University of Groningen

Language impairments and resting-state EEG in brain tumour patients

Wolthuis, Nienke

DOI:
[10.33612/diss.159333388](https://doi.org/10.33612/diss.159333388)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2021

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Wolthuis, N. (2021). *Language impairments and resting-state EEG in brain tumour patients: Revealing connections*. [Thesis fully internal (DIV), University of Groningen]. University of Groningen.
<https://doi.org/10.33612/diss.159333388>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Language impairments and resting-state EEG in brain tumour patients

Revealing connections

Nienke Wolthuis

**university of
 groningen**

faculty of arts

CLCG

umcg

Stichting Afasie Nederland

The work reported in this thesis has been carried out under the auspices of the Centre for Language and Cognition Groningen (CLCG) and the research school of Behavioural and Cognitive Neurosciences (BCN) at the University of Groningen, in collaboration with the University Medical Centre Groningen (UMCG) and the Erasmus MC University Medical Centre Rotterdam (Erasmus MC).

In addition, the EEG research reported in this thesis was financially supported by the Dutch Aphasia Foundation (Stichting Afasie Nederland).

The publication of this thesis was financially supported by the University of Groningen.

Groningen Dissertations in Linguistics 197

© 2021, Nienke Wolthuis

Cover design and layout by Daniëlle Balk – www.persoonlijkproefschrift.nl

Cover image by Boszud – www.shutterstock.com/g/Boszud

Printed by Ipskamp Printing (NL) – www.ipskampprinting.nl

university of
 groningen

Language impairments and resting-state EEG in brain tumour patients

Revealing connections

PhD thesis

to obtain the degree of PhD at the
University of Groningen
on the authority of the
Rector Magnificus Prof. C. Wijmenga
and in accordance with
the decision by the College of Deans.

This thesis will be defended in public on

Thursday 11 March 2021 at 14.30 hours

by

Nienke Wolthuis

born on 22 March 1991
in Zutphen

Supervisor

Prof. Y.R.M. Bastiaanse

Co-supervisors

Dr. D.D. Satoer

Dr. I. Bosma

Dr. J. Cherian Perumpillichira

Assessment committee

Prof. C.J. Stam

Prof. J.M.C. van Dijk

Prof. C. Papagno

*Voor opa en oma Schat
Jullie naam zegt genoeg*

Acknowledgements / Dankwoord

Dit proefschrift had niet tot stand kunnen komen zonder de inzet, hulp en support van veel verschillende mensen, die ik graag wil bedanken. There will be code-switching (het switchen tussen talen) in this section, but that will keep our brains flexible.

Allereerst wil ik de patiënten die meegedaan hebben aan het onderzoek bedanken. Uw bereidheid om deel te nemen aan de testonderzoeken vind ik fantastisch. Velen van u kwamen tot drie keer toe, zelfs in moeilijke of beroerde tijden, zonder dat daar iets tegenover stond. Ik heb hier veel bewondering voor. Daarnaast gaat mijn dank uit naar de mensen die deelgenomen hebben aan de controlegroep van het onderzoek. Voor alle deelnemers samen: heel hartelijk bedankt voor uw tijd en inzet. Het ga u goed.

Dan wil ik me graag richten tot mijn promotor prof. Roelien Bastiaanse en mijn co-promotoren dr. Djaina Satoer, dr. Ingeborg Bosma en dr. Joseph Cherian Perumpillichira.

Roelien, jij hebt veel bijgedragen aan mijn ontwikkeling als onderzoeker en neurolinguïst. Dat begon al in 2010 tijdens mijn eerste jaar van de bachelor Taalwetenschap aan de Rijksuniversiteit Groningen (RUG). Sindsdien heb ik veel geleerd van je kennis, ervaring en deskundigheid. Je hebt ervoor gezorgd dat alle ingrediënten aanwezig waren om dit project te laten slagen. Wat ben ik blij dat het gelukt is. Bedankt voor al je tijd, feedback en betrokkenheid tijdens alle stadia van het onderzoek, dat geleid heeft naar dit proefschrift.

Djaina, als mijn dagelijks begeleider heb je een groot aandeel gehad in dit project. Jaren geleden had jij een idee, stuurde me een aantal artikelen, en dat is uiteindelijk uitgegroeid tot dit proefschrift. Dankzij jou heb ik kennis en ervaring op kunnen doen in de klinische praktijk, zowel bij de polikliniek als in de operatiekamer. Daarnaast stond je altijd klaar om mijn vragen te beantwoorden en mijn stukken te lezen, die je tussen alle poliafspraken, operaties, onderwijs-, en onderzoeksactiviteiten door wist te plannen. Ik wil je enorm bedanken voor je begeleiding en het prettige contact tijdens dit hele traject.

Ingeborg, mede dankzij jou is dit onderzoeksproject van de grond gekomen. Bedankt voor je rol in de organisatie en implementatie van het onderzoek in het Universitair Medisch Centrum Groningen (UMCG), en voor je inzet bij de inclusie van patiënten. Daarnaast was jouw expertise op neuro(onco)logisch gebied onmisbaar in dit onderzoek. Ik kijk met plezier terug op onze gesprekken en de afspraken om artefactvrije segmenten in de elektro-encefalografie (EEG)-registraties te selecteren. Dank je wel voor de fijne begeleiding.

Joseph, thank you for all your contributions to this research project. For example, for teaching me how to look at EEG registrations and how to interpret the basic patterns (this already started during my master's thesis), for introducing me to – and making arrangements with – the KNF department at the Erasmus MC University Medical Centre Rotterdam (Erasmus MC), for the visual EEG analyses in this dissertation, and for your helpful feedback on my chapters. No matter the distance, you kept involved in this project, for which I am very grateful.

I would like to express my sincere appreciation to the members of the assessment committee: prof. Stam, prof. Papagno, and prof. van Dijk. Thank you for taking the time to evaluate my work and for the valuable comments that you shared. Also, I am grateful to

prof. Stam for creating the BrainWave software and making it available for researchers. The software, accompanied by useful documentation and literature, have contributed significantly to this project.

Er zijn veel mensen betrokken geweest bij de organisatie rondom dit onderzoek, de zogenoemde 'PLOTS-studie' (*Predicting Language Outcome after brain Tumour Surgery*), in het UMCG en het Erasmus MC. Voorafgaand aan de bedankjes per centrum, wil ik de mensen bedanken die, naast mijn promotor en co-promotoren, hebben bijgedragen aan (de totstandkoming van) het testprotocol: Elke de Witte, Evy Visch-Brink, Wencke Veenstra, Adrià Rofes en Fleur van Ierschoot. De EEG-registraties van dit onderzoek zijn mede mogelijk gemaakt door subsidie van Stichting Afasie Nederland.

Ik begin met het UMCG. Ik wil Wencke Veenstra bedanken voor het wegwijs maken met de procedures rondom wakkere hersenoperaties inclusief het afnemen van testonderzoeken. Ook heb ik de prettige gesprekken en de samenwerking m.b.t. scripties of gastcolleges erg gewaardeerd. Mijn dank gaat uit naar de neurochirurgen dr. Wagemakers, tevens co-investigator, en dr. Jeltrema voor het mogelijk maken van de inclusie en hun inzet daarbij. Daarnaast wil ik alle andere chirurgen bedanken waarmee contact is geweest voor de inclusie van patiënten. Ik dank dr. Drost en dr. van der Hoeven voor de afstemming over, en goedkeuring van, research EEG-registraties bij de KNF. Bovendien gaat mijn dank uit naar alle mensen die hebben bijgedragen aan de organisatie, planning en uitvoering van de EEG-registraties, zoals Esther, Goos, Janny, Harry, Greetje, Jan, Pieter en alle (andere) laboranten. Dank jullie wel voor de fijne samenwerking, jullie flexibiliteit, en het soepele verloop van de registraties. Ook wil ik de medewerkers van de polikliniek Neurologie bedanken, die me (na wat puzzelen) elke keer konden voorzien van een kamer voor de testonderzoeken. Dan kom ik bij Yvonne, Marga, Nadine en Bernie: bedankt voor het regelen van alle zaken rondom mijn werkplek, (technische) behoeftes, en aanstellingen. Ten slotte wil ik dr. Enting bedanken, de onafhankelijke arts van de PLOTS-studie in het UMCG. Zoals gezegd, dit alles had niet tot stand kunnen komen zonder de inzet en betrokkenheid van dr. Ingeborg Bosma.

Ook in het Erasmus MC hebben veel mensen bijgedragen aan dit project. Mijn dank gaat uit naar prof. Dirven, die ervoor gezorgd heeft dat de PLOTS-studie probleemloos van start kon gaan bij de afdeling Neurochirurgie, en naar Anja, die alle zaken rondom mijn aanstelling perfect geregeld heeft. Ik wil de neurochirurgen dr. Vincent en dr. Schouten bedanken voor hun bijdrage aan de studie, samen met alle andere chirurgen waarmee contact is geweest voor de inclusie van patiënten. Ik dank Marit en Dianne voor de afstemming rondom tests en patiëntafspraken. Ook ben ik dankbaar voor de hulp van Yvonne, Anneke, Monique en anderen bij de polikliniek Neurochirurgie en het OK planbureau. Speciale dank gaat uit naar dr. Marjan Scheltens voor het mogelijk maken van research EEG-registraties en de prettige samenwerking met de KNF daarna. Venny, Karla, Els, Monique, Irene, Ramona, en alle anderen die bijgedragen hebben aan de organisatie, planning en uitvoering van de EEG-registraties: ontzettend bedankt! Tafadzwa, it has been a long time ago, but I still appreciate the time you took to share your experience, making me familiar with the software to conduct network analyses. This has been very helpful. Ik wil prof. Marion Smits bedanken voor het nauwkeurig bepalen van alle pre- en postoperatieve tumorvolumes. Ook wil ik Tessa, Mariëlle, Cassandra

en Trisha bedanken. Jullie gaven me de ruimte om de testonderzoeken rustig uit te werken op de 22^{ste} van het Ee-gebouw (ik heb sportieve herinneringen aan toen de liften defect waren). Daarnaast dank ik dr. Dammers, de onafhankelijke arts van de PLOTS-studie in het Erasmus MC. Echter, deze hele organisatie was niet gelukt zonder de aanzet van dr. Joseph Cherian Perumpillichira en de grote toewijding van dr. Djaina Satoer.

I am indebted to many people at the University of Groningen. I thank the selection committee of the Centre for Language and Cognition Groningen (CLCG) for granting me the opportunity to start this PhD project in the first place. Also, I am very grateful to all the (former and present) members of the Neurolinguistics research group (not an exhaustive list): Adrià, Aida, Annie, Assunta, Atila, Ben, Camila, Dörte, Ellie, Fleur, Frank, Irene, Jakolien, Jidde, Juliana, Kaimook, Liset, Nathaniel, Nermina, Pauline, Roel, Roelant, Roelien, Sana, Sara, Seçkin, Serine, Srdan, Suzan, Svetlana, Teja, Toivo, Vânia, Weng, and Yulia. Thank you for sharing your knowledge and feedback, and for the pleasant non-academic talks over lunch or coffee. I enjoyed the time at the office over the years with Annie, Teja, Sara, Camila, Toivo, Pouran, Sana, Fleur, and Assunta, and people dropping by, such as Srdan and Frank. I very much appreciate the after-work drinks and dinners to keep in touch with you, as I was not around on a daily basis. Dan wil ik Christina, Alice, Gorus, Marijke en Diana (CLCG, GSH en BCN) graag bedanken, omdat zij ervoor gezorgd hebben dat mijn onderwijsactiviteiten, congresreizen en aanstellingszaken allemaal soepel verliepen.

Special thanks to Fleur and Annie, my conference buddies, friends, and now paranympths! We have shared many hilarious moments, challenging times, and academic milestones with each other. I am delighted that I will be able to finalise this PhD journey with you two by my side (digitally or live, let's see). Margreet en Nathalie, bedankt voor de gezellige bakjes koffie en de keren dat ik aan kon schuiven na werk in Groningen. Ook wil ik mijn waardering uitspreken voor het werk van Daniëlle Balk: wat heb je dit proefschrift prachtig vormgegeven.

I would like to thank my fellow students and friends from the EMCL, with whom I started this academic journey: Weng, Serine, Varsha, Frank, Michelle, Gabriele, Birgit, Chaya, to name a few. Frank, I want to start by saying: We did it!!! All simultaneously we graduated from the EMCL, started our PhD projects at the RUG, recently submitted our dissertations, and are about to defend our PhD theses on the same day! *Medaase* for the fun you brought to the entire journey, and for your support and friendship all this time. Michelle, I am very grateful to you, not only as a dear friend but also for proofreading my thesis and helping me out with my questions on English writing. I love how we can discuss work-related issues, as well as laugh about silly things far away from academics. *Baie dankie lieve vriendin, ek hoop ek sien jou binnekort weer.*

Waar golfbewegingen centraal staan in dit proefschrift, staan ze ook symbool voor de ups en downs waarmee dit promotieonderzoek gepaard ging. Ik ben enorm dankbaar voor de mensen in mijn naaste omgeving, die me op alle momenten zijn blijven steunen. Daarmee hebben jullie, al dan niet indirect, veel bijgedragen aan de afronding van het project.

Paulien en Charlotte, bedankt voor jullie betrokkenheid, de gezellige etentjes en de creatieve attenties in lastigere tijden. Jullie zijn toppers. Liselotte, bedankt voor de lachrimpel(tje)s die inmiddels zijn ontstaan bij mij, waar jij mede verantwoordelijk voor bent.

Ons contact doet me erg goed. Snel weer op fietsvakantie? Hilde, wat is het heerlijk om een vriendin 'van vroeger' (mattie uit de Achterhoek) hier in Amersfoort te hebben. Jij zorgde voor veel leuke afleiding, of het nou was met tennissen, wandelen, spelletjes doen, koffie leuten of bier drinken. Irene, ik wil je bedanken voor je gezelligheid, je luisterend oor en je support. Door onze vele (lunch)wandelingen was jij steeds op de hoogte van allerlei ontwikkelingen rondom dit onderzoek. En nu is het af! Mijn (oud)teamgenootjes Josanne, Irene, Marie-Catherine, Annemieke, Marjolein, Famke en Hilde: onze activiteiten op de baan en buiten de baan hebben me goed geholpen om met frisse energie verder te gaan. Dank jullie wel. Monique, Floris en Saskia, bedankt voor de gezellige avonden met borrels, etentjes, spelletjes of concertjes. De voetjes moeten snel weer van de vloer! Hilda-Marije, het is me een raadsel hoe we urenlang aan de telefoon kunnen hangen en nog niet uitgepraat zijn. Wél weet ik dat je me geweldig gesteund hebt bij de ups en downs in dit hele traject. Jouw positieve instelling en nuchtere kijk op zaken waren verhelderend. Ik wil je ontzettend bedanken en kijk ernaar uit om de afronding van dit proefschrift samen te vieren!

Dan wil ik graag mijn familie en schoonfamilie bedanken: John en Jolanda, Ellen en Irving, Loes en Reguilio, opa en oma Schat, oma Wolthuis, Joke en Bert, Hannanjah en Niels, Indira en Ronja.

Opa en oma Schat, door jullie heb ik in eerste instantie kennis gemaakt met de mooie stad Groningen. Jullie zijn een van de redenen waarom ik er graag wilde studeren, en dit leidde uiteindelijk tot een onderzoeksbaan aan de RUG. Al die tijd hebben jullie liefdevol en betrokken 'aan de zijlijn' gestaan. Dat waardeer ik erg. Verder wil ik jullie bedanken dat ik altijd gebruik mocht maken van de vertrouwde logeerkamer (wat een geluk om steeds te horen 'de kamer is nog vrij!'). Maak je geen zorgen dat mijn werk in Groningen nu afgerond is: ik blijf langskomen.

Lieve Ellen en Loes, wat bof ik met jullie als mijn grote zussen. Ellen, je bent erg betrokken bij je 'sis' en weet precies de dingen te zeggen waar ik weer mee verder kan. Loes, nu dit afgerond is, ben ik weer helemaal klaar voor een lange wandeling met Sisa of een middagvullend potje Monopoly. Bedankt dat je je netwerk inzette om de laatste deelnemers voor de studie te vinden. Zo fijn dat ik tijdens de werkzaamheden in Rotterdam twee adresjes had, waar ik altijd terecht kon.

Paps en mams, ik ben jullie enorm dankbaar. Zonder jullie onvoorwaardelijke liefde, steun en vertrouwen in mij, zou ik niet zijn wie – en waar – ik nu ben. Het is erg fijn om te weten dat, welke keuzes ik ook maak, en hoe dit promotieonderzoek ook was gelopen, jullie voor de volle 100% achter me staan en trots op me zijn. En ja, dat ben ik zelf ook.

En tot slot: Nivard, al ruim 8 jaar ben je een grote sprankel in mijn leven. Ik ben dol op je humor, je positiviteit en je mooie karakter. Je hebt me onwijs gesteund tijdens dit hele promotietraject. Daarnaast heb je op veel manieren bijgedragen aan de afronding van het schrijfwerk, zoals je relativerende opmerkingen en je adviezen ('less is more', hier weer mislukt), maar ook de potjes tafelvoetbal tussendoor en je heerlijke kookkunsten. Lieverd, bedankt voor alles. Wat er ook op ons pad komt, wij maken er samen iets moois van.

Contents

Acknowledgements / Dankwoord	6
List of abbreviations	13
PART I – Background & Proof of principle	15
Chapter 1	17
General introduction	
Chapter 2	25
Slow-wave activity in EEG/MEG as a marker of language impairment and recovery following brain injury – A review	
Chapter 3	43
Language impairments in brain tumour patients: The association with resting-state functional connectivity brain networks in EEG/MEG – A review	
Chapter 4	63
Slow-wave EEG activity and language functioning in glioma patients – A proof-of-principle study	
PART II - Results from the PLOTS study	75
<i>Predicting Language Outcome after brain Tumour Surgery</i>	
Chapter 5	77
Extensive language evaluation in low-grade glioma patients undergoing awake surgery	
Chapter 6	95
Pre- and postoperative language impairments in patients with grade I meningioma	
Chapter 7	113
Distinct slow-wave activity patterns in resting-state EEG and their relation to language functioning in low-grade glioma and meningioma patients	
Chapter 8	133
Resting-state functional connectivity networks in relation to pre- and postoperative language functioning in low-grade glioma and meningioma patients	
Chapter 9	163
General discussion	
References	171
Appendix A.....	185
Appendix B.....	187
Appendix C.....	191
Appendix D	195
Appendix E	203
Summary	227
Samenvatting	233
About the author.....	238
Groningen Dissertations in Linguistics (GRODIL)	239

List of abbreviations

(f)MRI = (functional) Magnetic Resonance Imaging
AAT = Aachen Aphasia Test
AD = Alzheimer's Disease
BC = maximum Betweenness Centrality (network measure^a)
C = Comprehension
Degr = maximum Degree fraction (network measure^a)
DES = Direct Electrical Stimulation
Diam = Diameter (network measure^a)
DIMA = Diagnostic Instrument for Mild Aphasia
Ecc = average Eccentricity (network measure^a)
ECG = Electrocardiography
EEG = Electroencephalography
EOG = Electrooculography
EORTC = European Organisation for Research and Treatment of Cancer
Erasmus MC = Erasmus MC University Medical Centre Rotterdam
FC = Functional Connectivity
FFT = Fast Fourier Transform
IDH = Isocitrate dehydrogenase (molecular marker)
Leaf = Leaf fraction (network measure^a)
LH = Left-Hemispheric
MEG = Magnetoencephalography
MST = Minimum Spanning Tree (type of FC network)
P = Production
PD = Parkinson's disease
PLI = Phase Lag Index (network measure^a)
PLOTS = Predicting Language Outcome after brain Tumour Surgery
PPA = Primary Progressive Aphasia
rC = relative average Clustering coefficient (network measure^a)
RH = Right-Hemispheric
rL = relative average path Length (network measure^a)
SAN = Stichting Afasie Nederland
SWI = Small-World Index (network measure^a)
T1 = Time point before surgery
T2 = Time point 2 months after surgery
T3 = Time point 1 year after surgery
TBI = Traumatic Brain Injury
TH = Tree Hierarchy (network measure^a)
UMCG = University Medical Centre Groningen
W = Weighted (type of FC network)
WHO = World Health Organisation
Note. Fp1, Fp2, F3, F4, F7, F8, T3, T4, T5, T6, C3, C4, P3, P4, O1, O2, Fz, Pz, Cz, A1 and A2 are electrode positions, see figures 7.1 (p. 121) and 8.1 (p. 139).
^aNetwork measures can be found in table 8.2 (p. 142).

PART I

Background & Proof of principle

Chapter 1

General introduction

Research objectives

Speaking to a friend, listening to the news, reading a book, or typing an e-mail; these are all examples of language use in daily life. A brain tumour can cause impairments in language functioning. Language impairments have an immense effect on everyday communication and negatively influence quality of life (Hilari, Needle, & Harrison, 2012). Considering that language covers a range of abilities, several language modalities can be affected. These include speech production, comprehension, reading, and writing. More specifically, impairments can manifest at different linguistic levels, such as phonology (concerning speech sounds), semantics (concerning meaning), and morphosyntax (concerning word and sentence structure, also called grammar). Therefore, it is important to take into account a wide range of language functions when studying the impact of a brain tumour on communication in daily life.

The current project concentrates on low-grade gliomas and meningiomas (see section *Brain tumours*). Low-grade glioma patients have reported language complaints, but previously used tests were not always able to detect (mild) language impairments. Therefore, it is unclear how exactly the different aspects of language are affected in these patients. Moreover, language functioning in meningioma patients is largely unknown. Hence, the first objective of this project is to gain more insight into language functioning in low-grade glioma and meningioma patients, using a comprehensive linguistic test protocol.

In relation to the first objective, it is useful to study factors that are associated with language functioning. Previous studies indicate that particular characteristics of electrical brain activity during a resting state are related to language impairments and language recovery in patients with other types of brain injury (chapters 2 and 3). These aspects of resting-state brain activity are slow-wave activity (activity in the delta and theta frequency bands) and functional connectivity brain networks (reflecting the extent to which brain areas functionally interact). Both can be analysed from registrations of electroencephalography (EEG): a sensitive, non-invasive, and inexpensive measurement of brain function, which is commonly used in (brain tumour) patients suspected of having epileptic seizures. Accordingly, our second objective is to reveal the as yet unexplored relation between the aforementioned characteristics in resting-state EEG and language functioning in low-grade brain tumour patients.

Patients with a low-grade glioma or meningioma generally undergo surgical resection. They are often young and have a relatively long life expectancy after surgery (Louis et al., 2007; Van Alkemade et al., 2012). Therefore, preservation of language functioning is crucial for these patients to resume daily activities and to return to work. In spite of that, language outcome after brain tumour surgery in language-related areas is variable, ranging from intact language functioning to severely impaired language functioning (e.g. Norrelgen, Jensdottir, & Östberg, 2020). An accurate preoperative risk estimation of postoperative language impairments could contribute to clinical care, such as patient counselling, planning of treatment, and language rehabilitation. Therefore, our third objective is to find predictors for language outcome after brain tumour surgery by analysing preoperative EEG.

The three main objectives of this project are:

- (1) to gain more insight into language functioning in low-grade glioma and meningioma patients;
- (2) to reveal whether/how language functioning is related to resting-state EEG characteristics;
- (3) to find predictors for language outcome after brain tumour surgery, based on preoperative EEG.

Next, background information on brain tumours, language functioning in brain tumour patients, and brain activity is provided, followed by an outline of the thesis.

Background

Brain tumours

A brain tumour is characterised by an accumulation of abnormal cells that proliferate, resulting in a growing mass of tissue infiltrating into, or pressing on, healthy brain structures. This project concentrates on primary (as opposed to metastatic) brain tumours, which start in the brain or its surrounding tissues. Furthermore, we study brain tumours that are low-grade, classified as grade I or II (World Health Organisation [WHO] classification; Louis et al., 2016), based on the type of cell that a tumour originates from (histology). Low-grade tumours have a relatively slow growth rate. The types of low-grade brain tumours studied in this project are gliomas and meningiomas. The two differ with regard to their origin and their effect on surrounding brain areas. However, both tumour types can affect crucial brain areas that are involved in sensorimotor or language functions, the so-called 'eloquent areas'.

Gliomas

Gliomas are intra-axial tumours, meaning that they lie within brain tissue (brain parenchyma). These infiltrative tumours originate from glial cells, brain cells that support and protect neurons. Gliomas are the most frequently occurring primary brain tumours. There are approximately 1000 new diagnoses of adult gliomas every year in The Netherlands (population of approximately 17 million), of which 20% are low-grade (Ho et al., 2014). Furthermore, low-grade gliomas affect relatively young individuals; the mean age at diagnosis is 42 years (Ho et al., 2014). A glioma is usually discovered when the patient develops symptoms such as epileptic seizures (most frequent), mild language and cognitive impairments, or headaches. However, it may take many years before symptoms of a low-grade glioma appear because of its slow growth rate (diameter expansion of approximately 4 mm a year; Mandonnet et al., 2008) in combination with neuroplasticity processes. Low-grade gliomas, which are generally grade II tumours in adults, eventually progress to higher grades of malignancy (grades III and IV; high-grade tumours). Also, they frequently infiltrate eloquent brain areas. To avoid further disruption of essential brain tissue, low-grade glioma patients typically undergo resective surgery which is done while they are awake.

Awake brain surgery with intraoperative mapping of functions is the gold standard treatment for patients with a presumed low-grade glioma in or near eloquent brain areas.

The goal is to maximise tumour resection and to preserve (language) functions. During the intraoperative procedure, the patient has to perform short tasks for monitoring of critical sensorimotor and language functions, while brain tissue is stimulated with tiny electrodes (direct electrical stimulation; DES). DES provokes temporary disruptions of function, which are observed via changes in task performance. This allows the identification of cortical and subcortical brain structures that are involved in sensorimotor and language functioning. Awake glioma surgery is associated with more extensive tumour resection and better preservation of language and cognitive functions than surgeries without intraoperative DES (De Witt Hamer, Robles, Zwinderman, Duffau, & Berger, 2012). Furthermore, the procedure is well tolerated by patients (Beez et al., 2013). Life expectancy after low-grade glioma surgery generally exceeds 5 years (Louis et al., 2007).

Meningiomas

Meningiomas are extra-axial tumours, meaning that they lie outside the brain parenchyma. These tumours arise from the meninges, which are protective membranes surrounding the brain. Even though meningiomas generally do not infiltrate brain tissue, they can compress adjacent brain areas. Meningiomas represent approximately one-third of all primary brain tumours, of which 90% are classified as grade I (Whittle, Smith, Navoo, & Collie, 2004; Wiemels, Wrensch, & Claus, 2010). Approximately 500 adults with a symptomatic meningioma are diagnosed every year in The Netherlands (The Netherlands Cancer Registry). However, many meningiomas are asymptomatic and remain undiagnosed. Therefore, the overall meningioma incidence is presumably at least twice as high (Larjavaara, Haapasalo, Sankila, Helen, & Auvinen, 2008). Symptomatic meningiomas are usually discovered between the age of 40 and 70 years (Radhakrishnan et al., 1995). They can manifest through a wide range of symptoms, depending on size and location. Possible symptoms include epileptic seizures, disturbed vision, sensorimotor dysfunction, cognitive decline, headaches, and other signs of increased intracranial pressure (Whittle et al., 2004). A large number of meningiomas are discovered incidentally by brain scans for other purposes (Whittle et al., 2004). Meningioma surgery is performed under general anaesthesia. Grade I meningioma patients have a relatively long life expectancy: more than half of the patients survive the first 20 years after surgery (Van Alkemade et al., 2012).

Language functioning in brain tumour patients

Previous studies show that glioma patients suffer from language impairments (for systematic reviews see: Satoer, Visch-Brink, Dirven, & Vincent, 2016; and Van Kessel, Baumfalk, Van Zandvoort, Robe, & Snijders, 2017). Performance on object naming and verbal fluency tests¹ is found to be most frequently impaired before surgery (Satoer et al., 2016). Language functioning tends to decline shortly after surgery. In the longer term, as assessed between 3 and 6 months after surgery, language performance tends to improve, although performance

1 Verbal fluency, in the form of category or letter fluency, is classified under language functioning instead of executive functioning in this project because the tests at least partly assess language processing (Aita et al., 2019; Whiteside et al., 2016).

on some tests (such as category fluency) remains impaired 1 year after surgery (Satoer et al., 2016, 2014). However, many studies investigated a mixed group of low-grade and high-grade glioma patients, whereas language impairments in low-grade glioma patients seem less severe than those in high-grade glioma patients (Campanella, Mondani, Skrap, & Shallice, 2009; Noll, Sullaway, Ziu, Weinberg, & Wefel, 2015). This difference is presumably due to the slow growth rate of a low-grade glioma, which allows for neuroplasticity and reorganisation of language functions (Desmurget, Bonnetblanc, & Duffau, 2007). Nonetheless, low-grade glioma patients report language complaints (Racine, Li, Molinaro, Butowski, & Berger, 2015). In order to detect the generally mild language impairments in these patients, a sensitive assessment is required, though most studies conducted classical language tests that are commonly used in stroke patients with more severe language impairment. Therefore, it is unclear how the various language abilities are affected specifically in low-grade glioma patients. This leads to the first objective of the present project.

With regard to meningioma patients, the majority of patients have impairments in several cognitive functions (e.g. verbal memory, working memory, attention, and executive functioning), as systematically reviewed by Meskal et al. (2016). However, previous literature on language functioning in meningioma patients is inconclusive². There are indications that language abilities before meningioma surgery, as assessed with a verbal fluency test, an object naming test, and/or the Token Test, are intact (Butts et al., 2017; Campanella, Fabbro, Ius, Shallice, & Skrap, 2015; Van Nieuwenhuizen et al., 2013), as well as indications that preoperative language abilities are impaired (Hendrix et al., 2017; Liouta, Koutsarnakis, Liakos, & Stranjalis, 2016; Tucha et al., 2003). Furthermore, language performance after meningioma surgery may not change (e.g. Abel et al., 2016) or may improve (e.g. Liouta et al., 2016). Previous studies mainly focused on cognitive functions, such as memory and attention. Consequently, language functions were assessed by only one or two tests. Hence, a detailed language assessment is needed to gain a better understanding specifically of language functioning in meningioma patients (objective 1).

Apart from a thorough assessment of language functioning, it is important to evaluate whether, and to what extent, patients experience language problems in daily life. Subjective language problems have rarely been taken into account in previous research. These are included in the current project to obtain a comprehensive language profile of low-grade glioma and meningioma patients. As language is our main focus, we study brain tumours that are located in the language-dominant hemisphere. In most individuals, this concerns the left hemisphere; adequate language functioning relies on a large-scale neural network, involving cortical areas (grey matter) and subcortical pathways (white matter), typically lateralised to the left hemisphere (Duffau, Moritz-Gasser, & Mandonnet, 2014). Consequently, brain tumour surgery in the language-dominant hemisphere can have considerable impact on language functioning.

2 The terminology on language and cognition is ambiguous. Some researchers consider language as one of the cognitive functions, like memory and attention, and propose a single mechanism for language and cognition (Croft & Cruse, 2004), whereas others see language and cognition as two separate (but interacting) abilities (Chomsky, 1995; Perlovsky, 2013). We follow the latter view throughout this thesis.

Predictors of postoperative language outcome

Language outcome after brain tumour surgery varies greatly between patients, ranging from intact language functioning to severe permanent language impairments (e.g. Norrelgen et al., 2020). Postoperative language outcome has an effect on the extent to which patients can resume domestic, social, and professional activities in the long term after surgery. Therefore, it is useful to identify factors that can predict the risk of language decline after brain tumour surgery.

Previously-reported risk factors for postoperative language impairment are preoperative aphasia, non-frontal tumour location, intraoperative complications, and language-positive stimulation sites within the tumour (Ilmberger et al., 2008). Furthermore, in patients without preoperative language impairments, submaximal object naming performance (within the normal range) has been shown to predict early postoperative language impairment (Ilmberger et al., 2008). However, predictors of long-term language outcome after brain tumour surgery are scarce.

In patients with non-tumour-related brain injury, characteristics of brain activity during a resting state seem to have prognostic value for the course of language functioning. For example, slow-wave activity (brain activity in the delta and theta frequency bands), evaluated 2 weeks post-stroke, is predictive of language outcome 8 weeks post-stroke (Szelies, Mielke, Kessler, & Heiss, 2002). Furthermore, functional connectivity brain networks, which are analysed from brain activity recordings and reflect the extent to which brain areas functionally interact, have been shown to predict the level of language recovery in stroke patients (Nicolo et al., 2015). Functional connectivity network characteristics have been demonstrated to relate to cognitive dysfunction in brain tumour patients (e.g. Bosma et al., 2009).

The current project investigates whether/how the two aspects of brain activity, slow-wave activity and functional connectivity network characteristics, are related to language functioning in brain tumour patients, and whether these predict language outcome after surgery (objectives 2 and 3). The next sections provide background information on brain activity, the corresponding frequency bands, and brain activity registration.

Brain activity

The brain contains billions of neurons which generate and transmit information through tiny electrical signals. When groups of neurons are similarly oriented and fire simultaneously, signals sum up and constitute brain activity that can be measured via electrical or magnetic fields (see section *Registration of brain activity*). Brain activity comprises spontaneous activation as well as responses to internal and external events. When brain waves are ongoing and repetitive, they are called 'neural oscillations' (for a review see Schnitzler & Gross, 2005). Spontaneous neural oscillations are continuously present, also during resting conditions. Moreover, resting-state brain activity can be seen as the baseline functioning of the brain, and has been found to be robust (Damoiseaux et al., 2006; Gusnard & Raichle, 2001). By convention, brain activity is classified based on its frequency (the number of oscillatory repetitions per second). Niedermeyer (1999) provides an overview of the frequency bands in adult brain activity, which are briefly introduced below.

Frequency bands

Activity in the alpha band (8-13 Hz) is usually most prominent in typical brain activity recordings during a relaxed, wakeful state. It is very noticeable over posterior regions, with a higher voltage over bilateral occipital areas. Alpha rhythm is best seen during relaxation with closed eyes, and it attenuates with eye opening and mental effort. Waveform morphology and amplitude vary over time. Beta activity (13-30 Hz) is relatively fast and has low amplitudes. It can be observed in almost every healthy adult. Beta waves are primarily found over frontal and central regions, but may also occur in posterior regions as fast alpha equivalent. Furthermore, gamma activity oscillates even faster, with frequencies above 30 Hz. Therefore, activity in the gamma band is difficult to discern by visual inspection of clinical registrations. Gamma activity rarely occurs in resting conditions, but it is commonly present during mental activity or task performance.

Theta activity (4-8 Hz) is relatively slow and not associated with a specific region. Only a small amount can be seen in the recording of a healthy, awake adult; larger amounts or persistent theta activity is abnormal. However, theta activity is prominent in states of drowsiness and sleep in adults, and in young children while awake. This also applies to activity in the delta band (0.5-4 Hz). Delta waves are the slowest brain oscillations with large amplitudes. They are typically observed during deep sleep in healthy adults but indicate brain dysfunction if present in an awake state. Activity in the theta and delta bands, referred to as slow-wave activity, is present in many patients with brain injury (chapter 2).

Registration of brain activity

Brain activity can be registered using electroencephalography (EEG). This non-invasive technique directly measures brain signals in real-time by electrodes affixed on the scalp. These signals are amplified, digitalised, and plotted as changes in voltage over time. EEG registration has high temporal resolution, but its spatial resolution is rather low. Alternatively, brain activity can be registered using magnetoencephalography (MEG), which combines high temporal resolution and relatively high spatial resolution. However, EEG has the advantage of being less expensive and more widely available than MEG. Moreover, EEG is frequently used in clinical settings when brain dysfunction or epileptic seizures are suspected. Hence, potential clinical application is feasible in the case that slow-wave activity and/or functional connectivity network characteristics in resting-state EEG are found to be predictive of language outcome after brain tumour surgery.

Outline of the thesis

An outline of the thesis is presented, indicating the research objective targeted in each chapter. The objectives are stated once again:

- (1) to gain more insight into language functioning in low-grade glioma and meningioma patients;
- (2) to reveal whether/how language functioning is related to resting-state EEG characteristics;
- (3) to find predictors for language outcome after brain tumour surgery, based on preoperative EEG.

Part I of the thesis comprises background information, literature reviews, and a proof-of-principle study. After the current introductory chapter, chapters 2 and 3 provide literature reviews on language functioning in relation to slow-wave activity and functional connectivity brain networks, respectively (preparation for objectives 2 and 3). Chapter 4 reports a proof-of-principle study on the paradigm we developed for relating slow-wave activity to language functioning in glioma patients (objective 2).

Part II of the thesis consists of prospective research, presenting results from the PLOTS study: Predicting Language Outcome after brain Tumour Surgery. This multidisciplinary project is a collaboration between the University of Groningen, the University Medical Centre Groningen, and the Erasmus MC University Medical Centre Rotterdam. Results on language functioning before and after brain tumour surgery are presented in chapter 5 for glioma patients, and in chapter 6 for meningioma patients (objective 1). Subsequently, chapter 7 demonstrates the relation between slow-wave activity and language functioning in these patients (objectives 2 and 3). Chapter 8 shows how functional connectivity brain networks are related to preoperative language functioning and postoperative language outcome in both patient groups (objectives 2 and 3). Finally, chapter 9 gives an overview of the main outcomes and their implications, followed by recommendations for clinical practice and future research.

Chapter 2

Slow-wave activity in EEG/MEG as a marker
of language impairment and recovery
following brain injury

A review

Abstract

Language impairments hinder everyday communication. They frequently occur after brain injury, not only when cortical areas are affected, but also when subcortical white matter pathways are damaged. The brain activity during resting state, registered with electroencephalography (EEG) or magnetoencephalography (MEG), in patients with brain injury often exhibits pathologically increased slow-wave activity: (focal) brain activity in the delta and theta frequency range (0.5-8 Hz). This is a sign of brain dysfunction, presumably caused by white matter injury. Furthermore, increased slow-wave activity has been shown to relate to poorer cognitive performance, but its association with language functioning is not well understood.

We reviewed the literature in order to examine the relation between slow-wave activity in EEG/MEG and language performance in adults with brain injury caused by stroke, neurodegenerative diseases, trauma, epilepsy or tumour. It was evaluated whether slow-wave activity is a marker of language impairment, and whether it has prognostic value for language outcome or recovery.

The majority of the 20 included studies show that slow-wave activity can be seen as a marker of language impairment. In stroke patients, the degree and localisation of slow-wave activity indicate the severity and type of language impairment. There are indications that slow-wave activity can predict language recovery in post-stroke aphasia, but very little is known about other patient populations. Hence, further investigations on this are needed. Potential future implications for clinical practice are discussed.

Introduction

Brain injury often results in language deficits, affecting verbal communication in daily life. Apart from cortical regions that are known to be involved in language functioning, specifically, a large part of the perisylvian region including the “classical” language areas (Broca’s and Wernicke’s area), an important prerequisite for adequate language functioning is the intactness of subcortical white matter tracts (Duffau et al., 2014). At a neurophysiological level, patients with brain injury frequently show slow-wave brain activity while awake (Schomer & Lopes da Silva, 2010). Increased localised slow-wave activity is presumed to be caused by white matter injury (Gloor, Ball, & Schaul, 1977). Accordingly, increased slow-wave activity can be present in various brain regions, and, depending on the lesion site, may be associated with different symptoms. Considering that white matter tracts are highly involved in language processes, a relation between the level of slow-wave activity and language functioning is suggested. We do not expect slow-wave activity to be specific for language, but it may be an indicator of language dysfunction and/or language recovery. In this review we discuss studies that examined the relation between slow-wave activity and language performance in patients with brain injury. We address the following questions: (1) whether slow-wave activity can be a marker of language impairment, and (2) if it has prognostic value for language functioning at a later stage.

Language impairments have a significant impact on everyday communication and, thus, affect quality of life (Hilari et al., 2012; Worrall & Holland, 2003). They can be caused by different types of brain injury, of which stroke is the most common cause (Miceli et al., 1981). Deficits can occur at each of the linguistic levels (e.g. phonology, syntax, semantics) of spoken and written language production and comprehension, according to Ellis and Young’s (1988) model for single words and Levelt’s (1989) model for sentence processing. With regard to its neural basis, language processing relies on a large-scale network, involving cortical areas and subcortical connections, and containing sub-networks for phonological, syntactic, and semantic processes (Duffau et al., 2014). Particularly, subcortical white matter pathways, such as the arcuate fasciculus (AF) and the inferior fronto-occipital fasciculus (IFOF), significantly contribute to language. If these tracts are spared after brain injury, possible language impairments may recover, despite damage to cortical language areas (Duffau et al., 2014). Injury to subcortical pathways could be the primary cause of (more permanent) language and cognitive deficits after brain surgery (Bello et al., 2007; Trinh et al., 2013). Apart from that, subcortical injury is thought to be responsible for alterations in brain activity, more specifically, the emergence of slow waves (Ball, Gloor, & Schaul, 1977; Gloor et al., 1977).

Electrical activity in the brain can be recorded non-invasively with electroencephalography (EEG) or magnetoencephalography (MEG), with high temporal accuracy. Brain activity can be described in terms of frequency bands: delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz), and gamma (>30 Hz; Niedermeyer, 1999), although the exact limits are not fixed (Boersma et al., 2011). Slow-wave activity refers to (focal) brain activity in the delta and theta frequency range (0.5–8 Hz), absolute or relative to the entire spectrum. This is commonly observed in infants and during sleep in adults. However, slow waves during an awake state

in adults are considered to be pathological, a marker of brain dysfunction, for example due to structural damage (e.g. De Jongh et al., 2003). Slow-wave activity in patients with brain injury is presumed to originate from injured tissue around the lesion, in particular subcortical white matter injury. Subcortical lesions seem to induce slow waves that are generated by cortical areas overlying the lesion (Ball et al., 1977; Gloor et al., 1977). This is supported by the finding that, after severe brain injury, increased slow-wave activity relates to the magnitude of white matter damage (Thatcher, 2006). It is proposed that lesions restricted to cortical areas do not induce slow-wave activity (Ball et al., 1977; Gloor et al., 1977).

The relation between slow-wave activity and language functioning is yet unclear. For cognitive functions, such as memory and attention, increased slow-wave activity is found to be related to poorer performance in patients with brain injury due to stroke (Schleiger et al., 2014; Schleiger, Wong, Read, Rowland, & Finnigan, 2017), Alzheimer's disease (Babiloni et al., 2007; Fernández et al., 2002; Van der Hiele et al., 2007), Parkinson's disease (Olde Dubbelink et al., 2013; Sinanovic, Kapidzic, Kovacevic, Hudic, & Smajlovic, 2005), trauma (Álvarez et al., 2008; Thatcher, Biver, McAlaster, Camacho, & Salazar, 1998), and tumour (Bosma, Stam, et al., 2008). Also, slow-wave activity has been demonstrated to have prognostic value for functional and cognitive outcome after brain injury. More specifically, enhanced slow-wave activity in stroke patients and preoperative brain tumour patients indicates poor functional outcome and recovery at a later (postoperative) stage (Finnigan & Van Putten, 2013; Oshino et al., 2007). Apart from that, presence and localisation of slow-wave activity in epilepsy patients before surgery predict memory function after temporal lobe surgery (Tuunainen et al., 1995).

We evaluated whether slow-wave activity is a marker of language impairment, and whether it has prognostic value for language outcome or recovery. For this purpose, we searched via WorldCat in various electronic databases (e.g. PubMed, MEDLINE, Web of Science, ScienceDirect) for studies in which slow-wave (delta and/or theta) activity from EEG or MEG recordings was analysed in relation to language performance in adult patients with brain injury (e.g. due to stroke, neurodegenerative diseases, trauma, tumour, etc.). Also, research on slow-wave activity and cognitive functions was examined in order to find out whether language tests were conducted as part of a larger cognitive assessment and whether these data were analysed separately. Brain activity had to be recorded in a wakeful state and regarded as spontaneous activation; studies with event-related potentials or analysis during particular linguistic processing phases were not included. Overall, we looked for very specific analyses, some of which would have been missed if we had followed a formal systematic approach. For example, many analyses within our scope were found via in-text references and by evaluating full-text articles even when there was no mention of these analyses in the abstract. Hence, our literature search resulted in an extensive, but not systematic, review.

Slow-wave activity and its relation to language performance

Twenty studies met the above-mentioned criteria. They are summarised in table 2.1, sorted on patients' neurological aetiology (stroke, neurodegenerative diseases, traumatic brain injury, epilepsy, and brain tumour). Although many of these studies have addressed additional questions, only analyses examining the relation between slow-wave activity and language are provided in this review.

Ten studies exclusively report significant relations between slow-wave activity and language. They show that increased slow-wave activity is related to poorer language performance and minimal slow-wave activity is related to better language performance (Chapman, Pool, Finitzo, & Hong, 1989; Claus et al., 2000; Finitzo, Pool, & Chapman, 1991; Jabbari, Maulsby, Holtzapple, & Marshall, 1979; Kielar, Shah-Basak, Deschamps, Jokel, & Meltzer, 2019; Meinzer et al., 2004; Olde Dubbelink et al., 2013; Szelies et al., 2002; Van der Hiele et al., 2007; Wolthuis et al., chapter 4). Seven studies report 'mixed findings', in which increased slow-wave activity is related to poorer language functioning, but not for all measures or analyses (Helkala et al., 1991; Hensel, Rockstroh, Berg, Elbert, & Schönle, 2004; Kim et al., 2012; Ranasinghe et al., 2017; Shah-Basak et al., 2019; Thatcher et al., 1998; Tikofsky, Kooi, & Thomas, 1960). Three studies report no significant relations between slow-wave activity and language performance (Capon, 1996; Duffy, McAnulty, & Albert, 1995; Tuunainen et al., 1995).

From all 20 studies, eight were performed with patients after stroke, of which the majority had post-stroke aphasia (one study included a small number of patients with traumatic brain injury and encephalitis as well), nine that included patients with neurodegenerative diseases (Alzheimer's, Parkinson's disease, or primary progressive aphasia), one included patients with traumatic brain injury, one included patients with epilepsy, and one that included patients with a brain tumour. The next section discusses whether the literature provides support for slow-wave activity to be a marker of language impairment for each patient group separately. Subsequently, the prognostic value of slow-wave activity for language outcome is evaluated.

Table 2.1. Overview of 20 studies that analysed slow-wave activity in relation to language functioning

Patients	N	Method	Timing EEG/MEG	Language assessment	Language Assessment/ therapy	Outcome measure(s)	Main results		Indication for Language marker	Progn. value
Tikofsky et al., 1960	33	EEG; dominant background frequency in (> 8.5 Hz) or below alpha range (< 8.5 Hz; theta); presence delta activity by visual inspection	Before or early in course of speech therapy	After speech therapy	Speech therapy of 2-24 months; standard clinical care	Progress after speech therapy according to speech therapy records	Before or early in the course of speech therapy, a slow, theta- band background frequency was indicative of poor language recovery after speech therapy; Presence of delta activity did not differ significantly between patients with no progress and patients with fair/good progress		+/-	+/-
Jabbari et al., 1979	53	EEG; degree of focal slow-wave activity by visual inspection	Around four times; < 2 weeks post- stroke, and every 4-6 months over a 8-24 month period	Around four times; 2-4 weeks post-stroke, and every 4-6 months over a 8-24 month period	PICA score (verbal, gestural and graphic aspects of language)	Extent of language recovery based on aphasia severity and PICA change	The degree of slow-wave activity in the initial EEG was correlated with the extent of language recovery; minimal slow-wave activity was associated with good recovery and a high level of slow-wave activity was associated with poor/no recovery. Broca's aphasia was associated with anterior slow-wave foci and Wernicke's aphasia was associated with posterior foci		+	+
Chapman et al., 1989	100	EEG; spectral analysis; average delta (0.5-3.5 Hz) amplitude	≥ 1 month post- stroke	≥ 1 month post-stroke	Severity ratings for fluency, comprehension, and expression	Group comparisons: severe language deficits versus no deficit	Aphasic patients had more LH delta activity (maximally over perisylvian areas) than non- aphasic patients; Global aphasia was associated with more delta activity in left temporoparietal areas com- pared to non-global aphasia; Specific language deficits were associated with increased delta activity in left frontotemporal areas (fluency) and left temporoparietal areas (comprehension and expression)		+	

Table 2.1. Continued

Patients	N	Method	Timing EEG/MEG	Language assessment	Language Assessment/ therapy	Outcome measure(s)	Main results	Indication for	
								Language marker	Progn. value
Finizto et al., 1991	Stroke (LH, RH, or bilateral); with (4/6) and without aphasia (5/4)	100 EEG; spectral analysis; absolute and relative delta (0.5-3.5 Hz) and theta (4-7.5 Hz) amplitude	≥ 1 month post- stroke	≥ 1 month post-stroke	Severity ratings for fluency and comprehension	Accuracy of correctly predicting presence of aphasia and severe language deficits, on the basis of EEG	A severe comprehension deficit could be correctly classified by enhanced delta amplitude over left parietal areas in 81% of the subjects; Aphasia could be correctly classified by quantitative EEG, including slow-wave activity, in 90% of the subjects, but this also required information from other frequency bands	+	+
Capon, 1996	LH stroke with aphasia (17); or RH stroke without aphasia (15)	32 EEG; spectral analysis; absolute and relative delta power; relative delta peak frequency	At least thrice; in the period of 1-3 months post- stroke	Four times; in the period of 0.5-3 months post-stroke	Aphasia index based on language production and comprehension	Change between last and first aphasia index	No significant correlation between delta power change and language improvement; Language outcome after 3 months could not be predicted by delta power from the initial EEG	-	-
Szelles et al., 2002	LH stroke; aphasia	23 EEG; spectral analysis; delta (0.5-3.5 Hz) and theta (4-7.5 Hz) power	Twice; 2 and 8 weeks post-stroke	Twice; 2 and 8 weeks post-stroke	AAT	Token Test (<10: good outcome; ≥10: poor outcome)	An increase of LH slow-wave power early post-stroke predicts poor language outcome, and little or no slow- wave activity predicts good language outcome	+	+
Hensel et al., 2004	LH stroke; aphasia	11 EEG; spectral analysis; delta (1-4 Hz) amplitude; delta dipole location and strength	Five times; every 4-5 months in a period of 1-3 months until 2 years post-stroke	Thrice; at the time of the first, third, and fifth EEG	AAT	Change in AAT profile	A decrease of LH delta activity changed parallel to the recovery of aphasia in the first year post-stroke; Patients with the highest levels of slow-wave activity in the initial EEG had the smallest language improvement, and patients with the least slow- wave activity had the largest improvement; however, the correlation was not significant	+	+/-

Table 2.1. Continued

Patients	N	Method	Timing EEG/MEG	Language		Main results	Indication for Language marker	Progn. value
				Language assessment	Assessment/ therapy			
Meinzer et al., 2004	LH stroke; chronic aphasia	28 MEG; delta (1-4 Hz) dipole density by source localisation	1 day before and 1 day after language therapy (≥1 year post-stroke)	1 day before and 1 day after language therapy (≥1 year post-stroke)	Therapy: CIAT or MB; Duration: 2 weeks; Intensity: 3 hours/day; Assessment: AAT	Change in AAT profile; Token test score	Delta activity decreased after language therapy, but not in all patients, while language improved significantly; The extent of change in LH delta activity correlated with the amount of improvement on both language measures	+
Helkala et al., 1991	Alzheimer's disease (19); Parkinson's disease with dementia (18)	37 EEG; spectral analysis; absolute delta (1.46-3.91 Hz) and theta (4.15-7.32 Hz) amplitude	Once	Once	Object naming; comprehension; category fluency; automatic speech	Idem	AD: delta activity was negatively correlated with comprehension, category fluency, and automatic speech; PD: no significant correlations	+/-
Duffy et al., 1995	Alzheimer's disease	60 EEG; spectral analysis; Relative theta (4.0-7.5 Hz) power	Once	Once	Items from the BNT; letter fluency	Idem	No significant correlations between theta power and language functioning	-
Claus et al., 2000	Alzheimer's disease	163 EEG; spectral analysis; absolute and relative delta (0.3-3.5 Hz) and theta (3.6-7.4 Hz) power	Once	Once	CAMCOG language subscale (language production and comprehension)	Idem	LH delta power was inversely related to language functioning	+
Van der Hiele et al., 2007	Mild cognitive impairment (18); Alzheimer's disease (16)	34 EEG; spectral analysis; relative theta (4-8 Hz) power	Once	Once	BNT; category and letter fluency; CAMCOG language subscale	Idem	Theta power was negatively correlated with language performance (category fluency and CAMCOG measure)	+
Kim et al., 2012	Alzheimer's disease	30 EEG; spectral analysis; relative delta (1-3 Hz) and theta (4-7 Hz) power; current source density	Once	Once	BNT; category fluency	Idem	No significant correlations between slow-wave power and language performance; Theta source activity was negatively correlated with BNT and category fluency scores	+/-

Table 2.1. Continued

Patients	N	Method	Timing EEG/MEG	Language assessment	Language Assessment/ therapy		Main results	Indication for Language marker	Progn. value
Olde Dubbelink et al., 2013	49	MEG: spectral analysis; relative delta (0.5-4 Hz) and theta (4-8 Hz) power	Twice with a 4-year interval	Twice with a 4-year interval	Category fluency	Idem	Theta power was negatively cor- related with category fluency	+	
Ranasinghe et al., 2017	39	MEG: spectral analysis; delta- theta (2-8 Hz) power	Once	Once	Assignment of the specific PPA variant was based on current diagnostic criteria	Group comparisons: logopenic, non-fluent, and semantic PPA vs. control	Logopenic PPA was associated with increased slow-wave power in frontal lobes, bilaterally; No effects were found for non-fluent and semantic PPA when corrected for grey matter volume	+/-	
Shah-Basak et al., 2019	22	MEG: spectral analysis; relative delta (1-4 Hz) and theta (4-7 Hz) power	Once	Once	Object and action naming, repetition, sentence production and comprehension, receptive vocabulary, clustered together	Group comparisons: PPA vs. control, and MCI vs. control; Language tests as one composite	Increased delta (and decreased alpha) power; i.e. surrounding LH language areas, distinguished PPA from the control group (no effect for MCI vs. control); No significant effects between slow-wave power and the lan- guage cluster in PPA, nor in MCI	+/-	
Kielar et al., 2019	13	MEG: spectral analysis; relative delta (1-4 Hz) and theta (4-7 Hz) power	Once	Once	Sentence comprehension during MEG, and offline letter fluency, repetition, and WAB subtests (spontaneous speech fluency, repetition, aphasia score, language score)	Group comparisons: PPA vs. control; Online sentence comprehension accuracy; Offline language scores	PPA was associated with increased delta and theta power in several LH brain areas; Increased theta power was associated with lower sentence comprehension accuracy; Theta power was negatively correlated with all offline language measures, except for letter fluency	+	

Table 2.1. Continued

Patients		N	Method	Timing EEG/MEG	Language assessment	Language Assessment/ therapy	Outcome measure(s)	Main results	Indication for Language marker	Progn. value
Thatcher et al., 1998	Traumatic brain injury	19	EEG; spectral analysis; delta (0.5-3.5 Hz) and theta (3.5-7 Hz) amplitude	10 days-11 years post-injury	10 days-11 years post- injury	BNT	The number of stimulus cues given on the BNT	Higher theta amplitude was related to poorer language performance Not significant for delta amplitude	+/-	
Tuunainen et al., 1995	Epilepsy; temporal lobe surgery	32	EEG; visual inspection delta and theta activity	< 1 year before and 1 year after surgery	2 weeks before and 1 year after surgery	Object naming; Token Test; (written) letter fluency	Change in language scores	Naming and Token Test performance did not change after surgery, and, therefore, changes could not be predicted from preoperative slow-wave activity; Letter fluency improved after surgery, but no relation with preoperative slow-wave activity was reported	-	
Wolthuis et al., chapter 4	Brain tumour (glioma); before (12) or after surgery (9)	21	EEG; visual inspection of delta (0.5-4 Hz) and theta activity (4-8 Hz); spectral analysis; relative slow-wave power	0-9 months before or after surgery	1-12 months before or after surgery	BNT; category and letter fluency; AAT subtests; Token Test; repetition, reading, writing	Mean composite language score (average z-score of all tests)	Higher levels of slow-wave activity were related to poorer language performance, and limited slow-wave activity was related to better language performance	+	

Note. + indicates a significant relation, evidencing slow-wave activity to be a marker of language impairment or to have prognostic value; - indicates no significant relation; +/- indicates a significant relation, but not for all measures or analyses performed; empty cells indicate that the matter was not investigated. Only details about slow-wave activity and language analyses are included; other study information is excluded. TBI = traumatic brain injury; AD = Alzheimer's Disease; PD = Parkinson's Disease; PPA = Primary Progressive Aphasia; LH = left-hemispheric; RH = right-hemispheric; EEG = electroencephalography; MEG = magnetoencephalography; PICA = Porch Index of Communicative Ability; BNT = Boston Naming Test; CAMCOG = Cambridge Cognitive Examination; CIAT = Constrained-Induced Aphasia Therapy; MB = Massed Model-Based Aphasia Therapy; AAT = Aachen Aphasia Test; WAB = Western Aphasia Battery

Marker of language impairment

Stroke

Patients with a unilateral stroke demonstrate more slow-wave activity than healthy adults (Assenza, Zappasodi, Pasqualetti, Vernieri, & Tecchio, 2013; Spironelli & Angrilli, 2009; Tecchio et al., 2005), most pronounced over perilesional areas (Chu, Braun, & Meltzer, 2015; Hensel et al., 2004; Meinzer et al., 2004; Spironelli & Angrilli, 2009; Tecchio et al., 2005). Six out of the eight studies in stroke patients show that the degree of slow-wave activity is an indicator of (the severity of) language impairment, as measured with aphasia test batteries or aphasia severity ratings (Chapman et al., 1989; Finitzo et al., 1991; Hensel et al., 2004; Jabbari et al., 1979; Meinzer et al., 2004; Szelies et al., 2002). Increased left-sided slow-wave activity generally marks a more severe aphasia.

In Chapman et al. (1989), slow-wave EEG activity was used to distinguish stroke patients with aphasia from stroke patients without aphasia. Aphasia was associated with more left-hemispheric delta activity, maximally over perisylvian areas. Also, the distribution of slow-wave activity over the scalp was an indication of aphasia type. Anterior foci of pronounced slow-wave activity were observed in non-fluent aphasic patients, whereas posterior foci of slow-wave activity were observed in fluent aphasic patients (Hensel et al., 2004; Jabbari et al., 1979). In addition, patients with global aphasia could be differentiated from patients with other types of aphasia by more delta activity in left temporoparietal areas (Chapman et al., 1989). With regard to specific language deficits, a severe fluency deficit was marked by increased delta activity in left frontotemporal areas, whereas severe comprehension and expression deficits were both associated with increased delta activity in left temporoparietal areas (Chapman et al., 1989; Finitzo et al., 1991). Apart from that, slow-wave activity in chronic aphasic patients was influenced by intensive language therapy: the magnitude of change in slow-wave activity after therapy, which was a decrease in most patients, was associated with the amount of language improvement (Meinzer et al., 2004).

One of the eight studies shows that presence of slow-wave activity indicates the degree of language impairment in post-stroke aphasia, but not for all measures of slow-wave activity (Tikofsky et al., 1960). Finally, one study reports no relation between slow-wave activity change and language improvement over a 3-month period post-onset (Capon, 1996). This may be explained by the fact that half of the group had a right-hemispheric stroke, no aphasia and presumably no language change.

Neurodegenerative diseases

Patients with suspected Alzheimer's disease demonstrate increased slow-wave activity, particularly in temporoparietal areas (Duffy et al., 1995; Fernández et al., 2002; Helkala et al., 1991; Kim et al., 2012; Van der Hiele et al., 2007). This is an indicator of the level of language functioning, as it negatively correlates with several language measures (a subscale of language production and comprehension, category fluency test, automatic speech assessment, but not for object naming; Claus et al., 2000; Helkala et al., 1991; Van der Hiele et al., 2007). Furthermore, one study reports mixed results, dependent on the measure of slow-wave

activity (Kim et al., 2012), and one study does not provide support for slow-wave activity to be a marker of language impairment in patients with Alzheimer's disease (Duffy et al., 1995).

Patients with Parkinson's disease show a progressive increase of generalised or localised slow-wave activity (Bosboom et al., 2006; Helkala et al., 1991; Olde Dubbelink et al., 2013; Sinanovic et al., 2005; Stoffers et al., 2007). In non-demented patients with Parkinson's disease, higher slow-wave power marks poorer language performance (category fluency; Olde Dubbelink et al., 2013). In demented patients with Parkinson's disease, no relation is found between slow-wave activity and language performance (naming, comprehension, and category fluency; Helkala et al., 1991).

