UNIVERSITY OF THESSALY
SCHOOL OF HEALTH SCIENCES

FACULTY OF MEDICINE

DEPARTMENT OF NEUROSURGERY
Director: Professor Kostas Fountas

Doctoral Dissertation

"THE ASSESSMENT OF LANGUAGE FUNCTIONS IN AWAKE CRANIOTOMIES"

by

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Speech-Language Therapist

Submitted with the aim to fulfil
part of the requirements of the
PhD title acquisition
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The approval of the PhD thesis by the Faculty of Medicine of the School of Health Sciences does not declare the approval of the author’s believes (according to the article 202, paragraph 2 of N.5343/1932).

Approved by the members of the Examination Committee (2η/22.09.2021 ΓΣΕΣ)

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2nd Examiner	**Ilias Papathanasiou** Professor, Speech-Language Pathology, Department of Speech and Language Therapy, University of Patras
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5th Examiner	**Konstantinos Paterakis** Associate Professor, Neurosurgery, Faculty of Medicine, University of Thessaly
6th Examiner	**Nikolaos Christodoulou** Associate Professor, Psychiatry, Faculty of Medicine, University of Thessaly
7th Examiner	**Damianos Sakas** Professor, Neurosurgery, Department of Neurosurgery, National & Kapodistrian University of Athens

Preface - Acknowledgements

About four years ago, I embarked on a journey into uncharted waters. The field of neurosurgery was unfamiliar to me, while my knowledge on awake brain surgery was superficial and limited. Today, after voyaging for a while in this ocean called "human brain", endowed with knowledge, emotions, and experience, not only do I not feel that this journey ends, but I am looking forward to what the future holds. Although it is well known that doctoral dissertations are lonely journeys, I was lucky enough to "travel" with some great people.

First, I would like to thank all people I worked with to carry out this project, and especially the three-member advisory committee for their support and guidance. I am particularly grateful to the principal supervisor, professor of neurosurgery Konstantinos Fountas, who gave me the opportunity to discover the incredible world of neurosurgery and enter the fascinating field of awake brain surgeries. The contribution of the third supervisor, neuroradiologist Eftychia Kapsalaki, was very important to acquire essential neuroimaging knowledge, which was necessary for the present dissertation. Of course, I would like to give special thanks to my mentor in speech-language pathology, who pushed me to take this step, guided me scientifically, and provided me with, not only academic but also psychological support, professor of speech-language pathology Ilias Papathanassiou.

I would also like to thank all the nursing and medical staff with whom I have collaborated in past years in the Department of Neurosurgery of the General University Hospital of Larissa. Particularly, the attending neurosurgeons Anastasia Tasiou, Mpampis Gatos, and Alexandros Brotis, as well as the intern neurosurgeons Thanos Paschalis, Alkis Tzanis, Christos Tzerefos, Xanthi Lamprianou, Vassilis Papastergiou, Diamantis Kalogeras, and Giannis Theofanis with whom I shared knowledge, experience, setbacks, and successes. Finally, I would like to express my gratitude to the former scientific partner of the department, neurosurgeon Iordanis Georgiadis for all his insights and assistance, especially during my first year in this doctorate program.

Inside the operating room, I had the chance to collaborate with some phenomenal scientists and professionals. I would especially like to thank the anesthesiologist Argyro Petsiti, for the valuable knowledge she provided regarding the field of anesthesiology, as well as for her excellent cooperation, especially during the awake stages. At this point I ought to mention the patients that I was lucky enough to meet. These great people have always shown courage, even in the most difficult times. The connection that I had with each patient underwent awake craniotomy was unique, and they all have a special place in my soul.

Finally, I would like to dedicate this work to the most important person in my life, my wife Cleopatra, and thank her for her support, love, and patience.

Brief Curriculum Vitae

Education

2017 – 2021

PhD Student

Department of Neurosurgery, Faculty of Medicine

University of Thessaly

2014 – 2016

Master of Science, Linguistics

Department of Linguistics, Faculty of Philology

University of Patras

Dissertation focused on neurolinguistics.

2010 – 2014

Bachelor of Science, Speech-Language Therapy

Department of Speech-Language Therapy

Technological Educational Institute of Patras (current University of Patras)

Thesis focused on language acquisition.

Academic awards and honors

2018 – 2021

Three-year scholarship to pursue a PhD, from the Greek State Scholarships Foundation (IKY). Project: "Strengthening Human Resources Research Potential via Doctorate Research" (MIS-5000432), implemented by the State Scholarships Foundation (IKY).

2014 & 2016

Graduated with First-Class Honors (Excellent) for both Bachelor's (grade: 8.51) and Master's (grade: 8.88) degrees.

Publications

(see Appendix C for dissertation related academic work and publications)

Papatzalas C, Papathanasiou I, Paschalis T, Tzerefos C, Kapsalaki E, Petsiti A, Fountas K. Left inferior longitudinal fascicle and reading: Exploring their relationship through a brain stimulation case study. Communic Dis Quart. Forthcoming 2021.

Papatzalas C, Fountas K, Kapsalaki E, Papathanasiou I. Language Disorders in Neurosurgery. In: Coppens P, Papathanasiou I, editors. Aphasia and Related Neurogenic Communication Disorders. 3rd ed. Burlington, MA: Jones and Bartlett Publishers; 2021. p. 581-601.

Papatzalas C, Fountas K, Kapsalaki E, Papathanasiou I. The use of standardized intraoperative language tests in awake craniotomies: A scoping review. Neuropsychol Rev. 2021 Mar 31:1-31. doi: 10.1007/s11065-021-09492-6. Epub ahead of print.

Papatzalas C, Fountas K, Brotis A, Kapsalaki E, Papathanasiou I. The Greek linguistic assessment for awake brain surgery: development process and normative data. Clin Linguist Phon. 2021 May 4;35(5):458-488. doi: 10.1080/02699206.2020.1792997. Epub 2020 Jul 15.

Georgiou, R., Papatzalas, C. Terzi, A. A non-finite period in early Cypriot Greek? In: Ralli A, Koutsoukos N & Bompolas S, (editors). Proceedings of the 6th International Conference on Modern Greek Dialects & Linguistic Theory. Patras, Greece: University of Patras; 2016. p. 52-62. doi: 10.26220/mgdlt.v6i1.2672

Conference presentations and posters

23 NOVEMBER 2019

Papatzalas C, Fountas K, Kapsalaki E, Papathanasiou I. The role of left inferior longitudinal fascicle in reading: evidence from a brain stimulation case study. Poster session presented at: Annual Convention of the American Speech-Language-Hearing Association; 2019 November 21-23; Orlando, FL.

6 MAY 2019

Papatzalas, C. Cortical & subcortical anatomy. Workshop session presented at: Functional anatomy workshop, Intracranial Glioma Workshop: from A to Z; 2019 May 6-8; Athens, Greece.

6 MAY 2019

Papatzalas C, Fountas K, Paschalis T, Tzerefos C, Kapsalaki E, Petsiti A, Papathanasiou I. The role of left inferior longitudinal fascicle in reading: evidence from a case study. e-Poster session presented at: Intracranial Glioma Workshop from A to Z; 2019 May 6-8; Athens, Greece.

28 SEPTEMBER 2014

Georgiou, R., Papatzalas, C. & Terzi, A. (2014, September). A non-finite period in early Cypriot Greek? Paper presented at the meeting of 6th International Conference on Modern Greek Dialects & Linguistic Theory, University of Patras, Greece.

Research experience

2017 – 2021

Doctoral researcher

Department of Neurosurgery, Faculty of Medicine, University of Thessaly, Greece

Development, standardization, and intraoperative administration of the first Greek intraoperative language assessment for awake brain surgery. Conduction of numerous psycholinguistic experiments on healthy and pathological populations.

MAY - JUNE 2016

Postgraduate student

Department of Linguistics, Faculty of Philology, University of Patras, Greece

Field research on healthy participants and patients with Alzheimer's disease in the context of master's dissertation. The investigation lasted for two months and included visits and sessions on a weekly basis to the private psychiatric clinic "Renaissance [Αναγέννηση]" M. Thomas (Larisa, Greece).

2013 – 2015

Undergraduate research assistant in Greece

Institute of Linguistics, University of Stuttgart, Germany

DFG-Projekt AL 554/7-1, Prof. Dr. Artemis Alexiadou (project leader)

Research assistant in Greece, responsible for collecting and transcribing spontaneous oral speech from two monolingual Greek speaking children (3-6 years old) and their parents. The investigation lasted for two years and included visits and sessions on monthly basis to participants' homes. http://ifla.uni-stuttgart.de/index.php?article_id=168&clang=1

Lectures and academic services

2017 - 2021

Invited speaker in several undergraduate and postgraduate courses of the Faculty of Medicine, University of Thessaly, and other institutions (**see Appendix C** of the current dissertation for details).

20-22 MAY 2016

Member of the organizing committee of the 4th Patras International Conference of Graduate Students in Linguistics (PICGL 4).

Department of Linguistics, Faculty of Philology, University of Patras, Greece.

19-23 AUGUST 2013

Attended the International Speech-Language Therapy Summer School in Patras organized by the Department of Speech-Language Therapy of the Technological Educational Institute of Patras and 18 other universities.

28-29 SEPTEMBER 2012
Member of the organizing committee of the 4th Language Disorders in Greek conference (4th LDG). Department of Speech-Language Therapy, Technological Educational Institute of Patras.

2010 – 2011
President of the Greek branch of the National Student Speech Language Hearing Association (Chapter President - TEI of Patras NSSLHA Chapter).

Professional credentials and memberships

17 FEBRUARY 2015
Credential ID to practice speech-language therapy in Greece: 44407/751. Issuing authority: Region of Western Greece.

Member of the Hellenic Society for Neuroscience (HSfN).

Member of the Greek Association of Speech-Language Therapists (ΣΕΛΛΕ).

Translations and editing

MAY 2015 – JULY 2016
Member of the Greek translating team of the textbook “Articulation and phonological disorders: Speech sound disorders in children” Bernthal J, Bankson N & Flipsen P, (2016).
Editor of the Greek version: Prof. Ilias Papathanasiou

MARCH 2015 – JUNE 2015
Language editing on the Greek version of the textbook “Dysphagia: Clinical management in adults and children” Groher & Crary (2015).
Editor of the Greek version: Prof. Ilias Papathanasiou

Doctoral Dissertation

"THE ASSESSMENT OF LANGUAGE FUNCTIONS IN AWAKE CRANIOTOMIES"

CHRISTOS G. PAPATZALAS
University of Thessaly, Faculty of Medicine, 2021

THREE-MEMBERED CONSULTATION COMMITTEE

1. **Kostas Fountas,** Professor of Neurosurgery, Department of Neurosurgery, Faculty of Medicine, School of Health Sciences, University of Thessaly ***(Supervisor)***

2. **Ilias Papathanasiou,** Professor of Speech-Language Pathology, Department of Speech-Language Therapy, School of Health Rehabilitation Sciences, University of Patras

3. **Eftychia Kapsalaki,** Professor of Neuroradiology, Faculty of Medicine, School of Health Sciences, University of Thessaly

Abstract

Background. Awake brain surgery (or awake craniotomy) is a type of surgical procedure performed on the brain, while the patient is fully awake and participates in various tasks. The mapping process (positive or negative) is typically conducted with direct electrical stimulation which is used to identify eloquent brain areas and protect them from the resection. Awake craniotomy is extremely valuable in diffuse brain tumors, in which the neurosurgical team must optimize the balance between tumor removal and risk of postsurgical tumor-related language disorders. The assessed functions may differ on each patient and range from simple motor skills to communication and emotions. Although the assessment of language is considered an essential part of awake brain surgery, this field is considered extremely heterogeneous.

Aims and objectives. The aims of the current doctoral dissertation were multiple. A review of the awake craniotomy literature was conducted to reveal gaps, strengths, and limitations of the current practice. The acquired information were utilized to develop a new Greek language test, specifically for intraoperative use. The test had to be standardized on Greek healthy population and validated on patients undergoing awake brain surgery, while its effectiveness was also addressed. Finally, a protocol comprised of the newly developed test, and other well-known cognitive and language tests, was used in order to investigate the pre-, intra-, and postoperative language abilities of several brain tumor patients.

Materials and Methods. In order to conduct the review, I used the extended PRISMA template for scoping reviews (PRISMA-ScR). Regarding the test development, I took into account all the special restrictions of the intraoperative language assessment, and I followed proposals of other, relative studies. The normative data were acquired from a sample of healthy participants consisting of 80 consecutively selected individuals, while 80 additional individuals participated in various experiments. Data from nine brain tumor patients were used to calculate convergent and discriminant validity. The language abilities of the 21 patients that went through awake craniotomy to our institution are presented in a case series study design. Finally, the data of 8 brain tumor patients were used in order to investigate the effectiveness of the test.

Results. The scoping review revealed great heterogeneity among different teams in assessment methodologies. Three standardized tests developed specifically for intraoperative use were analyzed and critically reviewed. Regarding the normative data of the developed Greek test (GLAABS), only a few interactions of demographic variables were found on the results. Most differences were found between age groups, in which older participants

performed slightly worse than younger ones. Concerning its clinical use, GLAABS assisted the neurosurgeons to achieve total and subtotal tumor resections in 64% of our patients. The postoperative results revealed that the performed awake craniotomies did not significantly alter the language abilities of our patients. The mean extent of resection (approximately 86%) was found to be similar with reports in the literature regarding awake craniotomies, and higher compared to reports for general anesthesia. With respect to the linguistic deficits, our findings agree with studies that suggest a high rate of new early deficits after awake craniotomy, which dramatically decrease after a few months, with or without speech-language therapy.

Conclusions. The findings from the current dissertation support the use of GLAABS in awake craniotomies in order to assist the neurosurgeons achieve greater resections without compromising the postsurgical neuropsychological functions of the patients.

ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΙΑΣ
ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ ΥΓΕΙΑΣ

ΤΜΗΜΑ ΙΑΤΡΙΚΗΣ

ΝΕΥΡΟΧΕΙΡΟΥΡΓΙΚΗ ΚΛΙΝΙΚΗ
Διευθυντής: καθηγητής Κωνσταντίνος Φουντάς

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«Η ΑΞΙΟΛΟΓΗΣΗ ΤΩΝ ΔΙΕΡΓΑΣΙΩΝ ΤΟΥ ΛΟΓΟΥ ΣΤΙΣ ΚΡΑΝΙΟΤΟΜΕΣ ΣΕ ΑΦΥΠΝΙΣΗ»

υπό

ΧΡΗΣΤΟΥ Γ. ΠΑΠΑΤΖΑΛΑ
Λογοθεραπευτή

Υπεβλήθη για την εκπλήρωση μέρους των
απαιτήσεων για την απόκτηση
Διδακτορικού Διπλώματος
Λάρισα, 2021

Επιχειρησιακό Πρόγραμμα
Ανάπτυξη Ανθρώπινου Δυναμικού,
Εκπαίδευση και Διά Βίου Μάθηση
Με τη συγχρηματοδότηση της Ελλάδας και της Ευρωπαϊκής Ένωσης

Το έργο συγχρηματοδοτείται από την Ελλάδα και την Ευρωπαϊκή Ένωση (Ευρωπαϊκό Κοινωνικό Ταμείο) μέσω του Επιχειρησιακού Προγράμματος «Ανάπτυξη Ανθρώπινου Δυναμικού, Εκπαίδευση και Διά Βίου Μάθηση», στο πλαίσιο της Πράξης «Ενίσχυση του ανθρώπινου ερευνητικού δυναμικού μέσω της υλοποίησης διδακτορικής έρευνας – 2ος Κύκλος» (MIS-5000432), που υλοποιεί το Ίδρυμα Κρατικών Υποτροφιών (ΙΚΥ).

Η έγκριση της διδακτορικής διατριβής από το Τμήμα Ιατρικής της Σχολής Επιστημών Υγείας του Πανεπιστημίου Θεσσαλίας δεν υποδηλώνει αποδοχή των απόψεων του συγγραφέα (σύμφωνα με τις διατάξεις του άρθρου 202, παράγραφος 2 του Ν.5343/1932).

Εγκρίθηκε από τα Μέλη της Επταμελούς Εξεταστικής Επιτροπής (2η/22.09.2021 ΓΣΕΣ)

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2ος Εξεταστής	**Ηλίας Παπαθανασίου** Καθηγητής, Λογοπαθολογία, Τμήμα Λογοθεραπείας, Πανεπιστήμιο Πατρών
3ος Εξεταστής	**Ευτυχία Καψαλάκη** Καθηγήτρια, Νευροακτινολογία, Τμήμα Ιατρικής, Πανεπιστήμιο Θεσσαλίας
4ος Εξεταστής	**Ευθύμιος Δαρδιώτης** Αναπληρωτής Καθηγητής, Νευρολογία, Τμήμα Ιατρικής, Πανεπιστήμιο Θεσσαλίας
5ος Εξεταστής	**Κωνσταντίνος Πατεράκης** Αναπληρωτής Καθηγητής, Νευροχειρουργική, Τμήμα Ιατρικής, Πανεπιστήμιο Θεσσαλίας
6ος Εξεταστής	**Νικόλαος Χριστιδούλου** Αναπληρωτής Καθηγητής, Ψυχιατρική, Τμήμα Ιατρικής, Πανεπιστήμιο Θεσσαλίας
7ος Εξεταστής	**Δαμιανός Σακάς** Καθηγητής, Νευροχειρουργική, Τμήμα Ιατρικής, Εθνικό και Καποδιστριακό Πανεπιστήμιο Αθηνών

Πρόλογος - Ευχαριστίες

Πριν από περίπου τέσσερα χρόνια, ξεκινούσα ένα ταξίδι, το οποίο ήταν ταξίδι σε αχαρτογράφητα νερά. Η επαφή μου με τις κρανιοτομές σε αφύπνιση ήταν επιφανειακή και η νευροχειρουργική, σαν επιστημονικό πεδίο, ανοικείο. Σήμερα, εφοδιασμένος με γνώσεις, συναισθήματα, και εμπειρίες, και έχοντας περιηγηθεί έστω και για λίγο σε αυτόν τον ωκεανό που ονομάζεται «ανθρώπινος εγκέφαλος» όχι μόνο δεν νιώθω ότι το ταξίδι σταματά, αλλά αδημονώ για την συνέχεια. Αν και είναι γνωστό ότι οι διδακτορικές διατριβές είναι μοναχικά ταξίδια, ήμουν αρκετά τυχερός να συναντήσω και να συμπορευτώ με μερικούς εξαιρετικούς ανθρώπους.

Πρώτα απ' όλα θα ήθελα να ευχαριστήσω όλα τα άτομα με τα οποία συνεργάστηκα για να φέρω εις πέρας τον παρόν έργο, και ιδιαίτερα την τριμελή συμβουλευτική επιτροπή για τη βοήθεια, την καθοδήγηση, και τις προοπτικές που μου παρείχαν. Αισθάνομαι ιδιαίτερη ευγνωμοσύνη προς τον πρώτο επιβλέποντα αυτής της έρευνας, καθηγητή νευροχειρουργικής Κωνσταντίνο Φουντά, ο οποίος μου έδωσε την ευκαιρία να γνωρίσω τον απίθανο κόσμο της νευροχειρουργικής και να εισέλθω στον συναρπαστικό χώρο των χειρουργείων για χωροκατακτητικές εξεργασίες του εγκεφάλου με την μέθοδο της κρανιοτομής σε αφύπνιση. Η συμβολή της δεύτερης συνεπιβλέπουσας, νευροακτινολόγου Ευτυχίας Καψαλάκη, ήταν επίσης σημαντική, καθώς κατάφερα να αποκτήσω ουσιώδεις νευροαπεικονιστικές γνώσεις, που ήταν απαραίτητες για την παρούσα διατριβή. Φυσικά, ιδιαίτερες ευχαριστίες θα ήθελα να δώσω στον πρώτο συνεπιβλέποντα και μέντορά μου στην λογοθεραπεία, ο οποίος με ώθησε να κάνω αυτό το βήμα, με καθοδήγησε επιστημονικά, και μου παρείχε όχι μόνο ακαδημαϊκή αλλά και ψυχολογική υποστήριξη, τον καθηγητή λογοπαθολογίας Ηλία Παπαθανασίου.

Θα ήθελα, επίσης, να ευχαριστήσω όλο το νοσηλευτικό και ιατρικό προσωπικό με το οποίο συνεργάστηκα τα τελευταία χρόνια στην κλινική νευροχειρουργικής του Πανεπιστημιακού Γενικού Νοσοκομείου Λάρισας. Οι επιμελητές νευροχειρουργικής Αναστασία Τάσιου, Μπάμπης Γάτος, και Αλέξανδρος Μπρότης, καθώς επίσης και οι ειδικευόμενοι νευροχειρουργοί Θάνος Πασχάλης, Άλκης Τζάνης, Χρήστος Τζερεφός, Ξανθή Λαμπριανού, Βασίλης Παπαστεργίου, Διαμαντής Καλογεράς, και Γιάννης Θεοφάνης αποδείχθηκαν όλοι άξιοι επιστήμονες και εξαιρετικοί συνεργάτες, με τους οποίους μοιράστηκα γνώση, εμπειρίες, επιτυχίες, αναποδιές, και χαρές. Τέλος, θα ήθελα να εκφράσω την ευγνωμοσύνη μου στον πρώην επιστημονικό συνεργάτη της κλινικής, νευροχειρουργό Ιορδάνη Γεωργιάδη ο οποίος μου παρείχε αμέριστη βοήθεια σε επιστημονικό αλλά και πρακτικό επίπεδο.

Κατά την παρουσία μου στην χειρουργική αίθουσα συνεργάστηκα άψογα με το εξαιρετικό νοσηλευτικό και τεχνικό προσωπικό των χειρουργείων, καθώς επίσης και με τα υπόλοιπα μέλη της ομάδας των κρανιοτομών σε αφύπνιση. Θα ήθελα να ευχαριστήσω

ιδιαίτερα την αναισθησιολόγο Αργυρώ Πετσίτη, για τις πολύτιμες γνώσεις που μου παρείχε σχετικά με την επιστήμη της αναισθησιολογίας, καθώς επίσης για την άψογη συνεργασία της, ειδικά κατά την διάρκεια των σταδίων αφύπνισης. Σε αυτό το σημείο πρέπει να αναφερθώ στους ασθενείς που είχα την τύχη να γνωρίσω. Πρόκειται για εξαιρετικούς ανθρώπους που πάντα έδειχναν θάρρος, ακόμα και στις πιο δύσκολες στιγμές. Η σύνδεση που ερχόταν με κάθε ασθενή που υποβαλλόταν σε κρανιοτομή σε αφύπνιση ήταν μοναδική, και όλοι τους έχουν μία ξεχωριστή θέση στην ψυχή μου.

Τέλος, θα ήθελα να αφιερώσω το παρόν έργο στον σημαντικότερο άνθρωπο στη ζωή μου, την γυναίκα μου Κλεοπάτρα, και να την ευχαριστήσω για την αμέριστη υποστήριξή της, την αγάπη της, και φυσικά την υπομονή της.

Σύντομο Ακαδημαϊκό Βιογραφικό

Εκπαίδευση

2017 – 2021

Υποψήφιος Διδάκτωρ

Κλινική Νευροχειρουργικής, Τμήμα Ιατρικής

Πανεπιστήμιο Θεσσαλίας

2014 – 2016

Μεταπτυχιακό Δίπλωμα Ειδίκευσης, Γλωσσολογία

Τομέας Γλωσσολογίας, Τμήμα Φιλολογίας

Πανεπιστήμιο Πατρών

Μεταπτυχιακή διατριβή στη νευρογλωσσολογία

2010 – 2014

Πτυχίο, Λογοθεραπεία

Τμήμα Λογοθεραπείας

Ανώτατο Τεχνολογικό Εκπαιδευτικό Ίδρυμα Πατρών (νυν Πανεπιστήμιο Πατρών)

Πτυχιακή έρευνα στην γλωσσική κατάκτηση

Ακαδημαϊκές διακρίσεις και υποτροφίες

2018 – 2021

Λήψη τριετούς υποτροφίας από το Ίδρυμα Κρατικών Υποτροφιών (ΙΚΥ) για διεξαγωγή διδακτορικής έρευνας. Πράξη «Ενίσχυση του ανθρώπινου ερευνητικού δυναμικού μέσω της υλοποίησης διδακτορικής έρευνας» MIS-5000432

2014 & 2016

Αριστούχος σε όλες τις ακαδημαϊκές σπουδές με βαθμούς 8.51 (Λογοθεραπεία, Πτυχίο) και 8.88 (Γλωσσολογία, ΜΔΕ) αντίστοιχα

Επιστημονικές δημοσιεύσεις

(στο Appendix C παρουσιάζεται αναλυτικά όλο το ακαδημαϊκό έργο και οι δημοσιεύσεις που σχετίζονται με την παρούσα διατριβή)

Papatzalas C, Papathanasiou I, Paschalis T, Tzerefos C, Kapsalaki E, Petsiti A, Fountas K. Left inferior longitudinal fascicle and reading: Exploring their relationship through a brain stimulation case study. Communic Dis Quart. Forthcoming 2021.

Papatzalas C, Fountas K, Kapsalaki E, Papathanasiou I. Language Disorders in Neurosurgery. In: Coppens P, Papathanasiou I, editors. Aphasia and Related Neurogenic Communication Disorders. 3rd ed. Burlington (MA): Jones and Bartlett Publishers; 2021. p. 581-601.

Papatzalas C, Fountas K, Kapsalaki E, Papathanasiou I. The use of standardized intraoperative language tests in awake craniotomies: A scoping review. Neuropsychol Rev. 2021 Mar 31:1-31. doi: 10.1007/s11065-021-09492-6. Epub ahead of print.

Papatzalas C, Fountas K, Brotis A, Kapsalaki E, Papathanasiou I. The Greek linguistic assessment for awake brain surgery: development process and normative data. Clin Linguist Phon. 2021 May 4;35(5):458-488. doi: 10.1080/02699206.2020.1792997. Epub 2020 Jul 15.

Georgiou, R., Papatzalas, C. Terzi, A. A non-finite period in early Cypriot Greek? In: Ralli A, Koutsoukos N & Bompolas S, (editors). Proceedings of the 6th International Conference on Modern Greek Dialects & Linguistic Theory. Patras, Greece: University of Patras; 2016. p. 52-62. doi: 10.26220/mgdlt.v6i1.2672

Προφορικές επιστημονικές παρουσιάσεις

23 ΝΟΕΜΒΡΙΟΥ 2019

Papatzalas C, Fountas K, Kapsalaki E, Papathanasiou I. The role of left inferior longitudinal fascicle in reading: evidence from a brain stimulation case study. Poster session presented at: Annual Convention of the American Speech-Language-Hearing Association; 2019 November 21-23; Orlando, FL.

6 ΜΑΙΟΥ 2019

Papatzalas, C. Cortical & subcortical anatomy. Workshop session presented at: Functional anatomy workshop, Intracranial Glioma Workshop: from A to Z; 2019 May 6-8; Athens, Greece.

6 ΜΑΙΟΥ 2019

Papatzalas C, Fountas K, Paschalis T, Tzerefos C, Kapsalaki E, Petsiti A, Papathanasiou I. The role of left inferior longitudinal fascicle in reading: evidence from a case study. e-Poster session presented at: Intracranial Glioma Workshop from A to Z; 2019 May 6-8; Athens, Greece.

28 ΣΕΠΤΕΜΒΡΙΟΥ 2014

Georgiou, R., Papatzalas, C. & Terzi, A. (2014, September). A non-finite period in early Cypriot Greek? Paper presented at the meeting of 6th International Conference on Modern Greek Dialects & Linguistic Theory, University of Patras, Greece.

Ερευνητική εμπειρία

2017 – 2021

Διδακτορικός ερευνητής

Κλινική Νευροχειρουργικής, Τμήμα Ιατρικής, Πανεπιστήμιο Θεσσαλίας

Ανάπτυξη, στάθμιση και διεγχειρητική χορήγηση του πρώτου Ελληνικού πρωτοκόλλου αξιολόγησης λόγου/ομιλίας για ασθενείς που υποβάλλονται σε κρανιοτομές σε αφύπνιση (awake craniotomies) για αφαιρέσεις όγκων. Το πλήθος των ψυχογλωσσολογικών πειραμάτων που διεξήχθησαν στα πλαίσια της παρούσας διδακτορικής έρευνας αφορούσαν ασθενείς και υγιή πληθυσμό και περιγράφονται με λεπτομέρεια στα επόμενα κεφάλαια.

