lamb	4	III	OO	N	5,27		7	5	3		4,86	5,19			vccvGv
55	**violenta**	violent	1	III	LFL	A	20,27	L	8	8	3	L	3,22	6,17			cvvcvccv
56	**invano**	in vain	1	II	LFS	F	13,16	L	6	6	3	S	1,54	6,34			vccvcv
57	**pesche**	peaches	4	II	OO	N	2,37		6	5	2		4,94	6,20			cvcccv
58	**lento**	slow	1	II	LFS	A	17,90	L	5	5	2	S	3,12	5,44			cvccv
59	**lancio**	throwing	4	II	OO	N	19,75		6	6	2		3,52	4,36			cvccvv
60	**racconta**	tells	1	II	HFL	V	123,74	H	8	7	3	L	3,36	6,40			cvGvccv
61	**bella**	nice	1	II	HFS	A	183,77	H	5	4	2	S	3,26	8,73			cvGv
62	**fenomeno**	phenomenon	3	III	CV	N	53,45		8	8	4		2,60	6,31			cvcvcvcv
63	**vissero**	lived	2	III	MO	V	1,84		7	7	3		1,70	20,49	4	3	cvGvcv
64	**intero**	whole	3	II	nCV	A	63,98		6	6	3		3,24	4,58			vccvcv
65	**aglio**	garlic	4	III	OO	N	13,16		5	4	2		4,92	4,49			vccvv
66	**sceso**	descended	4	II	OO	V	20,01		5	4	2		2,57	5,49			ccvcv

67	**naturali**	natural	3	II	CV	A	36,33		8	8	4		2,51	6,15			cvcvcvcv
68	**fascino**	charm	4	II	OO	N	39,23		7	6	3		2,42	6,01			cvccvcv
69	**ballavo**	danced	1	II	LFL	V	0,53	L	7	6	3	L	3,98	5,31			cvGvcv
70	**liquore**	liquor	4	III	OO	N	2,37		7	6	3		4,42	5,53			cvcvvcv
71	**donde**	whence	1	III	LFS	F	2,63	L	5	5	2	S	3,16	6,32			vccv
72	**banche**	banks	4	III	OO	N	45,55		6	5	2		4,52	6,15			cvcccv
73	**famosi**	famous	3	III	CV	A	23,43		6	6	3		3,20	5,57			cvcvcv
74	**attività**	activity	1	III	HFL	N	172,45	H	8	7	4	L	2,94	5,20			vGvcvcv
75	**arriverà**	arrive	3	III	nCVG	V	20,54		8	7	4		2,06	6,72			vGvcvcv
76	**ascesa**	rise	4	III	OO	N	10,00		6	5	3		2,64	6,29			vccvcv
77	**desidero**	wish	3	III	CV	V	7,11		8	8	4		2,32	6,87			cvcvcvcv
78	**quercia**	oak	4	III	OO	N	17,64		7	6	2		4,88	5,51			cvvccvv
79	**ridendo**	laughing	2	II	MO	V	6,85		7	7	3		3,92	5,28	3	4	cvcvccv
80	**ciuffo**	tuft	4	III	OO	N	7,90		6	5	2		4,60	4,55			cvvGv
81	**entrambi**	both	1	II	HFL	F	71,61	H	8	8	3	L	2,64	7,53			cvcvccvv
82	**cuoco**	cook	4	III	OO	N	9,21		5	5	2		4,33	12,20			cvvcv
83	**chiamò**	called	3	III	nCV	V	11,06		6	5	2		2,40	4,93			ccvvcv
84	**brutto**	bad	3	II	nCVG	A	33,17		6	5	2		3,42	4,77			ccvGv
85	**ferrovie**	railways	1	III	LFL	N	15,27	L	8	7	3	L	4,83	6,50			cvGvcvv
86	**semplice**	simple	1	II	HFL	A	120,58	H	8	8	3	L	2,50	6,48			cvccccvcv
87	**castello**	castle	3	III	nCVG	N	38,44		8	7	3		4,94	4,90			cvccvGv
88	**costruirono**	built	2	II	MO	V	1,84		11	11	4		3,10	7,24	8	3	cvccccvvcvcv
89	**grossa**	big	3	III	nCVG	A	26,85		6	5	2		4,08	5,51			ccvGv
90	**righe**	lines	4	II	OO	N	24,75		5	4	2		4,68	4,97			cvccv
91	**ecco**	here	1	III	HFS	F	231,68	H	4	3	2	S	1,69	3,60			vGv
92	**quota**	share	4	II	OO	N	63,45		5	4	2		2,86	5,34			cvvcv
93	**ultimi**	latest	1	III	HFS	A	193,51	H	6	6	3	S	3,53	5,05			vccvc
94	**sciopero**	strike	4	III	OO	N	20,27		8	7	3		3,76	6,62			ccvvcvcv
95	**discreto**	discreet	1	II	LFL	A	9,21	L	8	8	3	L	2,00	5,74			cvccccvcv
96	**giornale**	newspaper	4	II	OO	N	67,66		8	8	3		4,96	6,14			cvvccvcv
97	**seguono**	follow	2	II	MO	V	16,85		7	7	3		2,78	5,80	4	3	cvvvvcv
98	**prossima**	next	3	II	nCVG	A	65,29		8	7	3		2,44	5,45			ccvGvcv
99	**foglia**	leaf	4	III	OO	N	10,53		6	5	2		4,94	4,56			cvccvv

Presentation NR	Stimulus (IT)	Sublist	Assessment list	Assessment cluster	Letters	Graphemes	Syllables	Length	N-count	Orthography	Morphology	Mean reaction time	Consonant vowel order
1	nortedi	1	III	CL	7	7	3	L	0	C		6,52	cvccvcv
2	scrivate	2	III	MD	8	8	3		2		D	6,45	cccvcvcv
3	effista	1	III	UL	7	6	3	L	0	U		6,19	vGvccv
4	caroi	2	II	nMD	5	5	3		3		nD	4,62	cvcvv
5	mopie	1	III	CS	5	5	3	S	2	C		5,24	cvcvv
6	gettiva	2	II	MD	7	6	3		2		D	6,24	cvGvcv
7	chebo	1	II	US	5	4	2	S	1	U		5,25	ccvcv
8	cerote	2	III	nMD	6	6	3		3		nD	5,36	cvcvcv
9	paruntri	1	II	CL	8	8	3	L	0	C		7,40	cvcvcccv
10	pesivi	2	III	MD	6	6	3		3		D	8,46	cvcvcv
11	cirenghi	1	II	UL	8	7	3	L	0	U		6,73	cvcvcccv
12	ammusti	2	II	nMD	7	6	3		0		nD	5,94	vGvccv
13	rogli	1	II	US	5	4	2	S	7	U		4,87	cvccv
14	pulpoto	2	III	nMD	7	7	3		1		nD	5,50	cvccvcv
15	alfiria	1	II	CL	7	7	4	L	0	C		6,98	vccvcvv
16	cullito	2	II	MD	7	6	3		2		D	5,59	cvcGvcv
17	spivo	1	II	CS	5	5	2	S	4	C		8,55	ccvcv
18	selolo	2	III	nMD	6	6	3		1		nD	5,55	cvcvcv
19	sanodi	1	III	US	6	6	3	S	1	U		6,12	cvcvcv
20	fermiva	2	III	MD	7	7	3		1		D	6,40	cvccvcv
21	itte	1	III	US	4	3	2	S	2	U		4,26	vcGv
22	salvite	2	III	MD	7	7	3		1		D	5,49	cvccvcv
23	lopasira	1	III	CL	8	8	4	L	0	C		6,34	cvcvcvcv
24	gedatti	2	III	nMD	7	6	3		1		nD	5,89	cvcvGv
25	erriba	1	II	US	6	5	3	S	0	U		5,30	vGvcv
26	curete	2	II	MD	6	6	3		1		D	5,47	cvcvcv
27	sabomi	1	II	CS	6	6	3	S	2	C		6,38	cvcvcv
28	ammossi	2	II	nMD	7	5	3		3		nD	6,18	vGvGv
29	tenomato	1	II	CL	8	8	4	L	1	C		6,43	cvcvcvcv
30	sintoti	2	II	nMD	7	7	3		1		nD	5,64	cvccvcv
31	vallunde	1	II	UL	8	7	3	L	0	U		6,06	cvGvccv
32	capei	2	II	MD	5	5	2		4		D	4,37	cvcvv
33	seglioto	1	II	UL	8	7	3	L	0	U		8,25	cvccvvcv
34	atrasti	2	III	MD	7	7	3		1		D	5,90	vccvccv
35	ospe	1	III	CS	4	4	2	S	1	C		5,82	vccv
36	vivite	2	II	MD	6	6	3		3		D	6,58	cvcvcv
37	raschelo	1	III	UL	8	7	3	L	0	U		6,69	cvcccvcv
38	scrivule	2	III	nMD	8	8	3		0		nD	10,09	cccvcvcv
39	dirto	1	II	CS	5	5	2	S	4	C		5,03	cvccv
40	getruva	2	II	nMD	7	7	3		0		nD	8,00	cvccvcv