Finally, patients with primary progressive aphasia, a neurodegenerative language impairment, exhibit increased delta and theta activity, especially near left-hemispheric, language-related brain areas. This pattern distinguishes patients from healthy, age-matched individuals (Kielar et al., 2019; Shah-Basak et al., 2019). Furthermore, the logopenic variant of primary progressive aphasia, characterised by impaired word retrieval and repetition, is associated with increased slow-wave activity in the frontal lobes, bilaterally (Ranasinghe et al., 2017). Slow-wave power negatively correlates with several language measures (sentence comprehension, spontaneous speech fluency, repetition, aphasia score, language scores), but no significant correlation is found for letter fluency or a composite language measure (Kielar et al., 2019; Shah-Basak et al., 2019).

Traumatic brain injury

Patients with traumatic brain injury demonstrate increased activation in the delta and theta frequency bands (Haneef, Levin, Frost, & Mizrahi, 2013; Li et al., 2015; Thatcher, 2006). Increased theta activity is an indicator of poorer language performance, evidenced by a higher number of stimulus cues given in an object naming task. However, this is not significant for delta activity (Thatcher et al., 1998).

Epilepsy

Patients with temporal lobe epilepsy exhibit focal slow-wave activity over the temporal region, either unilateral or bilateral, which is present before and after brain surgery (Tuunainen et al., 1995). No relation between the amount of slow-wave activity and the level of language functioning is reported in Tuunainen et al. (1995; see section *Prognostic value*).

Brain tumour

Brain tumour patients demonstrate enhanced slow-wave activity, located in areas around the tumour (Baayen et al., 2003; De Jongh et al., 2003; Oshino et al., 2007) and, to a lesser extent, in the contralateral hemisphere (De Jongh et al., 2003; Oshino et al., 2007). High levels of slow-wave activity indicate poorer language functioning and little or no slow-wave activity indicates better language functioning, according to an overall language measure (including naming, fluency, comprehension, repetition, reading, and writing scores; Wolthuis et al., chapter 4).

Conclusion

Left-sided or bilateral slow-wave activity in patients with brain injury can be seen as a marker of language impairment, according to most studies. In post-stroke aphasic patients, the degree of slow-wave activity, particularly over left perilesional areas, is a marker of the severity of the language impairment. In addition, the localisation of slow-wave activity seems to be related to aphasia type, and to the presence of specific language deficits. Furthermore, the finding that slow-wave activity can be modulated by language therapy in the chronic phase looks promising for language recovery (Meinzer et al., 2004). In a broader view, it seems that patients with a language impairment (post-stroke aphasia and primary progressive aphasia) can be distinguished from healthy adults based on slow-wave activity patterns. Literature on other types of brain injury (neurodegenerative diseases without primary progressive aphasia, trauma, epilepsy surgery, and tumour), which generally have a lower incidence of language impairments, demonstrates that slow-wave activity signals the level of language (dys)functioning, although a small number of studies do not provide such support.

Prognostic value

For a relation between slow-wave activity and language to be clinically relevant, examination of the prognostic value of slow-wave activity is needed, in other words, the ability to predict language functioning at a later time point. This can be language recovery after acute brain damage, or language outcome after brain surgery. From the 20 studies described previously, six analysed slow-wave activity in relation to a later assessment of language (last column, table 2.1). Two studies indicate that slow-wave activity has prognostic value for the course of language recovery (Jabbari et al., 1979; Szelies et al., 2002), two studies describe mixed results (Hensel et al., 2004; Tikofsky et al., 1960), and two studies report an absence of such evidence (Capon, 1996; Tuunainen et al., 1995).

For the post-stroke aphasic patients in Jabbari et al. (1979), the severity of focal slow-wave activity in EEG, registered early after stroke and evaluated by visual inspection, was indicative of the extent of recovery from aphasia. Minimal slow-wave activity was indicative of good language recovery, and a high level of slow-wave activity was linked to poor or no recovery after 8 to 24 months. Szelies et al. (2002) assessed post-stroke aphasic patients 2 and 8 weeks post-onset with EEG and an aphasia test battery. An increase of delta and theta power in the affected left hemisphere was linked to poor language outcome at the second examination. Little or no slow-wave activity was associated with a good language outcome.

Among the two studies with mixed prognostic results (demonstrating a significant prognostic relation, but not for all tests or measures of slow-wave activity), Tikofsky et al. (1960) examined EEG and language recovery in a group of aphasic patients with different types of brain injury. All patients received speech therapy for a period of between 2 months and 2 years, and language recovery was determined by evaluating speech therapy records. A slow, theta-band (instead of alpha-band) background frequency around the start of speech therapy was indicative of a poor prognosis, that is, no progress after 2 to 24 months of

speech therapy. However, the relation between delta activity and language recovery failed to reach significance. Hensel et al. (2004) evaluated slow-wave EEG activity and language performance every 4-5 months in aphasic patients up to 2 years post-stroke. Patients with the highest levels of left-sided delta activity early after stroke had the smallest language improvement, and patients with the least left-sided delta activity had the largest language improvement. However, the correlation failed to reach significance, presumably due to the small sample size.

In two studies, language outcome could not be predicted by slow-wave activity. In patients who underwent epilepsy surgery by resection of mesial temporal structures, Tuunainen et al. (1995) found that object naming and Token Test performance had not changed 1 year after surgery and letter fluency performance had improved. No relations between these outcome measures and preoperative slow-wave activity were reported. This is not surprising because brain dysfunction and surgery took place in the mesial temporal lobe (including the amygdala and the hippocampus), which predominantly subserves memory functions. Therefore, slow-wave activity over temporal regions is not likely to reflect language functioning in this patient group. In Capon (1996), delta activity and aphasia index were regularly evaluated over a 3-month period in post-stroke hemiplegic patients with aphasia (left-hemispheric stroke) and without aphasia (right-hemispheric stroke). Language outcome could not be predicted by delta activity over the affected hemisphere from the initial EEG recording. This may be due to a methodological issue: the analysis was performed over the entire group, in which approximately half of the patients had a right-hemispheric stroke and no aphasia. Slow-wave activity in only the left, instead of the affected hemisphere, may have been a predictor for language functioning in this patient group, as left-hemispheric slow-wave activity has been shown to distinguish stroke patients with aphasia from stroke patients without aphasia (Chapman et al., 1989).

Conclusion

The reported findings on the prognostic value of slow-wave activity for language are diverse. There are indications that slow-wave activity can predict language functioning at a later time point, at least in post-stroke aphasic patients in the subacute and in the chronic phase. However, this does not seem to hold for all measures of slow-wave activity. It may be essential to take the location of slow-wave activity in the left hemisphere into account. Very little is known about the prognostic relevance of slow-wave activity in patients with brain injury other than stroke. In epilepsy patients, slow-wave activity over temporal regions does not predict language outcome after surgery, although language functioning does not decline after surgery and language impairments are less prevalent in these patients.

Discussion

Literature on slow-wave activity and language functioning in patients with brain injury suggests that presence and degree of slow-wave activity are markers of the existence and severity of language impairment, respectively. Higher amounts of slow-wave activity are

associated with poorer language functioning. Furthermore, in stroke patients, slow-wave activity in left anterior regions is related to non-fluent language use, whereas slow-wave activity in left posterior regions is related to fluent language use and comprehension deficits. Finally, there is support for slow-wave activity to have prognostic relevance, as it can predict the extent of language recovery after stroke. It is unknown whether this also holds for patients with other types of brain injury.

The notion of slow-wave activity being a marker of (the severity of) language impairment applies both to stroke patients and to patients with primary progressive aphasia. The minimum amount or level from which slow-wave activity indicates a language impairment after stroke is unclear and is highly dependent on the methodology. In patients with other types of brain pathology (neurodegenerative diseases without primary progressive aphasia, traumatic brain injury, epilepsy, and brain tumours), language was often assessed as part of a larger test battery, and information on language impairment was not included. Although the level of language functioning was described by test scores, there was no evaluation on when language performance was impaired. Hence, in these patient groups, there is support for slow-wave activity to be a marker of the level of language functioning. After applying a cut-off score for language impairment, slow-wave activity is expected to be a marker of language impairment in these patient groups as well, similar to stroke patients.

A few studies report no relation between slow-wave activity and language (Capon, 1996; Duffy et al., 1995; Tuunainen et al., 1995). Language test scores in Tuunainen et al. (1995; epilepsy) and in Duffy et al. (1995; Alzheimer's disease) were possibly too high (in the normal range, although this was not defined) to demonstrate a relation with slow-wave activity. Furthermore, in order to obtain indications for the level of language functioning, it may be necessary to evaluate slow-wave activity over the left, language dominant hemisphere, as opposed to the affected (left or right) hemisphere as in Capon (1996). Analyses including left-hemispheric stroke patients together with right-hemispheric stroke patients with increased right-sided slow-wave activity (without language impairment) can obscure effects at a group level.

Although all described types of brain injury co-occur with slow-wave activity, which is presumably induced by subcortical white matter damage (Ball et al., 1977; Gloor et al., 1977), the underlying brain pathologies are very different, which may partly explain differences between previous findings. For example, in cases of acute brain injury (e.g. stroke, trauma), it is more likely for both slow-wave activity and language impairment to be severe, possibly resulting in larger effects, compared to cases of brain injury due to a gradually evolving process (e.g. temporal lobe epilepsy, tumour). The major contrast between the two is that a gradually evolving process has had more opportunity (time) for neuroplasticity: the brain's ability to change, adapt and compensate for injury. Therefore, relations between slow-wave activity and language functioning or recovery may be less apparent in patients with non-acute brain injury than in patients with acute brain injury.

The presence of slow-wave activity is presumably not specific for language, nor for specific cognitive functions. However, for language processing in particular, the neural network is commonly left lateralised, primarily around the Sylvian fissure (Naidich, Hof,

Gannon, Yousry, & Yousry, 2001). Slow-wave activity over this region indicates dysfunction of the underlying (white matter) structures and, thus, can be seen as an indirect sign of poor language functioning. Markedly, the brain area over which slow-wave activity is most pronounced indicates the type of language deficit (Chapman et al., 1989). Apart from that, measures of whole-brain slow-wave activity are also indicative of language performance (Helkala et al., 1991; Thatcher et al., 1998; Van der Hiele et al., 2007; Wolthuis et al., chapter 4). It is expected that network analyses with EEG or MEG can provide additional information on the severity and recovery of language impairments (cf. Bosma et al., 2009 and Van Dellen et al., 2013 for cognitive functions).

Exploring the relation between slow-wave activity and language was not the main objective in most of the reviewed studies. Therefore, some analyses may not be optimal to answer the current questions. Furthermore, the methodologies varied considerably between studies. For language, various assessments have been used, ranging from extensive (aphasia) test batteries to single test scores. Not all assessments provide a comprehensive language profile. Also, it is unclear whether the specific tests are sufficiently sensitive to detect (mild) language deficits in all patient groups. In terms of the various language modalities that can be affected after brain injury (Ellis & Young, 1988; Levelt, 1989), slow-wave activity has been shown to relate to speech production (Helkala et al., 1991; Kiehl et al., 2019; Kim et al., 2012; Olde Dubbelink et al., 2013; Thatcher et al., 1998; Van der Hiele et al., 2007) and comprehension (Helkala et al., 1991; Kiehl et al., 2019; Meinzer et al., 2004; Szelies et al., 2002). Reading and writing have not been investigated or the scores were included in an overall language measure.

With regard to brain activity recordings, EEG has been used more often than MEG. MEG has higher spatial resolution, which is beneficial for assumptions on slow-wave activity localisation and its sources. However, EEG is more frequently used and better suited to clinical settings, as it is relatively inexpensive, widely available, and requires no constrictive head fixation. Furthermore, slow-wave activity is one of the standard categories for evaluating clinical EEG (next to epileptiform patterns, special patterns, etc.; see Lüders & Noachtar, 2000), so its measurement does not require much extra time. Apart from the recording technique (EEG vs. MEG), various ways to examine slow-wave activity have been used. A relation with language has been found for slow-wave activity using visual inspection (Jabbari et al., 1979), spectral analyses by using amplitude (Chapman et al., 1989; Finitzo et al., 1991; Helkala et al., 1991; Hensel et al., 2004; Thatcher et al., 1998) or power (squared amplitude; Claus et al., 2000; Kiehl et al., 2019; Olde Dubbelink et al., 2013; Ranasinghe et al., 2017; Shah-Basak et al., 2019; Szelies et al., 2002; Van der Hiele et al., 2007; Wolthuis et al., chapter 4), and dipole density or strength (Hensel et al., 2004; Kim et al., 2012; Meinzer et al., 2004). The latter quantitative approaches are more objective and less time consuming than visual analysis, although visual inspection is required to select artefact-free segments for quantitative analysis.

This review is the first to evaluate literature on slow-wave activity and language, aiming to uncover potential applications in clinical practice. Slow-wave activity as a marker of language impairment can, for example, be used after acute brain injury. Language assessments are

time consuming and are not possible when patients cannot cooperate with testing. In such cases, brain activity can be recorded without the need for active patient participation and can potentially help with other diagnostic purposes simultaneously. Moreover, there is evidence that slow-wave activity provides prognostic information about the course of language recovery in post-stroke aphasia. This can give directions for language intervention and aid patient counselling. It is unknown whether slow-wave activity also has prognostic relevance for language functioning in non-stroke patients with brain injury. If so, this would be especially useful for patients who already undergo EEG registration as part of their clinical work-up. In the future, slow-wave activity may be used to estimate the risk of language decline after brain surgery (cf. memory in Tuunainen et al., 1995). Hence, more insight into the prognostic value of slow-wave activity for language is warranted and requires further investigation.

Chapter 3

Language impairments in brain tumour patients: The association with resting-state functional connectivity brain networks in EEG/MEG

A review

Abstract

Many patients with brain tumours in eloquent areas suffer from language impairments, before and after surgery. These impairments cannot be explained solely by the structural injury caused by the tumour and its treatment. Therefore, it is informative to examine EEG/MEG-based networks of functional connectivity (FC), indicating the extent to which brain areas functionally interact. Resting-state FC brain networks have been shown to be associated with cognitive functioning. However, it is unclear whether these networks relate to language functioning in brain tumour patients.

This review discusses: (1) FC network analysis; (2) resting-state FC network alterations in brain tumour patients; (3) literature on the relation between FC network characteristics and cognitive functioning in brain tumour patients; (4) literature on the relation between FC network characteristics and language functioning in brain tumour patients and in patients with other brain pathologies.

Brain tumour patients have increased FC in lower frequency bands and decreased FC in higher frequency bands. These FC alterations relate to poorer language performance, as suggested by three out of four studies in brain tumour patients, and supported by findings in other patient groups. For brain tumour patients, however, this only applies to performance on verbal fluency tests, which only partly assess language.

Further investigation into how resting-state FC brain networks relate to different aspects of language functioning is needed to improve our understanding of the underlying neural mechanisms of language impairments. Also, FC network characteristics potentially predict language outcome after brain tumour surgery, which could benefit counselling and planning of surgical procedures.

Introduction

Language impairments in brain tumour patients

Intact language functioning is a prerequisite for communication in daily activities and contributes to quality of life (Liu, Page, Solheim, Fox, & Chang, 2009). The majority of patients with a tumour in eloquent brain areas report language problems, such as word finding difficulties (Racine et al., 2015; Satoer, Vincent, Smits, Dirven, & Visch-Brink, 2013). These language problems have been objectified with naming and verbal fluency tasks. In addition, impairments in comprehension, repetition, and writing have been found (Satoer et al., 2016).

Patients with a primary brain tumour, such as a low-grade glioma, a high-grade glioma or a meningioma, generally undergo surgical resection. Shortly after surgery, language performance may worsen in glioma patients. Language functioning improves in the longer term after surgery, but some aspects remain impaired compared to the preoperative level (Satoer et al., 2016). In meningioma patients, the effect of tumour resection on language functioning is largely unknown, but performance may not change (Abel et al., 2016) or may improve after surgery (Liouta et al., 2016). Overall, the incidence of postoperative language impairments in brain tumour patients ranges between 10 and 70% (Antonsson, Jakola, et al., 2018; Di Cristofori et al., 2018; Santini et al., 2012; Van Kessel et al., 2020).

Language impairments in brain tumour patients cannot be explained solely by the structural injury caused by the tumour or its treatment. In order to understand the underlying neural mechanisms of language problems, an examination of the extent to which brain areas functionally interact can be informative. This has already been shown to be a promising approach for understanding the impact on cognitive functions, such as attention, verbal memory, and executive functioning (Bosma et al., 2009).

Language processes require activation and cooperation of multiple specialised brain areas that are integrated in a large-scale, functionally interacting network (Duffau, 2014). A relatively new way of studying the consequences of an intracranial tumour on brain functioning is analysing functional connectivity (FC) networks (Bartolomei et al., 2006a). These networks represent the (strength of) functional interactions between brain regions and can be obtained from recordings of brain activity. FC network alterations in brain tumour patients have mainly been examined in relation to cognitive functions. It is yet unclear whether, or to what extent, alterations in FC networks are related to language functioning in brain tumour patients.³

In this review, we first introduce the principles of FC network analysis and describe resting-state FC network alterations in brain tumour patients. Subsequently, the relation between these network alterations and cognitive functioning is evaluated as a starting

3 The terminology on language and cognition is ambiguous. Some researchers consider language as one of the cognitive functions, like memory and attention, and propose a single mechanism for language and cognition (Croft & Cruse, 2004), whereas others see language and cognition as two separate (but closely interacting) abilities (Chomsky, 1995; Perlovsky, 2013). In this review, we follow the latter approach because our purpose is to evaluate whether FC alterations are specifically related to language.

point because cognitive functioning and language functioning both require a large-scale functionally interacting network. From there, we examine what is known about FC network characteristics in relation to language functioning in brain tumour patients and, as this has not been well studied before, in patients with other brain pathologies. The literature searches are performed via WorldCat in various electronic databases (e.g. PubMed, MEDLINE, Web of Science, ScienceDirect) to find analyses that meet our aforementioned scope, resulting in an extensive literature review, although not a systematic one.

Functional connectivity and resting-state brain activity

FC concerns the transmission of information throughout the brain, in other words, the functional interactions between brain areas. Structural (or anatomical) connections are a prerequisite for brain areas to functionally interact, however, this review focuses on FC rather than structural connectivity. FC is based on the synchronisation of electrical signals by neurons, characterised by any statistical interdependency between two signals of brain activity (Aertsen, Gerstein, Habib, & Palm, 1989). Two basic principles of information processing in the brain are functional segregation, also called short-distance FC (here: 'local FC'), and functional integration, also called long-distance FC (here: 'global FC'). Local FC is the ability for specialised processing to occur within a highly interconnected brain area, whereas global FC refers to the capacity to rapidly combine specialised information from distinct and remote brain areas (Rubinov & Sporns, 2010).

Local and global FC can be examined by using recordings of brain activity during a resting state. Resting-state brain activity can be seen as the baseline functioning of the brain, characterised by constantly changing, weakly synchronised networks, which have been found to be robust (Damoiseaux et al., 2006; Gusnard & Raichle, 2001).

Techniques for registration of brain activity

Analysis of FC brain networks at rest requires registrations of brain activity. For this, electroencephalography (EEG) and magnetoencephalography (MEG) recordings can be used. Both methods directly measure brain activity in real-time by electrical or magnetic fields. EEG and MEG enable examination of different frequency bands of brain activity (delta, theta, alpha, beta, and gamma). Alternatively, FC brain networks can be analysed with the use of functional magnetic resonance imaging (fMRI), but fMRI investigations are beyond the scope of this review.⁴ The process of FC network analysis with EEG/MEG data is described below.

4 fMRI measures brain activity indirectly by hemodynamic responses. These responses occur relatively slowly and, therefore, registration by fMRI is restricted to lower frequencies than EEG and MEG. To illustrate, commonly studied brain-related activity measured with EEG/MEG lies within the range of approximately 0.3-70 Hz (Niedermeyer, 1999), whereas brain-related activity registered with fMRI data lies within the range of approximately 0.01-0.08 Hz (band-pass filter used in Zhang et al., 2018). Because of these fundamental differences, fMRI-based FC networks are not comparable to EEG/MEG-based FC networks. Hence, literature on fMRI-based FC networks is not evaluated in this review.

(1) Functional connectivity network analysis

Network construction

FC brain networks can be studied and abstractly visualised by performing a FC network analysis on EEG/MEG registrations. The corresponding brain activity is commonly recorded in or over multiple brain areas, sometimes summarised into regions of interest. FC between brain areas is analysed by means of a FC measure. This calculates statistical interdependencies between the signal of one area and the signal of every other area, hence, for every pair of signals. All FC measures are based on correlation coefficients but differ in aspects such as linear or nonlinear relations, FC in the time or frequency domain, and amplitude-based or phase-based. An overview of FC measures can be found in Van Diessen et al. (2015), also see Pereda, Quiroga, and Bhattacharya (2005) for the statistical derivation.

A high correlation between two signals indicates strong synchronisation and represents a (strong) functional interaction between two brain areas. A low correlation indicates a weak interaction or no functional interaction between two brain areas. These values are organised in a correlation matrix (also called 'adjacency matrix'; figure 3.1). The rows and columns are labelled with the areas from which the signals were recorded and the colours in squares indicate the strength of the correlations. Next, the correlations between all pairs of signals are mapped onto a schematic representation of the brain, in which connecting lines between brain areas indicate functional interactions. A 'weighted' network shows the strength of functional interactions between brain areas by a thicker line for a stronger interaction. In an 'unweighted' or binary network, a functional interaction is either present (connecting line) or absent (no line), depending on a correlation threshold. The latter type of network analysis is illustrated in figure 3.1. More detailed explanations of FC network analysis can be found in Van Diessen et al. (2015), Van Straaten and Stam (2013), and Zhang, Lei, Wu, and Jiang (2014).

Figure 3.1. Example of a functional connectivity network analysis in the alpha frequency band obtained from EEG signals using BrainWave software (version 0.9.152.12.26; Stam, 2018). (A) EEG signals; (B) Correlation strength (red = high; blue = low) between every pair of EEG signals, presented in an adjacency matrix (weighted); (C) After applying a correlation threshold (above threshold = functional connection; below threshold = no functional connection), functional connections are mapped onto a schematic representation of the brain (unweighted network representation); (D) Quantification of the network organisation by network measures. Note: Fp1, Fp2, A1 and A2 electrodes are not included in the analysis to avoid contamination by muscle activity and cardiac rhythm artefacts. The correlation threshold (0.2) was arbitrarily chosen; the figure elements and mean values are for illustrative purposes only.

Quantification and modelling of the network architecture

The organisation of a FC network can be described by network measures, determining the network characteristics. Graph theory, a branch of mathematics, is frequently used to describe and quantify the properties of a network. Graph theory reduces complex networks to a 'graph', which is an abstract representation of the network, consisting of nodes ('vertices') and connections ('edges'). In FC network analysis of the brain, a node corresponds to the recording site (or region of interest) and represents the underlying brain area. A connection is the link between nodes, representing a functional interaction between brain areas. See the review by Stam and Van Straaten (2012) for the application of graph theory in FC network analysis of the brain.

Several types of network measures are used for the quantification of network configurations. Measures of centrality provide information on a local scale and examine the relative importance of individual elements (nodes or connections) in the network. 'Degree' is an example of a centrality measure for nodes. It indicates the number of connections a node has. Measures of local FC examine the presence of groups of nodes that are highly

interconnected, more than to the rest of the network; they are referred to as ‘clusters’ or ‘modules’. Detection of a cluster in a FC brain network indicates specialised processing within a densely interconnected brain area. An example of a local FC measure is the ‘clustering coefficient’, the extent to which neighbours of a node are connected to each other. Measures of global FC examine how well distant (groups of) nodes are connected in the network. This indicates the ease with which remote brain regions interact, including long-distance interhemispheric interactions. Measures of global FC are based on the concept of the shortest path: the smallest number of connections that have to be passed to get from one node to another. Hence, a short averaged ‘path length’ indicates high global FC. An overview of all types of network measures can be found in Rubinov and Sporns (2010).

Apart from network measures, different network models have been proposed to describe a network organisation. The ‘regular’ (or ‘ordered’) network model is characterised by high local FC and low global FC (Watts & Strogatz, 1998). In contrast, the ‘random’ network model has low local FC and high global FC, and connections between nodes are determined on a random basis (Erdős & Rényi, 1959). As both network models are not able to explain most of the properties of natural networks, an intermediate network model was introduced: the ‘small-world’ network (Watts & Strogatz, 1998). This model combines high local FC with high global FC, a balance which is observed in many other complex natural networks.

In healthy adults, the FC brain network has a small-world configuration, combining high levels of local clustering with strong global integration (Achard, Salvador, Whitcher, Suckling, & Bullmore, 2006; Bassett, Meyer-Lindenberg, Achard, Duke, & Bullmore, 2006; Stam, 2004). The next section describes how the organisation of FC brain networks is altered in brain tumour patients. Subsequently, literature on these alterations in relation to cognitive and language functioning is reviewed.

(2) Functional connectivity in brain tumour patients

Functional connectivity network characteristics

Several studies have investigated FC brain networks during a resting state with MEG in brain tumour patients. So far, EEG has not been used. Table 3.1 gives an overview of the FC findings for each frequency band.

Before surgery, Bartolomei et al. (2006b) found decreased FC in the broad band (0.5-60 Hz) and in the gamma band in a mixed group of brain tumour patients (meningiomas, low- and high-grade gliomas), compared to healthy individuals. These alterations were observed in multiple brain areas, not only in the affected hemisphere, but also in the contralateral hemisphere. When distinguishing local and global FC, the same group of patients had increased local and global FC in the lower or intermediate frequency bands (delta, theta, and alpha), and decreased global FC in the higher frequency bands (beta and gamma; Bartolomei et al., 2006a). In terms of graph theory, the patients had a more random network organisation compared to the ‘small-world’ configuration in healthy individuals (Bartolomei et al., 2006a). Furthermore, Van Dellen et al. (2012) found that FC in low-grade glioma patients differed

from healthy individuals only in the theta band, that is, increased local FC together with decreased global FC. No alterations were found in high-grade glioma patients. Lastly, Hu, Lei, Xu, Zou, and Liu (2013) found a decreased small-world index in a group of low- and high-grade glioma patients compared to healthy individuals, but only in the gamma band. Overall, previous studies indicate that, before surgery, brain tumour patients have altered FC network characteristics in both hemispheres, generally with increased FC in lower frequency bands, and decreased FC in higher frequency bands.

Two studies investigated FC in low-grade glioma patients of which the majority were assessed long-term after surgery. Comparable findings were reported: patients had higher FC in the delta and theta bands, and lower FC in the alpha, beta and gamma bands, compared to healthy individuals. However, one exceptional finding showed increased FC in the gamma band (Bosma, Douw, et al., 2008; Bosma et al., 2009).

The effect of tumour resection and postoperative neurological outcome

The effect of brain tumour surgery on FC has been investigated with resting-state MEG (table 3.1). Studies that compared preoperative FC with postoperative FC indicate that brain tumour patients have decreased global FC in the theta band (Douw et al., 2008), increased FC in the alpha band (Lizarazu et al., 2020; Van Dellen et al., 2013), and increased local and global FC in the beta band (Wang et al., 2010) after surgery. Considering that inverse patterns have been observed before surgery (increased FC in the theta band and decreased FC in the beta band; Bartolomei et al., 2006a), this suggests that FC tends to normalise after tumour resection.

MEG-based FC analysis on a smaller scale, focusing on the preoperative tumour area in specific, has been shown to be informative with regard to neurological outcome after surgery (Guggisberg et al., 2008; Martino et al., 2011; Tarapore et al., 2012). Resection of brain tumours with decreased alpha-band FC within the tumour area (compared to contralateral tissue) is associated with a low risk of inducing new neurological deficits (Guggisberg et al., 2008; Tarapore et al., 2012). Furthermore, resection of tumours with increased alpha-band FC within the tumour area is associated with a higher risk of postoperative deficits, in the short and long term after surgery (Tarapore et al., 2012). Hence, (peri)tumoural areas with decreased alpha-band FC seem to have reduced functionality and may, therefore, be resected without inducing new deficits, whereas (peri)tumoural areas with increased alpha-band FC suggest functional importance. This has been confirmed by Martino et al. (2011), who showed a 0% probability of finding positive language or sensorimotor sites during intraoperative Direct Electrical Stimulation (DES) in brain tumour patients with decreased alpha-band FC in the tumour area, as opposed to a 64% probability in patients with increased alpha-band FC in the tumour area. This suggests that preoperative FC analysis in tumour areas is related to intraoperative DES findings (Martino et al., 2011) and may predict neurological outcome after brain tumour surgery (Guggisberg et al., 2008; Tarapore et al., 2012).

Table 3.1. Functional connectivity alterations in brain tumour patients

Study	Participants	Method	FC alterations for each frequency band					
			Delta	Theta	Alpha	Beta	Gamma	Broad band
Before surgery – compared to healthy individuals								
Bartolomei et al. (2006b)	2 Men+5 LGG+10 HGG vs. 15 Healthy	rs MEG before surgery					↓	AH, CH
Bartolomei et al. (2006a)	2 Men+5 LGG+10 HGG vs. 15 Healthy	rs MEG before surgery	↑	↑	↑	↓	↓	
Van Dellen et al. (2012)	13 LGG vs. 36 Healthy	rs MEG before surgery	AH	AH	AH	AH, CH	AH, CH	
			-	↑↓	-	-	-	
				WB				
Hu et al. (2013)	12 HGG vs. 36 Healthy	rs MEG before surgery	-	-	-	-	-	
	13 LGG+7 HGG vs. 20 Healthy	rs MEG before surgery	-	-	-	-	↓	
							WB	
After surgery – compared to healthy individuals								
Bosma, Douw, et al. (2008)	17 LGG vs. 17 Healthy	rs MEG 1-19 years after surgery (except 3 patients) ^a	↑	↑	↓	-	↑	
			WB	WB	WB		WB	
Bosma et al. (2009)	17 LGG vs. 17 Healthy	rs MEG 1-19 years after surgery (except 2 patients) ^a	-	↑	-	↓	↓	
				WB		WB	WB	
Before vs. after surgery – within-group comparisons								
Douw et al. (2008)	2 Men+6 LGG+7 HGG	rs MEG before and 5-10 months after surgery	-	↓	-	-	-	
				WB				
Wang et al. (2010)	2 Men+6 LGG+7 HGG	rs MEG before and 5-10 months after surgery	-	-	-	↑		
						WB		
Van Dellen et al. (2013)	10 LGG	rs MEG before and 2-6 months after surgery	-	-	↑	-	-	
					WB			
Lizarazu et al. (2020)	12 LGG	rs MEG before, 3 months, and 6 months after surgery	-	-	↑	-	-	
					AH			

Note. ↑ indicates a FC increase (local and/or global); ↓ indicates a FC decrease (local and/or global); ↑↓ indicates a FC increase and a FC decrease, depending on the network measure; - indicates no difference; empty cells indicate that this band was not investigated. Abbreviations: Men = meningioma; LGG = low-grade glioma; HGG = high-grade glioma; rs = resting-state; MEG = magnetoencephalography; AH = affected hemisphere (tumour location); CH = contralateral hemisphere; WB = whole-brain analysis, or no distinction was made between the affected hemisphere and the contralateral hemisphere.

^a This study was classified in the category after surgery because the majority of the patient group was assessed after surgery.

The effect of tumour characteristics

A few studies have investigated effects of tumour characteristics on FC using resting-state MEG in brain tumour patients, all before surgery. Effects have been demonstrated for tumour location, grade, and molecular markers.

As for tumour location, left-hemispheric tumours are associated with a more severe FC loss in the broad, beta, and gamma bands than right-hemispheric tumours (Bartolomei et al., 2006b, 2006a). Although speculative, the left hemisphere may generally have a more extensive FC network than the right hemisphere (also see Raemaekers, Schellekens, Petridou, & Ramsey, 2018), indicating more connections at risk. This may link to the finding that left-hemispheric gliomas are associated with more severe cognitive impairments than right-hemispheric gliomas (Noll, Ziu, Weinberg, & Wefel, 2016).

With regard to tumour grade, Van Dellen et al. (2012) showed that patients with a low-grade (slow-growing) glioma had altered FC in the theta band compared to healthy individuals, whereas patients with a high-grade (fast-growing) glioma did not. The authors propose that it may take time for neuroplasticity effects to become evident on a global FC scale. This may explain why the FC network in high-grade glioma patients, who had a shorter time interval between the first symptoms and MEG registration, more closely resembles a healthy configuration than the FC network in low-grade glioma patients (Van Dellen et al., 2012).

The effect of glioma molecular markers on FC was investigated by Derks et al. (2019). Glioma patients with isocitrate dehydrogenase (IDH)-wildtype showed lower alpha-band FC than glioma patients with IDH-mutation. This difference could not be explained by age, presence of epilepsy, or tumour grade.

(3) Functional connectivity network characteristics and cognitive functioning

Brain tumour patients

Eight studies have investigated whether FC network alterations in resting-state MEG are related to cognitive functioning in brain tumour patients (Bosma, Douw, et al., 2008; Bosma et al., 2009; Derks et al., 2019; Hu et al., 2013; Lizarazu et al., 2020; Van Dellen et al., 2013, 2012; Van Nieuwenhuizen et al., 2018), of which seven report significant effects. These effects indicate relations between FC network characteristics and performance on tasks assessing verbal memory, working memory, information processing, psychomotor speed, attention, executive functioning, and intelligence, either preoperatively, postoperatively, or by postoperative change (before vs. after surgery) (Bosma, Douw, et al., 2008; Bosma et al., 2009; Derks et al., 2019; Hu et al., 2013; Van Dellen et al., 2013, 2012; Van Nieuwenhuizen et al., 2018). Various FC network characteristics in the delta, theta, alpha, beta, and gamma bands have been analysed in relation to these cognitive functions. More specific findings are described below, summarised into local FC and global FC for each frequency band.

In the delta band, no effects are reported for the preoperative stage (Hu et al., 2013). In the postoperative stage, however, high local and high global FC are associated with

poorer attention and working memory (Bosma, Douw, et al., 2008), whereas other analyses indicate that low local and low global FC are associated with poorer attention and executive functioning (Bosma et al., 2009). In the theta band, preoperative low local FC relates to poorer attention and verbal memory (Van Dellen et al., 2012), although one study reports no effects (Hu et al., 2013). Furthermore, contradictory results are reported for the postoperative stage: high global FC relating to poorer working memory and attention (Bosma, Douw, et al., 2008), low global FC relating to poorer working memory (Van Nieuwenhuizen et al., 2018), and no effects (Bosma et al., 2009).

In the alpha band, preoperative low global FC is associated with poorer verbal memory, information processing, psychomotor speed, attention, executive functioning (Derks et al., 2019), and intelligence quotients (Hu et al., 2013). In the postoperative stage, low local and low global FC is associated with poorer verbal memory; however, one exceptional finding in the lower alpha band indicates that high local FC is also correlated with poorer verbal memory (Bosma et al., 2009). Furthermore, an increase of alpha-band FC after glioma surgery coincides with cognitive improvement (verbal memory, working memory, attention, and executive functioning; Van Dellen et al., 2013). Other studies report no effects for the postoperative stage (Bosma, Douw, et al., 2008; Van Nieuwenhuizen et al., 2018), or no significant correlations between FC change and cognitive change after surgery (Lizarazu et al., 2020).

In the beta band, there are no relations between FC network characteristics and cognitive functioning preoperatively (Hu et al., 2013), nor postoperatively (Bosma, Douw, et al., 2008; Bosma et al., 2009). In the gamma band, no effects are reported for the preoperative stage (Hu et al., 2013). In the postoperative stage, measures of high local and high global FC are associated with poorer attention and information processing (Bosma, Douw, et al., 2008), or no effects are reported (Bosma et al., 2009).

In conclusion, pre- and postoperative FC findings in the (intermediate) alpha band generally point in the same direction: low FC relates to poorer cognitive performance, and FC and cognitive scores tend to increase in parallel after surgery. Relations are less clear for the lower frequency bands (delta and theta), as low and high FC are both associated with poorer cognitive functioning. In the higher frequency bands, most findings indicate no relations between FC and cognition (beta and gamma), apart from the finding that postoperative high FC relates to poorer performance (gamma).

Previously, in section 2, it was discussed that brain tumours alter FC brain networks, and it is known that brain tumour patients frequently suffer from (mild) cognitive impairments (Van Kessel et al., 2017). Many studies in the current section provide evidence for a relation between FC network characteristics and cognitive functioning in brain tumour patients. This suggests that altered FC network characteristics may be a marker of cognitive dysfunction in this patient group. Like cognitive functions, language also involves a large-scale functionally interacting brain network for adequate performance (Duffau, 2014). Again, FC networks are often affected in brain tumour patients, and many patients report language problems (Racine et al., 2015). The next section reviews literature on the relation between FC network characteristics and language functioning. As this has not been well investigated in brain tumour patients, we take into account patients with other brain pathologies as well.

(4) Functional connectivity network characteristics and language functioning

Brain tumour patients

Four studies have related FC brain networks to the level of language performance in brain tumour patients. Resting-state MEG was used in all four studies and they only included glioma patients. The four studies mainly focused on cognitive functions and were also mentioned in the previous section. Analyses on language are summarised in table 3.2. Note that verbal fluency, in the form of category or letter fluency, is considered a language test here. Although it is often used as a measure of executive functioning, it also assesses language processing (Aita et al., 2019; Whiteside et al., 2016).

First, Van Dellen et al. (2012) showed that FC alterations in the theta band, such as increased local FC, are related to poorer category fluency performance in low-grade glioma patients. No effects were found for high-grade glioma patients. Second, Hu et al. (2013) found that a more ‘small-world’-like FC network in the gamma band positively correlates with verbal fluency scores. Third, Derks et al. (2019) showed that lower global FC in the alpha band is related to poorer category fluency performance. Finally, Lizarazu et al. (2020) assessed left-hemispheric, low-grade glioma patients with object naming and semi-spontaneous speech ratings, and registered MEG before, 3 months after, and 6 months after surgery. No relations between FC change in the alpha band and language change scores were found, possibly because language performance did not significantly change between the time points.

To date, for brain tumour patients, FC network characteristics have been found to be related to language functioning: high (local) FC in the theta band and low (global) FC in the alpha and gamma bands are associated with poorer language functioning. However, this only applies to verbal fluency performance.

Other patient groups

Other brain pathologies such as stroke, neurodegenerative diseases, and traumatic brain injury (TBI) also induce widespread alterations in resting-state FC brain networks (Aerts, Fias, Caeyenberghs, & Marinazzo, 2016). These networks are highly dynamic. In case of recovery of neural injury, they tend to change towards healthy configurations by FC decreases in lower frequency bands and FC increases in higher frequency bands (Castellanos et al., 2010). We review the literature on these patient groups as well in order to improve our understanding of how FC network characteristics relate to language functioning. An overview of the findings is provided in table 3.3.

Dubovik et al. (2012) investigated FC in a group of left and right-hemispheric stroke patients, using high-density EEG registered once in the subacute stage (3 months post-onset). A decrease of alpha-band FC of the left inferior and left middle frontal gyrus with the rest of the brain was associated with poorer letter fluency performance. Furthermore, a decrease of alpha-band FC of the right inferior frontal gyrus with the rest of the brain was associated with better letter fluency performance. Furthermore, Nicolo et al. (2015) investigated FC in high-density EEG in left-hemispheric stroke patients with language impairments. In the

acute stage (2-3 weeks post-onset), high beta-band FC of the left inferior frontal gyrus with the rest of the brain, and high theta-band FC of the right inferior frontal gyrus with the rest of the brain were predictors of better language recovery in the subacute stage (3 months post-onset). With regard to neurodegenerative diseases, Dubovik, Bouzerda-Wahlen, et al. (2013) examined FC alterations in high-density EEG and category fluency performance, assessed once in patients with probable Alzheimer's disease. All effects were found in the alpha band. Lower FC of the left inferior frontal gyrus with the rest of the brain and lower left intrahemispheric FC were related to better language performance, unlike healthy individuals and stroke patients, who showed inverse patterns. Lower FC of the right inferior frontal gyrus with the rest of the brain and lower right intrahemispheric FC were related to poorer language performance. Ranasinghe et al. (2017) investigated FC with MEG registered once in patients with primary progressive aphasia (PPA), a neurodegenerative language impairment, and found distinct FC patterns for each PPA variant. Logopenic PPA, characterised by phonological impairments, was associated with decreased alpha- and beta-band FC in left posterior temporal and occipital areas, and increased bilateral delta- and theta-band FC in medial frontal and posterior parietal areas. Semantic PPA, characterised by semantic/comprehension impairments, was associated with decreased alpha- and beta-band FC in the left temporo-parietal junction. Non-fluent PPA, characterised by morphosyntactic impairments, was associated with decreased alpha- and beta-band FC in the left inferior frontal gyrus. Finally, Castellanos et al. (2010) studied FC with MEG registered before and after rehabilitation for severe cognitive impairments in patients with TBI. A decrease of delta-band FC was associated with an improvement of letter fluency performance after treatment.

In summary, relations between resting-state FC and language performance in patients with brain pathologies other than tumours were found in the delta, theta, alpha and beta bands. In the delta band, a decrease of FC over time was related to language improvement (Castellanos et al., 2010). In the theta band, high FC in the contralateral right hemisphere was related to better language functioning (Nicolo et al., 2015). In the alpha band, low FC in the left hemisphere was related to poorer language performance (Dubovik et al., 2012; Ranasinghe et al., 2017), and low FC in the right hemisphere was related to better language functioning (Dubovik et al., 2012), although patients with probable Alzheimer's disease showed opposite patterns (Dubovik, Bouzerda-Wahlen, et al., 2013). In the beta band, low FC in the affected left hemisphere was related to poorer language functioning and recovery (Nicolo et al., 2015; Ranasinghe et al., 2017).

Table 3.2. Overview of analyses on functional connectivity network characteristics in relation to language functioning in brain tumour patients

Study	Patients	FC analysis	Language assessment	Timing of EEG/MEG and language assessment	Main findings with regard to language
Van Dellen et al. (2012)	21 glioma patients with tumour-associated epilepsy (LH and RH, 11 LGG; 10 HGG)	Method: rs MEG; FC measure: phase lag index; Network measures: average weighted clustering coefficient, stability of network synchronisability; Freq. band: theta	Category fluency	Once: before surgery	LGG: Theta band: Altered FC network characteristics, e.g. increased local FC, are related to poorer category fluency performance; HGG: No significant relations
Hu et al. (2013)	20 glioma patients (LH and RH, 13 LGG; 7 HGG)	Method: rs MEG; FC measure: phase lag index; Network measure: 'small-world' index: clustering coefficient divided by the average path length; Freq. bands: delta, theta, alpha, beta, low gamma, high gamma	Verbal fluency (not further specified)	Once: before surgery	Gamma band: Decreased global FC is related to poorer verbal fluency performance
Derks et al. (2019)	54 glioma patients (LH and RH, 28 LGG; 26 HGG)	Method: rs MEG; FC measure: phase lag index; Network measure: global FC between 78 cortical regions; Freq. band: alpha	Category fluency	Once: before surgery and/or start adjuvant treatment	Alpha band: Lower global FC is associated with poorer category fluency performance
Lizarazu et al. (2020)	12 LH glioma patients undergoing awake surgery in language areas (all LGG)	Method: rs MEG; FC measure: imaginary coherence; FC analysis of peri-tumoural and contra-tumoural regions with the rest of the brain; Freq. band: alpha	Object naming and proficiency ratings of semi-spontaneous speech	Thrice: before, 3 months after, and 6 months after surgery	Alpha band: No relations between FC change and language change after surgery

Note. Only analyses between FC network characteristics and language are included, other study information is excluded. Abbreviations: FC = functional connectivity; EEG = electroencephalography; MEG = magnetoencephalography; rs = resting-state; LH = left-hemispheric, RH = right-hemispheric; LGG = low-grade glioma; HGG = high-grade glioma.

Table 3.3. Overview of analyses on functional connectivity network characteristics in relation to language functioning in patients with other brain pathologies

Study	Patients	FC analysis	Language assessment	Timing of EEG/MEG and language assessment	Main findings with regard to language
Dubovik et al. (2012)	14 unilateral stroke patients (LH and RH)	Method: rs high-density EEG; FC measure: imaginary coherence; FC analysis of the entire cortex, using adaptive spatial filters for normalised brain maps; Network measures: mean FC of each voxel and mean FC of ROIs; Freq. bands: delta, theta, alpha, beta	Letter fluency	Once: 3 months post-onset	Alpha band: FC of the left IFG and MFG with the rest of the brain is positively correlated with letter fluency performance; Alpha band: FC of the right IFG with the rest of the brain is negatively correlated with letter fluency performance
Nicolo et al. (2015)	14 LH stroke patients with a language impairment in the acute stage	Method: rs high-density EEG; FC measure: imaginary coherence; Network measures: weighted node degree of the left IFG and its contralateral homologue; Freq. bands: delta, low theta, high theta, low alpha, high alpha, low beta, high beta	Spontaneous speech, repetition, verbal fluency, comprehension, reading, and writing summarised into one score	Twice: 2-3 weeks and 3 months post-onset	Beta band: Higher FC of the left IFG with other brain areas in the acute stage is related to better language recovery; Theta band: Higher FC of the contralateral right IFG with other brain areas in the acute stage is related to better language recovery
Dubovik, Bouzerda-Wahlen, et al. (2013)	15 patients with Alzheimer's disease (early stage)	Method: rs high-density EEG; FC measure: imaginary coherence; FC analysis of the entire cortex, using adaptive spatial filters for normalised brain maps; Network measures: mean FC of each voxel and mean FC of ROIs; Freq. bands: delta, theta, alpha, beta	Category fluency	Once	Alpha band: Increased FC of the left IFG with the rest of the brain and increased left intrahemispheric FC are related to poorer category fluency performance; Alpha band: Increased FC of the right IFG with the rest of the brain and increased right intrahemispheric FC are related to better category fluency performance

Table 3.3. Continued

Study	Patients	FC analysis	Language assessment	Timing of EEG/MEG and language assessment	Main findings with regard to language
Ranasinghe et al. (2017)	39 patients with PPA (variants: 14 logopenic, 13 semantic, and 12 non-fluent)	Method: rs MEG; FC measure: imaginary coherence; FC analysis of the whole brain; Network measures: mean FC of each voxel and mean FC of ROIs; Freq. bands: delta-theta, alpha, beta	Aphasia batteries for assignment of aphasia variant (logopenic/non-fluent/semantic; based on diagnostic criteria)	Once	Distinct FC patterns for every variant of PPA; Logopenic: decreased alpha and beta FC in left posterior temporal and occipital areas, and increased delta-theta FC in medial frontal and posterior parietal areas, bilaterally; Semantic: decreased alpha and beta FC in the left temporo-parietal junction; Non-fluent: decreased alpha and beta FC in the left IFG
Castellanos et al. (2010)	15 TBI patients with severe cognitive impairments (LH, RH and bilateral)	Method: rs MEG; FC measure: wavelet coherence; Network measure: 'distance-to-control', the number and weight of connections combined, relative to a healthy population; Freq. bands: delta, theta, alpha, beta	Letter fluency	Twice: before and after neuropsychological rehabilitation	Delta band: After neuropsychological rehabilitation, a larger decrease of FC is related to larger language improvement

Note. Only analyses between FC network characteristics and language are included; other study information is excluded. Abbreviations: FC = functional connectivity; EEG = electroencephalography; MEG = magnetoencephalography; LH = left-hemispheric, RH = right-hemispheric; rs = resting-state; ROI = region of interest; IFG = inferior frontal gyrus; MFG = middle frontal gyrus; PPA = primary progressive aphasia; TBI = traumatic brain injury.

Discussion

Functional connectivity network characteristics and language functioning

There is a considerable amount of evidence that FC network characteristics in resting-state EEG/MEG are related to cognitive functioning in brain tumour patients, but the relation with language functioning in this patient group has received little attention. Three out of four studies that included language suggest that high (local) FC in the theta band and low (global) FC in the alpha and gamma bands are indicative of poorer language performance in glioma patients (Derks et al., 2019; Hu et al., 2013; Van Dellen et al., 2012). The interpretation of these findings in different frequency bands is not straightforward.

It is possible that high FC in lower frequency bands indicates more severe brain dysfunction, as brain activity in lower frequency bands (also called ‘slow-wave’ activity) is pathologically overrepresented in brain tumour patients (Baayen et al., 2003; De Jongh et al., 2003; Oshino et al., 2007). When brain activity is highly present in a particular frequency band, one is more likely to find statistical interdependencies between brain signals, which provide more opportunity for high FC (Aertsen et al., 1989). This may explain the high local FC in the theta band, and its association with poorer language functioning (Van Dellen et al., 2012).

Brain activity in higher frequency bands is generally reduced in brain tumour patients (Bosma, Stam, et al., 2008). This may account for low FC in higher frequency bands (Bartolomei et al., 2006b, 2006a; Bosma et al., 2009). Moreover, brain activity in higher frequency bands, especially in the gamma band, is important for engagement in specialised (language or cognitive) processes (Lopes da Silva, 2013). For this reason, one may expect a relation between decreased FC in higher frequency bands and poorer test performance in brain tumour patients. This was shown for language (Hu et al., 2013), but the opposite pattern was found for cognitive functioning: increased gamma-band FC relates to poorer attention and information processing (Bosma, Douw, et al., 2008). This could suggest distinct underlying neural mechanisms for language and cognitive processes.

FC in the intermediate alpha band and language functioning seem to follow the pattern of higher frequency bands, that is, lower FC relates to poorer language performance (Derks et al., 2019). This suggests that, when alpha-band FC in glioma patients increases between pre- and postoperative measurements (Lizarazu et al., 2020; Van Dellen et al., 2013), language scores increase in parallel. However, this is not confirmed by Lizarazu et al. (2020), who found no associations between alpha-band FC changes and language change scores. One explanation is that language performance in their patient group did not change after surgery. Although the language measures used (object naming and semi-spontaneous speech ratings) resemble language functioning in daily life better than verbal fluency tests, the specific tasks may not have been sufficiently sensitive to detect language changes in low-grade glioma patients.

The reported associations between FC in resting-state MEG and language functioning in brain tumour patients only apply to verbal fluency performance. However, verbal fluency tests are not a “pure” reflection of language skills, as executive functions are also involved (Aita et al., 2019; Whiteside et al., 2016). Therefore, it is still largely unknown how FC network characteristics specifically relate to language functioning in brain tumour patients. This needs

further investigation. As language covers a range of abilities, a comprehensive language assessment is needed to examine how FC networks relate to different language modalities (speech production, comprehension, reading, and writing) and linguistic levels (e.g. phonology, semantics, and morphosyntax).

Patients with other types of brain injury also demonstrate alterations in resting-state FC, which are related to language functioning. The following FC network characteristics in EEG or MEG are indicative of poorer language functioning or poorer recovery: increased delta-band FC (TBI: Castellanos et al., 2010), decreased theta-band FC in contralateral areas (stroke: Nicolo et al., 2015), decreased alpha-band FC in the left hemisphere and increased alpha-band FC in the right hemisphere (stroke: Dubovik et al., 2012; PPA: Ranasinghe et al., 2017; although contradictory to Dubovik, Bouzerda-Wahlen, et al., 2013 on Alzheimer's disease), decreased beta-band FC in the left hemisphere (stroke: Nicolo et al., 2015; PPA: Ranasinghe et al., 2017). These findings hold for verbal fluency and an overall measure of language functioning. The patterns by which FC relates to language functioning in these patient groups are broadly in line with those in brain tumour patients.

Despite the different aetiologies of brain injury, most of the findings on FC network characteristics and language functioning point in the same direction. Increased FC in lower frequency bands is generally associated with poorer language performance. Decreased FC in higher frequency bands is generally associated with poorer language performance. Moreover, it looks as though the brain localisation of altered FC is indicative of the type of language impairment, at least distinguishing phonological, semantic, and morphosyntactic impairments in PPA (Ranasinghe et al., 2017). Finally, it is promising that FC network characteristics during a resting state can predict language functioning at a later time point, as shown for language recovery following stroke (Nicolo et al., 2015).

Methodological variation

In order to provide a concise overview of the literature, we narrowed down previous findings to general FC terms, instead of providing all the methodological details. The various methodological approaches, for example regarding the recording technique, the FC measure, and the network measures (summarised into local and global FC, whether or not derived from graph theory) make the studies difficult to compare and may explain variation in the findings.

With regard to the different recording techniques, EEG has limited spatial resolution, in contrast to MEG. Therefore, an in-depth analysis of FC within a specific (tumour) area (cf. Guggisberg et al., 2008; Tarapore et al., 2012) is not possible with standard, 23-electrode EEG, whereas analysis of whole-brain FC networks is feasible (Van Diessen et al., 2015). Out of the two, EEG is widely available, less expensive and best suited for potential future implementation in standard clinical protocol. So far, there is not enough evidence that evaluating FC brain networks in resting-state EEG/MEG have significant (prognostic) value for language functioning in brain tumour patients, as only a few studies have addressed this. However, fMRI studies indicate that resting-state FC network characteristics in epilepsy patients may be used for preoperative language mapping (Doucet, Pustina, et al., 2015; Tanaka & Stufflebeam, 2016) and for predicting postoperative language outcome (Doucet,

Rider, et al., 2015). It remains unclear whether this also applies to FC network characteristics in EEG/MEG.

A complicating factor in FC network analysis is that the design often comes with multiple comparisons, comprising many frequency bands, multiple brain regions, and different behavioural tests or domains. Therefore, taking statistical precautions are important, but not always executed. Furthermore, FC network analysis is often performed in small patient groups, restricting statistical power. The combination of small sample sizes and heterogeneous disease and treatment characteristics may also explain why the effect of tumour characteristics on FC networks is not entirely clear (section 2).

In this review, only studies on FC brain networks during a resting state were discussed, even though there is quite some literature on FC brain networks during (language) task performance. The latter may be most relevant for language functioning, however, investigation of a resting state has several advantages. For example, it does not require complex paradigms or accurate task performance. Therefore, registration of resting-state brain activity is less demanding and less time consuming, especially for brain tumour patients with language problems, as opposed to registration of task-related brain activity. Also, brain activity during rest is often recorded for clinical purposes in patients with suspected brain function abnormalities and/or epileptic seizures (only applicable to EEG). This potentially makes resting-state FC network analysis relatively easy to implement in clinical procedures, unlike FC network analysis based on task-related brain activity.

Conclusions and future directions

To date, little is known about the relation between FC network characteristics in resting-state EEG/MEG and language functioning in brain tumour patients. Previous literature, including studies in other patient populations, suggest that increased FC in lower frequency bands and decreased FC in higher frequency bands are related to poorer language functioning. FC network analysis during a resting state seems to be a promising method that contributes to knowledge on the underlying neural mechanisms of language impairments. There is a need for future research to investigate how resting-state FC network characteristics relate to different aspects of language functioning in brain tumour patients, and whether these characteristics predict language outcome after surgery. More insight into these topics can improve patient counselling and may aid in planning the surgical procedure.

Chapter 4

Slow-wave EEG activity and language
functioning in glioma patients

A proof-of-principle study

Abstract

Introduction

Patients with a glioma in eloquent brain areas frequently suffer from language problems, before and after surgery. How these difficulties relate to their functional brain organisation can be studied with electroencephalography (EEG). Gliomas cause increased brain activity in lower frequency bands (0.5-8 Hz; slow-wave activity), which is correlated with cognitive dysfunction. However, relationship of this activity to language has not been investigated yet. In this retrospective proof-of-principle study, we examined whether the paradigm we developed for relating slow-wave activity to language functioning in glioma patients is feasible.

Method

Twenty-one presumed low-grade glioma patients, who underwent surgery, were included. Language and EEG data of these patients were available, obtained within 1 year preoperatively or postoperatively. Mean composite language z-scores were calculated, consisting of scores on tests for object naming, verbal fluency, comprehension, repetition, reading and/or writing. EEG recordings were analysed visually by categorising slow-wave activity and quantitatively by calculating relative slow-wave power during wakeful, resting conditions.

Results

Visual EEG analysis showed that patients with moderate/severe slow-wave activity had lower language scores than patients with normal/mild slow-wave activity. Quantitative EEG analysis revealed a significant negative correlation between slow-wave power and language scores.

Discussion

We demonstrate that the paradigm is suitable for the current project: slow-wave activity in resting-state EEG is related to language functioning in glioma patients. Limited slow-wave activity is associated with better language performance and increased slow-wave activity is associated with poorer language performance.

Introduction

Gliomas in eloquent brain areas can cause language deficits that impact everyday communication. This is evidenced by deficits in spontaneous speech, as well as impaired performance on tests assessing speech production, comprehension, reading, and writing (Satoer et al., 2016). Knowledge of the structural and functional organisation of the brain areas responsible for the different aspects of language, identified with non-invasive techniques, is of great importance when deciding to operate on a patient. The gold standard treatment for presumed low-grade gliomas in eloquent areas is an awake surgery procedure with direct electrical stimulation. Despite intensive language monitoring, about half of the patients suffer from language impairments after surgery (Santini et al., 2012). Several factors are associated with language functioning and the risk of postoperative language deficits, such as tumour location, language-positive sites within the tumour (Ilmberger et al., 2008), preoperative neural plasticity due to the nature of a slow growing tumour, and the peri- and postoperative adaptation to surgery (Duffau, 2014).

Electroencephalography (EEG) is a non-invasive technique which can be used to study brain activity. This method is relatively inexpensive and commonly used in clinical practice. It is as of yet unclear whether brain activity, specifically slow-wave activity, in the low-grade glioma patient population is associated with the perceived language deficits. Slow-wave activity refers to focal brain activity in the delta and theta range (0.5-8 Hz). Patients with a brain lesion frequently exhibit enhanced slow-wave activity during a wakeful resting state (Lüders & Noachtar, 2000). This is assumed to be a marker of brain dysfunction, generated by injured brain tissue around the lesion (Chu et al., 2015; De Jongh et al., 2003; Oshino et al., 2007). Increased slow-wave activity is associated with poorer cognitive functions in low-grade glioma patients (working memory, information processing, and executive functioning; Bosma, Stam, et al., 2008), and with the degree of language impairment in stroke patients (Chapman et al., 1989; Finitzo et al., 1991; Hensel et al., 2004).

For the current proof-of-principle study, we combined this information to investigate whether the paradigm we aim to develop for relating slow-wave EEG activity to language functioning in (presumed) low-grade glioma patients is feasible.

Method

Retrospective patient inclusion

Patient files (2004-2015) at the University Medical Centre Groningen (UMCG) and the Erasmus MC University Medical Centre Rotterdam (Erasmus MC) in the Netherlands were reviewed to search for patients who met the following inclusion criteria: (1) surgery for a glioma in or near eloquent brain areas; (2) radiologically 'presumed' low-grade glioma without contrast enhancement on MRI; (3) available language and EEG data: obtained within 1 year, either before or after surgery. Exclusion criteria were: (1) (history of) other neurological,

medical or psychiatric conditions known to affect language or cognition; (2) severe visual disorder or deafness; (3) mental retardation; (4) (history of) substance abuse.

The study was approved by the institutional ethical review board of the Erasmus MC, which was also applicable to the UMCG. No informed consent from the patients was required due to the retrospective nature of the study, and because asking permission could be a burden for patients and/or (surviving) relatives.

Language assessment

Patients were assessed by an experienced clinical linguist with the following standardised tests: the Boston Naming Test (Kaplan, Goodglass, & Weintraub, 2001), category fluency (producing words of a given category within 1 minute; Luteijn & Barelids, 2004), letter fluency (idem, but words starting with a given letter; Schmand, Groenink, & Van den Dungen, 2008), and subtests of the Aachen Aphasia Test (AAT; Dutch version; Graetz, De Bleser, & Willmes, 1992): the Token Test (executing tasks with geometric forms on verbal commands), repetition, reading aloud, and writing to dictation. Raw test scores were converted to z-scores, taking into account published normative data from a healthy control population. As not all patients completed all tests, a 'mean composite language score' was computed, consisting of the average z-score of the available language tests for each patient.

EEG

Clinical EEGs were recorded with 44-channel Schwarzer amplifiers (Natus Europe GmbH, Munich), placing 21 scalp electrodes according to the international 10-20 system. EEG analysis of slow-wave activity was performed visually, the gold standard in clinical evaluation, and quantitatively.

Visual EEG analysis was performed in BrainRT software (v.2.0; Rumst, Belgium, 2013) by one of the authors (PJC), a board-certified Clinical Neurophysiologist, who was blinded to the patients' medical records. The presence and characteristics of activity in the delta (0.5-4 Hz), theta (4-8 Hz), and alpha (8-12 Hz) frequency bands were determined with EEG data reformatted to display standard antero-posterior bipolar montage and common average montages. Subsequently, slow-wave activity was classified according to the Mayo Classification System (Mayo Clinic and Mayo Foundation, 1998), complemented by guidelines of Lüders and Noachtar (2000). From this, four categories were created: normal, mild, moderate, and severe slow-wave activity. See table 4.1 for their definitions. For analysis purposes, ensuring enough data for group comparisons, the categories 'normal' and 'mild' were grouped together, as well as the categories 'moderate' and 'severe'.