ΜΑΪΟΣ - ΙΟΥΝΙΟΣ 2016

Μεταπτυχιακός φοιτητής

Τομέας Γλωσσολογίας, Τμήμα Φιλολογίας, Πανεπιστήμιο Πατρών

Έρευνα πεδίου σε ασθενείς με νόσο Alzheimer στα πλαίσια εκπόνησης της μεταπτυχιακής διπλωματικής διατριβής. Η έρευνα περιλάμβανε επισκέψεις στην ιδιωτική ψυχιατρική κλινική «Αναγέννηση» του Μ. Θωμά στη Λάρισα και συνεδρίες με ασθενείς με νόσο Alzheimer.

2013 – 2015

Προπτυχιακός βοηθός έρευνας στην Ελλάδα

Institute of Linguistics, University of Stuttgart, Germany

DFG-Projekt AL 554/7-1, Prof. Dr. Artemis Alexiadou (project leader)

Βοηθός έρευνας στην Ελλάδα στο ερευνητικό πρόγραμμα DFG –Projekt AL 554/7-1 του Πανεπιστημίου Στουτγάρδης. Υπεύθυνος για τη συλλογή και απομαγνητοφώνηση αυθόρμητου προφορικού λόγου από δύο μονόγλωσσα παιδιά (3-6 ετών) με μητρική γλώσσα την Ελληνική και τους γονείς τους, σε μηνιαία βάση για διάστημα δύο ετών.

http://ifla.uni-stuttgart.de/index.php?article_id=168&clang=1

Ακαδημαϊκή δραστηριότητα

2017 - 2021

Παραχώρηση διαλέξεων ως καλεσμένος ομιλητής σε διάφορα προπτυχιακά και μεταπτυχιακά μαθήματα του τμήματος Ιατρικής του Πανεπιστημίου Θεσσαλίας αλλά και άλλων Ιδρυμάτων (**βλ. Appendix C** της παρούσας διατριβής)

20-22 ΜΑΪΟΥ 2016

Μέλος της Οργανωτικής Επιτροπής του 4ου Διεθνούς Συνεδρίου Μεταπτυχιακών Φοιτητών Γλωσσολογίας του Πανεπιστημίου Πατρών (4th PICGL – Patras International Conference of Graduate Students in Linguistics)
Πανεπιστήμιο Πατρών, Τμήμα Φιλολογίας, 20 – 22 Μαΐου 2016

19-23 ΑΥΓΟΥΣΤΟΥ 2013
Παρακολούθηση Διεθνούς Θερινού Σχολείου στη Λογοθεραπεία (Speech language Therapy Summer School in Patras)
Διοργάνωση: Τμήμα Λογοθεραπείας, ΑΤΕΙ Πατρών (συνδιοργάνωση με άλλα 18 Πανεπιστήμια)

28-29 ΣΕΠΤΕΜΒΡΙΟΥ 2012
Μέλος της Οργανωτικής Επιτροπής του 4ου Συνεδρίου Ελληνική Γλώσσα και Διαταραχές (4th LDG - Language Disorders in Greek).
ΑΤΕΙ Πατρών, Τμήμα Λογοθεραπείας, 28-29 Σεπτεμβρίου 2012

2010 – 2011
Πρόεδρος του παρατήματος της Αμερικανικής Ένωσης Φοιτητών Λογοπαθολογίας και Ακοολογίας στο ΤΕΙ Πατρών (Chapter President - TEI of Patras NSSLHA Chapter)

Επαγγελματικές πιστοποιήσεις και συνδρομές

17 ΦΕΒΡΟΥΑΡΙΟΥ 2015
Άδεια ασκήσεως επαγγέλματος Λογοθεραπευτή. Αρ. πρωτοκόλλου: 44407/751. Αρχή έκδοσης: Περιφέρεια Δυτικής Ελλάδος

Μέλος της Ελληνικής Εταιρίας Νευροεπιστημών (ΕΕΝ)

Μέλος του Συλλόγου Επιστημόνων Λογοθεραπευτών-Λογοπαθολόγων Ελλάδος (ΣΕΛΛΕ)

Επιμέλειες και μεταφράσεις

ΜΑΙΟΣ 2015 – ΙΟΥΛΙΟΣ 2016
Μέλος της μεταφραστικής ομάδας του επιστημονικού βιβλίου Articulation and phonological disorders: Speech sound disorders in children (Αρθρωτικές και Φωνολογικές διαταραχές: Οι διαταραχές των λεκτικών ήχων στα παιδιά) των Bernthal J, Bankson N & Flipsen P, (2016).
Επιμέλεια Ελληνικής έκδοσης: Δρ. Ηλίας Παπαθανασίου

ΜΑΡΤΙΟΣ 2015 – ΙΟΥΝΙΟΣ 2015

Γλωσσική επιμέλεια και διορθώσεις του επιστημονικού βιβλίου Dysphagia: Clinical management in adults and children (Δυσφαγία: Κλινική διαχείριση παιδιών και ενηλίκων) των Groher & Crary (2015). Επιμέλεια Ελληνικής έκδοσης: Δρ. Ηλίας Παπαθανασίου

Διδακτορική Διατριβή

«Η ΑΞΙΟΛΟΓΗΣΗ ΤΩΝ ΔΙΕΡΓΑΣΙΩΝ ΤΟΥ ΛΟΓΟΥ ΣΤΙΣ ΚΡΑΝΙΟΤΟΜΕΣ ΣΕ ΑΦΥΠΝΙΣΗ»

ΧΡΗΣΤΟΣ Γ. ΠΑΠΑΤΖΑΛΑΣ

Πανεπιστήμιο Θεσσαλίας, Τμήμα Ιατρικής, 2021

ΤΡΙΜΕΛΗΣ ΣΥΜΒΟΥΛΕΥΤΙΚΗ ΕΠΙΤΡΟΠΗ

2.1. **Κωνσταντίνος Φουντάς,** καθηγητής Νευροχειρουργικής, Τμήμα Ιατρικής, Σχολή Επιστημών Υγείας, Πανεπιστήμιο Θεσσαλίας ***(Επιβλέπων)***

2.2. **Ηλίας Παπαθανασίου,** καθηγητής Λογοπαθολογίας, Τμήμα Λογοθεραπείας, Σχολή Επιστημών Αποκατάστασης Υγείας, Πανεπιστήμιο Πατρών

2.3. **Ευτυχία Καψαλάκη,** καθηγήτρια Νευροακτινολογίας, Τμήμα Ιατρικής, Σχολή Επιστημών Υγείας, Πανεπιστήμιο Θεσσαλίας

Περίληψη

Θεωρητικό υπόβαθρο. Η κρανιοτομή σε αφύπνιση (awake craniotomy) είναι μία νευροχειρουργική επέμβαση για χωροκατακτητικές εξεργασίες του εγκεφάλου, όπου ο ασθενής αφυπνίζεται και αφού αποκτήσει πλήρη συνείδηση καλείται να συμμετάσχει σε διάφορες δοκιμασίες. Κατά το στάδιο αυτό επιτελείται η διαδικασία της χαρτογράφησης η οποία διεξάγεται με άμεσο ηλεκτρικό ερεθισμό (direct electrical stimulation) και έχει στόχο τον εντοπισμό ευγενών εγκεφαλικών περιοχών και κατ' επέκταση την προστασία τους από την εκτομή. Στους διηθητικούς όγκους, η διαδικασία αυτή μπορεί να είναι αρκετά απαιτητική καθώς ο νευροχειρουργός πρέπει να ισορροπεί ανάμεσα στην μέγιστη αφαίρεση του παθολογικού ιστού και τον κίνδυνο μετεγχειρητικών γλωσσικών διαταραχών (ογκολογική αφασία). Οι λειτουργίες που αξιολογούνται διαφέρουν σε κάθε ασθενή και κυμαίνονται από απλές κινητικές δεξιότητες έως επικοινωνία και συναισθήματα. Αν και η εκτίμηση της γλώσσας θεωρείται αναπόσπαστο κομμάτι των κρανιοτομών σε αφύπνιση αυτό το πεδίο θεωρείται εξαιρετικά ετερογενές.

Στόχος. Οι στόχοι της παρούσας διδακτορικής διατριβής ήταν πολλαπλοί. Αρχικά, διεξήχθη ανασκόπηση της βιβλιογραφίας σχετικά με την αξιολόγηση του λόγου κατά τη διάρκεια κρανιοτομών σε αφύπνιση, προκειμένου να αποκαλυφθούν κενά, δυνατά σημεία και περιορισμοί των υπαρχόντων πρακτικών. Οι πληροφορίες που αποκτήθηκαν χρησιμοποιήθηκαν για την ανάπτυξη ενός νέου, ελληνικού τεστ, ειδικά για διεγχειρητική χρήση. Το τεστ έπρεπε να σταθμιστεί σε ελληνικό υγιή πληθυσμό και να ελεγχθεί η εγκυρότητά του σε ασθενείς, ενώ εξετάστηκε επίσης η αποτελεσματικότητά του ως διεγχειρητικό αξιολογητικό εργαλείο. Τέλος, ένα πρωτόκολλο αποτελούμενο από το προαναφερθέν τεστ, καθώς επίσης και από άλλες γνωστές γνωστικές και γλωσσικές δοκιμασίες, χρησιμοποιήθηκε για τη διερεύνηση των προ-, δια- και μετεγχειρητικών γλωσσικών ικανοτήτων αρκετών ασθενών με χωροκατακτητικές εξεργασίες του εγκεφάλου.

Υλικά και μέθοδοι. Προκειμένου να διεξαχθεί ο έλεγχος της βιβλιογραφίας, χρησιμοποιήθηκε το εκτεταμένο πρότυπο PRISMA για διερευνητική ανασκόπηση (scoping review, PRISMA-ScR). Όσον αφορά την ανάπτυξη των δοκιμασιών, ελήφθησαν υπ' όψιν όλοι οι ειδικοί περιορισμοί της διεγχειρητικής γλωσσικής αξιολόγησης καθώς επίσης και προτάσεις άλλων, σχετικών μελετών. Οι νόρμες αποκτήθηκαν από ένα δείγμα υγιών συμμετεχόντων αποτελούμενο από 80 άτομα, ενώ 80 επιπλέον άτομα συμμετείχαν σε διάφορα πειράματα. Τα δεδομένα από 9 ασθενείς με όγκο στον εγκέφαλο χρησιμοποιήθηκαν για τον υπολογισμό της συμβατικής και διακριτικής εγκυρότητας (convergent and discriminant validity). Οι γλωσσικές ικανότητες των 21 ασθενών που υποβλήθηκαν σε κρανιοτομή σε αφύπνιση στην νευροχειρουργική κλινική του Πανεπιστημιακού Γενικού Νοσοκομείου Λάρισας παρουσιάζονται σε μορφή μελέτης σειράς περιπτώσεων (case series). Τέλος, τα δεδομένα 8 ασθενών με όγκο στον εγκέφαλο αξιοποιήθηκαν προκειμένου να διερευνηθεί η αποτελεσματικότητα του τεστ.

Αποτελέσματα. Η διερευνητική ανασκόπηση αποκάλυψε μεγάλη ετερογένεια στις μεθοδολογίες αξιολόγησης. Επίσης εντοπίστηκαν και αναλύθηκαν κριτικά τρία σταθμισμένα αξιολογητικά εργαλεία, ανεπτυγμένα ειδικά για διεγχειρητική χρήση. Η ανάλυση των δεδομένων στάθμισης του ελληνικού τεστ που αναπτύχθηκε στα πλαίσια της παρούσας διατριβής (GLAABS) αποκάλυψε ελάχιστες αλληλεπιδράσεις των δημογραφικών μεταβλητών στα αποτελέσματα. Οι περισσότερες διαφορές εντοπίστηκαν μεταξύ των ηλικιακών ομάδων, όπου οι ηλικιωμένοι συμμετέχοντες παρουσίασαν ελαφρώς χειρότερες επιδόσεις από τους νεότερους. Όσον αφορά την κλινική του χρήση, το GLAABS βοήθησε τους νευροχειρουργούς να επιτύχουν ολικές και υφολικές εκτομές όγκων στο 64% των ασθενών. Τα μετεγχειρητικά αποτελέσματα αποκάλυψαν ότι οι κρανιοτομίες σε αφύπνιση δεν άλλαξαν στατιστικώς σημαντικά τις γλωσσικές ικανότητες των ασθενών μας. Το μέσο εύρος εκτομής (περίπου 86%) βρέθηκε να είναι αφενός παρόμοιο με αναφορές στη βιβλιογραφία σχετικά με τις κρανιοτομές σε αφύπνιση και αφετέρου υψηλότερο σε σύγκριση με επεμβάσεις χωρίς αφύπνιση. Όσον αφορά τα γλωσσικά ελλείμματα, τα ευρήματά συμφωνούν με μελέτες που αναφέρουν υψηλό ποσοστό νέων πρώιμων ελλειμμάτων μετά από κρανιοτομή σε αφύπνιση, τα οποία μειώνονται δραματικά μετά από μερικούς μήνες, με ή χωρίς λογοθεραπεία.

Συμπεράσματα. Τα ευρήματα από τη παρούσα διατριβή υποστηρίζουν τη χρήση του GLAABS σε κρανιοτομίες σε αφύπνιση, προκειμένου να βοηθήσουν τους νευροχειρουργούς να επιτύχουν μεγαλύτερες εκτομές χωρίς να διακυβεύονται μετεγχειρητικά οι λειτουργίες του λόγου των ασθενών.

Contents

Chapter 1. General Introduction[1]

Awake brain surgery (or awake craniotomy) is a type of surgical procedure performed on the brain while the patient is fully awake and alert. After the initial sedation, the patient is awakened in order to respond to various tasks and assist the neurosurgical team to conduct the brain mapping procedure which will help to preserve functional tissue. Although the assessment of language functions is considered an essential part of awake brain surgery, the novel field of intraoperative language assessment is extremely heterogeneous.

For many decades most of neurosurgical teams have allowed the presence of only the absolutely necessary personnel (i.e., neurosurgeons, anesthesiologists, and nurses) inside the operating theatre. As a result, most of the reports in the literature regarding intraoperative language assessment were sparse and limited to general descriptions of the tests. Once various clinicians related to language (such as neuropsychologists, speech-language therapists, clinical linguists) gained access to the operating rooms, more detailed reports began to emerge. However, even today, the lack of international guidelines and communication between various teams continues to pose a major obstacle. Intraoperative language assessment is not an ordinary language assessment. It requires specialized education and clinical skills by the clinician who conducts it, and specialized standardized assessment tools, developed specifically for intraoperative use.

The purpose of mapping in awake craniotomies is to detect eloquent brain areas and create a "functional map" in order to protect them from the resection process. The assessed functions depend on the brain area (or areas) close or within the pathological tissue and range from simple motor skills, to communication and emotions. The notion "maximum resection, minimum deficits", which has been recently considered the ultimate goal in neurosurgery, denotes that neurosurgeons aim to balance between maximal possible resection of the pathological tissue while preserving eloquent structures of the brain and maintaining patients' quality of life [1,2]. During the past three decades, various methods have occasionally been used in order to achieve this goal. Preoperative functional magnetic resonance imaging (fMRI) and diffuse tensor imaging (DTI), preoperative transcranial magnetic stimulation (TMS), intraoperative neuronavigation and DTI, and intraoperative mapping with electrical stimulation (Figure 1.1, next page), have all been used to assist neurosurgeons' surgical plan [3]. Although many of these methods were introduced as promising, there is no longer any doubt that the gold standard -when comes to gliomas- is intraoperative mapping during awake craniotomy [1,2,4,5].

[1]A modified version of this chapter was published as a book chapter: "Papatzalas C, Fountas K, Kapsalaki E, Papathanasiou I. Language Disorders in Neurosurgery. In: Papathanasiou I, Coppens P, editors. Aphasia and related neurogenic communication disorders. 3rd ed. Burlington (MA): Jones and Bartlett Publishers; 2021. p. 581-601."

Figure 1.1
Functional map created in order to preserve language functions. The picture illustrates the mapping procedure that was followed in one of our patients (see Chapter 4). Electrical stimulation of the area assigned with “1” induced anomias, with “2” anomias again, and with “3” semantic and phonemic paraphasias.

The present dissertation discusses these issues and analyzes why proper language assessment with standardized and specialized tools can help the neurosurgeons increase the effectiveness of the surgery and lead to better quality of life for the patients undergoing awake craniotomy. Also, attempts have been made to explore the efficacy of language assessment during brain mapping and awake craniotomy using a specialized linguistic test. This test was developed specifically for intraoperative use and it was administered in 21 patients from the Department of Neurosurgery, University Hospital of Larisa (Greece).

The first chapter provides an introductory overview of some core definitions and notions that will be used later. The second chapter focuses on exploring the literature for standardized intraoperative language tests used by other neurosurgical teams and discusses the findings. The third chapter describes the process of developing and norming a language test, specialized for intraoperative use. The fourth chapter is a case series that describes a series of patients that underwent awake craniotomy in our institution and outlines their language profiles. The pathological population mainly consists of brain tumor patients, and this is why I focus on this disease. However, patients suffering from arteriovenous malformations (AVMs), and medical intractable epilepsy are also included. Finally, the fifth chapter investigates the effectiveness and validity of the intraoperative test presented in Chapter 3, while the last chapter provides a general discussion related to the entire thesis.

1.1. Neurosurgery and language disorders

The neurosurgery field is associated with the prevention, diagnosis, surgical treatment, and rehabilitation of the diseases that affect any part of the nervous system, including the brain, the spinal cord, and other structures of the peripheral nervous system. Surgical procedures of the central nervous system (CNS) and particularly of the brain represent a substantial and important portion of the entire neurosurgical workload [6]. Although the sequelae of traumatic brain injury (TBI) are also considered a significant part of the neurosurgical caseload, this chapter will not include them; instead, we will focus on the speech and language disorders associated with "craniotomies other than trauma in patients over 17 years of age" [6: p.507]. Particularly, in this chapter I will focus on deficits resulting from brain tumors or their surgical treatment, and I will briefly discuss the implications of surgical operations for arteriovenous malformations (AVMs) and medical intractable epilepsy.

Brain tumors are occupying masses that displace neural structures and may not cause neuronal damage for extended periods of time [7]. The most common brain tumors are gliomas, which, along with meningiomas, represent 60% of all brain tumors [8]. Gliomas originate from glial cells; they grow inside the brain parenchyma and invade adjacent structures. On the other hand, meningiomas mostly pressure the brain and are not considered invasive. However, this is true only for grade I meningiomas, as grade III meningiomas are considered invasive and malignant. Surgical removal of the tumor improves the median survival time and time to tumor recurrence; therefore, surgery is considered an effective therapeutic tool [9,10,11,12].

Contrary to diseases in which the brain lesion develops suddenly (such as strokes or TBIs), brain tumors typically grow slowly, allowing neuroplasticity to reorganize or relocate brain functions [2,13]. Severe speech and language deficits due to tumor occurrence are considered rare, while the symptoms from the surgical treatment tend to be transient (for more information, see Chapter 5). In order to better understand the tumor-related language disorders, it is necessary to provide an overview of the underlying mechanisms of brain tumors, specifically regarding gliomas.

1.2. Gliomas and glial cells

Gliomas are neuroepithelial masses caused by uncontrolled and abnormal proliferation of glial (supporting) cells of the brain and may not affect neurons functionality for a long time since the onset [7]. The brain mainly consists of two type of cells [14]: *glial cells* and *neurons*. Neurons receive and transmit electrical signals by sending information throughout the nervous system, which allows us to think, move, speak, and perceive the world around us. Glial cells, which outnumber neurons, have a supportive role by surrounding, insulating, and supplying nutrients and oxygen to neurons. Some common types are astrocytes, oligodendrocytes, microglia, and ependymal cells, and each type serves a different role [14]. Astrocytes, along with oligodendrocytes, make up the majority of glial cells. The former are responsible for several processes, such as providing the blood–brain barrier that prevents unwanted substances to seep in the brain, while the latter mainly form the myelin sheath around neurons' axons. Finally, the microglia are a macrophage-like type of cells, and the ependymal cells form the walls of the brain ventricles.

Gliomas, as their name states, originate from the glial cells. Typically, the diagnosis is defined by an integrated neuropathological term starting with the histopathological classification (e.g., astrocytoma), followed by the World Health Organization (WHO) grade (e.g., grade III) [15]. There are approximately 100 histologically distinct types of primary (not metastatic) brain and CNS tumors [16,17], but since it is beyond the scope of this chapter to discuss them all, I will only discuss the most frequent ones.

Regarding WHO grades, gliomas may vary from non-malignant grade I (e.g.: pilocytic astrocytoma) to highly aggressive grade IV, such as glioblastoma [8]. Low-grade gliomas (grade I and II) represent approximately the 15% of all gliomas [18]. These slow growing brain tumors can evolve in three possible ways. First, by *local growth*, which takes place before any anaplastic degeneration, and has been reported to be about 4mm per year [19]. Second, LGGs might *infiltrate* the white matter pathways of the ipsilateral, or in some cases the contralateral hemisphere via corpus callosum [20]. Finally, it is through *anaplastic transformations* (lasting approximately 7 to 8 years) that LGGs evolve to higher grades, and eventually become fatal, as the median survival time is around 10 years post-onset [21].

Gliomas can also be categorized in two major subgroups according to infiltration patterns they present [22]: *diffuse gliomas*, which typically are malignant (grade III and IV), and *non-diffuse gliomas*, which actually correspond to gliomas showing a more circumscribed and slower growth pattern. Diffuse gliomas are more common and characterized by fast cell reproduction as well as infiltration of nearby tissue [23]. The most common histopathological type is glioblastoma (or glioblastoma multiform), which accounts for approximately one-half of all gliomas [8]. Other less-frequent types are diffuse astrocytoma, pilocytic astrocytoma, anaplastic astrocytoma, oligodendroglioma, and oligoastrocytic and ependymal tumors, while neuronal and mixed neuronal-glial tumors are rare and typically low grade [24].

1.3. Neuroplasticity

Neuroplasticity refers to the ability of the brain to constantly reorganize itself in short-term, middle-term and long-term, and it takes place during phylogenesis, learning, and repairing after injury [25]. Post-lesional plasticity emerges after injury of the peripheral of central nervous system. Neuroplasticity can be observed in macroscopic (functional/behavioral) and macroscopic (ultrastructural) levels and has an essential role in *when* and *how* the symptoms from brain tumors manifest [13]. Numerous studies have reported patients with large brain tumors that lived normal lives and presented an almost normal neurological examination with only slight neuropsychological or linguistic symptoms, or no symptoms at all [26-28]. For instance, Papagno et al. [29] reported a case in which a patient with anaplastic oligodendroglioma (WHO grade III) in the left frontal lobe, whose volume was 118.5 cm^3, did not experience any cognitive or language deficit or personality disorder. According to Duffau [25] the explanation of such phenomena, especially in slow growing brain tumors, can be found in studying the mechanism of neuroplasticity.

Various preoperative functional neuroimaging studies have shown that slow growing brain tumors trigger a reorganization of the language cortical areas, allowing the patients to be free of overt symptoms even for long periods of time. Duffau [25] suggested a “temporospatial” hierarchical model, based on brain tumor and acute lesion studies, in which local reorganizations take place before remote compensations. The model consists of four patterns, from best to worst functional language outcome. In the first pattern, sensorimotor and/or language functions persist within the tumor. This phenomenon is possible when a tumor infiltrates functional brain tissue, but neurons have not yet degenerated [25,30]. This pattern has been observed in low-grade gliomas [31] and, interestingly, also in high-grade, more aggressive gliomas such as glioblastomas and anaplastic astrocytomas [30]. The mass effect, the invasion, and the anaplastic transformation will eventually lead to disruption of functioning neuronal architecture, although the exact time frame is not yet known [25,30]. The second pattern assumes a “within area” mechanism of reorganization, according to which eloquent areas are redistributed immediately around the tumor. Regarding language reorganization, this phenomenon has been observed in patients with gliomas located within the classical Broca’s area but without aphasia, in whom activation of the adjacent left inferior frontal cortex was demonstrated [32]. The third pattern is associated with redistribution of functions ipsilaterally, usually by recruiting other language association areas. For instance, two functional neuroimaging studies have reported activations in the left superior temporal gyrus for patients with gliomas within the Broca’s area [32,33]. Additionally, it has been reported that in case of slow-growing tumors, areas and structures that are not considered “essential” or “classic” for language (e.g., Brodmann’s area [BA] 46, BA 47, supplementary motor area [SMA], cerebellum, putamen) may also be recruited [32,34,35]. In the fourth pattern the contralateral hemisphere compensates for the lost functions, usually the opposite homologous area. This phenomenon may be possible due to a decrease of the transcallosal inhibition of the contralateral brain areas [25]. It has been observed that brain tumors in Broca’s area may trigger translocation to the non-dominant homologous area [36], and the same has been observed regarding Wernicke’s area [37]. It should be noted that a combination of two or more patterns may emerge. For instance, in a large functional neuroimaging study [38] it was observed a combination of the second (activation in left hemisphere) and fourth (activation in contralateral hemisphere) patterns in 60% of the participants. It should also be stressed that similar observations regarding the neuroplasticity patterns have been made for acute lesions too (such as strokes and TBIs)—that is, intrinsic reorganization within injured areas [33,39,40], recruitment of perilesional structures [33,35], recruitment of other regions involved in the language network [41], and recruitment of the contralateral hemisphere [41]. However, there are two major differences between acute lesions and slow-growing brain tumors [25]. It has been observed that in slow growing tumors the compensation within the same hemisphere is possible even by non-linguistic areas [35]. This phenomenon is not very common in acute lesions and it is not yet fully understood in brain tumors. Finally, regarding the fourth pattern, the compensation of the contralateral (non-dominant) hemisphere does not necessarily mark a poor recovery as it is has been proposed in post-stroke aphasia [33,42].

In awake craniotomies, neuroplasticity plays a major role. First, it highlights the importance of brain mapping during awake craniotomies because language has already reorganized to some extent preoperatively [25,29]. This is in line with evidence regarding relocated functions in cortical areas that are not related traditionally with speech or language [35]. Therefore, electrical stimulation and language mapping during awake craniotomy, if done right, can reveal any eloquent cortex inside or around the tumor. Additionally, it has been observed that in some cases there is an acute functional remapping which can take place within 15 to 60 minutes after resection starts [25]. This still poorly understood phenomenon may affect speech production (but not language per se) since it has been reported only for sensorimotor functions [43].

In conclusion, it is evident that atypical functional patterns resulting from neuroplasticity must be taken into consideration in surgical planning, in conducting the intraoperative assessment, and finally in postoperative therapeutic management [25,31].

1.4. Tumor-related language disorders

Aphasia is an acquired language disorder caused by brain damage in the dominant (typically left) hemisphere that affects communicational and social life of the patient [44]. In the current literature, the language deficits due to a brain tumor or its surgical removal are typically called tumor- or cancer-related aphasia in order to distinguish them from the more common post-stroke aphasia. Additional differences also include incidence and prevalence rates and neuropathology. Also, differences exist within the tumor-related aphasia subgroup between preoperative and postoperative language disorders.

Strokes are more common than brain tumors in the United States. There are approximately 795.000 new stroke cases every year [45] while new primary (not metastatic) brain tumor cases are only 18.500 [46]. Typically, metastatic tumors are excluded when studying brain tumors, and only a few studies include or study them specifically. This is mostly because metastatic brain tumors have a poor prognosis and a very low mean survival rate. Additionally, most neurosurgical teams avoid awake brain surgery on patients with metastatic tumors.

Language disorders are more common in primary brain tumors than in stroke patients. Research showed that 37% to 58% of the tumor patients will experience a form of aphasia either from the tumor growth or the surgical resection [47-49], whereas the rate is 21% to 38% for stroke patients [50].