Presentation NR	Stimulus (IT)	Stimulus (EN)	Sublist	Assessment list	Assessment cluster	Grammatical class	Frequency count main word	Letters main word	Graphemes main word	Syllables main word	Words in sentence	Mean reaction time	Consonant vowel order
1	**La mamma cuciva i pantaloni con l'ago.**	The mom sewed the pants with the needle.	1	II	H						8	18,22	
1	La mamma	The mom	1	II		N	113,47	5	4	2	8		cv cvG
1	cuciva	sewed	1	II		V	0,53	6	6	3	8		cvcvcv
1	i pantaloni	the pants	1	II		N	29,22	9	9	4	8		v cvccvcvcv
1	con	with	1	II		F	6629,06	3	3	1	8		cvc
1	l'ago	the needle	1	II	H	N	10,79	4	4	2	8		c'vcv
2	**Era l'una di notte quando ci siamo alzati.**	It was one at night when we got up.	1	II	H						9	19,64	
2	Era	It was	1	II		V	2485,87	3	3	2	9		vcv
2	l'una	one	1	II	H	N	8076,30	4	4	2	9		c'vcv
2	di notte	at night	1	II		A	286,45	5	4	2	9		cv cvGv
2	quando	when	1	II		F	1419,86	6	6	2	9		cvvccv
2	ci siamo alzati	we got up	1	II		V	2,90	6	6	3	9		cv cvvcv vccvcv
3	**Ogni inizio d'anno si fanno delle feste.**	Every beginning of the year they have a party.	1	II	H						8	19,45	
3	Ogni	Every	1	II		A	816,69	4	3	2	8		vccv
3	inizio d'	beginning of the	1	II		A	182,98	6	6	3	8		vcvcvv c
3	(d')anno	year	1	II	H	N	638,71	4	3	2	8		vGv
3	si fanno	they have	1	II		V	227,21	5	4	2	8		cv cvGv
3	delle	a	1	II		F	2346,85	5	4	2	8		cvGv
3	feste	party	1	II		N	31,86	5	5	2	8		cvccv
4	**Quando sono passati un mucchio d'anno si dimentica facilmente.**	Whenmany years have passed you forget easily.	1	II	H						10	30,47	
4	Quando	When	1	II		F	1419,86	6	6	2	10		cvvccv
4	sono passati	have passed	1	II		V	43,70	7	6	3	10		cvcv cvGvcv
4	un mucchio d'	many	1	II		A	9,74	7	5	2	10		vc cvGcvv c
4	(d')anni	years	1	II	H	N	1793,45	4	4	2	10		vGv
4	si dimentica	you forget	1	II		V	8,95	9	9	4	10		cv cvcvccvcv
4	facilmente	easily	1	II		A	43,70	10	10	4	10		cvcvccvccv
5	**Ho nascosto io l'etto di caramelle.**	I have hidden a pound of candy.	1	II	H						7	20,33	
5	Ho nascosto	have hidden	1	II		V	33,44	8	8	3	7		cv cvccvccv
5	io	I	1	II		F	886,72	2	2	1	7		vv
5	l'etto	a pound	1	II	H	N	2,37	5	4	2	7		c'vGv
5	di	of	1	II		F	31428,48	2	2	1	7		cv
5	caramelle	candy	1	II		N	4,21	9	8	4	7		cvcvcvGv
6	**Gianni ha acquistato una pelle d'orso.**	Gianni has bought a bearskin.	1	II	H						7	18,78	
6	Gianni	Gianno	1	II		N		6	5	2	7		cvvGv
6	ha acquistato	has bought	1	II		V	23,43	10	9	4	7		cv vccvvccvcv
6	una pelle	a skin	1	II		N	109,26	5	4	2	7		vcv cvGv
6	d'orso	of a bear	1	II	H	A	13,95	5	5	2	7		c'vccv
7	**Sul pavimento non c'era la cera.**	There was no wax on the floor.	1	II	H						7	15,49	
7	Sul	On	1	II		F	1132,88	3	3	1	7		cvc
7	pavimento	(the) floor	1	II		N	22,12	9	9	4	7		cvcvcvccv
7	non	no	1	II		A	9305,01	3	3	1	7		cvc
7	c'era	was	1	II	H	V	197,98	4	4	2	7		c'vcv
7	la cera	(the) wax	1	II	H	N	6,06	4	4	2	7		cv cvcv
8	**Venezia l'hanno visitata una sola volta.**	They have visited Venice only one time.	1	II	H						7	20,53	
8	Venezia	Venice	1	II		N	65,03	7	7	3	7		cvcvcvv
8	l'hanno visitata	they have visited	1	II	H	V	1598,88	6	4	4	7		c'cvGv cvcvcvcv
8	una (sola) volta	one time	1	II		N	676,89	5	5	2	7		vcv cvccv
8	sola	only	1	II		A	168,50	4	4	2	7		cvcv
9	**Il bambino non ha preso la merenda.**	The child has not taken the snack.	1	II	H						7	18,19	
9	Il bambino	The child	1	II		N	136,38	7	7	3	7		vc cvccvcv
9	non	not	1	II		A	9305,01	3	3	1	7		cvc
9	ha preso	has taken	1	II	H	V	147,44	5	5	2	7		cv ccvcv
9	la merenda	the snack	1	II		N	1,58	7	7	3	7		cv cvcvccv
10	**Valeria sa che Carlo non l'ama più.**	Valeria knows that Carlo does not love her anymore.	1	II	H						8	17,86	
10	Valeria	Valeria	1	II		N		7	7	4	8		cvcvcvv
10	sa	knows	1	II		V	230,10	2	2	1	8		cv
10	che	that	1	II		F	6395,80	3	2	1	8		ccv
10	Carlo	Carlo	1	II		N	146,91	5	5	2	8		cvccv
10	non	not	1	II		A	9305,01	3	3	1	8		cvc
10	l'ama	love her	1	II	H	V	50,55	4	4	2	8		c'vcv
10	più	anymore	1	II		A	4140,83	3	3	1	8		cvv
11	**Non v'era traccia alcuna.**	There was not any trace.	1	II	H						5	13,05	
11	Non	Not	1	II		A	9305,01	3	3	1	5		cvc
11	v'era	there was	1	II	H	V	1,05	4	4	2	5		cvcv
11	traccia	trace	1	II		N	32,12	7	7	2	5		ccvGvv
11	alcuna	any	1	II		A	63,71	6	6	3	5		vccvcv

Appendix B.2 Dutch stimuli lists

Appendix B.2a Dutch reading: Pre-operative version

Dutch | Word reading | Pre-operative

Presentation NR	Stimulus (NL)	Stimulus (EN)	Sublist	Assessment list	Assessment cluster	Grammatical class	Frequency count	Frequency	Letters	Phonemes	Syllables	Length	Imageability	Age of Acquisition	Mean reaction time	Morphological regularity	Orthographic regularity	Consonant vowel order
1	nadenken	to think	I	1	HFL	V	49,74	H	8	8	3	L	3,00	7,00	2,31			cvcvccvc
2	wijsheid	wisdom	I	1	LFL	N	11,09	L	8	6	2	L	2,66	9,00	2,28			cvvccvvc
3	spoot	spouted	I	2	IM	V	1,56		5	4	1		3,10	6,78	2,20	I		ccvvc
4	opdracht	commission	II	1	HFL	N	48,05	H	8	7	2	L	3,14	7,94	2,33			vcccvccc
5	valt	falls	II	1	HFS	V	152,99	H	4	4	1	S	3,54	4,46	1,74			cvcc
6	signaal	signal	II	3	IO	N	29,13	L	7	6	2		3,24	9,18	2,21		I	cvccvvc
7	verkeerd	wrong	II	1	HFL	A	115,51	H	8	7	2	L	2,66	6,96	2,50			cvccvvcc
8	trui	sweater	I	3	RO	N	11,62	L	4	3	1		4,82	4,83	1,70		R	ccvv
9	bukken	to bend	II	1	LFS	V	10,73	L	6	5	2	S	4,31	6,21	1,71			cvccvc
10	problemen	problems	I	1	HFL	N	232,64	H	9	9	3	L	2,21	7,00	2,04			ccvccvcvc
11	inmiddels	by now	I	1	LFL	F	7,52	L	9	8	3	L	1,55	9,70	2,22			vccvccvcc
12	etui	etui	I	3	IO	N	0,07	L	4	4	2		4,76	8,59	2,16		I	vcvv
13	dreigen	to threaten	I	1	LFL	V	3,96	L	7	6	2	L	2,90	9,36	2,00			ccvvcvc
14	vies	dirty	II	1	LFS	A	19,80	L	4	3	1	S	3,86	4,59	1,79			cvvc
15	rent	runs	I	2	RM	V	11,16		4	4	1		3,83	5,65	2,00	R		cvcc
16	nergens	nowhere	I	1	HFL	F	145,26	H	7	7	2	L	2,24	5,95	1,95			cvccvcc
17	bloedde	bled	II	2	RM	V	3,27		7	5	2		3,90	5,46	2,14	R		ccvvccv
18	meteen	immediately	I	1	HFS	F	218,46	H	6	5	2	S	2,10	8,06	1,91			cvcvvc
19	inclusief	including	II	1	LFL	A	12,78	L	9	8	3	L	2,41	11,06	2,04			vcccvcvvc
20	gooien	to throw	I	1	HFS	V	49,62	H	6	5	2	S	4,59	4,84	1,87			cvvvvc
21	cacao	cacao	II	3	IO	N	0,62	L	5	4	2		4,07	8,02	2,04		I	cvcvv
22	schrok	startled	II	2	IM	V	10,66		6	5	1		3,07	6,03	2,05	I		ccccvc
23	toneel	theater	I	1	LFS	N	12,81	L	6	5	2	S	4,41	6,89	1,84			cvcvvc
24	betalen	to pay	II	1	HFL	V	162,34	H	7	7	3	L	4,17	6,22	1,94			cvcvcvc
25	chaos	chaos	II	3	RO	N	15,80	L	5	4	2		3,41	10,16	1,97		R	ccvvc
26	opendoen	to open	II	1	LFL	V	8,07	L	8	7	3	L	4,00	5,83	2,23			vcvccvvc
27	avond	evening	I	1	HFS	N	180,61	H	5	5	2	S	4,10	4,92	1,75			vcvcc
28	ontkende	denied	II	2	RM	V	1,97		8	8	3		2,31	9,25	2,23	R		vccccvccv
29	zodra	once	II	1	HFS	F	85,43	H	5	5	2	S	1,62	8,00	1,77			cvccv
30	strik	bow	II	1	LFS	N	2,04	L	5	5	1	S	4,76	5,80	1,93			cccvc
31	viel	fell	I	2	IM	V	85,87		4	3	1		3,66	4,46	1,83	I		cvvc
32	kabouter	gnome	I	3	RO	N	1,78	L	8	7	3		4,93	5,20	2,09		R	cvcvvcvc
33	weven	to weave	I	1	LFS	V	0,66	L	5	5	2	S	4,14	8,78	1,96			cvcvc
34	scheef	askew	I	1	LFS	A	3,00	L	6	4	1	S	3,97	6,96	1,75			cccvvc
35	zwoer	swore	II	2	IM	V	3,61		5	4	1		1,83	7,78	2,08	I		ccvvc
36	mens	human	II	1	HFS	N	144,66	H	4	4	1	S	4,57	5,05	1,47			cvcc
37	lacht	laughs	I	2	RM	V	21,29		5	4	1		4,18	4,59	1,92	R		cvccc
38	microfoon	microphone	II	1	LFL	N	10,34	L	9	8	3	L	4,86	7,83	1,85			cvccvcvvc