Quantitative EEG analysis was performed in BrainVision Analyzer 2.0 (Brain Products GmbH, 2013) on eyes-closed, artefact-free EEG during wakeful resting conditions. Twenty 2-second epochs for each patient were selected by visual inspection (IB). Raw EEG data were resampled to 256 Hz and re-referenced to a new averaged reference consisting of 15 scalp electrodes: F3; F4; F7; F8; T3; T4; T5; T6; C3; C4; P3; P4; Pz; O1; and O2 (excluding: Fz and Cz because they were used as reference electrodes; Fp1 and Fp2 because they generally contain eye-blink artefacts and muscle activity). Subsequently, the data were filtered (band-

pass: 0.27-30 Hz, slope 24 dB/Oct; notch: 50 Hz, slope 24 dB/Oct). For every patient, spectral analysis was performed on the 20 epochs of 512 points by a Fast Fourier Transform (FFT) for all 15 electrodes. After averaging the 20 FFTs, relative slow-wave power was calculated by dividing the absolute power in the delta and theta range (0.5-8 Hz) by the absolute power in the total spectrum (0.5-70 Hz). Lastly, relative slow-wave power was averaged over the 15 electrodes.

Table 4.1. Classification of slow-wave activity in EEG by visual analysis

Degrees of slow-wave activity	Category from the Mayo Classification System ^a	Interpretation ^b
<u>Normal</u>		No abnormal slow-wave activity
<u>Mild</u>	- Dysrhythmia grade I - Dysrhythmia grade II	Intermittent nonspecific theta or delta slowing < 50% of the recording: focal, bilateral, or diffuse with amplitudes < 60 μ V
<u>Moderate</u>	- Dysrhythmia grade III - Delta grade I	Intermittent nonspecific theta or delta slowing > 50% of the recording: focal, bilateral, or diffuse with amplitudes > 60 μ V ^c Persistent polymorphic (irregular) delta slowing: focal, bilateral or diffuse with amplitudes < 30 μ V
<u>Severe</u>	- Delta grade II - Delta grade III	Persistent polymorphic (irregular) delta slowing: focal, bilateral or diffuse with amplitudes > 30 μ V

Note. Persistent asymmetry in amplitude or frequency of >50% between the hemispheres was also scored, but not included in the analysis.

^a Mayo Clinic and Mayo Foundation (1998).

^b Complemented by guidelines of Lüders and Noachtar (2000).

^c Dysrhythmia grade III can also refer to specific epileptiform activity (spikes, sharp waves and spike-waves as well as recorded ictal patterns). Even though this was scored during visual interpretation of EEG, it was not included for data analysis.

Statistical analysis

In IBM SPSS Statistics software (version 23, release 23.0.0.0), a one-sample *t* test was used to compare patients' mean composite language scores to normative data (*M* = 0.00). Possible effects of tumour and treatment-related factors on language performance, and later on slow-wave activity, were examined with independent-samples Mann-Whitney U tests. Language performance of the two groups from visual EEG analysis (normal/mild slow-wave activity and moderate/severe slow-wave activity) were compared to: (1) a healthy population with one-sample Wilcoxon Signed-rank tests; (2) each other by means of an independent-samples Mann-Whitney U test. Slow-wave power from quantitative EEG analysis was correlated with language performance by a Spearman's rho correlation test.

Results

Patient characteristics

Twenty-one glioma patients were included (13 female; mean age = 39 years), of which 12 with preoperative language and EEG data (preoperative patients) and 9 with postoperative language and EEG data (postoperative patients). No patient data were available of both pre- and postoperative EEG with language tests. Patient characteristics are shown in table 4.2.

Table 4.2. Demographic and clinical characteristics of the patient group (N = 21): number of patients (and percentage) or mean (and range)

Patients	
Female gender	13 (62%)
Mean age in years	39 (19-63)
Mean education ^a	5 (3-7)
Right-handed	19 (90%)
Preoperative patients	12 (57%)
Postoperative patients	9 (43%)
Mean time interval in months	
Language tests → surgery	1 (0-5)
EEG → surgery	5 (1-9)
Surgery → language tests	4 (0-12)
Surgery → EEG	1 (0-5)
Language tests ↔ EEG	5 (1-12)
Tumour location – left hemisphere	18 (86%)
Tumour location – lobe	
Frontal	6 (29%)
Fronto-temporal	3 (14%)
Temporal	5 (24%)
Temporo-insular	1 (5%)
Insular	2 (10%)
Temporo-parietal	1 (5%)
Parietal	2 (10%)
Temporo-occipital	1 (5%)
Tumour size	
≤ 5 cm	6 (29%)
> 5 cm	15 (71%)
Histology ^b	
Astrocytoma	7 (33%)
Anaplastic astrocytoma	1 (5%)
Oligodendroglioma	3 (14%)
Oligoastrocytoma	5 (24%)
Anaplastic oligodendroglioma	1 (5%)
Glioblastoma	4 (19%)

Table 4.2. Continued

Patients	
Grade	
Low-grade	15 (71%)
High-grade	6 (29%)
Diagnosis	
De novo	17 (81%)
Recurrent	4 (19%)
Use of anti-epileptic drugs	17 (81%)
Resection ^c	
≤ 90%	6 (67%)
> 90%	3 (33%)
Adjuvant therapy at the time of EEG ^c	
Radiotherapy	5 (56%)
Chemotherapy	3 (33%)

Note. Information on hemispheric language dominance (attested with fMRI) was not available in the majority of the patients.

^a Education was classified according to seven categories (1= incomplete primary education; 2= complete primary education; 3= primary education and < 2 years of low-level secondary education; 4= complete low-level secondary education; 5= complete average-level secondary education; 6= complete high-level secondary education; 7= complete university education; Verhage, 1964).

^b Based on the former 2007 WHO classification (Louis et al., 2007).

^c Only applicable to the postoperative patients.

Language performance

The patient group had a mean composite language z-score of -0.61 ($N = 21$, $SD = 0.70$), which was significantly lower than that of a healthy population ($t(20) = -4.04$, $p < 0.001$, $d = 0.71$). An overview of z-scores on each separate language test can be found in Appendix A. No effect of tumour and treatment-related factors on language performance was found with regard to tumour size, extent of resection, tumour grade, diagnosis (de novo versus recurrent), use of anti-epileptic drugs, and postoperative radiotherapy or chemotherapy ($p > 0.05$).⁵

Slow-wave activity

In the visual EEG analysis, 13 patients were classified as having normal/mild slow-wave activity and 8 patients had moderate/severe slow-wave activity. For quantitative EEG analysis, three patients had to be excluded due to the lack of sufficient artefact-free EEG segments. The remaining 18 patients had a mean (relative) slow-wave power of 0.61 ($SD = 0.24$). Patients with normal/mild slow-wave activity had a mean slow-wave power of 0.44 ($N = 10$, $SD = 0.17$) and patients with moderate/severe slow-wave activity had a mean slow-wave power of 0.83 ($N = 8$, $SD = 0.08$).

⁵ Tumour location was not investigated; all tumours were located in or near eloquent brain areas, expected to be involved in language and/or sensorimotor functioning.

Abnormal slow-wave activity was most pronounced in the affected hemisphere in all patients. Furthermore, there was no effect of tumour and treatment-related factors on the level of slow-wave power: tumour size, extent of resection, tumour grade, diagnosis (de novo versus recurrent), use of anti-epileptic drugs, and postoperative radiotherapy or chemotherapy ($p > 0.05$).

Associations between language performance and slow-wave activity

Visual EEG analysis

Compared to a healthy population, both patients with normal/mild slow-wave activity ($N = 13$, $Mdn = -0.38$) and patients with moderate/severe slow-wave activity ($N = 8$, $Mdn = -1.12$) had significantly lower mean composite language scores ($Z = 11$, $p = 0.016$ and $Z = 3$, $p = 0.036$, respectively). Patients with moderate/severe slow-wave activity had lower mean composite language scores than patients with normal/mild slow-wave activity (marginally significant; $U = 25$, $p = 0.053$, $d = 0.82$; see figure 4.1).

Quantitative EEG analysis

Mean composite language scores showed a significant negative correlation with slow-wave power ($r_s(16) = -.53$, $p = 0.025$).

Figure 4.1. Overall language performance according to visual EEG analysis: patients with normal/mild slow-wave activity (striped blue) and patients with moderate/severe slow-wave activity (aqua). Error bars represent standard errors.

* indicates a significantly lower score compared to a healthy population at the 0.05 level (2-tailed); † indicates a marginally significant difference between the groups.

Pre- and postoperative patients

With regard to language performance, mean composite language scores of preoperative patients ($N = 12$) did not differ significantly from a healthy population ($t(11) = -2.02, p = 0.068, d = 0.44$), but postoperative patients ($N = 9$) had significantly lower scores than a healthy population ($t(8) = -4.20, p = 0.003, d = 1.10$). No significant relations between slow-wave activity and language performance were found in pre- and postoperative patients as separate groups.

Discussion

This proof-of-principle study focused on the relation between slow-wave brain activity and language functioning in glioma patients. The results show that this principle is feasible: limited slow-wave activity in resting-state EEG is related to better language performance, and more pronounced slow-wave activity is related to poorer language performance. This applies to the overall language performance in presumed low-grade glioma patients, irrespective of the timing of the assessments (language and EEG recording before or after surgery). When examining the group more closely by separating pre- and postoperative patients, no relations between slow-wave activity and language performance are found, presumably due to small sample sizes.

These findings are in accordance with Bosma, Stam, et al. (2008), who showed that increased slow-wave activity correlates with poorer working memory, information processing, and executive functioning in (pre- and postoperative) low-grade glioma patients. With regard to language, a similar relation with slow-wave activity has previously been found in patients with traumatic brain injury (Thatcher et al., 1998), Alzheimer's disease (Helkala et al., 1991; Van der Hiele et al., 2007), Parkinson's disease (non-demented stage; Olde Dubbelink et al., 2013), and post-stroke aphasia (Hensel et al., 2004). Hensel et al. (2004) demonstrated that a decrease of left-hemispheric slow-wave activity coincides with language recovery during the first year post-stroke.

Language performance

Presumed low-grade glioma patients have poorer language performance than a healthy control group, but this does not hold for preoperative patients only. Previous findings by Papagno et al. (2011) and Santini et al. (2012) confirm that language impairments in glioma patients are less prevalent preoperatively than postoperatively. The lower incidence and the relatively mild character of preoperative language impairments in low-grade glioma patients can (partly) be explained by the slow tumour growth rate, which allows for the reorganisation of functions (Desmurget et al., 2007).

However, the present findings on language performance must be interpreted cautiously because the currently used tests do not provide a comprehensive language profile. Not all language skills were assessed (e.g., no test for sentence processing was included) and there was no measurement of language use in daily life (e.g. spontaneous speech). Furthermore, it is questionable whether the AAT subtests are sufficiently sensitive to detect the mild language deficits in this patient group (Satoer et al., 2014 and see Appendix A).

Tumour and treatment-related factors did not influence language performance in our sample. Previous studies have reported that high-grade tumours, large tumour volume, and tumour location in frontotemporal areas and/or involving subcortical white matter tracts are associated with poor language functioning, whereas other studies report no effects of these factors (Satoer et al., 2016). Moreover, anti-epileptic drugs and postoperative radio- and chemotherapy have been reported to negatively affect language and cognition (McAleer & Brown, 2015).

Slow-wave activity

Slow-wave activity was, as expected, maximally pronounced over the region corresponding to the tumour location. This has been demonstrated before (Baayen et al., 2003; De Jongh et al., 2003; Oshino et al., 2007) and can be explained by its origin in brain tissue adjacent to the tumour and surrounding oedematous areas (Fernández-Bouzas et al., 1999; Oshino et al., 2007). We did not find effects of other tumour or treatment-related factors on (the amount of) slow-wave activity, in contrast to De Jongh et al. (2003) who report that larger tumour volume and higher tumour grade are associated with higher slow-wave power. However, our patient selection is slightly biased because only presumed low-grade glioma patients who had an EEG recording on clinical indications were included.

For the analysis of slow-wave activity, we used relative instead of absolute slow-wave power because the former is less sensitive to effects of different recording systems (as EEG was recorded at different centres). A disadvantage, however, is that relative slow-wave power can be influenced by deviations in other, higher frequency bands. Moreover, previous studies that investigated slow-wave activity in brain tumour patients used a different technique: magnetoencephalography (MEG). Apart from high temporal resolution as in EEG, MEG enables detailed examination of the spatial distribution of brain oscillations, without distortion by skull and scalp. Downsides of MEG are its susceptibility to metal artefacts (e.g. dental implants), high cost and limited availability. Therefore, MEG is better suited for scientific research, whereas EEG is more appropriate for application in clinical context.

Associations between language performance and slow-wave activity

The current findings indicate that increased slow-wave activity relates to poorer overall language performance in glioma patients. This link contributes to knowledge of the underlying mechanisms of language problems in this patient group. High levels of slow-wave activity are assumed to arise from cortical deafferentation due to subcortical injury (Gloor et al., 1977). It is known that intact subcortical structures are crucial for the preservation of language in awake glioma surgery (Trinh et al., 2013). Hence, when language deficits are present, slow-wave activity may be postulated to be the intermediate between injured, subcortical brain tissue (by the tumour and its treatment) and apparent language problems, as suggested by Bosma, Stam, et al. (2008) for cognitive dysfunction.

A closer examination of cognitive functioning in their study (Bosma, Stam, et al., 2008) demonstrates that poor performance in working memory, information processing and executive functioning is associated with increased slow-wave activity. However, it has been

suggested that these cognitive domains make use of language skills (Baldo et al., 2005; Emerson & Miyake, 2003; Whiteside et al., 2016). As a glioma can affect cognitive functioning either directly, or indirectly via an underlying mechanism, we cannot exclude the possibility that the previously found relations between slow-wave activity and cognitive functions are caused by an underlying language deficit. In any case, it is essential to distinguish cause and effect in language and cognitive functioning, not only from a theoretical perspective, but also with regard to therapeutic intervention.

Conclusion

We demonstrated that our paradigm of relating slow-wave activity in resting-state EEG to language functioning in glioma patients is suitable: slow-wave activity is inversely related to language performance in a group of glioma patients who were assessed before or after surgery. This retrospective proof-of-principle study is the starting point for our prospective research, which is described in the next chapters. Recommendations from the current study have been taken into account in setting up our design to further investigate slow-wave activity and language functioning in brain tumour patients.

PART II

Results from the PLOTS study

Predicting Language Outcome after brain Tumour Surgery

Chapter 5

Extensive language evaluation in low-grade glioma patients undergoing awake surgery

Abstract

Introduction

Many patients with a glioma involving eloquent brain areas develop language impairments, but relatively little is known about how different language modalities and linguistic levels are affected, specifically in low-grade glioma patients. Our objective is to gain more insight into language functioning in these patients by using a comprehensive linguistic test protocol.

Method

Fifteen patients underwent awake surgery for a low-grade glioma in the language-dominant hemisphere. Language functioning was assessed before surgery (T1), 2 months after surgery (T2), and 1 year after surgery (T3). Standardised language tests were conducted, assessing the domains: word retrieval, phonology, semantics, and morphosyntax for speech production; comprehension of auditory and visual input; reading; and writing. Additionally, self-reported language problems were evaluated.

Results

Before surgery, the patient group had poorer performance than a healthy population for: word retrieval, phonology, semantics, and morphosyntax (trend) in speech production; comprehension of auditory input; and writing. Auditory comprehension improved after surgery. At the individual level, 9/15 (T1), 10/15 (T2), and 10/13 (T3) patients had language impairments. Self-reported language problems were present in 8/15 (T1), 10/15 (T2), and 8/13 (T3) patients. These complaints corresponded to the test results only at T1.

Discussion

Low-grade gliomas in the language-dominant hemisphere cause language impairments in almost all domains. Impairments may persist 1 year after surgery, but there is large inter-patient variation. This demonstrates the importance of extensive language testing before and after awake glioma surgery. Moreover, a thorough preoperative language assessment is essential for selecting the most suitable intraoperative tests in order to limit language impairment and preserve patients' quality of life.

Introduction

Gliomas are the most frequently occurring primary brain tumours with approximately 1000 new diagnoses a year in The Netherlands, of which 20% are low-grade (World Health Organisation [WHO] grade II; Ho et al., 2014; Louis et al., 2016). Low-grade gliomas grow relatively slowly, but typically infiltrate neural tissue important for sensorimotor and language functions. Patients with a low-grade glioma in these 'eloquent areas' usually undergo awake brain tumour surgery with continuous monitoring of sensorimotor and language abilities, to avoid removal of functional tissue while aiming for maximal tumour resection. Low-grade gliomas affect relatively young individuals, and their life expectancy after surgery generally exceeds 5 years (Louis et al., 2007). For this reason, preservation of quality of life is one of the main outcome measures after awake glioma surgery.

Low-grade gliomas in or near eloquent brain areas can cause language impairments, which negatively affect quality of life due to their impact on everyday communication (Hilari et al., 2012; Worrall & Holland, 2003). A systematic review by Van Kessel, Baumfalk, Van Zandvoort, Robe, and Snijders (2017) reports impaired language performance in preoperative glioma patients at the group level, and at the individual level in approximately 25% of the patients. When comparing abilities before surgery to those 3-6 months after surgery, language functioning in glioma patients may not change or may decline, as systematically reviewed by Satoer, Visch-Brink, Dirven, and Vincent (2016).

However, in the majority of previous studies, the patient group comprised both low-grade and high-grade glioma patients, where high-grade glioma patients seem to have poorer language functioning than low-grade glioma patients (Campanella et al., 2009; Noll et al., 2015). Apart from that, the assessments used may not have been optimal for detecting (mild) language impairments in low-grade glioma patients, for several reasons. First, assessments often examined only a few language abilities, whereas different language modalities (speech production, comprehension, reading, and writing) and linguistic levels (e.g. phonology, concerning speech sounds; semantics, concerning meaning; and morphosyntax, concerning word and sentence structure) can be impaired. Second, some of the classical language tests used may not be sufficiently sensitive to detect mild impairments because they have been designed to assess stroke-related language impairments, which are generally more severe than tumour-related language impairments (Anderson, Damasio, & Tranel, 1990). Third, many assessments did not include self-reported information, even though it is essential to evaluate whether patients experience language problems.

Recently, two Swedish research groups investigated language functioning extensively in presumed low-grade glioma patients, by using test batteries that were designed to detect subtle language impairments (Antonsson, Jakola, et al., 2018; Antonsson, Longoni, et al., 2018; Norrelgen et al., 2020). Before surgery, Antonsson, Longoni, et al. (2018) found impaired group-level performance for object naming and category fluency in patients with tumour locations in left language areas, left non-language areas, and right non-language areas. A few patients experienced language problems and only minor language impairments were identified by the assessment. Three months after surgery, category fluency performance worsened compared to the preoperative level (Antonsson, Jakola, et al., 2018). Furthermore,

Norrelgen et al. (2020) found no change in overall language performance 3 months and 1 year after awake surgery in left language areas, however, category fluency declined in the long-term after surgery. At the individual level, 13% (3 months) and 9% (1 year) of the patients had declined language functioning after surgery. Overall, these studies indicate mildly impaired language functioning in pre- and postoperative low-grade glioma patients.

Our goal is to gain more insight into the wide range of language abilities in Dutch-speaking low-grade glioma patients undergoing awake surgery. Accordingly, a thorough test battery specifically designed for detecting mild impairments is used to systematically assess language domains (created by combining language modalities and linguistic levels) before surgery, 2 months after surgery, and 1 year after surgery. We investigate: (1) whether glioma patients have impaired language abilities before surgery, and if so, which domains are affected; (2) whether their language abilities change in the short and long-term after surgery; (3) whether self-reported language problems correspond to language impairments as revealed by tests; and (4) whether tumour and treatment characteristics are associated with language performance before surgery and language change after surgery.

Method

Patients

Newly-diagnosed patients with a presumed low-grade glioma, who were planned to undergo awake surgery at the University Medical Centre Groningen (UMCG) or the Erasmus MC University Medical Centre Rotterdam (Erasmus MC), were invited to participate in the study. Inclusion criteria were: tumour location in the language-dominant hemisphere⁶ (if language lateralisation was unknown: right-handed patients with left-sided tumour); aged between 18 and 75; in case of epilepsy, seizures under control with anticonvulsants. Exclusion criteria were: non-native speaker of Dutch; history of a medical, neurological or psychiatric condition known to affect language or cognitive functioning; history of substance abuse; consistent use of dexamethasone preoperatively; previous brain surgery or cranial radiation therapy.

Tumour localisation and tumour size were determined by a neuroradiologist. For tumour size, the maximum diameters were measured in three directions, two in the axial plane and one in the sagittal plane, using T1 and T2-weighted images from MRI scans. Subsequently, tumour volume was estimated using the standard formula for an ellipsoid: the product of the three maximum diameters, divided by 2 (Sorensen et al., 2001). All patients underwent tumour resection with an awake procedure, during which language and sensorimotor functions were monitored according to local protocol.

No control group was included because pre-existing normative data from healthy individuals were used. This multicentre study was approved by the medical, ethical review board of the UMCG, which was also applicable to the Erasmus MC. All patients gave written informed consent.

6 Bilateral language activation in functional magnetic resonance imaging (fMRI) was also permitted for inclusion.

Procedure

The study had a longitudinal design, in which patients underwent an extensive language assessment at three time points: **T1** = before surgery (mean 33 days, range 6-83); **T2** = 2 months after surgery (mean 1.83, range 1.18-2.89); and **T3** = 12 months after surgery (mean 12.61, range 11.05-15.22). The language assessment was administered by a clinical linguist in the outpatient clinic at one of the participating medical centres. The total assessment took up to a maximum of 1.5 hours and breaks were taken when desired.

Language assessment

The assessment included administration of the Edinburgh Handedness Inventory (Oldfield, 1971) and a selection of standardised language tests: object naming (De Witte et al., 2015), action naming in sentence context (Rofes, 2012), the shortened Token Test (De Renzi & Faglioni, 1978), category fluency (Luteijn & Barelds, 2004), letter fluency (Schmand et al., 2008), reading and writing (Van Ierschoot, 2018), and subtests of the Diagnostic Instrument for Mild Aphasia (DIMA; Satoer et al., 2019): repetition, semantic odd-picture-out, sentence completion, and sentence judgement. The tests examine a wide range of linguistic abilities. They are presented in table 5.1, together with task descriptions of each test.

Furthermore, a short interview was held on current language complaints (if applicable). Additional information on self-reported language problems was obtained by conducting a questionnaire from the European Organisation for Research and Treatment of Cancer (EORTC) on quality of life: the brain module EORTC QLQ-BN20 (Osoba et al., 1996). This includes four questions on language functioning, namely, asking patients whether they have difficulty with: reading; finding the right words to express themselves; speaking; and communicating their thoughts. Answers were given on a 4-point scale from 'not at all' to 'very much'.

Data processing

Raw scores on the language tests were normalised by conversion to z-scores, using pre-existing normative data from a healthy population. Subsequently, eight language domains were created for the purpose of this study, as shown in table 5.2. This was done for two reasons: (1) to reduce the number of statistical comparisons; and (2) to examine all language modalities (speech production, comprehension, reading, and writing), three linguistic levels (phonology, semantics, and morphosyntax), and comprehension of two types of input (auditory and visual). A domain score equalled the average z-score of the tests in that domain for each patient.

For the evaluation of language performance of individual patients, a domain z-score ≤ -1.5 indicated an impairment. For each patient, the number of impaired domains before surgery was compared to the number of impaired domains after surgery. Patients were classified as 'improved' when this number decreased, 'worsened' when this number increased, and 'unchanged' when this number remained the same after surgery.

Information on experienced language problems was obtained from an interview and complemented by the language-related questions from the questionnaire. Categories of self-reported language problems were formed based on the patients' responses: word finding, speaking (producing words, formulating sentences, expressing thoughts), keeping up with conversations, articulation, comprehension, reading, and writing/typing.

Table 5.1. Overview of tests used in the language assessments

Tests	Linguistic abilities	Task description	Example
Object naming ^a (De Witte et al., 2015)	Word retrieval (nouns)	Naming objects depicted on black-and-white drawings with the introduction <i>This is...</i> (time limit: 4 sec.)	Dit is... <i>een emmer</i> (This is... <i>a bucket</i>)
Action naming in sentence context (Rofes, 2012)	Word retrieval (verbs) and morphology: 3rd person singular	Naming and inflecting verbs depicted on black-and-white drawings with the introduction <i>The (wo) man...</i> (time limit: 4 sec.)	De man... <i>rent</i> (The man... <i>runs</i>)
Token Test (De Renzi & Faglioni, 1978)	Auditory sentence comprehension	Executing tasks with geometric forms on verbal commands (shortened version)	Raak de grote witte cirkelen en het kleine groene vierkant aan. (Touch the large white circle and the small green square)
Category fluency (Luteijn & Barends, 2004)	Flexibility of lexical access by semantic searching	Producing words of a given category (animals; professions) within 60 sec.	
Letter fluency ^b (Schmand et al., 2008)	Flexibility of lexical access by phonological searching	Producing words starting with a given letter within 60 sec.	
Reading ^b (Van Ierschoot, 2018)	Reading	Reading sentences aloud ^c	De kinderen kunnen goed met elkaar overweg. (The children get along well with each other.)
Writing ^b (Van Ierschoot, 2018)	Writing	Writing sentences to dictation ^c	Mies kocht een lap stof op de markt. (Mies bought a piece of fabric at the market.)
Subtests of the Diagnostic Instrument for Mild Aphasia (DIMA; Satoer et al., 2019):			
- Repetition	Phonological ability	Repetition of 3-syllabic words, compound words, non-words, and sentences	De man zoekt zijn zomerjas zonder succes. (The man searches for his summer jacket without success)
- Semantic odd-picture-out	Semantic ability and word retrieval	Out of 3 black-and-white drawings, naming the noun or verb that semantically does not fit 2 other items (time limit: 4 sec.)	Pictures of 'borstel, hond, kat' (brush, dog, cat) → answer: borstel (brush)
- Sentence completion	Syntactic ability	Sentence completion	Iedere dag ... (Every day ...)
- Sentence judgement ^d	Differentiating phonological, semantic and syntactic violations from correct sentences	Correctness judgement of visually presented sentences with phonological violations, semantic violations, syntactic violations, or without violations	De gieter smeert een boterham. (The watering-can prepares a sandwich.) → incorrect; meaning not possible (semantic violation)

Note. For all tests, the normative data used was based on a healthy, Dutch population matched for age and education.

^aWhen this object naming test could not be administered (e.g. because of the 4 sec. time constraint), the Boston Naming Test (Kaplan et al., 2001) was used instead.

^bA parallel version of this test was used at T2. (The other tests only had one version available.)

^cOnly the sentence subtask because it has been shown to be the most sensitive subtask of the test (Van Ierschoot, 2018).

^dAccuracy scores; the sentence judgement test also includes the measurement of reaction times but these were not taken into account in this study.

Table 5.2. Language domains under investigation with their corresponding tests

Domains	Tests
1. Production-Word retrieval	Object naming
2. Production-Phonology	Repetition Letter fluency
3. Production-Semantics	Semantic odd-picture-out Category fluency
4. Production-Morphosyntax	Sentence completion Action naming in sentence context
5. Comprehension-Auditory input	Token Test
6. Comprehension-Visual input	Sentence judgement (accuracy)
7. Reading	Reading
8. Writing	Writing

Note. Although some language tests could assess more than one domain (e.g. action naming in morphosyntax and word retrieval), every test is classified in one domain only in order to minimise statistical dependencies between domains.

Statistical analysis

Patients' domain z-scores at T1 were compared to pre-existing normative data from a healthy population ($M = 0$) by one-sample Wilcoxon signed-rank tests. This was analysed one-sided, in order to test the hypothesis that glioma patients perform poorer than a healthy population. Subsequently, paired Wilcoxon signed-rank tests were used to investigate within-subject changes in domain scores over time, comparing T1-T2 (short-term effects), T2-T3 (recovery effects), and T1-T3 (long-term effects). Associations between self-reported language problems (present or absent) and a language impairment according to test results (present or absent) were examined with Fisher's exact tests for T1, T2, and T3. Fisher's exact tests were also used to investigate binary tumour and treatment-related variables (localisation-hemisphere, localisation-lobes, histology, volume, use of anti-epileptic drugs, extent of resection, chemo and/or radiotherapy) in relation to presence of a language impairment at T1 (yes or no), and to language change from T1 to T3 (improved/unchanged or worsened). All analyses were performed using IBM SPSS Statistics software (version 23, release 23.0.0.0).

Results

Demographic and clinical characteristics

Fifteen patients with a glioma in the language-dominant hemisphere (or with bilateral language representation) participated in the study. All gliomas were classified as WHO grade II (Louis et al., 2016). Demographic and clinical characteristics are shown in table 5.3. At the time of inclusion, gliomas were untreated and detected by epileptic seizures ($N = 13$) or incidentally ($N = 2$). When invited for T3, two patients declined further participation in the study due to severe side effects of adjuvant treatment.

Table 5.3. Demographic and clinical characteristics of the glioma patients: number of patients (and percentage) or mean (and range)

	Patients (N = 15)
Gender – female	5 (33%)
Mean age in years (range)	42.0 (22-60)
Mean education level ^a (range)	5.3 (4-7)
Handedness ^b	
Right	10 (67%)
Left	4 (27%)
Ambidextrous	1 (7%)
Mean ‘diagnosis → surgery’ in months (range)	20.8 (1.1-167.3)
Tumour histology ^c	
Diffuse astrocytoma	5 (33%)
Oligodendroglioma	10 (67%)
Tumour localisation, hemisphere	
Left	13 (87%)
Right	2 (13%)
Tumour localisation, lobes	
Frontal	5 (33%)
Fronto-temporal	1 (7%)
Fronto-parietal	1 (7%)
Temporal	1 (7%)
Temporo-insular	3 (20%)
Parietal	3 (20%)
Parieto-temporal	1 (7%)
Mean tumour volume before surgery in cm ³ (range)	51.0 (10.5-143.1)
Mean tumour volume after surgery in cm ³ (range)	11.4 (0.0-59.6)
Extent of resection ^d	
Partial: 20-89%	7 (47%)
Subtotal: 90-99%	6 (40%)
Total: 100%	2 (13%)
Use of anti-epileptic drugs at T1	13 (87%)
Use of anti-epileptic drugs at T3	12 (92%)
Postoperative treatment (ongoing or completed at T3; N = 13)	
None	3 (23%)
Radiotherapy only	1 (8%)
Chemotherapy only	1 (8%)
Both	8 (62%)

Note. Some variables add up to 101% due to rounding. T1 = before surgery; T3 = 1 year after surgery.

^a Education level was classified according to seven categories (1= incomplete primary education; 2= complete primary education; 3= primary education and < 2 years of low-level secondary education; 4= complete low-level secondary education; 5= complete average-level secondary education; 6= complete high-level secondary education; 7= complete university education; Verhage, 1964).

^b Handedness was assessed by the Edinburgh Handedness Inventory (Oldfield, 1971).

^c Based on the 2016 WHO (World Health Organisation) classification (Louis et al., 2016).

^d Extent of resection was determined by a neuroradiologist, based on pre- and postoperative tumour volumes.

Language performance before surgery (group level)

Figure 5.1 shows the language domain scores of the patient group at T1, and table 5.4 presents the corresponding comparisons to a healthy population. Glioma patients scored significantly lower than healthy individuals on domains of Production-Word retrieval, Production-Phonology, Production-Semantics, Comprehension-Auditory input, and Writing. A trend was found for Production-Morphosyntax ($p = 0.063$), indicating poorer scores in patients. For Reading, patients scored higher than a healthy population, as all but one patient made no errors on this test.

Figure 5.1. Language domain z-scores of glioma patients at T1. The horizontal line at 0 represents the average performance of a healthy population. Every box contains 50% of the data (interquartile range), including the median (thick black line), and the vertically extending lines (whiskers) represent the upper and lower quartiles of the data. 'O' indicates an outlier between 1.5-3 times the interquartile range, and '*' indicates an outlier > 3 times the interquartile range.

Abbreviations: P-WR = Production-Word retrieval; P-Phon = Production-Phonology; P-Sem = Production-Semantics; P-Mor = Production-Morphosyntax; C-Aud = Comprehension-Auditory input; C-Vis = Comprehension-Visual input; Read = Reading; Writ = Writing

Table 5.4. Language domain scores of glioma patients at T1 compared to a healthy population

Language domain	N	Mdn z-score	Comparisons to a healthy population		
			Z	p	r
Production-Word retrieval	15	-1.64	-1.99	0.023	<u>0.51</u>
Production-Phonology	15	-0.20	-2.27	0.012	<u>0.59</u>
Production-Semantics	15	-0.60	-1.87	0.031	0.48
Production-Morphosyntax	15	-0.25	-1.53	0.063	0.40
Comprehension-Auditory input	15	-0.69	-1.77	0.039	0.46
Comprehension-Visual input	13	0.19	0.32	0.376	0.09
Reading	14	0.28	2.67	0.004	<u>0.71</u>
Writing	13	-0.79	-2.16	0.016	<u>0.60</u>

Note. N = sample size; Mdn z-score = median z-score; Z = standardised test statistic of the one-sample Wilcoxon signed rank tests; p = p-value (one-sided); r = effect size ($r = Z/\sqrt{N}$). Significant effects ($p < 0.05$) are presented in bold font and large effect sizes (≥ 0.50 ; Cohen, 1992) are underlined.

Scores on the separate language tests can be found in Appendix B1.

Language change after surgery (group level)

T1→T2: Domain scores of Comprehension-Auditory input increased significantly ($N = 15$, $Mdn_{T1} = -0.69$, $Mdn_{T2} = 0.32$, $Z = -2.30$, $p = 0.022$, $r = 0.59$).

T2→T3: No significant changes in language domain scores were found. Large effect sizes, but with differences that were only marginally significant, were found for: Production-Morphosyntax ($N = 13$, $Mdn_{T2} = -0.20$, $Mdn_{T3} = -0.59$, $Z = -1.85$, $p = 0.064$, $r = 0.51$), indicating a decrease in scores; and Comprehension-Visual input ($N = 11$, $Mdn_{T2} = 0.19$, $Mdn_{T3} = 0.51$, $Z = -1.69$, $p = 0.091$, $r = 0.51$), indicating an increase in scores.

T1→T3: Domain scores of Comprehension-Auditory input increased significantly ($N = 13$, $Mdn_{T1} = -0.69$, $Mdn_{T3} = -0.18$, $Z = -2.07$, $p = 0.038$, $r = 0.57$).

Appendix B1 presents the language domain scores at each time point. Not all of these data points could be used for the within-subject comparisons described above because of missing data at one or both test moments.

Language impairments (individual level)

An overview of impaired language domains for each patient at all test moments can be found in table 5.5.

T1: Nine patients (60%) had a language impairment. Affected domains were Production-Word retrieval ($N = 8$), Production-Phonology ($N = 3$), Production-Semantics ($N = 3$), Production-Morphosyntax ($N = 3$), Comprehension-Auditory input ($N = 4$), Reading ($N = 1$), and Writing ($N = 3$).

T2: Ten patients (67%) had a language impairment; seven already had an impairment before surgery and three had no impairment before surgery. Affected domains were Production-Word retrieval ($N = 6$), Production-Phonology ($N = 3$), Production-Semantics ($N = 2$), Production-Morphosyntax ($N = 3$), Comprehension-Auditory input ($N = 3$), Comprehension-Visual input ($N = 2$), Reading ($N = 2$), and Writing ($N = 6$).

T3: Ten out of thirteen patients (77%) had a language impairment, one of whom had no impairment at earlier assessments. Affected domains were Production-Word retrieval ($N = 6$), Production-Phonology ($N = 5$), Production-Semantics ($N = 4$), Production-Morphosyntax ($N = 3$), Comprehension-Auditory input ($N = 3$), and Writing ($N = 6$).

Table 5.6 shows language change over time ($T1 \rightarrow T2$, $T2 \rightarrow T3$, and $T1 \rightarrow T3$) according to the number of impaired domains.

Table 5.5. Individual impaired language domains (z-score ≤ -1.5 , displayed in grey) at each time point

	pt1	pt2	pt3	pt4	pt5	pt6	pt7	pt8	pt9	pt10	pt11	pt12	pt13	pt14	pt15
T1	Production-Word retrieval														
	Production-Phonology														
	Production-Semantics														
	Production-Morphosyntax														
	Comprehension-Auditory input														
	Comprehension-Visual input														
T2	Reading														
	Writing														
	Production-Word retrieval														
	Production-Phonology														
	Production-Semantics														
	Production-Morphosyntax														
T3	Comprehension-Auditory input														
	Comprehension-Visual input														
	Reading														
	Writing														
	Production-Word retrieval														
	Production-Phonology														
T3	Production-Semantics														
	Production-Morphosyntax														
	Comprehension-Auditory input														
	Comprehension-Visual input														
	Reading														
	Writing														

Note. Grey-shaded cells indicate impaired domains, hyphens ('-') indicate unimpaired domains, and empty white cells indicate that the assessment did not take place. T1 = before surgery; T2 = 2 months after surgery; T3 = 1 year after surgery.
^a At T3, five z-scores for Reading (all -2.5) were below the cut-off for an impaired domain, however, it should not be interpreted as an impairment because the score is based on only 1 error in 6 sentences. The 'extreme' z-scores can be explained by the performance of a healthy population (on which the normative data are based), who made almost no errors on this test ($M_{errors} = 0.10$, $SD = 0.36$, range = 0 – 1). The aforementioned only applies to Reading at T3.

Table 5.6. Number of patients (and percentage) with unchanged, improved, and worsened language performance over time, based on the number of impaired domains

Time interval	Unchanged	Improved	Worsened
T1→T2	4 (27%)	4 (27%)	7 (47%)
T2→T3	4 (31%)	3 (23%)	6 (46%)
T1→T3	5 (38%)	0	8 (62%)

Note. Improved language functioning equals a decrease in the number of impaired domains, and worsened language functioning equals an increase in the number of impaired domains. (The T1→T2 interval adds up to 101% due to rounding.)

Self-reported language problems

T1: Eight patients (53%) experienced one or more speech-language problems in daily life. They reported difficulties with word finding ($N = 8$), speaking (producing words, formulating sentences, expressing thoughts; $N = 5$), reading ($N = 4$), and writing/typing ($N = 5$).

T2: Ten patients (67%) reported language problems, six of whom already had language complaints before surgery. They had difficulties with word finding ($N = 9$), speaking ($N = 9$), keeping up with conversations ($N = 3$), articulation ($N = 2$), comprehension ($N = 1$), reading ($N = 7$), and writing/typing ($N = 4$).

T3: Eight out of thirteen patients (62%) reported language problems. Compared to T1, six patients continued to have problems, four continued without problems, one recovered, and two reported new problems. Complaints included difficulties with word finding ($N = 7$), speaking ($N = 6$), keeping up with conversations ($N = 2$), reading ($N = 6$), and writing/typing ($N = 3$).

Self-reported language problems versus language impairments

The presence of self-reported language problems at T1 was significantly related to the presence of a language impairment according to the test battery at T1. No relations were found at T2 and T3 (table 5.7). Individual data on self-reported language problems and language impairments are presented in Appendix B2.

Table 5.7. Self-reported language problems compared to language impairments revealed by language assessments at T1, T2, and T3

		Self-reported language problems at T1		<i>p</i>
		No	Yes	
Language impairment at T1	No	5	1	0.041
	Yes	2	7	
		Self-reported language problems at T2		<i>p</i>
		No	Yes	
Language impairment at T2	No	1	4	0.600
	Yes	4	6	
		Self-reported language problems at T3		<i>p</i>
		No	Yes	
Language impairment at T3	No	2	1	0.510
	Yes	3	7	

Note. p = p -value of the Fisher's exact tests (two-sided). Significant effects ($p < 0.05$) are presented in bold font.

Effect of tumour and treatment characteristics

No effects of tumour and treatment characteristics (localisation-hemisphere, localisation-lobes, histology, volume at T1, use of anti-epileptic drugs at T1, extent of resection, and chemo and/or radiotherapy) were found on the presence of a language impairment at T1, nor on worsening of language performance (an increase in the number of impaired domains) from T1 to T3 (table 5.8).

Table 5.8. Tumour and treatment characteristics related to: (1) the presence of a language impairment at T1; and (2) worsening of language performance between T1 and T3

		Language impairment at T1			Increased no. of impaired domains from T1 to T3		
		No	Yes	<i>p</i>	No (improved/ unchanged)	Yes (worsening)	<i>p</i>
Localisation – hemisphere	Left	4	9	0.143	3	8	0.128
	Right	2	0		2	0	
Localisation – lobes	Fronto-temporo insular involvement	4	8	0.525	5	5	0.231
	Parietal	2	1		0	3	
Histology	Diffuse astrocytoma	2	3	1.000	3	2	0.293
	Oligodendroglioma	4	6		2	6	
Volume at T1	< 30cm ³	4	4	0.608	3	5	1.000
	≥ 30cm ³	2	5		2	3	
Use of anti-epileptic drugs at T1	Yes	4	9	0.143	3	8	0.128
	No	2	0		2	0	
Extent of resection	< 90%			-	1	5	0.266
	≥ 90%				4	3	
Chemo and/or radiotherapy	Yes			-	4	6	1.000
	No				1	2	

Note. *p* = *p*-value of the Fisher's exact tests (two-sided); '-' indicates that the test was not performed because the comparison is not informative.

Discussion

Language performance before surgery

The low-grade glioma patients in this study have impaired language functioning at the group level before surgery. Compared to a healthy population, patients have poorer performance in almost all domains: word retrieval, phonology, semantics, and morphosyntax (trend) in speech production; comprehension of auditory input; and writing. The patient group's reading performance is

better than that of a healthy population; this can be explained by the test being very easy, as the normative data hardly include any errors and all but one patient reached the maximum score. Impaired group-level performance in preoperative glioma patients has been reported in at least five previous studies (Van Kessel et al., 2017), although these often include low-grade and high-grade glioma patients. Antonsson, Longoni, et al. (2018) report that (presumed) low-grade glioma patients perform poorer than healthy individuals on only 2 out of 14 language (sub)tests (object naming and category fluency-animals subtest), as assessed with a battery that was designed for detecting mild impairments. The proportion of language measures that indicate impaired group performance is higher in the current study. This is presumably due to differences in tumour location: we studied tumours in the language-dominant hemisphere (eligible for awake surgery), whereas Antonsson, Longoni, et al. studied tumours in left language areas, left non-language areas, and right non-language areas. Interestingly, they reported language impairments in all three subgroups, and in comparable quantity (see the later section *Effect of tumour and treatment characteristics*).

With regard to the different language domains, impaired group-level performance in word retrieval, phonology, and semantics has previously been found in preoperative glioma patients, whereas impaired writing and comprehension of auditory input are less common (e.g. Satoer et al., 2014). Writing abilities have received little attention in patients undergoing awake glioma surgery (Van Ierschoot, Bastiaanse, & Miceli, 2018), and when these abilities are evaluated preoperatively, they usually appear to be unimpaired (Santini et al., 2012; Satoer et al., 2014). The currently-used writing test by Van Ierschoot (2018) is presumably more sensitive to detect writing impairments than previously-used writing subtests from aphasia batteries. It can, however, be helpful to expand the normative data of this test by increasing the control group size ($N = 51$; Appendix B1) to ensure valid interpretations on individual test performance. Furthermore, impairment of auditory comprehension, as assessed with the Token Test, is usually reported for stroke patients (De Renzi & Faglioni, 1978), but here we demonstrate impaired performance in low-grade glioma patients as well. There seems to be a discrepancy between impaired comprehension of auditory input and unimpaired comprehension of visual input. However, comprehension of the two different types of input is not directly comparable due to non-equivalent tasks. Comprehension of visual input was assessed by the sentence judgement test, which requires other linguistic abilities than the Token Test (table 5.1). Moreover, the sentence judgement task involves a 50% chance of choosing the correct answer, although we did not take reaction times into account to increase sensitivity of this test. The tests that were used to assess other language domains have more room for error and seem sufficiently sensitive for this patient group.

At the individual level, 60% of the patients in our sample had a language impairment before surgery, based on objective testing. This percentage is relatively high compared to what has been found in previous studies in preoperative (low-grade and high-grade) glioma patients, indicating language impairment in 25% of the patients (interquartile range 15-48%, minimum 3%, maximum 90%; Van Kessel et al., 2017). Hence, language impairments are more frequently present in the current study, despite the fact that it comprises low-grade glioma patients only, who tend to have better language functioning than high-grade glioma

patients (Campanella et al., 2009; Noll et al., 2015). The discrepancy with previous findings may be explained by differences in methodology. First, we report the percentage of patients with impaired performance in one or more domains, whereas Van Kessel et al. (2017) used a different approach (due to unavailability of individual data per test), which – according to the authors – usually yields an underestimation. Second, the current study includes category and letter fluency performance in language domains because the tests at least partly assess language processing (Aita et al., 2019; Whiteside et al., 2016). However, they are also commonly classified as an assessment of executive functioning, which is shown to be frequently impaired (Van Kessel et al., 2017). Third, we use tests that have been designed specifically for glioma patients and apply a $z < -1.5$ cut-off for individual patients in order to detect mild deficits. Finally, our specific selection criteria ensure that tumours are located in the hemisphere dominant for (or at least involved in) language processing. This is likely to contribute to a higher prevalence of language impairments, as opposed to studies that included all tumour locations.

Language change after surgery

Comprehension of auditory input is the only language domain in which performance changes significantly after awake glioma surgery. We demonstrate that auditory comprehension improves in the short and long term after surgery, as assessed by the Token Test. Thus, this test is sensitive to language change after glioma surgery in the current study (in contrast to Satoer et al., 2014), even though the Token Test is commonly used for detection of stroke-related language impairments (Anderson et al., 1990; De Renzi & Faglioni, 1978). Also, Token Test performance is indicative of the severity of language impairment (De Renzi & Faglioni, 1978). Hence, postoperative improvement on this test suggests that, at the group level, language impairment becomes less severe after glioma surgery.

Apart from auditory comprehension, all other language domains indicate unchanged performance after surgery. This is in line with previous studies, which report no change on the majority of language tests in the longer term (3-12 months) after surgery (Antonsson, Jakola, et al., 2018; Norrelgen et al., 2020; Satoer et al., 2016, 2014). However, postoperative decline has been reported for word retrieval (object naming; Satoer et al., 2016), phonological abilities (letter fluency; Satoer et al., 2016), and semantic abilities (category fluency; Antonsson, Jakola, et al., 2018; Norrelgen et al., 2020; Satoer et al., 2016, 2014).

In contrast to group-level performance, impaired domains at the individual level reveal that, compared to before surgery, language performance worsens in 62% and remains unchanged in 38% of the patients in the long term after surgery. The combination of many patients with more impaired domains after surgery (individual level) and reduced severity of language impairment after surgery (group level) seems contradictory, and stresses the importance of evaluating individual performance to complement group-level analyses in this type of research.

Self-reported language problems versus test performance

Presence (or absence) of self-reported language problems are in agreement with presence (or absence) of impaired test performance before surgery, as expected. However, the self-reported information after surgery shows no relation with the obtained test results. A weak congruence between subjective complaints and objective test results after brain tumour surgery has previously been reported for executive functioning (Van der Linden et al., 2020). For language functioning, a weak congruence has only been observed before brain tumour surgery (Antonsson, Longoni, et al., 2018; Pranckeviciene, Deltuva, Tamasauskas, & Bunevicius, 2017), in contrast to our results.

Remarkably, when there is incongruence between self-reported information and test performance in the current study, it does not concern one particular language domain; it is shown for word retrieval, speech production, comprehension, reading, and writing (Appendix B2). This suggests that the inconsistency between self-reported information and test performance after surgery cannot be explained by particular tests or domains. Alternatively, the low congruence may be due to under- or overestimation of one's own skills (Kruger & Dunning, 1999), the gap between everyday language use and artificial test situations (Satoer et al., 2018), or particular patient characteristics (Gehring, Taphoorn, Sitskoorn, & Aaronson, 2015). See chapter 6 for elaborate explanations on this topic.

Effect of tumour and treatment characteristics

The data show that tumour and treatment characteristics are not related to the presence of language impairment before surgery, nor to language change in the year after surgery. This partly conflicts with previous literature in glioma patients. For example, several studies report associations between tumour location and language functioning, in which (left) frontal, temporal, and insular locations and the involvement of subcortical language pathways are related to poorer language outcome after surgery (see the review by Satoer et al., 2016). The current study included three patients with a tumour that did not involve frontal, temporal, or insular areas, but solely parietal areas. Remarkably, all three patients showed worsening of language performance, whereas only half of the patients with a tumour involving fronto-temporo-insular areas showed worsening of language performance 1 year after surgery. These observations do not agree with previous findings, although the number of patients is very small. With regard to other tumour and treatment characteristics, such as tumour volume, extent of resection, and adjuvant treatment, relations with language functioning have only been reported for tumour volume (Papagno et al., 2012; Talacchi, Santini, Savazzi, & Gerosa, 2011). However, most studies report no effects of tumour and treatment characteristics⁷ (Santini et al., 2012; Satoer et al., 2013, 2014, 2012; Van Kessel et al., 2020), which is in line with our results.

7 Tumour grade is disregarded here because it is not applicable to the current patients, who all have a grade II glioma.

Conclusion

This study indicates that, before surgery, patients with a low-grade glioma in the language-dominant hemisphere have impaired language abilities for speech production (word retrieval, phonology, semantics, and a trend for morphosyntax), auditory comprehension, and writing. Group-level language functioning does not change in the short and long-term after surgery, apart from improvement of auditory comprehension. At the individual level, however, the majority of patients show language decline in the long term after surgery.

Overall, there is large variation between low-grade glioma patients with regard to the type and severity of language impairments. This underlines the importance of extensive language testing, including assessment of language modalities and linguistic levels, and evaluation of self-reported language problems. A thorough language assessment before awake glioma surgery provides a baseline for examining postoperative change, which may give directions for language intervention and patient counselling. Moreover, extensive language testing is crucial in order to determine the most suitable approach for intraoperative language monitoring, aiming to preserve patients' quality of life as effectively as possible.

Chapter 6

Pre- and postoperative language impairments
in patients with grade I meningioma

Abstract

Introduction

Intracranial, grade I meningiomas are slow-growing, non-infiltrative tumours, which induce compression of surrounding brain tissue. This frequently leads to impaired cognitive functions. For language functioning, however, it is yet unclear whether meningioma patients have complaints and/or impairments pre- and postoperatively, and if so, which language modalities and linguistic levels are affected.

Method

Ten patients with an untreated meningioma pressing on the left language-dominant hemisphere were included. They underwent language assessment at three time points: before surgery (T1), 2 months after surgery (T2), and 1 year after surgery (T3). The assessment included standardised tests evaluating the following domains: word retrieval, phonology, semantics, and morphosyntax for speech production; comprehension of auditory and visual input; reading; and writing. Additionally, self-reported language problems were evaluated.

Results

At the group level, meningioma patients had poorer word retrieval, morphosyntactic abilities, and writing performance than a healthy population. Language performance remained largely stable after surgery. At the individual level, however, 4/10 (T1), 4/10 (T2), and 5/8 (T3) patients had language impairments. Self-reported language problems were present in 6/10 (T1), 5/10 (T2), and 5/8 (T3) patients, although these complaints often did not correspond to the test results.

Discussion

Meningiomas can cause language impairments, despite the non-infiltrative nature of these tumours. Before and after surgery, many patients in this study had language complaints and/or impairments, affecting primarily expressive language domains (speech production and writing). Hence, attention must be paid to language abilities of left-sided meningioma patients for suitable counselling pre- and postoperatively.

Introduction

Different types of brain injury (e.g. stroke, trauma, and glioma) frequently lead to language impairments, which negatively affect everyday communication and quality of life (Hilari et al., 2012; Worrall & Holland, 2003). It is unclear whether this also applies to intracranial meningiomas. These extra-axial tumours, arising from the meninges, represent approximately one-third of all primary brain tumours (Wiemels et al., 2010). Ninety percent of meningiomas is classified as WHO (World Health Organisation) grade I (Whittle et al., 2004), associated with a relatively long life expectancy (Van Alkemade et al., 2012). Meningiomas generally do not infiltrate, but compress and distort, the surrounding brain tissue (Wei, Guo, & Mikulis, 2007). Furthermore, subcortical white matter pathways appear to be displaced, but do stay intact (Campanella, Ius, Skrap, & Fadiga, 2014). For these reasons, one may expect little or no impairments in cognitive functioning. However, there is evidence that such impairments do occur.

A systematic review by Meskal, Gehring, Rutten, and Sitskoorn (2016) indicates that the majority of meningioma patients suffer from impairment of one or more cognitive functions (e.g. memory, attention and executive functioning) before surgery. These functions tend to improve after surgery, but persistent impairments seem to be present in 44% of the patients (Meskal, Gehring, Van der Linden, Rutten, & Sitskoorn, 2015). Little is known about language functioning in meningioma patients. It is clinically relevant to gain knowledge on possible language impairments in this patient group because it could influence the course of patient counselling before and after surgery. For example, this information would enable an early start to suitable language intervention to improve patients' well-being and their ability to return to work after surgery.

Language covers a range of functions, including the modalities of speech production, comprehension, reading, and writing. Furthermore, language processing integrates at least three linguistic levels: phonology, concerning speech sounds; semantics, concerning meaning; and morphosyntax, concerning word and sentence structure. Hence, various language functions are potentially at risk in patients with a meningioma pressing on the language-dominant (usually left) hemisphere.

Some previous studies on cognition in meningioma patients have included a small number of language measures. Before surgery, performance on letter fluency (phonology) and category fluency (semantics) tests, which at least partly assess language processing (Aita et al., 2019; Whiteside et al., 2016), is reported to be impaired at the group and the individual level (Bommakanti et al., 2016; Hendrix et al., 2017; Liouta et al., 2016; Tucha et al., 2003), but intact performance has also been reported (Butts et al., 2017; Van Nieuwenhuizen et al., 2013). Similar contradictory findings have been reported for object naming (word retrieval) and the Token Test (auditory sentence comprehension; Butts et al., 2017; Campanella, Fabbro, Ius, Shallice, & Skrap, 2015; Di Cristofori et al., 2018). After surgery, performance on these tests may remain unchanged (Abel et al., 2016; Bommakanti et al., 2016; Campanella et al., 2015; Hendrix et al., 2017; Tucha et al., 2003) but improvement has also been described (Di Cristofori et al., 2018; Liouta et al., 2016). This summary suggests that previous findings are inconclusive, and that language has not yet been studied in sufficient detail.

Our objective is to gain more insight into language functioning in patients with a meningioma pressing on the left language-dominant hemisphere, by systematically assessing language domains (created by combining language modalities and linguistic levels). We investigate: (1) whether meningioma patients have impaired language abilities before surgery, and if so, which domains are affected; (2) whether their language abilities change in the short and long-term after surgery; (3) whether self-reported language problems correspond to language impairments as revealed by tests; and (4) whether tumour and treatment characteristics are associated with language performance before surgery and language change after surgery.

Method

Patients

Newly-diagnosed patients with a presumed WHO grade I meningioma pressing on the left hemisphere, who were planned to undergo surgery at the University Medical Centre Groningen (UMCG) or the Erasmus MC University Medical Centre Rotterdam (Erasmus MC), were invited to participate in the study. Inclusion criteria were: intracranial, supratentorial tumour location; diameter >3 cm; presumed left-hemispheric language dominance or right-handedness; aged between 18 and 75; in case of epilepsy, seizures under control with anticonvulsants. Exclusion criteria were: non-native speaker of Dutch; history of a medical, neurological or psychiatric condition known to affect language or cognitive functioning; history of substance abuse; consistent use of dexamethasone preoperatively; previous brain surgery or cranial radiation therapy.

Tumour localisation was classified based on the place of meningioma origin (convexity, falx, etc.), and according to the affected lobes. The latter differs from the convention of labelling extra-axial tumours according to the covering skull bone, but we consider the related cerebral lobes to be more relevant in the context of this study. For tumour size, a neuroradiologist measured the maximum diameters in three directions, two in the axial plane and one in the sagittal plane, using T1 and T2-weighted images from MRI scans. Subsequently, tumour volume was estimated using the standard formula for an ellipsoid: the product of the three maximum diameters, divided by 2 (Sorensen et al., 2001). All patients underwent tumour resection under general anaesthesia.

No control group was included because pre-existing normative data from healthy individuals were used. This multicentre study was approved by the medical, ethical review board of the UMCG, which was also applicable to the Erasmus MC. All patients gave written informed consent.

Procedure

The study had a longitudinal design, in which patients underwent an extensive language assessment at three time points: **T1** = before surgery (mean 20 days, range 1-48); **T2** = 2 months after surgery (mean 2.34, range 1.58-3.39); and **T3** = 12 months after surgery (mean 11.97, range 11.21-12.49). The language assessment was administered by a clinical linguist

in the outpatient clinic at one of the participating medical centres. The total assessment took up to a maximum of 1.5 hours and breaks were taken when desired.

Language assessment

The assessment included administration of the Edinburgh Handedness Inventory (Oldfield, 1971) and a selection of standardised language tests: object naming (De Witte et al., 2015), action naming in sentence context (Rofes, 2012), the shortened Token Test (De Renzi & Faglioni, 1978), category fluency (Luteijn & Barelds, 2004), letter fluency (Schmand et al., 2008), reading and writing (Van Ierschoot, 2018), and subtests of the Diagnostic Instrument for Mild Aphasia (DIMA; Satoer et al., 2019): repetition, semantic odd-picture-out, sentence completion, and sentence judgement. The tests examine a wide range of linguistic abilities. They are presented in table 6.1, together with task descriptions of each test.

Furthermore, a short interview was held on current language complaints (if applicable). Additional information on self-reported language problems was obtained by conducting a questionnaire from the European Organisation for Research and Treatment of Cancer (EORTC) on quality of life: the brain module EORTC QLQ-BN20 (Osoba et al., 1996). This includes four questions on language functioning, namely, asking patients whether they have difficulty with: reading; finding the right words to express themselves; speaking; and communicating their thoughts. Answers were given on a 4-point scale from 'not at all' to 'very much'.

Data processing

Raw scores on the language tests were normalised by conversion to z-scores, using pre-existing normative data from a healthy population. Subsequently, eight language domains were created for the purpose of this study, as shown in table 6.2. This was done for two reasons: (1) to reduce the number of statistical comparisons; and (2) to examine all language modalities (speech production, comprehension, reading, and writing), three linguistic levels (phonology, semantics, and morphosyntax), and comprehension of two types of input (auditory and visual). A domain score equalled the average z-score of the tests in that domain for each patient.

For the evaluation of language performance of individual patients, a domain z-score ≤ -1.5 indicated an impairment. For each patient, the number of impaired domains before surgery was compared to the number of impaired domains after surgery. Patients were classified as 'improved' when this number decreased, 'worsened' when this number increased, and 'unchanged' when this number remained the same after surgery.

Information on experienced language problems was obtained from an interview and complemented by the language-related questions from the questionnaire. Categories of self-reported language problems were formed based on the patients' responses: word finding, speaking (producing words, formulating sentences, expressing thoughts), keeping up with conversations, articulation, reading, and writing/typing.

Table 6.1. Overview of tests used in the language assessments

Tests	Linguistic abilities	Task description	Example
Object naming ^a (De Witte et al., 2015)	Word retrieval (nouns)	Naming objects depicted on black-and-white drawings with the introduction <i>This is...</i> (time limit: 4 sec.)	Dit is... <i>een emmer</i> (This is... <i>a bucket</i>)
Action naming in sentence context (Rofes, 2012)	Word retrieval (verbs) and morphology: 3rd person singular	Naming and inflecting verbs depicted on black-and-white drawings with the introduction <i>The (wo)man...</i> (time limit: 4 sec.)	De man... <i>rent</i> (The man... <i>runs</i>)
Token Test (De Renzi & Faglioni, 1978)	Auditory sentence comprehension	Executing tasks with geometric forms on verbal commands (shortened version)	Raak de grote witte cirkel en het kleine groene vierkant aan. (Touch the large white circle and the small green square)
Category fluency (Luteijn & Barends, 2004)	Flexibility of lexical access by semantic searching	Producing words of a given category (animals; professions) within 60 sec.	
Letter fluency ^b (Schmand et al., 2008)	Flexibility of lexical access by phonological searching	Producing words starting with a given letter within 60 sec.	
Reading ^b (Van lerschoot, 2018)	Reading	Reading sentences aloud ^c	De kinderen kunnen goed met elkaar overweg. (The children get along well with each other.)
Writing ^b (Van lerschoot, 2018)	Writing	Writing sentences to dictation ^c	Mies kocht een lap stof op de markt. (Mies bought a piece of fabric at the market.)
Subtests of the Diagnostic Instrument for Mild Aphasia (DIMA; Satoer et al., 2019):			
- Repetition	Phonological ability	Repetition of 3-syllabic words, compound words, non-words, and sentences	De man zoekt zijn zomerjas zonder succes. (The man searches for his summer jacket without success)
- Semantic odd-picture-out	Semantic ability and word retrieval	Out of 3 black-and-white drawings, naming the noun or verb that semantically does not fit 2 other items (time limit: 4 sec.)	Pictures of 'borstel, hond, kat' (brush, dog, cat) → answer: borstel (brush)
- Sentence completion	Syntactic ability	Sentence completion	Iedere dag... (Every day...)
- Sentence judgement ^d	Differentiating phonological, semantic and syntactic violations from correct sentences	Correctness judgement of visually presented sentences with phonological violations, semantic violations, syntactic violations, or without violations	De gieter smeert een boterham. (The watering can prepares a sandwich.) → incorrect; meaning not possible (semantic violation)

Note. For all tests, the normative data used was based on a healthy, Dutch population matched for age and education.