Language impairment is the most common symptom early symptom of brain tumors, as it is estimated that one-third of patients will exhibit aphasia symptoms before the tumor is diagnosed [51]. Patients who exhibit language deficits before surgical treatment are more likely to retain their symptoms after operation compared to those who do not exhibit preoperative language impairment [52]. However, permanent linguistic and cognitive deficits, even in later stages of the disease, are generally considered mild or nonexistent [7]. Severe symptoms are plausible, but are usually limited to aggressive, large, and infiltrative tumors (such as glioblastomas), and/or to later stages of the disease [53,54]. The types of errors that brain tumor patients produce during the preoperative phase are similar to aphasias resulting from other aphasia etiologies (such as acute lesions). Haas et al. [55] reported that the most common speech and language errors associated with tumors are semantic and phonological paraphasias, anomias, fragmentation of sentences, low mean length of utterance (MLU), syntactic errors, and circumlocutions, while neologisms, prosody disorders, and poor speed and fluency are considered rarer. Other disorders include pure alexia and Gerstmann syndrome [56,57].

Traditionally, it was believed that deficits in patients with brain tumors depend on the location and size of the tumor [53]. However, this has been challenged by newer studies that did not find an absolute relationship between brain tumor topography and type of language impairment [51,54,58]. In one of the first systematic studies of tumor-related language disorders, the linguistic performance (measured with Aachen Aphasia Test) of brain tumor patients was not directly correlated with tumor volume [55]. Davie et al. [58] found similar results; that is, although it is possible to list the symptoms associated with tumor-related language disorders, it is very difficult to accurately predict the type of language deficit from the topography of a tumor. There are numerous cases in the literature where patients displayed different types of language impairment secondary to brain tumors in the same location, or patients with similar lesion locations but very dissimilar symptoms, or no symptoms at all [7,55.59,60]. As already mentioned earlier in this chapter, the mechanism behind these unusual phenomena is *neuroplasticity*, which, combined with slow tumor growth rate, can delay the appearance or the severity of the symptoms significantly. By contrast, in post-stroke aphasia or TBIs, the damage occurs abruptly and catastrophically, and the functions are lost immediately before the brain begins the neuroplastic procedures [25].

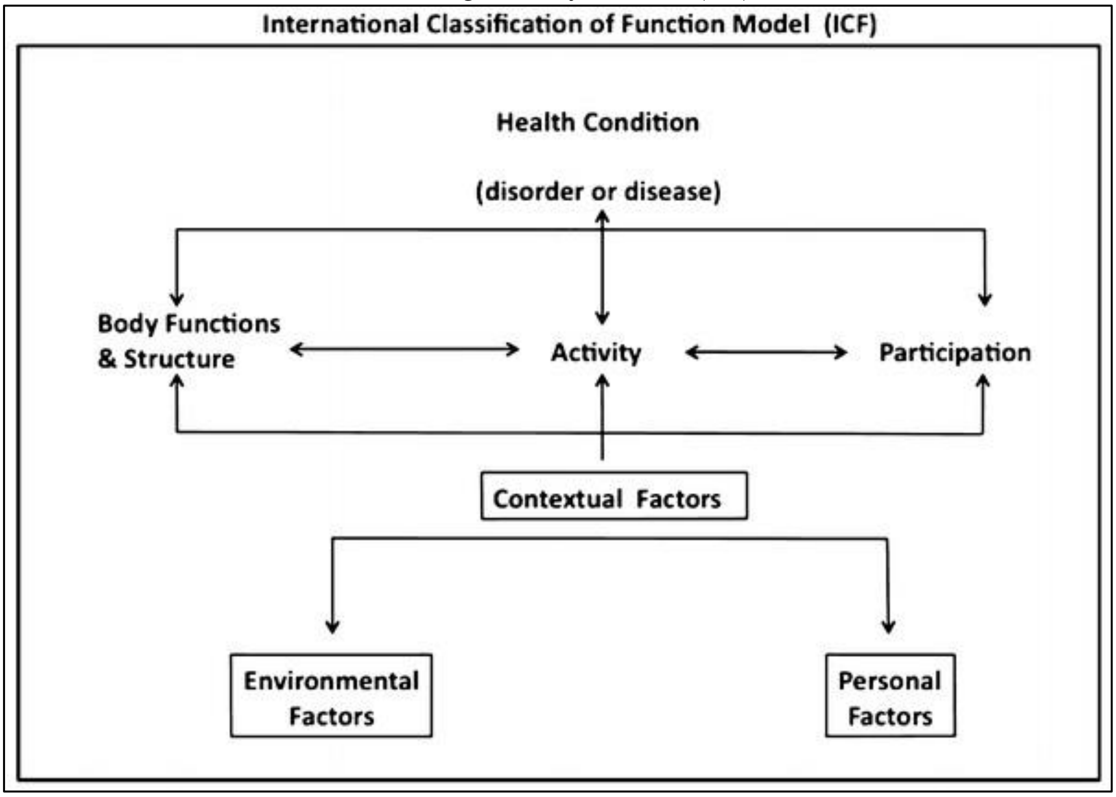
According to the traditional aphasia taxonomy (syndrome approach), anomic aphasia is the most common subtype due to brain tumor occurrence (before any surgical treatment), while global aphasia is the least frequent. Kazner [53], in one of the first studies focusing on language disorders due to brain tumors, reported that the most common symptom was anomia, although other symptoms were not ruled out. This finding was confirmed by numerous studies in the following decades, which reported anomic aphasia as the most common type of aphasia and Wernicke's as the second most common. Anomia (difficulty in retrieving words) is still considered the most common language error [7,48,55]. In general, it has been supported that resection of the tumors relieve from preoperative symptoms and it is uncommon to create new impairment [49,54,61]. Particularly, Whittle et al. [54] report that 23 out of 25 of their patients showed improved language function after resective surgery. However, their sample was very diverse comprising of glioblastomas, anaplastic gliomas, metastatic tumors and meningiomas. Also, they performed awake surgery only in 6 patients, while 19 went under general anesthesia. Davie et al. [58] investigated retrospectively the rates of postoperative aphasia and their subtypes in 358 brain tumor patients and found that the most common subtype was anomic aphasia (48%) with a great difference compared to the second Wernicke (13%). Third was conduction aphasia (10%), followed by Broca (9%), transcortical sensory (7%), global (5%), transcortical motor (5%) and transcortical mixed aphasia (3%). Similarly, Partovi et al. [13] reported that 23 of the 57 patients of their sample suffered from aphasic symptoms, although the authors do not provide information regarding the severity of symptoms. The deficits were due to tumor occurrence (before surgery), and no patient was diagnosed with global aphasia. These findings are in contrast to post-stroke aphasia, in which global aphasia is considered very common subtype (20-40%), while anomic rare (28-9%) [58,62-65].

Crossed aphasia is generally rare following strokes (less than 5% of right-handed patients with aphasia) and even rarer in patients with brain tumors, as only a few cases have been reported [66-68]. However, it is a disorder that may go unnoticed since the impairment in language is a result of a tumor in the right hemisphere, which is often considered non-dominant in right-handers. The possibility to go unnoticed is related to the fact that most neurosurgical teams do not consider language mapping in right-handed patients with right-hemisphere tumors, unless there are strong indications that the patient has the right hemisphere as dominant. These indications may be neuroimaging results (fMRI) or clinical signs (language deficits). Vassal et al. [67] suggest that when right hemisphere activations are observed in functional neuroimaging examinations (e.g., fMRI) in right-handers, even if the symptoms are mild (or occur only during focal seizures), awake craniotomy and language mapping should be considered.

Regarding iatrogenic language (and speech) disorders caused by surgical treatment, they are usually mild and transient (especially in case of awake craniotomy). Some common speech and language errors due to electrical stimulation are anomias, speech arrests, perseveration errors, phonological and semantic paraphasias, neologisms, dysfluencies, and dysarthrias [59,67,69]. Reading can be slow and effortful, and present paralexias (reading errors) or morphosyntactic errors [67,69]. According to Meyer et al. [70] the disruption of language sometimes can be present just as a delayed response (an anomic delay or word recalling problem). With regards to errors due to the resection itself, it has been reported that the type of error can be predicted by the location of the tumor [70]. For instance, resection of the left SMA may lead to a sudden inability to initiate language and movement, or resection of white matter tracts originating from the left frontal operculum may lead to language production deficiencies. The accurate identification and distinction between speech and language errors is not an easy task, considering that speech and language interact, are interdepended, and are represented and distributed in parallel [71,72]. It has been supported that a factor that may predict postoperative language deficits is the distance between the removed tissue and the nearest functional area. The 1-cm safety rule states that if the distance is less than 1 cm from the eloquent cortex, there is an increased risk of more permanent language deficits [47,73]. More details regarding the deficits after awake craniotomies will be discussed in the following chapters (especially in Chapters 4 and 5).

Tumor related language disorders can be described under the framework of International Classification of Functioning, Disability and Health (ICF) model [74] (Figure 1.2, next page). Regarding *body functions* and *structure*, the impairment in language results from tumor occurrence or its surgical removal and can be anomia, agrammatism, aphasic alexia, aphasic agraphia, auditory comprehension deficit, or other disorder. With respect to *activity*, the impact of language disorders on everyday life can be devastating as adequate communication abilities are mandatory for most daily activities. Therefore, after the treatment (which may involve surgery, radiotherapy, or chemotherapy), patient's everyday life may change dramatically [75]. The activity limitations from brain tumor may be also reflected in patient's *participation* in social life. Similarly to post-stroke aphasia, tumor-related language disorders may lead to social isolation, loss of employment, and reduced leisure activities [76]. Due to often fatal outcome of the disease and the low incidence of brain tumors (compared to post-stroke aphasia), the impact of the disease on patient's health-related quality of life (HRQOL) is generally considered understudied [75,77].

Figure 1.2
The International Classification of Functioning, Disability and Health (ICF) model [74].



1.5. Cognitive deficits in brain tumor patients

Cognition refers to the "higher" cerebral functions—that is perception, attention, thinking, reasoning, memory, and executive functions [78]. All brain tumor patients, regardless of the type of the tumor, primary or metastatic, are in high risk of compromised (non-linguistic) cognitive abilities. Assessment and monitoring of the cognitive functioning in brain tumor patients is important due to the special relationship between cognition and language. Moreover, adequate cognitive functions are required for the patient to perform most linguistic tasks; thus, a neuropsychologist should carry out an extensive cognitive assessment [79]. Preserving the cognitive functioning is also important to maintain well-being and quality of life postoperatively [80].

It has been reported that cognitive deficits are very common in patients with primary brain tumors and metastases prior to treatment, as it is estimated that 90% of patients will develop some form of cognitive disorder at some point during the disease [81,82]. The severity of the cognitive impairment is associated with tumor (location, size, histopathology etc.) and patient (age, physical condition etc.) characteristics [27]. Also, the types of deficits due to tumor occurrence depend on the characteristics of the tumor, such as location and size. However, it has been supported that brain tumors can also cause more general (non-linguistic) cognitive impairment affecting attention, memory, and executive functioning [83].

The iatrogenic deficits caused by the treatment of the tumor depend on the type of treatment. Surgical treatment, and particular awake craniotomies, may induce severe but transient cognitive impairments shortly after the operation [84]. The most commonly affected (non-linguistic) cognitive domains after the operation are memory and executive functions [85]. Radiotherapy may also lead to significant, but in most cases transient, cognitive impairments during the acute phase (radiation). Late cognitive impairments are more important because the radiation necrosis may lead to more permanent deficits, even dementia [86]. The cognitive deficits specifically due to chemotherapy are difficult to distinguish from those caused by radiation because most brain tumor patients are exposed to both types of therapy concurrently [78,80]. Deficits in later stages of the disease have been reported in glioma patients who received procarbazine, lomustine and vincristine chemotherapy [87]. The so-called "chemo brain" (or cancer-related cognitive impairment) refers to deficits in executive functions, learning, and memory, which along with deficits in visuospatial abilities, abstract reasoning and motor coordination are very common long-term impairments after treatment with systemic chemotherapy [88,89].

1.6. Awake craniotomies for AVM and intractable epilepsy

Language mapping with DES has been extensively used in epilepsy treatment [90-92] and less often in other diseases such as arteriovenous malformation resection [93,94].

Arteriovenous malformations

Arteriovenous malformation (AVM) is one of the four major types of vascular malformations and refers to a (mass-like) tangle of dysplastic blood vessels connecting arteries and veins in the brain without intervening capillaries [95]. Approximately, one-half of patients with AVMs may not experience symptoms until the AVM ruptures and results in a hemorrhage [95]. Neurological symptoms before rupture, when present, are typically mild and mostly associated with focal seizures; however, there is a smaller percentage of patients who may experience headaches, muscle weakness or other focal neurological deficits [96-98]. Some patients may experience more severe neurological symptoms such as paralysis, loss of vision, and dysarthria. Neurocognitive symptoms might be present in unruptured AVMs and can be present even if the patient does not exhibit other neurological symptoms [99]. These symptoms may include confusion and disorientation, cognitive disorders, unsteadiness, and more rarely aphasia. Neurological symptoms caused by a ruptured AVM might be more severe than hemorrhage attributed to other causes [95]. The treatment options for unruptured AVMs include microsurgery, embolization, stereotactic radiosurgery, and finally a multimodal approach combining one or more of the above options. Lately, several authors have argued that awake craniotomy may be a viable surgical treatment of AVMs [93,94]. Brain mapping during awake craniotomy may help in identifying motor or language cortex around the nidus and preserve its functions. Also, as Gabarros et al. [93] argued, mapping can guide the dissection subcortically and affect the neurosurgeon's decision for complete circumdissection of the AVM. Overall, language mapping during awake craniotomy is a valuable option when surgical treatment of unruptured AVM is planned, as it can assist the neurosurgeon in achieving an effective surgical cure with minimal risks of permanent postoperative language deficits [94].

Intractable (drug-resistant) epilepsy

Awake craniotomy to treat epilepsy became a popular treatment method almost a century ago, after World War I, mainly by Otfrid Foerster [100]. Although general anesthesia became again the gold standard in temporal lobe epilepsy after anatomically standardized resections were developed, awake craniotomy remains a valuable and essential technique [100].

Epilepsy is a very common neurological disorder which affects approximately 1% of the general population. This clinical condition induces significant physiological, neuropsychological, and social consequences for the patient [101,102]. About 35% of patients with epilepsy will ultimately develop medically intractable (or drug-resistant) epilepsy [102,103], which is defined as a "s failure of adequate trials of two tolerated and appropriately chosen and used antiepileptic drug (AED) schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom" [104: p.1073].

One possible treatment for this condition is temporal resective surgery under general anesthesia, an extremely safe procedure with mortality rates approaching zero [101]. The most common neurological complication after surgical treatment in mixed population (pediatric and adults) is the development of transient language deficit, with an incidence between 0.6 and 3.7% [105,106]. Other postoperative impairments include visual deficits, hemiparesis, aphasia, cerebral ischemic changes, and cranial nerve paresis or palsy [101]. Cognitive and neuropsychological complications are also possible after temporal lobe resective surgery, and typically include memory impairments, depression, and psychosis [101].

Brain mapping during awake craniotomy is now perceived as a method to minimize permanent postoperative cognitive and language deficits following temporal and extratemporal lobectomies for intractable epilepsy [90-92,107-109]. Similarly to awake surgery for brain tumors, in epilepsy, language is mapped by electrically stimulating cortical and subcortical areas and identifying eloquent areas [92,109]. The postoperative outcomes are generally considered positive as patients become seizure free while language deficits are typically transient, and permanent deficits are very rare [90,109].

1.7. Therapy decision and postoperative course

During the first preoperative session, the language specialist, either alone or with the support of a mental health clinician (psychologist, neuropsychologist, or social worker), will explain every step before and after the surgery. Also, they will describe the possible symptoms, how they are treated, and how the family should handle them.

Therapy is essential, and it has been found that if a patient does not receive treatment within 3 months after the surgery, their performance will remain lower than at the preoperative level [29]. The recommendations for therapy can be developed during the acute or the follow-up session, although the follow-up session provides a more complete picture of the patient's linguistic profile. The first days after operation several physiological and neurological phenomena (e.g., retraction, oedema, resection of eloquent brain tissue) do not allow safe conclusions. The deficits in this early, acute phase are typically transient and decrease quickly, thus a patient may underperform in linguistic tests immediately after operation and then start improving [54]. It has been suggested that it is better to make the decision for therapy at least two weeks after the surgery [69], although some neurosurgical teams prefer to start the therapy at the acute phase. The predictors of long-term functional outcome after awake craniotomy include patient characteristics (e.g., preoperative deficits, age and education), tumor characteristics (histopathology and location), surgery course (complications and history of previous craniotomy), and finally newly acquired postoperative deficits [110]. More information regarding this issue will be provided in Chapter 5.

Language therapy shows overall excellent results. Thomas et al. [111] reported that more than 80% of their participants developed some form of aphasia, which was associated with high levels of disorder awareness and anxiety. The same authors noted that language intervention had been quite successful, and proposed that the postsurgical recovery management of brain tumor patients should be conducted by interdisciplinary teams. Similarly, Duffau et al. [112] argued that postoperative therapeutic intervention (and particularly speech and language therapy) has very positive outcomes. In their study, all patients went through speech and language therapy and all demonstrated normal scores on BDAE during postoperative assessments (three months later). Additionally, they reported that all patients returned to the same social and occupational levels as before the operation.

1.8. Concluding remarks

The field of tumor-related language disorders is relatively novel for language clinicians such as speech language pathologists and clinical linguists. This subset of language disorders is currently understudied, especially compared to the more common acute lesion language disorders.

It is evident from the discussion presented in this chapter that the neuroplasticity mechanisms associated with brain tumors and brain tumor surgery determine the nature of the language symptoms. By studying these mechanisms, the researchers and the clinicians will gain a better understanding on the exact role of neuroplasticity on brain tumors. Also, they will shed light on how to use these mechanisms to perform more accurate mappings and provide better therapy interventions.

Chapter 2. Awake craniotomies and language assessment[2]

Abstract

Assessment of speech and language functions is an essential part of awake craniotomies. Although standardized and validated tests have several advantages compared to homemade (or mixed) batteries, in the literature it is unclear how such tests are used or whether they are used at all. In this chapter, I will present the results of a scoping review that was conducted in order to locate standardized and validated intraoperative language tests. Also, I will present and discuss various assessment methodologies reported in the literature. The inquiry included two databases (PubMED and MEDLINE), gray literature, and snowball referencing. Eighty-seven (n = 87) studies that report use of language tests and batteries were discovered, although most of them mention homemade tasks and tests borrowed from other settings. The tests that were found to meet the validation and standardization criteria were ultimately three (n = 3) and each one has its own advantages and disadvantages. Tests with high sensitivity and specificity not only can lead to better outcomes postoperatively, but they can also help us to gain a better understanding of the neuroanatomy of language.

2.1. Introduction

The surgical procedures with the patient in awake state originate from the field of medically intractable epilepsy treatment. In the beginning of the 1990s, they started to be reintroduced in oncological surgeries mostly by Mitchel Berger and George Ojemann [100]. These two pioneers developed the most common technique, which is used until today by most neurosurgical teams. The neurosurgeon and neuroscientist Hugues Duffau and his team in France evolved these methods and highlighted the importance of protecting the eloquent brain areas and preserving the patient's quality of life, while aiming for the maximal resection of the pathological tissue. Lately, this technique was named "resecting according to functional boundaries of tumor" [113]. The enormous development of this method in recent years now allows surgery to be performed on patients who were previously excluded, as their tumors were in the so-called "inoperable areas" [100].

Brain tumors and awake craniotomies

As it was mentioned in the previous chapter (Chapter 1, 1.2 Gliomas and glial cells), brain

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tumors grow mostly by compressing, displacing, and infiltrating normal neuronal tissue, which may remain functional for relatively long periods [7,59]. A common neurological symptom of intracranial tumors is the disruption of language functions, as it is estimated that 37-58% of patients with primary brain tumors will develop some form of aphasia [54]. The iatrogenic deficits in language may result from either electrical stimulation during the brain mapping process or surgical removal of the tumor. In the first case, the symptoms are always transient, while in the second, depending on the time that has passed since the operation, the symptoms and their severity may vary. Deficits in language that may appear in the immediate postoperative phase are typically transient, regardless of their severity, while permanent linguistic deficits after awake surgery are considered uncommon [114-116].

It is generally accepted that in most cases surgical treatment of brain tumors may increase life expectancy [117]. Contrary to the traditional surgical procedures where the patient is under general anesthesia, asleep-awake-asleep surgery allows continuous monitoring of the patient in an awake state in order to evaluate various functions (language, motor skills, emotion, non-linguistic cognition). As previously mentioned, the purpose of this procedure is to detect eloquent brain areas and create a "functional map" in order to protect them from the resection process. Two are the most common methods of brain mapping: i) direct electrical stimulation (DES), and ii) electrocorticography [118]. There are a lot of published articles reporting surgical guidelines and details about awake craniotomies but it falls outside the scope of the current chapter to discuss them all in detail (for more information, see Berger et al. [119], and Duffau [120]). In the next paragraphs I will discuss the basic principles and techniques of brain mapping with DES, especially regarding language. The procedure, quite simplified, is as follows: after the exposure of a specific brain region, the neurosurgeon administers small amounts of electrical current directly to the surface of a specific brain area, and inhibits its function. If the moment of stimulation this function is performed, it gets disrupted and the neurosurgeon manually tags the brain area as eloquent with a small sterile tag, thereby creating a functional map [114,121]. The amount of electrical current varies among surgical groups, but it is quite common to range between 2 and 10mA and to be administered for no more than 4 seconds [114,122-124]. Any speech or language error the patient produces due to electrical stimulation is transient, and the disruption typically does not last more than the stimulation. Brain mapping is not performed only to the cortex of the dominant hemisphere. There are several articles reporting mapping procedures on subcortical pathways [125,126] as well as on the right (non-dominant) hemisphere [127,128].

Today, when certain requirements are met, mapping with DES is a relatively safe procedure, which is well tolerated by most patients [129,130]. It is considered the gold standard in awake brain surgery, allowing maximal resection with minimal postoperative deficits [1,4,5]. According to De Witte et al. [3], there are several reasons for DES to be considered the best method to guide the surgical plan, as under ideal conditions it has optimal sensitivity and rarely produces false negative results, it provides information about essential for language brain areas, it is suited for both cortical and subcortical mapping, it can be used during subcortical resection, and finally it minimizes postoperative language impairment, since permanent deficits appear in less than 5% of the cases [1,2,28].

Brain mapping is not used only to map language functions per se. Studies report use of electrical stimulation in order to detect brain areas involving various aspects of speech, like fluency and voice [131,132], emotions [133], vision [134], non-linguistic cognitive functions [135], singing [136], and of course motor functions [137]. Unlike most studies focusing on monolingual patients, there are several studies on bilingual patients, which also suggest specific intraoperative tasks [138-140]. Additionally, language mapping with DES has been extensively used in epilepsy treatment [91,92] and less often in other diseases such as arteriovenous malformation resection [93,94]. With respect to age, there are not strict guidelines. Nonetheless, the patients between 15 to 65 years of age have traditionally been considered “good candidates” for awake craniotomy [141]. Children (under 15 years of age) have been associated with deprived cooperation capacity during the awake stage [142], as well as with other contraindicative anatomical, functional, and psychological factors [143], while older patients (over 65 years) have been linked with poor survival and increased perioperative mortality and morbidity [144]. Regarding the latter, the last few years emerging evidence [122] tend to reverse this view, and today aggressive tumor removal under awake craniotomy is not uncommon for older patients if their physical and cognitive status allows it. Under the appropriate circumstances, awake craniotomy constitutes a viable surgical treatment option for both age groups, and there is a growing number of studies in pediatric [145,146] and elderly populations [122] supporting it. Finally, it has to be emphasized that the decision for performing an awake craniotomy should be individualized and take into consideration the physical and psychological status of the patient, as well as the presence of any comorbidities.

Neuroimaging methods in awake craniotomies

During the 00’s, non-invasive structural and functional neuroimaging methods became very popular in mapping the human brain for a variety of functions, and also for guiding neurosurgeons in aggressive tumor resection.

Conventional magnetic resonance imaging (MRI) is still the most dominant method to obtain anatomical information of tumors, such as size, location, and boundaries [2,147]. Advanced imaging techniques, such as proton magnetic resonance spectroscopy (MRS), provide metabolic and other pathophysiological information of tumors and they are used clinically in differential diagnosis and decision making [148,149]. The employment of transcranial magnetic stimulation (TMS) may well localize the sensory-motor cortex, but its accuracy in identifying language-associated cortical areas still remains questionable [150]. Magnetoencephalography (MEG) along with magnetic source imaging (super imposition of magnetoencephalographic data on MRI) and functional magnetic resonance imaging (fMRI) are functional neuroimaging methods, which have been used preoperatively in order to localize eloquent cortical areas. The application of the former in neurosurgery field has been described by Mäkelä et al. [151] and for many years it was limited to sensorimotor preoperative mapping [152-154]. In the past few years, the use of MEG expanded to language [155,156] although for various reasons magnetoencephalography never reached the popularity of fMRI [157]. Functional MRI on the other hand, has been extensively used by numerous neurosurgical teams and institutions to assist their surgical planning [158-161]. By analyzing the blood-oxygen-level dependent signal clinicians locate the eloquent brain structures and create functional maps preoperatively. The neurosurgeons use these maps intraoperatively in order to protect the eloquent cortex. Since this method is non-invasive, it can be repeated with relatively low cost, contrary to other functional imaging techniques, such as positron emission tomography [3]. However, its use as the sole means of guiding the surgery is controversial as it has several disadvantages. De Witte et al. [3] summarize them as follows: a) fMRI does not provide information for subcortical functions, b) it cannot detect which regions are essential for certain language functions, d) it depends heavily on paradigms and statistical tools, and e) it has low sensitivity for language functions (but not for sensorimotor functions). Giussani et al. [162] reviewed nine language brain mapping studies that compared functional MRI techniques with DES methods. While these studies were not homogenous methodologically and varied a lot in many respects, authors found that sensitivity of fMRI regarding language ranged from 59 to 100%, while specificity ranged from 0 to 97%. Further evidence from other studies support the aforementioned finding, as they report approximately 66% sensitivity to identify language functions [116,163].

Language assessment in awake craniotomies

The behavioral evaluation process in awake neurosurgery is described in numerous articles [2,29,59,69,70,121,164]. Since the goal of this thesis is not to review exhaustively all the aspects of behavioral assessment, the author will focus on language for which an overview of the literature will be provided.

The clinician

Regarding the specialty of the clinician who conducts the linguistic or cognitive evaluations, the reports in the literature do not agree. Some teams use a speech-language therapist [69,70,114,123,146,166,167], while others use a neuropsychologist [129,145]. A limited number of studies report using both a speech-language therapist and a neuropsychologist [73,168] or other specialties such as an anesthesiologist [132]. The education and skills of such a clinician have been described by De Witte et al. [169] who emphasized the need for neurolinguistic background and basic knowledge of the language system. In this chapter, I will use the term "language specialist" for this member of the team, regardless of his or her educational background. Since the language specialist has to be the same at all phases of the assessment, the clinician is tasked with several duties intraoperatively [69,168]. The language specialist not only conducts the language evaluation during the mapping and resection processes, but also has to constantly communicate with the patient keeping him or her in a calm state and most importantly, has to recognize, interpret, and inform the neurosurgeon of any error that the patient may produce [69,112,169].

The administration procedure

Various assessment methodologies have been reported by different teams (for reviews of the practices used by different teams around the world, see Rofes et al. [170] or De Witte et al. [3]). Usually, the evaluation process is not limited to the day of the surgery; it starts days or even weeks before. In the current literature [3,29,59,69,171,172] three distinctive stages are mostly described: a) the preoperative, b) the intraoperative and c) the postoperative. However, there are some studies that report one more distinctive session which most of the times works as a separate "preparatory" phase for the intraoperative stage and takes place just one or two days before the surgery [69,173-175]. Usually during this phase the patient is trained on the intraoperative tasks and stimuli, in order to exclude those that the patient does not answer perfectly. This is important because the language specialist must ensure that the patient is able to easily perform the intraoperative tasks during the surgery and any errors he or she may commit will be due to electrical stimulation and not to previous disorders [67,69]. Still, it is not always clearly reported in the literature whether these sessions take place, even though this is strongly implied sometimes.