Dutch | Non-word reading | Pre-operative

Presentation NR	Stimulus (NL)	Sublist	Assessment list	Assessment cluster	Letters	Phonemes	Syllables	Length	N-count	Similarity to words	Mean reaction time	Consonant vowel order
1	beg	I	1	HNS	3	3	1	S	15	H	1,45	cvc
2	verkoerd	II	1	LNL	8	7	2	L	2	L	2,01	cvccvvcc
3	schuiden	II	1	HNL	8	6	2	L	6	H	1,91	cccvvcvc
4	hank	I	1	HNS	4	4	1	S	9	H	1,54	cvcc
5	straag	I	1	LNL	6	5	1	L	2	L	1,75	cccvvc
6	beum	I	1	LNS	4	3	1	S	3	L	1,42	cvvc
7	groek	II	1	HNS	5	4	1	S	7	H	1,68	ccvvc
8	bemaren	I	1	LNL	7	7	3	L	0	L	1,77	cvcvcvc
9	topa	II	1	LNS	4	4	1	S	1	L	1,55	cvcv
10	schanen	I	1	HNL	7	6	2	L	9	H	1,70	cccvcvc
11	ezo	I	1	LNS	3	3	2	S	1	L	1,65	vcv
12	schorken	I	1	HNL	8	7	2	L	5	H	2,02	cccvccvc

Presentation NR	Stimulus (NL)	Stimulus (EN)	Sublist	Assessment list	Assessment cluster	Grammatical class	Frequency count main word	Letters main word	Phonemes main word	Syllables main word	Words in sentence	Mean reaction time	Consonant vowel order
1	**De zwerver is aan het bedelen.**	The tramp is begging.	I	1	I						6	3,03	
1	De zwerver	The tramp	I	1		N	6,77	7	7	2	6		cv ccvccvc
1	is aan het	is	I	1		V	21669,76	2	2	1	6		vc vvc cvc
1	bedelen	begging	I	1	I	V	2,93	7	7	3	6		cvcvcvc
2	**Bob onderging een knie operatie.**	Bob underwent knee surgery.	I	1	NI						5	3,40	
2	Bob	Bob	I	1		N		3	3	1	5		cvc
2	onderging	underwent	I	1	NI	V	1,49	9	8	3	5		vccvccvcc
2	een (knie) operatie	surgery	I	1		N	44,16	8	8	4	5		vvc vcvcvcvv
2	knie	knee	I	1		A	10,24	4	3	1	5		ccvv
3	**De regels op de computer verspringen.**	The lines on the computer jump in.	I	1	NI						6	3,64	
3	De regels	The lines	I	1		N	83,77	6	6	2	6		cv cvcvcc
3	op	on	I	1		F	80868,80	2	2	1	6		vc
3	de computer	the computer	I	1		N	47,89	8	9	3	6		cv cvccvcvc
3	verspringen	jump in	I	1	NI	V	0,16	11	10	3	6		cvccccvccvc
4	**De auto wacht bij de overweg.**	The car waits at the train crossing.	II	1	I						6	3,24	
4	De auto	The car	II	1		N	458,00	4	3	2	6		cv vvcv
4	wacht	waits	II	1		V	834,29	5	4	1	6		cvccc
4	bij	at	II	1		F	2465,94	3	2	1	6		cvv
4	de overweg	the train crossing	II	1	I	N	8,67	7	7	3	6		cv vcvccvc
5	**De panda is een dier dat weinig voorkomt.**	The panda is an animal that does not appear often.	I	1	I						8	3,91	
5	De panda	The panda	I	1		N	0,96	5	5	2	8		cv cvccv
5	is	is	I	1		V	21669,76	2	2	1	8		vc
5	een dier	an aminal	I	1		N	28,10	4	3	1	8		vvc cvvc
5	dat	that	I	1		F	22080,40	3	3	1	8		cvc
5	weinig	not often	I	1		A	110,45	6	5	2	8		cvvcvc
5	voorkomt	does appear	I	1	I	V	5,67	8	7	2	8		cvvccvcc
6	**De kinderen kunnen goed met elkaar overweg.**	The children get along well with each other.	II	1	NI						7	3,67	
6	De kinderen	The children	II	1		N	474,49	8	8	3	7		cv cvccvcvc
6	kunnen	get	II	1		V	1704,80	6	5	2	7		cvGvc
6	goed	well	II	1		A	3488,11	4	3	1	7		cvvc
6	met	with	II	1		F	6813,26	3	3	1	7		cvc
6	elkaar	each other	II	1		F	578,08	6	5	2	7		vccvvc
6	overweg	along	II	1	NI	A	8,67	7	7	3	7		vcvccvc

Appendix B.2b Dutch reading: Post-operative version

Dutch | Word reading | Post-operative

Presentation NR	Stimulus (NL)	Stimulus (EN)	Sublist	Assessment list	Assessment Cluster	Grammatical class	Frequency count	Frequency	Letters	Phonemes	Syllables	Length	Imageability	Age of Acquisition	Mean reaction time	Morphological regularity	Orthographic regularity	Consonant vowel order
1	schok	shock	III	1	LFS	N	11,66	L	5	4	1	S	2,93	8,22	2,20			cccvc
2	betalen	to pay	II	1	HFL	V	162,34	H	7	7	3	L	4,17	6,22	1,94			cvcvcvc
3	houding	attiture	III	3	RO	N	20,08	L	7	5	2		3,24	9,72	2,12		R	cvvcvcc
4	verkeerd	wrong	II	1	HFL	A	115,51	H	8	7	2	L	2,66	6,96	2,50			cvccvvcc
5	klimaat	climate	III	1	LFL	N	4,12	L	7	6	2	L	2,76	9,54	2,12			ccvcvvc
6	zond	sent	III	2	IM	V	3,59		4	4	1		1,97	6,90	2,05	I		cvcc
7	opdracht	commission	II	1	HFL	N	48,05	H	8	7	2	L	3,14	7,94	2,33			vcccvccc
8	bloedde	bled	II	2	RM	V	3,27		7	5	2		3,90	5.46	2,14	R		ccvvccv
9	welkom	welcome	III	1	HFS	A	162,04	H	6	6	2	S	2,86	6,89	1,87			cvccvc
10	bukken	to bend	II	1	LFS	V	10,73	L	6	5	2	S	4,31	6,21	1,71			cvccvc
11	signaal	signal	II	3	IO	N	29,13	L	7	6	2		3,24	9,18	2,21		I	cvccvvc
12	opendoen	to open	II	1	LFL	V	8,07	L	8	7	3	L	4,00	5,83	2,23			vcvccvvc
13	chaos	chaos	II	3	RO	N	15,80	L	5	4	2		3,41	10,16	1,97		R	ccvvc
14	schrijven	to write	III	1	HFL	V	96,62	H	9	7	2	L	4,48	5,59	2,11			ccccvvcvc
15	zelden	rarely	III	1	LFS	F	12,60	L	6	6	2	S	1,93	8,44	1,90			cvccvc
16	cacao	cacao	II	3	IO	N	0,62	L	5	5	2		4,07	8,02	2,04		I	cvcvv
17	derhalve	therefore	III	1	LFL	F	0,85	L	8	8	3	L	1,34	12,11	2,15			cvccvccv
18	ontkende	denied	II	2	RM	V	1,97		8	8	3		2,31	9,25	2,23	R		vcccvccv
19	gezicht	face	III	1	HFL	N	183,63	H	7	6	2	L	4,76	5,14	1,78			cvcvccc
20	vies	dirty	II	1	LFS	A	19,80	L	4	3	1	S	3,86	4,59	1,79			cvvc
21	sliep	slept	III	2	IM	V	26,48		5	4	1		3,72	3.57	1,70	I		ccvvc
22	normaal	normal	III	1	HFL	A	120,06	H	7	6	2	L	2,10	7,34	1,81			cvccvvc
23	slaat	hits	III	2	RM	V	63,18		5	4	1		3,72	4,96	1,85	R		ccvvc
24	zodra	once	II	1	HFS	F	85,43	H	5	5	2	S	1,62	8,00	1,77			cvccv
25	uitkijken	to look out	III	1	LFL	V	11,73	L	9	7	3	L	3,07	7,61	2,00			vvccvvcvc
26	mens	human	II	1	HFS	N	144,66	H	4	4	1	S	4,57	5,05	1,47			cvcc
27	zwoer	swore	II	2	IM	V	3,61		5	4	1		1,83	7,78	2,08	I		ccvvc
28	inclusief	including	II	1	LFL	A	12,78	L	9	8	3	L	2,41	11,06	2,04			vcccvcvvc
29	strik	bow	II	1	LFS	N	2,04	L	5	5	1	S	4,76	5,80	1,93			cccvc
30	wast	washes	III	2	RM	V	3,91		4	4	1		3,79	4,96	2,16	R		cvcc
31	gevoel	feeling	III	1	HFS	N	128,27	H	6	5	2	S	2,32	7,17	1,93			cvcvvc
32	binden	to bind	III	1	LFS	V	8,99	L	6	6	2	S	3,48	7,71	1,96			cvccvc
33	mouw	sleeve	III	3	RO	N	4,18	L	4	3	1		4,83	5,10	1,64		R	cvvc
34	lezen	to read	III	1	HFS	V	107,80	H	5	5	2	S	4,31	5,65	1,69			cvcvc
35	journaal	news	III	3	IO	N	2,95	L	8	7	2		4,00	7,78	1,96		I	cvvccvvc
36	schrok	startled	II	2	IM	V	10,66		6	5	1		3,07	6,03	2,05	I		ccccvc
37	microfoon	microphone	II	1	LFL	N	10,34	L	9	8	3	L	4,86	7,83	1,85			cvccvcvvc
38	valt	falls	II	1	HFS	V	152,99	H	4	4	1	S	3,54	4,46	1,74			cvcc

Dutch | Non-word reading | Post-operative

Presentation NR	Stimulus (NL)	Sublist	Assessment list	Assessment cluster	Letters	Phonemes	Syllables	Length	N-count	Similarity to words	Mean reaction time	Consonant vowel order
1	grimaat	III	1	LNL	7	6	2	L	1	L	1,81	ccvcvvc
2	schuiden	II	1	HNL	8	6	2	L	6	H	1,91	cccvvcvc
3	groek	II	1	HNS	5	4	1	S	7	H	1,68	ccvvc
4	prucht	III	1	LNL	6	5	1	L	2	L	1,71	ccvccc
5	gra	III	1	LNS	3	3	1	S	0	L	1,45	ccv
6	rachten	III	1	HNL	7	6	2	L	10	H	1,75	cvcccvc
7	vlut	III	1	LNS	4	4	1	S	3	L	1,62	ccvc
8	nief	III	1	HNS	4	3	1	S	7	H	1,48	cvvc
9	verweeld	III	1	HNL	8	7	2	L	5	H	2,00	cvccvvcc
10	topa	II	1	LNS	4	4	1	S	1	L	1,55	cvcv
11	nak	III	1	HNS	3	3	1	S	15	H	1,32	cvc
12	verkoerd	II	1	LNL	8	7	2	L	2	L	2,01	cvccvvcc