^aWhen this object naming test could not be administered (e.g. because of the 4 sec. time constraint), the Boston Naming Test (Kaplan et al., 2001) was used instead.

^bA parallel version of this test was used at T2. (The other tests only had one version available.)

^cOnly the sentence subtask because it has been shown to be the most sensitive subtask of the test (Van lerschoot, 2018).

^dAccuracy scores; the sentence judgement test also includes the measurement of reaction times but these were not taken into account in this study.

Table 6.2. Language domains under investigation with their corresponding tests

Domains	Tests
1. Production-Word retrieval	Object naming
2. Production-Phonology	Repetition Letter fluency
3. Production-Semantics	Semantic odd-picture-out Category fluency
4. Production-Morphosyntax	Sentence completion Action naming in sentence context
5. Comprehension-Auditory input	Token Test
6. Comprehension-Visual input	Sentence judgement (accuracy)
7. Reading	Reading
8. Writing	Writing

Note. Although some language tests could assess more than one domain (e.g. action naming in morphosyntax and word retrieval), every test is classified in one domain only in order to minimise statistical dependencies between domains.

Statistical analysis

Patients' domain z-scores at T1 were compared to pre-existing normative data from a healthy population ($M = 0$) by one-sample Wilcoxon signed-rank tests. This was analysed one-sided, in order to test the hypothesis that meningioma patients perform poorer than a healthy population. Subsequently, paired Wilcoxon signed-rank tests were used to investigate within-subject changes in domain scores over time, comparing T1-T2 (short-term effects), T2-T3 (recovery effects), and T1-T3 (long-term effects). Associations between self-reported language problems (present or absent) and a language impairment according to test results (present or absent) were examined with Fisher's exact tests for T1, T2, and T3. Fisher's exact tests were also used to investigate binary tumour and treatment-related variables (localisation, volume, use of anti-epileptic drugs, and extent of resection) in relation to presence of a language impairment at T1 (yes or no), and to language change from T1 to T3 (improved/unchanged or worsened). All analyses were performed using IBM SPSS Statistics software (version 23, release 23.0.0.0).

Results

Demographic and clinical characteristics

Ten patients with a left-sided, grade I meningioma participated in the study. Demographic and clinical characteristics can be found in table 6.3. At the time of inclusion, the meningiomas were untreated and detected: by epileptic seizures ($N = 6$); by progressive (language and cognitive) complaints ($N = 1$); or incidentally ($N = 3$). At T3, there was a drop-out of two patients because they were no longer motivated to participate in the study.

Table 6.3. Demographic and clinical characteristics of the meningioma patients: number of patients (and percentage) or mean (and range)

	Patients (N = 10)
Gender – female	6 (60%)
Mean age in years (range)	58.6 (50-69)
Mean education level ^a (range)	5.4 (3-7)
Handedness ^b	
Right	9 (90%)
Ambidextrous	1 (10%)
Mean 'diagnosis → surgery' time in months (range)	8.0 (2.1-49.7)
Tumour localisation, lobes	
Frontal	6 (60%)
Parietal	3 (30%)
Parieto-occipital	1 (10%)
Tumour localisation, origin	
Convexity	6 (60%)
Falcine	2 (20%)
Intraventricular	1 (10%)
Skull base	1 (10%)
Mean tumour volume before surgery in cm ³ (range)	31.6 (6.2-90.2)
Mean tumour volume after surgery in cm ³ (range)	0.2 (0.0-1.5)
Extent of resection ^c	
Partial: 40-89%	1 (10%)
Subtotal: 90-99%	1 (10%)
Total: 100%	8 (80%)
Use of anti-epileptic drugs at T1	6 (60%)
Use of anti-epileptic drugs at T3 (N = 8)	7 (88%)

Note. T1 = before surgery; T3 = 1 year after surgery.

^a Education level was classified according to seven categories (1= incomplete primary education; 2= complete primary education; 3= primary education and < 2 years of low-level secondary education; 4= complete low-level secondary education; 5= complete average-level secondary education; 6= complete high-level secondary education; 7= complete university education; Verhage, 1964).

^b Handedness was assessed by the Edinburgh Handedness Inventory (Oldfield, 1971).

^c Extent of resection was determined by a neuroradiologist, based on pre- and postoperative tumour volumes.

Language performance before surgery (group level)

Figure 6.1 shows the language domain scores of the patient group at T1, and table 6.4 presents the corresponding comparisons to a healthy population. Meningioma patients scored significantly lower than healthy individuals on domains of Production-Word retrieval, Production-Morphosyntax, and Writing. For Reading, patients scored higher than a healthy population, as all but one patient made no errors on this test.

Figure 6.1. Language domain z-scores of meningioma patients at T1. The horizontal line at 0 represents the average performance of a healthy population. Every box contains 50% of the data (interquartile range), including the median (thick black line), and the vertically extending lines (whiskers) represent the upper and lower quartiles of the data. 'O' indicates an outlier between 1.5-3 times the interquartile range, and '*' indicates an outlier > 3 times the interquartile range.

Abbreviations: P-WR = Production-Word retrieval; P-Phon = Production-Phonology; P-Sem = Production Semantics; P-Mor = Production-Morphosyntax; C-Aud = Comprehension-Auditory input; C-Vis= Comprehension-Visual input; Read = Reading; Writ = Writing

Table 6.4. Language domain scores of meningioma patients at T1 compared to a healthy population

Language domain	N	Mdn z-score	Comparisons to a healthy population		
			Z	p	r
Production-Word retrieval	10	-0.58	-1.89	0.030	<u>0.60</u>
Production-Phonology	10	-0.12	-0.97	0.167	0.31
Production-Semantics	10	-0.48	-1.27	0.102	0.40
Production-Morphosyntax	10	-0.51	-2.81	0.003	<u>0.89</u>
Comprehension-Auditory input	10	0.07	0.05	0.480	0.02
Comprehension-Visual input	7	-0.07	0.17	0.433	0.06
Reading	9	0.28	1.73	0.042	<u>0.58</u>
Writing	9	-0.79	-1.98	0.024	<u>0.66</u>

Note. N = sample size; Mdn z-score = median z-score; Z = standardised test statistic of the one-sample Wilcoxon signed rank tests; p = p-value (one-sided); r = effect size ($r = Z/\sqrt{N}$). Significant effects ($p < 0.05$) are presented in bold font and large effect sizes (≥ 0.50 ; Cohen, 1992) are underlined.

Scores on the separate language tests can be found in Appendix C1.

Language change after surgery (group level)

T1→T2: No significant changes in language domain scores were found.

T2→T3: Domain scores of Production-Semantics increased significantly ($N = 7$, $Mdn_{-T2} = -0.47$, $Mdn_{-T3} = 0.47$, $Z = -2.37$, $p = 0.018$, $r = 0.89$). A large effect size, but with a difference that was only marginally significant, was found for Production-Morphosyntax ($N = 8$, $Mdn_{-T2} = -0.86$, $Mdn_{-T3} = -0.16$, $Z = -1.68$, $p = 0.092$, $r = 0.60$), indicating an increase in scores.

T1→T3: No significant changes in language domain scores were found. A large effect size, but a non-significant difference, was found for Production-Semantics ($N = 8$, $Mdn_{-T1} = -0.76$, $Mdn_{-T3} = 0.38$, $Z = -1.54$, $p = 0.123$, $r = 0.54$), indicating an increase in scores.

Appendix C1 presents the language domain scores at each time point. Not all of these data points could be used for the within-subject comparisons described above because of missing data at one or both test moments.

Language impairments (individual level)

An overview of impaired language domains for each patient at all test moments can be found in table 6.5.

T1: Four patients (40%) had a language impairment. Affected domains were Production-Word retrieval ($N = 1$), Production-Semantics ($N = 1$), and Writing ($N = 2$).

T2: Four patients (40%) had a language impairment; three already had an impairment before surgery and one had no impairment before surgery. Affected domains were Production-Word retrieval ($N = 3$), Production-Phonology ($N = 1$), Production-Semantics ($N = 1$), Production-Morphosyntax ($N = 2$), Comprehension-Auditory input ($N = 1$), and Writing ($N = 1$).

T3: Five out of eight patients (63%) had a language impairment, one of whom had no impairment at earlier assessments. Affected domains were Production-Word retrieval ($N = 2$), Production-Phonology ($N = 1$), Production-Morphosyntax ($N = 1$), and Writing ($N = 4$).

Table 6.6 shows language change over time (T1→T2, T2→T3, and T1→T3) according to the number of impaired domains.

Table 6.5. Individual impaired language domains (z-score ≤ -1.5 , displayed in grey) at each time point

	pt1	pt2	pt3	pt4	pt5	pt6	pt7	pt8	pt9	pt10
T1	Production-Word retrieval	-	-	-	-	-	-	-	-	-
	Production-Phonology	-	-	-	-	-	-	-	-	-
	Production-Semantics	-	-	-	-	-	-	-	-	-
	Production-Morphosyntax	-	-	-	-	-	-	-	-	-
	Comprehension-Auditory input	-	-	-	-	-	-	-	-	-
	Comprehension-Visual input	-	-	-	-	-	-	-	-	-
	Reading	-	-	-	-	-	-	-	-	a
	Writing	-	-	-	-	-	-	-	-	-
T2	Production-Word retrieval	-	-	-	-	-	-	-	-	-
	Production-Phonology	-	-	-	-	-	-	-	-	-
	Production-Semantics	-	-	-	-	-	-	-	-	-
	Production-Morphosyntax	-	-	-	-	-	-	-	-	-
	Comprehension-Auditory input	-	-	-	-	-	-	-	-	-
	Comprehension-Visual input	-	-	-	-	-	-	-	-	-
	Reading	-	-	-	-	-	-	-	-	-
	Writing	-	-	-	-	-	-	-	-	-
T3	Production-Word retrieval	-	-	-	-	-	-	-	-	-
	Production-Phonology	-	-	-	-	-	-	-	-	-
	Production-Semantics	-	-	-	-	-	-	-	-	-
	Production-Morphosyntax	-	-	-	-	-	-	-	-	-
	Comprehension-Auditory input	-	-	-	-	-	-	-	-	-
	Comprehension-Visual input	-	-	-	-	-	-	-	-	-
	Reading	-	-	-	-	-	-	-	-	a
	Writing	-	-	-	-	-	-	-	-	-

Note. Grey-shaded cells indicate impaired domains, hyphens ('-') indicate unimpaired domains, and empty white cells indicate that the assessment did not take place. T1 = before surgery; T2 = 2 months after surgery; T3 = 1 year after surgery.

^a The two z-scores for Reading (both -2.5) were below the cut-off for an impaired domain, however, it should not be interpreted as an impairment because the score is based on only 1 error in 6 sentences. The 'extreme' z-scores can be explained by the performance of a healthy population (on which the normative data are based), who made almost no errors on this test ($M_{\text{errors}} = 0.10$, $SD = 0.36$, range = 0 – 1). The aforementioned only applies to Reading.

Table 6.6. Number of patients (and percentage) with unchanged, improved, and worsened language performance over time, based on the number of impaired domains

Time interval	Unchanged	Improved	Worsened
T1→T2	6 (60%)	1 (10%)	3 (30%)
T2→T3	4 (50%)	2 (25%)	2 (25%)
T1→T3	4 (40%)	1 (12.5%)	3 (37.5%)

Note. Improved language functioning equals a decrease in the number of impaired domains and worsened language functioning equals an increase in the number of impaired domains.

Self-reported language problems

T1: Six patients (60%) experienced one or more speech-language problems in daily life. They reported difficulties with word finding ($N = 6$), speaking (producing words, formulating sentences, expressing thoughts; $N = 5$), articulation ($N = 1$), reading ($N = 5$), and writing/typing ($N = 2$).

T2: Five patients (50%) reported language problems, all of whom already had language complaints before surgery. They had difficulties with word finding ($N = 5$), speaking ($N = 3$), reading ($N = 4$), and writing/typing ($N = 3$).

T3: Five out of eight patients (63%) reported language problems. Compared to T1, four patients continued to have problems, two continued without problems, one recovered and one reported new problems. Complaints included difficulties with word finding ($N = 5$), speaking ($N = 5$), keeping up with conversations ($N = 3$), reading ($N = 4$), and writing/typing ($N = 3$).

Self-reported language problems versus language impairments

No relation was found between self-reported language problems and language impairments according to the test battery at T1, T2, and T3 (table 6.7). Individual data on self-reported language problems and language impairments are presented in Appendix C2.

Table 6.7. Self-reported language problems compared to language impairments revealed by language assessments at T1, T2, and T3

		Self-reported language problems at T1		
		No	Yes	<i>p</i>
Language impairment at T1	No	2	4	1.000
	Yes	2	2	
		Self-reported language problems at T2		
		No	Yes	<i>p</i>
Language impairment at T2	No	2	4	0.524
	Yes	3	1	
		Self-reported language problems at T3		
		No	Yes	<i>p</i>
Language impairment at T3	No	1	2	1.000
	Yes	2	3	

Note. *p* = *p*-value of the Fisher's exact tests (two-sided)

Effect of tumour and treatment characteristics

No effects of tumour and treatment characteristics (localisation, volume at T1, use of anti-epileptic drugs at T1, and extent of resection) were found on the presence of a language impairment at T1, nor on worsening of language performance (an increase in the number of impaired domains) from T1 to T3 (table 6.8). However, a non-significant observation suggests that the majority of patients with an anterior (frontal) tumour location had no language impairment, whereas the majority of patients with a posterior (parietal/parieto-occipital) tumour location had a language impairment at T1.

Table 6.8. Tumour and treatment characteristics related to: (1) the presence of a language impairment at T1; and (2) worsening of language performance between T1 and T3

		Language impairment at T1			Increased no. of impaired domains from T1 to T3		
		No	Yes	<i>p</i>	No (improved/ unchanged)	Yes (worsening)	<i>p</i>
Localisation ^a	Anterior	5	1	0.190	3	2	1.000
	Posterior	1	3		2	1	
Volume at T1	< 30cm ³	4	2	1.000	4	1	0.464
	≥ 30cm ³	2	2		1	2	
Use of anti-epileptic drugs at T1	Yes	4	2	1.000	4	2	1.000
	No	2	2		1	1	
Extent of resection	< 90%			-	1	0	1.000
	≥ 90%				4	3	

Note. *p* = *p*-value of the Fisher's exact tests (two-sided); '-' indicates that the test was not performed because the comparison is not informative.

^aAnterior indicates frontal locations and posterior indicates parietal and parieto-occipital locations.

Discussion

Language performance before surgery

The data show that patients with a left-sided, grade I meningioma have impaired language abilities before surgery, in different domains, but all involving expressive language. At the group level, patients have poorer performance than healthy individuals for word retrieval and morphosyntax (production), and writing, whereas no difference is found for phonology and semantics (production), and comprehension. The patient group's reading performance is better than that of a healthy population; this can be explained by the test being very easy, as the normative data hardly include any errors and all but one patient reached the maximum score.

At the individual level, 40% of the patients had a language impairment before surgery in our sample. Although this is a small group with specific selection criteria (right-handed, left-sided tumour, diameter >3cm), the percentage is similar to previous studies that report

impaired language performance before meningioma surgery: 35% in Bommakanti et al. (2016) and 41% in Di Cristofori et al. (2018).

Language impairments caused by grade I meningiomas do not seem to be as severe as those caused by other brain pathologies, such as glioma or stroke. This is presumably due to lack of (infiltrative) injury to the brain tissue surrounding the meningioma; however, the parenchyma can get compressed, distorted, and displaced (Wei et al., 2007). Moreover, the tumour grows over a long period due to the slow growth rate, providing opportunities for adaptation and reorganisation (Huttner et al., 2018). Therefore, language changes in meningioma patients can be subtle and gradual at first. These may not be noticed or could be attributed to other factors (e.g. aging or stress), until problems progress to a noticeable level which impacts daily life.

Language domains

This is the first study that investigates language functioning in meningioma patients in detail. Previous studies in this patient group have used only one or two language measures, instead of assessing all language domains separately.

Impairments in word retrieval have previously been found in preoperative meningioma patients (Di Cristofori et al., 2018), which is in line with our results. Morphosyntactic abilities and writing skills, however, have not been previously investigated in meningioma patients. Preoperative impairments in these domains should be taken into account when assessing and counselling this patient group.

For phonology and semantics, no differences between meningioma patients and a healthy population were found. This is surprising because previous studies show that letter fluency and category fluency performance is affected before meningioma surgery, as patients score significantly lower than a matched control group (Hendrix et al., 2017; Liouta et al., 2016; Tucha et al., 2003). However, the language domains used in the current study include more than just fluency tasks (see Appendix C1), which may explain the discrepancy with findings from previous studies. Moreover, verbal fluency tests do not solely assess language, but also executive functions, and their relation to language functioning in daily life is unclear. Auditory comprehension is not affected in the current group, in agreement with Campanella et al. (2015), who also used the Token Test. Nonetheless, another study reports impaired Token Test performance in 29% of elderly meningioma patients (Di Cristofori et al., 2018). A large age difference between their patient group ($M = 74$ years) and our patient group ($M = 58$ years) may account for this inconsistency. Unlike comprehension of auditory input, comprehension of visual input and reading abilities have not been investigated before. These are found to be spared in the current patient group.

Expressive versus receptive language

Interestingly, all receptive language domains (comprehension and reading) are unimpaired preoperatively. A possible explanation is that meningiomas generally have little effect on deep, subcortical tracts involved in comprehension and reading, as they usually do not infiltrate brain tissue, but rather compress it (Wei et al., 2007). This results in displaced, but intact,

sufficiently-functioning white matter tracts (Campanella et al., 2014). Hence, subcortical pathways known to be important for receptive language abilities, such as the inferior fronto-occipital fascicle for semantic judgement and reading (De Witte et al., 2015), are likely to be intact in this patient group. However, subcortical pathways known to be important for expressive language abilities (production and writing), such as the superior longitudinal fascicle for articulatory processing (De Witte et al., 2015), may be more vulnerable to being affected by the tumour mass because some are localised more superficially, closer to the cortex. In order to discover which language-related brain areas are still functionally connected, network analysis with recordings of brain activity may be useful (cf. Van Nieuwenhuizen et al., 2018 for cognitive functioning in meningioma patients).

An alternative explanation for the combination of intact receptive language abilities and impaired expressive language abilities, is that impairments in expressive language are easier to detect with language tests. That is, expressive language tests involve many speech and language processes and there is more room for error. In contrast, comprehension tests are less prone to errors because they do not require a verbal response and are often multiple choice. Hence, the chance to answer correctly is much higher. For example, the comprehension domain by visual input is assessed by a sentence judgement task with a 50% chance of choosing the correct answer. An exception is the Token Test (comprehension of auditory input), however, this test is not discriminative in meningioma patients, even though it is reputed to be the most sensitive test for detecting aphasia in stroke patients (De Renzi & Faglioni, 1978).

Language change after surgery

At group level, patients' language performance in all investigated domains remains unchanged at the short-term (2 months) and the long-term (1 year) after surgery. One exception (trend) indicates an improvement of semantic abilities 1 year postoperatively. Between 2 months and 1 year after surgery, there is an improvement of semantic abilities, as well as a tendency for morphosyntactic abilities to improve (trend).

Five previous studies also report no change in language abilities after meningioma surgery in domains of word retrieval, phonology, semantics, auditory comprehension, reading, and writing (range: 2-9 months after surgery; Abel et al., 2016; Bommakanti et al., 2016; Campanella et al., 2015; Hendrix et al., 2017; Tucha et al., 2003), whereas two studies report improvement in domains of word retrieval, phonology, semantics, and auditory comprehension (range: 2-12 months after surgery; Di Cristofori et al., 2018; Liouta et al., 2016). Hence, meningioma resection in the vicinity of eloquent brain areas does not seem to cause language deterioration at the group level.

However, performance at the individual level reveals that, compared to before surgery, language performance worsened in three out of eight patients (38%) at the long term after surgery (one patient improved and four patients remained unchanged). Also, between 2 months and 1 year after surgery, language performance worsened in two out of eight patients (25%), whereas group results indicate no change or improvement. This demonstrates the importance of examining individual performance, as it provides necessary complementary information, which can be missed in group-level analyses.

Self-reported language problems versus test performance

Presence (or absence) of self-reported language problems are in line with presence (or absence) of impaired test performance in only 40% of the patients before surgery. After surgery, this is 30% (at 2 months) and 50% (at 1 year). Hence, in many cases the self-reported information does not correspond to the obtained test results. Although remarkable, this is in line with previous literature. A low congruence between subjective complaints and objective test results has been reported for language (Antonsson, Longoni, et al., 2018; Pranckeviciene et al., 2017), and is a common finding for cognitive functioning in brain tumour patients (Gehring et al., 2015; Pranckeviciene et al., 2017; Van der Linden et al., 2020). In our study, incongruence is observed in both directions: (1) patients report *no language problems*, but have *impaired test performance*; (2) patients report *language problems*, but have *no impaired test performance*.

(1) No language problems and impaired test performance

Possible explanations for (1) are that patients are unaware of their decreased proficiency, gradual changes may be attributed to other factors, or methodological aspects of test interpretation can be considered.

First, patients may be unaware of deviant language abilities because their daily environment does not require particularly complex language skills. In this case, test performance may be impaired, but patients have no complaints because they are not hindered in their daily activities. Related to this, the presence or absence of complaints is highly dependent on the ability to reflect on one's own skills. This is well demonstrated by Kruger and Dunning (1999). They show that, when individuals with the same education level are less competent than their peers in a certain domain, this frequently coincides with the inability to realise it. Less competent individuals do not only overestimate their performance, they believe they perform above average. The reason for this is that the knowledge that is needed to perform a (language) task correctly, is the same knowledge that underlies the ability to recognise inadequate performance on this task.

Second, in patients with a slow-growing, grade I meningioma it can take up to 25 years before the tumour is detected and treated (Huttner et al., 2018). Gradual changes in language abilities may go unnoticed over this long period of time. Also, subtle language problems may be attributed to other factors, such as aging, fatigue or stress. Consequently, they are less likely to be mentioned in relation to their diagnosis.

Third, methodological choices may be of influence in phenomenon (1). Most of the selected language tests are specifically created for brain tumour patients, and are presumably more sensitive than 'classical' aphasia instruments. Additionally, a cut-off of $z < -1.5$, indicating an impairment, is used to detect mild impairments. One could argue that our definition of impaired language performance is too strict, leading to the combination of no complaints and impaired test performance. However, that would conflict with phenomenon (2) discussed below.

(2) Language problems and no impaired test performance

Phenomenon (2) indicates that in some of the patients with language complaints, a comprehensive language test battery reveals adequate performance. It has been found

previously in glioma patients that language complaints cannot always be objectified by conducting language assessments (Racine et al., 2015; Satoer et al., 2012). Explanations for (2) may have to do with the underestimation of one's own performance, certain patient characteristics, and/or the test situation being artificial.

First, it has been reported by Kruger and Dunning (1999) that individuals who are more competent than their peers tend to underestimate their own performance and ability. Hence, patients who have adequate or good language performance may underestimate their own abilities, and perhaps report subtle difficulties. Also, it is likely that patients pay very close attention to their brain functions after receiving the diagnosis of a brain tumour. As a consequence, they may be more inclined to notice and report subtle disturbances, possibly leading to more self-reported language problems, despite their test scores lying in the normal range.

Second, particular patient characteristics can be associated with a higher incidence of self-reported language problems. For cognition, it has been shown that more (severe) self-reported problems are associated with increased psychological distress, fatigue, motor dysfunction, and female gender in brain tumour patients (Gehring et al., 2015; Pranckeviciene et al., 2017). As impaired test performance is associated with different characteristics (Gehring et al., 2015), a combination of the former factors may result in a higher number of self-reported language problems, sometimes in combination with intact test performance.

Third, phenomenon (2) can partly be explained by the fact that conducting language tests is an artificial situation. It is not representative of language use in daily life. Everyday language use is unrestricted and requires integration of different linguistic levels, which is more complex and demanding than assessing linguistic levels in isolation. Spontaneous speech analysis resembles everyday language abilities better than formal language testing, and can make a valuable contribution to the test results (Rofes et al., 2018; Satoer et al., 2018). Another possible explanation, partly conflicting with (1), is that some of the language tests are not suitable or sufficiently sensitive for the reported complaints by this patient group.

Effect of tumour and treatment characteristics

Tumour and treatment characteristics are not significantly related to language functioning in this patient group. This contrasts previous findings in larger groups that demonstrated effects of meningioma localisation and volume on language performance ($N = 70$ in Abel et al., 2016; $N = 48$ in Butts et al., 2017; and $N = 54$ in Liouta et al., 2016). Hence, the absence of significant effects in the current study is presumably due to the small sample size.

For tumour localisation, it is observed that the majority of patients with an anterior (frontal) meningioma does not have a language impairment, whereas the majority of patients with a posterior (parietal/parieto-occipital) meningioma does have a language impairment (all affecting expressive language domains) before surgery. This is unexpected because frontal regions are highly involved in expressive language functioning (De Witte et al., 2015). Additionally, anterior meningiomas are reported to be associated with poorer expressive language performance than posterior meningiomas (Liouta et al., 2016). We do not have a straightforward explanation for the contradictory finding in the current study, apart from the small sample size.

Conclusion and recommendation

Meningiomas can cause language impairments, despite the non-infiltrative nature of these tumours. Impairments concern expressive language abilities: speech production and writing. Language performance after meningioma surgery remains largely unchanged, although some patients show long-term language deterioration.

Our findings demonstrate the importance of assessing language abilities in patients with a left-sided meningioma, also with regard to individual postoperative changes. Assessments require at least speech production and writing tests, combined with self-reported information regarding language problems. As the congruence between self-reported language problems and test results appears to be weak, taking only one or the other into account could lead to inadequate conclusions.

To date in clinical practice, language functioning before and after meningioma surgery is not always evaluated. In view of suitable counselling and patients' quality of life, our study underlines that language impairments in meningioma patients are not to be ignored.

Chapter 7

Distinct slow-wave activity patterns in resting-state EEG and their relation to language functioning in low-grade glioma and meningioma patients

Abstract

Introduction

Brain tumours frequently cause language impairments. Also, brain tumours are likely to co-occur with localised abnormal slow-wave brain activity, but it is unclear whether this applies specifically to low-grade brain tumours. We investigate whether low-grade glioma and meningioma patients have increased slow-wave activity in resting-state electroencephalography (EEG), and if so, whether this relates to preoperative language functioning and postoperative language outcome.

Method

Patients with a glioma ($N = 15$) or meningioma ($N = 10$) infiltrating into/pressing on the language-dominant hemisphere underwent extensive language testing before and 1 year after surgery. EEG was registered preoperatively, postoperatively (glioma patients only), and once in healthy individuals. Slow-wave activity in delta and theta frequency bands was evaluated visually and quantitatively by spectral power at three levels over the scalp: the whole brain, the affected hemisphere, and the affected area.

Results

Glioma patients had increased delta activity (affected area) and increased theta activity (all levels) before and after surgery. Meningioma patients had no increased slow-wave activity compared to healthy individuals. Before glioma surgery, increased theta activity was related to the presence of language impairment, in particular to poorer word retrieval and morphosyntactic performance. Preoperative slow-wave activity was not related to postoperative language outcome.

Discussion

Low-grade gliomas and meningiomas have a different effect on resting-state brain activity. The findings suggest that increased theta activity can be considered a marker of language impairment in glioma patients, but slow-wave activity is not predictive of language outcome after surgery.

Introduction

Approximately 10 per 100.000 individuals are diagnosed with a primary brain tumour every year (De Robles et al., 2015). When located in the left hemisphere, it is estimated that nearly half of these tumours cause language impairments (Davie, Hutcheson, Barringer, Weinberg, & Lewin, 2009). Language impairments have an immense impact on everyday domestic, social and professional activities, and, thus, on the quality of life (Hilari et al., 2012). They can affect different language modalities (speech production, comprehension, reading, and writing) and linguistic levels, such as phonology (concerning speech sounds), semantics (concerning meaning) and morphosyntax (concerning word and sentence structure). Adequate language functioning relies on a large-scale, usually left-lateralised neural network, involving a large part of the perisylvian cortex and the underlying white matter pathways (Duffau et al., 2014). White matter pathways have been shown to be especially crucial for language; injury to these subcortical tracts greatly increases the risk of language decline and permanent impairments after brain tumour surgery (Bello et al., 2007; Trinh et al., 2013).

Brain injury, principally white matter injury, is known to co-occur with increased slow-wave activity: an excess of focal brain activity in the delta (0.5-4 Hz) and theta (4-8 Hz) frequency bands (Lüders & Noachtar, 2000). Increased slow-wave activity is considered pathological, indicative of brain dysfunction, when present in adults during wakeful, resting conditions (Lüders & Noachtar, 2000). Slow waves are presumed to be induced by injured tissue around the lesion, specifically by white matter injury, and generated by cortical areas overlying the lesion (Ball et al., 1977; Gloor et al., 1977). Increased slow-wave activity has been observed in brain tumour patients (Baayen et al., 2003; De Jongh et al., 2003; Oshino et al., 2007). However, these investigations concerned heterogeneous groups of brain tumour patients, including different tumour types and grades. It is unclear whether increased slow-wave activity is evident in low-grade brain tumour patients, more specifically, low-grade glioma and meningioma patients, in whom the tumour has developed over a long time.

Gliomas are intra-axial, infiltrative tumours, representing the most frequently occurring primary brain tumours, of which 20% are low-grade (World Health Organisation [WHO] grade II; Ho et al., 2014; Louis et al., 2016). One-third of primary brain tumours concern meningiomas; these are extra-axial, non-infiltrative tumours, of which 95% are low-grade (WHO grade I; Wiemels, Wrensch, & Claus, 2010). Low-grade gliomas and meningiomas are both slow-growing, but their different histopathological nature has distinct effects on peritumoural brain tissue (infiltration versus compression), possibly reflected by slow-wave activity patterns. Patients with a low-grade brain tumour are usually young individuals with a relatively long life expectancy after surgery (Ho et al., 2014; Van Alkemade et al., 2012). Preservation of language functioning is crucial in these patients for successfully carrying out daily activities and returning to work.

Considering the involvement of white matter injury in the manifestation of language impairments as well as in the emergence of abnormal slow-wave activity, a relation between slow-wave activity and language functioning is expected. This has not yet been studied in brain tumour patients, apart from one retrospective study. Wolthuis et al. (chapter 4) demonstrated

that increased slow-wave activity was related to poorer language performance, according to a composite language score including naming, verbal fluency, comprehension, repetition, reading, and writing. However, it concerned a heterogeneous patient group of low-grade and high-grade glioma patients who were assessed before or after surgery. On top of that, the time interval between registration of brain activity and language assessment was relatively long. Hence, the relation between slow-wave activity and language functioning in low-grade brain tumour patients is to be further investigated.

For cognitive functions, it has been shown that increased slow-wave activity in low-grade glioma patients is associated with poorer working memory, information processing, and executive functioning (Bosma, Stam, et al., 2008). Also, slow-wave activity in brain tumour patients has been studied in relation to clinical symptoms (mostly sensorimotor impairments) and functional outcome after surgery. Oshino et al. (2007) demonstrated that the localisation of increased focal slow-wave activity corresponds to the brain areas which are responsible for the manifested symptoms. This was more apparent for delta activity than for theta activity. Furthermore, a larger area of increased delta activity was related to poorer functional outcomes after brain tumour surgery (Oshino et al., 2007).

In patients with non-tumour-related brain injury, for example due to stroke or neurodegenerative disease, slow-wave activity has been associated with the level of language performance, which often corresponded to the severity of language impairment (Chapman et al., 1989; Claus et al., 2000; Finitzo et al., 1991; Hensel et al., 2004; Jabbari et al., 1979; Kiehl et al., 2019; Meinzer et al., 2004; Olde Dubbelink et al., 2013; Szekely et al., 2002; Van der Hiele et al., 2007). Moreover, slow-wave activity has been used to predict the course of language recovery in post-stroke aphasia. Little or no slow-wave activity was indicative of good language recovery, whereas a high level of slow-wave activity was indicative of poor language recovery (Hensel et al., 2004; Jabbari et al., 1979; Szekely et al., 2002; Tikofsky et al., 1960). For a review, see chapter 2.

The current study investigates whether slow-wave activity has clinical relevance for the course of language functioning in patients undergoing low-grade glioma or meningioma surgery. We use electroencephalography (EEG) for brain activity registration because it is relatively inexpensive and commonly used in clinical practice. Hence, potential novel findings are clinically applicable and may aid in perisurgical patient care, such as treatment planning, counselling, and language rehabilitation. Additionally, we attempt to gain more insight into the underlying neural mechanisms of language impairments, for which the main language modalities and linguistic levels (combined into 'language domains') are taken into account.

Our research questions are:

- (1) Do low-grade glioma and meningioma patients have more slow-wave activity than healthy individuals in their EEG preoperatively and 1 year postoperatively?
- (2) If so, is increased preoperative slow-wave activity related to: preoperative language functioning, and 1 year postoperative language outcome?

Method

Participants

Patients with a presumed low-grade glioma and patients with a presumed grade I meningioma, who were planned to undergo surgery at the University Medical Centre Groningen (UMCG) or the Erasmus MC University Medical Centre Rotterdam (Erasmus MC), were invited to participate in the study.

Inclusion criteria were:

- intracranial, supratentorial, untreated tumour infiltrating into or pressing on the language-dominant hemisphere⁸ (if language lateralisation was unknown: right-handed patients with left-sided tumour);
- tumour diameter >3 cm (meningiomas only);
- aged between 18 and 75 years;
- in case of epilepsy, seizures under control with anticonvulsants.

Exclusion criteria were:

- non-native speaker of Dutch;
- history of a medical, neurological or psychiatric condition known to affect language or cognitive functioning;
- history of substance abuse;
- consistent use of dexamethasone preoperatively;
- previous brain surgery or cranial radiation therapy.

Glioma patients underwent tumour resection with an awake procedure and meningioma patients underwent surgery under general anaesthesia. Healthy volunteers (aged between 18 and 75; often proxies of the patients) were invited to participate in the control group. The same exclusion criteria applied for this group. This multicentre study was approved by the medical, ethical review board of the UMCG, which was also applicable to the Erasmus MC. All participants gave written informed consent.

Matching for age, gender and education

The patient groups were compared to the healthy control group with regard to age (Mann-Whitney U test), gender (Fisher's exact test) and education (Mann-Whitney U test). No differences were found for age, gender and education between the glioma patient group ($N = 15$) and the healthy control group ($N = 15$). For the meningioma patient group, no differences were found for gender and education, but age differed significantly between meningioma patients ($N = 10$, $M = 58.6$) and the healthy participants ($N = 15$, $M = 42.3$), $U = 22$, $p = 0.002$. Therefore, the youngest healthy participants were excluded from the group

⁸ Bilateral language activation in functional magnetic resonance imaging (fMRI) was also permitted for inclusion.

until there was no longer a significant age difference between the meningioma patients and the control group. This resulted in a control group of 9 healthy participants for comparisons to the meningioma patient group.

Procedure

Both patient groups underwent extensive language assessment at three time points: T1 = before surgery (glioma patients: mean 33 days, range 6-83; meningioma patients: mean 20 days, range 1-48); T2 = 2 months after surgery (reported elsewhere; chapters 5 and 6); and T3 = 12 months after surgery (glioma patients: mean 12.61, range 11.05-15.22; meningioma patients: mean 11.97, range 11.21-12.49). EEG registration was performed at T1 and at T3 in glioma patients, at T1 in meningioma patients, and once in healthy participants.

Language assessment

A selection of standardised language tests was conducted, assessing a wide range of linguistic abilities. Tests included object naming (De Witte et al., 2015), action naming in sentence context (Rofes, 2012), the shortened version of the Token Test (De Renzi & Faglioni, 1978), category fluency (Luteijn & Barelds, 2004), letter fluency (Schmand et al., 2008), reading and writing (Van lerschot, 2018), and subtests of the Diagnostic Instrument for Mild Aphasia (DIMA; Satoer et al., 2019): repetition, semantic odd-picture-out, sentence completion, and sentence judgement. Task descriptions have been reported previously (chapters 5 and 6).

Raw scores were normalised by conversion to z-scores, using pre-existing normative data from a healthy population. Subsequently, eight language domains were created for the purpose of this study, as shown in table 7.1. This was done for two reasons: (1) to reduce the number of statistical comparisons; and (2) to examine all language modalities (speech production, comprehension, reading, and writing), three linguistic levels (phonology, semantics, and morphosyntax), and comprehension of two types of input (auditory and visual). A domain score equalled the average z-score of the tests in that domain for each patient. Domain scores below -1.5 indicated an impairment.

Table 7.1. Language domains under investigation with their corresponding tests

Domains	Tests
1. Production-Word retrieval	Object naming
2. Production-Phonology	Repetition Letter fluency
3. Production-Semantics	Semantic odd-picture-out Category fluency
4. Production-Morphosyntax	Sentence completion Action naming in sentence context
5. Comprehension-Auditory input	Token Test
6. Comprehension-Visual input	Sentence judgement (accuracy)
7. Reading	Reading
8. Writing	Writing

EEG registration

EEG was registered using 44-channel Schwarzer amplifiers (Natus Europe GmbH, Munich). Twenty-one scalp electrodes were applied according to the International 10-20 System, with or without caps according to local protocol. Additional polygraphic channels were applied for artefact detection: electrooculography (EOG; two diagonally placed electrodes for eye movements), electrocardiography (ECG; chest electrode), and respiration (abdominal movements). EEG was recorded with electrode impedances $\leq 5 \text{ k}\Omega$, a sampling frequency of 500 Hz, and with Cz as reference electrode.

At least 5 minutes of eyes-closed, resting-state EEG were registered for every participant. If there were many artefacts, the duration was prolonged to 10 minutes. Participants were instructed to try to refrain from moving and to stay alert. Alertness was continuously monitored and acoustic stimuli were given when signs of drowsiness appeared. For (glioma) patients with suspected epileptiform activity, the resting-state registration was followed by the standard clinical EEG registration of at least 30 minutes.

Analysis of slow-wave activity

Evaluation of slow-wave activity was performed visually, the gold standard in clinical evaluation, and quantitatively, for investigating a relation to language performance.

Visual EEG analysis was performed in BrainRT software (v.2.0; Rumst, Belgium, 2013) by one of the authors (PJC), a board-certified clinical neurophysiologist, who was blinded to the participants' medical situation (brain tumour or healthy). The presence and characteristics of activity in the delta (0.5-4 Hz), theta (4-8 Hz), and alpha (8-12 Hz) frequency bands were determined with EEG data reformatted to display standard antero-posterior bipolar montage and common average montages. Subsequently, slow-wave activity was classified according to the Mayo Classification System (Mayo Clinic and Mayo Foundation, 1998), complemented by guidelines of Lüders and Noachtar (2000). From this, four categories were created: normal, mild, moderate, and severe slow-wave activity. See table 7.2 for their definitions. As pathological slow-wave activity is generally pronounced over a region of brain injury (De Jongh et al., 2003), the categories of visual EEG analysis are presented in relation to quantitatively-analysed slow-wave activity over the affected area as described below.

Quantitative EEG analysis was performed in BrainVision Analyzer 2.0 (Brain Products GmbH, 2013). Artefact-free EEG was selected by visual inspection (IB) and was segmented into 20 2-second epochs for each participant. Raw EEG data were re-referenced to a new averaged reference consisting of 16 scalp electrodes: F3; F4; F7; F8; T3; T4; T5; T6; C3; C4; P3; P4; O1; O2; Fz; and Pz (excluding: Cz [reference electrode]; Fp1 and Fp2 [to minimise excess muscle activity and eye movement artefacts]; A1 and A2 [do not register brain activity]). Subsequently, the data were filtered (band-pass: 0.27-30 Hz, slope 24 dB/Oct; notch: 50 Hz, slope 24 dB/Oct). For every patient, spectral analysis was performed on the 20 epochs of 1000 points by a Fast Fourier Transform (FFT) for all 16 electrodes. After averaging the 20 FFTs, absolute power in the delta (0.5-4 Hz) and theta range (4-8 Hz) was normalised by dividing both by the absolute power in the total spectrum (0.5-70 Hz). Hence, quantitative analysis of slow-wave activity resulted in relative power values in the delta and theta band separately.

Table 7.2. Classification of slow-wave activity in EEG by visual analysis

Degrees of slow-wave activity	Category derived from the Mayo Classification System ^a	Interpretation ^b
<u>Normal</u>		No abnormal slow-wave activity
<u>Mild</u>	- Dysrhythmia grade I - Dysrhythmia grade II	Intermittent nonspecific theta or delta slowing < 50% of the recording: focal, bilateral, or diffuse with amplitudes < 60 μ V
<u>Moderate</u>	- Dysrhythmia grade III - Delta grade I	Intermittent nonspecific theta or delta slowing > 50% of the recording: focal, bilateral, or diffuse with amplitudes > 60 μ V ^c Persistent polymorphic (irregular) delta slowing: focal, bilateral or diffuse with amplitudes < 30 μ V
<u>Severe</u>	- Delta grade II - Delta grade III	Persistent polymorphic (irregular) delta slowing: focal, bilateral or diffuse with amplitudes > 30 μ V

Note. Persistent asymmetry in amplitude or frequency of >50% between the hemispheres was also scored, but not included in the analysis.

^a Mayo Clinic and Mayo Foundation (1998).

^b Complemented by guidelines of Lüders and Noachtar (2000).

^c Dysrhythmia grade III can also refer to specific epileptiform activity (spikes, sharp waves and spike-waves as well as recorded ictal patterns). Even though this was scored during visual interpretation of EEG, it was not included for data analysis.

In order to examine slow-wave activity at different spatial levels over the scalp, three measures were created. First, a whole-brain measure was computed, consisting of the mean activity of the 16 remaining scalp electrodes. Subsequently, two ‘tumour-specific’ measures were created, taking into account the tumour localisation of individual patients: (1) ‘Affected hemisphere’, consisting of the mean activity of 7 electrodes on the side of the tumour (F3, F7, T3, T5, C3, P3, and O1 for left-sided tumours and F4, F8, T4, T6, C4, P4, and O2 for right-sided tumours); and (2) ‘Affected area’, consisting of the mean activity of electrodes over the region of the tumour, which was classified by a neuro-radiologist. This corresponded to one or two of the following regions (based on EEG regions as used in Gallego-Jutglà et al., 2015): left frontal (F3); right frontal (F4); left temporal (mean of F7, T3, and T5); right temporal (mean of F8, T4, and T6); left parietal (C3); right parietal (C4); left occipital (mean of P3 and O3); and right occipital (mean of P4 and O2; see figure 7.1).

Statistical analysis

Analyses were performed using IBM SPSS Statistics software (version 23, release 23.0.0.0). For delta and theta activity over the whole brain, the patient groups were compared to the control groups by using Mann-Whitney U tests. As the two tumour-specific measures could only be calculated for patients, they were compared to the median of the whole-brain measure of the control groups, by using one-sample Wilcoxon signed rank tests. This was performed after confirmation that the control groups had no differences between the left and the right hemisphere ($N = 15$, delta: $Z = -1.307$, $p = 0.191$, theta: $Z = -1.367$, $p = 0.172$; $N = 9$, delta: $Z = -0.771$, $p = 0.441$, theta: $Z = -0.475$, $p = 0.635$). Only the slow-wave activity measures for

which patients showed significantly more delta/theta activity than healthy individuals were used in the analysis with language functioning. Language was analysed in terms of impaired (z-score ≤ -1.5 on one or more language domains) or unimpaired: slow-wave activity of patients with language impairment was compared to slow-wave activity of patients without language impairment with Mann-Whitney U tests. Also, the separate language domain scores were analysed in relation to slow-wave activity with Kendall's tau-b correlation coefficients⁹. A Bonferroni correction for the number of slow-wave activity measures was applied in the correlation analyses (adapted significance level). A significance level of 0.05 was used in all other tests.

Figure 7.1. Electrode positions according to the International 10-20 System and their involvement in the slow-wave activity measures. The five red-circled electrodes were excluded from all analyses. 'Whole brain' included the 16 remaining electrodes, whereas 'Affected hemisphere' and 'Affected area' included the electrodes corresponding to the individual tumour location of each patient.

Results

Participants

Demographic and clinical characteristics of the 15 glioma patients (matched to 15 healthy individuals) and the 10 meningioma patients (matched to 9 healthy individuals) can be found in table 7.3. At T3, there was a drop-out of two glioma patients, due to severe side effects of adjuvant treatment, and two meningioma patients, because they were no longer motivated to participate in the study.

9 The Kendall's tau-b test was selected because it best handles the combination of small sample sizes and many ties (patients with identical language scores) in the data, which do not meet the assumptions for parametric testing.

Table 7.3. Demographic and clinical characteristics of the participants: number of participants (and percentage) or mean (and range)

	Glioma patients (N = 15)	Control group matched to glioma patients (N = 15)	Meningioma patients (N = 10)	Control group matched to meningioma patients (N = 9)
Gender – female	5 (33%)	6 (40%)	6 (60%)	4 (44%)
Mean age in years (range)	42.0 (22-60)	42.3 (20-59)	58.6 (50-69)	53.8 (46-59)
Mean education level ^a (range)	5.3 (4-7)	5.4 (4-7)	5.4 (3-7)	5.2 (4-7)
Handedness ^b				
Right	10 (67%)	12 (80%)	9 (90%)	8 (89%)
Left	4 (27%)	3 (20%)	0	1 (11%)
Ambidextrous	1 (7%)	0	1 (10%)	0
Mean ‘diagnosis → surgery’ time in months (range)	20.8 (1.1-167.3)	NA	8.0 (2.1-49.7)	NA
Tumour histology and grade ^c				
Diffuse astrocytoma, grade II	5 (33%)	NA	NA	NA
Oligodendroglioma, grade II	10 (67%)	NA	NA	NA
Meningioma, grade I	NA	NA	10 (100%)	NA
Tumour localisation, hemisphere				
Left	13 (87%)	NA	10 (100%)	NA
Right ^d	2 (13%)	NA	0	NA
Tumour localisation, lobes				
Frontal	5 (33%)	NA	6 (60%)	NA
Fronto-temporal	1 (7%)	NA	0	NA
Fronto-parietal	1 (7%)	NA	0	NA
Temporal	1 (7%)	NA	0	NA
Temporo-insular	3 (20%)	NA	0	NA
Parietal	3 (20%)	NA	3 (30%)	NA
Parieto-temporal	1 (7%)	NA	0	NA
Parieto-occipital	0	NA	1 (10%)	NA
Extent of resection ^e				
Partial: 20-89%	7 (47%)	NA	1 (10%)	NA
Subtotal: 90-99%	6 (40%)	NA	1 (10%)	NA
Total: 100%	2 (13%)	NA	8 (80%)	NA
Use of anti-epileptic drugs at T1	13 (87%)	NA	6 (60%)	NA
Use of anti-epileptic drugs at T3	12/13 (92%)	NA	7/8 (88%)	NA
Postoperative glioma treatment (chemo/radiotherapy ongoing or completed at T3)	10/13 (77%)	NA	NA	NA

Note. NA = not applicable; T1 = before surgery; T3 = 1 year after surgery. Some variables add up to 101% due to rounding.

^a Education level was classified according to seven categories (1= incomplete primary education; 2= complete primary education; 3= primary education and < 2 years of low-level secondary education; 4= complete low-level secondary education; 5= complete average-level secondary education; 6= complete high-level secondary education; 7= complete university education; Verhage, 1964).

^b Handedness was assessed by the Edinburgh Handedness Inventory (Oldfield, 1971).

^c Based on the 2016 WHO (World Health Organisation) classification (Louis et al., 2016).

^d The two right-hemispheric glioma patients had bilateral language activation in fMRI.

^e Extent of resection was determined by a neuroradiologist, based on pre- and postoperative tumour volumes.

Language performance

Glioma patients

T1 & T3: Pre- and postoperative language domain z-scores are presented in table 7.4. Chapter 5 provides the specifics of the language performance in this patient group.

Meningioma patients

T1 & T3: Pre- and postoperative language domain z-scores are presented in table 7.5. Chapter 6 provides the specifics of the language performance in this patient group.

Table 7.4. Language domain z-scores of glioma patients at T1 and T3, including comparisons to normative data from a healthy population

Language domain	T1: Language z-scores				Comparisons to a healthy population		T3: Language z-scores				Comparisons to a healthy population	
	N	Mdn	Min	Max	Z	p	N	Mdn	Min	Max	Z	p
P-Word Retrieval	15	-1.64	-10.71	0.83	-1.99	0.023	13	0.02	-7.18	0.88	-1.23	0.110
P-Phonology	15	-0.20	-5.28	0.95	-2.27	0.012	13	-0.84	-5.62	0.85	-2.20	0.014
P-Semantics	15	-0.60	-5.14	1.11	-1.87	0.031	13	-0.70	-3.99	0.91	-1.85	0.032
P-Morphosyntax	15	-0.25	-8.33	0.74	-1.53	0.063	13	-0.59	-5.38	0.86	-2.41	0.008
C-Auditory Input	15	-0.69	-4.98	0.83	-1.77	0.039	13	-0.18	-3.97	0.83	-0.88	0.191
C-Visual Input	13	0.19	-1.05	0.56	0.32	0.376	12	0.38	-0.72	0.57	0.94	0.173
Reading	14	0.28	-5.28	0.28	2.67	0.004	13	0.28	-2.50	0.28	-0.69	0.247
Writing	13	-0.79	-6.12	0.55	-2.16	0.016	13	-0.79	-7.45	0.55	-2.78	0.003

Note. P = production; C = comprehension; N = sample size; Mdn = median; Min = minimum value; Max = maximum value; Z = standardised test statistic of the one-sample Wilcoxon signed rank tests; p = p-value (one-sided). Significant effects ($p < 0.05$) are presented in bold font.

Table 7.5. Language domain z-scores of meningioma patients at T1 and T3, including comparisons to normative data from a healthy population

Language domain	T1: Language z-scores				Comparisons to a healthy population		T3: Language z-scores				Comparisons to a healthy population	
	N	Mdn	Min	Max	Z	p	N	Mdn	Min	Max	Z	p
P-Word Retrieval	10	-0.58	-1.64	0.42	-1.89	0.030	8	-0.58	-8.44	0.88	-1.40	0.081
P-Phonology	10	-0.12	-1.34	1.16	-0.97	0.167	8	-0.11	-1.61	1.31	-0.14	0.445
P-Semantics	10	-0.48	-1.58	1.03	-1.27	0.102	8	0.38	-1.34	1.43	1.26	0.104
P-Morphosyntax	10	-0.51	-1.29	-0.35	-2.81	0.003	8	-0.16	-3.77	0.43	-1.12	0.132
C-Auditory Input	10	0.07	-0.69	0.83	0.05	0.480	8	0.07	-1.19	0.83	0.28	0.390
C-Visual Input	7	-0.07	-1.18	0.74	0.17	0.433	6	0.30	-0.53	0.51	0.73	0.232
Reading	9	0.28	-2.50	0.28	1.73	0.042	8	0.28	-2.50	0.28	1.51	0.066
Writing	9	-0.79	-6.12	0.55	-1.98	0.024	8	-1.45	-6.12	0.55	-1.69	0.046

Note. P = production; C = comprehension; N = sample size; Mdn = median; Min = minimum value; Max = maximum value; Z = standardised test statistic of the one-sample Wilcoxon signed rank tests; p = p-value (one-sided). Significant effects ($p < 0.05$) are presented in bold font.

Slow-wave activity

Glioma patients

T1: By visual EEG examination, nine patients (60%) had no abnormal slow-wave activity ('normal' in table 7.2), five patients (33%) had a mild degree of slow-wave activity, and one patient (7%) had a severe degree of slow-wave activity. For every degree, figure 7.2a shows the corresponding quantitative EEG results, namely, the median ratios of delta and theta activity over the affected area.

Quantitative EEG analysis revealed that glioma patients had significantly more delta activity over the affected area ($Mdn_G = 0.450$) compared to the whole-brain measure of the control group ($Mdn_C = 0.324$), $Z = 2.158$, $p = 0.016$, $r = 0.56$. No differences between the groups were found for delta activity over the whole brain and the affected hemisphere. Therefore, delta activity over the whole brain and the affected hemisphere at T1 were not analysed in relation to language performance.

In the theta band, glioma patients showed significantly more activity over the whole brain ($Mdn_G = 0.132$, $Mdn_C = 0.110$, $U = 68.0$, $p = 0.034$, $r = 0.34$), the affected hemisphere ($Mdn_G = 0.135$, $Mdn_C = 0.110$, $Z = 2.784$, $p = 0.003$, $r = 0.72$), and the affected area ($Mdn_G = 0.149$, $Mdn_C = 0.110$, $Z = 2.897$, $p = 0.002$, $r = 0.75$) than healthy individuals. See Appendix D1.

T3: One year after surgery, eleven glioma patients underwent a second EEG registration. Visual EEG examination showed that five patients (46%) had no abnormal slow-wave activity, four patients (36%) had a mild degree of slow-wave activity, one patient (9%) had a moderate degree of slow-wave activity, and one patient (9%) had a severe degree of slow-wave activity. For every degree, figure 7.2b shows the corresponding, quantitatively-analysed median ratios of delta and theta activity over the affected area.

Quantitative EEG analysis revealed that glioma patients had significantly more delta activity over the affected area ($Mdn_G = 0.370$) at T3 compared to the whole-brain measure of the control group ($Mdn_C = 0.324$), $Z = 1.778$, $p = 0.038$, $r = 0.54$. No differences between the groups were found for delta activity over the whole brain and the affected hemisphere.

In the theta band, glioma patients showed significantly more activity over the whole brain ($Mdn_G = 0.139$, $Mdn_C = 0.110$, $U = 47.0$, $p = 0.035$, $r = 0.36$), the affected hemisphere ($Mdn_G = 0.149$, $Mdn_C = 0.110$, $Z = 2.223$, $p = 0.013$, $r = 0.67$), and the affected area ($Mdn_G = 0.160$, $Mdn_C = 0.110$, $Z = 2.667$, $p = 0.004$, $r = 0.80$) than healthy individuals. See Appendix D1.

Meningioma patients

T1: Visual EEG examination revealed that seven patients (70%) had no abnormal slow-wave activity, two patients (20%) had a mild degree of slow-wave activity, and one patient (10%) had a moderate degree of slow-wave activity. For every degree, figure 7.3 shows the corresponding, quantitatively-analysed median ratios of delta and theta activity over the affected area.

Quantitative EEG analysis demonstrated that delta and theta activity over the whole brain, the affected hemisphere, and the affected area in meningioma patients did not differ from the whole-brain measure of the control group (Appendix D2). Therefore, slow-wave activity in meningioma patients was not analysed in relation to language performance.

T3: Meningioma patients did not undergo EEG registration at T3.

Figures 7.2a (left) and 7.2b (right). Quantitatively-analysed slow-wave activity (relative delta and theta power) over the affected area for every degree of slow-wave activity from visual EEG examination in glioma patients at T1 (left) and at T3 (right).

Figure 7.3. Quantitatively-analysed slow-wave activity (relative delta and theta power) over the affected area for every degree of slow-wave activity from visual EEG examination in meningioma patients at T1. (N.B. Meningioma patients did not undergo EEG registration at T3.)

Slow-wave activity at T1 and language performance at T1

Only those slow-wave activity measures for which patients had significantly more delta/theta activity than healthy individuals were used to examine whether increased preoperative slow-wave activity is related to preoperative language functioning.

Glioma patients

Impaired vs. unimpaired language performance

No difference in delta activity over the affected area was found between glioma patients with and without language impairment at T1.

In the theta band, glioma patients with language impairment ($N = 9$) had significantly more activity over the whole brain ($Mdn_{Imp} = 0.178$, $Mdn_{Unimp} = 0.122$, $U = 8.5$, $p = 0.029$, $r = 0.56$; see figure 7.4), the affected hemisphere ($Mdn_{Imp} = 0.185$, $Mdn_{Unimp} = 0.125$, $U = 10.0$, $p = 0.045$, $r = 0.52$), and the affected area ($Mdn_{Imp} = 0.214$, $Mdn_{Unimp} = 0.131$, $U = 10.0$, $p = 0.045$, $r = 0.52$) compared to glioma patients without language impairment ($N = 6$) at T1. See Appendix D3.

Figure 7.4. Boxplots of theta activity over the whole brain for glioma patients with language impairment ($N = 9$) and glioma patients without language impairment ($N = 6$) at T1. The boxes contain 50% of the data (interquartile range), including the median (black horizontal line), and the vertically extending lines (whiskers) present the upper and lower quartiles of the data. '*' indicates an outlier > 3 times the interquartile range.

Language domains

No significant correlations were found between delta activity over the affected area and the language domain scores at T1.

Theta activity over the whole brain, the affected hemisphere, and the affected area all showed a significant negative correlation with Production-Word Retrieval scores ($N = 15$, $\tau = -0.57$, $p = 0.004$; $N = 15$, $\tau = -0.57$, $p = 0.004$; $N = 15$, $\tau = -0.51$; $p = 0.010$). Also, theta activity over the affected hemisphere showed a significant negative correlation with

Production-Morphosyntax scores ($N = 15$, $\tau = -0.53$, $p = 0.006$), whereas correlations for the whole brain ($N = 15$, $\tau = -0.47$, $p = 0.017$) and the affected area ($N = 15$, $\tau = -0.44$; $p = 0.025$) lost significance after Bonferroni correction. See Appendix D3.

Meningioma patients

Slow-wave activity in meningioma patients was not analysed in relation to language performance because patients did not have more delta and theta activity than the control group (Appendix D2).

Slow-wave activity at T1 and language outcome at T3

Only those slow-wave activity measures for which patients had significantly more delta/theta activity than healthy individuals were used to examine whether increased preoperative slow-wave activity is related to 1 year postoperative language outcome.

Glioma patients

Impaired vs. unimpaired language performance

No differences in slow-wave activity at T1 were found between glioma patients with and without language impairment at T3. See Appendix D4.

Language domains

No significant correlations were found between delta activity over the affected area at T1 and language scores at T3.

This also applied to the theta band, for which negative correlations between activity over the whole brain ($N = 15$, $\tau = -0.51$, $p = 0.019$), the affected hemisphere ($N = 15$, $\tau = -0.53$, $p = 0.013$), and the affected area ($N = 15$, $\tau = -0.48$; $p = 0.026$) and Production-Word Retrieval scores at T3 lost significance after Bonferroni correction. See Appendix D4.

Discussion

This study indicates that low-grade glioma patients have increased slow-wave activity compared to healthy individuals, before and 1 year after surgery. Before surgery, increased slow-wave activity is associated with the presence of language impairment and with poor language performance in specific language domains. Slow-wave activity before surgery is not related to language outcome after surgery. Furthermore, meningioma patients have no increased slow-wave activity compared to healthy individuals.

Slow-wave activity

Glioma patients

Glioma patients show more delta activity over the affected area, and more theta activity over the whole brain, the affected hemisphere, and the affected area before surgery. Pathologically increased slow-wave activity has already been shown to occur preoperatively in mixed patient groups with different tumour types and grades (Baayen et al., 2003; De Jongh et al., 2003; Oshino et al., 2007) and is now confirmed specifically for low-grade glioma patients. Nevertheless, there is much individual variation in the level of slow-wave activity, also confirmed by visual EEG examination.

Explanations for the observed slow-wave activity patterns will be discussed for the delta and theta band separately. Presence of increased delta activity only over the affected area is in line with previous studies, which also report increased delta activity predominantly over the area corresponding to the tumour location (Baayen et al., 2003; De Jongh et al., 2003; Oshino et al., 2007). Moreover, the findings are supported by Fernández-Bouzas et al. (1999), who show that sources of delta activity are localised in the tumour margins. This explains why we did not find enhanced delta activity over the entire affected hemisphere, nor over the whole brain. Literature on acute brain injury reports that increased localised delta activity is presumed to originate from injured tissue around the lesion, in particular, subcortical white matter injury. Subcortical lesions appear to induce delta waves that are generated by pyramidal neurons in cortical areas overlying the lesion (partial cortical deafferentation; Ball et al., 1977; Gloor et al., 1977). Furthermore, after severe traumatic brain injury, the extent of delta activity is related to the magnitude of white matter injury (Thatcher, 2006). Although low-grade gliomas do not cause acute injury (rather slowly developing injury), gliomas predominantly affect subcortical white matter because that contains more glial cells than cortical grey matter (Larjavaara et al., 2007). Therefore, it is plausible that, also in glioma patients, white matter injury contributes significantly to emerging delta activity.