The main goals of the speech and language evaluation prior to surgery depend on the needs of each team or institution. Typically, at this stage the language specialist seeks to gain a brief overview of the patient's clinical characteristics, identify any linguistic deficit, set an assessment baseline, familiarize the patient with the whole process, and ultimately build a trustful relationship [29,59,67,69,70]. The time during which this stage takes place may range from one day prior to the operation [122,124,129,176] to several days or weeks before [166,177]. With regard to the tests and tasks used, reports from various studies can be divided in two major categories: a) those who use different tests in order to establish a baseline, usually standardized batteries like the Boston Diagnostic Aphasia Examination (BDAE), the Aachen Aphasia Test (AAT), the Mount Wilga High Level Language Test, the Comprehensive Aphasia Test (CAT), or the Standard Language Test of Aphasia [166,176,178,179] and b) those who use the same set of tests for all the stages, including intraoperative [125,180]. Some of the tasks commonly mentioned in the latter (b) category are Dénomination Orale 80 (DO80) and Pyramids and Palm Trees Test (PPTT) as well as experimental and homemade tasks. Figure 2.1 provides a schematic representation of the two main approaches in language assessment.

Postoperative assessment is usually performed with the same tools as the preoperative phase and aims to evaluate the patient on the basis of preoperative performance. The majority of studies suggest two evaluations after the operation. One in the immediate postoperative period, that is 3-4 days after the procedure, and one as a follow-up few months later [67,114,123,168].

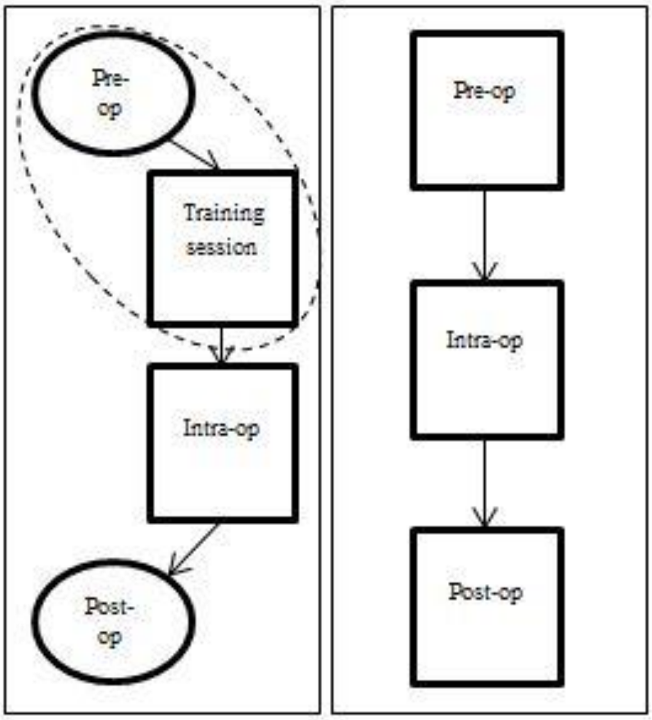


Figure 2.1
Schematic representation of the two main methods of language assessment.

Different types of shapes (squares and ovals) represent different materials. On the left, pre- and postoperative tests are different from the intraoperative test. A separate "preparatory" session takes place a few days before, in order to train the patient and allow the language specialist to select tasks. On the right, the same tests are used for all the stages of the procedure.

Intraoperative stage consists of two phases, brain mapping and tumor resection; although this distinction is not always clear in the literature. It has been suggested that these two intraoperative phases should be treated and assessed differently by the language specialist [79]. The variety in intraoperative procedures and tests among various neurosurgical teams extends from assessment of automated-formulaic speech [181] to assessment with standardized batteries [79]. Most studies, however, stand somewhere in between as they use blends of homemade tasks and formal standardized tests [26,69,70,122,124,125,179,182]. As Rofes et al. [183] argue, such combinations have several limitations as they often lack clear purpose, reliability, consistency, and normative data. It is also common for some studies to fail to assess the full spectrum of language, as they investigate very specific aspects, narrowing their scope, for instance only syntax [184], or only auditory comprehension of single words [90]. Another major drawback of many mixed sequences of tasks is that they do not specify exactly how they take into account the *constraints of intraoperative assessment*. These limitations have been described as: the linguistic and cognitive load that has to be processed by the patient, the limitation in response time (4 seconds), the visual complexity of the given stimuli, and the impact that anesthesia has to cognition [3,185]. Regarding anesthesia, it has been reported that during the awake stage can induce some degree of disorientation, confusion, and increase reaction times [186-188]. Patients' reactions have the lowest performance during the first minutes after extubation. Their performance is gradually getting better as they wake up, reaching their highest performance after the first 20 minutes [187].

Standardization and validity

As discussed above, some teams or institutions use standardized tests, either individually or as parts of larger, mixed batteries. Standardized tests are defined as norm-referenced or criterion-referenced measures of performance that include clearly defined procedures for administration [189]. Criterion-referenced tests measure the performance of an individual against a predetermined criterion, in case of awake craniotomies, patient's perioperative score [190]. In norm-referenced tests, which are the most common in speech and language pathology field, scores are interpreted with reference to the scores from a normative sample [191]. For the purposes of this chapter, as standardized are considered the tests that are both criterion and norm based.

Validity is a theoretical concept that refers to the extent a test accurately measures what it is supposed to measure. There is no doubt that currently there are numerous validation and reliability frameworks related to speech and language assessment (e.g., content validity, discriminant validity, predictive validity, test-retest reliability). According to the writing committee of the Academy of Neurologic Communication Disorders and Sciences Practice Guidelines Group [189], a test in order to accurately detect impairment must have at least discriminant and concurrent validity. Discriminant validity refers to the degree that a test is able to distinguish a typical from a pathological communication behavior, and as it will be evident later in this article, it is very helpful in intraoperative tests. On the other hand, concurrent validity refers to the degree that the results of a new test agree with the results of a valid and well-established test.

In addition to validity and the typical standardized characteristics, tests that are intended for intraoperative use need to have some extra features. As it has been already proposed [3,185.192], an integrated, specialized and standardized language battery should take into account the constraints of intraoperative assessment, the complexity of language system and brain areas supporting it, and finally it should have the flexibility to assess a different linguistic process every time the neurosurgeon moves to a new area either for stimulation or resection. Two other very important features of an intraoperative assessment tool, which can have a direct impact on surgery effectiveness, are sensitivity and specificity. High sensitivity is associated with low rate of Type II (false negative) errors and requires accurate clinico-anatomical correlations. The occurrence of many Type II errors means that the patient responded to the tasks correctly, but a wrong function was assessed the moment of stimulation. In order to keep sensitivity high, correct responses need to result from stimulation of true non-eloquent areas and not from wrong functions assessed. Otherwise the neglected eloquent areas are at risk of been removed, which can lead to increased permanent linguistic deficits. High specificity on the other hand is associated with low rate of Type I (false positive) errors. These errors occur when the patient produces speech or language errors that do not result from stimulation or resection processes, but from other, unrelated factors (e.g., fatigue, lack of prior knowledge, dialectal differences). In the event of high Type I error rate, non-eloquent areas will be unnecessarily marked and preserved as eloquent, which may affect the extent of tumor resection. This can be avoided by removing, before the operation, any stimuli that are not answered flawlessly by the patient or within the given time limit. To keep rates of Type I and II errors low, preoperative personalization of tests on each patient, as well as the use of intraoperative tests with rigorous administration procedures and accurate clinico-anatomical correlations are extremely important. A sufficient number of tasks that evaluate different linguistic processes can also help in this direction. As Duffau [113] argues, the more different functions evaluated the more eloquent areas will be maintained, leading to larger and safer resections. All the aforementioned features can have a positive impact on life expectancy and quality of life of the patient and also help us to gain valuable insights regarding clinico-anatomical relationships and the brain connectome [3,113,193,183].

This chapter

This chapter provides an overview of the history and context of functional mapping and where language mapping sits within it. From the analysis provided in the previous sections, it can be concluded that a modern and comprehensive intraoperative language assessment tool has to be standardized (norm and criterion based), evaluate many, if not all, language functions, and assess all the corresponding brain structures involved. Furthermore, it should be developed so it can cope with the particular conditions of awake craniotomies as they were discussed in the preceding sections.

The main goal of this chapter is to present the findings of the scoping review I conducted in order to detect and analyze standardized intraoperative language tests. Detailed description of the materials and methods that were used for this review is provided in the next section. The third section of the current chapter (Results) includes an overview of the articles that were examined for eligibility, and a detailed, critical analysis of the tests that were found to fulfill the criteria. By identifying the gaps of the current literature and highlighting the strengths and limitations of the under-examination tests, this part of the thesis attempts to contribute in the production of more specialized and methodologically rigorous tests.

2.2. Materials and Methods

I performed a scoping review of the literature using the framework proposed by Arksey et al. [194] and the extended PRISMA template for scoping reviews (PRISMA-ScR [195]). This method is considered best suited for summarizing findings, exploring the extent of research, and identifying research gaps [196]. The framework includes five steps: a) identifying the research question, b) identifying relevant studies, c) study selection, d) charting the data, and e) collating, summarizing, and reporting the results. In order to verify that all the necessary items were reported, the PRISMA-ScR checklist was used.

The inquiry included two databases, gray literature, and snowball referencing and was conducted April through June 2019. The two databases were PubMED and MEDLINE, and the keywords were as follows: “standardized language test”, “intraoperative language assessment”, “linguistic protocol”, “awake surgery”, “language mapping”, “brain tumor”, and “direct electrical stimulation”. The included articles were written in English and published after 1999.

The search strategy that was followed consisted of the following steps: a) investigation for the aforementioned key-terms and recording of the number of articles, b) selection of articles that were relevant judging by their titles, c) screening of the records and selection of those that mentioned intraoperative language tests, d) assessment of all the relevant articles for eligibility in order to locate standardized tests, and e) analysis of the studies that reported standardized language tests and critical review of the reported tests. Records that went through the assessment step had to mention intraoperative language testing in their abstracts. Articles had to meet the following criteria in order to be included in the final step and be reviewed extensively:

- Report or describe in detail tests focusing on language
- Tests had to be developed specifically for intraoperative use
- Tests had to be standardized (norm and criterion based) and validated (discriminant and concurrent validity)
- Used for language mapping with DES

I chose to chart and categorize data according to how close they were to the research question and not by assessing the quality of their methodology. This process took place during the assessment for eligibility procedure and the articles were divided in four groups. The first group (Type S) is the target group and consists of the studies included in qualitative analysis, since they describe the use of standardized intraoperative language tests developed from scratch specifically for awake craniotomies. The largest group (Type M) consists of articles reporting a blend of homemade and standardized tasks, not standardized as a single intraoperative protocol, but used extensively in the operating theatres. Additionally, they take into consideration some or all of the intraoperative constraints. Most of them were retrospective designs. The third group (Type E) consists of studies with experimental intraoperative tests. However, since they were experimental designs, they had narrow scope on language, for example they were investigating only auditory comprehension or only syntax. Finally, the last group (Type P) consists of studies reporting tasks that were developed for intraoperative assessment but are not used yet. A “narrative” charting approach was used for the studies in Type S group, and a descriptive-analytical method in order to find their strengths and weaknesses. Both methods have been described by Arksey et al. [194]. The data charting forms were constructed in Microsoft Excel program and they included the following information:

- Details regarding publication (authors, year, journal name if it was needed)
- Specifics about tasks or tests (name of the tests, number of tasks, the language function involved, standardization on healthy population, validation)
- The population they were used on (e.g., brain tumor patients, epilepsy patients, vascular malignancies, mixed population)
- Details about the procedure (mention of tasks for subcortical mapping and resection process, preparatory phase)

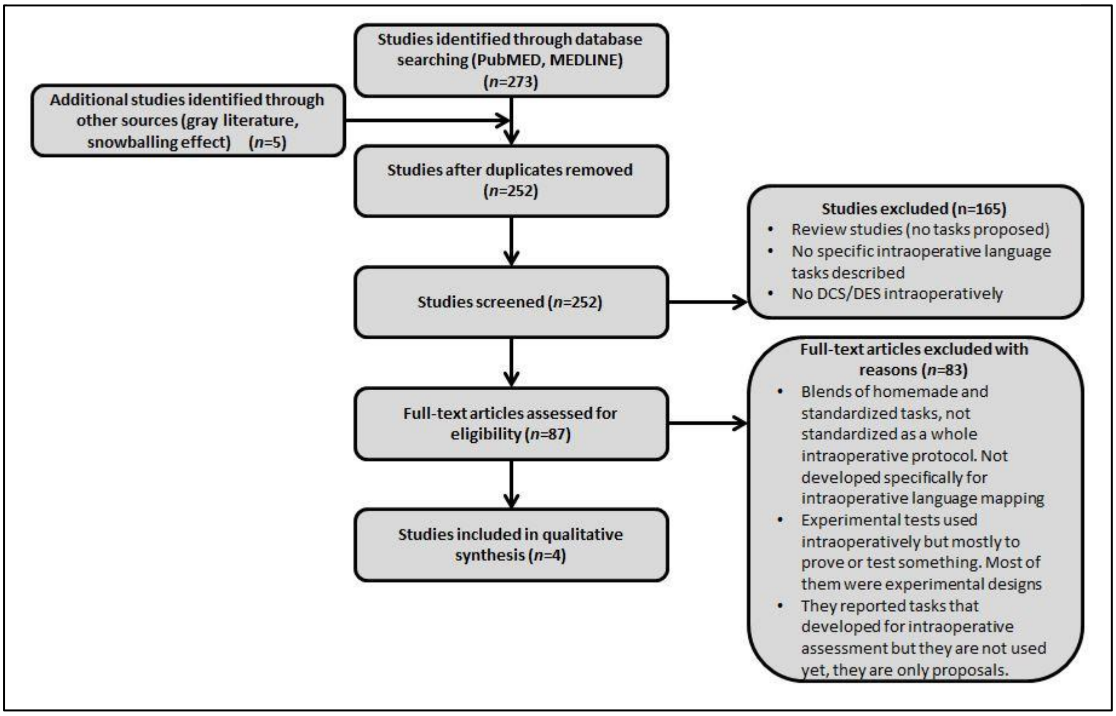
All the studies included in these four groups (i.e., the records that were accessed for eligibility) went through the charting process. Nevertheless, only the tests described in Type S studies were critically reviewed.

2.3. Results

The initial database investigations returned a total of 20.785 results. After manual examination of the titles 273 relevant articles were identified. Five (*n* = 5) additional records were added from other sources (gray literature, snowballing effect). Finally, the duplicates (*n* = 26) were removed and the screening process of the 252 articles began. During the screening process 165 records were excluded for various reasons, which are demonstrated in Figure 2.2.

Figure 2.2

The search strategy that was used.



The remaining 87 articles (84 from databases and 3 from other sources) were studied extensively in order to be decided if they met the inclusion criteria. From this process only four studies (*n* = 4) were identified to meet the eligibility criteria. Since two of them refer to the same test, the extensive review included three tests (*n* = 3). Table 2.1 (next page) demonstrates the 87 records that were assessed for eligibility and it is followed by an overview of the articles divided into their respective categories.

Table 2.1
Charted data for the 87 articles that were assessed for eligibility.

Study	Intraoperative language tasks or tests	Developed specifically for awake craniotomies	Standardized	Validated	Used in brain mapping (DES)	Type of study
1. Ilmberger et al. [176]	naming (with carrier phrase)	no	not reported	not reported	yes, BT	M
2. De Witte et al. [174]	repetition from DuLIP 2 semantic tasks from DuLIP naming (with carrier phrase) from CAT-NL & BNT reading from PALPA verb generation from a Flemish-Dutch protocol action naming from a Flemish-Dutch protocol automated-formulaic speech (homemade)	no except DuLIP tasks	yes	not reported	yes, BT	M
3. Herbet et al. [171]	automated speech (counting 0-10) naming - DO80 non-verbal semantics - PPTT reading aloud	no (not specified for reading)	yes (not specified for reading)	not reported	yes, BT	M
4. Kilbride [197]	picture naming repetition sentence completion reading (words) color identification self-midline command automated speech (days, months, counting)	not specified	not reported	not reported	yes, MP	M
5. Zhang et al. [109]	naming from C-WAB spontaneous speech from C-WAB comprehension from C-WAB repetition (homemade) reading (homemade) writing (homemade)	only the homemade tasks	only C-WAB tasks	not reported	yes, Ep	M
6. Saito et al. [198]	picture naming reading (words) verb generation	not specified	not reported	not reported	yes, BT	M
7. Ille et al. [199]	object naming (with carrier phrase)	not specified	not reported	not reported	yes, BT	M
8. Bilotta et al. [200]	object naming action naming famous people naming reading	not specified	not reported	not reported	yes, BT	M
9. Pallud et al. [123]	counting (1-10) naming (with carrier phrase) - DO80	no	yes	no	yes, BT	M
10. Zemmoura et al. [124]	counting (1-10) reading - MT86 test naming (with carrier phrase) - DO80	no	yes	no	yes, BT	M
11. Motomura et al. [201]	naming	not specified	not specified for linguistic	not reported	yes, BT	M

	counting (and other non-linguistic tasks)		tasks			
12. Trimble et al. [166]	monologue automatic speech word association language sequencing tasks explanation of idioms	not specified	not reported	not reported	yes, BT	M
13. Sobottka et al. [202]	verb generation picture naming	yes	not reported	not reported	yes, BT	M
14. Meyer et al. [70]	picture naming reading of words repetition	not specified	not reported	not reported	yes, BT	M
15. Duffau et al. [114]	counting naming (with carrier phrase) - DO80	no	yes	no	yes, BT	M
16. Sierpowska et al. [140]	simplified naming task (Havas et al. 2015) semantic pairs task (adapted from Jefferies et al. 2009) non-verbal semantics - PPTT	only naming task	yes	not reported	yes, BT	M
17. Lubrano et al. [179]	naming	not specified	not reported	not reported	yes, BT	M
18. Grossman et al. [122]	naming visual verb generation auditory verb generation speech comprehension free speech (during resection)	not specified	not reported	not reported	yes , BT (elderly)	M
19. Delion et al. [146]	naming (with carrier phrase) - DO80 hypnosis by psychiatrist	no	yes	no	yes , BT (pediatric)	M
20. Picht et al. [203]	naming (with carrier phrase) from AAT	no	yes	no	yes, BT	M
21. Costello [181]	counting backwards (100-0)	no	no	no	yes, BT	M
22. Leal et al. [204]	counting naming reading	not specified	not reported	not reported	yes, BT	M
23. Skrap et al. [205]	**all tasks come from standardized batteries** naming repetition (words & non-words) phonemic discrimination phonological discrimination praxis (apraxia) reading (words & non-words) auditory comprehension digit span phonological fluency action naming picture description automatic speech (and other non-linguistic tasks)	test developed only for rese- ction, not mapping	yes	not specified	only for resection	M
24. Whittle et al. [206]	counting	not specified	not reported	not reported	yes, BT	M

	naming reading					
25. Gabarros et al. [93]	counting (0-10) object naming reading (words)	not specified	not reported	not reported	yes, AVM	M
26. Ott et al. [207]	naming – DO80 digit span from WAIS-III semantic & phonological fluency from Regensburg fluency test	no	yes	not reported	yes, BT	M
27. Spena et al. [115]	naming (with carrier phrase) form AAT or DO80	no	yes	not reported	yes, BT	M
28. Kemerdere et al. [131]	counting (1-10) naming (with carrier phrase) - DO80 non-verbal semantics - PPTT	no	yes	not reported	yes, BT	M
29. Low et al. [208]	counting object naming	not specified	not reported	not reported	yes, BT	M
30. Kim et al. [209]	verbal and visual tasks	not specified	not reported	not reported	yes, BT	M
31. Bello et al. [210]	counting object naming from Laiacona, et al. (1993) verb naming from BADA famous people naming from Rizzo et al. (2002)	no	yes	not reported	yes, BT	M
32. Gonen et al. [211]	naming verb generation comprehension semantic retrieval (definition to noun)	not specified	not reported	not reported	yes, BT	M
33. Schapiro et al. [132]	counting naming	not specified	not reported	not reported	yes, BT	M
34. Gil-Robles et al. [212]	naming reading symbol recognition (cognitive task)	not specified	not reported	not reported	yes, BT	M
35. Vassal et al. [67]	naming – DO80	no	yes	not reported	yes, BT	M
36. Roux et al. [139]	naming – DO80 reading	no (not reported for reading task, only for DO80)	yes	not reported	yes, BT	M
37. Bello et al. [125]	counting object naming from Laiacona, et al. (1993) verb naming from BADA famous people naming from Rizzo et al. (2002) sentence comprehension from Parisi and Pizzamiglio (1970) word comprehension from Laiacona, et al. (1993)	no	yes	not reported	yes, BT	M
38. Lucas et al. [138]	confrontational naming	not specified	not reported	not reported	yes, BT	M
39. Sanai et al. [12]	counting (1-50) object naming reading words	not specified	not reported	not reported	yes, BT	M
40. Gil Robles et al. [213]	counting naming – DO80	no	yes	not reported	yes, BT	M
41. Kuchcinski et al. [160]	counting (0-10) naming – DO80	not specified	not reported	not reported	yes, BT	M

		spontaneous speech					
42.	Fujii et al. [178]	object naming	not specified	not reported	not reported	yes, BT	M
43.	Bilotta et al. [177]	object naming verb naming famous people naming	not specified	not reported	not reported	yes, BT	M
44.	Spena et al. [214]	counting naming reading	not specified	not reported	not reported	yes, BT	M
45.	Moritz-Gasser et al. [180]	naming – DO80 non-verbal semantics - PPTT	no	yes	not reported	yes, BT	M
46.	Sarubbo et al. [215]	counting picture naming	not specified	not reported	not reported	yes, BT	M
47.	Sakurada et al. [216]	naming objects	not specified	not reported	not reported	yes, BT	M
48.	Tomasino et al. [182]	counting verb generation - S&V set object naming (with carrier phrase) - S&V set	not specified	not specified (S&V set is standardized but it is unknown if the procedure the authors used is)	not reported	yes, BT	M
49.	Krieg et al. [217]	counting naming (with carrier phrase)	not specified	not reported	not reported	yes, BT	M
50.	Kinoshita et al. [218]	naming – DO80	no	yes	not reported	yes, BT	M
51.	Vidorreta et al. [219]	naming (with carrier phrase)– DO80	no	yes	not reported	yes, BT	M
52.	Duffau et al. [2]	counting (0-10) naming (with carrier phrase) – DO80	no	yes	not reported	yes, BT	M
53.	Polczynska et al. [220]	object naming	not specified	not reported	not reported	yes, BT	M
54.	Borius et al. [173]	naming sentence reading translation (L2->L1)	not specified	not reported	not reported	yes, BT	M
55.	Duffau et al. [26]	counting (0-10) naming (with carrier phrase) - DO80 reading sentences	no (not specified for reading)	yes (not specified for reading)	not reported	yes, BT	M
56.	Roux et al. [221]	counting (0-10) naming (with carrier phrase) - DO80 reading sentences	no (not specified for reading)	yes (not specified for reading)	not reported	yes, BT	M
57.	Corina et al. [222]	object naming from S&V set	yes	yes	not reported	yes, MP	M
58.	Tonn [116]	object naming (with carrier phrase)	not specified	not reported	not reported	yes, BT	M
59.	Balogun et al. [145]	counting object naming	not specified	not reported	not reported	yes, BT (pediatric)	M
60.	Hervey-Jumper et al. [129]	automated speech (counting, letters) object naming reading spelling comprehension (and other non-linguistic tasks)	not specified	not reported	not reported	yes, BT	M
61.	Eisner et al. [223]	object naming (with carrier phrase)	not specified	not specified	not reported	yes, BT	M
62.	Kin et al. [224]	picture naming auditory naming (definition to word)	not specified	not reported	not reported	yes, BT	M

63. Hulou et al. [127]	tasks not described (patient was observed by the anesthesiologist)	not specified	not reported	not reported	yes, BT	M
64. Spena et al. [225]	counting reading object naming writing auditory naming (definition to word)	not specified	not reported	not reported	yes, BT	M
65. Robert [69]	naming task (200 pictures) from PALPA & BNT auditory naming (definition to word) semantic odd word out calculation spontaneous speech	PALPA & BNT are not (not specified for the rest homemade tasks)	yes (PALPA & BNT)	not reported	yes, BT	M
66. De Witte et al. [226]	DuLIP for cortical mapping QMT (experimental) for subcortical	yes (both)	yes (DuLIP only)	yes (DuLIP only)	yes, BT	E (QMT)
67. Sierpowska et al. [175]	**experimental tasks for language switching:** single language naming language switching condition	yes	no (images used may be standardized but the whole procedure is not)	not reported	yes. BT	E (language switching)
68. Martino et al. [227]	counting (0-50) object naming – DO80 verbal memory test (experimental)	only verbal memory test	only DO80	not reported	yes, BT	E (short-term memory)
69. Alarcon et al. [90]	single word auditory comprehension (SWAC)	yes	not reported	not reported	no, Ep	E (comprehension only)
70. Hirsch et al. [159]	picture naming auditory naming (naming by definition)	yes	not reported	not reported	yes, BT	E (fMRI accuracy)
71. Chang et al. [228]	counting (1-50) naming - DO80 (timed) non-verbal semantics – PPTT	no	yes	not reported	yes, BT	E (PPTT as a deficit predictor)
72. Krieg et al. [229]	object naming (with carrier phrase, timed)	no	yes	not reported	yes, BT	E (rTMS vs DCS)
73. Papagno et al. [230]	naming (object & action) from Catricala et al. (2013) verbal fluency from Novelli et al. (1986) comprehension of sentences from Cecchetto et al. (2012) token test from De Renzi and Faglioni (1978) repetition from BADA digit span	only digit span	yes	not reported	yes, BT	E (verbal short term memory)
74. Ries et al. [184]	picture-word interference (experimental) sentence generation (experimental)	yes	no	not reported	yes, BT	E (syntax)
75. Lubrano et al. [231]	naming (with carrier phrase) reading (sentences) writing	only writing task	not specified	not reported	yes. BT	E (writing)
76. Corina et al. [91]	object naming action naming (vignettes)	yes	yes	not reported	yes, MP	E (designed for awakes but used e-xtra-op)

77. Chang et al. [232]	counting (0-10) repetition (Leonard et al. 2019) naming (Corina et al. 2010) sentence production (experimental) (and some extra tasks for some cases)	no (but modified properly for awake craniotomy)	yes	not reported	yes, MP	E (localiza-tion of syn-tax)
78. Serafini et al. [92]	visual-object naming (with carrier phrase) auditory naming (with carrier phrase) sentence completion	yes	only visual-obj. naming task (not specified for experimental tasks)	not reported	yes, Ep	E (auditory vs visual na-ming)
79. Jung et al. [150]	counting object naming verb naming	not specified	not reported	not reported	yes, BT	E (nTMS vs DCS)
80. Wager et al. [167]	stroop test (experimental)	no (but modified properly for awake craniotomy)	yes	not reported	yes, BT	E (stroop task)
81. De Witte et al. [233]	DuLIP (and extra cognitive tasks)	yes	yes	not reported	yes, BT	E (pilot)
82. Faulkner et al. [234]	picture naming verb generation picture-word verification real word repetition non-word repetition stroop task letter fluency category fluency articulatory agility	yes but only for preoperative assessment	yes	yes	no	P (only for pre-op pha-se)
83. Polczynska [192]	**tasks for dominant and non-dominant hemispheres:** sentence production sentence completion singular to plural spontaneous speech metaphor to picture association semantic odd word out find the synonym sentence production with different prosodies prosody to semantics auditory association	yes	no	not reported	no	P (never used intra-op)
84. Rofes et al. [172]	counting (0-10) object naming (ECCO) verb naming (VISC)	yes	yes	yes	yes, BT	S
85. Rofes et al. [183]	object naming (ECCO) verb naming (VISC)	yes	yes	yes	yes, BT	S
86. De Witte et al. [79]	17 linguistic tasks covering phonology, semantics & syntax reading, auditory comprehension & repetition speech (articulation & oral motor planning)	yes	yes	yes	yes, BT	S
87. Dragoy et al. [235]	object naming verb naming	yes	yes	yes	yes, BT	S

Leg.: *BT* = brain tumors, *Ep* = epilepsy, *MP* = mixed population, *AVM* = arteriovenous malformation, *PALPA* = Psycholinguistic Assessments of Language Processing in Aphasia [236], *CAT-NL* = Comprehensive Aphasia Test [237], *BNT* = Boston Naming Test [238], *DO80* = Dénomination Orale 80 [239], *PPTT* = Pyramids and Palm Trees Test [240], *C-WAB* = Chinese-Western Aphasia Test [241], *MT86* = Montreal-Toulouse-86 [242], *AAT* = Aachen Aphasia Test [243], *WAIS-III* = Wechsler Adult Intelligence Scale-III [244], *BADA* = Batteria per l'Analisi del Deficit Afasico [245], *S&V* = Snodgrass and Vanderwart set of images [246], *QMT* = Quick Mixed Test [226], *VISC* = Verb production In Sentence Context [183], *DES* = direct electrical stimulation, *rTMS* = repetitive transcranial magnetic stimulation, *nTMS* = navigated transcranial magnetic stimulation

Type S category

Four (*n* = 4) studies report intraoperative use of standardized tests in awake craniotomies according to the criteria previously presented. Two of these studies come from the same team using the same test, which basically means that the tests are three:

- ECCO and Verb production In Sentence Context (VISC) tests [172,183]
- Dutch Linguistic Intraoperative Protocol [79]
- Russian Intraoperative Naming Test [235]

These tests are controlled for a variety of psycholinguistic and grammatical variables, and they take into consideration the constraints of the intraoperative assessment. Further details about these tests are provided later in this article.