Presentation NR	Stimulus (NL)	Stimulus (EN)	Sublist	Assessment list	Assessment cluster	Grammatical class	Frequency count main word	Letters main word	Phonemes main word	Syllables main word	Words in sentence	Mean reaction time	Consonant vowel order
1	**De leider moet iedereen een rol toe bedelen.**	The leader must assign everyone a role.	III	1	NI							3,03	
1	De leider	The leader	III	1		N	45,76	6	5	2	8		cv cvvcvc
1	moet	must	III	1		V	3929,38	4	3	1	8		cvvc
1	iedereen	everyone	III	1		F	698,71	8	6	3	8		vvcvcvvc
1	een rol	a role	III	1		N	54,01	3	3	1	8		vvc cvc
1	toe bedelen	assign	III	1	NI	V	2,93	7	7	3	8		cvv cvcvcvc
2	**De kinderen kunnen goed met elkaar overweg.**	The children get along well with each other.	II	1	NI							3,67	
2	De kinderen	The children	II	1		N	474,49	8	8	3	7		cv cvccvcvc
2	kunnen	get	II	1		V	1704,80	6	5	2	7		cvGvc
2	goed	well	II	1		A	3488,11	4	3	1	7		cvvc
2	met	with	II	1		F	6813,26	3	3	1	7		cvc
2	elkaar	each other	II	1		F	578,08	6	5	2	7		vccvvc
2	overweg	along	II	1	NI	F	8,67	7	7	3	7		vcvccvc
3	**Zij keken naar de zon die onderging.**	They looked at the sun that was setting.	III	1	I							3,40	
3	Zij	They	III	1		N	755,65	3	2	1	7		cvv
3	keken	looked	III	1		V	12,12	5	5	2	7		cvcvc
3	naar	at	III	1		F	4447,55	4	3	1	7		cvvc
3	de zon	the sun	III	1		N	68,67	3	3	1	7		cv cvc
3	die	that	III	1		F	7204,60	3	2	1	7		cvv
3	onderging	was setting	III	1	I	V	1,49	9	8	3	7		vccvccvcc
4	**Het leger voorkomt de ramp.**	The army prevents the disaster.	III	1	NI							2,93	
4	Het leger	The army	III	1		N	107,98	5	5	2	5		cvc cvcvc
4	voorkomt	prevents	III	1	NI	V	5,67	8	7	2	5		cvvccvcc
4	de ramp	the disaster	III	1		N	25,89	4	4	1	5		cv cvcc
5	**De atleet verbrak het record verspringen.**	The athlete broke the long jump record.	III	1	I							4,05	
5	De atleet	The athlete	III	1		N	2,58	6	5	2	6		cv vccvvc
5	verbrak	broke	III	1		V	1,23	7	7	2	6		cvcccvc
5	het record	the record	III	1		N	10,13	6	5	2	6		cvc cvcvcc
5	verspringen	long jump	III	1	I	N	0,16	11	10	3	6		cvccccvccvc
6	**De auto wacht bij de overweg.**	The car waits at the train crossing.	II	1	I							3,24	
6	De auto	The car	II	1		N	458,00	4	3	2	6		cv vvcv
6	wacht	waits	II	1		V	834,29	5	4	1	6		cvccc
6	bij	at	II	1		F	2465,94	3	2	1	6		cvv
6	de overweg	the train crossing	II	1	I	N	8,67	7	7	3	6		cv vcvccvc

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Appendix B.2c Dutch spelling: Pre-operative version

Dutch | Word spelling | Pre-operative

Presentation NR	Stimulus (NL)	Stimulus (EN)	Sublist	Assessment list	Assessment cluster	Grammatical class	Frequency count	Frequency	Letters	Graphemes	Syllables	Length	Imageability	Age of Acquisition	Mean reaction time	Morphological regularity	Orthographic regularity	Consonant vowel order
1	kamer	room	1	II	HFS	N	275,24	H	5	5	2	S	4,69	4,75	6,73			cvcvc
2	vervoeren	to transport	1	I	LFL	V	6,93	L	9	8	3	L	3,62	8,33	7,18			cvccvvcvc
3	douche	shower	3	II	IO	N	22,25		6	4	1		4,90	6,03	5,14		I	cvvccv
4	inderdaad	indeed	1	I	HFL	F	172,31	H	9	8	3	L	1,86	7,50	8,11			vccvccvvc
5	hoest	coughs	2	II	RM	V	2,88		5	4	1		4,14	5,77	6,63	R		cvvcc
6	tevens	in addition	1	I	LFS	F	4,16	L	6	6	2	S	1,48	10,30	5,38			cvcvcc
7	gelei	jelly	3	I	IO	N	0,71		5	4	2		3,97	8,20	10,59		I	cvcvv
8	schelen	to differ	1	I	HFL	V	93,55	H	7	6	2	L	2,18	8,78	5,68			cccvcvc
9	tram	tram	1	II	LFS	N	1,81	L	4	4	1	S	4,76	7,59	6,31			ccvc
10	dacht	thought	2	II	IM	V	5,28		5	4	1		2,31	5,53	5,75	I		cvccc
11	waarheid	truth	1	II	HFL	N	189,39	H	8	6	2	L	2,39	6,71	7,65			cvvccvvc
12	denkt	thinks	2	II	RM	V	375,56		5	5	1		2,89	5,53	6,00	R		cvccc
13	aangaande	regarding	1	II	LFL	F	1,90	L	9	7	3	L	1,45	11,61	7,83			vvccvvccv
14	onderzoek	research	1	I	HFL	N	109,88	H	9	8	3	L	3,24	8,78	6,59			vccvccvvc
15	belde	called	2	I	RM	V	78,71		5	5	2		3,48	6,03	6,06	R		cvccv
16	neef	nephew	1	I	HFS	N	48,48	H	4	3	1	S	4,28	5,37	4,53			cvvc
17	blut	broke	1	I	LFS	A	12,51	L	4	4	1	S	3,66	9,15	4,71			ccvc
18	gram	gram	3	I	RO	N	6,20		4	4	1		3,45	7,62	5,78		R	ccvc
19	zowel	both	1	II	LFS	F	15,41	L	5	5	2	S	1,55	7,78	5,27			cvcvc
20	liep	walked	2	I	IM	V	71,37		4	3	1		3,59	4,14	6,47	I		cvvc
21	raar	weird	1	II	HFS	A	84,89	H	4	3	1	S	2,75	6,46	5,14			cvvc
22	steiger	scaffolding	3	II	IO	N	1,28		7	6	2		4,86	9,27	6,76		I	ccvvcvc
23	regenen	to rain	1	II	LFL	V	7,94	L	7	7	3	L	4,52	4,90	5,51			cvcvcvc
24	vandaan	from	1	II	HFL	F	165,88	H	7	6	2	L	1,82	9,06	6,35			cvccvvc
25	routine	routine	3	II	RO	N	7,32		7	6	3		2,41	10,61	5,71		R	cvvcvcv
26	vieren	to celebrate	1	I	HFS	V	47,70	H	6	5	2	S	3,72	6,34	6,51			cvvcvc
27	mijzelf	myself	1	I	LFL	F	14,77	L	7	6	2	L	4,24	5,56	6,45			cvvcvcc
28	kreeg	received	2	II	IM	V	169,93		5	4	1		2,55	4,84	5,03	I		ccvvc
29	schouder	sholder	1	I	LFL	N	18,57	L	8	6	2	L	4,93	5,65	5,57			cccvvcvc
30	hakte	chopped	1	I	LFS	V	1,56	L	5	5	2	S	3,86	8,01	5,66			cvccv
31	cognac	cognac	3	II	RO	N	7,82		6	6	2		4,62	10,95	6,64		R	cvccvc

Dutch | Non-word spelling | Pre-operative

Presentation NR	Stimulus (NL)	Sublist	Assessment list	Assessment cluster	Letters	Graphemes	Syllables	Length	N-count	Similarity to words	Mean reaction time	Consonant vowel order
1	wussen	1	I	HNL	6	5	2	L	10	H	5,12	cvGvc
2	doep	1	I	HNS	4	3	1	S	13	H	4,96	cvvc
3	kruiter	1	II	LNL	7	6	2	L	1	L	6,35	ccvvcvc
4	deven	1	I	HNS	5	5	2	S	14	H	4,71	cvcvc
5	kelft	1	I	LNS	5	5	1	S	2	L	4,90	cvccc
6	maspel	1	I	LNL	6	6	2	L	0	L	5,14	cvccvc
7	kroek	1	II	HNS	5	4	1	S	7	H	4,73	ccvvc
8	ulp	1	II	LNS	3	3	1	S	0	L	4,47	vcc
9	schullen	1	II	HNL	8	6	2	L	5	H	5,50	cccvGvc
10	nif	1	I	LNS	3	3	1	S	2	L	3,86	cvc

Presentation NR	Stimulus (NL)	Stimulus (EN)	Sublist	Assessment list	Assessment cluster	Grammatical class	Frequency count main word	Letters main word	Graphemes main word	Syllables main word	Words in sentence	Mean reaction time	Consonant vowel order
1	**Jan schaatst op het ijs.**	Jan skates on the ice.	I	1	D						5	12,23	
1	Jan	Jan	I	1		N		3	3	1	5		cvc
1	schaatst	skates	I	1		V	0,55	8	6	1	5		cccvvccc
1	op	on	I	1		F	8068,91	2	2	1	5		vc
1	het ijs	the ice	I	1	D	N	58,70	3	2	1	5		cvc vvc
2	**Mies kocht een lap stof op de markt.**	Mies bought a piece of fabric at the market.	II	1	ND						8	17,97	
2	Mies	Mies	II	1		N		4	3	1	8		cvvc
2	kocht	bought	II	1		V	24,79	5	4	1	8		cvccc
2	een lap	a piece of	II	1	ND	N	3,43	3	3	1	8		vvc cvc
2	stof	fabric	II	1		A	29,25	4	4	1	8		ccvc
2	op	at	II	1		F	8068,91	2	2	1	8		vc
2	de markt	the market	II	1		N	19,03	5	5	1	8		cv cvccc
3	**In de zomer blijft het langer licht.**	In summer it stays light for longer.	I	1	ND						7	16,29	
3	In	In	I	1		F	8822,71	2	2	1	7		vc
3	de zomer	(the) summer	I	1		N	42,90	5	5	2	7		cv cvcvc
3	blijft	stays	I	1		V	265,27	6	5	1	7		ccvvcc
3	het	it	I	1		N	24433,98	3	3	1	7		cvc
3	langer	for longer	I	1		A	104,16	6	5	2	7		cvccvc
3	licht	light	I	1	ND	A	103,64	5	4	1	7		cvccc
4	**Zij heeft een gebroken hart.**	She has a broken hart.	I	1	D						5	14,16	
4	Zij	She	I	1		N	755,65	3	2	1	5		cvv
4	heeft	has	I	1		V	3657,28	5	4	1	5		cvvcc
4	een hart	a hart	I	1	D	N	196,37	4	4	1	5		vvc cvcc
4	gebroken	broken	I	1		A	66,04	8	8	2	5		cvccvcvc
5	**De onderzoeker heeft een groot lab.**	The researcher has a big lab.	II	1	D						6	18,96	
5	De onderzoeker	The researcher	II	1		N	3,59	1	10	4	6		cv vccvccvvcvc
5	heeft	has	II	1		V	3657,28	5	4	1	6		cvvcc
5	een lab	a lab	II	1	D	N	35,17	3	3	1	6		vvc cvc
5	groot	big	II	1		F	237,51	5	4	1	6		ccvvc