Increased theta activity is observed at all three spatial levels in our glioma patient group. This is in agreement with the findings of Oshino et al. (2007), who reported that enhanced theta activity is present more diffusely than delta activity in preoperative brain tumour patients. An explanation for the difference in spatial distribution between delta and theta activity is that theta activity is not restricted to the tumour margins, but relates directly to regions of oedema (Fernández-Bouzas et al., 1999, 1997). Considering that oedema is usually manifested around the tumour area, theta activity naturally covers a more widespread

region than delta activity. Interestingly, theta activity appears to indicate less severe brain dysfunction than delta activity and the state of underlying brain tissue may be reversible (Oshino et al., 2007). Hence, increased delta activity and increased theta activity seem to represent two different pathological, neurophysiological processes (Fernández-Bouzas et al., 1999), which have their own spatial distribution and can relate to clinical symptoms in their own way (Oshino et al., 2007).

This is the first study demonstrating that increased slow-wave activity is still present 1 year after glioma surgery. Moreover, the slow-wave activity patterns are identical to those before surgery (more delta activity over the affected area, and more theta activity over the whole brain, the affected hemisphere, and the affected area). De Jongh et al. (2003) reported similar patterns of delta activity preoperatively compared to 8 months postoperatively in a subgroup of patients with different types of low-grade brain tumours. Together, the findings suggest that in the long term after brain tumour surgery, brain tissue around the surgical cavity and/or residual tumour is (still) injured or oedematous, despite much of the tumour having been resected. Alternatively, increased slow-wave activity 1 year after surgery may be associated with adjuvant treatment, which the majority of glioma patients in our study received around the time of testing (Nokia, Anderson, & Shors, 2012).

Meningioma patients

Unlike glioma patients, preoperative meningioma patients have no abnormal slow-wave activity at the group level. The results are similar to those of Oshino et al. (2007). In their study, extra-axial tumours (all meningiomas) were associated with less delta activity and less consistent delta source locations than intra-axial tumours (gliomas and metastatic tumours), while taking tumour size and surrounding oedema into account. The difference between tumour types is presumably due to the fact that meningiomas have a less destructive effect on surrounding brain tissue, especially with regard to subcortical tissue. As opposed to gliomas, meningiomas generally compress and distort surrounding brain tissue without infiltrating it, and white matter pathways tend to be displaced but intact (Campanella et al., 2014). Therefore, meningiomas coincide with minimal or no white matter injury, which is believed to co-occur with minimal or no delta activity (Gloor et al., 1977), in line with our results.

At the individual level, three out of ten patients show an abnormal degree of slow-wave activity by visual EEG examination. Increased slow-wave activity in these patients is possibly linked to larger oedema size, according to post-hoc observations and previous research. Two meningioma patients in Baayen et al. (2003) demonstrated enhanced slow-wave activity patterns similar to those of glioma patients, and both had moderate to strong oedema. Nevertheless, in general our results indicate limited or no abnormal slow-wave activity in meningioma patients. Hence, its evaluation in relation to language functioning does not seem beneficial.

Slow-wave activity and language functioning

Preoperative language performance

Glioma patients with language impairment have similar delta activity, but more theta activity over the whole brain, the affected hemisphere and the affected area, as opposed to glioma patients without language impairment. This suggests that impaired and unimpaired language functioning can be differentiated on the basis of the level of theta activity, which is a novel finding in brain tumour patients. Similar results have been reported for other patient groups. In patients after stroke, the usefulness of slow-wave activity in quantitative EEG for the classification of aphasia and non-aphasia has been demonstrated (Chapman et al., 1989; Finitzo et al., 1991). Furthermore, post-stroke aphasic patients can be differentiated from post-stroke non-aphasic patients by increased left-hemispheric delta activity, maximally over perisylvian areas (Chapman et al., 1989). The localisation of enhanced slow-wave activity is in agreement with the current results, as the affected hemisphere is generally the left hemisphere and the affected area commonly lies around the Sylvian fissure. However, the frequency band (delta instead of theta) that Chapman et al. (1989) report is not in line with our findings. This may be explained by the different types of brain injury (acute versus non-acute), and by the fact that Chapman et al. (1989) did not include theta activity. Also patients with non-acute, neurodegenerative language impairment (i.e., primary progressive aphasia) can be differentiated from healthy, age-matched individuals by slow-wave activity patterns, more specifically, by increased delta activity and increased theta activity over left-hemispheric language-related areas (Kielar et al., 2019; Shah-Basak et al., 2019). Overall, previous studies and the current study point in the same direction: increased slow-wave activity, at least theta activity, is a sign of language impairment.

When considering different language domains, increased theta activity appears to be associated with poorer word retrieval (for all three spatial levels) and morphosyntactic abilities (for the affected hemisphere, and a tendency for the affected area and the whole brain). The relation between increased theta activity and poorer word retrieval, as assessed with object naming, has previously been found in patients with Alzheimer's disease (Kim et al., 2012), although not consistently (Duffy et al., 1995; Helkala et al., 1991; Van der Hiele et al., 2007), and in patients with traumatic brain injury (Thatcher et al., 1998). No significant correlations have been reported for delta activity, like in the current study. Interestingly, object naming is the most frequently used test in glioma patients undergoing awake surgery (De Witte & Mariën, 2013) and high performance on this test is associated with good quality of life and return to work after glioma surgery (Moritz-Gasser, Herbet, Maldonado, & Duffau, 2012). The relation between increased theta activity and poorer morphosyntactic abilities, as assessed with action naming in sentence context and sentence completion, has not been investigated before. Previous studies did not assess morphosyntax or did not analyse it separately in relation to slow-wave activity (Shah-Basak et al., 2019). In general, morphosyntactic performance is only occasionally tested in brain tumour patients, even though it contributes important information to perioperative language assessments, as it reflects communication at the sentence level.

Postoperative language outcome

Even though preoperative slow-wave activity has previously been shown to have prognostic value for functional outcome after brain tumour surgery (Oshino et al., 2007), our study indicates that this does not apply to language outcome. Slow-wave activity in low-grade glioma patients is not predictive of 1 year postoperative language impairment, nor is it predictive of performance in separate language domains. Regarding the latter, there was only a tendency for more theta activity to be associated with poorer word retrieval outcome (as assessed with object naming), which should be interpreted with extreme caution.

Several studies in stroke patients have shown that increased slow-wave activity is indicative of poorer language recovery 2-24 months post-stroke. Evidence has been provided for delta activity (Hensel et al., 2004), theta activity (Tikofsky et al., 1960), and delta-theta activity combined (Jabbari et al., 1979; Széles et al., 2002). The discrepancy with our results is presumably due to the difference in neurological aetiology and the extent of language impairment it induced: an acute stroke, which caused language impairment in all patients (previous studies), versus a slow-growing tumour and its surgical resection, which caused language impairment only in some of the patients (current study). The lower occurrence of language impairment in low-grade glioma patients can be explained by the fact that a slow-growing tumour allows for neuroplasticity processes and reorganisation of (language) function. Moreover, a brain tumour is generally associated with less severe brain injury and less severe language impairment than a stroke in the same location (Anderson et al., 1990). For this reason, it is more probable to detect a relation between slow-wave activity and language outcome in stroke patients than in low-grade glioma patients.

Methodological considerations

The current results should be interpreted with caution because the sample sizes are small and there is a high level of inter-individual variability in language scores and slow-wave activity. With regard to language, we examine performance in eight language domains separately because language covers a wide range of abilities, which can be impaired independently. We believe that the evaluation of language functioning requires a combination of sensitive tests assessing different language modalities (speech production, comprehension, reading, and writing) and linguistic levels (at least phonology, semantics, and morphosyntax); conducting an object naming test alone is not sufficient. However, disadvantages of our elaborate approach are that it is time-consuming and it leads to many statistical tests in relation to slow-wave activity.

The slow-wave activity results may have been influenced by usage of anti-epileptic drugs at T1 and T3 and adjuvant treatment at T3 (Duncan, 1987; Nokia et al., 2012), even though all registrations are visually inspected and controlled for their quality. Furthermore, EEG registration comes with a few challenges. Namely, EEG is sensitive to conductivity errors, as conductivity of the skull and other tissues can blur the signal. As a consequence, one cannot be certain that the signal registered at the scalp originates from the brain area exactly underneath. In addition, by following the standard clinical procedure, EEG was registered with 21 scalp electrodes, which underlines the limited spatial resolution. However, an advantage of EEG in this context is that many brain tumour patients already undergo EEG registration as

part of their diagnostic examination, due to suspected epileptic seizures. In those instances, evaluation of slow-wave activity does not require much extra time, and could provide language-related information simultaneously.

Conclusion

This is the first prospective study to report on slow-wave brain activity in low-grade glioma and meningioma patients, and its relation to language functioning. We show that glioma patients, unlike meningioma patients, have increased slow-wave activity in resting-state EEG. Before and 1 year after glioma surgery, delta activity is increased over the affected (tumour) area, and theta activity is increased over the whole brain, the affected hemisphere, and the affected area. At the same time, patients suffer from language impairments. The data suggest that increased theta activity can serve as a marker of language impairment in glioma patients. Also, more theta activity is associated with poorer word retrieval and morphosyntactic performance. However, the level of slow-wave activity before surgery does not seem to have prognostic value for language outcome after glioma surgery. The search for predictors of language outcome remains important because new insights may aid (peri) surgical procedures and potentially help to prevent language decline.

Chapter 8

Resting-state functional connectivity networks
in relation to pre- and postoperative language
functioning in low-grade glioma and meningioma
patients

Abstract

Introduction

Preservation of language functioning in patients undergoing brain tumour surgery is essential because language impairments negatively impact the quality of life. Apart from that, brain tumour patients have alterations in functional connectivity (FC), the extent to which brain areas functionally interact. We studied FC networks in relation to language functioning in glioma and meningioma patients.

Method

Patients with a low-grade glioma ($N = 15$) or meningioma ($N = 10$) infiltrating into/pressing on the language-dominant hemisphere underwent extensive language testing before and 1 year after surgery. Resting-state EEG was registered preoperatively, postoperatively (glioma patients only), and once in healthy individuals. After analysing FC in theta and alpha frequency bands, weighted networks and Minimum Spanning Trees were quantified by various network measures.

Results

FC network characteristics did not differ between patients and healthy individuals, but visual inspection revealed higher theta-band FC and lower alpha-band FC in both patient groups. Preoperative FC network characteristics (theta: hub presence and global FC; alpha: a small-world-like network configuration) were related to preoperative language functioning (production-morphosyntax and comprehension) in glioma patients. Furthermore, higher theta-band FC before surgery was associated with poorer word retrieval 1 year after surgery. In meningioma patients, FC networks were not related to language functioning.

Discussion

We demonstrate that preoperative FC networks are informative for pre- and postoperative language functioning in glioma patients, but not for language functioning in meningioma patients. However, the matter requires further investigation, considering the small sample sizes and the exploratory design. FC networks can potentially be useful in clinical settings, for example, by predicting postoperative language outcome.

Introduction

Primary brain tumours in the left hemisphere are estimated to cause language impairment in nearly half of all patients (Davie et al., 2009). Language abilities are essential for everyday communication and for participation in society, hence, impairments negatively affect the quality of life (Hilari et al., 2012). As language covers a range of functions, several language modalities (speech production, comprehension, reading, and writing) and linguistic levels (e.g. phonology, concerning speech sounds; semantics, concerning meaning; and morphosyntax, concerning word and sentence structure) are at risk in brain tumour patients.

The most frequently occurring primary brain tumours are gliomas and meningiomas. Gliomas are intra-axial, infiltrative tumours of which 20% are low-grade (World Health Organisation [WHO] grade II; Ho et al., 2014; Louis et al., 2016). Meningiomas are extra-axial, non-infiltrative tumours of which 95% are low-grade (WHO grade I; Wiemels, Wensch, & Claus, 2010). Patients with a low-grade glioma involving eloquent brain areas generally undergo surgical resection by an awake procedure, whereas patients with a meningioma are operated on under general anaesthesia. Patients of both groups are usually young individuals with a relatively long life expectancy after surgery (Ho et al., 2014; Van Alkemade et al., 2012). Preservation of language functioning is crucial in these patients for successfully carrying out daily activities and returning to work. The incidence of language impairments after brain tumour surgery ranges between 10 and 70% (Antonsson, Jakola, et al., 2018; Di Cristofori et al., 2018; Santini et al., 2012; Van Kessel et al., 2020). Hence, it is important to gain more insight into the underlying mechanisms of language impairments in this group of patients to potentially prevent postoperative language decline.

The consequences of an intracranial tumour, and its treatment, on brain functioning can be studied by functional connectivity (FC) networks, analysed from recordings of resting-state brain activity (Bartolomei et al., 2006a). FC concerns the extent to which brain areas functionally interact, which is reflected by the level of synchronisation of brain activity signals, characterised by any statistical interdependency between two signals (Aerts et al., 1989).¹⁰ In brain tumour patients before surgery, FC tends to be increased in lower frequency bands (delta and theta) and decreased in higher frequency bands (beta and gamma) compared to healthy individuals (Bartolomei et al., 2006b, 2006a; Hu et al., 2013; Van Dellen et al., 2012). For the (intermediate) alpha band, FC in brain tumour patients may be higher or lower than in a healthy population (Bartolomei et al., 2006a; Bosma, Douw, et al., 2008), but appears to increase between pre- and postoperative assessments (Lizarazu et al., 2020; Van Dellen et al., 2013).

FC network alterations in brain tumour patients, as investigated with resting-state magnetoencephalography (MEG), have been shown to relate to poorer cognitive functioning, such as verbal memory, working memory, attention, and executive functioning (Bosma,

¹⁰ The interpretation of FC network configurations is dependent on the investigated frequency band; brain activity in the delta and theta bands is considered pathological (this is usually absent in healthy adults while awake), whereas brain activity in the alpha and beta bands indicates normal physiological brain rhythms (Niedermeyer, 1999).

Douw, et al., 2008; Bosma et al., 2009; Derks et al., 2019; Hu et al., 2013; Van Dellen et al., 2013, 2012; Van Nieuwenhuizen et al., 2018). However, literature on language functioning in relation to FC network characteristics is scarce. It has been reported that FC network alterations in the theta, alpha, and gamma bands are associated with poorer performance on a verbal fluency test in glioma patients (Derks et al., 2019; Hu et al., 2013; Van Dellen et al., 2012).¹¹ Furthermore, Lizarazu et al. (2020) assessed left-hemispheric, low-grade glioma patients with an object naming test and semi-spontaneous speech ratings, and registered resting-state MEG before, 3 months after, and 6 months after surgery. No relations between FC change in the alpha band and language change scores were found, possibly because language performance did not significantly change between the time points. Nonetheless, studies in patients with non-tumour-related brain injury show that FC network characteristics predict the type of language impairment and the course of language recovery (Castellanos et al., 2010; Nicolo et al., 2015; Ranasinghe et al., 2017).

For brain tumour patients, it is largely unknown whether, or to what extent, FC network characteristics during a resting state are related to language functioning. In order to investigate this, we assess language domains (created by combining language modalities and linguistic levels) and register brain activity by using electroencephalography (EEG), a non-invasive, inexpensive, and frequently applied technique in clinical practice.

Our research questions are:

- (1) Do FC network characteristics in low-grade glioma and meningioma patients, preoperatively and 1 year postoperatively, differ from those in healthy individuals?
- (2) Are preoperative FC network characteristics related to preoperative language functioning?
- (3) More specifically, which network characteristics are associated with language impairments?
- (4) Are preoperative FC network characteristics related to 1 year postoperative language outcome?

Method

Participants

Patients with a presumed low-grade glioma and patients with a presumed grade I meningioma, who were planned to undergo surgery at the University Medical Centre Groningen (UMCG) or the Erasmus MC University Medical Centre Rotterdam (Erasmus MC), were invited to participate in the study.

11 Verbal fluency, in the form of category or letter fluency, is classified under language functioning instead of executive functioning here because the tests at least partly assess language processing (Aita et al., 2019; Whiteside et al., 2016).

Inclusion criteria were:

- intracranial, supratentorial, untreated tumour infiltrating into or pressing on the language-dominant hemisphere¹² (if language lateralisation was unknown: right-handed patients with left-sided tumour);
- tumour diameter >3 cm (meningiomas only);
- aged between 18 and 75 years;
- in case of epilepsy, seizures under control with anticonvulsants.

Exclusion criteria were:

- non-native speaker of Dutch;
- history of a medical, neurological or psychiatric condition known to affect language or cognitive functioning;
- history of substance abuse;
- consistent use of dexamethasone preoperatively;
- previous brain surgery or cranial radiation therapy.

Glioma patients underwent tumour resection with an awake procedure and meningioma patients underwent surgery under general anaesthesia. Healthy volunteers (aged between 18 and 75; often proxies of the patients) were invited to participate in the control group. The same exclusion criteria applied for this group. This multicentre study was approved by the medical, ethical review board of the UMCG, which was also applicable to the Erasmus MC. All participants gave written informed consent.

Matching for age, gender and education

The patient groups were compared to the healthy control group with regard to age (Mann-Whitney U test), gender (Fisher's exact test) and education (Mann-Whitney U test). No differences were found for age, gender and education between the glioma patient group ($N = 15$) and the healthy control group ($N = 15$). For the meningioma patient group, no differences were found for gender and education, but age differed significantly between meningioma patients ($N = 10$, $M = 58.6$) and the healthy participants ($N = 15$, $M = 42.3$), $U = 22$, $p = 0.002$. Therefore, the youngest healthy participants were excluded from the group until there was no longer a significant age difference between the meningioma patients and the control group. This resulted in a control group of 9 healthy participants for comparisons to the meningioma patient group.

Procedure

Both patient groups underwent extensive language assessment at three time points: T1 = before surgery (glioma patients: mean 33 days, range 6-83; meningioma patients: mean 20 days, range 1-48); T2 = 2 months after surgery (reported elsewhere; chapters 5

12 Bilateral language activation in functional Magnetic Resonance Imaging (fMRI) was also permitted for inclusion.

and 6); and T3 = 12 months after surgery (glioma patients: mean 12.61, range 11.05-15.22; meningioma patients: mean 11.97, range 11.21-12.49). EEG registration was performed at T1 and at T3 in glioma patients, at T1 in meningioma patients, and once in healthy participants.

Language assessment

A selection of standardised language tests was conducted, assessing a wide range of linguistic abilities. Tests included object naming (De Witte et al., 2015), action naming in sentence context (Rofes, 2012), the shortened version of the Token Test (De Renzi & Faglioni, 1978), category fluency (Luteijn & Barelds, 2004), letter fluency (Schmand et al., 2008), reading and writing (Van Ierschoot, 2018), and subtests of the Diagnostic Instrument for Mild Aphasia (DIMA; Satoer et al., 2019): repetition, semantic odd-picture-out, sentence completion, and sentence judgement. Task descriptions have been reported previously (chapters 5 and 6).

Raw scores were normalised by conversion to z-scores, using pre-existing normative data from a healthy population. Subsequently, eight language domains were created for the purpose of this study, as shown in table 8.1. This was done for two reasons: (1) to reduce the number of statistical comparisons; and (2) to examine all language modalities (speech production, comprehension, reading, and writing), three linguistic levels (phonology, semantics, and morphosyntax), and comprehension of two types of input (auditory and visual). A domain score equalled the average z-score of the tests in that domain for each patient. Domain scores below -1.5 indicated an impairment.

Table 8.1. Language domains under investigation with their corresponding tests

Domains	Tests
1. Production-Word retrieval	Object naming
2. Production-Phonology	Repetition Letter fluency
3. Production-Semantics	Semantic odd-picture-out Category fluency
4. Production-Morphosyntax	Sentence completion Action naming in sentence context
5. Comprehension-Auditory input	Token Test
6. Comprehension-Visual input	Sentence judgement (accuracy)
7. Reading	Reading
8. Writing	Writing

EEG registration

EEG was registered using 44-channel Schwarzer amplifiers (Natus Europe GmbH, Munich). Twenty-one scalp electrodes were applied according to the International 10-20 System, with or without caps according to local protocol. Electrode positions are shown in figure 8.1. Additional polygraphic electrodes were applied for artefact detection: electrooculography (EOG; two diagonally placed electrodes for eye movements), electrocardiography (ECG; chest

electrode), and respiration (abdominal movements). EEG was recorded with impedances ≤ 5 k Ω , a sampling frequency of 500 Hz, and with Cz as reference electrode.

At least 5 minutes of eyes-closed, resting-state EEG were registered for every participant. If there were many artefacts, the duration was prolonged to 10 minutes. Participants were instructed to try to refrain from moving and to stay alert. Alertness was continuously monitored and acoustic stimuli were given when signs of drowsiness appeared. For (glioma) patients with suspected epileptiform activity, the resting-state registration was followed by the standard clinical EEG registration of at least 30 minutes.

EEG processing

Artefact-free EEG for analysis was selected by visual inspection (IB) and segmented into five epochs of 8.19 seconds (4096 samples) for each participant. Using BrainVision Analyzer 2.0 (Brain Products GmbH, 2013), EEG data were re-referenced to a new averaged reference consisting of 16 scalp electrodes: F3; F4; F7; F8; T3; T4; T5; T6; C3; C4; P3; P4; O1; O2; Fz; and Pz (excluding: Cz [reference electrode]; Fp1 and Fp2 [to minimise excess muscle activity and eye movement artefacts]; A1 and A2 [do not register brain activity]). Only these 16 electrodes were included for FC network analysis, described below (for more detailed explanations on FC network analysis see Van Diessen et al., 2015; Van Straaten & Stam, 2013; and Zhang, Lei, Wu, & Jiang, 2014).

Figure 8.1. Electrode positions according to the International 10-20 System. The five red-circled electrodes were excluded from all analyses.

Functional connectivity (FC) network analysis

FC network analysis was performed in BrainWave software (version 0.9.152.12.26; Stam, 2018) for every EEG segment. The mean values of 5 segments for each participant were used in further (statistical) analyses. FC networks were analysed in the theta (4-8 Hz) and alpha (8-13 Hz) frequency bands. These bands were selected based on previous literature (Derks et al., 2019; Van Dellen et al., 2012) and because of practical considerations. That is, brain activity in the theta and alpha bands is consistently present (as opposed to the delta band) in awake EEG registrations, is not close to the frequencies of muscle contraction artefacts (as opposed to the beta and gamma bands), and can be easily ascertained by visual inspection.

FC network analysis was performed with the phase lag index (PLI), a correlation coefficient that measures synchronisation of brain activity between different brain regions, by the consistency with which one signal is leading or lagging in phase with respect to another signal (Stam, Nolte, & Daffertshofer, 2007). As this is a phase-based technique, it does not depend on the amplitude of the signal. Other advantages of the PLI are that it analyses nonlinear relations and that it is relatively insensitive to the effects of volume conduction, a phenomenon denoting that the activity recorded over different brain regions can be influenced by one single underlying source (Stam et al., 2007).

Analysis with the PLI results in values between 0 and 1 for every pair of signals. A PLI close to 0 demonstrates no/very weak synchronisation between two signals recorded from different electrode sites, which indicates no/very weak functional interaction between the underlying brain areas. A PLI close to 1 indicates strong synchronisation between two signals and a strong functional interaction between the underlying brain areas. PLI values form the basis for the FC networks, for both weighted and Minimum Spanning Tree (MST) networks, which provide complementary information. The organisation of FC networks was quantified by network measures. Scores on these measures were referred to as network characteristics.

Graph theory and network measures

All network measures used are based on graph theory. This is a mathematical approach by which a complex network is reduced to a 'graph', an abstract representation of the network. A graph consists of nodes (also called 'vertices') and connections, which are links between nodes (also called 'edges'). In our case, nodes refer to the electrode sites, which represent the underlying brain areas, and connections represent functional interactions between the underlying brain areas.

Different aspects of the network organisation were evaluated by using network measures. First, connectivity of individual nodes was examined. Nodes with many connections and a central position in the network are called 'hubs'. Subsequently, short-distance or local FC, and long-distance or global FC were examined. Lastly, efficiency of the entire network configuration was examined.

Table 8.2 gives an overview of the network measures used, including examples corresponding to figure 8.2. The first part of the table quantifies the original weighted networks, and the latter part quantifies the MST networks.

Weighted networks

Weighted networks take the exact PLI values, the synchronisation strength between signals, into account. Hence, it provides insight into all connections, weak and strong, on a continuous scale. For the visualisation of weighted networks, several correlation thresholds were applied. PLI values above such threshold were included as connecting lines in a schematic representation of the brain, and PLI values below the threshold were not included in the network figure. Weighted network figures were created at the group level and at the individual level.

Network measures that quantify weighted networks are influenced by network density, that is, the number of connections, while the number of nodes is equal between participants (Van Diessen et al., 2015). Therefore, weighted network measures were normalised by dividing their absolute values by the mean values of 50 surrogate random networks of the same density. This increased the comparability between networks.

Minimum Spanning Tree (MST) networks

The MST (Stam et al., 2014) is a subnetwork of the weighted network. It has the same number of nodes as the weighted network (16 in our analysis), but the number of connections is limited to the number of nodes minus one (15 in our analysis). Every node gets connected to at least one other node in the MST, without forming cycles. The selection of connections to be included in the MST follows the principle of minimum cost, which is the inverse FC strength ($1/\text{PLI}$ value). To illustrate, the highest PLI value between any of the 16 nodes, which indicates the strongest functional connection, has the lowest cost, and is, therefore, the first to be included in the MST. Next, the connection with the second highest PLI value is included, and so forth, while taking into account the above-mentioned criteria (all nodes have to be connected, no cycles, restricted number of connections). Creation of the MST was performed by Kruskal's algorithm (Kruskal, 1956) in BrainWave software.

As the MST is a binary network, it is independent of an (arbitrarily-chosen) correlation threshold. Where a weighted network looks different for every other correlation threshold, the derived MST network always has one unique representation. Furthermore, MST networks are insensitive to the effect of network density because the number of nodes and connections remain the same. Both properties make MST networks well suited for comparisons between participants. A disadvantage of the MST network is that it includes a small portion of connections and does not provide information on weaker connections or local FC with cycles.

Table 8.2. Network measures used for the quantification of the functional connectivity (FC) brain networks

Measure	Evaluation of	Description	Interpretation	Example in figure 8.2
<i>Weighted (W) network analysis</i>				
PLI:	Phase Lag Index	Functional connectivity	High PLI → high whole-brain FC	NA
rC:	relative average Clustering coefficient	Local FC	High rC → high local FC	NA
rL:	relative average path Length	Global FC	Low rL → high global FC	NA
SWI:	Small-World Index	Entire network configuration	High SWI → optimal network organisation (high local and high global FC)	NA
<i>Minimum Spanning Tree (MST) network analysis</i>				
Degr:	maximum Degree fraction	Connectivity of individual nodes	High Degr → presence of one/more hubs in the network	Node 6 has the maximum degree fraction: 4/9
Ecc:	average Eccentricity	Connectivity of individual nodes	Low Ecc → presence of one/more hubs in the network	Nodes 1 and 6 have the lowest eccentricity: 3/9

Table 8.2. Continued

Measure	Evaluation of	Description	Interpretation	Example in figure 8.2
BC: maximum Betweenness Centrality	Connectivity of individual nodes	Betweenness centrality of a node: the number of paths going through that node divided by the total number of paths ^a . Maximum betweenness centrality: the highest BC of all nodes	High BC → presence of one/more hubs in the network	Node 6 has the maximum betweenness centrality: 38/45
Leaf:	Leaf fraction	Leaf number: the number of nodes in the network that have only one connection (degree = 1); Leaf fraction: leaf number divided by the total number of nodes	High Leaf → high local FC	Leaf fraction: 5/10
Diam:	Diameter	The number of connections in the longest path ^a between any two nodes in the network, and for normalisation, divided by the maximum number of connections	Low Diam → high global FC	Diameter: 5/9
TH:	Tree Hierarchy	The balance between diameter reduction (a star-like configuration) and prevention from overloading central nodes (a line-like configuration): TH = leaf number / (2 * (no. of nodes - 1) * max BC)	Low TH ^b → line-like configuration (no risk of overloading central nodes) High TH ^b → star-like configuration (efficient FC)	Tree hierarchy: 5 / (2 * (10 - 1) * (38/45))

Note. When measures were averaged for all channels or nodes, this concerned the 16 remaining channels (electrode positions) as shown in figure 8.1. NA = not applicable.

^a A path between any two nodes in a MST network is by definition the shortest path between these two nodes because the MST network only has one path between every two nodes (no cycles). Therefore, terms such as the 'longest shortest path' were avoided.

^b TH close to 0 was considered to be low and TH close to 0.5 was considered to be high because TH ≥ 0.5 was not applicable in our data. See Boersma et al. (2013) for the full TH interpretation.

Figure 8.2. Example MST network with 10 nodes, corresponding to the explanations in table 8.2-last column.

Statistical analysis

Apart from visual inspection of network configurations, statistical tests were performed for each research question using IBM SPSS Statistics software (version 23, release 23.0.0.0). (1) Network characteristics of patient groups were compared to those of the control groups by Mann-Whitney U tests. (2) Kendall's tau-b correlation analyses were performed between preoperative network characteristics and preoperative language domain z-scores. (3) Network characteristics of patients with language impairment (z-score ≤ -1.5 on one or more language domains) were compared to those of patients without language impairment by means of Mann-Whitney U tests. Additionally, Degr and BC values were used to calculate which nodes were most often highly connected in patients with language impairment. (4) Kendall's tau-b correlation analyses were performed between preoperative network characteristics and 1 year postoperative language domain z-scores. A Bonferroni correction for the number of network measures was applied in all tests, using a significance level of 0.005.

Results

Participants

Demographic and clinical characteristics of the 15 glioma patients (matched to 15 healthy individuals) and the 10 meningioma patients (matched to 9 healthy individuals) can be found in table 8.3. At T3, there was a drop-out of two glioma patients, due to severe side effects of adjuvant treatment, and two meningioma patients, because they were no longer motivated to participate in the study.

Table 8.3. Demographic and clinical characteristics of the participants: number of participants (and percentage) or mean (and range)

	Glioma patients (N = 15)	Control group matched to glioma patients (N = 15)	Meningioma patients (N = 10)	Control group matched to meningioma patients (N = 9)
Gender – female	5 (33%)	6 (40%)	6 (60%)	4 (44%)
Mean age in years (range)	42.0 (22-60)	42.3 (20-59)	58.6 (50-69)	53.8 (46-59)
Mean education level ^a (range)	5.3 (4-7)	5.4 (4-7)	5.4 (3-7)	5.2 (4-7)
Handedness ^b				
Right	10 (67%)	12 (80%)	9 (90%)	8 (89%)
Left	4 (27%)	3 (20%)	0	1 (11%)
Ambidextrous	1 (7%)	0	1 (10%)	0
Mean 'diagnosis → surgery' time in months (range)	20.8 (1.1-167.3)	NA	8.0 (2.1-49.7)	NA
Tumour histology and grade ^c				
Diffuse astrocytoma, grade II	5 (33%)	NA	NA	NA
Oligodendroglioma, grade II	10 (67%)	NA	NA	NA
Meningioma, grade I	NA	NA	10 (100%)	NA
Tumour localisation, hemisphere				
Left	13 (87%)	NA	10 (100%)	NA
Right ^d	2 (13%)	NA	0	NA
Tumour localisation, lobes				
Frontal	5 (33%)	NA	6 (60%)	NA
Fronto-temporal	1 (7%)	NA	0	NA
Fronto-parietal	1 (7%)	NA	0	NA
Temporal	1 (7%)	NA	0	NA
Temporo-insular	3 (20%)	NA	0	NA
Parietal	3 (20%)	NA	3 (30%)	NA
Parieto-temporal	1 (7%)	NA	0	NA
Parieto-occipital	0	NA	1 (10%)	NA
Extent of resection ^e				
Partial: 20-89%	7 (47%)	NA	1 (10%)	NA
Subtotal: 90-99%	6 (40%)	NA	1 (10%)	NA
Total: 100%	2 (13%)	NA	8 (80%)	NA
Use of anti-epileptic drugs at T1	13 (87%)	NA	6 (60%)	NA
Use of anti-epileptic drugs at T3	12/13 (92%)	NA	7/8 (88%)	NA
Postoperative glioma treatment (chemo/radiotherapy ongoing or completed at T3)	10/13 (77%)	NA	NA	NA

Note. NA = not applicable; T1 = before surgery; T3 = 1 year after surgery. Some variables add up to 101% due to rounding.

^a Education level was classified according to seven categories (1= incomplete primary education; 2= complete primary education; 3= primary education and < 2 years of low-level secondary education; 4= complete low-level secondary education; 5= complete average-level secondary education; 6= complete high-level secondary education; 7= complete university education; Verhage, 1964).

^b Handedness was assessed by the Edinburgh Handedness Inventory (Oldfield, 1971).

^c Based on the 2016 WHO (World Health Organisation) classification (Louis et al., 2016).

^d The two right-hemispheric glioma patients had bilateral language activation in fMRI.

^e Extent of resection was determined by a neuroradiologist, based on pre- and postoperative tumour volumes.

Language performance

Glioma patients

T1 & T3: Pre- and postoperative language domain z-scores are presented in table 8.4. Chapter 5 provides the specifics of the language performance in this patient group.

Meningioma patients

T1 & T3: Pre- and postoperative language domain z-scores are presented in table 8.5. Chapter 6 provides the specifics of the language performance in this patient group.

Table 8.4. Language domain z-scores of glioma patients at T1 and T3, including comparisons to normative data from a healthy population

Language domain	T1: Language z-scores				Comparisons to a healthy population		T3: Language z-scores				Comparisons to a healthy population	
	N	Mdn	Min	Max	Z	p	N	Mdn	Min	Max	Z	p
P-Word Retrieval	15	-1.64	-10.71	0.83	-1.99	0.023	13	0.02	-7.18	0.88	-1.23	0.110
P-Phonology	15	-0.20	-5.28	0.95	-2.27	0.012	13	-0.84	-5.62	0.85	-2.20	0.014
P-Semantics	15	-0.60	-5.14	1.11	-1.87	0.031	13	-0.70	-3.99	0.91	-1.85	0.032
P-Morphosyntax	15	-0.25	-8.33	0.74	-1.53	0.063	13	-0.59	-5.38	0.86	-2.41	0.008
C-Auditory Input	15	-0.69	-4.98	0.83	-1.77	0.039	13	-0.18	-3.97	0.83	-0.88	0.191
C-Visual Input	13	0.19	-1.05	0.56	0.32	0.376	12	0.38	-0.72	0.57	0.94	0.173
Reading	14	0.28	-5.28	0.28	2.67	0.004	13	0.28	-2.50	0.28	-0.69	0.247
Writing	13	-0.79	-6.12	0.55	-2.16	0.016	13	-0.79	-7.45	0.55	-2.78	0.003

Note. P = production; C = comprehension; N = sample size; Mdn = median; Min = minimum value; Max = maximum value; Z = standardised test statistic of the one-sample Wilcoxon signed rank tests; p = p-value (one-sided). Significant effects ($p < 0.05$) are presented in bold font.

Table 8.5. Language domain z-scores of meningioma patients at T1 and T3, including comparisons to normative data from a healthy population

Language domain	T1: Language z-scores				Comparisons to a healthy population		T3: Language z-scores				Comparisons to a healthy population	
	N	Mdn	Min	Max	Z	p	N	Mdn	Min	Max	Z	p
P-Word Retrieval	10	-0.58	-1.64	0.42	-1.89	0.030	8	-0.58	-8.44	0.88	-1.40	0.081
P-Phonology	10	-0.12	-1.34	1.16	-0.97	0.167	8	-0.11	-1.61	1.31	-0.14	0.445
P-Semantics	10	-0.48	-1.58	1.03	-1.27	0.102	8	0.38	-1.34	1.43	1.26	0.104
P-Morphosyntax	10	-0.51	-1.29	-0.35	-2.81	0.003	8	-0.16	-3.77	0.43	-1.12	0.132
C-Auditory Input	10	0.07	-0.69	0.83	0.05	0.480	8	0.07	-1.19	0.83	0.28	0.390
C-Visual Input	7	-0.07	-1.18	0.74	0.17	0.433	6	0.30	-0.53	0.51	0.73	0.232
Reading	9	0.28	-2.50	0.28	1.73	0.042	8	0.28	-2.50	0.28	1.51	0.066
Writing	9	-0.79	-6.12	0.55	-1.98	0.024	8	-1.45	-6.12	0.55	-1.69	0.046

Note. P = production; C = comprehension; N = sample size; Mdn = median; Min = minimum value; Max = maximum value; Z = standardised test statistic of the one-sample Wilcoxon signed rank tests; p = p-value (one-sided). Significant effects ($p < 0.05$) are presented in bold font.

Functional connectivity (FC) networks and language functioning

The results regarding FC network characteristics in relation to language functioning are presented in the next sections for each research question consecutively.

(1) Do FC network characteristics in low-grade glioma and meningioma patients, preoperatively and 1 year postoperatively, differ from those in healthy individuals?

Glioma patients

T1: In the theta band, visual inspection of the group-average weighted networks revealed that left-hemispheric glioma patients had more (and, therefore, generally stronger) functional connections than healthy individuals (figures 8.3A and 8.3C). Furthermore, visual inspection of the group-average MST networks revealed that patients had more left-sided FC, whereas healthy individuals had slightly more right-sided FC. Statistically, the FC (weighted and MST) network characteristics in glioma patients did not significantly differ from those in healthy individuals (Appendix E1).

In the alpha band, visual inspection of the group-average weighted networks revealed that left-hemispheric glioma patients had fewer (and, therefore, generally weaker) functional connections than healthy individuals (figures 8.4A and 8.4C). Furthermore, visual inspection of the group-average MST networks revealed that patients had more right-sided FC, whereas healthy individuals had relatively symmetrical/slightly more left-sided FC. Statistically, the FC (weighted and MST) network characteristics in glioma patients did not differ from those in healthy individuals (Appendix E1).

T3: In the theta band, visual inspection of the group-average weighted networks revealed that left-hemispheric glioma patients had more (and, therefore, generally stronger) functional connections than healthy individuals (figures 8.3B and 8.3C). Furthermore, visual inspection of the group-average MST networks revealed that patients had a relatively symmetrical network, whereas healthy individuals had slightly more right-sided FC. Statistically, the FC (weighted and MST) network characteristics in glioma patients did not differ from those in healthy individuals. Appendix E1 presents all comparisons, one of which lost significance after Bonferroni correction (applying to W-SWI).

In the alpha band, visual inspection of the group-average weighted networks revealed that left-hemispheric glioma patients had fewer (and, therefore, generally weaker) functional connections than healthy individuals (figures 8.4B and 8.4C). Furthermore, visual inspection of the group-average MST networks revealed that both patients and healthy individuals had relatively symmetrical/slightly more left-sided FC. Statistically, the FC (weighted and MST) network characteristics in postoperative glioma patients did not differ from those in healthy individuals (Appendix E1).

Figures 8.3 and 8.4. Theta-band (fig. 8.3) and alpha-band (fig. 8.4) FC network illustrations: two weighted networks with different correlation thresholds (chosen for illustrational purposes only) and the MST network, averaged for each group: preoperative glioma patients (8.3A, 8.4A), postoperative glioma patients (8.3B, 8.4B), and healthy individuals (8.3C, 8.4C). Two right-hemispheric glioma patients are excluded from these networks for better interpretation of the network configurations. Abbreviations: MST = Minimum Spanning Tree; T1 = before surgery; T3 = 1 year after surgery; LH = left-hemispheric.

Meningioma patients

T1: In the theta band, visual inspection of the group-average weighted networks revealed that left-hemispheric meningioma patients had more (and, therefore, generally stronger) functional connections than healthy individuals (figures 8.5A and 8.5B). Furthermore, visual inspection of the group-average MST networks revealed that patients and healthy individuals both had slightly more right-sided FC. Statistically, the FC (weighted and MST) network characteristics in meningioma patients did not differ from those in healthy individuals (Appendix E2).

In the alpha band, visual inspection of the group-average weighted networks revealed that meningioma patients had fewer (and, therefore, generally weaker) functional connections than healthy individuals (figures 8.6A and 8.6B). Furthermore, visual inspection of the group-average MST networks revealed that patients and healthy individuals both had relatively symmetrical FC. Statistically, the FC (weighted and MST) network characteristics in meningioma patients did not differ from those in healthy individuals (Appendix E2).

T3: Meningioma patients did not undergo EEG registration at T3.

Figures 8.5 and 8.6. Theta-band (fig. 8.5) and alpha-band (fig. 8.6) FC network illustrations: two weighted networks with different correlation thresholds (chosen for illustrational purposes only) and the MST network, averaged for left-hemispheric meningioma patients (8.5A, 8.6A) and healthy individuals (8.5B, 8.6B). MST = Minimum Spanning Tree.

In conclusion: FC network characteristics in glioma and meningioma patients did not differ statistically from those in healthy individuals, although visual inspection revealed increased theta-band FC and decreased alpha-band FC in both patient groups.

(2) Are preoperative FC network characteristics related to preoperative language functioning?

Glioma patients

Correlation analyses

In the theta band, MST-Degr negatively correlated with C-Visual Input ($\tau = -0.73, p = 0.001$), and MST-Diam positively correlated with P-Morphosyntax ($\tau = 0.55, p = 0.005$). These results indicate that hub presence and higher global FC at T1 related to poorer language performance at T1 in glioma patients. Correlations with $p < 0.05$ that lost significance after Bonferroni correction are shown in Appendix E3 (for FC networks: W-PLI, W-rL, W-SWI, MST-Ecc, MST-BC, MST-Leaf, MST-Diam, and MST-TH; for language: P-Word Retrieval, P-Semantics, P-Morphosyntax, C-Auditory Input, C-Visual Input, and Writing).

In the alpha band, W-SWI negatively correlated with C-Visual Input ($\tau = -0.60, p = 0.005$). This result indicates that a more small-world-like network configuration at T1 related to poorer language performance at T1 in glioma patients. Correlations that lost significance after Bonferroni correction are shown in Appendix E3 (for FC networks: W-rC, W-SWI, MST-Ecc, MST-Diam, and MST-TH; for language: C-Visual Input and P-Morphosyntax).

Individual FC networks and language impairments

For examination of individual FC networks in relation to language impairments, Appendix E9 presents an overview of the tumour locations (MRI images), the weighted networks using three different thresholds, the MST networks, and the presence/absence of impaired language domains for every patient.

Meningioma patients

Correlation analyses

In the theta band and in the alpha band, no significant correlations were found between FC (weighted and MST) network measures at T1 and language scores at T1 within the meningioma patient group. One correlation lost significance after Bonferroni correction (applying to W-SWI and C-Visual Input); see Appendix E4.

Individual FC networks and language impairments

For examination of individual FC networks in relation to language impairments, Appendix E10 presents an overview of the tumour locations (MRI images), the weighted networks using three different thresholds, the MST networks, and the presence/absence of impaired language domains for every patient.

In conclusion: Preoperative FC network characteristics in the theta band (hub presence and higher global FC) and in the alpha band (a more small-world-like network configuration) were related to poorer preoperative language performance (production-morphosyntax and comprehension-visual input) in glioma patients. No relations were found in meningioma patients.

(3) Which network characteristics are associated with language impairments?

Glioma patients

Patients with and without language impairment

There were nine glioma patients with language impairment ($z\text{-score} \leq -1.5$ on one or more language domains) and six glioma patients without language impairment preoperatively. In the theta band and in the alpha band, no differences in FC (weighted and MST) network characteristics were found between glioma patients with and without language impairment. Appendix E5 presents all comparisons, three of which lost significance after Bonferroni correction (MST-Ecc, MST-Diam, and MST-TH in the theta band).

Connectivity of individual nodes in patients with language impairment

Nodes (electrode positions; figure 8.1) with the highest Degr and the highest BC indicate the most connected and most centrally positioned nodes in the MST network. In order to further investigate network characteristics of patients with language impairment, the nodes with the highest Degr and the highest BC rankings were selected for every patient with impaired language performance. Consecutively for each node, the percentage of patients with that node having the highest Degr/BC was calculated (as in Boersma et al., 2013). These percentages are given in figure 8.7. (Two right-hemispheric glioma patients were not included here because they were unimpaired.)

In the theta band, T5, P3, and Pz most often had the highest Degree/BC rankings, representing the most connected nodes in the MST network of glioma patients with language impairment (figure 8.7A). The electrode positions overlies left posterior temporal and left parieto-occipital brain areas that seem to be highly connected in this frequency band¹³.

In the alpha band, O2, P4 and C4 most often had the highest Degree/BC rankings, representing the most connected nodes in the MST network of glioma patients with language impairment (figure 8.7B). The electrode positions overlies right parieto-occipital brain areas that seem to be highly connected in this frequency band.

13 Proposed links between electrode positions at the scalp and FC of the underlying brain areas have to be interpreted with great caution (see *Limitations and future directions*).

Figure 8.7. Overview of most connected nodes in MST networks in the theta band (A) and in the alpha band (B) in preoperative glioma patients with language impairment ($N = 9$). For each node, the y-axis expresses the percentage of patients who have the highest Degree/Betweenness Centrality (BC) ranking for that node in their MST network. If a patient's network has two or more nodes with a shared highest ranking, all shared highest rankings are included in the figure.

Meningioma patients

Patients with and without language impairment

There were four meningioma patients with language impairment and six meningioma patients without language impairment preoperatively. In the theta band and in the alpha band, no differences in FC (weighted and MST) network characteristics were found between meningioma patients with and without language impairment. Appendix E6 presents all comparisons, one of which lost significance after Bonferroni correction (W-rL in the theta band).

Connectivity of individual nodes in patients with language impairment

In the theta band, C3 most often had the highest Degree/BC rankings, representing the most connected node in the MST network of meningioma patients with language impairment (figure 8.8A). The electrode position overlies the left parietal brain area that seems to be highly connected in this frequency band.

In the alpha band, T6 most often had the highest Degree/BC rankings, representing the most connected node in the MST network of meningioma patients with language impairment (figure 8.8B). The electrode position overlies the right posterior temporal brain area that seems to be highly connected in this frequency band.

Figure 8.8. Overview of most connected nodes in MST networks in the theta band (A) and in the alpha band (B) in preoperative meningioma patients with language impairment ($N = 4$). For each node, the y-axis expresses the percentage of patients who have the highest Degree/Betweenness Centrality (BC) ranking for that node in their MST network. If a patient's network has two or more nodes with a shared highest ranking, all shared highest rankings are included in the figure.

In conclusion: No discriminative FC network characteristics were found between (glioma/meningioma) patients with and without language impairment. However, language impairments appeared to be associated with high theta-band FC in left-sided brain areas and high alpha-band FC in right-sided brain areas.

(4) Are preoperative FC network characteristics related to 1 year postoperative language outcome?

Glioma patients

Correlation analyses

In the theta band, MST-Ecc and MST-Diam at T1 both positively correlated with P-Word Retrieval at T3 ($\tau = 0.69$, $p = 0.001$; $\tau = 0.73$, $p = 0.001$). These results indicate that hub presence and higher global FC before surgery related to poorer language outcome after glioma surgery. Correlations that lost significance after Bonferroni correction are shown in Appendix E7 (for FC networks: W-PLI, W-rC, MST-Degr, MST-Leaf, and MST-TH; for language: P-Word Retrieval and Writing).

In the alpha band, no significant correlations were found between FC (weighted and MST) network measures at T1 and language scores at T3 within the glioma patient group (Appendix E7).

Meningioma patients

Correlation analyses

In the theta band, no significant correlations were found between FC (weighted and MST) network measures at T1 and language scores at T3 within the meningioma patient group. Correlations that lost significance after Bonferroni correction are shown in Appendix E8 (for FC networks: W-PLI; for language: P-Word Retrieval and P-Semantics).

In the alpha band, no significant correlations were found. Correlations that lost significance after Bonferroni correction are shown in Appendix E8 (for FC networks: MST-Degr, MST-Ecc, MST-BC, and MST-Diam; for language: P-Word Retrieval and Writing).

In conclusion: In glioma patients, two preoperative FC network characteristics (hub presence and higher global FC in the theta band) were related to poorer language outcome (production-word retrieval) 1 year after surgery. No relations were found in meningioma patients.

Result summary

An overview of all results is presented in table 8.6.

Table 8.6. Result summary for every research question

Freq. band	Glioma patients	Meningioma patients
<i>(1) Do FC network characteristics in patients differ from those in healthy individuals?</i>		
Theta	T1: No. - Visual inspection: higher FC in patients. - Statistical analysis: no sig. differences. T3: No. - Visual inspection: higher FC in patients. - Statistical analysis: no sig. differences.	T1: No. - Visual inspection: higher FC in patients. - Statistical analysis: no sig. differences. T3: NA
Alpha	T1: No. - Visual inspection: lower FC in patients. - Statistical analysis: no sig. differences. T3: No. - Visual inspection: lower FC in patients. - Statistical analysis: no sig. differences.	T1: No. - Visual inspection: lower FC in patients. - Statistical analysis: no sig. differences. T3: NA
<i>(2) Are preoperative FC network characteristics related to preoperative language functioning?</i>		
Theta	Yes. - Statistical analysis: MST-Degr negatively correlated with C-Visual Input, and MST-Diam positively correlated with P-Morphosyntax (indicating that hub presence and higher global FC related to lower language scores).	No. - Statistical analysis: no sig. correlations.
Alpha	Yes. - Statistical analysis: W-SWI negatively correlated with C-Visual Input (indicating that a more small-world-like network configuration related to lower language scores).	No. - Statistical analysis: no sig. correlations.
<i>(3) Which network characteristics are associated with language impairments?</i>		
Theta	- Statistical analysis: no discriminative characteristics found. - Most connected MST nodes associated with language impairment: T5, P3, Pz.	- Statistical analysis: no discriminative characteristics found. - Most connected MST node associated with language impairment: C3.
Alpha	- Statistical analysis: no discriminative characteristics found. - Most connected MST nodes associated with language impairment: O2, P4, C4.	- Statistical analysis: no discriminative characteristics found. - Most connected MST node associated with language impairment: T6.
<i>(4) Are preoperative FC network characteristics related to 1 year postoperative language outcome?</i>		
Theta	Yes. - Statistical analysis: MST-Ecc and MST-Diam positively correlated with P-Word Retrieval at T3 (indicating that hub presence and higher global FC related to poorer language outcome).	No. - Statistical analysis: no sig. correlations.
Alpha	No. - Statistical analysis: no sig. correlations.	No. - Statistical analysis: no sig. correlations.

Note. Sig. = significant ($p < 0.005$; corrected for multiple comparisons); T1 = before surgery; T3 = 1 year after surgery; NA = not applicable because meningioma patients did not undergo EEG registration at T3. P = production; C = comprehension; FC = functional connectivity; W = weighted: these network measures quantify weighted FC networks; MST = Minimum Spanning Tree: these network measures quantify Minimum Spanning Tree FC networks. W-SWI = small-world index; MST-Degr = MST-maximum degree; MST-Ecc = MST-eccentricity, mean of all nodes; MST-Diam = MST-diameter.

Discussion

This is the first study to report on FC networks in relation to pre- and postoperative language functioning in glioma and meningioma patients. The outcomes for each research question are discussed below.

(1) Do FC network characteristics in low-grade glioma and meningioma patients, preoperatively and 1 year postoperatively, differ from those in healthy individuals?

Glioma and meningioma patients

We found no statistical evidence that resting-state FC networks in glioma or meningioma patients differ from those in healthy individuals. However, visual inspection of group-average FC networks reveals higher (increased) theta-band FC and lower (decreased) alpha-band FC in both patient groups before surgery. Postoperative EEG was registered in glioma patients only, for whom the observed FC patterns preoperatively are identical to those 1 year postoperatively.

For the theta band, the visually inspected increased FC is in line with previous research, in which MEG was used. Studies report increased theta-band FC before and after brain tumour surgery (Bosma, Douw, et al., 2008; Bosma et al., 2009; Van Dellen et al., 2012), particularly in the affected hemisphere (Bartolomei et al., 2006a). Higher theta-band FC specifically in the affected (left) hemisphere may also be the case in the current glioma patients before surgery, according to the group-average MST network, but this is not observed in the current meningioma patients. Higher FC in the theta band is likely to be indicative of more severe brain dysfunction, similar to brain activity in lower (delta and theta) frequency bands. This so-called 'slow-wave activity' during wakeful, resting conditions in adults generally represent pathological brain rhythms (Lüders & Noachtar, 2000), and it has been shown to be overrepresented in brain tumour patients (different tumour types and grades; Baayen et al., 2003; De Jongh et al., 2003; Oshino et al., 2007). When brain activity is highly present in a particular frequency band, one is more likely to find statistical interdependencies between brain signals, which provide more opportunities for high FC (Aertsen et al., 1989). This may explain the observed increase in theta-band FC in both patient groups. Furthermore, increased theta-band FC may be related to epileptogenesis, a process by which the brain develops epilepsy. Our sample sizes were too small to verify this, but Douw et al. (2010) show that higher theta-band FC, especially in the temporal lobe, is associated with higher seizure frequency in glioma patients.

For the alpha band, the visually inspected decreased FC differs in its interpretation from the aforementioned because brain activity in the alpha band is representative of normal physiological brain rhythms (Lüders & Noachtar, 2000). This may explain a decrease of alpha-band FC in brain tumour patients. Decreased alpha-band FC has previously been found in low-grade glioma patients (Bosma, Douw, et al., 2008), and in patients with other types of brain injury, such as traumatic brain injury (Castellanos et al., 2010) and stroke (Dubovik, Ptak, et al., 2013). One study, however, has reported an increase of alpha-band FC in brain tumour patients (a mixed group of preoperative meningioma, low-grade glioma, and high-

grade glioma patients; Bartolomei et al., 2006a). FC in higher frequency bands (beta and gamma) is generally reduced in brain tumour patients (Bartolomei et al., 2006b, 2006a; Bosma et al., 2009; Hu et al., 2013). Hence, when the brain is affected by a tumour, FC in the alpha band may change in parallel with FC in higher frequency bands.

Although our observations are in line with previous literature, they should be interpreted with caution. Firstly, because we found no statistical evidence to support these observations, which may be due to considerable inter-subject variability in combination with small sample sizes. Secondly, visual inspection is a subjective method. Lastly, the possibility that the observed patterns in group-average FC networks rely on outliers cannot be ruled out.

(2) Are preoperative FC network characteristics related to preoperative language functioning?

Glioma patients

Three preoperative FC network characteristics, two in the theta band and one in the alpha band, show a relation to preoperative language performance in glioma patients. In the theta band, hub presence and higher global FC are associated with poorer language functioning before surgery. The direction of this relationship is to be expected, considering that higher theta-band FC indicates more severe brain dysfunction (previous section). Similar findings are reported by Van Dellen et al. (2012), who demonstrated that FC alterations in the theta band, such as increased local FC, were related to poorer language performance in preoperative low-grade glioma patients. This applied to category fluency performance (production-semantics at the word level), whereas the current study shows associations with morphosyntax (production) and comprehension of visual input, both of which concern language functioning at the sentence level. Morphosyntactic performance showed a tendency towards impaired performance at the group level, but comprehension of visual input was unimpaired in the glioma patient group. Notwithstanding, two characteristics of high theta-band FC relate to poorer language functioning in glioma patients.

In the alpha band, a more small-world-like network configuration, which represents the combination of high local and high global FC, is associated with poorer language performance (comprehension of visual input) before surgery. This result is inconsistent with previous findings, which demonstrated that lower global FC in the alpha band was related to poorer language performance, as assessed with category fluency, in a group of preoperative low-grade and high-grade glioma patients (Derks et al., 2019). In addition, low alpha-band FC was related to poorer performance in several cognitive functions (e.g. verbal memory, information processing, and attention; Derks et al., 2019). The contrast with our result can be explained by the language task that was used to assess comprehension of visual input: sentence judgement (accuracy scores). This test was presumably too easy because it has a 50% chance of selecting the correct answer. Moreover, comprehension of visual input was the only language domain for which all patients were unimpaired preoperatively (chapter 5). Consequently, the correlation is based on small variation in unimpaired language performance and, therefore, may not be very informative.

The majority of FC network characteristics show no relation to language functioning in glioma patients. However, many correlations lost significance after correcting for multiple comparisons. These correlations involved all FC network characteristics in the theta and/or alpha band and most of the language domains. Furthermore, nearly all of the correlations were in the direction of higher theta-band/lower alpha-band FC relating to poorer language scores (Appendix E3).

Meningioma patients

Preoperative FC network characteristics are not related to preoperative language functioning, also according to the uncorrected data, in the current meningioma patient group. This is presumably due to the nature of the tumour; meningiomas generally do not infiltrate the surrounding brain tissue (Wei et al., 2007). Therefore, they do not have a large direct destructive effect on brain tissue, which may be reflected by little or no FC alterations. Meningiomas can, however, cause language impairments, despite the absence of infiltrative injury (chapter 6). Yet, unchanged FC is likely to be the cause of the lack of associations with language performance.

(3) Which network characteristics are associated with language impairments?

Glioma and meningioma patients

The results indicate that there are no preoperative FC network characteristics specifically associated with preoperative language impairments in these patient groups. This can, at least partly, be explained by the small sample sizes. The comparisons that lost significance after correction for multiple comparisons point in the direction that, in glioma patients, a language impairment is associated with hub presence, higher global FC, and a more star-like network configuration in the theta band, compared to the absence of language impairment. Language impairment in meningioma patients may be associated with higher global FC in the theta band, compared to patients with no language impairment.

A more descriptive analysis of individual nodes in the MST network suggests that, in left-hemispheric tumour patients with language impairment, theta-band FC is frequently highest in left-sided brain areas and alpha-band FC is frequently highest in right-sided brain areas. This has to be interpreted with caution because the analysis is based on language-impaired subgroups, and the original numbers of glioma and meningioma patients were already small.

Overall, there are indications that FC brain networks can signify presence of language impairment in brain tumour patients, although this lacks statistical support. In patients with non-tumour-related, but neurodegenerative language impairment (i.e., primary progressive aphasia), the localisation of altered FC in resting-state MEG has been shown to be indicative of the type of language impairment, at least distinguishing phonological, semantic, and morphosyntactic impairments (Ranasinghe et al., 2017). It is possible that investigating FC of specific brain areas can provide more accurate insights into language impairments in brain tumour patients as well.

(4) Are preoperative FC network characteristics related to 1 year postoperative language outcome?

Glioma patients

Two preoperative FC network characteristics are shown to relate to postoperative language outcome: hub presence and higher global FC in the theta band are associated with poorer word retrieval performance 1 year after surgery. Markedly, five out of six correlations that lost significance after correction for multiple comparisons also involved word retrieval; higher overall FC strength, higher local FC, hub presence, and a more star-like network configuration in the theta band may additionally relate to poorer performance after surgery. Hence, several features of high FC in the 'pathological' theta band preoperatively seem to be predictive of poor word retrieval long-term postoperatively. Word retrieval was assessed with object naming, which is the most frequently used test in glioma patients undergoing awake surgery (De Witte & Mariën, 2013). Interestingly, high performance on this test is associated with good quality of life and return to work after glioma surgery (Moritz-Gasser et al., 2012). The sixth correlation that lost significance after correction involves writing performance; higher overall FC strength in the theta band before surgery may be associated with poorer writing after surgery. It is important to investigate this further because awake glioma surgery can induce writing impairments (Van Ierschoot et al., 2018). In the current patient group, the number of preoperative versus 1 year postoperative writing impairments had doubled (chapter 5). Hence, the intraoperative procedure may benefit from a well-suited risk estimation on the basis of FC networks prior to surgery.

Alpha-band FC has no relation to language outcome in our study. This is in line with Lizarazu et al. (2020), who found no association between FC change in the alpha band and language change scores (object naming and semi-spontaneous speech ratings) between pre- and postoperative assessments in left-hemispheric, low-grade glioma patients. A reason for this may be that language performance did not change after surgery. The current study used language outcome scores at T3, instead of language change scores (T3-T1), because performance at T3 is most relevant for the postoperative approach, such as initiation of language intervention. To illustrate, a patient who shows no language change between pre- and postoperative assessments can either have continued unimpaired performance or persistent language impairments that require attention.

Meningioma patients

Preoperative FC network characteristics in the theta and alpha bands are not related to postoperative language outcome in meningioma patients. Correlations that lost significance after correction suggest that higher overall FC strength in the theta band, as well as hub presence and higher global FC in the alpha band, are associated with poorer language functioning (word retrieval, semantics, and writing) 1 year after surgery. Future research can uncover whether these will be supported when studying a larger patient group.

Limitations and future directions

This study is underpowered, due to the combination of small groups, many variables and, as a consequence, many statistical comparisons that accompanied our exploratory design. However, the outcomes can assist in the selection of variables in future studies. Language domains that appear most promising in relation to FC networks are word retrieval (as assessed with object naming), morphosyntax, and comprehension of visual input when using a sufficiently sensitive test. FC network characteristics that appear most promising in relation to language functioning are MST degree, eccentricity and diameter in the theta band, and weighted small-world index in the alpha band. Although the large number of network measures complement each other in quantifying FC network configurations, a disadvantage is that they are not all independent of each other (Van Diessen et al., 2015). This is another reason for limiting the number of network measures in future research.