Type M category

Sixty-five (*n* = 65) studies belong to this category. Some of them come from the same team or same institution. For example, the studies from Duffau et al. [114], Herbet et al. [171], and Zemmoura et al. [124] were conducted in the same institution (Université de Montpellier) and by the same neurosurgical team. In these cases, the reported tests and procedures are very similar and therefore, some studies that describe the exact same assessment protocol were excluded. However, these similarities reflect only a small portion of the studies and in general there is a considerable variation in assessment procedures and tests. Many studies report intraoperative testing with only a naming or an automated speech task [67,114,123,138,145,179,199]. On the other hand, there are reports of various mixtures of tests that use homemade and tasks borrowed from well-known standardized batteries [26,69,70,109,129,166,171,182,197,198,209,210]. With regards to assessment procedures, most of the studies in this group report a preoperative "preparatory" phase [129,131,171,174,176,179,209,213,222] in which the patient is trained for the intraoperative assessment, and all the incorrectly answered stimuli are removed. It should be noted that the categorization of the articles in Type S and Type M groups was based on the amount of information they shared in their published articles, and not the tests they used per se. For example, Gonen et al. [211] mention that their tasks were used before but they do not provide further information (e.g., about norming data of the stimuli). Tests used in cases like the latter were treated as not standardized. In contrast with homemade tasks, well-known standardized tests borrowed from other pathologies and settings (such as AAT, DO80 and C-WAB) are undeniably normed, therefore, authors do not discuss further task details in their studies. Concerning validation status, records that are tagged as "not reported" indicates that no information or evidence are provided in order to consider these tests as validated.

Type E category

This group includes 16 studies that were mostly experimental in the sense that they were designed to test a specific function (e.g., *syntax* [184], and *verbal memory* [227]) or to report a particular finding (e.g., *language switching* [175] and *writing* [231]). Additionally, this group includes studies reporting experimental tests (e.g., Quick Mixed Test [226]), as well as studies comparing mapping methods, for instance navigated transcranial magnetic stimulation with DES [150], or fMRI with DES [159]. Similarly, with Type M records, the information about norming data of stimuli are not available in most records. Of the two studies that mention data for stimuli norms, one used normed stimuli from databases [184], whilst only Corina et al. [91] shared some information about the grammatical and psycholinguistic variables they took into consideration.

Type P category

This small group includes two (n = 2) studies reporting proposals for intraoperative assessment of brain tumor patients [192,234]. Only one of them is standardized [234], although authors do not provide information regarding norming data of the stimuli. Since there were no reports of intraoperative use for any of the proposed tests, these records were excluded from further analysis.

Critical review of the tests

Below, can be found an analytical description of the three standardized tests extracted from Type S category.

De Witte et al. [79] - Dutch Linguistic Intraoperative Protocol

De Witte et al. [79] use a neurolinguistic approach to develop a battery for awake craniotomies in eloquent brain areas. It consists of 17 linguistic tasks evaluating various language domains (phonology, semantics, syntax, morphology), functions (production of speech, naming, comprehension, reading, repetition), and speech systems (articulation, motor programming). Regarding morphology, authors do not clearly state that it is independently assessed, but some of the proposed tasks (such as sentence completion) involve several morphological processes [118]. All tasks require adequate cognitive abilities, so the authors suggest also an extensive non-linguistic cognitive assessment. All tasks were developed while taking into account the constraints of awake craniotomies as described by the same team [3].

Most of the stimuli included in DuLIP tasks, come from Dutch databases (e.g., CELEX, SUBTLEX-NL, Positie woordenboek), or other language tests, so norming data are assumed. However, this does not apply to all tasks as there are tasks in DuLIP that were made from scratch. Regarding these tasks, information about norming data of the stimuli, such as frequency, imageability, age of acquisition, and visual complexity are sparse. On the other hand, some psycholinguistic variables, like word length, syllable structure, or morphosyntactic features, are reported although not consistently, for all the homemade tasks. In particular, *repetition of words* task is controlled for syllable length and structure, stress pattern, and order of presentation, *reading with phonological odd word out* task only for the syllable structure, *reading with semantic odd word out* task for word length, *action naming* task for the morphosyntactic features of the verbs, *verb generation* task for syntactic (person, number, transitivity) and morphological (different noun-verb stems) features of the elicited verbs, *semantic fluency* task for the included categories, and finally *syntactic sentence judgment* task is controlled for the grammatical errors included. Furthermore, *object naming* and *action naming* tasks are normed for picture-name agreement (over 80%), while all tasks intended for stimulation phase are normed for response time (4 seconds). The authors also tried to avoid stimuli that can be associated with negative thoughts, such as death, brain cancer, and so forth. Lastly, in the description of some tasks there are references to procedures and routes according to cognitive neuropsychological models for single word processing, although no clear connection is made, which suggests a more "loose" association.

Normative data come from 250 adult volunteers, while the pathological population includes five (n = 5) brain tumor patients. Normal sample consists of healthy, native, Dutch-speaking participants, with no neurological or cognitive deficits (according to Mini Mental State Examination [247]), or drug abuse history. Concerning validity, the authors refer to DuLIP as a "valid approach", and in the literature it is characterized as "validated in clinical population" [235]. However, in their article, the authors only offer a description of DuLIP's clinical application in five patients and they do not report the exact validation methods they followed, as Rofes et al. [183] do. DuLIP is considered double-referenced standardized test (norm and criterion based), as it comes with a well-defined administration protocol, it includes normative data, and it assumes a preparatory session. The authors propose a certain procedure with three stages (pre-, intra-, postoperative). During the preoperative stage, after the whole test is administered, the language specialist selects some tasks in order to intraoperatively use them. The selection of tasks needs to be based on the preoperative social, linguistic, and cognitive level of the patient, and also on the characteristics of the tumor. In regard to the clinico-anatomical correlations of the tasks, these are based on the neurolinguistic model they propose in the same article. Most tasks are presented digitally via PowerPoint. Thus, any stimulus that the patient does not respond is excluded from the intraoperative process. During the intraoperative stage, and particularly during the brain mapping, tasks are serially administered depending on the cortical brain area that is stimulated, while for the subcortical mapping they suggest a parallel administration for some functions (e.g., semantic odd-picture out and motor evaluation, with the patient touching the screen).

Concerning its limitations, the authors report some minor issues regarding the specificity of some tasks and their clinico-anatomical correlations. They also address the issue of duration, since the administration of this test intraoperatively can substantially prolong the surgical time. However, this is reasonable considering a comparison with a single object naming test. Language is a very complex system involving numerous brain areas, so a test that tries to cover most of them will require more time. One more limitation is related to the clinico-anatomical correlations of each task. The proposed neurolinguistic model is based almost exclusively on DES studies and most of these studies were retrospective or involved only a few participants. In order to strengthen and verify the suggested function-location relationships, additional studies with larger populations are needed. Furthermore, studies from other fields, such as neuroimaging, may provide additional valuable insights in this regard.

Rofes et al. [172] and Rofes et al. [183] – ECCO and VISC tests

Rofes et al. [183] created a language test for brain mapping, which is addressed to Italian-speaking participants. This is a relatively shorter test as it includes two tasks, an object naming (ECCO) and a verb naming (VISC) task. The images included in the former were extracted from the Snodgrass and Vanderwart [246] collection, whilst with respect to the latter new images were created by a graphic designer. The authors took into consideration all the limitations of intraoperative assessment and normed all stimuli for several psycholinguistic variables. All stimuli are controlled for frequency of occurrence, age of acquisition, imageability and word length in phonemes, whilst verbs are also controlled for instrumentality, transitivity, actionality, number of internal arguments, and regularity. Both tasks are normed for response time (4 seconds) and picture-name agreement. All images are black and white drawings, and are presented in PowerPoint slides with an introductory phrase which the patient has to read. For verb naming, it is a pronominal form (“Lui/Lei…”) and for object naming a carrier phrase (“Ecco la…”). In a subsequent follow-up study by the same team [172], the authors attempted to associate their test with the cognitive neuropsychological model for processing of single words, although it is not specified which adaptation of the model is used.

In total, 75 participants were involved in the standardization and stimuli norming processes. However, tasks were separately standardized and the authors did not specify the actual number of participants, who took the entire test. Fourteen (*n* = 14) patients with post-stroke aphasia were included in the validation purposes. Authors describe in detail the procedures they followed in order to establish concurrent and discriminant (divergent) validity. With respect to the first, they used the Communicative Abilities in Daily Living 2 test and, for the second one they used the Attentive Matrices test. I consider this test as double-referenced standardized (norm and criterion based), as it comes with a well-defined administration protocol, it includes normative data, and it assumes a preparatory session.

Rofes et al. [172] specify a procedure for intraoperative administration and add one more automated-formulaic speech task (counting from 0-10). With respect to the assessment procedure, they propose a preoperative session with an extensive linguistic and cognitive assessment, during which the intraoperative test is also administered. This stage is used as a "preparatory" phase (training of the patient and selection of stimuli). They do not report selection of tasks based on tumor and patient characteristics or alternating tasks intraoperatively according to the area of stimulation. The entire test, including these three tasks, was administered to all patients. Intraoperatively, the two naming tasks can also be used for subcortical mapping. However, regarding resection they do not specify if any task was administered during tumor removal.

Summarizing, it is evident that the Italian test (ECCO and VISC) has been developed with a rigorous methodology. The authors do not explicitly mention any limitation and they argue that the three tasks approach (counting, object naming, and finite verb naming), can efficiently assess the language faculty in a relatively short time. However, as it is discussed in this chapter, a small number of tasks may undermine the test's sensitivity.

Dragoy et al. [235] - Russian Intraoperative Naming Test

Similarly to the test presented above, Dragoy et al. [235] developed a relatively short test for brain mapping during awake craniotomies, which focuses on specific brain areas. It consists of two tasks: one for object naming (50 items), and one for verb naming (50 items), and evaluates lexical and grammatical aspects of language. In the first task (object naming), the patient names images with objects by using nouns, while in the second one (verb naming) names actions by using verbs. Stimuli were extracted from a Russian normative database, and they are controlled for picture name agreement, visual complexity, object or action familiarity, age of acquisition, imageability, image-word agreement, frequency, and word length in syllables. According to the authors, they took into account all the limitations of awake craniotomy and assessment during brain mapping in order to develop their tasks.

Norming data for this test derive from 100 healthy, Russian-speaking participants, and they are available on the webpage of the database. The authors claim that their stimuli can be answered by the typical population in 3-4 seconds, but they do not specify the procedure they followed in order to ensure that. In order to check clinical feasibility and validity, they used their test on 20 brain tumor patients undergoing awake brain surgery. Similarly with the DuLIP test, the authors refer to their test as validated without providing any further evidence.

With respect to the methods of administration, the authors describe the methodology that followed in their clinical population. Preoperatively, it is used along with an extensive neuropsychological assessment. They also mention a preparatory phase in the preoperative stage, during which the patient is trained and the proper stimuli are selected. In line with De Witte et al. [79], Dragoy et al. [235] report a clinico-anatomical model for intraoperative task selection, although it is significantly limited compared to DuLIP test. That model recommends the verb naming task for frontal tumors, and the object naming task for temporal tumors (Chen et al. [248], Damasio et al. [249], Shapiro et al. [250]). Intraoperatively, the selected tasks can be used during cortical and subcortical mapping, as well as during tumor resection. Stimuli were presented digitally with the pictures changing every 3 seconds. They report the use of a carrier phrase, which was given orally by the examiner (instead of the written carrier phrase used in Rofes et al. [183]). I will consider the Russian test as standardized (norm and criterion based), as it provides normative data and assumes a preparatory session, however information regarding exact validation procedures are missing.

Overall, the Russian test is structurally similar to the Italian test (two task approach), and in terms of procedures, it has more similarities to the DuLIP test (clinico-anatomical model). However, several oversights regarding its development methodology were found, especially compared to the other two tests, that raise questions about its reliability and its validity.

Summarizing the results

Our results suggest that the Italian test is the most methodologically rigorous developed, while the DuLIP test [79] is generally the most comprehensive. The DuLIP test provides tasks for mapping and resection of both cortical and subcortical areas, and tasks that cover the majority of language domains (semantics, syntax, morphology, phonology) and functions (speaking, comprehension, reading, repetition, naming), as well as most aspects of speech. Even the word level, where the Italian and Russian tests are restricted, it is not covered in the same range by the three tests.

The DuLIP test extends to several grammatical categories (e.g., nouns, verbs, adjectives, pronouns) through many different tasks. All tests appear to be double-referenced standardized and validated, although only the Italian test [172,183] provides the proper evidence. In terms of procedures, the DuLIP and the Russian tests suggest different tasks for different brain areas, whilst all three tests suggest a preparatory phase that allows the task pre-selection and personalization of stimuli. Table 2.2 summarizes the features of the three tests.

Table 2.2
Comparative presentation of the three standardized intraoperative language tests and protocols reported in this chapter.

	De Witte et al. [79]	Rofes et al. [172] & Rofes et al. [183]	Dragoy et al. [235]
Number of Tasks	17	3[a]	2
Mapping Tasks	different tasks for cortical and subcortical mapping	yes, but not specific tasks for the subcortical mapping	yes, but not specific tasks for the subcortical mapping
Resection Tasks	different tasks for resection	yes, but not specific tasks for the resection process	yes, but not specific tasks for the resection process
Standardization status	norm and criterion based	norm and criterion based	norm and criterion based
Validation	methods not specified	discriminant and concurrent validity	methods not specified
Population (healthy and pathological)	250 healthy, 8 pathological (brain tumors)	75 healthy, 17 pathological (14 post-stroke aphasia, 3 brain tumors)	100 healthy (only for stimuli standardization), 20 pathological (brain tumors)
Language domains and speech systems covered	language: phonology, semantics, syntax morphology speech: articulation, motor planning	language: (lexical-) semantics, syntax speech: articulation (indirectly)	language: (lexical-) semantics, syntax speech: articulation (indirectly)
Language functions covered	speaking, comprehension, reading, repetition, naming	speaking, naming, reading	speaking, naming
Clinico-anatomical model	yes, neurolinguistic, based mostly on DES studies [79]	not provided	yes, based on based on stroke-related studies [248-250]
Association with cognitive neuropsychological models	yes, loose relationship	yes, loose relationship	not provided

[a] The tasks that the authors developed are actually two. The third task they propose is an automated speech task (counting).

2.4. Discussion

In line with other reviews [3,185], the study behind this chapter also found great variation regarding tests and procedures used in language assessment during brain mapping in awake craniotomies. As it is demonstrated in the results, it is evident that most of the neurosurgical teams and institutions use at least one naming task, sometimes combined with an automated speech task. It is also common in bilingual studies to use reading and translating of paragraphs in order to conduct the mapping process.

Regarding the research question, three standardized tests that meet the requirements in order to be reviewed critically were found. The criteria defined that each test had to be developed specifically for intraoperative use, standardized (norm and criterion based) and validated, used in awake craniotomies, and adapted to the special circumstances of brain mapping with DES (e.g., time and cognitive processing constraints). In order to achieve these goals I used the scoping review methodology (for more information, see Methods section).

It is evident from the exploration of the literature that there are several studies that report use of standardized tests (e.g., DO80, or subtests of AAT) either alone or as a part of larger batteries; however these tests cannot be included in group “Type S”, since they do not meet all the criteria (Figure 2.2). For example, these tests have not been specifically designed for patients undergoing awake craniotomy or have not been developed for intraoperative employment. In most cases, they are borrowed from other pathologies (e.g., post-stroke aphasia), something that can result in a misleading assessment of the patient’s communicative profile [189]. Regarding homemade tasks, usually normative data for the stimuli are not available, thus it is unknown whether they have been controlled for various psycholinguistic and grammatical variables (e.g., frequency of occurrence, age of acquisition, word length, etc). Even in cases where well-known, standardized tests are used it is not clear whether they have been normed for response time. Thus, it is unknown if healthy population can respond to each task within the given timeframe (i.e., 4 seconds). Although all the three critically reviewed tests, provide some amount of information with respect to the grammatical and psycholinguistic data of the stimuli, the Italian test provides the most comprehensive details.

It is unclear why in awake craniotomy context mixed assessment tools that employ tasks and norms from different populations are so prevalent. A possible explanation may be the lack of standardized, specialized, and language-specific tests, which is not surprising given that the intraoperative assessment of speech and language by specialized clinicians is undoubtedly less common compared to other settings. Moreover, awake craniotomies are highly specialized, technically demanding, and often expensive surgical operations, therefore not easily available in some countries. Another reason may lie on the need for individualized intraoperative assessments according to the patient’s and tumor characteristics (e.g., size and anatomic location). It is very unlikely, that individual tasks which can cover only a narrow range of the language system, can assess the full spectrum of human communication; therefore, in the cases where the existing test is inadequate, clinicians are led to use homemade tasks in order to fill any possible gaps. Considering the above, one could argue that it is more convenient to combine parts from different standardized tests or integrate specific homemade tasks, than to develop and standardize a specialized test. However, as this is extensively discussed in the current chapter, this strategy may well carry several risks.

Norms are essential because they ensure that patient’s scores from the awake stage are not only comparable to his or her perioperative performance, but also to normal, healthy population. This is particularly important considering that any impairment in language occurred prior to the operation, which is not uncommon according to Davie et al. [58], may compromise the results of the intraoperative procedure. On the other hand, regarding intraoperative use, only norm-referenced standardized tests may hide some pitfalls. As they rely solely in norms, sometimes they can become impersonal and this could limit their ability to capture the unique characteristics of an individual’s communicative abilities [189]. To avoid that, it is critical for both the test and the language specialist to be able to identify impairments in specific language domains or functions not only compared to the healthy population but also to the patient’s perioperative performance. This criterion can be ensured with a session where the clinician personalizes the test on the patient, by removing incorrect responded stimuli and recording the answers. All the three tests that were critically reviewed assume a preparatory session before the surgery and all provide normative data. Therefore, are both norm and criterion based, and better suited for intraoperative language assessment during awake surgery than only criterion-referenced tests.

As mentioned in the Introduction section, sensitivity is a characteristic related with low rate of Type II errors, while specificity with low rate of Type I. In order to reach the “holy grail” of awake brain surgery, that is maximum resection with minimum deficits, brain mapping need to have both at the highest possible level. For example, if a task has high sensitivity but low specificity it will fail to distinguish between true errors, caused by the stimulation or the tumor resection, and errors resulting from reasons not related with the brain mapping. This scenario can lead to reduced extent of resection. Contrarily, a task with low sensitivity and high specificity will fail to identify eloquent areas as such, which can lead to increased permanent linguistic deficits. Regarding the types of errors produced intraoperatively by the patient (such as anomias, semantic paraphasias, speech arrests, etc.), one could argue that they could provide some indications about the subsystem that is disrupted. However, this may not always be reliable since it exclusively relies on the interpretation of the error by the examiner. A limitation that all the tests included in Type S group carry, is that they do not provide detailed information about their sensitivity and specificity, therefore their predictive value is unknown.

Generally, object naming is a task with high sensitivity in brain mapping which is why (among other reasons) it is so widely used in awake craniotomies [2]. According to Gatignol et al. [251], it is reproducible across languages, requires exactly the same cognitive stimuli regardless of the language, and recruits well-understood cognitive processes. However, this view does not take into account the linguistic and cultural differences among different normative samples. Although it fails to assess language beyond the word level (for example syntactic features), it involves several language domains (for example morphology, lexical-semantics, phonology), all the subsystems supporting speech (articulation, voice, prosody, resonance, respiration), and other, non-linguistic cognitive abilities (e.g., visuospatial processing, executive functions). However, not all these functions are involved equally, in the same degree. Thus, during stimulation one or more of these functions and subsystems may be disrupted, but little information is provided regarding which of them is essential and which supplementary. It should be noted that in object naming tasks even if a carrier phrase such as "*This is a ...*" is used, not all grammatical aspects of the language (e.g., Subject-Verb Agreement) are evaluated, since it is an automated phrase that uses a copular verb (is) which is a special grammatical case that does not carry significant morphosyntactic load. Also, important language functions above the word level, like suprasegmental features (e.g., intonation and phrase prosody) are ignored.

Given the complexity of human language, it is very hard to isolate and examine a specific language domain or function (for example only grammar). Nevertheless, some tasks can narrow their scope of assessment. For example, a phonological odd word out task with auditory stimuli is highly specified to assess phonological processing. Similarly, all the so called “essential language areas” support more than one language function, although not all of them are involved in the same degree (some of them more, some of them less). This is one of the main reasons why preoperative fMRI cannot be reliably used for surgical planning, because it fails to distinguish between essential and supplementary areas [3,252].

The fact that automated speech and object naming tasks involve numerous brain areas and language functions makes them effective tools to detect eloquent brain areas. However, this feature can compromise the sensitivity of these tasks and increase Type II errors if they are not used correctly. For instance, if an object naming task is used to map brain areas related to other language functions (e.g., verb naming) patient is prone to produce false negative errors, which can increase permanent postoperative deficits. This is more relevant in brain tumors where neuroplastic changes can relocate functions and reshape our knowledge about clinico-anatomical correlations [25,29]. The impact of intraoperative language assessment on postoperative quality of life and life expectancy amplifies the need for tests that provide accurate clinico-anatomical correlations and distinguish between essential and supplementary areas for every function of the language system. From the three reviewed tests, DuLIP [79] seems to provide these characteristics more consistently.

Based on all the information that was extracted from the review and the analysis that followed, I would like to highlight the following points as important parts of a valid language assessment in awake craniotomy context. First, a detailed neuropsychological evaluation with standardized tests and diagnostic batteries should be conducted preoperatively to set the baseline and detect severe language or cognitive impairment. An individualized intraoperative assessment should be carefully planned for the mapping and resection processes according to the surgical plan, patient's characteristics (i.e., age, education, bilingual status), lesion's characteristics (i.e., type of pathology, size, anatomic location), and possible neuroplastic variations due to the slow, chronic tumor growth. The assessment should include a perioperative preparatory session in order to detect and exclude from further procedures stimuli which were incorrectly answered. Preferably, the intraoperative test should be developed specifically for language mapping, while the clinico-anatomical correlations ought to be based on the suggestions of the current neurolinguistic literature. Also, it should be standardized and normed on a healthy population comprised by native speakers of the particular language, and properly validated, at least for concurrent and discriminant validity. The included stimuli should be controlled for various psycholinguistic and grammatical variables, and comply with the particular conditions that emerge in the demanding intraoperative setting (e.g., time frame for mapping tasks, possible impact of anesthesia on patient's cognition, patient's fixed position, and space insufficiency inside the operating theatre). Finally, a detailed neuropsychological assessment with the preoperative tests should be conducted several weeks or months after the operation since several neurophysiological phenomena during the acute postoperative phase may affect the patient's performance.

Regarding the clinical usability of each test, an important issue that frequently arises is the time each test requires inside the operating room. Although at first glance DuLIP, which consists of considerable more tasks compared to the other two, seems to need much more time to be administered, it is highly unlike that all 17 tasks will be used simultaneously. According to the model they propose in their article, it is extremely uncommon to use more than four or five tasks in a single surgery. Therefore, although DuLIP may need more time to be administered, as it evaluates more language functions than the other two, the difference in administration time is not as big as it initially seems.

A possible shortcoming of the current scoping review is that the investigation was limited to two databases. In order to surpass that limitation, gray literature and snowball referencing were also included. The fact that only three tests were found also limits the review, so safe conclusions are difficult to be drawn. Future studies that will bring additional tests to the surface may shed light on which language functions are most frequently affected in brain tumor patients and by which lesions. This can reduce the duration of mapping and resection processes without risking reduced sensitivity and specificity.

Concluding remarks

In the present chapter I investigated the literature through a scoping review in order to find and analyze standardized and validated language tests used in awake craniotomies. The three tests that were critically reviewed show some advantages and disadvantages. According to the analysis in the discussion section, it is evident that larger tests cover more language functions, which may lead to higher sensitivity at the cost of increased administration time. The Italian test (ECCO and VISC) report a rigorous methodology and provides all the necessary evidence regarding stimuli norming data and validation procedures. The neurolinguistic model proposed by the team behind DuLIP suggests on average two or three tasks for each cortical or subcortical structure, and thus it is reasonable to presume that the duration of the mapping process will not greatly differ from the other two tests. Comprehensive perioperative sessions will diminish Type I errors while accurate correlations between functions, tasks and neuroanatomy will keep Type II error rate low. This is not an easy task considering the neuroplastic mechanisms involved in brain tumors. In this regard, the collaboration of researchers, clinicians, neurosurgeons and the other specialties involved in intraoperative language mapping is very important and can lead to more accurate and efficient tests.

Chapter 3. Developing and norming an intraoperative test[3]

Abstract

Assessing a variety of language functions intraoperatively can affect the extent of the tumor resection as well as the patient's postoperative quality of life. Although most published intraoperative tests presume preoperative sessions where tasks are personalized to each patient, normative data are essential since they can ensure that the presented stimuli can be responded appropriately. In this chapter, I describe the development and standardization procedures of the first Greek linguistic test, designed specifically for brain mapping during awake craniotomies. The tasks are developed to comply with the special conditions and restrictions of language assessment inside the operating room. Each task is controlled for various psycholinguistic and lexical variables and it is associated with specific neuroanatomical areas and linguistic processes. Population consists of 80 right-handed, healthy, Greek-speaking individuals aged 20-60 years. Only a few main effects and interactions of demographic variables were found on the results. Most differences were found between age groups, since older participants tend to perform slightly worse than younger ones. Therefore, percentiles and cut-off scores were calculated separately for each demographic group. Finally, I will outline the procedures of administration on brain tumor patients which underwent awake craniotomy, but only briefly since the clinical application of the test is described with detail in the next chapter.

3.1. Introduction

Two quite popular tests for evaluating language intraoperatively are object naming and automated speech. However, as discussed in previous chapter (Chapter 2) using only these two tasks may increase the risk of Type II (false negative) errors which may result in reduced sensitivity of the mapping procedure. Thus, additional tasks that will cover more linguistic functions and may lead the neurosurgeon to identify and preserve more eloquent brain areas [3]. It has been argued that this process can create a direct link between the quality of language assessment intraoperatively and the patient's life expectancy and postoperative quality of life [193].