Appendix B.2d Dutch spelling: Post-operative version

Dutch | Word spelling | Post-operative

Presentation NR	Stimulus (NL)	Stimulus (EN)	Sublist	Assessment list	Assessment Cluster	Grammatical class	Frequency count	Frequency	Letters	Graphemes	Syllables	Length	Imageability	Age of Acquisition	Mean reaction time	Morphological regularity	Orthographic regularity	Consonant vowel order
1	raar	weird	1	II	HFS	A	84,89	H	4	3	1	S	2,75	6,46	5,14			cvvc
2	lichaam	body	1	III	HFL	N	147,54	H	7	5	2	L	4,72	6,09	6,49			cvccvvc
3	denkt	thinks	2	II	RM	V	375,56		5	5	1		2,89	5,53	6,00	R		cvccc
4	getij	tide	3	III	IO	N	1,35		5	4	2		3,36	9,57	7,51		I	cvcvv
5	bedoelen	to mean	1	III	LFL	V	8,07	L	8	7	3	L	2,07	7,44	6,11			cvcvvcvc
6	steiger	scaffolding	3	II	IO	N	1,28		7	6	2		4,86	9,27	6,76		I	ccvvcvc
7	geinig	funny	1	III	LFS	A	1,62	L	6	5	2	S	2,75	10,94	6,21			cvvcvc
8	aangaande	regarding	1	II	LFL	F	1,90	L	9	7	3	L	1,45	11,61	7,83			vvccvvccv
9	cognac	cognac	3	II	RO	N	7,82		6	6	2		4,62	10,95	6,64		R	cvccvc
10	luisteren	to listen	1	III	HFL	V	99,41	H	9	8	3	L	3,38	4,83	6,78			cvvccvcvc
11	routine	routine	3	II	RO	N	7,32		7	6	3		2,41	10,61	5,71		R	cvvcvcv
12	alhoewel	although	1	III	LFL	F	9,24	L	8	8	3	L	1,38	9,35	7,34			vccvvcvc
13	duidelijk	celar	1	III	HFL	A	170,82	H	9	9	3	L	2,45	7,44	7,37			cvvcvcvvc
14	hoest	coughs	2	II	RM	V	2,88		5	4	1		4,14	5,77	6,63	R		cvvcc
15	tussen	between	1	III	HFS	F	249,95	H	6	5	2	S	3,31	6,61	5,91			cvGvc
16	waarheid	truth	1	II	HFL	N	189,39	H	8	6	2	L	2,39	6,71	7,65			cvvccvvc
17	dacht	thought	2	II	IM	V	5,28		5	4	1		2,31	5,53	5,75	I		cvccc
18	zowel	both	1	II	LFS	F	15,41	L	5	5	2	S	1,55	7,78	5,27			cvcvc
19	waardevol	valuable	1	III	LFL	A	8,48	L	9	8	3	L	2,79	10,61	8,57			cvvccvcvc
20	lukt	manages	2	III	RM	V	102,75		4	4	1		2,14	6,46	4,43	R		cvcc
21	gezag	authority	1	III	LFS	N	11,66	L	5	5	2	S	2,86	9,12	5,06			cvcvc
22	vandaan	from	1	II	HFL	F	165,88	H	7	6	2	L	1,82	9,06	6,35			cvccvvc
23	toga	gown	3	III	RO	N	1,46		4	4	2		4,72	11,79	5,44		R	cvcv
24	zoal	like	1	III	LFS	F	5,79	L	4	4	2	S	1,45	7,82	4,43			cvvc
25	kamer	room	1	II	HFS	N	275,24	H	5	5	2	S	4,69	4,75	6,73			cvcvc
26	hing	hang	2	III	IM	V	15,00		4	3	1		3,52	6,03	6,35	I		cvcc
27	koffie	coffee	1	III	HFS	N	133,30	H	6	4	2	S	4,86	6,11	5,44			cvGvv
28	regenen	to rain	1	II	LFL	V	7,94	L	7	7	3	L	4,52	4,90	5,51			cvcvcvc
29	douche	shower	3	II	IO	N	22,25		6	4	1		4,90	6,03	5,14		I	cvvccv
30	kreeg	got	2	II	IM	V	169,93		5	4	1		2,55	4,84	5,03	I		ccvvc
31	tram	tram	1	II	LFS	N	1,81	L	4	4	1	S	4,76	7,59	6,31			ccvc

Dutch | Non-word spelling | Post-operative

Presentation NR	Stimulus (NL)	Sublist	Assessment list	Assessment cluster	Letters	Graphemes	Syllables	Length	N-count	Similarity to words	Mean reaction time	Consonant vowel order
1	kroek	1	II	HNS	5	4	1	S	7	H	4,73	ccvvc
2	bekalen	1	III	LNL	7	7	3	L	0	L	7,11	cvcvcvc
3	ulp	1	II	LNS	3	3	1	S	0	L	4,47	vcc
4	mer	1	III	HNS	3	3	1	S	16	H	3,84	cvc
5	kruiter	1	II	LNL	7	6	2	L	1	L	6,35	ccvvcvc
6	munst	1	III	LNS	5	5	1	S	3	L	5,45	cvccc
7	gussen	1	III	HNL	6	5	2	L	10	H	5,24	cvGvc
8	slun	1	III	LNS	4	4	1	S	1	L	4,37	ccvc
9	bist	1	III	HNS	4	4	1	S	11	H	4,78	cvcc
10	schullen	1	II	HNL	8	6	2	L	5	H	5,50	cccvcGvc

Presentation NR	Stimulus (NL)	Stimulus (EN)	Sublist	Assessment list	Assessment cluster	Grammatical class	Frequency count main word	Letters main word	Graphemes main word	Syllables main word	Words in sentence	Mean reaction time	Consonant vowel order
1	**De onderzoeker heeft een groot lab.**	The researcher has a big lab.	II	1	D						6	18,96	
1	De onderzoeker	The researcher	II	1		N	3,59	11	10	4	6		cv vccvccvvcvc
1	heeft	has	II	1		V	3657,28	5	4	1	6		cvvcc
1	een lab	a lab	II	1	D	N	35,17	3	3	1	6		vvc cvc
1	groot	big	II	1		F	237,51	3	4	1	6		ccvvc
2	**De auto reed te hard.**	The car drove too fast.	III	1	ND						5	11,05	
2	De auto	The car	III	1		N	458,00	4	3	1	5		cv vvcv
2	reed	drove	III	1		V	40,75	4	3	1	5		cvvc
2	te	too	III	1		A	7846,62	2	2	1	5		cv
2	hard	fast	III	1	ND	A	159,46	4	4	1	5		cvcc
3	**Dirk ligt op het strand.**	Dirk lies on the beach.	III	1	D						5	12,73	
3	Dirk	Dirk	III	1		N		4	4	1	5		cvcc
3	ligt	lies	III	1	D	V	277,27	4	4	2	5		cvcc
3	op	on	III	1		F	8068,91	2	2	1	5		vc
3	het strand	the beach	III	1		N	40,16	6	6	1	5		cvc cccvcc
4	**De rechter stelt een hoge eis.**	The judge sets a high claim.	III	1	ND						6	14,45	
4	De rechter	The judge	III	1		N	63,28	7	6	2	6		cv cvcccvc
4	stelt	sets	III	1		V	54,29	5	5	1	6		ccvcc
4	een eis	a claim	III	1	ND	N	12,07	3	2	1	6		vvc vvc
4	hoge	high	III	1		A	47,43	4	4	1	6		cvcv
5	**Mies kocht een lap stof op de markt.**	Mies bought a piece of fabric at the market.	II	1	ND						8	17,97	
5	Mies	Mies	II	1		N		4	3	1	8		cvvc
5	kocht	bought	II	1		V	24,79	5	4	1	8		cvccc
5	een lap	a piece of	II	1	ND	N	3,43	3	3	1	8		vvc cvc
5	stof	fabric	II	1		A	29,25	4	4	1	8		ccvc
5	op	at	II	1		F	8068,91	2	2	1	8		vc
5	de markt	the market	II	1		N	19,03	5	5	1	8		cv cvccc

A

Appendix B.3 Abbreviation glossary

Appendix B.3a Abbreviations reading

Glossary Reading

Category	Abbreviation	Description
Assessment cluster	HFL	High Frequency Long
	HFS	High Frequency Short
	LFL	Low Frequency Long
	LFS	Low Frequency Short
	MI	Morphological Irregularity
	MR	Morphological Regularity
	Ocg	Orthography with c/g letters
	Ogem	Orthography with geminate consonants
	Ostress	Orthography with irregular stress
	CV	Consonant-Vowel structure
	nCV	no CV structure
	MD	Morphological Decomposable
	nMD	not Morphological Decomposable
	RO	Regular Orthography
	IO	Irregular Orthography
	RM	Regular Morphology
	IM	Irregular Morphology
	HS	High similarity to words
	LS	Low similarity to words
	HNL	High N-count Long
	HNS	High N-count Short
	LNL	Low N-count Long
	LNS	Low N-count Short
	PS	Penultimate Stress
	nPS	no Penultimate Stress
	Cl	Clitic pronoun
	I	Initial stress
	NI	Not Initial stress
Grammatical class	N	Noun
	V	Verb
	A	Adjective
	F	Function word
Frequency	H	High
	L	Low
Length	L	Long
	S	Short
Orthographic regularity	R	Regular
	I	Irregular
Morphological regularity	R	Regular
	I	Irregular
Similarity to words	H	High similarity to words
	L	Low similarity to words
Consonant vowel order	c	consonant
	v	cowel
	G	geminate consonant