FC networks in the current study may have been influenced by tumour and treatment-related factors, such as tumour location, volume, histology, use of anti-epileptic drugs, and adjuvant treatment (only applicable to glioma patients at T3), but the sample sizes were too small to control for these variables. Apart from that, there were some EEG-related challenges. EEG registration is sensitive to conductivity errors, as conductivity of the skull and other tissues can blur the signal. Consequently, signals that are registered at the scalp may not originate from the brain areas directly underneath them. Moreover, electrical conduction properties of the human head vary between individuals. This results in differences in total FC strength, as measured with the PLI, and may explain the high level of inter-subject variability in the weighted FC network figures (Appendices E9 and E10). We normalised the other weighted FC network measures to increase comparability between networks, although network comparisons are still not completely unbiased by using this method (Stam et al., 2014). MEG may be preferred to EEG for FC network investigations, which will reduce the previous problems and increase spatial resolution. However, it is more expensive and less suited for clinical settings than EEG. Overall, future studies on this topic are likely to benefit from larger sample sizes and fewer variables, carefully selected on the basis of previous work.

Conclusion

To summarise, this study indicates that:

- (1) FC network characteristics in glioma and meningioma patients do not differ statistically from those in healthy individuals, but group-average network observations reveal higher theta-band FC and lower alpha-band FC in both patient groups.
- (2) In glioma patients, unlike in meningioma patients, three preoperative FC network characteristics are associated with preoperative language functioning, for example, higher global FC in the theta band relates to poorer morphosyntactic abilities.
- (3) There is no statistical evidence that language impairments are associated with specific FC network characteristics, however, theta-band FC appears highest in left-sided brain areas and alpha-band FC appears highest in right-sided brain areas in glioma and meningioma patients with language impairment.

- (4) Higher theta-band FC before surgery is related to poorer word retrieval 1 year after glioma surgery, but FC network characteristics in meningioma patients are not predictive of postoperative language outcome.

Overall, we present the first indications that FC networks are informative for language functioning in glioma patients undergoing surgery, but not (yet) to an extent that the outcomes are clinically applicable. Continuation of this line of research, especially the search for predictors of language outcome, has the potential to improve perisurgical patient care, such as treatment planning, counselling, and language rehabilitation.

Chapter 9

General discussion

Main outcomes in context

This thesis has presented literature reviews and proof-of-principle research (part I), followed by results from the PLOTS study (Predicting Language Outcome after brain Tumour Surgery; part II). Both parts contribute to our three research objectives:

- (1) to gain more insight into language functioning in low-grade glioma and meningioma patients;
- (2) to reveal whether/how language functioning is related to resting-state EEG characteristics;
- (3) to find predictors for language outcome after brain tumour surgery, based on preoperative EEG.

The main findings and implications for each objective are discussed below.

(1) Language functioning in low-grade glioma and meningioma patients

Language impairments in glioma patients had already been reported previously (see the reviews by Satoer et al., 2016 and Van Kessel et al., 2017), but language functioning in meningioma patients was largely unknown. The present PLOTS study demonstrates that the majority of patients with a low-grade glioma in the language-dominant hemisphere experience language problems and have impaired performance on language tests before surgery. Impairments are present in more aspects of language than previously reported; almost all language modalities and linguistic levels are affected (speech production [word retrieval, phonology, semantics, and a trend for morphosyntax], auditory comprehension, and writing). After surgery, auditory comprehension improves at the group level, but individual language impairments persist or worsen in many patients (chapter 5). These results underline the importance of extensive language testing in patients undergoing awake glioma surgery. Moreover, a detailed preoperative language assessment is crucial for treatment planning (selecting the best suitable tests for intraoperative language monitoring) and postoperative language assessments give directions for language intervention (e.g. enabling an early start), all in order to minimise language impairment and to preserve quality of life.

Furthermore, in patients with a left-sided grade I meningioma, our results show that more than half of the patients experience language problems before surgery, despite the non-infiltrative nature of the tumour. Impairments manifest primarily in expressive language abilities (speech production [word retrieval and morphosyntax] and writing). Language performance after meningioma surgery remains largely unchanged, although some patients show long-term language decline (chapter 6). These impairments and their impact on daily life should not be overlooked. Language functioning is not always tested in current clinical practice. The present findings emphasise the necessity of assessing language abilities in left-hemispheric meningioma patients to optimise counselling of patients and their proxies, and to evaluate the need for language intervention.

Another finding, applicable to both patient groups, is that self-reported language problems are not always in agreement with the language test results (chapters 5 and 6). This incongruence is observed in both directions: there are patients who report no problems and

have impaired test performance, and patients who report language problems and have no impaired test performance. Although remarkable, a similar incongruence has been reported previously in brain tumour patients for language as well as cognitive functioning (Antonsson, Longoni, et al., 2018; Gehring et al., 2015; Prankeviciene et al., 2017; Van der Linden et al., 2020). This implies that a task-related explanation for the observed inconsistency is unlikely. Alternative explanations, as discussed in chapter 6, concern under- or overestimation of one's own skills (Kruger & Dunning, 1999), the gap between everyday language use and artificial test situations (Satoer et al., 2018), and particular patient characteristics (Gehring et al., 2015). Nevertheless, the discrepancy between subjective and objective language measures indicates that it is helpful to evaluate self-reported language problems in addition to formal language testing because taking only one or the other into account could lead to inadequate conclusions and lower patient satisfaction. Hence, both types of information should be considered.

Low-grade glioma patients and meningioma patients have been described as separate groups throughout this thesis in order to provide insight into language functioning of both patient groups independently. No direct comparisons between the two, i.e. comparing the impact of intra- versus extra-axial tumours, were made because of the small sample sizes and many potentially confounding factors, such as differences in age, neuropathology, tumour size and location, surgical procedure, extent of resection, adjuvant treatment, and use of anti-epileptic drugs. Despite that, one can speculate that language impairments in meningioma patients are somewhat less frequently occurring, less severe, and restricted to fewer language modalities (speech production and writing), than those in low-grade glioma patients. However, when comparing the language performance of the current patient groups to previous literature on low-grade brain tumour patients (e.g. Antonsson, Longoni, et al., 2018; Norrelgen et al., 2020), language impairments are more frequently present, are more severe, and are more widespread (i.e. affecting more language abilities) in the current project. This can be explained by the following: we only included patients with tumour locations in the language-dominant hemisphere, we used language tests that are designed for detection of mild impairments, and we assessed a higher number of language abilities. Our extensive and systematic approach of assessing language is time consuming, but provides a comprehensive language profile of individual patients, which aids personalised perisurgical procedures.

Altogether, the present findings contribute to a better understanding of language impairments that are induced by primary low-grade brain tumours and their treatment. It is important to note that language performance in glioma and meningioma patients shows large inter-individual variation, varying from unimpaired performance to severe impairments pre- and/or postoperatively. This further demonstrates the need for implementing routine language assessments, before and after brain tumour surgery in the language-dominant hemisphere, to enable a well-suited clinical approach for each patient.

(2) Language functioning in relation to resting-state EEG characteristics

This section discusses two aspects of resting-state brain activity, namely slow-wave activity and functional connectivity (FC) network characteristics, which have been analysed from EEG registrations described in chapters 4, 7 and 8.

Slow-wave activity

The relation between slow-wave activity and language functioning had not been studied previously in brain tumour patients. However, in patients with non-tumour-related brain injury, slow-wave activity (degree and localisation) had been shown to be a marker of language impairment (severity and type; chapter 2). Our proof-of-principle study demonstrates that such analyses are feasible in glioma patients as well, and indicates that increased slow-wave activity is associated with poorer language functioning in a group of pre- and postoperative patients (chapter 4). Furthermore, the PLOTS study reveals that low-grade glioma patients have a localised increase in delta activity and a widespread increase in theta activity. Moreover, increased theta activity is related to the presence of language impairment, in particular to poorer speech production (word retrieval and morphosyntax) in preoperative low-grade glioma patients (chapter 7). Even though meningioma patients suffer from language impairments as well (chapter 6), they have no increased slow-wave activity, presumably because this tumour has a limited (direct) destructive effect on surrounding brain tissue (chapter 7). Hence, increased theta activity can be considered a marker of language impairment in glioma patients, but not in meningioma patients.

FC network characteristics

Previously, a few studies in brain tumour patients reported that alterations in FC networks are associated with poorer verbal fluency performance, but relations to performance on other language tests were unknown (chapter 3). The PLOTS study indicates that FC network characteristics in low-grade glioma and meningioma patients do not differ statistically from those in healthy individuals, which may be explained by inter-individual variation in small groups. However, visual inspection reveals that both patient groups have increased theta-band FC and decreased alpha-band FC before surgery. With regard to language functioning, we add to previous knowledge by showing that preoperative FC network characteristics (theta band: hub presence and global FC; alpha band: a small-world-like network configuration) are related to preoperative speech production (morphosyntax) and comprehension abilities in glioma patients. There are indications of more relations between FC network characteristics and language domains; the corresponding results almost reached significance in our design of limited statistical power (see *Limitations*). FC networks in meningioma patients are not related to language functioning (chapter 8).

Slow-wave activity and FC network characteristics

The presented relations between language functioning and resting-state EEG characteristics are predominantly found in the theta band: increased theta activity and higher theta-band FC are associated with poorer language functioning in glioma patients (chapters 7 and 8). An overrepresentation of brain activity and FC in the theta band during wakeful, resting conditions is indicative of pathological brain rhythms (applicable only to adults; Lüders & Noachtar, 2000) and may be related to epileptogenesis (the process by which the brain develops epilepsy; Douw et al., 2010). Furthermore, brain dysfunction associated with theta activity is believed to reflect a potentially reversible state (Oshino et al., 2007), which

seems promising for language recovery. In other frequency bands, we report no relations with language functioning (delta band – slow-wave activity; chapter 7) or they are less pronounced (alpha band – FC networks; chapter 8).

Another similarity between the slow-wave activity results (chapter 7) and the FC network results (chapter 8) is that both aspects of resting-state brain activity show no relation to language functioning in meningioma patients. An explanation for this is that meningiomas do not seem to induce the previously mentioned EEG alterations, presumably due to the extra-axial nature of the tumour. There is usually no infiltrative injury to parenchyma, but brain tissue surrounding the meningioma can get compressed, distorted, and displaced (Campanella et al., 2014; Wei et al., 2007). Also, grade I meningiomas have a slow growth rate, providing opportunities for adaptation and reorganisation (Huttner et al., 2018). Despite all of this, our research shows that left-hemispheric meningioma patients suffer from language impairments (chapter 6). This suggests that language functioning can be affected by neural changes even when these are not (yet) detectable in resting-state EEG registrations. Alternatively, it is possible that the currently conducted EEG analyses are not sufficiently sensitive to measure meningioma-related changes, and/or that the patient group is too small to detect neural effects at the group level.

Slow-wave activity and FC network characteristics have been described as separate aspects of brain activity throughout the thesis. However, the two are not independent of each other, as FC network analyses are based on brain activity patterns. This explains the conformity of findings for the theta band in chapters 7 and 8. Apart from that, we currently believe that every frequency band has to be analysed and interpreted separately, in contrast to our combined delta-theta band analysis in chapter 4 (also performed in other studies, e.g. Ranasinghe et al., 2017). Our revised view is supported by the study described in chapter 7, which demonstrates that delta activity and theta activity have their own spatial distribution, are likely to reflect two distinct pathological, neurophysiological processes (Fernández-Bouzas et al., 1999), and are different in their relation to language impairments (chapter 7) and other clinical symptoms (Oshino et al., 2007).

Overall, the outcomes corresponding to objective (2) indicate that specific characteristics in resting-state EEG are informative for language functioning in glioma patients undergoing surgery. These findings improve our understanding of the underlying neural mechanisms of language problems in these patients. The next section discusses whether slow-wave activity measures and/or FC network characteristics predict postoperative language outcome.

(3) Predictors for language outcome after brain tumour surgery

Slow-wave activity

In previous literature there were indications that slow-wave activity in resting-state EEG had the ability to predict the course of language recovery in post-stroke aphasia (chapter 2). We show that the level of slow-wave EEG activity in glioma and meningioma patients before surgery is not predictive of language outcome after surgery (chapter 7). The discrepancy between previous research and our results is presumably due to the difference in neurological aetiology and the extent of language impairment it induced: an acute stroke, which caused

language impairment in all patients (previous research), versus a slow-growing tumour and its surgical resection, which caused language impairment in some of the patients (current research).

FC network characteristics

Similar to slow-wave activity, resting-state FC networks had previously been demonstrated to predict language recovery in stroke patients only (chapter 3). The PLOTS study contributes to this knowledge that two FC network characteristics are predictive of language functioning in low-grade glioma patients: higher theta-band FC (hub presence and global FC) before surgery is associated with poorer language outcome (word retrieval) 1 year after surgery. Preoperative FC networks in meningioma patients show no relation to postoperative language outcome (chapter 8).

Slow-wave activity and FC network characteristics

The current project identifies two predictors of language outcome after glioma surgery, both indicating that high theta-band FC is associated with an increased risk of postoperative language impairment. Apart from these two, a number of other slow-wave activity measures and FC network characteristics show promising results but do not sustain corrections for multiple comparisons in our exploratory design (chapters 7 and 8). These specific variables can, therefore, not yet be ruled out as predictors, and it would be worthwhile to investigate them further (see *Future research*).

Predictors derived from resting-state EEG measures are suitable for use in clinical settings because EEG is widely available and relatively inexpensive. Moreover, a number of brain tumour patients already undergo EEG registration as part of their clinical examination, due to suspected epileptic seizures. In those instances, evaluation of slow-wave activity and FC networks may not require much extra time, and can provide language-related information simultaneously. Continuation of studying predictors of language outcome after brain tumour surgery has the potential to improve perisurgical procedures, such as treatment planning, patient counselling, and language rehabilitation, in order to minimise or prevent postoperative language impairments.

Limitations

A limitation of this project is the small sample sizes. The reason for this is that the in- and exclusion criteria were quite specific in order to study relatively homogeneous patient groups (e.g. newly-diagnosed tumours located in the language-dominant hemisphere) and to avoid confounding factors (e.g. effects of consistent dexamethasone use). Therefore, only a limited number of patients from the two participating medical centres were eligible for participation in the PLOTS study. The small sample sizes led to restricted statistical power, which was further reduced by the many tests and corrections in our exploratory design. Corrections for multiple comparisons were made for the number of EEG measures. These measures

were not independent of each other because the same raw EEG data were used in different ways. Throughout the thesis, we did not correct for the number of language measures. This is because we aimed to study the different language functions separately, by language measures that are independent of each other (a language test score was used for one domain only, not more). The corrections for the number of EEG measures had a large influence on the results. To illustrate, we currently report three significant correlations between preoperative FC network characteristics and preoperative language performance in glioma patients, instead of 21 without corrections (Appendix E3). The statistical analysis was complemented by descriptive analyses to enable a broader view on the topic.

With regard to the language assessment, almost all tests were sufficiently sensitive and suitable for the present patient groups. An exception, however, was the sentence judgement task, which was presumably too easy, although we did not take reaction times into account to increase sensitivity. Contrastingly, the reading and writing tests were very sensitive for detecting impairments. Some patients had extremely low z-scores (minimum value $z = -23$), partly because the available normative data from a healthy population included almost no errors. The pre-existing normative data that were used for the transformation of patients' raw scores to z-scores are based on different groups of healthy individuals for every test (Appendix B1), whereas one large group for all tests would have been preferable.

Furthermore, EEG registration has disadvantages, such as low spatial resolution, especially when following the standard clinical procedure which includes 21 scalp electrodes. This leads to limited precision in investigations of specific brain regions (chapter 7). In addition, EEG registration is sensitive to conductivity errors (discussed in chapter 8) and is possibly influenced by differences in head tissue thickness between individuals. This partly explains the high level of inter-subject variation in the slow-wave activity and FC network results, as normalisation procedures do not always completely eliminate such confounding effects (Stam et al., 2014). Also, mental activity during the investigated 'resting state' differs between individuals (e.g. mental relaxation versus overthinking a problem), which is likely to be reflected by variation in brain activity recordings. Apart from that, brain activity may have been affected by the use of anti-epileptic drugs and postoperative adjuvant treatment (Duncan, 1987; Nokia et al., 2012), even though all registrations were visually inspected and controlled for their quality.

Clinical recommendations

In reference to chapter 6, we encourage an increase of awareness amongst clinicians with regard to the occurrence of language complaints and impairments induced by left-hemispheric meningiomas and their treatment. Furthermore, we advocate for the implementation of a standard clinical language assessment to screen for impairments in left-hemispheric meningioma patients pre- and postoperatively. Such assessments are already common practice in most centres that treat low-grade glioma patients with awake brain surgery. For both patient groups, it is important that language assessments include tests that are sufficiently

sensitive for detection of mild impairments. In view of the fact that language impairments manifest in different language modalities and at different linguistic levels (chapters 5 and 6), we propose that assessments at least examine speech production, comprehension, reading, and writing, taking phonology, semantics, and morphosyntax into account. Written language abilities in particular are not often assessed, even though these appear to be problematic in a number of patients (chapters 5 and 6). Moreover, formal language testing has to be complemented by evaluating self-reported language problems because language test performance does not always correspond to experienced language problems (chapters 5 and 6). Apart from language assessments, the risk of postoperative language decline may be communicated to low-grade brain tumour patients and their proxies, especially considering that language impairments can persist up to 1 year after surgery (chapters 5 and 6).

Future research

Further investigation into language functioning in a larger group of meningioma patients is needed to establish the incidence and severity of language impairments in these patients. The use of language tests designed for brain tumour patients, combined with a systematic approach to assess language abilities, can help to study different aspects of language functioning in glioma and meningioma patients. In addition, it can be valuable to evaluate spontaneous speech because it better resembles language use in daily life than formal language testing. Moreover, the current research shows that group-level performance and individual performance can give different impressions of language functioning (chapter 5), and, therefore, should both be reported.

Another important recommendation for future research is that glioma patients and meningioma patients have to be studied as two separate groups. Reason for this is that gliomas and meningiomas, which differ in (intra- versus extra-axial) tumour location and histopathological nature, are associated with diverse clinical presentations. Our research indicates that gliomas and meningiomas do not only induce different effects at the behavioural level (chapters 5 and 6), but also at a neurophysiological level (chapters 7 and 8). Hence, analyses of both patient groups combined should be avoided.

Future projects could study the relation between resting-state EEG characteristics and language functioning by changing from an exploratory approach to a more hypothesis-based approach. That is, the present outcomes (chapters 7 and 8) can assist in the selection of variables for future study designs. This applies to the delta, theta, and alpha frequency bands, however, investigation of higher frequency bands (beta, gamma) can also be useful (cf. Bosma, Douw, et al., 2008 for cognitive functioning). Moreover, it is essential to study the clinical applicability of resting-state EEG, such as examining whether FC network characteristics, possibly analysed via an automatised procedure, can be used as a prognostic tool for language outcome after brain tumour surgery. In order to continue this line of research in larger patient groups, it is beneficial to establish (international) collaborations between medical centres. It's a small world after all (Walt Disney; chapters 3 and 8).

References

References

- Abel, T. J., Manzel, K., Bruss, J., Belfi, A. M., Howard, M. A., & Tranel, D. (2016). The cognitive and behavioral effects of meningioma lesions involving the ventromedial prefrontal cortex. *Journal of Neurosurgery*, 124, 1568–1577. <https://doi.org/10.3171/2015.5.JNS142788>
- Achard, S., Salvador, R., Whitcher, B., Suckling, J., & Bullmore, E. (2006). A Resilient, Low-Frequency, Small-World Human Brain Functional Network with Highly Connected Association Cortical Hubs. *Journal of Neuroscience*, 26(1), 63–72. <https://doi.org/10.1523/JNEUROSCI.3874-05.2006>
- Aerts, H., Fias, W., Caeyenberghs, K., & Marinazzo, D. (2016). Brain networks under attack: robustness properties and the impact of lesions. *Brain*, 139(12), 3063–3083. <https://doi.org/10.1093/brain/aww194>
- Aertsen, A. M. H. J., Gerstein, G. L., Habib, M. K., & Palm, G. (1989). Dynamics of neuronal firing correlation: modulation of “effective connectivity.” *Journal of Neurophysiology*, 61(5), 900–917. <https://doi.org/10.1152/jn.1989.61.5.900>
- Aita, S. L., Beach, J. D., Taylor, S. E., Borgogna, N. C., Harrell, M. N., & Hill, B. D. (2019). Executive, language, or both? An examination of the construct validity of verbal fluency measures. *Applied Neuropsychology: Adult*, 26(5), 441–451. <https://doi.org/10.1080/23279095.2018.1439830>
- Álvarez, X. A., Sampedro, C., Figueroa, J., Tellado, I., González, A., García-Fantini, M., ... Moessler, H. (2008). Reductions in qEEG slowing over 1 year and after treatment with Cerebrolysin in patients with moderate-severe traumatic brain injury. *Journal of Neural Transmission*, 115(5), 683–692. <https://doi.org/10.1007/s00702-008-0024-9>
- Anderson, S. W., Damasio, H., & Tranel, D. (1990). Neuropsychological impairments associated with lesions caused by tumor or stroke. *Archives of Neurology*, 47(4), 397–405. <https://doi.org/10.1001/archneur.1990.00530040039017>
- Antonsson, M., Jakola, A., Longoni, F., Carstam, L., Hartelius, L., Thordstein, M., & Tisell, M. (2018). Post-surgical effects on language in patients with presumed lowgrade glioma. *Acta Neurologica Scandinavica*, 137, 469–480. <https://doi.org/10.1111/ane.12887>
- Antonsson, M., Longoni, F., Jakola, A., Tisell, M., Thordstein, M., & Hartelius, L. (2018). Pre-operative language ability in patients with presumed low-grade glioma. *Journal of Neuro-Oncology*, 137(1), 93–102. <https://doi.org/10.1007/s11060-017-2699-y>
- Assenza, G., Zappasodi, F., Pasqualetti, P., Vernieri, F., & Tecchio, F. (2013). A contralesional EEG power increase mediated by interhemispheric disconnection provides negative prognosis in acute stroke. *Restorative Neurology and Neuroscience*, 31(2), 177–188. <https://doi.org/10.3233/RNN-120244>
- Baayen, J. C., De Jongh, A., Stam, C. J., De Munck, J. C., Jonkman, J. J., Kasteleijn-Nolst Trenité, D. G. A., ... Vandertop, W. P. (2003). Localization of slow wave activity in patients with tumor-associated epilepsy. *Brain Topography*, 16(2), 85–93. <https://doi.org/10.1023/B:BRAT.00000006332.71345.b7>
- Babiloni, C., Cassetta, E., Binetti, G., Tombini, M., Del Percio, C., Ferreri, F., ... Rossini, P. M. (2007). Resting EEG sources correlate with attentional span in mild cognitive impairment and Alzheimer's disease. *European Journal of Neuroscience*, 25(12), 3742–3757. <https://doi.org/10.1111/j.1460-9568.2007.05601.x>
- Baldo, J. V., Dronkers, N. F., Wilkins, D., Ludy, C., Raskin, P., & Kim, J. (2005). Is problem solving dependent on language? *Brain and Language*, 92(3), 240–250. <https://doi.org/10.1016/j.bandl.2004.06.103>
- Ball, G. J., Gloor, P., & Schaul, N. (1977). The cortical electromicrophysiology of pathological delta waves in the electroencephalogram of cats. *Electroencephalography and Clinical Neurophysiology*, 43(3), 346–361. [https://doi.org/10.1016/0013-4694\(77\)90258-9](https://doi.org/10.1016/0013-4694(77)90258-9)

- Bartolomei, F., Bosma, I., Klein, M., Baayen, J. C., Reijneveld, J. C., Postma, T. J., ... Stam, C. J. (2006a). Disturbed functional connectivity in brain tumour patients: Evaluation by graph analysis of synchronization matrices. *Clinical Neurophysiology*, 117(9), 2039–2049. <https://doi.org/10.1016/j.clinph.2006.05.018>
- Bartolomei, F., Bosma, I., Klein, M., Baayen, J. C., Reijneveld, J. C., Postma, T. J., ... Stam, C. J. (2006b). How do brain tumors alter functional connectivity? A magnetoencephalography study. *Annals of Neurology*, 59(1), 128–138. <https://doi.org/10.1002/ana.20710>
- Bassett, D. S., Meyer-Lindenberg, A., Achard, S., Duke, T., & Bullmore, E. (2006). Adaptive reconfiguration of fractal small-world human brain functional networks. *Proceedings of the National Academy of Sciences*, 103(51), 19518–19523. <https://doi.org/10.1073/pnas.0606005103>
- Beez, T., Boge, K., Wager, M., Whittle, I., Fontaine, D., Spena, G., ... Sabel, M. (2013). Tolerance of awake surgery for glioma: a prospective European Low Grade Glioma Network multicenter study. *Acta Neurochirurgica*, 155(7), 1301–1308. <https://doi.org/10.1007/s00701-013-1759-0>
- Bello, L., Gallucci, M., Fava, M., Carrabba, G., Giussani, C., Acerbi, F., ... Gaini, S. M. (2007). Intraoperative subcortical language tract mapping guides surgical removal of gliomas involving speech areas. *Neurosurgery*, 60(1), 67–80. <https://doi.org/10.1227/01.NEU.0000249206.58601.DE>
- Boersma, M., Smit, D. J. A., Boomsma, D. I., De Geus, E. J. C., Delemarre-van de Waal, H. A., & Stam, C. J. (2013). Growing trees in child brains: Graph theoretical analysis of electroencephalography-derived minimum spanning tree in 5- and 7-year-old children reflects brain maturation. *Brain Connectivity*, 3(1), 50–60. <https://doi.org/10.1089/brain.2012.0106>
- Boersma, M., Smit, D. J. A., De Bie, H. M. A., Van Baal, G. C. M., Boomsma, D. I., De Geus, E. J. C., ... Stam, C. J. (2011). Network analysis of resting state EEG in the developing young brain: Structure comes with maturation. *Human Brain Mapping*, 32(3), 413–425. <https://doi.org/10.1002/hbm.21030>
- Bommakanti, K., Somayajula, S., Suvarna, A., Purohit, A. K., Mekala, S., Chadawaladi, S. K., & Gaddamanugu, P. (2016). Pre-operative and post-operative cognitive deficits in patients with supratentorial meningiomas. *Clinical Neurology and Neurosurgery*, 143, 150–158. <https://doi.org/10.1016/j.clineuro.2016.02.033>
- Bosboom, J. L. W., Stoffers, D., Stam, C. J., Van Dijk, B. W., Verbunt, J., Berendse, H. W., & Wolters, E. C. (2006). Resting state oscillatory brain dynamics in Parkinson's disease: An MEG study. *Clinical Neurophysiology*, 117(11), 2521–2531. <https://doi.org/10.1016/j.clinph.2006.06.720>
- Bosma, I., Douw, L., Bartolomei, F., Heimans, J. J., Van Dijk, B. W., Postma, T. J., ... Klein, M. (2008). Synchronized brain activity and neurocognitive function in patients with low-grade glioma: a magnetoencephalography study. *Neuro-Oncology*, 10(5), 734–744. <https://doi.org/10.1215/15228517-2008-034>
- Bosma, I., Reijneveld, J. C., Klein, M., Douw, L., Van Dijk, B. W., Heimans, J. J., & Stam, C. J. (2009). Disturbed functional brain networks and neurocognitive function in low-grade glioma patients: a graph theoretical analysis of resting-state MEG. *Nonlinear Biomedical Physics*, 3(1), 9. <https://doi.org/10.1186/1753-4631-3-9>
- Bosma, I., Stam, C. J., Douw, L., Bartolomei, F., Heimans, J. J., Van Dijk, B. W., ... Reijneveld, J. C. (2008). The influence of low-grade glioma on resting state oscillatory brain activity: A magnetoencephalography study. *Journal of Neuro-Oncology*, 88(1), 77–85. <https://doi.org/10.1007/s11060-008-9535-3>
- Butts, A. M., Weigand, S., Brown, P. D., Petersen, R. C., Jack, C. R. J., Machulda, M. M., & Cerhan, J. H. (2017). Neurocognition in individuals with incidentally-identified meningioma. *Journal of Neuro-Oncology*, 134(1), 125–132. <https://doi.org/10.1007/s11060-017-2495-8>

- Campanella, F., Fabbro, F., Ius, T., Shallice, T., & Skrap, M. (2015). Acute effects of surgery on emotion and personality of brain tumor patients: surgery impact, histological aspects, and recovery. *Neuro-Oncology*, 17(8), 1121–1131. <https://doi.org/10.1093/neuonc/nov065>
- Campanella, F., Mondani, M., Skrap, M., & Shallice, T. (2009). Semantic access dysphasia resulting from left temporal lobe tumours. *Brain*, 132(1), 87–102. <https://doi.org/10.1093/brain/awn302>
- Campanella, M., Ius, T., Skrap, M., & Fadiga, L. (2014). Alterations in fiber pathways reveal brain tumor typology: a diffusion tractography study. *PeerJ*, 2, e497. <https://doi.org/10.7717/peerj.497>
- Capon, A. P. (1996). Quantitative EEG with brain mapping in strokes: Is it useful for prognosis? *Brain Topography*, 9(2), 77–82. <https://doi.org/10.1007/BF01200707>
- Castellanos, N. P., Paúl, N., Ordóñez, V. E., Demuynck, O., Bajo, R., Campo, P., ... Maestú, F. (2010). Reorganization of functional connectivity as a correlate of cognitive recovery in acquired brain injury. *Brain*, 133(8), 2365–2381. <https://doi.org/10.1093/brain/awq174>
- Chapman, S. B., Pool, K. D., Finitzo, T., & Hong, C. T. (1989). Comparison of language profiles and electrocortical dysfunction in aphasia. In T. Prescott (Ed.), *Advances in Clinical Aphasiology* (pp. 41–59). San Diego, CA: College Hill Press.
- Chomsky, N. (1995). *The Minimalist Program*. Cambridge, MA: MIT Press.
- Chu, R. K. O., Braun, A. R., & Meltzer, J. A. (2015). MEG-based detection and localization of perilesional dysfunction in chronic stroke. *NeuroImage: Clinical*, 8, 157–169. <https://doi.org/10.1016/j.nicl.2015.03.019>
- Claus, J. J., Ongerboer De Visser, B. W., Bour, L. J., Walstra, G. J. M., Hijdra, A., Verbeeten Jr., B., ... Van Gool, W. A. (2000). Determinants of quantitative spectral electroencephalography in early Alzheimer's disease: cognitive function, regional cerebral blood flow, and computed tomography. *Dementia and Geriatric Cognitive Disorders*, 11(2), 81–89. <https://doi.org/10.1159/000017219>
- Cohen, J. (1992). A Power Primer. *Psychological Bulletin*, 112(1), 155–159. <https://doi.org/10.1037//0033-2909.112.1.155>
- Croft, W., & Cruse, D. A. (2004). *Cognitive Linguistics*. Cambridge, MA: Cambridge University Press. <https://doi.org/10.1017/CBO9780511803864>
- Damoiseaux, J. S., Rombouts, S. A. R. B., Barkhof, F., Scheltens, P., Stam, C. J., Smith, S. M., & Beckmann, C. F. (2006). Consistent resting-state networks across healthy subjects. *Proceedings of the National Academy of Sciences*, 103(37), 13848–13853. <https://doi.org/10.1073/pnas.0601417103>
- Davie, G. L., Hutcheson, K. A., Barringer, D. A., Weinberg, J. S., & Lewin, J. S. (2009). Aphasia in patients after brain tumour resection. *Aphasiology*, 23(9), 1196–1206. <https://doi.org/10.1080/02687030802436900>
- De Jongh, A., Baayen, J. C., De Munck, J. C., Heethaar, R. M., Vandertop, W. P., & Stam, C. J. (2003). The influence of brain tumor treatment on pathological delta activity in MEG. *NeuroImage*, 20(4), 2291–2301. <https://doi.org/10.1016/j.neuroimage.2003.07.030>
- De Renzi, E., & Faglioni, P. (1978). Normative data and screening power of a shortened version of the Token Test. *Cortex*, 14(1), 41–49. [https://doi.org/10.1016/S0010-9452\(78\)80006-9](https://doi.org/10.1016/S0010-9452(78)80006-9)
- De Robles, P., Fiest, K. M., Frolkis, A. D., Pringsheim, T., Atta, C., St. Germaine-Smith, C., ... Jette, N. (2015). The worldwide incidence and prevalence of primary brain tumors: A systematic review and meta-analysis. *Neuro-Oncology*, 17(6), 776–783. <https://doi.org/10.1093/neuonc/nou283>
- De Witt Hamer, P. C., Robles, S. G., Zwinderman, A. H., Duffau, H., & Berger, M. S. (2012). Impact of intraoperative stimulation brain mapping on glioma surgery outcome: A meta-analysis. *Journal of Clinical Oncology*, 30(20), 2559–2565. <https://doi.org/10.1200/JCO.2011.38.4818>

- De Witte, E., & Mariën, P. (2013). The neurolinguistic approach to awake surgery reviewed. *Clinical Neurology and Neurosurgery*, 115(2), 127–145. <https://doi.org/10.1016/j.clineuro.2012.09.015>
- De Witte, E., Satoer, D., Robert, E., Colle, H., Verheyen, S., Visch-Brink, E., & Mariën, P. (2015). The Dutch Linguistic Intraoperative Protocol: A valid linguistic approach to awake brain surgery. *Brain and Language*, 140, 35–48. <https://doi.org/10.1016/j.bandl.2014.10.011>
- Derks, J., Kulik, S., Wesseling, P., Numan, T., Hillebrand, A., van Dellen, E., ... Douw, L. (2019). Understanding cognitive functioning in glioma patients: The relevance of IDH-mutation status and functional connectivity. *Brain and Behavior*, 9(4), 1–9. <https://doi.org/10.1002/brb3.1204>
- Desmurget, M., Bonnetblanc, F., & Duffau, H. (2007). Contrasting acute and slow-growing lesions: A new door to brain plasticity. *Brain*, 130(4), 898–914. <https://doi.org/10.1093/brain/awl300>
- Di Cristofori, A., Zarino, B., Bertani, G., Locatelli, M., Rampini, P., Carrabba, G., & Caroli, M. (2018). Surgery in elderly patients with intracranial meningioma: neuropsychological functioning during a long term follow-up. *Journal of Neuro-Oncology*, 137(3), 611–619. <https://doi.org/10.1007/s11060-018-2754-3>
- Doucet, G. E., Pustina, D., Skidmore, C., Sharan, A., Sperling, M. R., & Tracy, J. I. (2015). Resting-state functional connectivity predicts the strength of hemispheric lateralization for language processing in temporal lobe epilepsy and normals. *Human Brain Mapping*, 36(1), 288–303. <https://doi.org/10.1002/hbm.22628>
- Doucet, G. E., Rider, R., Taylor, N., Skidmore, C., Sharan, A., Sperling, M., & Tracy, J. I. (2015). Presurgery resting-state local graph-theory measures predict neurocognitive outcomes after brain surgery in temporal lobe epilepsy. *Epilepsia*, 56(4), 517–526. <https://doi.org/10.1111/epi.12936>
- Douw, L., Baayen, H., Bosma, I., Klein, M., Vandertop, P., Heimans, J., ... Reijneveld, J. (2008). Treatment-related changes in functional connectivity in brain tumor patients: A magnetoencephalography study. *Experimental Neurology*, 212(2), 285–290. <https://doi.org/10.1016/j.expneurol.2008.03.013>
- Douw, L., Van Dellen, E., De Groot, M., Heimans, J. J., Klein, M., Stam, C. J., & Reijneveld, J. C. (2010). Epilepsy is related to theta band brain connectivity and network topology in brain tumor patients. *BMC Neuroscience*, 11, 103. <https://doi.org/10.1186/1471-2202-11-103>
- Dubovik, S., Bouzerda-Wahlen, A., Nahum, L., Gold, G., Schnider, A., & Guggisberg, A. G. (2013). Adaptive reorganization of cortical networks in Alzheimer's disease. *Clinical Neurophysiology*, 124(1), 35–43. <https://doi.org/10.1016/j.clinph.2012.05.028>
- Dubovik, S., Pignat, J. M., Ptak, R., Aboulafia, T., Allet, L., Gillabert, N., ... Guggisberg, A. G. (2012). The behavioral significance of coherent resting-state oscillations after stroke. *NeuroImage*, 61(1), 249–257. <https://doi.org/10.1016/j.neuroimage.2012.03.024>
- Dubovik, S., Ptak, R., Aboulafia, T., Magnin, C., Gillabert, N., Allet, L., ... Guggisberg, A. G. (2013). EEG alpha band synchrony predicts cognitive and motor performance in patients with ischemic stroke. *Behavioural Neurology*, 26(3), 187–189. <https://doi.org/10.3233/BEN-2012-129007>
- Duffau, H. (2014). The huge plastic potential of adult brain and the role of connectomics: New insights provided by serial mappings in glioma surgery. *Cortex*, 58, 325–337. <https://doi.org/10.1016/j.cortex.2013.08.005>
- Duffau, H., Moritz-Gasser, S., & Mandonnet, E. (2014). A re-examination of neural basis of language processing: Proposal of a dynamic hodotopical model from data provided by brain stimulation mapping during picture naming. *Brain and Language*, 131, 1–10. <https://doi.org/10.1016/j.bandl.2013.05.011>

References

- Duffy, F. H., McAnulty, G. B., & Albert, M. S. (1995). Temporoparietal electrophysiological differences characterize patients with Alzheimer's disease : A split-half replication study. *Cerebral Cortex*, 5(3), 215–221. <https://doi.org/10.1093/cercor/5.3.215>
- Duncan, J. S. (1987). Antiepileptic Drugs and the Electroencephalogram. *Epilepsia*, 28(3), 259–266. <https://doi.org/10.1111/j.1528-1157.1987.tb04216.x>
- Ellis, A. W., & Young, A. W. (1988). *Human cognitive neuropsychology*. Hove and London: Lawrence Erlbaum.
- Emerson, M. J., & Miyake, A. (2003). The role of inner speech in task switching: A dual-task investigation. *Journal of Memory and Language*, 48(1), 148–168. [https://doi.org/10.1016/S0749-596X\(02\)00511-9](https://doi.org/10.1016/S0749-596X(02)00511-9)
- Erdős, P., & Rényi, a. (1959). On random graphs. *Publicationes Mathematicae*, 6, 290–297. <https://doi.org/10.2307/1999405>
- Fernández-Bouzas, A., Harmony, T., Bosch, J., Aubert, E., Fernández, T., Valdés, P., ... Casián, G. (1999). Sources of abnormal EEG activity in the presence of brain lesions. *Clinical Electroencephalography*, 30(2), 46–52. <https://doi.org/10.1177/155005949903000205>
- Fernández-Bouzas, A., Harmony, T., Marosi, E., Fernández, T., Silva, J., Rodríguez, M., ... Casián, G. (1997). Evolution of cerebral edema and its relationship with power in the theta band. *Electroencephalography and Clinical Neurophysiology*, 102(4), 279–285. [https://doi.org/10.1016/S0013-4694\(96\)96049-6](https://doi.org/10.1016/S0013-4694(96)96049-6)
- Fernández, A., Maestú, F., Amo, C., Gil, P., Fehr, T., Wienbruch, C., ... Ortiz, T. (2002). Focal temporoparietal slow activity in Alzheimer's disease revealed by magnetoencephalography. *Society of Biological Psychiatry*, 52(7), 764–770. [https://doi.org/10.1016/S0006-3223\(02\)01366-5](https://doi.org/10.1016/S0006-3223(02)01366-5)
- Finitzo, T., Pool, K. D., & Chapman, S. B. (1991). Quantitative electroencephalography and anatomoclinical principles of aphasia. *Annals of the New York Academy of Sciences*, 620, 57–72. <https://doi.org/10.1111/j.1749-6632.1991.tb51574.x>
- Finnigan, S., & Van Putten, M. J. A. M. (2013). EEG in ischaemic stroke: Quantitative EEG can uniquely inform (sub-)acute prognoses and clinical management. *Clinical Neurophysiology*, 124(1), 10–19. <https://doi.org/10.1016/j.clinph.2012.07.003>
- Gallego-Jutglà, E., Solé-Casals, J., Vialatte, F.-B., Elgendi, M., Cichocki, A., & Dauwels, J. (2015). A hybrid feature selection approach for the early diagnosis of Alzheimer's disease. *Journal of Neural Engineering*, 12(1), 016018. <https://doi.org/10.1088/1741-2560/12/1/016018>
- Gehring, K., Taphoorn, M. J. B., Sitskoorn, M. M., & Aaronson, N. K. (2015). Predictors of subjective versus objective cognitive functioning in patients with stable grades II and III glioma. *Neuro-Oncology Practice*, 2(1), 20–31. <https://doi.org/10.1093/nop/npu035>
- Gloor, P., Ball, G., & Schaul, N. (1977). Brain lesions that produce delta waves in the EEG. *Neurology*, 27, 326–333. <https://doi.org/10.1212/WNL.27.4.326>
- Graetz, P., De Bleser, R., & Willmes, K. (1992). *Akense Afasietest, Dutch edition*. Lisse: Swets and Zeitlinger.
- Guggisberg, A. G., Honma, S. M., Findlay, A. M., Dalal, S. S., Kirsch, H. E., Berger, M. S., & Nagarajan, S. S. (2008). Mapping functional connectivity in patients with brain lesions. *Annals of Neurology*, 63(2), 193–203. <https://doi.org/10.1002/ana.21224>
- Gusnard, D. A., & Raichle, M. E. (2001). Searching for a baseline: Functional imaging and the resting human brain. *Nature Reviews Neuroscience*, 2, 685–694. <https://doi.org/10.1038/35094500>
- Haneef, Z., Levin, H. S., Frost, J. D., & Mizrahi, E. M. (2013). Electroencephalography and quantitative electroencephalography in mild traumatic brain injury. *Journal of Neurotrauma*, 30(8), 653–656. <https://doi.org/10.1089/neu.2012.2585>

- Helkala, E. L., Laulumaa, V., Soikkeli, R., Partanen, J., Soininen, H., & Riekkinen, P. J. (1991). Slow-wave activity in the spectral analysis of the electroencephalogram is associated with cortical dysfunctions in patients with Alzheimer's disease. *Behavioral Neuroscience*, 105(3), 409–415. <https://doi.org/10.1037/0735-7044.105.3.409>
- Hendrix, P., Hans, E., Griessenauer, C. J., Simgen, A., Oertel, J., & Karbach, J. (2017). Neurocognitive Function Surrounding the Resection of Frontal WHO Grade I Meningiomas: A Prospective Matched-Control Study. *World Neurosurgery*, 98, 203–210. <https://doi.org/10.1016/j.wneu.2016.10.095>
- Hensel, S., Rockstroh, B., Berg, P., Elbert, T., & Schönle, P. W. (2004). Left-hemispheric abnormal EEG activity in relation to impairment and recovery in aphasic patients. *Psychophysiology*, 41(3), 394–400. <https://doi.org/10.1111/j.1469-8986.2004.00164x>
- Hilari, K., Needle, J. J., & Harrison, K. L. (2012). What are the important factors in health-related quality of life for people with aphasia? A systematic review. *Archives of Physical Medicine and Rehabilitation*, 93(1), S86–95. <https://doi.org/10.1016/j.apmr.2011.05.028>
- Ho, V. K. Y., Reijneveld, J. C., Enting, R. H., Bienfait, H. P., Robe, P., Baumert, B. G., & Visser, O. (2014). Changing incidence and improved survival of gliomas. *European Journal of Cancer*, 50(13), 2309–2318. <https://doi.org/10.1016/j.ejca.2014.05.019>
- Hu, X. H., Lei, T., Xu, H. Z., Zou, Y. J., & Liu, H. Y. (2013). Resting-state magnetoencephalography study of “small world” characteristics and cognitive dysfunction in patients with glioma. *OncoTargets and Therapy*, 6, 311–313. <https://doi.org/10.2147/OTT.S42471>
- Huttner, H. B., Bergmann, O., Salehpour, M., El Cheikh, R., Nakamura, M., Tortora, A., ... Frisén, J. (2018). Meningioma growth dynamics assessed by radiocarbon retrospective birth dating. *EBioMedicine*, 27, 176–181. <https://doi.org/10.1016/j.ebiom.2017.12.020>
- Ilmberger, J., Ruge, M., Kreth, F.-W., Briegel, J., Reulen, H.-J., & Tonn, J.-C. (2008). Intraoperative mapping of language functions: a longitudinal neurolinguistic analysis. *Journal of Neurosurgery*, 109(4), 583–592. <https://doi.org/10.3171/JNS/2008/109/10/0583>
- Jabbari, B., Maulsby, R. L., Holtzapple, P. A., & Marshall, N. K. (1979). Prognostic value of EEG in acute vascular aphasia: a long term clinical-EEG study of 53 patients. *Clinical Electroencephalography*, 10(4), 190–197. <https://doi.org/10.1177/155005947901000403>
- Kaplan, E., Goodglass, H., & Weintraub, S. (2001). *The Boston Naming Test (second edition)*. Philadelphia, PA: Lippincott Williams and Wilkins. https://doi.org/10.1007/978-0-387-79948-3_869
- Kielar, A., Shah-Basak, P. P., Deschamps, T., Jokel, R., & Meltzer, J. A. (2019). Slowing is slowing: Delayed neural responses to words are linked to abnormally slow resting state activity in primary progressive aphasia. *Neuropsychologia*, 129(June), 331–347. <https://doi.org/10.1016/j.neuropsychologia.2019.04.007>
- Kim, J.-S., Lee, S.-H., Park, G., Kim, S., Bae, S.-M., Kim, D.-W., & Im, C.-H. (2012). Clinical implications of quantitative electroencephalography and current source density in patients with Alzheimer's disease. *Brain Topography*, 25, 461–474. <https://doi.org/10.1007/s10548-012-0234-1>
- Kruger, J., & Dunning, D. (1999). Unskilled and Unaware of It: How Difficulties in Recognizing One's Own Incompetence Lead to Inflated Self-Assessments. *Journal of Personality and Social Psychology*, 77(6), 1121–1134. <https://doi.org/10.1037/0022-3514.77.6.1121>
- Kruskal, J. B. (1956). On the shortest spanning subtree of a graph and the traveling salesman problem. *Proceedings of the American Mathematical Society*, 7(1), 48–50. <https://doi.org/10.1090/S0002-9939-1956-0078686-7>

- Larjavaara, S., Haapasalo, H., Sankila, R., Helen, P., & Auvinen, A. (2008). Is the incidence of meningiomas underestimated? A regional survey. *British Journal of Cancer*, 99(1532-1827 (Electronic)), 182–184. <https://doi.org/10.1038/sj.bjc.6604438>
- Larjavaara, S., Mäntylä, R., Salminen, T., Haapasalo, H., Raitanen, J., Jääskeläinen, J., & Auvinen, A. (2007). Incidence of gliomas by anatomic location. *Neuro-Oncology*, 9(3), 319–325. <https://doi.org/10.1215/15228517-2007-016>
- Levelt, W. J. M. (1989). *Speaking: From Intention to Articulation*. Cambridge, MA: MIT Press.
- Li, L., Pagnotta, M. F., Arakaki, X., Tran, T., Strickland, D., Harrington, M., & Zouridakis, G. (2015). Brain activation profiles in mTBI: Evidence from combined resting-state EEG and MEG activity. *Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBS)*, 6963–6966. <https://doi.org/10.1109/EMBC.2015.7319994>
- Liouta, E., Koutsarnakis, C., Liakos, F., & Stranjalis, G. (2016). Effects of intracranial meningioma location, size, and surgery on neurocognitive functions: a 3-year prospective study. *Journal of Neurosurgery*, 124(6), 1578–1584. <https://doi.org/10.3171/2015.6.JNS1549>
- Liu, R., Page, M., Solheim, K., Fox, S., & Chang, S. M. (2009). Quality of life in adults with brain tumors: current knowledge and future directions. *Neuro-Oncology*, 11(3), 330–339. <https://doi.org/10.1215/15228517-2008-093>
- Lizarazu, M., Gil-Robles, S., Pomposo, I., Nara, S., Amoruso, L., Quiñones, I., & Carreiras, M. (2020). Spatiotemporal dynamics of postoperative functional plasticity in patients with brain tumors in language areas. *Brain and Language*, 202, 104741. <https://doi.org/10.1016/j.bandl.2019.104741>
- Lopes da Silva, F. (2013). EEG and MEG: Relevance to neuroscience. *Neuron*, 80(5), 1112–1128. <https://doi.org/10.1016/j.neuron.2013.10.017>
- Louis, D. N., Ohgaki, H., Wiestler, O. D., Cavenee, W. K., Burger, P. C., Jouvet, A., ... Kleihues, P. (2007). The 2007 WHO classification of tumours of the central nervous system. *Acta Neuropathologica*, 114(2), 97–109. <https://doi.org/10.1007/s00401-007-0243-4>
- Louis, D. N., Perry, A., Reifenberger, G., von Deimling, A., Figarella-Branger, D., Cavenee, W. K., ... Ellison, D. W. (2016). The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. *Acta Neuropathologica*, 131(6), 1–18. <https://doi.org/10.1007/s00401-016-1545-1>
- Lüders, H. O., & Noachtar, S. (2000). *Atlas and classification of electroencephalography*. Philadelphia, PA: W. B. Saunders.
- Luteijn, F., & Barelds, D. P. F. (2004). *Groninger Intelligentie Test - 2 (GIT-2)*. Amsterdam: Pearson.
- Mandonnet, E., Pallud, J., Clatz, O., Taillandier, L., Konukoglu, E., Duffau, H., & Capelle, L. (2008). Computational modeling of the WHO grade II glioma dynamics: Principles and applications to management paradigm. *Neurosurgical Review*, 31(3), 263–268. <https://doi.org/10.1007/s10143-008-0128-6>
- Martino, J., Honma, S. M., Findlay, A. M., Guggisberg, A. G., Owen, J. P., Kirsch, H. E., ... Nagarajan, S. S. (2011). Resting functional connectivity in patients with brain tumors in eloquent areas. *Annals of Neurology*, 69(3), 521–532. <https://doi.org/10.1002/ana.22167>
- Mayo Clinic and Mayo Foundation. (1998). *Clinical Examinations in Neurology*. Baltimore, MD: Mosby.
- McAleer, M. F., & Brown, P. D. (2015). Neurocognitive function following therapy for low-grade gliomas. *Seminars in Radiation Oncology*, 25(3), 210–218. <https://doi.org/10.1016/j.semradonc.2015.02.005>
- Meinzer, M., Elbert, T., Wienbruch, C., Djundja, D., Barthel, G., & Rockstroh, B. (2004). Intensive language training enhances brain plasticity in chronic aphasia. *BMC Biology*, 2, 20. <https://doi.org/10.1186/1741-7007-2-20>

- Meskal, I., Gehring, K., Rutten, G.-J. M., & Sitskoorn, M. M. (2016). Cognitive functioning in meningioma patients: a systematic review. *Journal of Neuro-Oncology*, 128(2), 195–205. <https://doi.org/10.1007/s11060-016-2115-z>
- Meskal, I., Gehring, K., Van der Linden, S. D., Rutten, G.-J. M., & Sitskoorn, M. M. (2015). Cognitive improvement in meningioma patients after surgery: clinical relevance of computerized testing. *Journal of Neuro-Oncology*, 121(3), 617–625. <https://doi.org/10.1007/s11060-014-1679-8>
- Miceli, G., Caltagirone, C., Gainotti, G., Masullo, C., Silveri, M. C., & Villa, G. (1981). Influence of age, sex, literacy and pathologic lesion on incidence, severity and type of aphasia. *Acta Neurologica Scandinavica*, 64(5), 370–382. <https://doi.org/10.1111/j.1600-0404.1981.tb04416.x>
- Moritz-Gasser, S., Herbet, G., Maldonado, I. L., & Duffau, H. (2012). Lexical access speed is significantly correlated with the return to professional activities after awake surgery for low-grade gliomas. *Journal of Neuro-Oncology*, 107(3), 633–641. <https://doi.org/10.1007/s11060-011-0789-9>
- Naidich, T. P., Hof, P. R., Gannon, P. J., Yousry, T. A., & Yousry, I. (2001). Anatomic substrates of language: emphasizing speech. *Neuroimaging Clinics of North America*, 11(2), 305–341.
- Nicolo, P., Rizk, S., Magnin, C., Pietro, M. Di, Schnider, A., & Guggisberg, A. G. (2015). Coherent neural oscillations predict future motor and language improvement after stroke. *Brain*, 138(10), 3048–3060. <https://doi.org/10.1093/brain/awv200>
- Niedermeyer, E. (1999). The normal EEG of the waking adult. In E. Niedermeyer & F. Lopes da Silva (Eds.), *Electroencephalography: basic principles, clinical applications, and related fields* (4th ed., pp. 149–173). Philadelphia, PA: Williams and Wilkins.
- Nokia, M. S., Anderson, M. L., & Shors, T. J. (2012). Chemotherapy disrupts learning, neurogenesis and theta activity in the adult brain. *European Journal of Neuroscience*, 36(11), 3521–3530. <https://doi.org/10.1111/ejn.12007>
- Noll, K. R., Sullaway, C., Ziu, M., Weinberg, J. S., & Wefel, J. S. (2015). Relationships between tumor grade and neurocognitive functioning in patients with glioma of the left temporal lobe prior to surgical resection. *Neuro-Oncology*, 17(4), 580–587. <https://doi.org/10.1093/neuonc/nou233>
- Noll, K. R., Ziu, M., Weinberg, J. S., & Wefel, J. S. (2016). Neurocognitive functioning in patients with glioma of the left and right temporal lobes. *Journal of Neuro-Oncology*, 128(2), 1–9. <https://doi.org/10.1007/s11060-016-2114-0>
- Norrelgen, F., Jensdottir, M., & Östberg, P. (2020). High-level language outcomes three and twelve months after awake surgery in low grade glioma and cavernoma patients. *Clinical Neurology and Neurosurgery*, 195, 105946. <https://doi.org/10.1016/j.clineuro.2020.105946>
- Olde Dubbelink, K. T. E., Stoffers, D., Deijen, J. B., Twisk, J. W. R., Stam, C. J., & Berendse, H. W. (2013). Cognitive decline in Parkinson's disease is associated with slowing of resting-state brain activity: A longitudinal study. *Neurobiology of Aging*, 34(2), 408–418. <https://doi.org/10.1016/j.neurobiolaging.2012.02.029>
- Oldfield, R. C. (1971). The Assessment and Analysis of Handedness: The Edinburgh Inventory. *Neuropsychologia*, 9(1), 97–113. [https://doi.org/10.1016/0028-3932\(71\)90067-4](https://doi.org/10.1016/0028-3932(71)90067-4)
- Oshino, S., Kato, A., Wakayama, A., Taniguchi, M., Hirata, M., & Yoshimine, T. (2007). Magnetoencephalographic analysis of cortical oscillatory activity in patients with brain tumors: Synthetic aperture magnetometry (SAM) functional imaging of delta band activity. *NeuroImage*, 34(3), 957–964. <https://doi.org/10.1016/j.neuroimage.2006.08.054>

References

- Osoba, D., Aaronson, N. K., Muller, M., Sneeuw, K., Hsu, M.-A., Yung, W. K. A., ... Newlands, E. (1996). The development and psychometric validation of a brain cancer quality-of-life questionnaire for use in combination with general cancer-specific questionnaires. *Quality of Life Research*, 5(1), 139–150. Retrieved from <https://www.jstor.org/stable/4034790>
- Papagno, C., Casarotti, A., Comi, A., Gallucci, M., Riva, M., & Bello, L. (2012). Measuring clinical outcomes in neuro-oncology. A battery to evaluate low-grade gliomas (LGG). *Journal of Neuro-Oncology*, 108(2), 269–275. <https://doi.org/10.1007/s11060-012-0824-5>
- Papagno, C., Miracapillo, C., Casarotti, A., Romero Lauro, L. J., Castellano, A., Falini, A., ... Bello, L. (2011). What is the role of the uncinate fasciculus? Surgical removal and proper name retrieval. *Brain*, 134(2), 405–414. <https://doi.org/10.1093/brain/awq283>
- Pereda, E., Quiroga, R. Q., & Bhattacharya, J. (2005). Nonlinear multivariate analysis of neurophysiological signals. *Progress in Neurobiology*, 77(1–2), 1–37. <https://doi.org/10.1016/j.pneurobio.2005.10.003>
- Perlovsky, L. (2013). Language and cognition—joint acquisition, dual hierarchy, and emotional prosody. *Frontiers in Behavioral Neuroscience*, 7(123), 1–3. <https://doi.org/10.3389/fnbeh.2013.00123>
- Pranckeviciene, A., Deltuva, V. P., Tamasauskas, A., & Bunevicius, A. (2017). Association between psychological distress, subjective cognitive complaints and objective neuropsychological functioning in brain tumor patients. *Clinical Neurology and Neurosurgery*, 163, 18–23. <https://doi.org/10.1016/j.clineuro.2017.10.007>
- Racine, C. A., Li, J., Molinaro, A. M., Butowski, N., & Berger, M. S. (2015). Neurocognitive Function in Newly Diagnosed Low-grade Glioma Patients Undergoing Surgical Resection With Awake Mapping Techniques. *Neurosurgery*, 77(3), 371–379. <https://doi.org/10.1227/NEU.0000000000000779>
- Radhakrishnan, K., Mokri, B., Parisi, J. E., O'Fallon, W. M., Sunku, J., & Kurland, L. T. (1995). The trends in incidence of primary brain tumors in the population of Rochester, Minnesota. *Annals of Neurology*, 37(1), 67–73. <https://doi.org/10.1002/ana.410370113>
- Raemaekers, M., Schellekens, W., Petridou, N., & Ramsey, N. F. (2018). Knowing left from right: asymmetric functional connectivity during resting state. *Brain Structure and Function*, 223(4), 1909–1922. <https://doi.org/10.1007/s00429-017-1604-y>
- Ranasinghe, K. G., Hinkley, L. B., Beagle, A. J., Mizuiri, D., Honma, S. M., Welch, A. E., ... Nagarajan, S. S. (2017). Distinct spatiotemporal patterns of neuronal functional connectivity in primary progressive aphasia variants. *Brain*, 140(10), 2737–2751. <https://doi.org/10.1093/brain/awx217>
- Rofes, A. (2012). *The verb in sentence context test: Standardization and application in awake neurosurgery*. (Unpublished master's dissertation). University of Groningen, The Netherlands.
- Rofes, A., Talacchi, A., Santini, B., Pinna, G., Nickels, L., Bastiaanse, R., & Miceli, G. (2018). Language in individuals with left hemisphere tumors: Is spontaneous speech analysis comparable to formal testing? *Journal of Clinical and Experimental Neuropsychology*, 40(7), 722–732. <https://doi.org/10.1080/13803395.2018.1426734>
- Rubinov, M., & Sporns, O. (2010). Complex network measures of brain connectivity: Uses and interpretations. *NeuroImage*, 52(3), 1059–1069. <https://doi.org/10.1016/j.neuroimage.2009.10.003>
- Santini, B., Talacchi, A., Squintani, G., Casagrande, F., Capasso, R., & Miceli, G. (2012). Cognitive outcome after awake surgery for tumors in language areas. *Journal of Neuro-Oncology*, 108(2), 319–326. <https://doi.org/10.1007/s11060-012-0817-4>
- Satoer, D., De Witte, E., Bastiaanse, R., Vincent, A., Mariën, P., & Visch-Brink, E. (2019). Diagnostic Instrument for Mild Aphasia (DIMA): standardization and clinical application. *Conference Abstract: Academy of Aphasia 55th Annual Meeting*. <https://doi.org/10.3389/conf.fnhum.2017.223.00103>