The characteristics of a modern comprehensive language test that is intended for intraoperative use have been described in previous chapter. However, it should be stressed

[3] A modified version of this chapter was published as: "Papatzalas C, Fountas K, Brotis A, Kapsalaki E, Papathanasiou I. The Greek linguistic assessment for awake brain surgery: development process and normative data. Clin Linguist Phon. 2021 May 4;35(5):458-488. doi: 10.1080/02699206.2020.1792997."

that in addition to normative and validation data these assessment tools should have features to counter the particular conditions arising in intraoperative assessments. Also, their stimuli should be controlled for linguistic complexity through various psycholinguistic and lexical variables. Finally, these tests should have the flexibility to rapidly proceed to a different linguistic function every time the neurosurgeon moves to a new area either for stimulation or resection. Resection is a different process, and its assessment should be treated slightly different than mapping [79,205]. The errors detected through the continuous assessment of the patient during the resection of the pathological tissue, can warn the neurosurgeon that the resection approaches eloquent cortex. The resection part of the awake assessment is not free of constraints. The patient remains on a fixed position and anesthesia may still affect his or her cognitive abilities (although this is not common). Additionally, the patient may experience headache, dizziness or other discomforts as the neurosurgeon removes the pathological tissue so it may be difficult to concentrate and process complex stimuli. Moreover, the patient’s linguistic abilities may start to decline after a certain amount of time either because functions are maintained within the tumor, or because the resection is close to the borders of the tumor. On the other hand, the time limit of four seconds does not apply to the resection stage. However, as in the case of mapping tasks, stimuli should be controlled with respect to their linguistic and cognitive demands. To this end, tasks that involve comprehension and spontaneous speech may be more relevant to detect lesions due to resection, especially at latter phases of the awake stage.

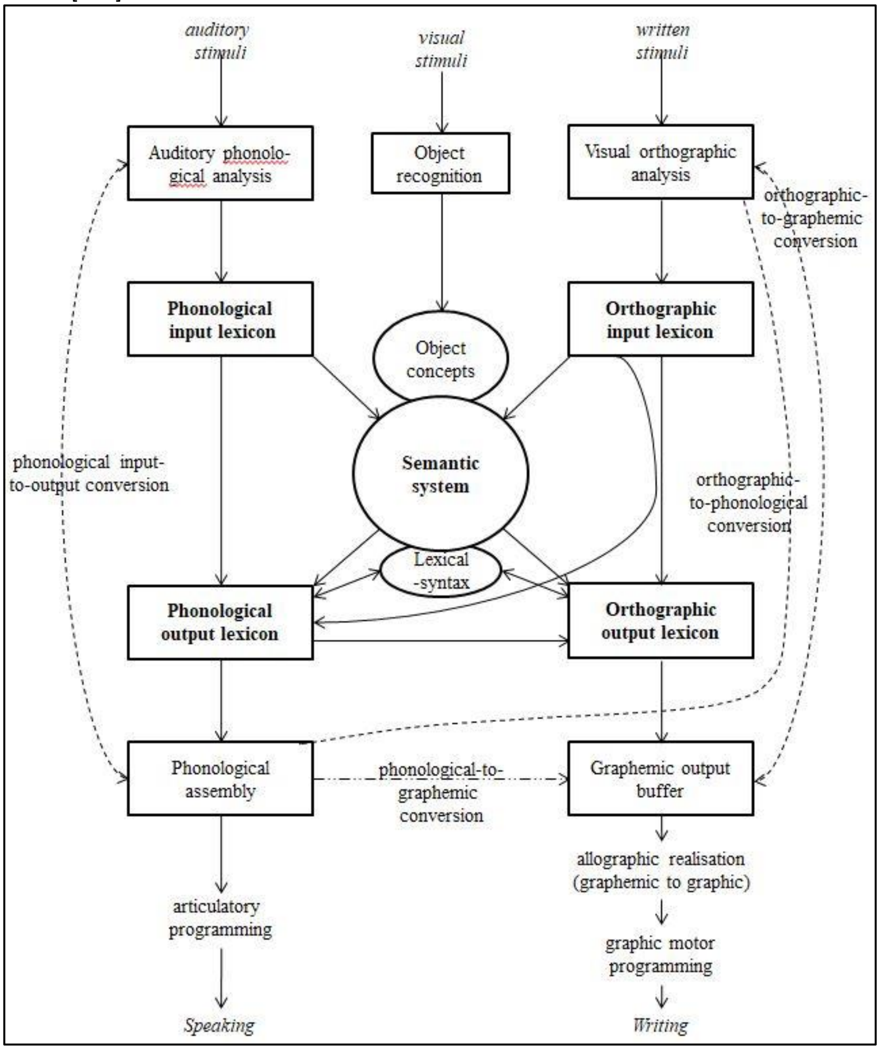
This chapter describes the development and norming procedure followed for the Greek Linguistic Assessment for Awake Brain Surgery (GLAABS) which is the first intraoperative (norm and criterion based) standardized test in Greek. This test includes specific administration procedures and linguistic tasks evaluating various language functions and brain areas and it is based on articles reporting similar tests and methods [59,60,69,79,112,125,166,183,192,197]. It is designed for use mainly inside the operating room, to assist brain mapping, but it can also be used preoperatively and postoperatively to indicate abnormal language performance. Before the description of the test, in the next sections I provide an overview of the cognitive neuropsychological and neurolinguistic models that were utilized in the development of the test.

Cognitive Neuropsychological Models of Language

Cognitive models for single words and sentences provide a comprehensive theoretical framework and are widely used in the assessment of language disorders. Their utilization in developing accurate and effective tests is important as they correlate specific cognitive functions with language domains. This is especially relevant today, since there is an increased need for more elaborate tests in the neurosurgical field [253].

With respect to single word processing and word retrieval the model proposed by Whitworth et al. [254] was used (Figure 3.1), which is in fact a development of the older “logogen model” [255]. Following Rofes et al. [253] the *lexical-syntax* process was also considered and it was relevant to thirteen (n = 13) tasks.

Figure 3.1
Cognitive model for single word processing, based on Whitworth et al. [254] and Rofes et al. [253].



Sentence level processing should be treated differently from word level processing, since the latter does not require the range of grammatical functions and working memory needed for sentences [256]. With respect to comprehension and production of language in sentence level, the model proposed by Bock et al. [257] was considered (which is a newer version of Garrett’s [256]). The tasks relative to this model were three for comprehension and one for production. Table 3.1 (next page) demonstrates the correlations between the main linguistic function aimed by each task and the relative routes or processes involved.

Table 3.1
GLAABS tasks and the key functions they involve.

Task	Function Aimed	Stim	Route (or process) targeted
Word repetition	Repetition	O	Phonological route, via the lexicons[a]
Motor planning	Motor planning of articulation (praxis)	O	Phonological input-to-out conversion & articulatory programming
Phonological odd-word out	Phonological processing	W	Orthographic-phonological route, via the lexicons
		O	Phonological route, via the lexicons
Semantic odd-word out	Semantic processing, reading	W	Orthographic-phonological route
Semantic odd-image out	Semantic processing, object recognition	V	Visual-phonological route
		O	Phonological route
Verb naming	Lexical-syntactic interface	V	Visual-phonological route, via the lexical-syntax
Object naming	Semantics, object recognition	V	Visual-phonological route[b]
Semantic association	Semantics processing, reading	W	Orthographic-phonological route
		O	Phonological route
Sentence completion (with word)	(morpho-)Syntax, reading	W	Orthographic-phonological route, via the lexical- syntax[c]
Verb generation	Semantics, syntax, object recognition	V	Visual-phonological route, via the lexical-syntax
		O	Phonological route, via the lexical-syntax
Sentence completion (with sentences)	Syntax, connected speech	O	-[d]
Phonological judgment	Phonology (comprehen-sion)	O	Phonological encoding
Semantic judgment	Semantics (comprehen-sion)	O	Functional processing (lexical selection)
Grammaticality judgment	Syntax (comprehension)	O	Functional processing (function assignment) & positional processing
Phonological fluency	Phonology	O	Phonological output lexicon
Semantic fluency	Semantics	O	Semantic system
Action fluency (verbs)	Lexical-syntactic	O	Lexical-syntax

The GLAABS tasks and their relation to the language processing models for words and sentences. I use the term "route" to refer to a standard group of processes: a) *phonological route* (auditory phonological analysis, phonological input lexicon, semantic system, phonological output lexicon, phonological assembly, articulatory programming), b) *orthographic-phonological route* (visual orthographic analysis, orthographic input lexicon, semantic system, phonological output lexicon, phonological assembly, articulatory programming), c) *visual-phonological route* (object recognition, object concepts, semantic system, phonological output lexicon, phonological assembly, articulatory programming). The presence of a deviation from the standard is denoted with the phrase "via the…". For example, the term "*phonological route, via the lexicons"* is used to indicate that this route links the two phonological lexicons and bypasses the semantic system. Leg: *Stim* = Stimulus, *V* = Visual, *W* = Written, *O* = Oral.
[a] if words are repeated as pseudowords, no access to the lexicons is needed
[b] in case of carrier phrase lexical-syntax process is also involved
[c] in this task sentence comprehension processes are also involved
[d] almost all language production and comprehension processes are involved in this task

Despite the fact that some tasks can focus on specific cognitive or linguistic processes, it is very difficult to accurately assess a single process with a single task [254]. In order to do that, one might need several other tasks that focus on different routes, processes and structures. The same holds for GLAABS tasks: although the cognitive and linguistic functions involved in each task are more than one, each task aims on those that carry the heavier load. For example, the *verb naming* task involves the *visual-phonological route, via the lexical-syntax*. That means that object recognition, object concepts, and all the word retrieval processes (semantic system, lexical-syntax, phonological output lexicon, and phonological assembly) are involved to some degree. In order to check if the *lexical-syntax* in particular is impaired, the examiner might need additional tasks, which will engage a similar route but will not require access to lexical-syntactic/grammatical features, e.g., *object naming task (without a carrier phrase)*. The same holds for sentence level, for both production and comprehension.

Clinico-anatomical correlations

It is generally accepted that there are no clear-cut correlations regarding cognitive tasks, brain areas, and linguistic functions. One specific brain area (e.g., the left inferior frontal gyrus - LIFG) may involve more than one linguistic functions, and one task (e.g., the sentence completion with a word task) may involve more than one brain areas [252]. However, most linguistic functions are supported more heavily by certain brain areas, which are considered *essential*, and less by others, which are considered *supplementary* [3,252]. Also, tasks can focus on specific linguistic domains if they are controlled for specific psycholinguistic variables [258]. For example, in the *phonological odd-word out* task, which aims on phonological processing, stimuli have to match for all psycholinguistic variables (semantics, syntax, length, frequency, etc), except the ones that involve phoneme processing. Thus, although it is difficult for tasks to be specific to a single linguistic function or brain area, they can focus on specific *essential* brain areas and linguistic functions.

The clinico-anatomical correlations of GLAABS (Table 3.2) are currently based on the neurolinguistic model proposed by De Witte et al. [79]. It should be noted that although this model links specific brain areas to linguistic functions and tasks, some of them may involve additional cortical or subcortical structures (e.g., occipital lobes are involved in all visual

Table 3.2
Clinico-anatomical correlations.

Brain region	Linguistic (or relative to language) functions
Cortical	
Inferior frontal gyrus	Articulatory processing, syntax, writing, executive functions[a]
Post. middle frontal gyrus	Action naming, writing
Post. superior frontal gyrus (SMA)	Language initiation
Precentral gyrus (PMA)	Motor network, motor aspects of speech
Post. superior temporal gyrus	Semantics, auditory comprehension, naming of living objects
Mid.-post. superior temporal sulcus	Phonological network
Ant. middle temporal sulcus	Famous face naming, memory
Mid. inferior temporal gyrus	Lexical interface, naming of non-living objects
Supramarginal gyrus	Reading, naming, semantics, memory
Angular gyrus	Reading, writing, calculation
Subcortical (white matter tracts)	
Subcallosal fascicle	Initiation of speech
Inferior fronto-occipical fascicle	Semantics, reading, judgment
Inferior longitudinal fascicle	Reading, phonology & semantics
Superior longitudinal fascicle (& arcuate fascicle)	Processing of articulation, phonology
Uncinate fascicle	Famous face naming, semantics
Corticospinal tract	Motor speech

Clinico-anatomical correlations based on neurolinguistic model proposed by De Witte et al. [79]. Leg.: *post.* = posterior, *mid.* = middle, *ant.* = anterior, *SMA* = supplementary motor area, *PMA* = primary motor area.
[a] Alvarez et al. [259]

tasks, such as reading). The correlations are based on studies with DES, which are quite effective in the identification of brain areas that are essential or supplementary to language [252].

3.2. Materials and methods

Development of the test

General principles

As described in the introduction, all the special conditions and restrictions of language mapping in awake craniotomies were taken into consideration. The time frame for mapping tasks is four seconds (4'') for presentation, process, and response to stimuli. Regarding possible mental fatigue and cognitive limitations due to anesthesia, I controlled the stimuli for visual and linguistic complexity in order to have 90% agreement in responses (except verbal fluency tasks). The fixed position of the patient and the limited space inside the operating room are affecting the presentation of the tasks with visual (object or written) stimuli. This challenge was addressed by creating digital versions of visual tasks, which can be presented via laptop or tablet. Finally, special record forms were created so that the examiner can easily record the answers/score.

For the needs of the present dissertation I developed 15 tasks to test different linguistic functions and I used another two (*n* = 2) verbal fluency tasks that are widely use and standardized in healthy Greek population [260]. The development process was based heavily on the proposals of De Witte et al. [79], Rofes [258], Bello et al. [125], and Polczynska [192]. Mapping and resection processes are treated differently, therefore GLAABS includes both timed tasks and tasks free of time restriction (the latter focus more on comprehension). The timed tasks are ten (*n* = 10) and best suited for the mapping process. Eight of them use visual stimuli (PowerPoint slides) programmed to change every 4000m/s (4 seconds). Following methodologies of similar tests [124,258], I placed a blank slide containing a large X in the center accompanied by a beep sound for 500m/s between each stimulus. In order to check the *auditory input route*, most of the timed tasks involving visual stimuli can also be given orally by the examiner. Tasks limited to the resection process do not have a time restriction and six (*n* = 6) of them have auditory stimuli provided by the language specialist, while the other three (*n* = 3) are verbal fluency tasks. For tasks that use visual-written stimuli, the "open sans" theme fonts were used since it is the easiest to read [261]. The *verb generation task* incorporates both visual and written stimuli, and the slides contain the image of an object and below a written word. For the tasks with images the Snodgrass et al. [246] colored pictures set was used [262]. For this set of pictures, normative and psycholinguistic data (imageability, visual complexity etc.) are already available in Greek [263]. The *verb naming* task employs the black and white drawings made by the famous Greek sketch artist “Stathis”[4]. In order to explore their psycholinguistic features separate experiments were conducted (see section 2.1.4 Group C tasks, subsection *Verb generation*). For tasks involving sentences, proper nouns were avoided as they are harder to recall [264]. In order to decrease perseveration errors and production of false positives, most of the stimuli were pseudo-randomly placed and, even though it was not always possible, I tried to avoid placing consecutively stimuli with visual, semantic, phonological and/or syntactic similarities. For some specific tasks extra experiments were conducted to check differences between oral and visual-written stimuli. These experiments were applied to ten (n = 10) healthy participants and relate to the following tasks: *phonological odd-word out*, *semantic odd-image out*, *semantic association*, and *verb generation*. Regarding the *semantic odd-word out* task, it was revealed that, when the task is given orally, it takes longer than 4 seconds for the participants to answer each target, thus its oral administration during mapping procedures is discouraged. The population for these experiments consisted of three (n = 3) females and seven (n = 7) males, with average age of 38 years, average years of education 14, and cognitive abilities above normal range (MoCA score >27). The results did not differ from the original stimuli, whether it was written or visual, since all oral stimuli had an above 90% agreement in answers.

For development purposes, I divided the tasks into five major groups based on the type of the expected response (Table 3.3, next page). In order to control complexity and cognitive/linguistic load for Groups A, B, and D that require a specific answer, I selected stimuli that have a 90% agreement in responses according to piloting experiments and previously published normative data. Group C and E tasks do not require a specific response; however, there are some restrictions regarding which answers are considered correct.

Group A tasks

Group A tasks consist of two tasks in which only exact repetitions were considered correct answers. The patient has to repeat the oral stimuli one (repetition task) or more times (motor planning task). Both tasks are more appropriate for brain mapping.

Word Repetition

This is a mapping task in which patients are asked to repeat the word they hear. Sixty-five (n = 65) words are presented orally with increasing difficulty based on syllable structure, phonological similarity, and frequency[5]. Forty words have simple syllabic structure, that is,

[4] Drawings were developed for the program “Teaching Greek Sign Language as First Language and Personalized Educational Program for Kids with Hearing Impairment” http://www.pi-schools.gr/programs/seppe/ppe/Eidiki_Agogi/ppe28.htm.
[5] In this article I use this term to refer to frequency of occurrence in Greek (written) language and particularly to the Zipf scale [267], which is the most appropriate statistic to measure word frequency in psychological research [270].

Table 3.3
Tasks of GLAABS.

Group	Expected answer	Tasks	Studies reported
Group A	Repetition	Word repetition	Chang et al. [232] De Witte et al. [79] Kilbride [197] Meyer et al. [70] Papagno et al. [230] Skrap et al. [205]
		Motor planning	De Witte et al. [79] Skrap et al. [205]
Group B	Specific response	Phonological odd-word out	De Witte et al. [79] Skrap et al. [205]
		Semantic odd-word out	De Witte et al. [79] Polczynska [192] Robert [69] Sierpowska et al. [140]
		Semantic odd-image out	De Witte et al. [79]
		Naming of Verbs	Bello et al. [125] Bilotta et al. [177] De Witte et al. [79] Dragoy et al. [235] Jung et al. [150] Lubrano et al. [265] Rofes et al. [183]
		Object naming [a]	Corina et al. [222] De Witte et al. [79] Duffau et al. [2] Hervey-Jumper et al. [129] Moritz-Gasser et al. [180] Polczynska et al. [220] Robert [69] Rofes et al. [172] Roux and Tremoulet [221] Sarubbo et al. [215] Tomasino et al. [182]
Group C	Open-ended	Semantic association	De Witte et al. [79] Trimble et al. [166]
		Sentence completion (with word)	De Witte et al. [79] Ojemann et al. [266] Polczynska [192] Serafini et al. [92]
		Verb generation	De Witte et al. [79] Gonen et al. [211] Grossman et al. [122] Saito et al. [198] Sobottka et al. [202] Tomasino et al. [182]
		Sentence completion (sentences)	De Witte et al. [79]
Group D	Closed-ended	Phonological judgment	De Witte et al. [79]
		Semantic judgment	De Witte et al. [79] Gonen et al. [211] Skrap et al. [205]
		Grammaticality judgment	De Witte et al. [79] Zanin et al. [118]
Group E	Verbal fluency	Phonological fluency	De Witte et al. [79] Skrap et al. [205] Ott et al. [207]
		Semantic fluency	De Witte et al. [79] Ott et al. [207]
		Action fluency (verbs)	De Witte et al. [79]

The GLAABS tasks are divided in five groups according to the expected answer. In the right column the studies where tasks are mentioned or described are alphabetically listed.
[a] Almost every language mapping study reports a naming test, however it falls beyond the scope of the current study to mention them all (for a comprehensive review see Rofes et al. [185]).

they contain only CV type syllables. Half of them (*n* = 20) are phonologically dissimilar and frequent (*M* = 4,529, *SD* = 0,410, *RANGE* = 3,764-5,194) and half (*n* = 20) similar and infrequent (*M* = 2,883, *SD* = 0,654, *RANGE* = 1,327-3,925). The rest of the 20 words contain consonant clusters and 15 of them are dissimilar and frequent (*M* = 4,205, *SD* = 0,755, *RANGE* = 2.327-5,392) while only 5 similar and infrequent (*M* = 2,917, *SD* = 0,290, *RANGE* = 2,504 3,282). All selected words are three-syllable and controlled for phoneme length and grammatical category (all nouns). Their lexical properties (including frequency) are coming from the GreekLex 2.0 database [267]. Words were placed in a manner that no consecutive words share the same stress pattern or have a semantic or phonological relation.

Motor planning

In this diadochokinesis task, patients are asked to produce a sequence of syllables, given to them orally, five times. Six (*n* = 6) sequences in total are included and following Pierce et al. [268], three have serial sequencing (e.g., /tatata/) and three alternating (e.g., /pataka/).

Group B tasks

In Group B a specific target-response is expected by the patient, according to normative data acquired from healthy population and pilot experiments. Tasks in this group are better suited for mapping, although they can also be used during resection.

Phonological odd-word out

In this task the patient is asked to read the phonologically non-matching word (e.g., *βάση* /’va.si/ ‘base’, *τάση* /’ta.si/ ‘trend’, *χώρα* /’xo.ɾa/ ‘country’, *φάση* /’fa.si/ ‘phase’). The stimuli can be given orally or visually and consist of 23 Power Point slides each one containing four written words. All the words and their lexical data (including frequency) are extracted from GreekLex 2.0 database [267]. The words in each slide are matched for length in phonemes, frequency in written language, syllable structure, orthographic transparency, and grammatical category. However, one of the words is the “odd” one that differs from the rest only from a phonological perspective as it contains different consonants and a different last vowel. Presentation order was pseudo-randomized with increasing difficulty according to the variables described above (length, syllable structure, and frequency). Concreteness and imageability should not affect performance as reading is not semantically mediated in this task [269]. According to the cognitive neuropsychological framework for single word processing and the analysis provided by Whitworth et al. [254], the direct lexical route does not involve the semantic system. The processed words can be identified and read aloud without access to the semantic system or the use of semantic knowledge. The words are recognized in the orthographic input lexicon and their phonology is retrieved from the phonological output lexicon. Since only real words are processed in the lexicons, a key element which can affect this process is frequency. More frequent words are more likely to use the direct lexical route and not pass through the semantic system thus only frequent words were included in this task (*M* = 3,603, *SD* = 0,876, *RANGE* = 1.327-5,925) according to GreekLex 2.0 database [267].

Semantic odd-word out

This task is similar to the phonological odd-word out; now patients exclude the word that does not match semantically (e.g., *τράτα* 'fishing boat', *πεύκο* 'pine tree', *λεύκα* 'poplar tree', *έλατο* 'fir tree'). It consists of 20 slides, each one containing four written words with one being semantically dissimilar. Only written stimuli can be used in the brain mapping process. The words were taken from the GreekLex 2.0 database [267] and they were divided in two large superordinate categories, biological and non-biological, according to Rosch et al. [271]. Then, they were further divided in smaller subordinate categories according to their common semantic features (e.g., fruits, trees, birds). Each slide contains four words that were all matched for length[6], frequency, and grammatical category. The non-matching word belonged to the opposite superordinate category (i.e., biological or non-biological[7]). The slides were arranged with increasing difficulty and were pseudo-randomized based on the superordinate category of the target-word of each slide, which alters between biological and non-biological.

Semantic odd-image out

In this task, patients have to exclude the semantically non-matching image by naming it. The pictures used were taken from Rossion et al. [262] set (colorized version of Snodgrass et al. [246]) for which there are already normative data in Greek [263]. Images were divided into semantic categories according to their common features (e.g., fruit, body parts, tools, etc). All pictures in each slide are matched for familiarity, picture-name agreement, imageability, length in letters and visual complexity, while the non-matching image and its corresponding word differs only in terms of category. Slides were pseudo-randomized so there are no consecutive (target) words with phonological and semantic similarities.

Verb (Action) Naming

Patients are asked to name the presented action using a verb. Stimuli are visual, consisting of 38 black and white drawings placed on PowerPoint slides. All pictures are matched for various psycholinguistic variables. Picture-name agreement, age of acquisition, and imageability data were obtained through pilot experiments in healthy adults based on Rofes [258] methodology (see next paragraph). Data regarding frequency in written language were

[6]It was not possible to match perfectly in number of phonemes or syllables so I tried to match them at least in terms of number of letters.
[7]Unfortunately it was not possible to apply this rule to every slide of this task.

obtained from the Corpus of Greek Texts [272]. The dominant verbs for every picture are also controlled for several grammatical variables. None of the verbs is reflexive or unaccusative, whilst all verbs have an external argument and assign an agent θ-role to their subjects. Thirty pictures elicit two place (transitive) verbs, while eight elicit one place unergative verbs. Slides were placed on pseudo-randomized order with increasing difficulty based on picture-naming agreement rates.

In order to gather the psycholinguistic information of the stimuli a psycholinguistic experiment was conducted based on the methodology described by Rofes [258]. Initially, the 74 original images that represented actions (see footnote 5) were checked for visual complexity. This procedure was carried out with lossless GIF compression method which is based on algorithmic information theory and image compression [273]. Specifically, lossless compression was applied on all PNG files. The lower the compression rate of the images, the more complex visually are considered. This process resulted in exclusion of two images with high visual complexity.

Subsequently, the 72 images were placed on power point slides and were administered by the first author to the experiment population consisted of ten (*n* = 10) healthy individuals. Half of the participants were males and half females with average age 32 years (range 30-40) and average education 17 years (ranged 14-22). This process resulted into 41 images that had above 80% agreement in responses, i.e., the participants produced the same verb. One more verb (clap) was also excluded due to the fact that produced a light verb construction.

Then, imageability and age of acquisition were calculated for the 40 dominant verbs of each image. For these two experiments, I used on-line questionnaires made with Google forms and administered them to 50 individuals in total (25 for imageability and 25 for age of acquisition). None of the participants had history of drug abuse, neurological problems or non-corrected vision (self-reported). Age ranged from 21 to 60 years old and education from 12 to 22 years of education. The two questionnaires contained the 41 verbs in written form and 10 control verbs (different for each questionnaire). Regarding imageability, participants had to answer, based on a likert scale (1-5), how difficult it was to imagine the action of the given verb. The controls were some very abstract verbs, such as categorize, differentiate, define etc. The 41 verbs had an average score of 1,2 (*SD* = 0,30), while controls had average 3,9 (*SD* = 0,51). Regarding age of acquisition, participants had to choose from the given age groups (0-3, 4-6, 7-10, 10-12, 12 and above) in which age they learned the meaning of each verb. Controls for this questionnaire were 10 less frequent verbs that are not likely to be acquired in younger ages (e.g., conclude, philosophize, document). The 41 verbs had an average score of 1,4 (*SD* = 0,24) and control verbs had 3,8 (*SD* = 0,43). The above results indicated that the used verbs had high imageability and young age of acquisition. Two additional images were excluded due to the 90% threshold for correct answers, reducing the final number of images to 38.

Object Naming

This is the most common type of linguistic task in awake craniotomies. Patients are asked to name the presented object orally. The stimuli consist of 109 images presented in PowerPoint slides. The pictures were taken from Rossion et al. [262] (colorized version of Snodgrass et al. [246]. As mentioned previously, normative and psycholinguistic data were already available for the Greek population [263]. The stimuli are controlled for familiarity, picture-name agreement, imageability and visual complexity; they were arranged in a pseudo-randomized order in order to avoid (target) words with phonological and semantic similarities appearing consecutively.

Group C tasks

The tasks included in Group C are open-ended, meaning that although there are some criteria in order to consider a response correct, there are still many possible answers. For example, in the sentence completion task, the sentence "Mount Olympus is very …" has many possible responses (e.g., tall, cold, beautiful, etc), but they have to be semantically appropriate adjectives (or words acting as adjectives), in the proper morpho-syntactic form (e.g., 1SG.NOM). Answers such as "Mount Olympus is very … *window*" are considered ungrammatical and therefore errors. Most of Group C tasks (semantic association, sentence completion with words, and verb generation) are best suited for mapping, even though using them during resection is not irrelevant. In contrast, the *sentence completion (with sentence)* task can only be used during the resection process.

Semantic association

In this task, patients are asked to produce a word that matches the two given written words (e.g., stimuli: cow, sheep, response: donkey). The task consists of 19 slides that can be presented orally or visually and each one contains two words belonging to the same semantic category (e.g., animals). There is not a single correct answer here; the produced word should belong to the proper category. First, it had to be decided which semantic categories would be included. Although, categories deriving from verbal fluency tasks were initially used [260], after the pilot administrations it was decided to change this because the results were inconsistent. Instead I preferred more general categories. The words in each category (taken from the GreekLex 2.0) are matched in terms of length and frequency. The slides were pseudo-randomized but consecutive similar semantic categories were avoided.