Appendix B.3b Abbreviations spelling

Glossary Spelling

Category	Abbreviation	Description
Assessment cluster	CV	Consonant-Vowel order
	HFL	High Frequency Long
	HFS	High Frequency Short
	LFL	Low Frequency Long
	LFS	Low Frequency Short
	OO	Opaque orthography
	MO	Morphology
	RO	Regular Orthography
	IO	Irregular Orthography
	RM	Regular Morphology
	IM	Irregular Morphology
	nCV	no CV structure
	nCVG	no CV structure, with a gemminate consonant
	MD	Morphological Decomposable
	nMD	not Morphological Decomposable
	CS	Common orthography Short
	CL	Common orthography Long
	US	Uncommon orthography Short
	UL	Uncommon orthography Long
	HNL	High N-count Long
	HNS	High N-count Short
	LNL	Low N-count Long
	LNS	Low N-count Short
	H	Homophone
	D	Dominant homophone
	ND	Non-Dominant homophone
Grammatical class	N	Noun
	V	Verb
	A	Adjective
	F	Function word
Frequency	H	High
	L	Low
Length	L	Long
	S	Short
Orthography	U	Uncommon
	C	Common
Morphology	D	Decomposable
	nD	not Decomposable
Orthographic regularity	R	Regular
	I	Irregular
Morphological regularity	R	Regular
	I	Irregular
Similarity	H	High similarity to words
	L	Low similarity to words
Consonant vowel order	c	consonant
	v	cowel
	G	geminate consonant

Appendix C

Scoring

Appendix C.1 Scoring forms for written language assessment

Appendix C.1.1a Example of a scoring form for reading words

PT: ....

Datum: ....

WRITING WORDS I - ERRORS

Nr	Stimulus	CORRECT	NO RESPONSE	ELLIPSIS	WORD Segmental	NON-WORD Segmental	PHONOLOGICALLY PLAUSIBLE	PHONOLOGICALLY RELATED	DIACRITIC	MORPHOLOGICAL-SYNTACTIC	OTHER	STIMULUS REPETITION	CASE MIXING	ILL-FORMED LETTERS	SELF-CORRECTED Correct	SELF-CORRECTED Wrong	UNCLASSIFIED ERROR	*Response*
Ex1	*idea*	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
Ex2	*pilota*	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
1	fascino	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
2	soffre	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
3	nera	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
4	orlo	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
5	equo	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
6	piacere	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
7	lento	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
8	pesche	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
9	scrivo	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
10	mani	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
11	vile	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
12	prezzi	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
13	numerose	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
14	modella	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
15	trova	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
16	intero	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
17	paesi	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
18	ognuno	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
19	quota	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
20	persero	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
21	cognato	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
22	stacca	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
23	asciutto	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
24	cielo	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
25	chiarire	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
26	usciere	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
27	saluta	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
28	coniuge	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
29	concluse	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
30	aquila	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
31	vieta	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
32	cero	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
33	lavora	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
34	perfetto	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
35	giornale	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
36	invano	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
37	finito	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
38	maschi	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
39	riescono	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
40	bestia	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
41	costruirono	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
42	sopra	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

Appendix C.1.1b Example of a scoring form for reading non-words

PT: ....
Datum: ....
WRITING NON-WORDS I - ERRORS

Nr	Stimulus	***CORRECT***	*NO RESPONSE*	*ELLIPSIS*	*WORD Segmental*	*NON-WORD Segmental*	*PHONOLOGICALLY PLAUSIBLE*	*PHONOLOGICALLY RELATED*	*DIACRITIC*	*OTHER*	*STIMULUS REPETITION*	*CASE MIXING*	*ILL-FORMED LETTERS*	*SELF-CORRECTED Correct*	*SELF-CORRECTED Wrong*	*UNCLASSIFIED ERROR*	*Response*
Ex1	*nesco*	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
Ex2	*firio*	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
1	vivite	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
2	cescia	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
3	pedovi	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
4	ledria	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
5	abitire	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
6	paruntri	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
7	abutive	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
8	cioreli	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
9	getruva	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
10	vallunde	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
11	cullito	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
12	chebo	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
13	veveta	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
14	viosile	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
15	aiupotte	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
16	rogli	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
17	aiutette	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
18	tenomato	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
19	gettiva	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
20	cirenghi	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
21	sedono	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
22	seltunda	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
23	capei	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
24	pefi	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
25	curete	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
26	dirto	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
27	femmida	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
28	erriba	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
29	cantevi	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
30	spivo	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
31	ammusti	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
32	sabomi	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
33	apressi	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
34	egne	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
35	ammossi	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
36	tasciolo	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
37	caroi	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
38	seglioto	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
39	sintoti	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
40	alfiria	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

Appendix C.1.1c Example of a scoring form for reading sentences

PT: ....
Datum: ....
WRITING SENTENCES I - ERRORS

Nr	Stimulus	CORRECT	NO RESPONSE	OMISSION	WORD ADDITION	WORD Substitution	ELLIPSIS	WORD Segmental	NON-WORD Segmental	PHONOLOGICALLY PLAUSIBLE	PHONOLOGICALLY RELATED	DIACRITIC	MORPHOLOGICAL-SYNTACTIC	OTHER	PUNCTUATION	STIMULUS REPETITION	CASE MIXING	ILL-FORMED LETTERS	SELF-CORRECTED Correct	SELF-CORRECTED Wrong	UNCLASSIFIED ERROR	*Response*
Ex1	*Marco mangiava una pera.*	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
1	La mamma	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
1	cuciva	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
1	i pantaloni	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
1	con	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
1	l'ago	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
2	Era	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
2	l'una	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
2	di notte	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
2	quando	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
2	ci siamo alzati	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
3	Ogni	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
3	inizio d'	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
3	(d')anno	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
3	si fanno	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
3	delle	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
3	feste	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
4	Quando	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
4	sono passati	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
4	un mucchio d'	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
4	(d')anni	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
4	si dimentica	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
4	facilmente	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
5	Ho nascosto	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
5	io	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
5	l'etto	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
5	di	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
5	caramelle	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

Appendix C.1.2a Example of a scoring form for spelling words

PT: ....
Datum: ....
WRITING WORDS I - ERRORS

Nr	Stimulus	CORRECT	NO RESPONSE	ELLIPSIS	WORD Segmental	NON-WORD Segmental	PHONOLOGICALLY PLAUSIBLE	PHONOLOGICALLY RELATED	DIACRITIC	MORPHOLOGICAL-SYNTACTIC	OTHER	STIMULUS REPETITION	CASE MIXING	ILL-FORMED LETTERS	SELF-CORRECTED Correct	SELF-CORRECTED Wrong	UNCLASSIFIED ERROR	*Response*
Ex1	*idea*	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
Ex2	*pilota*	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
1	fascino	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
2	soffre	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
3	nera	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
4	orlo	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
5	equo	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
6	piacere	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
7	lento	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
8	pesche	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
9	scrivo	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
10	mani	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
11	vile	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
12	prezzi	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
13	numerose	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
14	modella	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
15	trova	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
16	intero	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
17	paesi	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
18	ognuno	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
19	quota	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
20	persero	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
21	cognato	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
22	stacca	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
23	asciutto	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
24	cielo	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
25	chiarire	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
26	usciere	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
27	saluta	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
28	coniuge	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
29	concluse	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
30	aquila	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
31	vieta	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
32	cero	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
33	lavora	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
34	perfetto	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
35	giornale	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
36	invano	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
37	finito	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
38	maschi	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
39	riescono	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
40	bestia	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
41	costruirono	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
42	sopra	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
43	fasce	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
44	comincia	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
45	naturali	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
46	cicogna	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
47	cambieremo	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
48	chimera	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
49	sincera	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
50	calore	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
51	fresca	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

Appendix C.1.2b Example of a scoring form for spelling non-words

PT: ....
Datum: ....
WRITING NON-WORDS I - ERRORS

Nr	Stimulus	**CORRECT**	NO RESPONSE	ELLIPSIS	WORD Segmental	NON-WORD Segmental	PHONOLOGICALLY PLAUSIBLE	PHONOLOGICALLY RELATED	DIACRITIC	OTHER	STIMULUS REPETITION	CASE MIXING	ILL-FORMED LETTERS	SELF-CORRECTED Correct	SELF-CORRECTED Wrong	UNCLASSIFIED ERROR	*Response*
Ex1	*nesco*	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
Ex2	*firio*	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
1	vivite	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
2	cescia	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
3	pedovi	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
4	ledria	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
5	abitire	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
6	paruntri	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
7	abutive	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
8	cioreli	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
9	getruva	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
10	vallunde	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
11	cullito	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
12	chebo	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
13	veveta	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
14	viosile	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
15	aiupotte	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
16	rogli	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
17	aiutette	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
18	tenomato	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
19	gettiva	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
20	cirenghi	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
21	sedono	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
22	seltunda	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
23	capei	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
24	pefi	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
25	curete	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
26	dirto	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
27	femmida	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
28	erriba	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
29	cantevi	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
30	spivo	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
31	ammusti	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
32	sabomi	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
33	apressi	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
34	egne	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
35	ammossi	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
36	tasciolo	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
37	caroi	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
38	seglioto	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
39	sintoti	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
40	alfiria	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

Appendix C.1.2c Example of a scoring form for spelling sentences

PT: ....

Datum: ....