- Satoer, D., Vincent, A., Ruhaak, L., Smits, M., Dirven, C., & Visch-Brink, E. (2018). Spontaneous speech in patients with gliomas in eloquent areas: Evaluation until 1 year after surgery. *Clinical Neurology and Neurosurgery*, 167, 112–116. <https://doi.org/https://doi.org/10.1016/j.clineuro.2018.02.018>
- Satoer, D., Vincent, A., Smits, M., Dirven, C., & Visch-Brink, E. (2013). Spontaneous speech of patients with gliomas in eloquent areas before and early after surgery. *Acta Neurochirurgica*, 155(4), 685–692. <https://doi.org/10.1007/s00701-013-1638-8>
- Satoer, D., Visch-Brink, E., Dirven, C., & Vincent, A. (2016). Glioma surgery in eloquent areas: can we preserve cognition? *Acta Neurochirurgica*, 158(1), 35–50. <https://doi.org/10.1007/s00701-015-2601-7>
- Satoer, D., Visch-Brink, E., Smits, M., Kloet, A., Looman, C., Dirven, C., & Vincent, A. (2014). Long-term evaluation of cognition after glioma surgery in eloquent areas. *Journal of Neuro-Oncology*, 116(1), 153–160. <https://doi.org/10.1007/s11060-013-1275-3>
- Satoer, D., Vork, J., Visch-Brink, E., Smits, M., Dirven, C., & Vincent, A. (2012). Cognitive functioning early after surgery of gliomas in eloquent areas. *Journal of Neurosurgery*, 117(5), 831–838. <https://doi.org/10.3171/2012.7.JNS12263>
- Schleiger, E., Sheikh, N., Rowland, T., Wong, A., Read, S., & Finnigan, S. (2014). Frontal EEG delta/alpha ratio and screening for post-stroke cognitive deficits: The power of four electrodes. *International Journal of Psychophysiology*, 94(1), 19–24. <https://doi.org/10.1016/j.ijpsycho.2014.06.012>
- Schleiger, E., Wong, A., Read, S., Rowland, T., & Finnigan, S. (2017). Poststroke QEEG informs early prognostication of cognitive impairment. *Psychophysiology*, 54(2), 301–309. <https://doi.org/10.1111/psyp.12785>
- Schmand, B., Groenink, S. C., & Van den Dungen, M. (2008). Letter fluency: Psychometrische eigenschappen en Nederlandse normen. *Tijdschrift Voor Gerontologie En Geriatrie*, 39, 65–77. <https://doi.org/10.1007/BF03078128>
- Schnitzler, A., & Gross, J. (2005). Normal and pathological oscillatory communication in the brain. *Nature Reviews Neuroscience*, 6, 285–296. <https://doi.org/10.1038/nrn1650>
- Schomer, D. L., & Lopes da Silva, F. (2010). Part III Clinical EEG: General. In *Niedermeyer's Electroencephalography: Basic Principles, Clinical Applications, and Related Fields* (6th ed., pp. 267–464). Wolters Kluwer Health.
- Shah-Basak, P. P., Kielar, A., Deschamps, T., Verhoeff, N. P., Jokel, R., & Meltzer, J. (2019). Spontaneous oscillatory markers of cognitive status in two forms of dementia. *Human Brain Mapping*, 40(5), 1594–1607. <https://doi.org/10.1002/hbm.24470>
- Sinanovic, O., Kapidzic, A., Kovacevic, L., Hudic, J., & Smajlovic, D. (2005). EEG frequency and cognitive dysfunction in patients with Parkinson's disease. *Medicinski Arhiv*, 59(5), 286–287.
- Sorensen, A. G., Patel, S., Harmath, C., Bridges, S., Synnott, J., Sievers, A., ... Weisskoff, R. (2001). Comparison of Diameter and Perimeter Methods for Tumor Volume Calculation. *Journal of Clinical Oncology*, 19(2), 551–557. <https://doi.org/10.1200/JCO.2001.19.2.551>
- Spironelli, C., & Angrilli, A. (2009). EEG delta band as a marker of brain damage in aphasic patients after recovery of language. *Neuropsychologia*, 47(4), 988–994. <https://doi.org/10.1016/j.neuropsychologia.2008.10.019>
- Stam, C. J. (2004). Functional connectivity patterns of human magnetoencephalographic recordings: A "small-world" network? *Neuroscience Letters*, 355(1–2), 25–28. <https://doi.org/10.1016/j.neulet.2003.10.063>
- Stam, C. J. (2018). BrainWave [Computer software]. Retrieved from <http://home.kpn.nl/stam7883/brainwave.html>

- Stam, C. J., Nolte, G., & Daffertshofer, A. (2007). Phase lag index: Assessment of functional connectivity from multi channel EEG and MEG with diminished bias from common sources. *Human Brain Mapping*, 28(11), 1178–1193. <https://doi.org/10.1002/hbm.20346>
- Stam, C. J., Tewarie, P., Van Dellen, E., Van Straaten, E. C. W., Hillebrand, A., & Van Mieghem, P. (2014). The trees and the forest: Characterization of complex brain networks with minimum spanning trees. *International Journal of Psychophysiology*, 92(3), 129–138. <https://doi.org/10.1016/j.ijpsycho.2014.04.001>
- Stam, C. J., & Van Straaten, E. C. W. (2012). The organization of physiological brain networks. *Clinical Neurophysiology*, 123(6), 1067–1087. <https://doi.org/10.1016/j.clinph.2012.01.011>
- Stoffers, D., Bosboom, J. L. W., Deijen, J. B., Wolters, E. C., Berendse, H. W., & Stam, C. J. (2007). Slowing of oscillatory brain activity is a stable characteristic of Parkinson's disease without dementia. *Brain*, 130(7), 1847–1860. <https://doi.org/10.1093/brain/awm034>
- Szelies, B., Mielke, R., Kessler, J., & Heiss, W. D. (2002). Prognostic relevance of quantitative topographical EEG in patients with poststroke aphasia. *Brain and Language*, 82(1), 87–94. [https://doi.org/10.1016/S0093-934X\(02\)00004-4](https://doi.org/10.1016/S0093-934X(02)00004-4)
- Talacchi, A., Santini, B., Savazzi, S., & Gerosa, M. (2011). Cognitive effects of tumour and surgical treatment in glioma patients. *Journal of Neuro-Oncology*, 103(3), 541–549. <https://doi.org/10.1007/s11060-010-0417-0>
- Tanaka, N., & Stufflebeam, S. M. (2016). Presurgical Mapping of the Language Network Using Resting-state Functional Connectivity. *Topics in Magnetic Resonance Imaging*, 25(1), 19–23. <https://doi.org/10.1097/RMR.0000000000000073>
- Tarapore, P. E., Martino, J., Guggisberg, A. G., Owen, J., Honma, S. M., Findlay, A., ... Nagarajan, S. S. (2012). Magnetoencephalographic imaging of resting-state functional connectivity predicts postsurgical neurological outcome in brain gliomas. *Neurosurgery*, 71(5), 1012–1022. <https://doi.org/10.1227/NEU.0b013e31826d2b78>
- Tecchio, F., Zappasodi, F., Pasqualetti, P., Tombini, M., Salustri, C., Oliviero, A., ... Rossini, P. M. (2005). Rhythmic brain activity at rest from rolandic areas in acute mono-hemispheric stroke: A magnetoencephalographic study. *NeuroImage*, 28(1), 72–83. <https://doi.org/10.1016/j.neuroimage.2005.05.051>
- Thatcher, R. W. (2006). Electroencephalography and Mild Traumatic Brain Injury. In S. Slobounov & W. Sebastianelli (Eds.), *Foundations of Sport-Related Brain Injuries* (pp. 241–265). New York: Springer-Verlag.
- Thatcher, R. W., Biver, C., McAlaster, R., Camacho, M., & Salazar, A. (1998). Biophysical linkage between MRI and EEG amplitude in closed head injury. *NeuroImage*, 7, 352–367. <https://doi.org/10.1006/nimg.1998.0330>
- Tikofsky, R. S., Kooi, K. A., & Thomas, M. H. (1960). Electroencephalographic findings and recovery from aphasia. *Neurology*, 10, 154–156. <https://doi.org/10.1212/WNL.10.2.154>
- Trinh, V. T., Fahim, D. K., Shah, K., Tummala, S., McCutcheon, I. E., Sawaya, R., ... Prabhu, S. S. (2013). Subcortical injury is an independent predictor of worsening neurological deficits following awake craniotomy procedures. *Neurosurgery*, 72(2), 160–169. <https://doi.org/10.1227/NEU.0b013e31827b9a11>
- Tucha, O., Smely, C., Preier, M., Becker, G., Paul, G. M., & Lange, K. W. (2003). Preoperative and postoperative cognitive functioning in patients with frontal meningiomas. *Journal of Neurosurgery*, 98(1), 21–31. <https://doi.org/10.3171/jns.2003.98.1.0021>

- Tuunainen, A., Nousiainen, U., Hurskainen, H., Leinonen, E., Pilke, A., Mervaala, E., ... Riekkinen, P. (1995). Preoperative EEG predicts memory and selective cognitive functions after temporal lobe surgery. *Journal of Neurology, Neurosurgery, and Psychiatry*, 58, 674–680. <https://doi.org/10.1136/jnnp.58.6.674>
- Van Alkemade, H., De Leau, M., Dieleman, E. M. T., Kardaun, J. W. P. F., Van Os, R., Vandertop, W. P., ... Stalpers, L. J. A. (2012). Impaired survival and long-term neurological problems in benign meningioma. *Neuro-Oncology*, 14(5), 658–666. <https://doi.org/10.1093/neuonc/nos013>
- Van Dellen, E., De Witt Hamer, P. C., Douw, L., Klein, M., Heimans, J. J., Stam, C. J., ... Hillebrand, A. (2013). Connectivity in MEG resting-state networks increases after resective surgery for low-grade glioma and correlates with improved cognitive performance. *NeuroImage: Clinical*, 2(1), 1–7. <https://doi.org/10.1016/j.nicl.2012.10.007>
- Van Dellen, E., Douw, L., Hillebrand, A., Ris-Hilgersom, I. H. M., Schoonheim, M. M., Baayen, J. C., ... Reijneveld, J. C. (2012). MEG Network Differences between Low- and High-Grade Glioma Related to Epilepsy and Cognition. *PLoS ONE*, 7(11). <https://doi.org/10.1371/journal.pone.0050122>
- Van der Hiele, K., Vein, A. A., Reijntjes, R. H. A. M., Westendorp, R. G. J., Bollen, E. L. E. M., Van Buchem, M. A., ... Middelkoop, H. A. M. (2007). EEG correlates in the spectrum of cognitive decline. *Clinical Neurophysiology*, 118(9), 1931–1939. <https://doi.org/10.1016/j.clinph.2007.05.070>
- Van der Linden, S. D., Gehring, K., De Baene, W., Emons, W. H. M., Rutten, G.-J. M., & Sitskoorn, M. M. (2020). Assessment of Executive Functioning in Patients with Meningioma and Low-Grade Glioma: A Comparison of Self-Report, Proxy-Report, and Test Performance. *Journal of the International Neuropsychological Society*, 26(2), 187–196. <https://doi.org/10.1017/S1355617719001164>
- Van Diessen, E., Numan, T., Van Dellen, E., Van der Kooi, A. W., Boersma, M., Hofman, D., ... Stam, C. J. (2015). Opportunities and methodological challenges in EEG and MEG resting state functional brain network research. *Clinical Neurophysiology*, 126(8), 1468–1481. <https://doi.org/10.1016/j.clinph.2014.11.018>
- Van Ierschoot, F. (2018). *Written language in awake surgery – Monitoring of reading and spelling in glioma patients undergoing awake surgery*. (Doctoral dissertation). University of Trento, Italy, and University of Groningen, The Netherlands. Retrieved from <https://nvneuropsychy.nl/uploads/prijzen/inzendingen/5abe08aaf035957a7a9e38858a3ce0b7.pdf>
- Van Ierschoot, F., Bastiaanse, R., & Miceli, G. (2018). Evaluating Spelling in Glioma Patients Undergoing Awake Surgery: a Systematic Review. *Neuropsychology Review*, 28(4), 470–495. <https://doi.org/10.1007/s11065-018-9391-7>
- Van Kessel, E., Baumfalk, A. E., Van Zandvoort, M. J. E., Robe, P. A., & Snijders, T. J. (2017). Tumor-related neurocognitive dysfunction in patients with diffuse glioma: a systematic review of neurocognitive functioning prior to anti-tumor treatment. *Journal of Neuro-Oncology*, 134(1), 9–18. <https://doi.org/10.1007/s11060-017-2503-z>
- Van Kessel, E., Snijders, T. J., Baumfalk, A. E., Ruis, C., van Baarsen, K. M., Broekman, M. L., ... Robe, P. A. (2020). Neurocognitive changes after awake surgery in glioma patients: a retrospective cohort study. *Journal of Neuro-Oncology*, 146, 97–109. <https://doi.org/10.1007/s11060-019-03341-6>
- Van Nieuwenhuizen, D., Ambachtsheer, N., Heimans, J. J., Reijneveld, J. C., Peerdeman, S. M., & Klein, M. (2013). Neurocognitive functioning and health-related quality of life in patients with radiologically suspected meningiomas. *Journal of Neuro-Oncology*, 113(3), 433–440. <https://doi.org/10.1007/s11060-013-1132-4>

References

- Van Nieuwenhuizen, D., Douw, L., Klein, M., Peerdeman, S. M., Heimans, J. J., Reijneveld, J. C., ... Hillebrand, A. (2018). Cognitive functioning and functional brain networks in postoperative WHO grade I meningioma patients. *Journal of Neuro-Oncology*, 140(3), 605–613. <https://doi.org/10.1007/s11060-018-2987-1>
- Van Straaten, E. C. W., & Stam, C. J. (2013). Structure out of chaos: Functional brain network analysis with EEG, MEG, and functional MRI. *European Neuropsychopharmacology*, 23(1), 7–18. <https://doi.org/10.1016/j.euroneuro.2012.10.010>
- Verhage, F. (1964). *Intelligentie en leeftijd: Onderzoek bij Nederlanders van 12 tot 77 jaar*. Assen: Van Gorkum.
- Wang, H., Douw, L., Hernández, J. M., Reijneveld, J. C., Stam, C. J., & Van Mieghem, P. (2010). Effect of tumor resection on the characteristics of functional brain networks. *Physical Review E - Statistical, Nonlinear, and Soft Matter Physics*, 82(2), 1–14. <https://doi.org/10.1103/PhysRevE.82.021924>
- Watts, D. J., & Strogatz, S. H. (1998). Collective dynamics of “small-world” networks. *Nature*, 393(6684), 440–442. <https://doi.org/10.1038/30918>
- Wei, C. W., Guo, G., & Mikulis, D. J. (2007). Tumor Effects on Cerebral White Matter as Characterized by Diffusion Tensor Tractography. *Canadian Journal of Neurological Sciences*, 34(1), 62–68. <https://doi.org/10.1017/s0317167100005801>
- Whiteside, D. M., Kealey, T., Semla, M., Luu, H., Rice, L., Basso, M. R., & Roper, B. (2016). Verbal Fluency: Language or Executive Function Measure? *Applied Neuropsychology: Adult*, 23(1), 29–34. <https://doi.org/10.1080/23279095.2015.1004574>
- Whittle, I. R., Smith, C., Navoo, P., & Collie, D. (2004). Meningiomas. *The Lancet*, 363(9420), 1535–1543. [https://doi.org/10.1016/S0140-6736\(04\)16153-9](https://doi.org/10.1016/S0140-6736(04)16153-9)
- Wiemels, J., Wrensch, M., & Claus, E. B. (2010). Epidemiology and etiology of meningioma. *Journal of Neuro-Oncology*, 99(3), 307–314. <https://doi.org/10.1007/s11060-010-0386-3>
- Worrall, L., & Holland, A. (2003). Editorial: Quality of life in aphasia. *Aphasiology*, 17(4), 329–332. <https://doi.org/10.1080/02687030244000699>
- Zhang, N., Xia, M., Qiu, T., Wang, X., Lin, C., Guo, Q., ... Zhou, L. (2018). Reorganization of cerebro-cerebellar circuit in patients with left hemispheric gliomas involving language network: A combined structural and resting-state functional MRI study. *Human Brain Mapping*, 39(12), 4802–4819. <https://doi.org/10.1002/hbm.24324>
- Zhang, X., Lei, X., Wu, T., & Jiang, T. (2014). A review of EEG and MEG for brainnetome research. *Cognitive Neurodynamics*, 8(2), 87–98. <https://doi.org/10.1007/s11571-013-9274-9>

Appendix A

Appendix to chapter 4

Appendix A – Overview language scores

Mean z-scores (and standard deviations) for each separate language test and comparisons to a healthy population ($M = 0.00$)

	N	M (SD)
Mean composite language z-score	21	-0.61 (0.70)***
<i>Individual language tests</i>		
Object naming	21	-1.36 (1.68)**
Category fluency	20	-0.93 (0.81)***
Letter fluency	20	-0.81 (1.17)**
Token Test (AAT)	15	-0.50 (1.82)
Repetition (AAT)	11	-0.18 (0.98)
Reading (AAT)	10	0.03 (1.01)
Writing (AAT)	10	0.22 (0.51)

Note. AAT = Aachen Aphasia Test.

* Significantly lower than a healthy population at the 0.05 level (2-tailed)

** Significantly lower than a healthy population at the 0.01 level (2-tailed)

*** Significantly lower than a healthy population at the 0.001 level (2-tailed)

Appendix B

Appendix to chapter 5

Appendix B1 – Language performance in glioma patients

Language domain z-scores of glioma patients at T1, T2, and T3

Language domain	T1				T2				T3				Normative data ^c	
	N	Mdn	Min	Max	N	Mdn	Min	Max	N	Mdn	Min	Max	Max	N
Separate tests														
Production-Word retrieval ^a	15	-1.64	-10.71	0.83	15	-0.63	-8.19	0.88	13	0.02	-7.18	0.88		145
Object naming														
Production-Phonology ^b	15	-0.20	-5.28	0.95	15	-0.34	-8.73	0.74	13	-0.84	-5.62	0.85		
Letter fluency	15	-0.60	-3.00	1.20	15	-0.90	-2.60	1.00	13	-0.50	-2.60	1.10		570
Repetition	15	-0.07	-7.86	0.78	15	-0.07	-14.87	0.78	13	-0.85	-8.64	0.78		103
Production-Semantics ^b	15	-0.60	-5.14	1.11	15	-0.42	-3.02	1.07	13	-0.70	-3.99	0.91		
Category fluency	15	-0.65	-3.10	1.55	15	-0.60	-2.45	1.25	13	-0.80	-2.75	2.00		464, 394 ^d
Semantic odd-picture-out	15	-0.64	-8.28	1.21	15	0.19	-3.70	1.21	13	-0.64	-5.22	1.21		104
Production-Morphosyntax ^b	15	-0.25	-8.33	0.74	15	-0.20	-4.35	0.86	13	-0.59	-5.38	0.86		
Action naming	14	-0.29	-16.41	1.05	15	0.38	-4.95	1.29	13	-0.38	-5.62	1.29		143
Sentence completion	15	0.43	-3.75	0.43	15	0.43	-3.75	0.71	13	-0.25	-5.14	0.43		105
Comprehension-Auditory input ^a	15	-0.69	-4.98	0.83	15	0.32	-5.23	0.83	13	-0.18	-3.97	0.83		100
Token Test														
Comprehension-Visual input ^a	13	0.19	-1.05	0.56	14	0.14	-2.01	0.57	12	0.38	-0.72	0.57		104
Sentence judgement														
Reading ^a	14	0.28	-5.28	0.28	15	0.61	-5.57	0.61	13	0.28	-2.50	0.28		51
Reading														
Writing ^a	13	-0.79	-6.12	0.55	14	-0.72	-23.09	0.59	13	-0.79	-7.45	0.55		51
Writing														

Note. T1 = before surgery; T2 = 2 months after surgery; T3 = 1 year after surgery; N = sample size; Mdn = median; Min = minimum value; Max = maximum value.

^a The language domain includes one test only, therefore, the domain scores are identical to the test scores.

^b Domain scores are composed of the scores on the separate tests presented below the domains.

^c For every test, the pre-existing normative data were based on a group of healthy, Dutch individuals, of which the sample size is provided.

^d The first number concerns the subtest Animals; the second number concerns the subtest Professions.

Appendix B2 –Self-reported language problems and test performance: individual data

Language altogether: Presence (1) or absence (0) of self-reported language problems, and language impairment according to tests for each patient at T1, T2, and T3

	pt1	pt2	pt3	pt4	pt5	pt6	pt7	pt8	pt9	pt10	pt11	pt12	pt13	pt14	pt15
T1	Self-reported language problems														
	1	1	1	0	1	0	1	0	0	0	1	0	0	1	1
T2	Impaired test performance														
	1	1	0	0	1	0	1	1	0	0	1	1	0	1	1
T2	Self-reported language problems														
	0	1	1	1	1	1	0	1	0	0	1	0	1	1	1
T3	Impaired test performance														
	1	0	0	0	1	1	0	1	1	1	1	1	0	1	1
T3	Self-reported language problems														
	0	1	1	0	1	1	1	0	0	0	1	0	1	1	1
T3	Impaired test performance														
	1	1	1	0	1	1	1	0	0	1	1	1	0	1	1

Note. Impaired test performance is defined as $z \leq -1.5$ in one or more language domains. Empty cells indicate that the assessment did not take place.

Separate language domains: Presence (1) or absence (0) of self-reported language problems, and language impairment according to tests for each patient at T1, T2, and T3

	pt1	pt2	pt3	pt4	pt5	pt6	pt7	pt8	pt9	pt10	pt11	pt12	pt13	pt14	pt15
Word retrieval	Self-reported language problems														
	1	1	1	0	1	0	1	0	0	0	1	0	0	1	1
	Impaired test performance														
	1	1	0	0	0	0	1	1	0	0	1	1	0	1	1
Production	Self-reported language problems														
	0	0	0	0	1	0	1	0	0	0	1	0	0	1	1
	Impaired test performance														
	0	1	0	0	1	0	0	1	0	0	1	0	0	1	1
T1 Comprehension	Self-reported language problems														
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Impaired test performance														
	0	0	0	0	1	0	0	1	0	0	1	0	0	0	1
Reading	Self-reported language problems														
	0	0	0	0	1	0	1	0	0	0	1	0	0	0	1
	Impaired test performance														
	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Writing	Self-reported language problems														
	1	0	0	0	1	0	1	0	0	0	1	0	0	0	1
	Impaired test performance														
	0			0	1	0	0	0	0	0	1	0	0	0	1

	pt1	pt2	pt3	pt4	pt5	pt6	pt7	pt8	pt9	pt10	pt11	pt12	pt13	pt14	pt15
Word retrieval	Self-reported language problems	0	1	1	1	0	1	0	1	0	0	1	0	1	1
	Impaired test performance	1	0	0	0	0	0	0	1	0	0	1	1	0	1
	Self-reported language problems	0	1	0	1	1	1	0	1	0	0	1	0	1	1
	Impaired test performance	0	0	0	0	1	0	0	1	0	0	1	0	0	0
T2 Comprehension	Self-reported language problems	0	0	0	0	0	0	0	0	0	0	0	0	0	1
	Impaired test performance	0	0	0	0	0	0	0	1	1	0	1	0	0	0
	Self-reported language problems	0	1	0	1	1	0	0	1	0	0	1	0	1	0
	Impaired test performance	0	0	0	0	1	0	0	0	0	0	1	0	0	0
Reading	Self-reported language problems	0	0	0	0	1	0	0	0	0	0	1	0	0	0
	Impaired test performance	0	0	0	0	1	0	0	0	0	0	1	0	0	0
	Self-reported language problems	0	0	1	0	0	1	0	0	0	0	1	0	0	1
	Impaired test performance	0	0	0	1	1	0	0	1	1	1	1	0	0	0
Writing	Self-reported language problems	0	1	0	0	1	0	0	0	0	0	1	0	0	0
	Impaired test performance	0	0	0	1	1	0	0	1	1	1	1	0	0	0
	Self-reported language problems	0	1	1	0	0	1		0	0	1	0	1	1	1
	Impaired test performance	1	1	0	0	0	0	0	0	0	1	1	0	1	1
T3 Word retrieval	Self-reported language problems	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Impaired test performance	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Self-reported language problems	0	0	0	0	1	1	0	0	0	1	0	1	1	1
	Impaired test performance	0	0	0	0	1	0	0	0	1	1	1	0	1	1
T3 Comprehension	Self-reported language problems	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Impaired test performance	0	0	0	0	0	0	0	0	0	0	1	0	0	1
	Self-reported language problems	0	0	1	0	1	1	0	0	0	1	0	0	1	1
	Impaired test performance	1	1	0	0	1	0	0	0	1	1	0	0	0	0
Reading	Self-reported language problems	0	0	1	0	0	0	0	0	0	0	1	0	0	0
	Impaired test performance	0	0	1	0	0	0	0	0	0	0	1	0	0	0
	Self-reported language problems	0	0	1	0	0	0	0	0	0	1	0	1	0	0
	Impaired test performance	0	0	1	0	1	1	0	0	1	1	0	0	0	1
Writing	Self-reported language problems	0	0	1	0	1	1	0	0	1	1	0	0	0	1
	Impaired test performance	0	0	1	0	1	1	0	0	1	1	0	0	0	1
	Self-reported language problems	0	1	1	0	0	1		0	0	1	0	1	1	1
	Impaired test performance	1	1	0	0	0	0	0	0	0	1	1	0	1	1

Note. Impaired test performance is defined as $z \leq -1.5$. Empty cells indicate that the assessment did not take place. Test performance in Production domains (Phonology, Semantics and Morphosyntax) were combined, as well as test performance in Comprehension domains (Auditory input and Visual input), because there were no such distinctions in the self-reported information. Two categories of self-reported problems, Articulation and Keeping up with conversations, were not taken into account here because they were not formally tested.

Appendix C

Appendix to chapter 6

Appendix C1 – Language performance in meningioma patients

Language domain z-scores of meningioma patients at T1, T2, and T3

Language domain Separate tests	T1				T2				T3				Normative data ^c	
	N	Mdn	Min	Max	N	Mdn	Min	Max	N	Mdn	Min	Max	N	
Production-Word retrieval ^a	10	-0.58	-1.64	0.42	10	-0.71	-23.75	0.83	8	-0.58	-8.44	0.88	145	
Object naming														
Production-Phonology ^b	10	-0.12	-1.34	1.16	10	0.01	-3.34	1.11	8	-0.11	-1.61	1.31		
Letter fluency	10	-0.70	-2.80	1.20	9	-0.70	-2.10	1.10	8	-0.20	-2.50	1.50	570	
Repetition	10	0.54	-0.85	1.11	10	0.54	-3.34	1.11	8	0.72	-2.22	1.11	103	
Production-Semantics ^b	10	-0.48	-1.58	1.03	9	-0.16	-3.95	1.25	8	0.38	-1.34	1.43		
Category fluency	10	-0.58	-2.40	1.35	9	-0.30	-1.20	1.25	8	0.03	-2.35	1.65	464, 394 ^d	
Semantic odd-picture-out	9	0.19	-2.17	1.21	8	0.19	-6.75	1.21	8	0.89	-0.64	1.21	104	
Production-Morphosyntax ^b	10	-0.51	-1.29	-0.35	10	-0.42	-8.68	0.68	8	-0.16	-3.77	0.43		
Action naming	10	-0.58	-2.29	0.89	10	-0.25	-9.41	0.65	8	-0.08	-5.36	0.38	143	
Sentence completion	10	-0.61	-2.18	0.71	10	-0.25	-7.95	0.71	8	-0.25	-2.18	0.71	105	
Comprehension-Auditory input ^a														
Token Test	10	0.07	-0.69	0.83	10	0.20	-3.72	0.83	8	0.07	-1.19	0.83	100	
Comprehension-Visual input ^a														
Sentence judgement	7	-0.07	-1.18	0.74	6	0.33	-0.29	0.51	6	0.30	-0.53	0.51	104	
Reading ^a														
Reading	9	0.28	-2.50	0.28	9	0.61	-0.63	0.61	8	0.28	-2.50	0.28	51	
Writing ^a														
Writing	9	-0.79	-6.12	0.55	9	0.59	-13.88	0.59	8	-1.45	-6.12	0.55	51	

Note. T1 = before surgery; T2 = 2 months after surgery; T3 = 1 year after surgery; N = sample size; Mdn = median; Min = minimum value; Max = maximum value.

^a The language domain includes one test only, therefore, the domain scores are identical to the test scores.

^b Domain scores are composed of the scores on the separate tests presented below the domains.

^c For every test, the pre-existing normative data were based on a group of healthy, Dutch individuals, of which the sample size is provided.

^d The first number concerns the subtest Animals; the second number concerns the subtest Professions.

Appendix C2 – Self-reported language problems and test performance: individual data

Language altogether: Presence (1) or absence (0) of self-reported language problems, and language impairment according to tests for each patient at T1, T2, and T3

		pt1	pt2	pt3	pt4	pt5	pt6	pt7	pt8	pt9	pt10
T1	Total										
	Self-reported language problems	0	1	1	0	1	1	0	1	0	1
	Impaired test performance	0	0	1	1	0	0	1	0	0	1
T2	Total										
	Self-reported language problems	0	1	1	0	0	1	0	1	0	1
	Impaired test performance	0	0	1	1	0	0	1	0	1	0
T3	Total										
	Self-reported language problems		0	1	0		1	1	1	0	1
	Impaired test performance		1	1	0		0	1	0	1	1

Note. Impaired test performance is defined as $z \leq -1.5$ in one or more language domains. Empty cells indicate that the assessment did not take place.

Separate language domains: Presence (1) or absence (0) of self-reported language problems, and language impairment according to tests for each patient at T1, T2, and T3

			pt1	pt2	pt3	pt4	pt5	pt6	pt7	pt8	pt9	pt10	
T1	Word retrieval	Self-reported language problems	0	1	1	0	1	1	0	1	0	1	
		Impaired test performance	0	0	0	0	0	0	1	0	0	0	
	Production	Self-reported language problems	0	0	1	0	1	1	0	1	0	1	
		Impaired test performance	0	0	0	1	0	0	0	0	0	0	
	Comprehension	Self-reported language problems	0	0	0	0	0	0	0	0	0	0	
		Impaired test performance	0	0	0	0	0	0	0	0	0	0	
	Reading	Self-reported language problems	0	1	1	0	0	1	0	1	0	1	
		Impaired test performance		0	0	0	0	0	0	0	0	1	
	Writing	Self-reported language problems	0	0	1	0	0	0	0	0	0	1	
		Impaired test performance		0	1	0	0	0	0	0	0	1	
	T2	Word retrieval	Self-reported language problems	0	1	1	0	0	1	0	1	0	1
			Impaired test performance	0	0	1	0	0	0	1	0	1	0
Production		Self-reported language problems	0	1	1	0	0	0	0	0	0	1	
		Impaired test performance	0	0	1	1	0	0	0	0	0	0	
Comprehension		Self-reported language problems	0	0	0	0	0	0	0	0	0	0	
		Impaired test performance	0	0	1	0	0	0	0	0	0	0	
Reading		Self-reported language problems	0	0	1	0	0	1	0	1	0	1	
		Impaired test performance		0	0	0	0	0	0	0	0	0	
Writing		Self-reported language problems	0	0	1	0	0	1	0	0	0	1	
		Impaired test performance		0	1	0	0	0	0	0	0	0	
T3		Word retrieval	Self-reported language problems		0	1	0		1	1	1	0	1
			Impaired test performance		0	1	0		0	0	0	1	0
	Production	Self-reported language problems		0	1	0		1	1	1	0	1	
		Impaired test performance		0	1	0		0	0	0	0	0	
	Comprehension	Self-reported language problems		0	0	0		0	0	0	0	0	
		Impaired test performance		0	0	0		0	0	0	0	0	
	Reading	Self-reported language problems		0	1	0		1	0	1	0	1	
		Impaired test performance		0	0	0		0	0	0	0	1	
	Writing	Self-reported language problems		0	1	0		0	1	0	0	1	
		Impaired test performance		1	1	0		0	1	0	0	1	

Note. Impaired test performance is defined as $z \leq -1.5$. Empty cells indicate that the assessment did not take place. Test performance in Production domains (Phonology, Semantics and Morphosyntax) were combined, as well as test performance in Comprehension domains (Auditory input and Visual input), because there were no such distinctions in the self-reported information. Two categories of self-reported problems, Articulation and Keeping up with conversations, were not taken into account here because they were not formally tested.

Appendix D

Appendix to chapter 7

Appendix D1 – Slow-wave activity in glioma patients

T1: before surgery

Whole-brain and tumour-specific measures of slow-wave activity in glioma patients compared to the whole-brain measure of the control group

	Glioma patients (N = 15)			Control group (N = 15)					
	Whole brain			Whole brain			Comparisons ^a		
	<i>Mdn</i>	<i>Min</i>	<i>Max</i>	<i>Mdn</i>	<i>Min</i>	<i>Max</i>	<i>U</i>	<i>p</i>	<i>r</i>
Delta	0.370	0.150	0.534	0.324	0.212	0.590	103.0	0.357	0.07
Theta	0.132	0.054	0.295	0.110	0.084	0.183	68.0	0.034	0.34
	Affected hemisphere			Whole brain			Comparisons ^b		
	<i>Mdn</i>	<i>Min</i>	<i>Max</i>	<i>Mdn</i>	<i>Min</i>	<i>Max</i>	<i>Z</i>	<i>p</i>	<i>r</i>
Delta	0.408	0.157	0.548	0.324	0.212	0.590	1.420	0.078	0.37
Theta	0.135	0.052	0.285	0.110	0.084	0.183	2.784	0.003	0.72
	Affected area			Whole brain			Comparisons ^b		
	<i>Mdn</i>	<i>Min</i>	<i>Max</i>	<i>Mdn</i>	<i>Min</i>	<i>Max</i>	<i>Z</i>	<i>p</i>	<i>r</i>
Delta	0.450	0.215	0.615	0.324	0.212	0.590	2.158	0.016	0.56
Theta	0.149	0.055	0.322	0.110	0.084	0.183	2.897	0.002	0.75

Note. *Mdn* = median; *Min* = minimum value; *Max* = maximum value; *U* = test statistic of the Mann-Whitney U tests; *Z* = standardised test statistic of the one-sample Wilcoxon signed rank tests; *p* = p-value (one-sided); *r* = effect size ($r = Z/\sqrt{N}$). Significant effects ($p < 0.05$) are presented in bold font.

^a Comparisons with Mann-Whitney U tests.

^b Slow-wave activity over the affected hemisphere and the affected area in glioma patients was compared to the median of the whole-brain measure of the control group by one-sample Wilcoxon signed rank tests because the control group does not have affected hemispheres or areas.

T3: 1 year after surgery

Whole-brain and tumour-specific measures of slow-wave activity at T3 in glioma patients compared to the whole-brain measure of the control group

	Glioma patients (N = 11)			Control group (N = 15)					
	Whole brain			Whole brain			Comparisons ^a		
	<i>Mdn</i>	<i>Min</i>	<i>Max</i>	<i>Mdn</i>	<i>Min</i>	<i>Max</i>	<i>U</i>	<i>p</i>	<i>r</i>
Delta	0.315	0.219	0.482	0.324	0.212	0.590	77.0	0.400	0.06
Theta	0.139	0.069	0.329	0.110	0.084	0.183	47.0	0.035	0.36
	Affected hemisphere			Whole brain			Comparisons ^b		
	<i>Mdn</i>	<i>Min</i>	<i>Max</i>	<i>Mdn</i>	<i>Min</i>	<i>Max</i>	<i>Z</i>	<i>p</i>	<i>r</i>
Delta	0.336	0.216	0.466	0.324	0.212	0.590	0.979	0.164	0.30
Theta	0.149	0.068	0.324	0.110	0.084	0.183	2.223	0.013	0.67
	Affected area			Whole brain			Comparisons ^b		
	<i>Mdn</i>	<i>Min</i>	<i>Max</i>	<i>Mdn</i>	<i>Min</i>	<i>Max</i>	<i>Z</i>	<i>p</i>	<i>r</i>
Delta	0.370	0.218	0.638	0.324	0.212	0.590	1.778	0.038	0.54
Theta	0.160	0.089	0.367	0.110	0.084	0.183	2.667	0.004	0.80

Note. *Mdn* = median; *Min* = minimum value; *Max* = maximum value; *U* = test statistic of the Mann-Whitney U tests; *Z* = standardised test statistic of the one-sample Wilcoxon signed rank tests; *p* = p-value (one-sided); *r* = effect size ($r = Z/\sqrt{N}$). Significant effects ($p < 0.05$) are presented in bold font.

^a Comparisons with Mann-Whitney U tests.

^b Slow-wave activity over the affected hemisphere and the affected area in glioma patients was compared to the median of the whole-brain measure of the control group by one-sample Wilcoxon signed rank tests because the control group does not have affected hemispheres or areas.

Appendix D2 – Slow-wave activity in meningioma patients

T1: before surgery

Whole-brain and tumour-specific measures of slow-wave activity in meningioma patients compared to the whole-brain measure of the control group

	Meningioma patients (N = 10)			Control group (N = 9)					
	Whole brain			Whole brain			Comparisons ^a		
	<i>Mdn</i>	<i>Min</i>	<i>Max</i>	<i>Mdn</i>	<i>Min</i>	<i>Max</i>	<i>U</i>	<i>p</i>	<i>r</i>
Delta	0.341	0.101	0.535	0.324	0.212	0.398	42.0	0.421	0.06
Theta	0.118	0.067	0.186	0.110	0.084	0.149	36.0	0.249	0.17
	Affected hemisphere			Whole brain			Comparisons ^b		
	<i>Mdn</i>	<i>Min</i>	<i>Max</i>	<i>Mdn</i>	<i>Min</i>	<i>Max</i>	<i>Z</i>	<i>p</i>	<i>r</i>
Delta	0.325	0.103	0.537	0.324	0.212	0.398	-0.153	0.439	0.05
Theta	0.121	0.069	0.188	0.110	0.084	0.149	0.866	0.193	0.27
	Affected area			Whole brain			Comparisons ^b		
	<i>Mdn</i>	<i>Min</i>	<i>Max</i>	<i>Mdn</i>	<i>Min</i>	<i>Max</i>	<i>Z</i>	<i>p</i>	<i>r</i>
Delta	0.322	0.087	0.581	0.324	0.212	0.398	-0.255	0.400	0.08
Theta	0.128	0.079	0.231	0.110	0.084	0.149	1.244	0.107	0.39

Note. *Mdn* = median; *Min* = minimum value; *Max* = maximum value; *U* = test statistic of the Mann-Whitney U tests; *Z* = standardised test statistic of the one-sample Wilcoxon signed rank tests; *p* = p-value (one-sided); *r* = effect size ($r=Z/\sqrt{N}$).

^a Comparisons with Mann-Whitney U tests.

^b Slow-wave activity over the affected hemisphere and the affected area in glioma patients was compared to the median of the whole-brain measure of the control group by one-sample Wilcoxon signed rank tests because the control group does not have affected hemispheres or areas.

T3: 1 year after surgery

Not applicable; meningioma patients did not undergo a postoperative EEG registration.

Appendix D3 – Slow-wave activity at T1 and language performance at T1 in glioma patients

Impaired vs. unimpaired language performance

Slow-wave activity at T1: patients with language impairment compared to patients without language impairment at T1

	Patients with language impairment (N = 9)			Patients without language impairment (N = 6)			Comparisons		
	<i>Mdn</i>	<i>Min</i>	<i>Max</i>	<i>Mdn</i>	<i>Min</i>	<i>Max</i>	<i>U</i>	<i>p</i>	<i>r</i>
Delta-Affected area ^a	0.370	0.219	0.615	0.477	0.215	0.606	21.0	0.480	0.18
Theta-Whole brain	0.178	0.095	0.295	0.122	0.054	0.132	8.5	0.029	0.56
Theta-Affected hemisphere	0.185	0.106	0.285	0.125	0.052	0.135	10.0	0.045	0.52
Theta-Affected area	0.214	0.099	0.322	0.131	0.055	0.149	10.0	0.045	0.52

Note. *Mdn* = median; *Min* = minimum value; *Max* = maximum value; *U* = test statistic of the Mann-Whitney U tests; *p* = p-value (two-sided); *r* = effect size ($r=Z/\sqrt{N}$). Significant effects ($p < 0.05$) are presented in bold font.

^aIn the delta band, activity over the whole brain and the affected hemisphere were not taken into account because glioma patients at T1 did not have more delta activity over those regions than the control group (see Appendix D1).

Language domains

Correlation analyses between slow-wave activity at T1 and language domain scores at T1

Language scores at T1	Delta ^a			Theta			Theta			Theta		
	Affected area			Whole brain			Affected hemisphere			Affected area		
	N	T	p	N	T	p	N	T	p	N	T	p
Production-Word Retrieval	15	0.10	0.616	15	-0.57	0.004	15	-0.57	0.004	15	-0.51	0.010
Production-Phonology	15	0.14	0.458	15	-0.14	0.457	15	-0.12	0.552	15	-0.10	0.620
Production-Semantics	15	0.14	0.458	15	-0.05	0.804	15	-0.13	0.488	15	-0.10	0.620
Production-Morphosyntax	15	0.14	0.487	15	-0.47	0.017	15	-0.53	0.006	15	-0.44	0.025
Comprehension-Auditory Input	15	0.22	0.269	15	0.14	0.481	15	0.09	0.651	15	0.15	0.451
Comprehension-Visual Input	13	0.12	0.576	13	0.07	0.755	13	0.03	0.901	13	0.11	0.619
Reading	14	-0.09	0.710	14	0.18	0.456	14	0.26	0.264	14	0.26	0.264
Writing	13	0.05	0.845	13	-0.27	0.239	13	-0.33	0.150	13	-0.21	0.360

Note. N = group size; T = Kendall's tau-b correlation coefficient; p = p-value (two-sided). Significant correlations after Bonferroni correction ($p < 0.0125$) are presented in bold font. Correlations that lost significance after Bonferroni correction ($p < 0.05$) are presented in italics.

^a In the delta band, activity over the whole brain and the affected hemisphere were not taken into account because glioma patients at T1 did not have more delta activity over those regions than the control group (see Appendix D1).

N.B. The previous analyses were not performed for meningioma patients because they did not have more slow-wave activity than healthy individuals.

Appendix D4 – Slow-wave activity at T1 and language outcome at T3 in glioma patients

Impaired vs. unimpaired language performance

Slow-wave activity at T1: patients with language impairment compared to patients without language impairment at T3

	Patients with language impairment (N = 10)			Patients without language impairment (N = 3)			Comparisons		
	Mdn	Min	Max	Mdn	Min	Max	U	p	r
Delta-Affected area ^a	0.413	0.219	0.615	0.526	0.215	0.606	12.0	0.612	0.14
Theta-Whole brain	0.160	0.054	0.295	0.123	0.114	0.132	7.5	0.204	0.35
Theta-Affected hemisphere	0.173	0.052	0.285	0.126	0.124	0.132	8.5	0.271	0.31
Theta-Affected area	0.200	0.055	0.322	0.131	0.131	0.137	9.0	0.310	0.28

Note. Mdn = median; Min = minimum value; Max = maximum value; U = test statistic of the Mann-Whitney U tests; p = p-value (two-sided); r = effect size ($r = Z/\sqrt{N}$).

^aIn the delta band, activity over the whole brain and the affected hemisphere were not taken into account because glioma patients at T1 did not have more delta activity over those regions than the control group (see Appendix D1).

Language domains

Correlation analyses between slow-wave activity at T1 and language outcome at T3

Language scores at T3	Delta			Theta Whole brain			Theta Affected hemisphere			Theta Affected area		
	Affected area											
	N	T	p	N	T	p	N	T	p	N	T	p
Production-Word Retrieval	13	0.33	0.123	13	-0.51	0.019	13	-0.53	0.013	13	-0.48	0.026
Production-Phonology	13	0.26	0.222	13	-0.16	0.462	13	-0.09	0.669	13	-0.07	0.760
Production-Semantics	13	0.18	0.393	13	-0.03	0.903	13	-0.01	0.951	13	0.01	0.951
Production-Morphosyntax	13	-0.04	0.854	13	-0.01	0.951	13	0.00	1.000	13	0.05	0.806
Comprehension-Auditory Input	13	0.09	0.664	13	-0.15	0.494	13	-0.16	0.456	13	-0.08	0.710
Comprehension-Visual Input	12	0.14	0.532	12	0.18	0.442	12	0.13	0.577	12	0.16	0.486
Reading	13	0.18	0.464	13	0.04	0.883	13	0.09	0.714	13	0.04	0.883
Writing	13	0.13	0.567	13	0.07	0.750	13	0.03	0.899	13	0.12	0.611

Note. N = group size; T = Kendall's tau-b correlation coefficient; p = p-value (two-sided). Correlations with *p* < 0.05 are presented in italics. No correlations remained significant after Bonferroni correction (*p* < 0.0125).

^a In the delta band, activity over the whole brain and the affected hemisphere were not taken into account because glioma patients at T1 did not have more delta activity over those regions than the control group (see Appendix D1).

N.B. The previous analyses were not performed for meningioma patients because they did not have more slow-wave activity than healthy individuals.

Appendix E

Appendix to chapter 8

Appendix E1 – FC network characteristics: glioma patients vs. healthy individuals

T1: before surgery

Theta- and alpha-band FC network characteristics in preoperative glioma patients compared to healthy individuals

	Glioma patients at T1 (N = 15)			Healthy individuals (N = 15)			Comparisons	
	<i>Mdn</i>	<i>Min</i>	<i>Max</i>	<i>Mdn</i>	<i>Min</i>	<i>Max</i>	<i>U</i>	<i>p</i>
Theta band								
W-PLI	0.123	0.107	0.207	0.130	0.100	0.153	112.0	1.000
W-rC	0.998	0.978	1.106	1.023	0.974	1.073	99.0	0.595
W-rL	0.901	0.884	0.955	0.909	0.887	0.950	89.0	0.345
W-SWI	1.106	1.089	1.173	1.114	1.090	1.149	103.0	0.713
MST-Degr	0.347	0.280	0.427	0.333	0.293	0.427	100.0	0.624
MST-Ecc	0.375	0.330	0.439	0.373	0.312	0.433	111.0	0.967
MST-BC	0.728	0.657	0.796	0.726	0.694	0.787	109.0	0.902
MST-Leaf	0.600	0.453	0.627	0.573	0.493	0.640	95.0	0.486
MST-Diam	0.467	0.400	0.547	0.467	0.387	0.533	109.0	0.902
MST-TH	0.398	0.311	0.439	0.398	0.330	0.452	90.0	0.367
Alpha band								
W-PLI	0.142	0.103	0.245	0.185	0.104	0.495	74.0	0.116
W-rC	1.012	0.973	1.083	1.015	0.970	1.101	105.0	0.775
W-rL	0.907	0.887	0.957	0.917	0.888	0.936	97.0	0.539
W-SWI	1.119	1.077	1.188	1.119	1.065	1.181	106.0	0.806
MST-Degr	0.347	0.293	0.480	0.360	0.293	0.493	96.5	0.512
MST-Ecc	0.374	0.312	0.420	0.381	0.299	0.427	102.0	0.683
MST-BC	0.714	0.673	0.819	0.731	0.653	0.813	97.0	0.539
MST-Leaf	0.613	0.520	0.680	0.587	0.507	0.720	111.5	0.967
MST-Diam	0.467	0.387	0.520	0.480	0.373	0.547	104.0	0.744
MST-TH	0.403	0.378	0.475	0.398	0.352	0.486	104.5	0.744

Note. *Mdn* = median; *Min* = minimum value; *Max* = maximum value; *U* = test statistic of the Mann-Whitney U tests; *p* = p-value (two-sided). W = weighted: these network measures quantify weighted FC networks; MST = Minimum Spanning Tree: these network measures quantify Minimum Spanning Tree FC networks. FC = functional connectivity; PLI = Phase lag index, mean of all 16 remaining electrodes; rC = relative average clustering coefficient; rL = relative average path length; SWI = small-world index; MST-Degr = MST-maximum degree; MST-Ecc = MST-eccentricity, mean of all nodes; MST-BC = MST-maximum betweenness centrality; MST-Leaf = MST-leaf fraction; MST-Diam = MST-diameter; MST-TH = MST-tree hierarchy.

T3: 1 year after surgery

Theta- and alpha-band FC network characteristics in 1 year postoperative glioma patients compared to healthy individuals

	Glioma patients at T3 (N = 11)			Healthy individuals (N = 15)			Comparisons	
	<i>Mdn</i>	<i>Min</i>	<i>Max</i>	<i>Mdn</i>	<i>Min</i>	<i>Max</i>	<i>U</i>	<i>p</i>
Theta band								
W-PLI	0.133	0.121	0.209	0.130	0.100	0.153	65.0	0.384
W-rC	1.002	0.979	1.058	1.023	0.974	1.073	63.0	0.330
W-rL	0.908	0.881	0.965	0.909	0.887	0.950	80.0	0.919
W-SWI	1.102	1.083	1.152	1.114	1.090	1.149	42.0	0.036
MST-Degr	0.320	0.267	0.360	0.333	0.293	0.427	58.5	0.217
MST-Ecc	0.397	0.347	0.446	0.373	0.312	0.433	59.0	0.237
MST-BC	0.707	0.669	0.773	0.726	0.694	0.787	47.5	0.069
MST-Leaf	0.533	0.493	0.627	0.573	0.493	0.640	56.0	0.180
MST-Diam	0.493	0.427	0.560	0.467	0.387	0.533	59.5	0.237
MST-TH	0.375	0.329	0.450	0.398	0.330	0.452	74.0	0.683
Alpha band								
W-PLI	0.139	0.095	0.245	0.185	0.104	0.495	50.0	0.097
W-rC	1.029	0.964	1.080	1.015	0.970	1.101	77.0	0.799
W-rL	0.916	0.891	0.949	0.917	0.888	0.936	77.0	0.799
W-SWI	1.126	1.049	1.181	1.119	1.065	1.181	77.0	0.799
MST-Degr	0.347	0.280	0.413	0.360	0.293	0.493	62.0	0.305
MST-Ecc	0.386	0.333	0.422	0.381	0.299	0.427	69.0	0.507
MST-BC	0.716	0.646	0.771	0.731	0.653	0.813	73.0	0.646
MST-Leaf	0.587	0.520	0.653	0.587	0.507	0.720	79.0	0.878
MST-Diam	0.480	0.413	0.520	0.480	0.373	0.547	58.0	0.217
MST-TH	0.403	0.376	0.438	0.398	0.352	0.486	72.5	0.610

Note. *Mdn* = median; *Min* = minimum value; *Max* = maximum value; *U* = test statistic of the Mann-Whitney *U* tests; *p* = *p*-value (two-sided). Comparisons with *p* < 0.05 are presented in italics. There were no significant effects after Bonferroni correction (*p* < 0.005). W = weighted: these network measures quantify weighted FC networks; MST = Minimum Spanning Tree: these network measures quantify Minimum Spanning Tree FC networks. FC = functional connectivity; PLI = Phase lag index, mean of all 16 remaining electrodes; rC = relative average clustering coefficient; rL = relative average path length; SWI = small-world index; MST-Degr = MST-maximum degree; MST-Ecc = MST-eccentricity, mean of all nodes; MST-BC = MST-maximum betweenness centrality; MST-Leaf = MST-leaf fraction; MST-Diam = MST-diameter; MST-TH = MST-tree hierarchy.

Appendix E2 – FC network characteristics: meningioma patients vs. healthy individuals

T1: before surgery

Theta- and alpha-band FC network characteristics in preoperative meningioma patients compared to healthy individuals

	Meningioma patients at T1 (N = 10)			Healthy individuals (N = 9)			Comparisons	
	<i>Mdn</i>	<i>Min</i>	<i>Max</i>	<i>Mdn</i>	<i>Min</i>	<i>Max</i>	<i>U</i>	<i>p</i>
Theta band								
W-PLI	0.134	0.113	0.449	0.129	0.100	0.153	37.0	0.549
W-rC	1.004	0.952	1.061	1.019	0.974	1.029	40.0	0.720
W-rL	0.904	0.888	1.012	0.905	0.893	0.922	44.0	0.968
W-SWI	1.097	1.051	1.156	1.112	1.091	1.136	30.0	0.243
MST-Degr	0.333	0.267	0.547	0.334	0.320	0.400	42.0	0.842
MST-Ecc	0.378	0.296	0.429	0.384	0.322	0.422	39.5	0.661
MST-BC	0.722	0.707	0.874	0.729	0.694	0.762	44.0	0.968
MST-Leaf	0.540	0.453	0.653	0.560	0.493	0.640	41.5	0.780
MST-Diam	0.474	0.360	0.547	0.480	0.400	0.533	40.5	0.720
MST-TH	0.375	0.321	0.435	0.402	0.330	0.427	39.0	0.661
Alpha band								
W-PLI	0.169	0.107	0.274	0.251	0.122	0.495	27.0	0.156
W-rC	1.015	0.976	1.068	1.001	0.970	1.057	37.0	0.549
W-rL	0.909	0.889	0.944	0.917	0.888	0.927	45.0	1.000
W-SWI	1.121	1.045	1.160	1.102	1.065	1.160	37.0	0.549
MST-Degr	0.347	0.280	0.493	0.373	0.307	0.440	38.0	0.604
MST-Ecc	0.361	0.311	0.459	0.381	0.331	0.427	42.0	0.842
MST-BC	0.738	0.670	0.798	0.735	0.684	0.808	42.5	0.842
MST-Leaf	0.587	0.480	0.693	0.587	0.507	0.693	44.0	0.968
MST-Diam	0.447	0.373	0.587	0.480	0.400	0.547	45.0	1.000
MST-TH	0.401	0.350	0.464	0.393	0.361	0.486	44.0	0.968

Note. *Mdn* = median; *Min* = minimum value; *Max* = maximum value; *U* = test statistic of the Mann-Whitney U tests; *p* = p-value (two-sided). W = weighted: these network measures quantify weighted FC networks; MST = Minimum Spanning Tree: these network measures quantify Minimum Spanning Tree FC networks. FC = functional connectivity; PLI = Phase lag index, mean of all 16 remaining electrodes; rC = relative average clustering coefficient; rL = relative average path length; SWI = small-world index; MST-Degr = MST-maximum degree; MST-Ecc = MST-eccentricity, mean of all nodes; MST-BC = MST-maximum betweenness centrality; MST-Leaf = MST-leaf fraction; MST-Diam = MST-diameter; MST-TH = MST-tree hierarchy.

Appendix E3 – FC network characteristics at T1 and language at T1 in glioma patients

Correlation analyses between FC network measures at T1 and language domain z-scores at T1 in glioma patients

		W-PLI	W-rC	W-rL	W-SWI	MST-Degr	MST-Ecc	MST-BC	MST-Leaf	MST-Diam	MST-TH
Theta band											
P-Word Retrieval (N = 15)	<i>T</i>	-	-	-	-	-	0.43	-	-0.42	0.45	-0.50
	<i>p</i>						.031		.038	.026	.012
P-Phonology (N = 15)	<i>T</i>	-	-	-	-	-	-	-	-	-	-
	<i>p</i>										
P-Semantics (N = 15)	<i>T</i>	-	-	-	-	-	0.40	-	-	0.50	-
	<i>p</i>						.037			.011	
P-Morphosyntax (N = 15)	<i>T</i>	-0.39	-	-	-	-	0.46	-	-	0.55	-
	<i>p</i>	.047					.019			.005	
C-Auditory Input (N = 15)	<i>T</i>	-	-	-0.42	-	-	-	-	-	-	-
	<i>p</i>			.035							
C-Visual Input (N = 13)	<i>T</i>	-	-	-	-0.44	-0.73	-	-0.44	-	-	-
	<i>p</i>				.040	.001		.040			
Reading (N = 14)	<i>T</i>	-	-	-	-	-	-	-	-	-	-
	<i>p</i>										
Writing (N = 13)	<i>T</i>	-0.56	-	-	-	-	-	-	-	0.47	-
	<i>p</i>	.016								.042	
Alpha band											
P-Word Retrieval (N = 15)	<i>T</i>	-	-	-	-	-	-	-	-	-	-
	<i>p</i>										
P-Phonology (N = 15)	<i>T</i>	-	-	-	-	-	-	-	-	-	-
	<i>p</i>										
P-Semantics (N = 15)	<i>T</i>	-	-	-	-	-	-	-	-	-	-
	<i>p</i>										
P-Morphosyntax (N = 15)	<i>T</i>	-	-	-	0.39	-	-	-	-	-	-
	<i>p</i>				.047						
C-Auditory Input (N = 15)	<i>T</i>	-	-	-	-	-	-	-	-	-	-
	<i>p</i>										
C-Visual Input (N = 13)	<i>T</i>	-	-0.50	-	-0.60	-	0.44	-	-	0.44	-0.46
	<i>p</i>		.022		.005		.040			.046	.034
Reading (N = 14)	<i>T</i>	-	-	-	-	-	-	-	-	-	-
	<i>p</i>										
Writing (N = 13)	<i>T</i>	-	-	-	-	-	-	-	-	-	-
	<i>p</i>										

Note. Only the tests with $p < 0.05$ are presented. N = group size; T = Kendall's tau-b correlation coefficient; p = p-value (two-sided). Significant correlations after Bonferroni correction ($p < 0.005$) are presented in bold font. P = production; C = comprehension; W = weighted; these network measures quantify weighted FC networks; MST = Minimum Spanning Tree: these network measures quantify Minimum Spanning Tree FC networks. FC = functional connectivity; PLI = Phase lag index, mean of all 16 remaining electrodes; rC = relative average clustering coefficient; rL = relative average path length; SWI = small-world index; MST-Degr = MST-maximum degree; MST-Ecc = MST-eccentricity, mean of all nodes; MST-BC = MST-maximum betweenness centrality; MST-Leaf = MST-leaf fraction; MST-Diam = MST-diameter; MST-TH = MST-tree hierarchy.

Appendix E4 – FC network characteristics at T1 and language at T1 in meningioma patients

Correlation analyses between FC network measures at T1 and language domain z-scores at T1 in meningioma patients

		W-PLI	W-rC	W-rL	W-SWI	MST-Degr	MST-Ecc	MST-BC	MST-Leaf	MST-Diam	MST-TH
Theta band											
P-Word Retrieval (N = 10)	<i>T</i>	-	-	-	-	-	-	-	-	-	-
	<i>p</i>										
P-Phonology (N = 10)	<i>T</i>	-	-	-	-	-	-	-	-	-	-
	<i>p</i>										
P-Semantics (N = 10)	<i>T</i>	-	-	-	-	-	-	-	-	-	-
	<i>p</i>										
P-Morphosyntax (N = 10)	<i>T</i>	-	-	-	-	-	-	-	-	-	-
	<i>p</i>										
C-Auditory Input (N = 10)	<i>T</i>	-	-	-	-	-	-	-	-	-	-
	<i>p</i>										
C-Visual Input (N = 7)	<i>T</i>	-	-	-	-0.68	-	-	-	-	-	-
	<i>p</i>				.033						
Reading (N = 9)	<i>T</i>	-	-	-	-	-	-	-	-	-	-
	<i>p</i>										
Writing (N = 9)	<i>T</i>	-	-	-	-	-	-	-	-	-	-
	<i>p</i>										
Alpha band											
P-Word Retrieval (N = 10)	<i>T</i>	-	-	-	-	-	-	-	-	-	-
	<i>p</i>										
P-Phonology (N = 10)	<i>T</i>	-	-	-	-	-	-	-	-	-	-
	<i>p</i>										
P-Semantics (N = 10)	<i>T</i>	-	-	-	-	-	-	-	-	-	-
	<i>p</i>										
P-Morphosyntax (N = 10)	<i>T</i>	-	-	-	-	-	-	-	-	-	-
	<i>p</i>										
C-Auditory Input (N = 10)	<i>T</i>	-	-	-	-	-	-	-	-	-	-
	<i>p</i>										
C-Visual Input (N = 7)	<i>T</i>	-	-	-	-	-	-	-	-	-	-
	<i>p</i>										
Reading (N = 9)	<i>T</i>	-	-	-	-	-	-	-	-	-	-
	<i>p</i>										
Writing (N = 9)	<i>T</i>	-	-	-	-	-	-	-	-	-	-
	<i>p</i>										

Note. Only the tests with $p < 0.05$ are presented. N = group size; T = Kendall's tau-b correlation coefficient; p = p-value (two-sided). There were no significant correlations after Bonferroni correction ($p < 0.005$). P = production; C = comprehension; W = weighted: these network measures quantify weighted FC networks; MST = Minimum Spanning Tree: these network measures quantify Minimum Spanning Tree FC networks. FC = functional connectivity; PLI = Phase lag index, mean of all 16 remaining electrodes; rC = relative average clustering coefficient; rL = relative average path length; SWI = small-world index; MST-Degr = MST-maximum degree; MST-Ecc = MST-eccentricity, mean of all nodes; MST-BC = MST-maximum betweenness centrality; MST-Leaf = MST-leaf fraction; MST-Diam = MST-diameter; MST-TH = MST-tree hierarchy.