Sentence completion (with word)

In this task, the patient is asked to complete the given sentence by producing a word. The presentation of the stimuli can be written or oral depending on which functions need to be assessed. In the first case, the examinee silently reads the incomplete sentence and produces an appropriate word, while in the second the sentence is presented orally by the examiner. Below I provide five examples (1) in the original language (Greek) which are followed by a free/loose translation in English:

(1) a. Ο σκύλος δαγκώνει το … *(noun)*
"The dog bites the _____"
b. Κάνε ησυχία γιατί το παιδί … *(verb)*
"Keep quiet because the child is ______"
c. Η ζάχαρη είναι πολύ… *(adjective)*
"Sugar is very _____"
d. Πάω για ύπνο, αύριο ξυπνάω … *(adverb)*
"I am going to bed, tomorrow I wake up _____
e. Άσε μην πας εσύ, θα πάω … *(pronoun)*
"Leave it, _____ will go"

The stimuli consist of 21 slides and each slide contains a sentence in which the last word (target) was replaced with an ellipsis (three dots). For every sentence there is a wide range of possible answers; however, the produced word must be semantically, morphologically, and syntactically correct. I included five grammatical categories (parts of speech) and matched the number of sentences for each condition with the rate that these categories appear in the Greek language. Since data for oral language were not available, the GreekLex 2.0 database was used. Eventually, the task contains nine sentences targeting nouns, five targeting adjectives, three targeting verbs, two targeting adverbs and two targeting pronouns. The sentences for each condition are matched for word order, number of words and number of phonemes. The presentation order is pseudo-randomized and I avoided placing the same grammatical category of the target word consecutively.

Verb generation

Patients are asked to produce a single verb that is associated with the object presented (e.g., object: *chair*, response: *sit*). The stimuli consist of 15 slides that contain a picture of an object and its written form. The written form is provided in order to differentiate the task from *object naming* and urge the examinee to focus on a relevant verb and not the noun. Although the pictures came from the same set as *object naming* and *semantic odd-image out*, care was taken not to use the same stimuli.

Normative data for these images already exist [263], but the dominant verb and the verb generation agreement (VGA) had to be calculated according to the methodologies proposed by Kurlald et al. [274] and Thompson-Schill et al. [275]. The pre-selection of images included the simplest ones in terms of visual complexity (*M* = 2.3, *SD* = 0.291, *RANGE* = 1.8-2.7, out of 5 scale) and the most familiar ones (*M* = 4.5, *SD* = 0.293, *RANGE* = 3.9-5.0, out of 5 scale) for the Greek population. After excluding the images that had been used in other tasks and those that were most likely to elicit morphologically related verbs, the number of images was amounting to 40. Sixteen (*n* = 16) of them represented objects that could act on their own whilst 24 needed an external force in order to act. These 40 images comprised the verb generation task that was used in the standardization process of GLAABS. Then, the extracted data were used to determine the verb generation agreement (VGA). This feature derives from the percentage rate of the most dominant response and the information from the H-statistic (see Snodgrass et al. [246]). Low H values indicate high agreement in responses and as the value increases the VGA decreases. For example, the theoretical value of a 0.0 indicates perfect agreement, while a value of a 1.0 indicates that an image generated exactly two verbs with equal frequency [274]. The initial plan was to include only images in which the dominant verb had agreement over 80% and the H value was below 1.5 [274,275]. However, this was impossible as the images presented low VGA and high H-stat. Therefore, images with H-stat below 2.0 (*M* = 1.21, *SD* = 0.51) and a VGA over 90% (*M* = 93%, *SD* = 0.02) were preferred. However, these images were eliciting more than one dominant verb. In other words, I kept the images in which the first three most dominant verbs had cumulatively over 90% agreement rate. The images with the highest association [275] were two (*n* = 2) and elicited only one dominant verb. Five (*n* = 5) images showed moderate association, since they could elicit two dominant verbs, and eight (*n* = 8) images had low association as three or more dominant verbs were possible. The final number of stimuli amounted to 15 images.

Summing up, the images are controlled in terms of familiarity and visual complexity, but they are not matched for picture-name agreement since the corresponding name is provided in written form. Given the cognitive challenges of awake craniotomies mentioned earlier, and the increased cognitive demands of verb generation tasks [274], unfamiliar and complex pictures were avoided. Slides were placed with increasing difficulty according to the number of possible verbs that the target could elicit.

Sentence completion (with sentences)

Patients are asked to produce a sentence in order to complete a given incomplete sentence. Below I demonstrate two examples (2) in the original language (Greek) followed by a free/loose translation in English:

(2) a. Τα καλοκαιρινά βράδια μου αρέσει να …
"On summer nights I like to _____"
b. Την τελευταία φορά στον κινηματογράφο …
"The last time at the cinema …"

Stimuli are presented only orally, and the patient's response has to be correct with regards to semantics, syntax, and morphology. Patients are encouraged to use as many words and sentences as they want, since this task is focused more on eliciting spontaneous-connected speech. It consists of 22 incomplete sentences and it is the only task from this group not used for mapping but only resection, since it exceeds the 4 seconds time frame.

Group D tasks

Tasks in Group D are closed-ended, meaning only "correct" or "wrong" responses are possible. Stimuli in all Group D tasks are provided orally by the examiner and no PowerPoint presentations are used. Patients are advised to avoid detecting the type or position of the error and only answer if the given sentence is correct or not. These tasks can be used only during resection, since they are untimed.

Phonological judgment

Patients have to decide whether the orally given sentence (e.g., *το κορίτσι άνοιξε τα ζ̲ώρα του* /to koˈɾitsi ˈanikse ta ˈzoɾa tu/ 'the girl opened her presents') is "pronounced correctly" or not. The example I provide contains an error where the phoneme /ð/ is pronounced as /z/. The stimuli consist of 21 pseudo-randomized sentences; thirteen contain a phonological error, while eight are correct. The sentences are controlled for sentence structure (Subject-Verb-Object word order[8]) and length in phonemes. The errors used in the erroneous sentences are common in phonological disorders in Greek population [276,277].

Semantic judgment

In this task, patients are asked to decide whether the orally given sentence is semantically correct (contains the "right words"). The stimuli consist of 23 sentences; thirteen contain semantic errors. The methodology used to develop this task is based on Kim and Thompson [279]. The sentences are controlled for length in phonemes, sentence structure (SVO) and grammatical features of the main verbs (transitive, inflected in past tense, having an internal and an external argument). In terms of θ-roles, six sentences (n = 6) have a semantic violation in *theme* (e.g., *η γιαγιά πότισε τα αεροπλάνα* 'grandma watered the airplanes'), while four (n =

[8] Although traditional grammarians assume the SVO word order as the standard for the Greek language, in recent years this has been questioned. For more information see Roussou & Tsimpli [278].

4) have violations in *agent* (e.g., *η κρεμάστρα ζωγράφισε ένα ποτάμι* ‘the hanger painted a river’) and three (*n* = 3) in *target* (e.g., ο σερβιτόρος έδωσε τον καφέ στην πένσα ‘the waiter gave/brought the coffee to the pliers’). Care has been taken so the sentence containing the error exhibits only semantic violations not pragmatic; thus, I selected the most implausible and anomalous sentence type as proposed by Kim et al. [279].

Grammaticality judgment.

This is a common task in which patients are asked to answer if the orally administered sentence is correct or not in terms of syntax. Stimuli consist of 20 pseudo-randomized sentences; thirteen are not grammatical, i.e., they contain a syntactic or morpho-syntactic (not only morphological) error. This task was developed based on studies regarding post-stroke aphasia and the sentences were generated with verbs that have been used in similar tasks [280,281]. Regarding the types of grammatical errors contained in the stimuli, frequent errors from agrammatic Greek patients were selected [280-282]. Most of the ungrammatical sentences carry errors in inflection (*n* = 11). Three are related to Aspect (3a), four to Tense (3b), and four to Agreement (3c). Moreover, there are four (*n* = 4) errors regarding complementizers and particles (3d), four (*n* = 4) errors for case marking (3e), and one irreversible sentence contains an error in word order (3f).

(3) a. Aspect

την	Τρίτη	**έχανα**	το	ρολόι	μου
the	Tuesday	**lose-IMPERF**	the	watch	my

‘*I was losing my watch last Tuesday’

b. Tense

χθες	**βράδυ**	αυτός	**σπάει**	πιάτα
last	**night**	he	**break-PRES**	dish

‘*Last night he breaks dishes’

c. Agreement

οι	**φωτιές**	**καίμε**	το	δάσος
the	**fires**	**burn-1PL**	the	woods

‘*The fires (we) burn the woods’

d. Complementizers

το	αγοράκι	λέει	**να**	κρυώνει
the	boy	say-3SG	**to**	cold

‘*The boy says to cold’

e. Case marking

η	κυρία	πλέκει	**ο**	**σκούφος**

the	lady	knit	**the**	**knit cap-NOM**

‘*The lady knits the knit cap’

f. Irreversible sentence

το	**ψωμί**	κόβει	**το**	**κορίτσι**
the	**bread**	slice-3SG	**the**	**girl**

‘*The bread slices the girl’

Group E tasks

Finally, tasks in Group E require production of words based on a given criterion, e.g., only animals. Even though there is freedom in responses, patients have to respond in 60 seconds, while words from other categories are considered errors and are not counted. All three tasks are used only during resection.

Fluency Tasks.

In the *action (verb) fluency* task, patients are asked to produce as many verbs as they can in 60 seconds. No data were available in Greek so far.

Regarding *phonological* and *semantic fluency* tasks, there are already data for Greek healthy population published by Kosmidis et al. [260]. In these two tasks, which are based on *Controlled Word Association Task* [283], in 60 seconds the patient has to produce words according to a given category (e.g., animals). The categories for semantic fluency are *fruits*, *animals* and *items*, while for phonological fluency words that start with the Greek letters “χ, σ, α” (/x, ç/, /s/, /a/).

Standardization procedure

Population

Our healthy population consists of eighty (*n* = 80) consecutively selected healthy individuals (Table 3.4, next page), and it is a convenience sample. The inclusion criteria for the participants were the following: a) Greek native speakers, b) right-handed, c) no neurological history, d) no history of psychotropic substances abuse, e) not un-corrected vision, f) no cognitive deficits. Information regarding lateralization (b) gathered with the Edinburgh Handedness Inventory (EHI) [284], and information regarding cognitive status (f) with the Montreal Cognitive Assessment (MoCA) [285,286]. For criteria (a), (c), (d) and (e) the information was provided by the participants themselves (self-reported).

Participants were equally divided in four age groups, i.e., 20 in the 20-29 age group, 20 in the 30-39, and so on. Half of the participants in each age group were males and half females, resulting in 40 males and 40 females in total. Half of the male group (*n* = 20) had up to 12 years of education and the rest over 12. The same goes for the female group. I ruled out ages below 20 and beyond 60, since awake craniotomies are usually limited to this range [141,146]. The subjects participated anonymously, as no information that could possibly lead to the participant's true identity was requested. The data collection is in accordance with the guidelines of the Helsinki's Declaration for ethics in medical research [287].

Table 3.4
Demographics of healthy population.

	Average	SD	Range
Age	39,6	11,9	20-60
Education	14,8	3,1	12-22
MoCA score	27,5	1,3	24-30

	Group	*n*
Total number of participants		80
Gender	M	40
	F	40
Age groups	20-29	20
	30-39	20
	40-49	20
	50-60	20
Education	+12	40
	-12	40
Lateralization	right-hand	80
	left-hand 0	
Area of living	Larisa	43
	Achaia	28
	Attica	4
	Karditsa	2
	Magnesia	1
	Trikala	1
	Sporades	1

Demographic characteristics of the sample I used in order to obtain normative data. Leg.: *SD* = standard deviation, *MoCA* = Montreal Cognitive Assessment, *M* = male, *F* = female.

In addition to the participants comprising the normal sample, 80 more healthy individuals participated in various piloting experiments to norm the stimuli. Fifty (n = 50) participants (age range: 21-60 years, education range: 12-22 years) were involved in obtaining the psycholinguistic properties of the action images (imageability and age of acquisition), whilst regarding the picture-name agreement the data were obtained from 10 healthy individuals (age range: 30-40 years, education range: 14-22 years). Ten (n = 10) additional participants were included in order to verify that *phonological odd-word out*, *semantic odd-image out*, *semantic association*, and *verb generation* tasks did not elicit different answers when given orally (average age: 38 years, average education: 14 years). Finally, 10 more participants were recruited to pilot the final version of GLAABS and test the procedure protocol. All tasks were administered to 10 healthy participants (average age: 37 years, average education: 14 years) in order to check for errors in procedures and detect stimuli with lower than 90% agreement.

Administration procedure and scoring

The standardization procedure took place between 2018 and 2019, and was carried out by the same examiner (first author, C.P.) with the same hardware (laptop), in a single session for every participant. Sessions took place in a quiet, usually isolated room in the hometowns of the participants, mainly in Patras and Larisa, Greece. Initially, a general description of the process was provided while avoiding details regarding the test itself or its purpose. Then, the examiner explicitly stated that the only biographical information required were age, gender, and years of education. After the participant consented (with written consent) to proceed, every subject was registered with a consecutive number and the administration procedure started. Specific instructions and two different examples were given for every task.

The results were then recorded in real-time on special case report forms and no audio records were kept. I followed Rofes [258] methodology for keeping records, as all responses were recorded in special forms but, depending on the test, only the following were counted as correct: (a) responses corresponding to the expected target response, (b) those that were possible and were found in pilot trials or other studies with similar stimuli, (c) those produced within the four seconds time frame, when necessary. After the collection of the normative data, the correct answers were scored with 1 and the false ones with 0 in order to conduct the statistics and determine the cut-off scores.

Statistics

Data analyses were conducted with SPSS (SPSS Statistics for Windows, Version 17.0) and R software [288]. For statistical reasons the participants were divided into two gender groups (males, females), two education groups (below and above 12 years of education), and four age groups (20-29, 30-39, 40-49, 50-60).

Initially, mean, median, standard deviation, standard error, and range of the participants' scores were calculated for each task. Afterwards, I checked for main effects and interactions of the demographic variables on scores (two-way ANOVA). Since the data are not normally distributed (Shapiro-Wilk, $p < 0,05$) and the results in most tasks are positively skewed (for more details see Results section), non-parametric tests were used to investigate for differences between age, gender, and education groups (Mann-Whitney U for two groups, Kruskal-Wallis for more than two groups). Finally, for the post-hoc analysis the Dwass-Steel-

Critchlow-Fligner test was used. Cut-off scores and descriptive statistics were also calculated for each group combination separately.

Determination of cut-off scores

Even though this test is not designed to detect specific speech-language pathologies, cut-off scores are important in order to help us decide preoperatively but mainly intraoperatively when a performance in a certain task is significantly below the average. This is particularly important in awake craniotomies, where severe preoperative linguistic deficits are considered contraindications.

In terms of percentiles, some very commonly used cut-off scores in clinical practice are, the 2nd [289], and the 5th percentile [290]. In terms of standard deviations on the other hand, when data are normally distributed, the 2nd percentile corresponds to approximately 2SDs below the average [291]. The differences in literature regarding the appropriate cut-off scores are expected considering that cut-off scores should result from sensitivity and specificity of each test. These two features according to Friberg [292] can determine the overall accuracy of a test.

As mentioned earlier, GLAABS can be used in two settings, that is, inside the operating room to assist brain mapping, and before and after the surgery to indicate language impairment. Since the aims and procedures in these two settings are very dissimilar, calculating sensitivity and specificity separately may lead to better overall accuracy. Regarding its use as an intraoperative assessment tool, there are several reasons that render it challenging to calculate sensitivity and specificity (e.g., assessments on the same patient cannot be repeated, brain mapping with DES is not applied to normal population, during the mapping process it is very difficult to accurately verify which speech errors are true positives). Therefore, it is difficult to calculate discriminant validity, since sensitivity and specificity in this case are unknown. Also, the concurrent validity, which is also an important validation method, cannot yet be measured for GLAABS as there are no similar tests in Greek.

Regarding its secondary role as an assessment tool to detect language impairment outside the operating theatres, GLAABS should be used with caution as its sensitivity and specificity are not yet measured. That being said, in order to set the cut-off scores, the method proposed by Ingraham et al. [293] was employed. I applied relatively strict criteria in order to decide the cut-off scores for three reasons:

i. It is recommended by Ingraham et al. [293] for tests with approximately fifteen tasks.

ii. By setting strict criteria the chances of false-positive results are reduced; therefore, there are low chances to exclude patients from awake surgery. This is even more important, considering that subjects are expected to complete the test easily (normal population have >90% success in all tasks).

iii. Loose criteria, may reduce the specificity; thus, individuals without any language impairment would appear as pathological. This may also lead to unnecessary exclusion of patients from subsequent surgery due to false negative results.

According to the above analysis which is based on the model proposed by Ingraham et al. [293], the most appropriate method for GLAABS's number of tasks, which will help us identify as "abnormal" the 5% of the sample, is the cut-off score of 2SDs below the average in at least two tasks. Since the normative data are skewed, the 2nd percentile rather than the standard deviation is preferred. At this point, it should be highlighted that this model is only a guide and cannot fully replace the correct clinical judgment.

3.3. Results

Effect of demographic variables

Two-way (factorial) ANOVAs were performed to check if the demographic variables (age, gender, and years of education) or a combination of these variables had an effect on the participants' performance on GLAABS (depended variables). The results (Table 3.5, next page) revealed significant main effects of gender on *phonological judgment* (F = 14.215, p < 0.001) and age on *phonological odd-word out* (F = 2.839, p = 0.044), *semantic association* (F = 3.829, p = 0.013) and *syntactic judgment* (F = 3.434, p = 0.021). Regarding education, it was found that there is a significant main effect on *action fluency* scores (F = 9.170, p = 0.003), and a marginally significant effect on *phonological judgment* (F = 3.769, p = 0.056). After checking for interaction effects between age, gender, and education, it was found that there is a significant interaction among education and gender on *phonological judgment* scores (F = 4.632, p = 0.035), as the effect of education differs according to participant's gender (males with lower education scored lower). Finally, the analysis revealed a marginal (but not significant) interaction between age and gender on the *semantic odd-image out* (F = 2.312, p=0.083) and *verb naming* tasks (F = 2.434, p = 0.072).

As discussed previously (section 2.3), data do not follow normal distribution and most are positively skewed; therefore, central tendency indices are not particularly useful for clinical use and percentile ranks are preferred [294]. This is the reason why Bonferroni corrected pairwise post-hoc analysis was unnecessary. Instead I checked for differences between demographic groups with non-parametric tests (see next section). It should be mentioned that even though most non-parametric tests use the *median* value instead of *mean*, I often refer to the latter as it is sometimes more indicative.

Table 3.5
Summary of effects and interactions of demographic variables.

		Main effect			Interaction		
		AG	GE	ED	AG*GE	AG*ED	ED*GE
Word repetition	*F*	-	-	-	-	-	-
	p	n/s	n/s	n/s	n/s	n/s	n/s
Motor planning	*F*	-	-	-	-	-	-
	p	n/s	n/s	n/s	n/s	n/s	n/s
Phon. odd-word out	*F*	2.839	-	-	-	-	-
	p	0.044**	n/s	n/s	n/s	n/s	n/s
Semantic odd-word out	*F*	-	-	-	-	-	-
	p	n/s	n/s	n/s	n/s	n/s	n/s
Semantic odd-image out	*F*	-	-	-	2.312	-	-
	p	n/s	n/s	n/s	0.083*	n/s	n/s
Verb naming	*F*	-	-	-	2.434	-	-
	p	n/s	n/s	n/s	0.072*	n/s	n/s
Object naming	*F*	-	-	-	-	-	-
	p	n/s	n/s	n/s	n/s	n/s	n/s
Semantic association	*F*	3.829	-	-	-	-	-
	p	0.013**	0.066*	n/s	n/s	n/s	n/s
Sentence completion (words)	*F*	-	-	-	-	-	-
	p	n/s	n/s	n/s	n/s	n/s	n/s
Verb generation	*F*	-	-	-	-	-	-
	p	n/s	n/s	n/s	n/s	n/s	n/s
Sentence completion (sentences)	*F*	-	-	-	-	-	-
	p	n/s	n/s	n/s	n/s	n/s	n/s
Phonological judgment	*F*	-	14.215	3.769	-	-	4.632
	p	n/s	0.001***	0.056	n/s	n/s	0.035**
Semantic judgment	*F*	-	-	-	-	-	-
	p	n/s	n/s	n/s	n/s	n/s	n/s
Grammaticality judgment	*F*	3.434	-	-	-	-	-
	p	0.021**	n/s	n/s	n/s	n/s	n/s
Action fluency (verbs)	*F*	-	-	9.170	-	-	-
	p	n/s	n/s	0.003***	n/s	n/s	n/s

Leg.: *AG* = age group, *GE* = gender, *ED* = education, *n/s* = not significant, * = marginally significant (p < 0.100), ** = significant (p < 0.050), *** = highly significant (p < 0.010)

Differences between groups

The differences between the two gender groups were investigated with Mann-Whitney U test (Shapiro-Wilk, $p < 0.05$). The analysis revealed no significant differences between the two gender groups in performance in most tasks (Table 3.6, next page). However, in the *phonological judgment* task, females scored on average slightly higher ($M = 20.95$) than males ($M = 20.63$), which is considered statistically significant ($p < 0.001$).

Analysis of the education groups with Mann-Whitney U test revealed that the two groups did not significantly differ in their performance in all tasks except one (Table 3.6). For the *action fluency* task, analysis showed a significant difference ($p = 0.004$) between groups, as the +12 years of education group produced more verbs ($M = 28.80$) compared to the -12 years of education group ($M = 24.45$).

Table 3.6
Summary of significant differences between gender, education and age groups.

Gender	Females			Males			M-W	
	Mean	SD	Median	Mean	SD	Median	*U*	*p*
Phonological judgment	20.95	0.22	21.00	20.63	0.49	21.00	540	<0.001***
Education	**-12 years of ed.**			**+12 years of ed.**			**M-W**	
	Mean	SD	Median	Mean	SD	Median	*U*	*p*
Action fluency (verbs)	24.45	5.20	24.50	28.80	7.33	28.00	504	0.004***

Age	K-W		Post-Hoc (D-S-C-F)	
	χ^2	*p*	Age groups (mean)	*p*
Phonological odd-word out	9.53	0.023**	20-29 (20.9) and 40-49 (22.3)	0.026**
			30-39 (22.95) and 40-49 (22.3)	0.008***
Semantic odd-image out	8.47	0.037**	30-39 (24.95) and 40-49 (24.7)	0.040**
			30-39 (24.95) and 50-60 (24.5)	0.004***
Semantic association	14.77	0.002***	30-39 (18.75) and 40-49 (18.4)	0.034**
			20-29 (18.3) and 50-60 (17.8)	0.028**
			30-39 (18.75) and 50-60 (17.8)	0.001***
			40-49 (18.4) and 50-60 (17.8)	0.036**
Grammaticality judgment	9.30	0.025**	20-29 (19.8) and 50-60 (19.3)	0.029**
			30-39 (19.9) and 50-60 (19.3)	0.005***

This table presents only the results that exhibited statistically significant differences. In post-hoc D-S-C-F results, values inside brackets refer to the mean scores. Leg.: *SD* = standard deviation, *M-W* = Mann-Whitney U test, *K-W* = Kruskal-Wallis, *D-S-C-F* = Dwass-Steel-Critchlow-Fligner test
* = marginally significant ($p < 0.100$), ** = significant ($p < 0.050$), *** = highly significant ($p < 0.010$)

Age groups were compared with the Kruskal-Wallis statistical test which is better suited when there are more than two groups. For post-hoc testing the Dwass-Steel-Critchlow-Fligner test was employed. Analyses showed statistically significant differences among age groups at the *phonological odd-word out*, *semantic odd-image out*, *semantic association*, and *grammaticality judgment* tasks respectively (Table 3.6). Post-hoc analyses revealed the following significant differences: a) in the *phonological odd-word out* task the 40-49 age group scored significantly lower than the 20-29 ($p = 0.026$) and 30-39 ($p = 0.008$) groups, b) in the *semantic odd-image out* task the 40-49 and 50-60 age groups scored significantly lower than the 30-39 age group (*p* values are 0.04 and 0.004 respectively), c) in the *semantic association* task the 50-60 age group had the worst performance compared to the other age groups while the 40-49 age group scored significantly worse only compared to the 30-39 ($p = 0.034$) age group, d) in the *grammaticality judgment* task the 50-60 age group scored significantly lower than the 20-29 ($p = 0.029$) and 30-39 ($p = 0.005$) age groups. Additional detailed tables for the normative data and the investigation regarding differences between groups are provided in Appendix B.

Cut-off scores

As discussed in Methodology, in order to consider a performance as deviant from typical, an individual has to perform in at least two tasks below the 2nd percentile, which is the cut-off score. Table 3.7 shows cut-off and maximum scores, medians, means, and standard deviations for the (normal) population. Since there were significant differences between age, gender, and education in several tasks, these values were calculated separately for each group (Appendix B). Semantic and phonological fluency tasks are not mentioned here, since there are already normative data for Greek healthy population [260]. Finally, the cut-off scores are rounded since each point corresponds to one correct answer.

Table 3.7
Cut-off scores (2%ile), Range, Mean, and SD for healthy population.

Tasks	Cut-off	Range	Mean	St. Deviation
Word repetition	60	60-60	60	0,000
Motor planning	6	5-6	6	0,112
Phonological odd-word out	20	17-23	22,7	0,818
Semantic odd-word out	17	16-20	19,6	0,733
Semantic odd-image out	23	22-25	24,7	0,582
Verb naming	34	33-38	37,3	1,052
Object naming	105	103-109	108,4	0,984
Semantic association	14	14-19	18,3	0,949
Sentence completion (with word)	19	19-21	20,6	0,589
Verb generation	9	9-15	13,8	1,277
Sentence completion (with sentences)	2,6	2,5-8,9	4,5	1,344
Phonological judgment	20	20-21	20,8	0,412
Semantic judgment	22	22-23	23	0,157
Grammaticality judgment	18	17-20	19,6	0,700
Action fluency (verbs)	15	14-47	26,6	6,681

3.4. Discussion

From the analyses of the normative data, I found only a few main effects and interactions of demographic variables on the test scores. Regarding age, even though the results indicate light impact of age on GLAABS scores, older participants tend to perform slightly worse than younger ones. In terms of statistical significance this is true only for four tasks. Gender and education demonstrated significant effects on the *phonological judgment* and the *action fluency* tasks respectively. Specifically, in the *action fluency* task, the more educated participants produced significantly more verbs than the less educated, while in *phonological judgment* task it was found an interaction between gender and education; the more educated females performed better than less educated males. Although these differences seem to have little impact on cut-off scores, the percentiles were calculated separately for each demographic group. Also, it is advised that specific cut-off scores should be considered only for tasks in which significant differences among groups were found.

GLAABS is a norm and criterion referenced standardized intraoperative language assessment tool, designed mainly to assist language mapping during awake craniotomies. With respect to the 11 criteria reported by Friberg [292] regarding the overall level of psychometric validity of tests, GLAABS as an intraoperative assessment tool meet at least five criteria (criteria 1, 2, 3, 5, 7), while three are in question (4, 6, 9). The remaining three (criteria 8, 10, 11) concern concurrent validity, and test-retest and inter-examiner reliability, which are difficult to measure in the case of GLAABS. In its secondary role as a test used outside the operating theatres, even though it is not a diagnostic tool, GLAABS can detect atypical linguistic performance, which -in most- cases indicate impairment. Following the Ingraham et al. [293] proposals, scores below the 2nd percentile in at least two of the 17 tasks of GLAABS, indicate pathological performance. It should be emphasized that since severe impairment in speech and language is a counter-indication for awake craniotomy, in case of abnormal scores preoperatively the patient should be re-evaluated with additional tests before being considered a candidate for awake craniotomy.

Clinical application of GLAABS

During the development of the test, preliminary versions of GLAABS were administered in several brain tumor patients that underwent awake craniotomies. In this section I will only provide an overview of the administration procedures followed in these cases, as detailed descriptions will be presented in the following chapters.