WRITING SENTENCES I - ERRORS

Nr	Stimulus	CORRECT	NO RESPONSE	OMISSION	WORD ADDITION	WORD Substitution	ELLIPSIS	WORD Segmental	NON-WORD Segmental	PHONOLOGICALLY PLAUSIBLE	PHONOLOGICALLY RELATED	DIACRITIC	MORPHOLOGICAL-SYNTACTIC	OTHER	PUNCTUATION	STIMULUS REPETITION	CASE MIXING	ILL-FORMED LETTERS	SELF-CORRECTED Correct	SELF-CORRECTED Wrong	UNCLASSIFIED ERROR	*Response*
Ex1	*Marco mangiava una pera.*	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
1	La mamma	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
1	cuciva	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
1	i pantaloni	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
1	con	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
1	l'ago	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
2	Era	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
2	l'una	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
2	di notte	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
2	quando	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
2	ci siamo alzati	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
3	Ogni	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
3	inizio d'	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
3	(d')anno	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
3	si fanno	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
3	delle	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
3	feste	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
4	Quando	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
4	sono passati	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
4	un mucchio d'	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
4	(d')anni	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
4	si dimentica	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
4	facilmente	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
5	Ho nascosto	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
5	io	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
5	l'etto	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
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Appendix C.2 Glossaries

Appendix C.2a Glossary of error classification system for reading

Reading	
Central errors	
No response	No (non-)word is read aloud
Omission	The omission of a word in a sentence
Word addition	The addition of one or more words in a sentence
Word substitution	The substitution of the target (non-)word with another (non-)word
Ellipsis	A fragment of the (non-)word is read aloud; e.g., only the first letters are read aloud
Word segmental error	Substitution, addition or omission of a part of the target (non-)word, in such a way that another word is read aloud
Non-word segmental error	Substitution, addition or omission of a part of the target (non-)word, in such a way that a non-word is read aloud
Stress misplacement	The word is read aloud while placing the stress on the wrong syllable
Circumlocution	The word is described without reading the word aloud
Morphological-Syntactic error	The word is read aloud with an error in the root and/or affix
Self-corrected correct	The patient corrects him/herself after an error, e.g., by explicitly saying it or by starting over after an error
Self-corrected incorrect	The patient fails an attempt to correct him/herself after an error - resulting in a wrong response
Central error not defined	Central error that does not fall in any of the other categories
Other errors	
Non-fluent reading	Repeated attempts to read a (non-)word aloud / the patient is stuck on a specific letter in a (non-)word
Syllabic reading	The (non-)word is read aloud syllable by syllable
Tremor	The (non-)word is read aloud with a tremor in his voice; e.g., a shaking voice
Speed	The (non-)word is read aloud faster or slower than at baseline
Volume	The (non-)word is read aloud at a louder or lower voice than at baseline
Deviant pronunciation of phoneme	The (non-)word is read aloud while one or more phonemes is pronounced in a different way, compared to baseline or compared to other words

Appendix C.2b Glossary of error classification system for spelling

Spelling	
Central errors	
No response	No (non-)word is spelled out
Omission	The omission of a word in a sentence
Word addition	The addition of one or more words in a sentence
Word substitution	The substitution of the target (non-)word with another (non-)word
Ellipsis	A fragment of the (non-)word is spelled; e.g., only the first letters are written down
Word segmental error	Substitution, addition or omission of a part of the target (non-)word, in such a way that another word is spelled out
Non-word segmental error	Substitution, addition or omission of a part of the target (non-)word, in such a way that a non-word is spelled out
Phonological related error	*Further distinction of segmental errors when a (non-)word is spelled out that is phonologically related to the target word*
Phonological plausible error	A (non-)word with a phonological plausible but incorrect spelling is spelled out
Diacritic	Substitution, addition or omission of a diacritic in the target word
Morphological-Syntactic error	The word is spelled out with an error in the root and/or affix
Self-corrected correct	The patient corrects him/herself after an error, e.g., by explicitly saying it or by starting over after an error
Self-corrected incorrect	The patient fails an attempt to correct him/herself after an error - resulting in a wrong response
Central error not defined	Central error that does not fall in any of the other categories
Peripheral errors	
Case mixing	The (non-)word is spelled out with individual letters in a word in inconsistent cases
Ill-formed letter	The (non-)word is spelled out with one or more ill-formed letters
Unclassifiable error	Error that could be either a central error or a peripheral error, e.g., a *m* written as a *n*

E

Epilogue

Acknowledgments

This thesis is the result of quite an incredible journey. A journey that was mine, but certainly would not have been possible without many other people.

First of all, I would like to express my gratitude to the patients who participated in the studies. The courage and confidence they showed in undergoing awake surgery was truly inspiring and served as my greatest motivation throughout my PhD. I also thank all healthy volunteers who wanted to contribute to improve clinical care for brain tumor patients.

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Prof. Roux, as a renowned expert in spelling in awake surgery, I was honored that you accepted to be on my review committee. Your very detailed and constructive review from a neurosurgical perspective has been very helpful in finalizing the thesis.

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About the author

Fleur Céline van Ierschot was born on December 27th 1988 in Tilburg, the Netherlands. She completed her secondary school (VWO) at the Theresialyceum in Tilburg in 2006. After a year in which she developed a strong interest for neuropsychology and photography in Florence (Italy), she started her studies of Psychology at the University of Groningen and of Photography at the Photoacademy. In 2012 she obtained her Master's of Science degree in Clinical Neuropsychology. In her pursuit to acquire more knowledge in the field of neuroscience, Fleur continued with a master of Cognitive and Clinical Neuroscience at Goldsmiths University of London (United Kingdom). She graduated with distinction (cum laude) in 2013. Returned to the Netherlands, she started a job as research assistant in the research group Cancer and Cognition at the Netherlands Cancer Institute / Antoni van Leeuwenhoek. In 2014 she was awarded with an Erasmus Mundus Joint Doctoral fellowship to start her PhD studies within the International Doctorate for Experimental Approaches to Language And Brain (IDEALAB), which gave her the possibility to continue focusing on cognition and cancer, while concentrating on brain tumor patients in an international setting. During her PhD, Fleur conducted her research at the Center for Mind/Brain Sciences (CIMeC, Trento, Italy), Center for Language and Cognition Groningen (Groningen, the Netherlands), and the Centre of Excellence in Cognition and its Disorders (Sydney, Australia). She worked in close collaboration with the Spedali Civili di Brescia (Brescia, Italy), Azienda Ospedaliera Universitaria Integrata Verona, Borgo Trento (Verona, Italy), and the University Medical Center Groningen (Groningen, the Netherlands). Within IDEALAB, Fleur received doctoral training from Universities of Trento, Groningen, Newcastle, Potsdam & Macquarie University. The author hopes to continue working in the field she is passionate about, focusing on clinical neuropsychology in awake surgery practice.

Thesis summary

One of the main aims of awake surgery for glioma patients is to preserve quality of life, while maximizing tumor resection. Focusing on an important yet understudied aspect of quality of life, this thesis investigates to what extent written language may be affected by a glioma or glioma surgery. The studies in this thesis have provided a better understanding of written language in neurosurgical practice. In particular, it has contributed to prediction and prevention of written language disorders in glioma patients undergoing awake surgery, and it has resulted in a valid examination tool to carefully monitor reading and spelling in this patient group.

Chapter 1 presents a general introduction to awake surgery for glioma patients and language monitoring in neurosurgical practice. It describes that assessments have mainly focused on spoken language, while written language is also indispensable for human communication. The multifaceted processes of reading and spelling are introduced in a cognitive model, and the functional neuroanatomy of reading and its application in awake surgery is discussed.

In **Chapter 2**, the functional and neural correlates of spelling are described, and the applicability of current neuroanatomical theories for glioma patients is investigated in a systematic literature review. We evaluated the incidence of dysgraphia in glioma patients, the type of spelling errors in light of tumor location, and the specificity of spelling sites with respect to other language functions. Only nine studies reported details on spelling assessment in glioma patients undergoing awake surgery. Post-operative and persistent dysgraphia was frequently found after glioma surgery, and intra-operative stimulation elicited isolated spelling interferences in more than a third of the patients. This study indicated that glioma data converged with anatomo-functional knowledge of spelling can aid neurosurgical practice.

Chapter 3 aims to evaluate the sensitivity of a commonly used clinical language battery to assess written language deficits in brain tumor patients. Fourteen glioma patients were retrospectively included. Quantitative and qualitative analyses of performance on the short clinical subtests before and after surgery revealed large individual variability in error patterns and error types, but did not allow to identify which underlying processes were damaged. Results show that current clinical evaluations are not always suitable to detect subtle deficits in glioma patients.

Chapter 4 describes the development of the written language battery for glioma patients. A cognitive model that distinguishes multiple underlying components of reading and spelling served as the foundation to design a sensitive and specific theory-driven assessment tool. The battery includes word, non-word and sentence tasks for reading and spelling, and was standardized in a population of Italian and Dutch neurologically healthy adults. Norms, imageability ratings, mean reaction times and inter-rater reliability from healthy participant data provide guidelines for the use of the battery in neurosurgical practice.

Chapter 5 reports on the validation and clinical application of the written language battery for glioma patients. We examine whether better accounts can be provided by evaluations of reading and spelling performance by using the written language battery compared to short subtests from a commonly used clinical battery. Results of two glioma cases demonstrate that the written language battery for glioma patients is more sensitive than a current clinical examination, and that damaged components can be identified using the new battery. The written language battery for glioma patients is a valid test to evaluate reading and spelling, and feasible to apply before, during and after awake surgery to target patient-tailored treatment in neurosurgical practice.

Chapter 6 focuses on how preservation of written language may be obtained in glioma patients. Reading and spelling were inspected in 18 glioma patients before and after surgery, and we weighted the value of different intra-operative assessments at an individual level. This study shows that substantial written language impairments can arise in glioma patients, yet that preservation of written language functioning is feasible when we implement detailed testing and conduct careful analyses. Written language can be preserved via task-specific intra-operative assessment, but preservation may not generalize towards non-monitored (written) language tasks.

Chapter 7 addresses the possible influence of lesion site, timing of assessments and cognitive profiles on interpreting pre- and post-operative written language performance in glioma patients. Error profiles converged in most cases with expectations based on lesion and neuroimaging studies given the specific glioma location. Post-operative written language performance differed over time, and was characterized by a decline directly after surgery followed by increase to pre-operative baseline at long-term assessments. The specific relation with impairments on other cognitive domains could not be established. Results connote that knowledge about the neural correlates of reading and spelling can be exploited to predict post-operative impairments and to guide intra-operative assessment. Interpretations of written language performance require careful considerations of individual parameters.

Chapter 8 provides a general discussion of the main findings and gives directions for clinical practice and future studies. In this thesis, thorough evaluations of written language revealed that reading and spelling functions are vulnerable to be damaged by a glioma and glioma surgery. It was demonstrated that the written language battery for glioma patients facilitates identification of damaged components of written language, and that the flexible battery can be used to target patient-tailored treatment, to predict and prevent reading and spelling disorders after awake surgery for glioma treatment, and to expand anatomo-functional knowledge of reading and spelling.