Appendix E5 – Glioma patients with vs. without language impairment

Theta- and alpha-band FC network characteristics of glioma patients with vs. without language impairment before surgery

	Glioma patients with language impairment at T1 (N = 9)			Glioma patients without language impairment at T1 (N = 6)			Comparisons	
	<i>Mdn</i>	<i>Min</i>	<i>Max</i>	<i>Mdn</i>	<i>Min</i>	<i>Max</i>	<i>U</i>	<i>p</i>
Theta band								
W-PLI	0.135	0.114	0.207	0.121	0.107	0.146	15.0	0.181
W-rC	1.010	0.978	1.106	0.996	0.987	1.037	22.0	0.607
W-rL	0.901	0.885	0.955	0.902	0.884	0.908	23.0	0.689
W-SWI	1.121	1.089	1.163	1.104	1.097	1.173	27.0	1.000
MST-Degr	0.373	0.293	0.427	0.347	0.280	0.373	17.0	0.272
MST-Ecc	0.369	0.330	0.388	0.396	0.343	0.439	9.5	0.036
MST-BC	0.728	0.657	0.796	0.726	0.708	0.754	27.0	1.000
MST-Leaf	0.613	0.520	0.627	0.560	0.453	0.614	11.5	0.066
MST-Diam	0.453	0.400	0.480	0.494	0.427	0.547	6.0	0.012
MST-TH	0.422	0.379	0.439	0.385	0.311	0.417	9.0	0.036
Alpha band								
W-PLI	0.166	0.108	0.245	0.139	0.103	0.197	19.0	0.388
W-rC	1.012	0.973	1.083	1.030	1.008	1.054	19.0	0.388
W-rL	0.911	0.887	0.929	0.905	0.888	0.957	18.0	0.328
W-SWI	1.106	1.077	1.170	1.122	1.093	1.188	17.0	0.272
MST-Degr	0.333	0.294	0.480	0.360	0.293	0.427	25.5	0.864
MST-Ecc	0.374	0.312	0.410	0.383	0.335	0.420	22.0	0.607
MST-BC	0.735	0.676	0.819	0.703	0.673	0.787	17.0	0.272
MST-Leaf	0.613	0.520	0.667	0.573	0.520	0.680	20.5	0.456
MST-Diam	0.467	0.387	0.520	0.473	0.413	0.520	24.0	0.776
MST-TH	0.407	0.378	0.429	0.388	0.381	0.475	25.0	0.864

Note. *Mdn* = median; *Min* = minimum value; *Max* = maximum value; *U* = test statistic of the Mann-Whitney *U* tests; *p* = *p*-value (two-sided). Comparisons with *p* < 0.05 are presented in italics. There were no significant effects after Bonferroni correction (*p* < 0.005). W = weighted: these network measures quantify weighted FC networks; MST = Minimum Spanning Tree: these network measures quantify Minimum Spanning Tree FC networks. FC = functional connectivity; PLI = Phase lag index, mean of all 16 remaining electrodes; rC = relative average clustering coefficient; rL = relative average path length; SWI = small-world index; MST-Degr = MST-maximum degree; MST-Ecc = MST-eccentricity, mean of all nodes; MST-BC = MST-maximum betweenness centrality; MST-Leaf = MST-leaf fraction; MST-Diam = MST-diameter; MST-TH = MST-tree hierarchy.

Appendix E6 – Meningioma patients with vs. without language impairment

Theta- and alpha-band FC network characteristics of meningioma patients with vs. without language impairment before surgery

	Meningioma patients with language impairment at T1 (N = 4)			Meningioma patients without language impairment at T1 (N = 6)			Comparisons	
	<i>Mdn</i>	<i>Min</i>	<i>Max</i>	<i>Mdn</i>	<i>Min</i>	<i>Max</i>	<i>U</i>	<i>p</i>
Theta band								
W-PLI	0.134	0.124	0.138	0.131	0.113	0.449	12.0	1.000
W-rC	0.991	0.966	1.038	1.013	0.952	1.061	10.0	0.762
W-rL	0.896	0.888	0.898	0.915	0.896	1.012	2.0	0.038
W-SWI	1.110	1.079	1.156	1.092	1.051	1.122	7.0	0.352
MST-Degr	0.347	0.320	0.386	0.327	0.267	0.547	8.0	0.476
MST-Ecc	0.375	0.339	0.405	0.388	0.296	0.429	10.0	0.762
MST-BC	0.729	0.707	0.737	0.717	0.707	0.874	11.5	0.914
MST-Leaf	0.567	0.520	0.640	0.527	0.453	0.653	8.0	0.476
MST-Diam	0.467	0.413	0.507	0.487	0.360	0.547	9.0	0.610
MST-TH	0.393	0.367	0.435	0.361	0.321	0.409	6.0	0.257
Alpha band								
W-PLI	0.143	0.110	0.211	0.212	0.107	0.274	8.0	0.476
W-rC	1.016	0.976	1.034	1.012	0.980	1.068	11.0	0.914
W-rL	0.902	0.894	0.911	0.916	0.889	0.944	7.0	0.352
W-SWI	1.125	1.093	1.140	1.121	1.045	1.160	11.0	0.914
MST-Degr	0.373	0.307	0.493	0.347	0.280	0.427	7.5	0.352
MST-Ecc	0.373	0.311	0.418	0.361	0.325	0.459	12.0	1.000
MST-BC	0.768	0.670	0.798	0.732	0.686	0.751	7.5	0.352
MST-Leaf	0.587	0.560	0.693	0.580	0.480	0.667	8.5	0.476
MST-Diam	0.467	0.373	0.520	0.447	0.400	0.587	12.0	1.000
MST-TH	0.405	0.378	0.437	0.392	0.350	0.464	10.0	0.762

Note. *Mdn* = median; *Min* = minimum value; *Max* = maximum value; *U* = test statistic of the Mann-Whitney U tests; *p* = p-value (two-sided). Comparisons with *p* < 0.05 are presented in italics. There were no significant effects after Bonferroni correction (*p* < 0.005). W = weighted: these network measures quantify weighted FC networks; MST = Minimum Spanning Tree: these network measures quantify Minimum Spanning Tree FC networks. FC = functional connectivity; PLI = Phase lag index, mean of all 16 remaining electrodes; rC = relative average clustering coefficient; rL = relative average path length; SWI = small-world index; MST-Degr = MST-maximum degree; MST-Ecc = MST-eccentricity, mean of all nodes; MST-BC = MST-maximum betweenness centrality; MST-Leaf = MST-leaf fraction; MST-Diam = MST-diameter; MST-TH = MST-tree hierarchy.

Appendix E7 – FC network characteristics at T1 and language outcome at T3 in glioma patients

Correlation analyses between FC network measures at T1 and language outcome (domain z-scores) at T3 in glioma patients

		W-PLI	W-rC	W-rL	W-SWI	MST-Degr	MST-Ecc	MST-BC	MST-Leaf	MST-Diam	MST-TH
Theta band											
P-Word Retrieval (N = 13)	<i>T</i>	-0.57	-0.44	-	-	-0.49	0.69	-	-0.57	0.73	-0.49
	<i>p</i>	.008	.042			.022	.001		.009	.001	.023
P-Phonology (N = 13)	<i>T</i>	-	-	-	-	-	-	-	-	-	-
	<i>p</i>										
P-Semantics (N = 13)	<i>T</i>	-	-	-	-	-	-	-	-	-	-
	<i>p</i>										
P-Morphosyntax (N = 13)	<i>T</i>	-	-	-	-	-	-	-	-	-	-
	<i>p</i>										
C-Auditory Input (N = 13)	<i>T</i>	-	-	-	-	-	-	-	-	-	-
	<i>p</i>										
C-Visual Input (N = 12)	<i>T</i>	-	-	-	-	-	-	-	-	-	-
	<i>p</i>										
Reading (N = 13)	<i>T</i>	-	-	-	-	-	-	-	-	-	-
	<i>p</i>										
Writing (N = 13)	<i>T</i>	-0.47	-	-	-	-	-	-	-	-	-
	<i>p</i>	.036									
Alpha band											
P-Word Retrieval (N = 13)	<i>T</i>	-	-	-	-	-	-	-	-	-	-
	<i>p</i>										
P-Phonology (N = 13)	<i>T</i>	-	-	-	-	-	-	-	-	-	-
	<i>p</i>										
P-Semantics (N = 13)	<i>T</i>	-	-	-	-	-	-	-	-	-	-
	<i>p</i>										
P-Morphosyntax (N = 13)	<i>T</i>	-	-	-	-	-	-	-	-	-	-
	<i>p</i>										
C-Auditory Input (N = 13)	<i>T</i>	-	-	-	-	-	-	-	-	-	-
	<i>p</i>										
C-Visual Input (N = 12)	<i>T</i>	-	-	-	-	-	-	-	-	-	-
	<i>p</i>										
Reading (N = 13)	<i>T</i>	-	-	-	-	-	-	-	-	-	-
	<i>p</i>										
Writing (N = 13)	<i>T</i>	-	-	-	-	-	-	-	-	-	-
	<i>p</i>										

Note. Only the tests with $p < 0.05$ are presented. N = group size; T = Kendall's tau-b correlation coefficient; p = p-value (two-sided). Significant correlations after Bonferroni correction ($p < 0.005$) are presented in bold font. P = production; C = comprehension; W = weighted; these network measures quantify weighted FC networks; MST = Minimum Spanning Tree: these network measures quantify Minimum Spanning Tree FC networks. FC = functional connectivity; PLI = Phase lag index, mean of all 16 remaining electrodes; rC = relative average clustering coefficient; rL = relative average path length; SWI = small-world index; MST-Degr = MST-maximum degree; MST-Ecc = MST-eccentricity, mean of all nodes; MST-BC = MST-maximum betweenness centrality; MST-Leaf = MST-leaf fraction; MST-Diam = MST-diameter; MST-TH = MST-tree hierarchy.

Appendix E8 – FC network characteristics at T1 and language outcome at T3 in meningioma patients

Correlation analyses between FC network measures at T1 and language outcome (domain z-scores) at T3 in meningioma patients

		W-PLI	W-rC	W-rL	W-SWI	MST-Degr	MST-Ecc	MST-BC	MST-Leaf	MST-Diam	MST-TH
Theta band											
P-Word Retrieval (N = 8)	<i>T</i>	-0.57	-	-	-	-	-	-	-	-	-
	<i>p</i>	.048									
P-Phonology (N = 8)	<i>T</i>	-	-	-	-	-	-	-	-	-	-
	<i>p</i>										
P-Semantics (N = 8)	<i>T</i>	-0.57	-	-	-	-	-	-	-	-	-
	<i>p</i>	.048									
P-Morphosyntax (N = 8)	<i>T</i>	-	-	-	-	-	-	-	-	-	-
	<i>p</i>										
C-Auditory Input (N = 8)	<i>T</i>	-	-	-	-	-	-	-	-	-	-
	<i>p</i>										
C-Visual Input (N = 6)	<i>T</i>	-	-	-	-	-	-	-	-	-	-
	<i>p</i>										
Reading (N = 8)	<i>T</i>	-	-	-	-	-	-	-	-	-	-
	<i>p</i>										
Writing (N = 8)	<i>T</i>	-	-	-	-	-	-	-	-	-	-
	<i>p</i>										
Alpha band											
P-Word Retrieval (N = 8)	<i>T</i>	-	-	-	-	-0.64	0.57	-	-	0.59	-
	<i>p</i>					.026	.048			.044	
P-Phonology (N = 8)	<i>T</i>	-	-	-	-	-	-	-	-	-	-
	<i>p</i>										
P-Semantics (N = 8)	<i>T</i>	-	-	-	-	-	-	-	-	-	-
	<i>p</i>										
P-Morphosyntax (N = 8)	<i>T</i>	-	-	-	-	-	-	-	-	-	-
	<i>p</i>										
C-Auditory Input (N = 8)	<i>T</i>	-	-	-	-	-	-	-	-	-	-
	<i>p</i>										
C-Visual Input (N = 6)	<i>T</i>	-	-	-	-	-	-	-	-	-	-
	<i>p</i>										
Reading (N = 8)	<i>T</i>	-	-	-	-	-	-	-	-	-	-
	<i>p</i>										
Writing (N = 8)	<i>T</i>	-	-	-	-	-	-	-0.75	-	-	-
	<i>p</i>							.014			

Note. Only the tests with $p < 0.05$ are presented. N = group size; T = Kendall's tau-b correlation coefficient; p = p-value (two-sided). There were no significant correlations after Bonferroni correction ($p < 0.005$). P = production; C = comprehension; W = weighted: these network measures quantify weighted FC networks; MST = Minimum Spanning Tree: these network measures quantify Minimum Spanning Tree FC networks. FC = functional connectivity; PLI = Phase lag index, mean of all 16 remaining electrodes; rC = relative average clustering coefficient; rL = relative average path length; SWI = small-world index; MST-Degr = MST-maximum degree; MST-Ecc = MST-eccentricity, mean of all nodes; MST-BC = MST-maximum betweenness centrality; MST-Leaf = MST-leaf fraction; MST-Diam = MST-diameter; MST-TH = MST-tree hierarchy.

Appendix E9 – Individual FC networks of glioma patients

Glioma patients before surgery: Theta band

Overview of individual MRI scans, FC weighted networks (using three different thresholds) and FC MST networks in the theta band for every glioma patient preoperatively. If patients had a language impairment, the last column shows which language domains were affected.

	MRI scan ^a		Weighted network Threshold 0.120		Weighted network Threshold 0.160		Weighted network Threshold 0.200		MST network		Impaired language domain(s)
	L	R	L	R	L	R	L	R	L	R	
1											P-Word Retrieval

2											P-Word Retrieval P-Semantics

3

MRI = magnetic resonance imaging; FC = functional connectivity; MST = minimum spanning tree; L = left; R = right; P = production; C = comprehension.
^aBrain tumour images were obtained from T2-weighted (dark fluid, flair, or turbo spin echo) MRI scans. The image of the largest tumour diameter in the transverse plane was selected, in which left is left and right is right (in contrast to the neuroradiological convention) to match the network images.

Glioma patients before surgery: Alpha band

Overview of individual MRI scans, FC weighted networks (using three different thresholds) and FC MST networks in the alpha band for every glioma patient preoperatively. If patients had a language impairment, the last column shows which language domains were affected.

	MRI scan ^a		Weighted network Threshold 0.120		Weighted network Threshold 0.160		Weighted network Threshold 0.200		MST network		Impaired language domain(s)
	L	R	L	R	L	R	L	R	L	R	
1											P-Word Retrieval
2											P-Word Retrieval P-Semantics
3

P-Semantics
C-Auditory Input
Reading
Writing

P-Word Retrieval

MRI = magnetic resonance imaging; FC = functional connectivity; MST = minimum spanning tree; L = left; R = right; P = production; C = comprehension.

Brain tumour images were obtained from T2-weighted (dark fluid, flair, or turbo spin echo) MRI scans. The image of the largest tumour diameter in the transverse plane was selected, in which left is left and right is right (in contrast to the neuroradiological convention) to match the network images.

Appendix E10 – Individual FC networks of meningioma patients

Meningioma patients before surgery: Theta band

Overview of individual MRI scans, FC weighted networks (using three different thresholds) and FC MST networks in the theta band for every meningioma patient preoperatively. If patients had a language impairment, the last column shows which language domains were affected.

MRI scan ^a		Weighted network Threshold 0.120		Weighted network Threshold 0.160		Weighted network Threshold 0.200		MST network		Impaired language domain(s)
L	R	L	R	L	R	L	R	L	R
-
-
Writing

MRI = magnetic resonance imaging; FC = functional connectivity; MST = minimum spanning tree; L = left; R = right; P = production; C = comprehension.
^a Brain tumour images were obtained from T2-weighted (dark fluid, flair, or turbo spin echo) MRI scans. The image of the largest tumour diameter in the transverse plane was selected, in which left is left and right is right (in contrast to the neuroradiological convention) to match the network images.

Meningioma patients before surgery: Alpha band

Overview of individual MRI scans, FC weighted networks (using three different thresholds) and FC MST networks in the alpha band for every meningioma patient preoperatively. If patients had a language impairment, the last column shows which language domains were affected.

MRI scan ^a	Weighted network Threshold 0.120		Weighted network Threshold 0.160		Weighted network Threshold 0.200		MST network		Impaired language domain(s)		
	L	R	L	R	L	R	L	R			
1											-
2											-
3											Writing

Reading
Writing

MRI = magnetic resonance imaging; FC = functional connectivity; MST = minimum spanning tree; L = left; R = right; P = production; C = comprehension.
a Brain tumour images were obtained from T2-weighted (dark fluid, flair, or turbo spin echo) MRI scans. The image of the largest tumour diameter in the transverse plane was selected, in which left is left and right is right (in contrast to the neuroradiological convention) to match the network images.

Summary

Intact language functions are crucial in domestic, social, and professional activities. A brain tumour can cause language impairments, which have a serious impact on everyday communication and negatively affect quality of life (Hilari, Needle, & Harrison, 2012). Considering that language covers a range of abilities, several language modalities (speech production, comprehension, reading, and writing) and linguistic levels (e.g. phonology, concerning speech sounds; semantics, concerning meaning; and morphosyntax, concerning word and sentence structure) are at risk in brain tumour patients. However, relatively little is known about how these different language modalities and linguistic levels are affected, specifically in patients with a low-grade glioma. Furthermore, it is unclear whether language impairments are present in patients with a meningioma. This thesis concentrates on language functioning in low-grade glioma and meningioma patients.

Gliomas are intra-axial tumours, meaning that they lie within brain tissue (brain parenchyma). These tumours frequently infiltrate brain areas that are involved in sensorimotor or language functions, the so-called 'eloquent areas'. Meningiomas are extra-axial tumours, which arise from the meninges and lie outside the brain parenchyma. Even though they generally do not infiltrate brain tissue, meningiomas can compress adjacent brain areas. Patients with a presumed low-grade glioma or meningioma in or near eloquent brain areas usually undergo surgical resection, after which they have a relatively long life expectancy. Language outcome after brain tumour surgery has an effect on the extent to which patients can resume their daily activities and return to work. However, postoperative language functioning varies greatly between patients (e.g. Norrelgen, Jensdottir, & Östberg, 2020). Therefore, it is useful to search for predictors of language outcome after brain tumour surgery.

In that regard, we study two aspects of resting-state brain activity that, based on previous literature, may be associated with language (dys)functioning in brain tumour patients. The first aspect is slow-wave activity: activity in the delta and theta frequency bands, presumably caused by white matter injury. The second concerns functional connectivity (FC) brain networks, reflecting the extent to which brain areas functionally interact. Both can be analysed from registrations of electroencephalography (EEG). This is a non-invasive and inexpensive measurement of brain function, which is commonly used in clinical practice. Hence, potential clinical application is feasible in the case that slow-wave activity and/or FC network characteristics in resting-state EEG are found to be predictive of language outcome after brain tumour surgery.

Chapter 1 in part I of the thesis introduces the three main objectives:

- (1) to gain more insight into language functioning in low-grade glioma and meningioma patients;
- (2) to reveal whether/how language functioning is related to resting-state EEG characteristics;
- (3) to find predictors for language outcome after brain tumour surgery, based on preoperative EEG.

Furthermore, background information on brain tumours, language functioning in brain tumour patients, and brain activity is provided, followed by an outline of the thesis.

In **chapter 2**, we review the literature in order to examine the relation between slow-wave activity during a resting state (registered with EEG or magnetoencephalography; MEG), and language performance in adults with brain injury (caused by stroke, neurodegenerative diseases, trauma, epilepsy or tumour). The majority of the 20 included studies show that slow-wave activity can be seen as a marker of language impairment. In stroke patients, the degree and localisation of slow-wave activity indicate the severity and type of language impairment. There are indications that slow-wave activity can predict the course of language recovery in post-stroke aphasia. It is unknown whether slow-wave activity also has prognostic value for language outcome or recovery in patients with brain injury other than stroke.

Chapter 3 introduces FC network analysis and describes how resting-state FC brain networks are altered in brain tumour patients. Subsequently, a literature review is presented to evaluate whether and how FC network characteristics are related to cognitive and language functioning in brain tumour patients and, only for language, in patients with other brain pathologies. Brain tumour patients seem to have increased FC in lower frequency bands and decreased FC in higher frequency bands. These FC alterations relate to poorer language performance, as suggested by three out of four studies in brain tumour patients, and supported by findings in other patient groups. For brain tumour patients, however, this concerns performance on verbal fluency tests, which only partly assess language. Hence, it is unclear how FC network characteristics relate to different aspects of language functioning before and after brain tumour surgery.

Chapter 4 presents a proof-of-principle study to examine whether the paradigm we developed for relating slow-wave activity to language functioning in glioma patients is feasible. Twenty-one presumed low-grade glioma patients were retrospectively included. Language scores and resting-state EEG data were obtained within 1 year preoperatively or postoperatively. The results showed that patients with moderate/severe slow-wave activity had lower language scores than patients with normal/mild slow-wave activity, based on visual EEG analysis. Quantitative EEG analysis revealed a significant negative correlation between slow-wave activity and language scores. In conclusion, the paradigm is suitable for the current project: slow-wave activity in resting-state EEG is inversely related to language functioning in glioma patients. This retrospective study is the starting point for our prospective research.

Part II of the thesis presents results from the PLOTS study: *Predicting Language Outcome after brain Tumour Surgery*.

Chapter 5 describes a study on language functioning in glioma patients undergoing awake brain surgery. Fifteen patients with a grade II glioma in the language-dominant hemisphere underwent a thorough and sensitive language test battery at three time points: before surgery, 2 months after surgery, and 1 year after surgery. Before surgery, the patient group had impaired language abilities for speech production (word retrieval, phonology, semantics, and a trend for morphosyntax), auditory comprehension, and writing. Group-level language performance did not change after surgery, apart from improvement of auditory comprehension. Language impairments and self-reported language problems were present at each time point in the majority of patients, but the test results corresponded to the self-

reported language problems only preoperatively. Overall, low-grade gliomas in the language-dominant hemisphere induce impairments in almost all language modalities and linguistic levels. The findings underline the importance of extensive language testing before and after awake glioma surgery.

The study presented in **chapter 6** follows the same procedure to examine language functioning in meningioma patients, specifically 10 patients with a grade I meningioma pressing on the left language-dominant hemisphere. Before surgery, the patient group had impaired language abilities for speech production (word retrieval and morphosyntax) and writing. Group-level language performance remained largely stable after surgery. Language impairments and self-reported language problems were present at each time point in approximately half of the patients. However, the test results often did not correspond to the self-reported language problems, suggesting that both should be evaluated for valid conclusions on language functioning. It is discussed that, despite the non-infiltrative nature of meningiomas, these tumours can cause language impairments, affecting primarily expressive language abilities. Hence, attention must be paid to language abilities of left-sided meningioma patients for suitable counselling pre- and postoperatively.

In **chapter 7**, we investigate whether low-grade glioma patients ($N = 15$) and meningioma patients ($N = 10$) have increased slow-wave activity in resting-state EEG, and if so, whether this relates to pre- and postoperative language functioning. EEG was registered preoperatively (all patients) and 1 year postoperatively (glioma patients only). Additionally, 15 healthy individuals underwent EEG registration. Glioma patients had increased delta activity and increased theta activity before and after surgery. Before glioma surgery, increased theta activity was related to the presence of language impairment, in particular to poorer word retrieval and morphosyntactic performance. Preoperative slow-wave activity was not related to postoperative language outcome in glioma patients. Meningioma patients had no increased slow-wave activity compared to healthy individuals. Thus, low-grade gliomas and meningiomas seem to have a different effect on resting-state brain activity. Increased theta activity can be considered a marker of language impairment in glioma patients, but it is not predictive of language outcome after surgery.

Chapter 8 presents a study on resting-state FC brain networks in relation to pre- and postoperative language functioning in low-grade glioma and meningioma patients. The study procedure is identical to that in previous chapters. The characteristics of FC networks did not differ between patients and healthy individuals, but visual inspection revealed higher theta-band FC and lower alpha-band FC in both patient groups. In glioma patients, three preoperative FC network characteristics (theta band: hub presence and global FC; alpha band: a small-world-like network configuration) were related to preoperative language functioning (production-morphosyntax and comprehension). Furthermore, higher theta-band FC before surgery (hub presence and global FC) was associated with poorer word retrieval 1 year after surgery. In meningioma patients, FC networks were not related to language functioning. Overall, we demonstrate that, in glioma patients only, FC networks are informative for preoperative language functioning and can predict postoperative language outcome. However, the matter requires further investigation in larger patient groups.

Chapter 9 discusses the main findings for each research objective. The outcomes corresponding to objective (1), as obtained by using an extensive and sufficiently sensitive language test battery, contribute to a better understanding of language impairments that are induced by low-grade gliomas or meningiomas and their treatment. In both patient groups, a variety of language abilities are affected. Many patients are presented with language impairments 1 year after surgery, but there is large interpatient variation. Our findings emphasise the significance of conducting standard clinical language assessments before and after brain tumour surgery in the language-dominant hemisphere to optimise patient counselling and to evaluate the need for language intervention. With regard to objective (2), the outcomes indicate that specific aspects of resting-state brain activity (increased theta activity and particular FC network characteristics) are associated with poorer language functioning in glioma patients before surgery. There is no evidence for such relations in meningioma patients. In reference to objective (3), this project identifies two predictors of language outcome after glioma surgery. Both indicate that high theta-band FC in resting-state EEG is associated with an increased risk of postoperative language impairment. This line of research has the potential to improve perisurgical procedures, such as treatment planning, patient counselling, and language rehabilitation, in order to minimise or prevent language decline. Finally, the chapter discusses limitations, clinical recommendations, and directions for future research.

Samenvatting

Intacte taalfuncties zijn cruciaal voor huiselijke, sociale en werkgerelateerde activiteiten. Een hersentumor kan taalstoornissen veroorzaken die een negatieve invloed hebben op de alledaagse communicatie en de kwaliteit van leven (Hilari, Needle & Harrison, 2012). Taal omvat veel vaardigheden. Zo zijn er verschillende taalmodaliteiten (productie, begrip, lezen en schrijven) en linguïstische niveaus (bijv. fonologie, dat betrekking heeft op spraakklanken; semantiek, dat betrekking heeft op betekenis; en morfosyntaxis, dat betrekking heeft op woord- en zinsstructuur) die risico lopen bij patiënten met een hersentumor. Desondanks is er relatief weinig bekend over hoe de verschillende taalmodaliteiten en linguïstische niveaus gestoord zijn specifiek bij patiënten met een laaggradig glioom. Daarnaast is het onduidelijk of er taalstoornissen voorkomen bij patiënten met een meningeoom. Dit proefschrift richt zich op het talig functioneren van laaggradig glioom- en meningeoompatiënten.

Gliomen zijn intra-axiale tumoren, wat betekent dat ze in het hersenweefsel (hersenparenchym) gelegen zijn. Deze tumoren infiltreren vaak hersengebieden die betrokken zijn bij sensorische-, motorische-, of taalfuncties, de zogenoemde 'eloquente gebieden'. Meningeomen zijn extra-axiale tumoren, die vanuit het hersenvlies ontstaan en buiten het hersenparenchym gelegen zijn. Hoewel ze het hersenweefsel doorgaans niet infiltreren, kunnen meningeomen drukken op omliggende hersengebieden. Patiënten met een verondersteld laaggradig glioom of meningeoom in of nabij eloquente hersengebieden ondergaan vaak een chirurgische resectie, waarna ze een relatief lange levensverwachting hebben. De taaluitkomst na een hersentumoroperatie heeft effect op de mate waarin patiënten hun dagelijkse activiteiten, zoals hun werk, kunnen hervatten. Het postoperatief talig functioneren varieert echter sterk tussen patiënten (bijv. Norrelgen, Jensdottir & Östberg, 2020). Daarom is het nuttig om te zoeken naar voorspellers voor de taaluitkomst na een hersentumoroperatie.

In dat verband bestuderen we twee aspecten van de hersenactiviteit in rust die, gebaseerd op eerdere literatuur, gerelateerd kunnen zijn aan het talig (dys)functioneren van hersentumorpatiënten. Het eerste aspect is trage activiteit: hersenactiviteit in de delta en θ frequentiebanden, vermoedelijk veroorzaakt door schade aan de witte stof. Het tweede betreft functionele connectiviteit (FC) hersennetwerken, die de mate van functionele interactie tussen hersengebieden weergeven. Beide kunnen worden geanalyseerd vanuit registraties met elektro-encefalografie (EEG). Dit is een niet-invasieve en relatief goedkope meting van de hersenactiviteit, die veel gebruikt wordt in de klinische praktijk. Hierdoor zullen potentiële klinische toepassingen haalbaar zijn in het geval dat trage activiteit en/of FC netwerkeigenschappen in rust-EEG voorspellend zijn voor de taaluitkomst na een hersentumoroperatie.

Hoofdstuk 1 in deel I van het proefschrift introduceert de drie hoofddoelen:

- (1) het verkrijgen van meer inzicht in het talig functioneren van laaggradig glioom- en meningeoompatiënten;
- (2) het onthullen of/hoe het talig functioneren gerelateerd is aan rust-EEG karakteristieken;
- (3) het vinden van voorspellers voor de taaluitkomst na een hersentumoroperatie, op basis van preoperatief EEG.

Verder wordt achtergrondinformatie gegeven over hersentumoren, taalvaardigheden bij hersentumorpatiënten en hersenactiviteit, gevolgd door een overzicht van het proefschrift.

In **hoofdstuk 2** reviewen we de literatuur om de relatie te onderzoeken tussen trage activiteit in rust (geregistreerd met EEG of magneto-encefalografie; MEG) en taalvaardigheden bij volwassenen met hersenletsel (veroorzaakt door een beroerte, neurodegeneratieve ziekte, trauma, epilepsie of tumor). Het merendeel van de 20 geïnccludeerde studies toont aan dat trage activiteit gezien kan worden als een marker van taalstoornissen. Bij patiënten met een beroerte duiden de mate en de lokalisatie van trage activiteit op de ernst en het type van de taalstoornis. Verder zijn er aanwijzingen dat trage activiteit het verloop van taalherstel bij afasie na een beroerte kan voorspellen. Het is onbekend of trage activiteit ook prognostische waarde heeft voor de taaluitkomst of het taalherstel bij patiënten met ander hersenletsel dan een beroerte.

Hoofdstuk 3 introduceert FC netwerkanalyse en beschrijft hoe FC hersennetwerken in rust aangepast zijn bij hersentumoriënten. Vervolgens wordt een literatuuronderzoek gepresenteerd, waarin bestudeerd wordt of/hoe FC netwerkeigenschappen gerelateerd zijn aan cognitief en talig functioneren bij hersentumoriënten en, alleen voor taal, bij patiënten met andere hersenpathologieën. Hersentumoriënten lijken verhoogde FC in lagere frequentiebanden en verlaagde FC in hogere frequentiebanden te hebben. Deze FC patronen zijn gerelateerd aan slechtere taalvaardigheden, wat blijkt uit drie van de vier studies bij hersentumoriënten en wordt ondersteund door bevindingen bij andere patiëntgroepen. Voor hersentumoriënten geldt dit echter alleen voor de prestatie op verbale fluency (woordvlotheid) tests, die niet uitsluitend taalfuncties onderzoeken. Het is daarom onduidelijk hoe FC netwerkeigenschappen relateren aan verschillende aspecten van het talig functioneren voor en na een hersentumoroperatie.

Hoofdstuk 4 presenteert een proof-of-principle studie om te onderzoeken of het paradigma, dat we ontwikkeld hebben voor het relateren van trage activiteit aan het talig functioneren van glioompatiënten, uitvoerbaar is. Eenentwintig patiënten met een verondersteld laaggradig glioom werden retrospectief geïnccludeerd. Taalscores en rust-EEG data waren binnen 1 jaar preoperatief of postoperatief verkregen. De resultaten laten zien dat patiënten met matige/ernstige trage activiteit lagere taalscores hadden dan patiënten met normale/milde trage activiteit, op basis van de visuele EEG analyse. De kwantitatieve EEG analyse toont een significante negatieve correlatie tussen trage activiteit en taalscores. De conclusie is dat het paradigma bruikbaar is voor het onderhavige project: trage activiteit in rust-EEG heeft een inverse relatie met het talig functioneren van glioompatiënten. Deze retrospectieve studie is het uitgangspunt voor ons prospectieve onderzoek.

Deel II van het proefschrift presenteert resultaten van de PLOTS-studie: *Predicting Language Outcome after brain Tumour Surgery*.

Hoofdstuk 5 beschrijft een studie over het talig functioneren van glioompatiënten die een wakkere hersenoperatie ondergaan. Vijftien patiënten met een graad II glioom in de taaldominante hemisfeer ondergingen een uitgebreide en sensitieve taaltestbatterij op drie meetmomenten: voor de operatie, 2 maanden na de operatie en 1 jaar na de operatie. Voor de operatie had de patiëntengroep gestoorde taalvaardigheden voor productie (woordvinding, fonologie, semantiek en een trend voor morfosyntaxis), begrip (auditief) en schrijven. De

taalprestaties op groepsniveau veranderden niet na de operatie, met uitzondering van een verbetering van het auditieve begrip. Taalstoornissen en zelfgerapporteerde taalproblemen kwamen op elk meetmoment bij het merendeel van de patiënten voor, maar de testresultaten kwamen alleen preoperatief overeen met de zelfgerapporteerde taalproblemen. Al met al veroorzaken laaggradige gliomen in de taaldominante hemisfeer stoornissen in bijna alle taalmodaliteiten en linguïstische niveaus. De bevindingen benadrukken de noodzaak van grondige taalonderzoeken voor en na wakkere glioomoperaties.

De studie in **hoofdstuk 6** volgt dezelfde procedure om het talig functioneren van meningeoompatiënten te onderzoeken, specifiek van 10 patiënten met een graad I meningeoom drukkend op de linker taaldominante hemisfeer. Voor de operatie had de patiëntengroep gestoorde taalvaardigheden voor productie (woordvinding en morfosyntaxis) en schrijven. De taalprestaties op groepsniveau bleven relatief stabiel na de operatie. Taalstoornissen en zelfgerapporteerde taalproblemen kwamen op elk meetmoment bij ongeveer de helft van de patiënten voor. Echter, de testresultaten kwamen vaak niet overeen met de zelfgerapporteerde taalproblemen, wat erop wijst dat beide meegenomen moeten worden om gegronde conclusies over taalvaardigheden te kunnen trekken. De discussie bespreekt dat, ondanks de niet-infiltrerende aard van meningeomen, deze tumoren taalstoornissen kunnen veroorzaken, die voornamelijk expressieve taalfuncties treffen. Er moet daarom gelet worden op het talig functioneren van linkszijdig meningeoompatiënten voor passende begeleiding pre- en postoperatief.

In **hoofdstuk 7** onderzoeken we of laaggradig glioompatiënten (N = 15) en meningeoompatiënten (N = 10) toegenomen trage activiteit in rust-EEG hebben, en zo ja, of dit gerelateerd is aan het pre- en postoperatief talig functioneren. EEG werd preoperatief (alle patiënten) en 1 jaar postoperatief (alleen glioompatiënten) geregistreerd. Daarnaast ondergingen 15 gezonde deelnemers een EEG-registratie. Glioompatiënten hadden toegenomen delta activiteit en toegenomen θ activiteit voor en na de operatie. Toegenomen θ activiteit voor de glioomoperatie was gerelateerd aan de aanwezigheid van taalstoornissen, in het bijzonder slechtere woordvinding en morfosyntactische vaardigheden. Preoperatieve trage activiteit was niet gerelateerd aan de postoperatieve taaluitkomst bij glioompatiënten. Meningeoompatiënten hadden geen toegenomen trage activiteit vergeleken met gezonde deelnemers. Kortom, laaggradige gliomen en meningeomen lijken een verschillend effect te hebben op de hersenactiviteit in rust. Toegenomen θ activiteit kan gezien worden als een marker van taalstoornissen bij glioompatiënten, maar het is niet voorspellend voor de taaluitkomst na de operatie.

Hoofdstuk 8 presenteert een studie over FC hersennetwerken in rust en hun relatie tot het pre- en postoperatief talig functioneren van glioom- en meningeoompatiënten. De procedure is identiek aan dat in vorige hoofdstukken. De FC netwerkeigenschappen verschilden niet tussen patiënten en gezonde deelnemers, maar de visuele inspectie onthulde verhoogde θ -band FC en verlaagde alfa-band FC in beide patiëntgroepen. Bij glioompatiënten waren drie preoperatieve FC netwerkeigenschappen (θ -band: hub aanwezigheid en globale FC; alfa band: een 'small-world' netwerkconfiguratie) gerelateerd aan preoperatieve taalvaardigheden (productie-morfosyntaxis en begrip). Bovendien was

verhoogde θ -band FC voor de operatie (hub aanwezigheid en globale FC) geassocieerd met slechtere woordvinding 1 jaar na de glioomoperatie. Bij meningeoompatiënten waren de FC netwerken niet gerelateerd aan de taalvaardigheden. Al met al demonstreren we dat, alleen bij glioompatiënten, FC netwerken informatief zijn voor het preoperatief talig functioneren en dat ze de taaluitkomst na de operatie kunnen voorspellen. Verder onderzoek bij grotere patiëntgroepen is echter noodzakelijk.

Hoofdstuk 9 bespreekt de belangrijkste bevindingen voor elk onderzoeksdoel. De uitkomsten behorende bij doel (1), die verkregen zijn met behulp van een uitgebreide en sensitieve taaltestbatterij, dragen bij aan een beter inzicht in taalstoornissen ten gevolge van laaggradige gliomen of meningeomen en hun behandeling. Beide patiëntgroepen tonen stoornissen in een verscheidenheid aan taalfuncties. Veel patiënten hebben taalstoornissen 1 jaar na de operatie, maar er is een grote variatie tussen patiënten. Onze bevindingen moedigen aan tot het afnemen van standaard klinische taalonderzoeken voor en na hersentumoroperaties in de taaldominante hemisfeer, om patiëntenbegeleiding te optimaliseren en te beoordelen of er gestart moet worden met taaltherapie. De resultaten behorende bij doel (2) duiden erop dat specifieke aspecten van hersenactiviteit in rust (toegenomen θ activiteit en bepaalde FC netwerkeigenschappen) geassocieerd zijn met slechtere taalvaardigheden bij glioompatiënten voor de operatie. Er is geen bewijs voor dergelijke relaties bij meningeoompatiënten. Met betrekking tot doel (3) constateert dit project twee voorspellers voor de taaluitkomst na een glioomoperatie. Beide laten zien dat verhoogde θ -band FC in rust-EEG geassocieerd is met een verhoogd risico op postoperatieve taalstoornissen. Deze onderzoeksrichting heeft de potentie om klinische procedures, zoals behandelingsplanning, patiëntenbegeleiding en taalrevalidatie, te verbeteren om taalachteruitgang te beperken of te voorkomen. Tot slot bespreekt het hoofdstuk beperkingen van het onderzoek, aanbevelingen voor de klinische praktijk en suggesties voor toekomstig onderzoek.

About the author

Nienke Wolthuis was born on 22 March 1991 in Zutphen, Gelderland, The Netherlands. In 2009, she graduated from her pre-university education at the Isendoorn College in Warnsveld. After taking a gap year for travelling and volunteering abroad, she studied for a Bachelor of Arts in Linguistics at the University of Groningen from 2010 to 2013. During this time, she assisted in aphasia research projects at the Erasmus MC University Medical Centre Rotterdam and worked on the development of a new digital language test at the University of Groningen. In 2013, she started the Erasmus Mundus programme European Master in Clinical Linguistics (EMCL) at the universities of Potsdam (Germany), Eastern Finland, and Groningen (The Netherlands), and graduated with a Master of Science in 2015. Subsequently, Nienke started her PhD project in Neurolinguistics at the Centre for Language and Cognition Groningen (CLCG), University of Groningen, in collaboration with the Neurology and Neurosurgery departments at the University Medical Centre Groningen and the Erasmus MC University Medical Centre Rotterdam. This multidisciplinary PhD project, which was supervised by Prof. Roelien Bastiaanse, Dr. Djaina Satoer, Dr. Ingeborg Bosma, and Dr. Joseph Cherian Perumpillichira, led to the dissertation '*Language impairments and resting-state EEG in brain tumour patients: Revealing connections*'. During her PhD trajectory, Nienke completed many courses at the Graduate School for the Humanities (GSH) and at the research school of Behavioural and Cognitive Neurosciences (BCN) in Groningen. Furthermore, she was engaged in BA and MA thesis supervision, gave guest lectures, and presented research output at international conferences. Nienke, her partner Nivard, and their many silverfish are living at their nice home in Amersfoort. At the time of printing this dissertation, Nienke is about to start her new position at the ALS Centre Netherlands, University Medical Centre Utrecht.

Groningen Dissertations in Linguistics (GRODIL)

1. Henriëtte de Swart (1991). *Adverbs of Quantification: A Generalized Quantifier Approach*.
2. Eric Hoekstra (1991). *Licensing Conditions on Phrase Structure*.
3. Dicky Gilbers (1992). *Phonological Networks. A Theory of Segment Representation*.
4. Helen de Hoop (1992). *Case Configuration and Noun Phrase Interpretation*.
5. Gosse Bouma (1993). *Nonmonotonicity and Categorical Unification Grammar*.
6. Peter I. Blok (1993). *The Interpretation of Focus*.
7. Roelien Bastiaanse (1993). *Studies in Aphasia*.
8. Bert Bos (1993). *Rapid User Interface Development with the Script Language Gist*.
9. Wim Kosmeijer (1993). *Barriers and Licensing*.
10. Jan-Wouter Zwart (1993). *Dutch Syntax: A Minimalist Approach*.
11. Mark Kas (1993). *Essays on Boolean Functions and Negative Polarity*.
12. Ton van der Wouden (1994). *Negative Contexts*.
13. Joop Houtman (1994). *Coordination and Constituency: A Study in Categorical Grammar*.
14. Petra Hendriks (1995). *Comparatives and Categorical Grammar*.
15. Maarten de Wind (1995). *Inversion in French*.
16. Jelly Julia de Jong (1996). *The Case of Bound Pronouns in Peripheral Romance*.
17. Sjoukje van der Wal (1996). *Negative Polarity Items and Negation: Tandem Acquisition*.
18. Anastasia Giannakidou (1997). *The Landscape of Polarity Items*.
19. Karen Lattewitz (1997). *Adjacency in Dutch and German*.
20. Edith Kaan (1997). *Processing Subject-Object Ambiguities in Dutch*.
21. Henny Klein (1997). *Adverbs of Degree in Dutch*.
22. Leonie Bosveld-de Smet (1998). *On Mass and Plural Quantification: The case of French 'des'/'du'-NPs*.
23. Rita Landeweerd (1998). *Discourse semantics of perspective and temporal structure*.
24. Mettina Veenstra (1998). *Formalizing the Minimalist Program*.
25. Roel Jonkers (1998). *Comprehension and Production of Verbs in aphasic Speakers*.
26. Erik F. Tjong Kim Sang (1998). *Machine Learning of Phonotactics*.
27. Paulien Rijkhoek (1998). *On Degree Phrases and Result Clauses*.
28. Jan de Jong (1999). *Specific Language Impairment in Dutch: Inflectional Morphology and Argument Structure*.
29. H. Wee (1999). *Definite Focus*.
30. Eun-Hee Lee (2000). *Dynamic and Stative Information in Temporal Reasoning: Korean tense and aspect in discourse*.
31. Ivilin P. Stoianov (2001). *Connectionist Lexical Processing*.
32. Klarien van der Linde (2001). *Sonority substitutions*.
33. Monique Lamers (2001). *Sentence processing: using syntactic, semantic, and thematic information*.
34. Shalom Zuckerman (2001). *The Acquisition of "Optional" Movement*.
35. Rob Koeling (2001). *Dialogue-Based Disambiguation: Using Dialogue Status to Improve Speech Understanding*.

36. Esther Ruigendijk (2002). *Case assignment in Agrammatism: a cross-linguistic study.*
37. Tony Mullen (2002). *An Investigation into Compositional Features and Feature Merging for Maximum Entropy-Based Parse Selection.*
38. Nanette Bienfait (2002). *Grammatica-onderwijs aan allochtone jongeren.*
39. Dirk-Bart den Ouden (2002). *Phonology in Aphasia: Syllables and segments in level-specific deficits.*
40. Rienk Withaar (2002). *The Role of the Phonological Loop in Sentence Comprehension.*
41. Kim Sauter (2002). *Transfer and Access to Universal Grammar in Adult Second Language Acquisition.*
42. Laura Sabourin (2003). *Grammatical Gender and Second Language Processing: An ERP Study.*
43. Hein van Schie (2003). *Visual Semantics.*
44. Lilia Schürcks-Grozeva (2003). *Binding and Bulgarian.*
45. Stasinios Konstantopoulos (2003). *Using ILP to Learn Local Linguistic Structures.*
46. Wilbert Heeringa (2004). *Measuring Dialect Pronunciation Differences using Levenshtein Distance.*
47. Wouter Jansen (2004). *Laryngeal Contrast and Phonetic Voicing: A Laboratory Phonology.*
48. Judith Rispens (2004). *Syntactic and phonological processing in developmental dyslexia.*
49. Danielle Bougaïré (2004). *L'approche communicative des campagnes de sensibilisation en santé publique au Burkina Faso: Les cas de la planification familiale, du sida et de l'excision.*
50. Tanja Gaustad (2004). *Linguistic Knowledge and Word Sense Disambiguation.*
51. Susanne Schoof (2004). *An HPSG Account of Nonfinite Verbal Complements in Latin.*
52. M. Begoña Villada Moirón (2005). *Data-driven identification of fixed expressions and their modifiability.*
53. Robbert Prins (2005). *Finite-State Pre-Processing for Natural Language Analysis.*
54. Leonoor van der Beek (2005) *Topics in Corpus-Based Dutch Syntax.*
55. Keiko Yoshioka (2005). *Linguistic and gestural introduction and tracking of referents in L1 and L2 discourse.*
56. Sible Andringa (2005). *Form-focused instruction and the development of second language proficiency.*
57. Joanneke Prenger (2005). *Taal telt! Een onderzoek naar de rol van taalvaardigheid en tekstbegrip in het realistisch wiskundeonderwijs.*
58. Neslihan Kansu-Yetkiner (2006). *Blood, Shame and Fear: Self-Presentation Strategies of Turkish Women's Talk about their Health and Sexuality.*
59. Mónika Z. Zempléni (2006). *Functional imaging of the hemispheric contribution to language processing.*
60. Maartje Schreuder (2006). *Prosodic Processes in Language and Music.*
61. Hidetoshi Shiraishi (2006). *Topics in Nivkh Phonology.*
62. Tamás Biró (2006). *Finding the Right Words: Implementing Optimality Theory with Simulated Annealing.*
63. Dieuwke de Goede (2006). *Verbs in Spoken Sentence Processing: Unraveling the Activation Pattern of the Matrix Verb.*

64. Eleonora Rossi (2007). *Clitic production in Italian agrammatism*.
65. Holger Hopp (2007). *Ultimate Attainment at the Interfaces in Second Language Acquisition: Grammar and Processing*.
66. Gerlof Bouma (2008). *Starting a Sentence in Dutch: A corpus study of subject- and object-fronting*.
67. Julia Klitsch (2008). *Open your eyes and listen carefully. Auditory and audiovisual speech perception and the McGurk effect in Dutch speakers with and without aphasia*.
68. Janneke ter Beek (2008). *Restructuring and Infinitival Complements in Dutch*.
69. Jori Mur (2008). *Off-line Answer Extraction for Question Answering*.
70. Lonneke van der Plas (2008). *Automatic Lexico-Semantic Acquisition for Question Answering*.
71. Arjen Versloot (2008). *Mechanisms of Language Change: Vowel reduction in 15th century West Frisian*.
72. Ismail Fahmi (2009). *Automatic term and Relation Extraction for Medical Question Answering System*.
73. Tuba Yarbay Duman (2009). *Turkish Agrammatic Aphasia: Word Order, Time Reference and Case*.
74. Maria Trofimova (2009). *Case Assignment by Prepositions in Russian Aphasia*.
75. Rasmus Steinkrauss (2009). *Frequency and Function in WH Question Acquisition. A Usage-Based Case Study of German L1 Acquisition*.
76. Marjolein Deunk (2009). *Discourse Practices in Preschool. Young Children's Participation in Everyday Classroom Activities*.
77. Sake Jager (2009). *Towards ICT-Integrated Language Learning: Developing an Implementation Framework in terms of Pedagogy, Technology and Environment*.
78. Francisco Dellatorre Borges (2010). *Parse Selection with Support Vector Machines*.
79. Geoffrey Andogah (2010). *Geographically Constrained Information Retrieval*.
80. Jacqueline van Kruiningen (2010). *Onderwijsontwerp als conversatie. Probleemoplossing in interprofessioneel overleg*.
81. Robert G. Shackleton (2010). *Quantitative Assessment of English-American Speech Relationships*.
82. Tim Van de Cruys (2010). *Mining for Meaning: The Extraction of Lexico-semantic Knowledge from Text*.
83. Therese Leinonen (2010). *An Acoustic Analysis of Vowel Pronunciation in Swedish Dialects*.
84. Erik-Jan Smits (2010). *Acquiring Quantification. How Children Use Semantics and Pragmatics to Constrain Meaning*.
85. Tal Caspi (2010). *A Dynamic Perspective on Second Language Development*.
86. Teodora Mehotchewa (2010). *After the fiesta is over. Foreign language attrition of Spanish in Dutch and German Erasmus Student*.
87. Xiaoyan Xu (2010). *English language attrition and retention in Chinese and Dutch university students*.
88. Jelena Prokić (2010). *Families and Resemblances*.

89. Radek Šimík (2011). *Modal existential wh-constructions*.
90. Katrien Colman (2011). *Behavioral and neuroimaging studies on language processing in Dutch speakers with Parkinson's disease*.
91. Siti Mina Tamah (2011). *A Study on Student Interaction in the Implementation of the Jigsaw Technique in Language Teaching*.
92. Aletta Kwant (2011). *Geraakt door prentenboeken. Effecten van het gebruik van prentenboeken op de sociaal-emotionele ontwikkeling van kleuters*.
93. Marlies Kluck (2011). *Sentence amalgamation*.
94. Anja Schüppert (2011). *Origin of asymmetry: Mutual intelligibility of spoken Danish and Swedish*.
95. Peter Nabende (2011). *Applying Dynamic Bayesian Networks in Transliteration Detection and Generation*.
96. Barbara Plank (2011). *Domain Adaptation for Parsing*.
97. Cagri Coltekin (2011). *Catching Words in a Stream of Speech: Computational simulations of segmenting transcribed child-directed speech*.
98. Dörte Hessler (2011). *Audiovisual Processing in Aphasic and Non-Brain-Damaged Listeners: The Whole is More than the Sum of its Parts*.
99. Herman Heringa (2012). *Appositional constructions*.
100. Diana Dimitrova (2012). *Neural Correlates of Prosody and Information Structure*.
101. Harwintha Anjarningsih (2012). *Time Reference in Standard Indonesian Agrammatic Aphasia*.
102. Myrte Gosen (2012). *Tracing learning in interaction. An analysis of shared reading of picture books at kindergarten*.
103. Martijn Wieling (2012). *A Quantitative Approach to Social and Geographical Dialect Variation*.
104. Gisi Cannizzaro (2012). *Early word order and animacy*.
105. Kostadin Cholakov (2012). *Lexical Acquisition for Computational Grammars. A Unified Model*.
106. Karin Beijering (2012). *Expressions of epistemic modality in Mainland Scandinavian. A study into the lexicalization-grammaticalization-pragmaticalization interface*.
107. Veerle Baaijen (2012). *The development of understanding through writing*.
108. Jacolien van Rij (2012). *Pronoun processing: Computational, behavioral, and psychophysiological studies in children and adults*.
109. Ankelien Schippers (2012). *Variation and change in Germanic long-distance dependencies*.
110. Hanneke Loerts (2012). *Uncommon gender: Eyes and brains, native and second language learners, & grammatical gender*.
111. Marjoleine Sloos (2013). *Frequency and phonological grammar: An integrated approach. Evidence from German, Indonesian, and Japanese*.
112. Aysa Arylova. (2013) *Possession in the Russian clause. Towards dynamicity in syntax*.
113. Daniël de Kok (2013). *Reversible Stochastic Attribute-Value Grammars*.
114. Gideon Kotzé (2013). *Complementary approaches to tree alignment: Combining statistical and rule-based methods*.

115. Fridah Katushemererwe (2013). *Computational Morphology and Bantu Language Learning: an Implementation for Runyakitara*.
116. Ryan C. Taylor (2013). *Tracking Referents: Markedness, World Knowledge and Pronoun Resolution*.
117. Hana Smiskova-Gustafsson (2013). *Chunks in L2 Development: A Usage-based Perspective*.
118. Milada Walková (2013). *The aspectual function of particles in phrasal verbs*.
119. Tom O. Abuom (2013). *Verb and Word Order Deficits in Swahili-English bilingual agrammatic speakers*.
120. Gülsen Yılmaz (2013). *Bilingual Language Development among the First Generation Turkish Immigrants in the Netherlands*.
121. Trevor Benjamin (2013). *Signaling Trouble: On the linguistic design of other-initiation of repair in English conversation*.
122. Nguyen Hong Thi Phuong (2013). *A Dynamic Usage-based Approach to Second Language Teaching*.
123. Harm Brouwer (2014). *The Electrophysiology of Language Comprehension: A Neurocomputational Model*.
124. Kendall Decker (2014). *Orthography Development for Creole Languages*.
125. Laura S. Bos (2015). *The Brain, Verbs, and the Past: Neurolinguistic Studies on Time Reference*.
126. Rimke Groenewold (2015). *Direct and indirect speech in aphasia: Studies of spoken discourse production and comprehension*.
127. Huiping Chan (2015). *A Dynamic Approach to the Development of Lexicon and Syntax in a Second Language*.
128. James Griffiths (2015). *On appositives*.
129. Pavel Rudnev (2015). *Dependency and discourse-configurationality: A study of Avar*.
130. Kirsten Kolstrup (2015). *Opportunities to speak. A qualitative study of a second language in use*.
131. Güliz Güneş (2015). *Deriving Prosodic structures*.
132. Cornelia Lahmann (2015). *Beyond barriers. Complexity, accuracy, and fluency in long-term L2 speakers' speech*.
133. Sri Wachyunni (2015). *Scaffolding and Cooperative Learning: Effects on Reading Comprehension and Vocabulary Knowledge in English as a Foreign Language*.
134. Albert Walsweer (2015). *Ruimte voor leren. Een etnografisch onderzoek naar het verloop van een interventie gericht op versterking van het taalgebruik in een knowledge building environment op kleine Friese basisscholen*.
135. Aleyda Lizeth Linares Calix (2015). *Raising Metacognitive Genre Awareness in L2 Academic Readers and Writers*.
136. Fathima Mufeeda Irshad (2015). *Second Language Development through the Lens of a Dynamic Usage-Based Approach*.
137. Oscar Strik (2015). *Modelling analogical change. A history of Swedish and Frisian verb inflection*.

138. He Sun (2015). *Predictors and stages of very young child EFL learners' English development in China*.
139. Marieke Haan (2015). *Mode Matters. Effects of survey modes on participation and answering behavior*.
140. Nienke Houtzager (2015). *Bilingual advantages in middle-aged and elderly populations*.
141. Noortje Joost Venhuizen (2015). *Projection in Discourse: A data-driven formal semantic analysis*.
142. Valerio Basile (2015). *From Logic to Language: Natural Language Generation from Logical Forms*.
143. Jinxing Yue (2016). *Tone-word Recognition in Mandarin Chinese: Influences of lexical-level representations*.
144. Seçkin Arslan (2016). *Neurolinguistic and Psycholinguistic Investigations on Evidentiality in Turkish*.
145. Rui Qin (2016). *Neurophysiological Studies of Reading Fluency. Towards Visual and Auditory Markers of Developmental Dyslexia*.
146. Kashmiri Stec (2016). *Visible Quotation: The Multimodal Expression of Viewpoint*.
147. Yinxing Jin (2016). *Foreign language classroom anxiety: A study of Chinese university students of Japanese and English over time*.
148. Joost Hurkmans (2016). *The Treatment of Apraxia of Speech. Speech and Music Therapy, an Innovative Joint Effort*.
149. Franziska Köder (2016). *Between direct and indirect speech: The acquisition of pronouns in reported speech*.
150. Femke Swarte (2016). *Predicting the mutual intelligibility of Germanic languages from linguistic and extra-linguistic factors*.
151. Sanne Kuijper (2016). *Communication abilities of children with ASD and ADHD. Production, comprehension, and cognitive mechanisms*.
152. Jelena Golubović (2016). *Mutual intelligibility in the Slavic language area*.
153. Nynke van der Schaaf (2016). *"Kijk eens wat ik kan!" Sociale praktijken in de interactie tussen kinderen van 4 tot 8 jaar in de buitenschoolse opvang*.
154. Simon Šuster (2016). *Empirical studies on word representations*.
155. Kilian Evang (2016). *Cross-lingual Semantic Parsing with Categorical Grammars*.
156. Miren Arantzeta Pérez (2017). *Sentence comprehension in monolingual and bilingual aphasia: Evidence from behavioral and eye-tracking methods*.
157. Sana-e-Zehra Haidry (2017). *Assessment of Dyslexia in the Urdu Language*.
158. Srđan Popov (2017). *Auditory and Visual ERP Correlates of Gender Agreement Processing in Dutch and Italian*.
159. Molood Sadat Safavi (2017). *The Competition of Memory and Expectation in Resolving Long-Distance Dependencies: Psycholinguistic Evidence from Persian Complex Predicates*.
160. Christopher Bergmann (2017). *Facets of native-likeness: First-language attrition among German emigrants to Anglophone North America*.
161. Stefanie Keulen (2017). *Foreign Accent Syndrome: A Neurolinguistic Analysis*.
162. Franz Manni (2017). *Linguistic Probes into Human History*.

163. Margreet Vogelzang (2017). *Reference and cognition: Experimental and computational cognitive modeling studies on reference processing in Dutch and Italian.*
164. Johannes Bjerva (2017). *One Model to Rule them all. Multitask and Multilingual Modelling for Lexical Analysis: Multitask and Multilingual Modelling for Lexical Analysis.*
165. Dieke Oele (2018). *Automated translation with interlingual word representations.*
166. Lucas Seuren (2018). *The interactional accomplishment of action.*
167. Elisabeth Borleffs (2018). *Cracking the code - Towards understanding, diagnosing and remediating dyslexia in Standard Indonesian.*
168. Mirjam Günther-van der Meij (2018). *The impact of degree of bilingualism on L3 development English language development in early and later bilinguals in the Frisian context.*
169. Ruth Koops van 't Jagt (2018). *Show, don't just tell: Photo stories to support people with limited health literacy.*
170. Bernat Bardagil-Mas (2018). *Case and agreement in Panará.*
171. Jessica Overweg (2018). *Taking an alternative perspective on language in autism.*
172. Lennie Donné (2018). *Convincing through conversation: Unraveling the role of interpersonal health communication in health campaign effectiveness.*
173. Toivo Glatz (2018). *Serious games as a level playing field for early literacy: A behavioural and neurophysiological evaluation.*
174. Ellie van Setten (2019). *Neurolinguistic Profiles of Advanced Readers with Developmental Dyslexia.*
175. Anna Pot (2019). *Aging in multilingual Netherlands: Effects on cognition, wellbeing and health.*
176. Audrey Rousse-Malpat (2019). *Effectiveness of explicit vs. implicit L2 instruction: a longitudinal classroom study on oral and written skills.*
177. Rob van der Goot (2019). *Normalization and Parsing Algorithms for Uncertain Input.*
178. Azadeh Elmianvari (2019). *Multilingualism, Facebook and the Iranian diaspora.*
179. Joëlle Ooms (2019). *"Don't make my mistake": Narrative fear appeals in health communication.*
180. Annerose Willemsen (2019). *The floor is yours: A conversation analytic study of teachers' conduct facilitating whole-class discussions around texts.*
181. Frans Hiddink (2019). *Early childhood problem-solving interaction: Young children's discourse during small-group work in primary school.*
182. Hessel Haagsma (2020). *A Bigger Fish to Fry: Scaling up the Automatic Understanding of Idiomatic Expressions.*
183. Juliana Andrade Feiden (2020). *The Influence of Conceptual Number in Coreference Establishing: An ERP Study on Brazilian and European Portuguese.*
184. Sirkku Lesonen (2020). *Valuing variability: Dynamic usage-based principles in the L2 development of four Finnish language learners.*
185. Nathaniel Lartey (2020). *A neurolinguistic approach to the processing of resumption in Akan focus constructions.*

186. Bernard Amadeus Jaya Jap (2020). *Syntactic Frequency and Sentence Processing in Standard Indonesian*.
187. Ting Huang (2020). *Learning an L2 and L3 at the same time: help or hinder?*.
188. Anke Herder (2020). *Peer talk in collaborative writing of primary school students: A conversation analytic study of student interaction in the context of inquiry learning*.
189. Ellen Schep (2020). *Attachment in interaction: A conversation analytic study on dinner conversations with adolescents in family-style group care*.
190. Yulia Akinina (2020). *Individual behavioural patterns and neural underpinnings of verb processing in aphasia*.
191. Camila Martinez Rebolledo (2020). *Comprehending the development of reading difficulties in children with SLI*.
192. Jakolien den Hollander (2021). *Distinguishing a phonological encoding disorder from Apraxia of Speech in individuals with aphasia by using EEG*.
193. Rik van Noord (2021). *Character-based Neural Semantic Parsing*.
194. Anna de Koster (2021). *Acting Individually or Together? An Investigation of Children's Development of Distributivity*.
195. Frank Tsiwah (2021). *Time, tone and the brain: Behavioral and neurophysiological studies on time reference and grammatical tone in Akan*.
196. Amélie la Roi (2021). *Idioms in the Aging Brain*.
197. Nienke Wolthuis (2021). *Language impairments and resting-state EEG in brain tumour patients: Revealing connections*.

GRODIL

Center for Language and Cognition Groningen (CLCG)

P.O. Box 716

9700 AS Groningen

The Netherlands