PhD portfolio

Erasmus Mundus Joint Doctorate 2014 - 2018

International Doctorate for Experimental Approaches to Language and Brain (IDEALAB), at the University of Trento and University of Groningen, in collaboration with Macquarie University, University of Newcastle & University of Potsdam
Supervisors: Prof. Dr. Gabriele Miceli and Prof. Dr. Roelien Bastiaanse

COURSES

IDEALAB winterschool: Computational modelling	Sydney, 2017
IDEALAB winterschool: Introduction to fMRI	Sydney, 2017
IDEALAB winterschool: Introduction to MEG	Sydney, 2017
IDEALAB winterschool: Introduction to EMOTIV	Sydney, 2017
IDEALAB winterschool: Introduction to EEG	Sydney, 2017
Neurosurgical Dissection course:"The white matters"	Graz, 2016
Academic writing for PhD students: A publishing course	Groningen, 2016
IDEALAB Summerschool: Abstract Writing	Potdam, 2015
IDEALAB Summerschool: Scientific Publishing	Potdam, 2015
IDEALAB Summerschool: Workshop on Aphasia	Potdam, 2015
IDEALAB Summerschool: Dyslexia	Potdam, 2015
IDEALAB Summerschool: Statistics R	Potdam, 2015
IDEALAB Summerschool: Ethics and Research Ethics	Potdam, 2015
Research communication: Figures and posters	Rovereto, 2015
Research communication: Data visualisation	Rovereto, 2015
Being a PhD student at CIMeC	Rovereto, 2015
Italian language course	Trento, 2014
Neurobiology of reading	Rovereto, 2014
Ethics of research in Neuroscience	Rovereto, 2014
Time management	Rovereto, 2014
Introduction to the PhD program	Rovereto, 2014
IDEALAB Summerschool: Scientific Writing	Potdam, 2014
IDEALAB Summerschool: Ethics	Potdam, 2014

ATTENDED TALKS

Colloquia

IDEALAB winterschool: Critical issue in cognitive sciences	Sydney, 2017
CLCG colloquium: Anatomo-functional variability in the brain	Groningen, 2016
IDEALAB winterschool: Serial position in written and spoken language	Bressanone, 2016
IDEALAB winterschool: Language and the striatum	Bressanone, 2016
IDEALAB winterschool: Pre- and post-lexical representations	Bressanone, 2016
IDEALAB winterschool: Semantic spaces in the brain	Bressanone, 2016
IDEALAB summerschool: Cross-linguistic research on aphasia	Potsdam, 2015
IDEALAB summerschool: Developmental language disorders	Potsdam, 2015
CIMeC colloquium: Advanced models for diffusion imaging and tractography	Rovereto, 2015
IDEALAB winterschool: The reading brain	Bressanone, 2015
IDEALAB winterschool: The contribution of medial PFC to semantics	Bressanone, 2015
IDEALAB winterschool: The phonological loop	Bressanone, 2015
CIMeC colloquium: Thus in the beginning all the world was America	Rovereto, 2015
CIMeC colloquium: Individual variation in resting temptation	Rovereto, 2015

Conferences

Society for the Neurobiology of Language	Baltimore, 2017
Federation of European Societies of Neuropsychology	Maastricht, 2017
European Low Grade Glioma Network	Bilbao, 2017
Science of Aphasia	Venice, 2016
European Low Grade Glioma Network	Graz, 2016
European Workshop on Cognitive Neuropsychology	Bressanone, 2016
Science of Aphasia	Aveiro, 2015
The brain and gliomas	Brescia, 2015
Connect brain	Trento, 2015
Images of the mind	Milan, 2015
European Low Grade Glioma Network	Paris, 2015
European Workshop on Cognitive Neuropsychology	Bressanone, 2015

TEACHING ACTIVITIES

Lecturing

MSc Clinical linguistics: language testing in awake brain surgery — Groningen, 2016
MSc Clinical linguistics: language testing in awake brain surgery — Groningen, 2017

Supervising

MSc Clinical linguistics: one student (Dutch/English) — Groningen, 2017
LM Psicologia - Neuroscienze: two students (Italian) — Rovereto, 2017
BA Taalwetenschap: one student (Dutch) — Groningen, 2016
LM Psicologia - Neuroscienze: two students (Italian/English) — Rovereto, 2015

HONOURS AND AWARDS

People's Choice Award, Three Minute Thesis Competition — Sydney, 2017
EU Funded Fellowship for Erasmus Mundus Joint Doctorate — 2014 - 2017

CIMEC PARTICIPATION

IDEALAB winterschool assistance — Rovereto, 2016
IDEALAB winterschool assistance — Rovereto, 2015

PUBLICATIONS

Van Ierschot, F.C., Bastiaanse, Y.R.M., Miceli, G. (Submitted). Assessing spelling in glioma patients undergoing awake surgery: A systematic review. *Submitted to Neuropsychology Review (August 2017)*

The European Low-Grade Glioma Network (contributor). (2017) Evidence-based medicine in glioma: molecular biology is only part of the story. *Lancet Oncology, 18*(8), DOI: http://dx.doi.org/10.1016/S1470-2045(17)30510-7

PROCEEDINGS

Van Ierschot, F., Veenstra, W., Santini, B., Wagemakers, M., Jeltema, H-R., Pinna, G., Bastiaanse, R., Miceli, G. (2017). Selective involvement of posteriori perisylvian regions in sublexica processing: Evidence from brain tumor patients. *Society for the Neurobiology of Language, Abstract book C36,* p.130.

Van Ierschot, F., Miozzo, A. Santini, Spena, G., Talacchi, A., Miceli, G. (2017). The necessity of theory-driven written language assessment in awake glioma surgery. *The Federation of European Societies of Neuropsychology, Abstract book ID 325,* p.24.

Van Ierschot, F.C., Miozzo, A., Santini, B., Spena, G., Talacchi, A., Miceli, G. (2016). Language preservation in brain tumour patients undergoing awake surgery: Does monitoring object naming suffice to spare other language skills? *Stem-, spraak- en taalpathologie. 21*, 136-140.

CONFERENCE PRESENTATIONS

Van Ierschot, F., Veenstra, W., Santini, B., Wagemakers, M., Jeltema, H-R., Pinna, G., Bastiaanse, R., Miceli, G. (9 November 2017). Selective involvement of posteriori perisylvian regions in sublexica processing: Evidence from brain tumor patients. *Poster presentation at the 9th Annual Meeting of the Society for the Neurobiology of Language,* Baltimore, USA.

Van Ierschot, F.C., & Miceli, G. (20 October 2017).Preserving spelling in the brain tumor patients: Two cases spelled out. *Poster presentation at 10th year CIMeC anniversary*, Rovereto, Italy.

Van Ierschot, F., Miozzo, A. Santini, Spena, G., Talacchi, A., Miceli, G. (13 October 2017). The necessity of theory-driven written language assessment in awake glioma surgery. *Oral presentation at the 6th Scientific meeting of the Federation of European Societies of Neuropsychology,* Maastricht, the Netherlands.

Van Ierschot, F.C., Veenstra, W.S., Miozzo, A., Santini, B., Wagemakers, M., Spena, G., Pinna, G., Bastiaanse, Y.R.M., Miceli, G. (2 June 2017). Task-specific preservation of written language through intra-operative assessment. *Oral presentation at the European Low Grade Glioma Network meeting*, Bilbao, Spain.

Van Ierschot, F.C., Miozzo, A., Santini, B., Spena, G., Talacchi, A., Miceli, G. (28 September 2016). Language preservation in brain tumour patients undergoing awake surgery: Does monitoring object naming suffice to spare other language skills? *Oral presentation at the Science of Aphasia Conference*, Venice, Italy.

Van Ierschot, F.C., Miozzo, A., Spena, G., Santini, B., Jeltema, J.R., Wagemakers, M., Bastiaanse, Y.R.M., Miceli, G. (3 June 2016). Reading and writing in glioma patients: The necessity of detailed monitoring. *Oral presentation at the international European Low Grade Glioma Network meeting*, Graz, Austria.

Van Ierschot, F.C., Miceli, G. (24 – 29 January 2016). Reading and writing in glioma patients: Towards a detailed assessment. *Poster presentation at the 34th European Workshop on Cognitive Neuropsychology*, Bressanone, Italy.

Van Ierschot, F.C., Miozzo, A., Spena, G., Miceli, G. (2 October 2015). Reading and writing assessments in glioma patients undergoing awake surgery. *Poster presentation at CIMeC Doctoral School day*, Rovereto, Italy.

Van Ierschot, F.C., Miozzo, A., Spena, G., Fontanella, M.M., Miceli, G. (24 – 26 September 2015). Reading and writing assessments in glioma patients undergoing awake surgery. *Poster presentation at The Brain and Gliomas: when connections are crucial conference*, Brescia, Italy.

PRESENTATIONS / INVITED TALKS

Van Ierschot, F.C. (7 April 2017). Awake surgery and the preservation of written language. *Invited speaker at Brown Bag CIMeC*, Rovereto, Italy.

Van Ierschot, F.C. (15 February 2017). Written language monitoring in awake surgery spelled out. *Oral presentation at the IDEALAB Winterschool,* Sydney, Australia.

Van Ierschot, F.C., (6 February 2017). Language preservation in adult brain tumour patients who undergo awake surgery. I*nvited speaker at the Behavioural Science Unit at Kids Cancer Centre*, Sydney, Australia.

Van Ierschot, F.C. (20 April 2016). Reading and writing after awake surgery: A case study. *Invited speaker at Research group Neurolinguistics*, Groningen, the Netherlands.

Van Ierschot, F.C. (19 January 2016). Reading and writing in glioma patients: Towards a detailed assessment. *Oral presentation at the IDEALAB Winterschool*, Rovereto, Italy.

Van Ierschot, F.C. (11 November 2015). Valutazione di scrittura e lettura. *Invited speaker at Il Centro Medico di Foniatria*, Padova, Italy.

Van Ierschot, F.C. (12 September 2015). Intra-operative mapping of reading and writing. *Oral presentation at the IDEALAB Summerschool*, Potsdam, Germany.

Van Ierschot, F.C. (1 September 2015). Written language assessment in glioma patients. *Invited speaker at the Department of Neuroscience - Section of Neurosurgery*, Verona, Italy.

Van Ierschot, F.C. (27 September 2014). Intra-operative mapping of reading and writing circuits in awake craniotomy. *Oral presentation the IDEALAB Summerschool*, Potsdam, Germany.

Van Ierschot, F.C. (14 May 2014). Reading and writing in awake craniotomy. *Invited speaker at Research group Neurolinguistics*, Groningen, the Netherlands.

MONITORING OF READING AND SPELLING IN GLIOMA PATIENTS UNDERGOING AWAKE SURGERY

F.C. VAN IERSCHOT