Preoperatively, all patients went under preoperative language and cognitive assessment with standardized assessment batteries in Greek, by the same speech language pathologist/therapist. The same examiner conducted the assessments in all stages (pro-, peri-, intra-, postoperative). Three were the main objectives in preoperative assessments: a) identify atypical linguistic performance, b) set the linguistic baseline for the patients and then compare this baseline with their postoperative performance, and c) collect information about the patient and the tumor that was needed intraoperatively. The perioperative assessments were conducted two-three days before the surgery, in order to practice and familiarize the patients with the intraoperative procedure, as well as to personalize the tasks by excluding stimuli that were not answered flawlessly and/or within the time limit. This is a crucial step in order to diminish the false positive results (Type I errors) of brain mapping, which can reduce the extent of tumor resection. Task selection and administration order were determined according to the following factors: a) tumor characteristics (location, size, and boundaries), b) surgical plan and surgical approach, c) possible neuroplastic changes of the brain, and d) patient's characteristics (education level, age, preoperative linguistic/cognitive deficit). This procedure was also important, since irrelevant tasks could increase the risk of false negative results (Type II errors), which in turn could lead to increased permanent postoperative deficits. Intraoperatively, the GLAABS test was employed in order to assist brain mapping by evaluating specific linguistic functions associated with the stimulated brain regions. A similar procedure was involved in the resection process, even though the exact assessment methods differed slightly (see Introduction section). Postoperative assessments were conducted with the same tests as preoperatively, usually four weeks after the surgery. During the acute phase, various postoperative phenomena (e.g., oedema, impact of anaesthesia) may occur and affect the clinical picture; therefore, patients were assessed only informally and briefly in order to monitor their progress.

All cases were patients of the Neurosurgery Clinic of the University Hospital of Larisa (Greece). The leading neurosurgeon was the supervisor of this dissertation (K.F). This was a very useful process that helped us gain valuable experience in order to conclude to the final version and administration procedures of the test.

Concluding remarks

Although the work presented in this chapter is fairly innovative, it does not come without limitations. The normative data come from a sample of eighty (n = 80) healthy participants, and although it has been argued that even a sample size of 50 participants can be adequate [295], a bigger sample may increase the accuracy of the standard scores estimation [296]. Moreover, the following facts should not be overlooked: a) in addition to being norm-referenced GLAABS is also criterion-referenced since each patient serves as his or her own baseline through the perioperative stage and b) the test is designed to mainly assist brain mapping and not to detect a specific pathology. It should be noted that 80 additional participants were involved in various experiments during the development of the test and stimuli norming procedures, but they cannot be included in the final normative sample. Concerning its use outside the operating rooms, GLAABS has not yet been officially validated and its overall identification accuracy (sensitivity and specificity) remains unknown even though it has been used with pathological population (mainly oncological patients).

An important issue regarding the brain mapping process that needs to be addressed in future research is the sensitivity and specificity of intraoperative tests to detect speech or language errors, which is closely related to the clinician's ability to accurately interpret them. Since it is difficult to eliminate the impact of the human factor involved in this process, focusing the efforts more on setting strict objective criteria would be extremely valuable. The minimal clinically important difference (MCID) is a term used in therapy settings and can be defined as the smallest difference in score, which a patient will perceive as beneficial and will maintain, in the absence of troublesome side effects and unaffordable cost [297]. In the field of mapping in awake craniotomies, what is considered to be a mistake caused by stimulation and what a transient difficulty caused by some other factor (e.g., lack of knowledge, anaesthesia, normal dysfluency) is a very important issue. Identifying the minimal difference that makes an utterance normal or pathological resulting from the stimulation is very important in order to reduce Type I (false positive) errors. These errors can reduce specificity and consequently the extent of the tumor resection. On the other hand, increasing sensitivity and reducing Type II (false negative) errors is equally important to increase the effectiveness of awake craniotomy, as high sensitivity is related with decreased permanent postoperative deficits. Future research should also focus on the development of more accurate neurolinguistic models which will be accompanied with more accurate clinico-anatomical correlations. This is not an easy task, but these directions can ultimately lead to more effective awake craniotomies that in turn will result in greater and more precise tumor resections with minimal postoperative deficits.

Chapter 4. Intraoperative assessment with GLAABS: A case series[9]

Abstract

This chapter is essentially a case series study, which presents, in a narrative way a series of cases that underwent awake craniotomy. Particular focus is given on patients' speech and language abilities, described in detail with regards to all surgery stages (pre-, peri-, intra-, and postoperatively). The population comprises of brain tumor patients, although patients with intractable epilepsy and arteriovenous malformations are also included. Preoperatively, patients who exhibited deficits presented only mild or very mild symptoms and their overall quality of life was not significantly affected. Intraoperatively (and perioperatively), all cases were assessed with the Greek Language Assessment for Awake Brain Surgery (GLAABS), or its preliminary versions, which helped the neurosurgeons to achieve total and subtotal tumor resections in 64% of our patients. The various findings from the intraoperative assessments are discussed and compared to similar findings reported in the literature.

4.1. Introduction

During the course of the current doctoral research 22 awake craniotomies were performed on 21 patients in our institution, and in all cases GLAABS (or its preliminary versions) was employed. In this chapter, I will describe these cases and their language profiles, along with the entire protocol that aimed to assist the neurosurgeons to improve the effectiveness of the surgeries. The word "protocol" is used here to denote the specific materials and methods that were used in each assessment stage of the surgeries, which were in a great degree common for all cases. In all cases, the examiner who conducted the assessments was a speech language therapist, the author of the present dissertation (unless otherwise specified). Before the detailed presentation of the cases, it would be helpful to provide the definitions of the key-terms used in error analysis of impaired speech and language, which are also adopted in this dissertation.

Core definitions of the speech and language errors

In scientific fields that study human communication and its pathology (such as neurolinguistics and speech-language pathology) there are specific terms to describe specific

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[9]A part of this chapter was first presented as a poster: "Papatzalas C, Fountas K, Kapsalaki E, Papathanasiou I. The role of left inferior longitudinal fascicle in reading: evidence from a brain stimulation case study. Poster session presented at: Annual Convention of the American Speech-Language-Hearing Association; 2019 November 21-23; Orlando, FL."

The same part it is accepted for publication as a journal article: "Papatzalas C, Papathanasiou I, Paschalis T, Tzerefos C, Kapsalaki E, Petsiti A, Fountas K. Left inferior longitudinal fascicle and reading: Exploring their relationship through a brain stimulation case study. Communic Dis Quart. Forthcoming 2021."

errors related to comprehension and production of speech and language. The majority of the terms that are widely used today were developed during the 1980s and 1990s, mainly to describe symptoms of aphasia and more generally, acquired communication disorders.

In the context of intraoperative mapping with DES, accurate labeling and interpretation of the errors induced by the electrical stimulation is very important [164]. For instance, differential diagnosis between a speech arrest and an anomic error may inform the neurosurgeon if the stimulated area involves motor or language functions and help him identify eloquent cortical and subcortical areas. At this point, it should be stressed that the presence of a symptom/error (e.g., anomia) does not always indicate the presence of an aphasic syndrome; in that case anomic aphasia. This is particularly true in tumor-related language disorders emerging postsurgically, in which transient deficits are very common.

Anomias (or anomic errors)

The term **anomia** refers to the inability of an individual to recall a word while he or she knows its nature and function [298]. These errors are more prominent during naming tasks and connected (free) speech [299] wherein often, instead of the target word, patients produce circumlocutions or abstract utterances (e.g., “that thing”) [298]. These word-finding difficulties can occur in any grammatical class, although they are more common in content (e.g., nouns and verbs) rather functional words [300-302]. Anomias occur not only in anomic aphasia but also in other aphasia subtypes, maybe due to the fact that there are numerous brain areas involved in naming process [300].

Paraphasias (semantic or phonemic paraphasias)

Paraphasias are language errors that refer to the “distortion of the semantic or phonological content of a word” [303]. The term *semantic paraphasia* (also known as verbal or lexical paraphasia) is used here to describe an error, in which an incorrect word is semantically related to the target word [299]. For instance, an individual may produce the word *chair* instead of “table” which is the intended word. On the other hand, the term *phonemic paraphasia* (also known as literal or phonological paraphasia) describes an error, in which the incorrect produced word is phonologically similar to the targeted word (e.g., *fort* instead of “fork”). This type of error is frequently escorted by consecutive (and usually unsuccessful) attempts from the patient to produce the word correctly, a phenomenon called “conduite d'approche” [304,305].

Neologisms (and jargon speech)

The term **neologism** describes a produced word that is incomprehensible and bears little or no resemblance to the targeted word. In some studies there is a distinction between *phonological neologisms* in which the produced word shares some phonological similarities with the intended word (although is still unconceivable), and *abstruse neologisms* in which the produced word cannot be identified at all [299]. In this dissertation I will not make this distinction and all the incomprehensible utterances, which the examiner cannot predict the target word, will be referred to as *neologisms*.

Paralexias (or paralexic errors)

Paralexias occur during reading and are manifested by the substitution of a target word with another word [306]. There are several different types of paralexias, named after the corresponding type of alexias (or "acquired dyslexias") [307]. Reading errors in which the misread word is related phonologically to the target word (e.g., *cat* instead of "hat"), are called *phonological paralexias*. On the other hand, *semantic paralexias* denote a reading error that is similar in meaning with the target word (e.g., *foot* instead of "hand"). Some other less known paralexias are *morphological paralexias* which have the same word-stem with the target (e.g., *uptake* instead of "mistake"), *visual paralexias* which involve words that appear visually similar to the target (e.g., *report* instead of "resort"), and finally, *regularization paralexias* wherein an irregular word (having low grapheme-phoneme correspondence) is spelled as regular. In the current chapter, in order to describe the patients' reading errors, I will mainly use the terms *phonological*, *semantic*, and *visual paralexias* [308].

Perseveration errors

The term **perseveration error** will be used to refer to the type of speech errors that denote a continuous unintentional recurrence of a previously uttered word [309]. Although there are several subtypes of perseveration errors (see Sandson et al. [309] for a review) in our case series, we mostly encountered *recurrent perseveration* that emerge immediately after the original word (or some moments later), when there is an attempt for a new utterance [310].

Agrammatic errors (and agrammatic speech)

Errors at the sentence level are called **agrammatic errors** and they are the clinical manifestations of *agrammatism*, which typically occur in Broca's aphasia [311]. Agrammatism typically causes "telegraphic speech" which is "marked by simplified grammatical structure and omissions of function words and inflectional markers" [312 p74]. According to Grodzinsky [313], agrammatism does not denote the omission of function words (or closed-class) but rather their mis-selection. Agrammatic errors can emerge in both production and comprehension of sentences. Comprehension errors can be elicited with various tasks, such as sentence-picture matching or grammaticality judgment. Regarding production level, as mentioned previously, the most prominent symptom is the unique agrammatical speech pattern which denotes a reduced variety in grammatical forms (e.g., embedded sentences), omission of function words, omission of main verbs, and slow rate of speech [311]. Additionally, as it has been demonstrated for Greek [282] and other languages [313] which are characterized by rich inflectional morphology, agrammatic errors may reflect selection of the wrong inflectional morpheme, e.g., *agorazi* (buy-PRES) instead of "agorase" (buy-PAST). In the present dissertation, the term **agrammatic error** will be used to denote single errors and the term **agrammatic speech** the speech pattern of agrammatism as they were both presented above.

Speech arrests

Speech arrests are also very common in the context of intraoperative language mapping and they are defined as the patient's inability to produce an utterance, while the rest of his or her linguistic functions are intact [314]. The main difference between anomias and speech arrests is that the former concerns the inability to produce a specific word, while a whole utterance will be disturbed when the latter is present [164]. For instance, in a naming task that demands a carrier phrase (e.g., "That is a…"), if the patient is able to produce the introductory phrase but not the name of the specific item, then the error is most likely anomia. On the other hand, if the patient is totally unable to utter any word including the carrier phrase, then the error is speech arrest.

Apraxia errors

One of the first and most common definitions of the term **apraxia of speech** (AOS) is attributed to Darley et al. [315] who defined this speech disorder as "a disorder of motor speech programming manifested primarily by errors of articulation" [316 p428]. Apraxia of speech does not involve muscle strength, tone, range of motion (as in dysarthria), or language abilities (as in aphasia) [316]. Although it is still debatable if the errors occurring in AOS are unique or not, they present some special characteristics that result from the disturbance of the ability to coordinate the sequential articulatory movements of speech [317]. Ogar et al. [316] describe these errors mainly as articulatory and prosodic in nature, although the latter is considered a secondary symptom. Perhaps the most common feature of errors in AOS is the excessive inconsistency [318]. An apraxic patient may misarticulate a word on one utterance, and articulate the same word accurately on another occasion. Despite the lack of predictability, apraxia errors are more common in phonologically complex words with consonant clusters, or infrequent words [318]. Currently, there is no specific clinical term that is widely used for the speech errors of AOS (e.g., “apractic errors”). In the current dissertation I will use the term *apraxia error* to denote a misarticulation with the characteristics of AOS. However, since it is common for brain tumor patients to exhibit transient symptoms, the use of this term will not necessarily presuppose the existence of the disorder per se (AOS).

Dysarthria

Dysarthria is a well-known group of diverse and, in many cases, chronic motor speech disorders “characterized by slow, weak, imprecise and/or uncoordinated movements of the speech musculature” [319]. They can result from lesions to the peripheral or the central nervous system, and each type of dysarthria (*flaccid, spastic, ataxic, hypokinetic, hyperkinetic, unilateral UNM,* and *mixed*) has different clinical manifestations and auditory perceptual characteristics [318]. They can affect any of the subsystems supporting speech production (respiration, phonation, resonance, articulation, and prosody) and their most common characteristic, which is used for differential diagnosis with AOS, is the consistency of symptoms. The speech errors in all types of dysarthrias are consistent and predictable [316].

Aprosodia

Prosody is an important component of human communication, in which the right (non-dominant) hemisphere is heavily involved [320,321]. Prosody provides the rhythm of language and modulates the suprasegmental parameters of speech, namely pitch, loudness, and duration, in order to convey communicative intents [322]. An important prosodic feature (along with lexical and phrasal prosody) is intonation, which is a sentence level phenomenon that denotes pitch variations during the course of an utterance [323,324]. The term *linguistic prosody* includes sentence mood (e.g., question or statement), and lexical and emphatic intonation, and it is distinguished from *affective (or emotional) prosody* which conveys information about speaker’s feelings (e.g., anger, sadness, or happiness) [325]. **Aprosodia** has been described as a monotonous speech pattern, resulting from flattening the intonational curve [320]. The most prominent errors regarding affective prosody associate with the expression of positive emotions (such as joy or surprise), while with regards to linguistic prosody, with sentence mood [326]. Finally, aprosodic speech may present atypical speech rate and affect paralinguistic features such as facial expressions [320,327]. The term **aprosodia** will be used here to describe the condition wherein a patient has difficulties to comprehend or produce variations in tone of voice that intend to convey a communicative intention (linguistic or an emotional).

Pragmatic errors

Pragmatics refer to the language domain that provides the necessary skills to understand and express communication intentions in a given context [328]. These skills include non-literal (figurative) language, and conversational discourse. Damage to the right (non-dominant) hemisphere may cause **pragmatic impairments** in comprehension and production levels and particularly in figurative language (metaphors), turn-taking during conversation, eye contact maintaining, stay on-topic, adaptation of message to the linguistic context, and finally in recognition of shared knowledge between speakers [325,329]. Particularly regarding comprehension, a very common error is to fail to interpret correctly indirect speech acts such as asking someone to increase the heat in room by saying "It's cold in here".

This chapter

The case series study design is essentially a descriptive study that follows a group of patients who have a similar diagnosis or undergoing the same procedure over a certain period of time, and discusses the recorded data [330]; therefore, they are based on retrospective observations and typically there is no control group [330,331]. In cognitive neuropsychology and neurolinguistics, case studies and case series were always an important part. According to Schwartz et al. [332], in these fields, the main goal of case series is to explain the variation of primary measures taken by a patient sample in order to draw conclusions about the functional organization of language and cognition. Although data from the sample are not always aggregated, patients can be analyzed together in order to identify quantitative trends in the sample [331.332].

In the current chapter, I will present the case reports of patients who went through awake craniotomy in our institution (Neurosurgery Department of University Hospital of Larisa, Greece). Herein, my research questions do not focus on whether the surgical treatment was more effective or safer than some other treatment rather investigate the language profiles of the patients.

4.2. Methods

In this section I will demonstrate the materials and methods that were employed in order to compose this chapter.

Participants

During the three-year period from 2017 to 2020, 30 individuals went through preoperative cognitive and linguistic examination, while our team performed 22 awake craniotomies in 21 patients of the Neurosurgery Department of the General University Hospital of Larissa (Table 4.1).

Table 4.1
Demographic characteristics of patients.

	Case number	Age	Gender	Hand-edness	Educa-tion	Patho-logy	Hemi-sphere	First language
1	P2	35	M	R	12	BT	left	el
2	P3	59	F	R	6	BT	left	el
3	P4	38	M	R	18	BT	left	el
4	P5[a]	39	F	R	14	BT	left	el
5	P7	44	F	R	12	BT	left	bg (2nd el)
6	P8	32	M	R	16	BT	left	el
7	P9	31	F	R	14	BT	left	el
8	P11	38	F	R	12	BT	left	el
9	P12	26	M	R	12	BT	left	el
10	P13	40	M	R	12	BT	left	el
11	P16	44	M	R	12	BT	left	el
12	P17	32	M	R	12	BT	left	el
13	P18	44	F	R	12	BT	right	el
14	P20	41	F	R	12	BT	left	el
15	P21	39	M	R	12	BT	right	el
16	P22	18	M	R	6	E	left	el (2nd bg, 3rd ro)
17	P23	50	M	R	12	BT	left	el
18	P25	36	F	R	16	AVM	right	bg (2nd el)
19	P26	32	M	L	16	BT	right	el
20	P27	40	F	R	12	BT	left	el
21	P30	39	M	R	12	AVM	left	el

Demographic features of the patients underwent awake craniotomy in our institution between 2017 and 2020. Leg.: *M* = male, *F* = female, *R* = right-handed, *L* = left-handed, *BT* = brain tumor, *E* = epilepsy, *AVM* = arteriovenous malformation, *el* = Greek, *bg* = Bulgarian, *ro* = Romanian.
[a] Patient P5 underwent awake craniotomy twice.

The reasons why these nine (n=9) patients did not undergo awake craniotomy in our clinic are illustrated in Table 4.2. One patient chose another institution (P29), five did not fulfill the criteria to be considered good candidates for awake craniotomy (P1, P10, P14, P19, P28), while in three cases (P6, P15, P24) the awakening process was aborted and the neurosurgeons continued with general anesthesia since there was a great risk of severe complications.

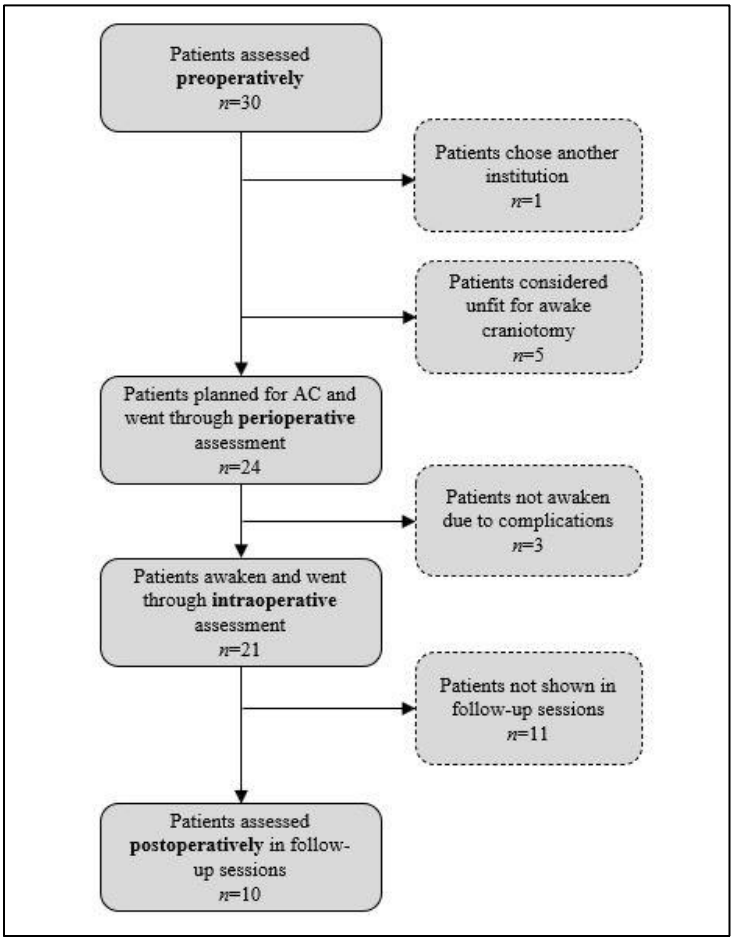
Table 4.2
Clinical characteristics of patients not included in this study.

	Case number	Age	Gender	Hand-edness	Educa-tion	Patho-logy	Hemi-sphere	Reason
1	P1	18	M	R	11	E	left	unfit for AC
2	P6	41	M	R	12	BT	right	intra-op complications
3	P10	51	F	R	12	BT	left	unfit for AC
4	P14	44	M	R	12	BT	left	unfit for AC
5	P15	30	M	R	12	BT	left	intra-op complications
6	P19	41	M	R	16	BT	right	unfit for AC
7	P24	43	F	R	12	BT	right	intra-op complications
8	P28	31	M	R	6	E	left	unfit for AC
9	P29	40	F	R	12	BT	right	chose another institution

Demographic features of the patients that did not undergo awake craniotomy in our institution (i.e., only preoperative assessment is available). Leg.: *M* = male, *F* = female, *R* = right-handed, *L* = left-handed, *BT* = brain tumor, *E* = epilepsy, *AC* = awake craniotomy

Ten patients (P11, P12, P13, P16, P17, P18, P20, P21, P27, P30) went through postoperative assessment in a follow-up session, while for 11 patients this was not possible, since due to various reasons they did not show up at the scheduled appointments (Figure 4.1). One patient (P16) did not conclude the assessment as he reported mental fatigue and aborted after 25 minutes.

Figure 4.1
Flowchart representing the selection of the patients.



Detailed case reports will be presented only for the 21 patients who underwent awake craniotomy, intraoperative evaluation, and language mapping. Although most of the patients were operated for brain tumors (*n* = 18), two patients with AVMs and one patient with drug-resistant epilepsy are also included (see Table 4.1). In 17 patients the lesion was located in the left (dominant) hemisphere, while in the other four the lesion concerned the right (non-dominant). The chronologically first seven patients (P2, P3, P4, P5, P7, P8, P9) were assessed intraoperatively with preliminary versions of GLAABS, as the test was still under construction. Also, the administration of the test during language mapping was performed together with another member of the team with a different specialty (psychologist). Regarding patients with lesions in the right (non-dominant hemisphere), in addition to GLAABS, an experimental intraoperative test (i.e., right hemisphere test; eRHT) was also administered. This test was developed in order to assess functions of the right hemisphere and it is briefly presented in Appendix A.

Assessment tools

Preoperative and postoperative assessment tools

The preoperative and postoperative evaluations were performed with valid and standardized assessment tools that have been reported in similar studies [7,54,67,69,112,115]. Moreover, they are widely used in speech, language, and cognitive disorders assessment (Table 4.3).

Table 4.3
The tests used in preoperative and postoperative assessments.

Test	Function Assessed	Translation and Normative data in Greek
EHI	Handedness	-
BNT	Language (naming)	Simos et al. [294]
BDAE	Language (speech, comprehension, repeating, reading, writing)	Papathanasiou et al. [333]
MoCA	Cognition (brief estimation)	Konstantopoulos et al. [285], Kounti et al. [334]
SAQoL-39g	Quality of life (poststroke aphasia)	Efstratiadou et al. [335], Kartsona et al. [336]
MEC	Right hemisphere language functions (discontinued)	*no normative data in Greek population*
Mount Wilga	High order language functions (discontinued)	*no normative data in Greek population*

Leg.: *EHI* = Edinburgh Handedness Inventory, *BNT* = Boston Naming Test, *BDAE* = Boston Diagnostic Aphasia Examination, *MoCA* = Montreal Cognitive Assessment, *SAQoL-39g* = Stroke and Aphasia quality of Life, *MEC* = Montreal Evaluation of Communication

The Edinburgh Handedness Inventory (EHI) [284] was used in order to measure patients' handedness. This questionnaire consists of 10 questions about examinee's hand preference. The final handedness quotient was calculated with the Online Tool for Handedness Assessment [337].

Speech and language were assessed with Boston Naming Test (BNT) [294,338], and Boston Diagnostic Aphasia Examination (BDAE) [312,333]. The former (BNT) is a naming test, typically incorporated in BDAE as a subtest. It evaluates visual confrontation naming of common objects, whilst the skills required to execute this task presuppose intact visual-phonological route. However, access to the semantic system is not always required [294]. This test was administered according to the instructions proposed by the authors that conducted the Greek adaptation/standardization and the 5th percentile of the cued and uncued responses was used as the cut-off score to indicate pathological performance [294]. Nevertheless, in the current chapter special references to the cued responses will be made where needed. The Greek version of BDAE [333] on the other hand, is a much bigger test that consists of 28 subtests divided in five major components[10] (*conversational discourse and description, auditory comprehension, production of speech, reading,* and *writing*). The first part includes the subjective evaluation of examinee's fluency, description and conversational discourse abilities, which determine if the examinee is fluent or non-fluent [333]. The rest components evaluate the most important language functions and are scored objectively with a specific scoring system for each task. Normative data regarding Greek healthy population were collected by Papathanasiou et al. [333]. I considered the lowest available percentile (10^{th}) as the cut-off score to determine normal or abnormal performance. The BDAE's *severity rating scale* is used in order to rate the severity of speech and language symptoms (Table 4.4). A score of 0 corresponds to "no usable speech or auditory comprehension" while a score of 5 to "minimal discernible speech handicap". Moreover, in cases of language impairment postoperatively the *rating scale profile of speech characteristics* is used to diagnose specific aphasia types. A deviation from the Greek version is that the *repetition* tasks were isolated and calculated separately, since these tasks measure an important skill, which easily can get disrupted by subcortical damage or stimulation.

Table 4.4
Aphasia severity scale (BDAE).

Score	Description	Severity level
0	No usable speech or auditory comprehension.	-
1	All communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. The information range that can be exchanged is limited, and the listener carries the burden of communication.	Extremely severe
2	Conversation about familiar subjects is possible with help from the listener. There are frequent failures to convey the idea, but the patient shares the burden of communication.	Severe
3	The patient can discuss almost all everyday problems with little or no assistance. Reduction of speech and/or comprehension however makes conversation about certain material difficult or impossible.	Moderate
4	Some obvious loss of fluency in speech or facility of comprehension without significant limitation on ideas expressed or form of expression.	Mild
5	Minimal discernible speech handicap; the patient may have subjective difficulties that are not obvious to the listener.	Very mild

In order to briefly evaluate cognitive skills, Montreal Cognitive Assessment (MoCA) was administered to most patients. The MoCA is a brief cognitive assessment tool, sensitive to mild stages of cognitive impairment [286]. According to the original MoCA authors, the 10-minute period that this test lasts is adequate for the examiner to gain an estimation of the examinee's visuospatial abilities, memory (working, short-term, and delayed recall), executive functions, attention, language (naming, repetition, and fluency), verbal abstraction, and orientation to time and place [286]. The authors suggest that scores below the cut-off score of 26/30 are indications for mild cognitive impairment. However, Konstantopoulos et

[10]This classification is based on the original (English) version [312].

al. [285] provide normative data from Greek healthy population and propose as normal a cut-off score of 25/30 or over.

The Stroke and Aphasia Quality of Life 39g (SAQoL-39g) [339] was used to evaluate patient's overall functionality and quality of life. This (originally English) questionnaire that measures health-related quality of life of post-stroke patients, has been translated and adapted in Greek by Kartsona et al. [336] while the psychometric properties of the Greek version have been studied by Efstratiadou et al. [335]. It is unknown whether the SAQoL-39g, which is mainly used in patients with post-stroke aphasia, has also been used previously in patients with tumor-related aphasia. The questionnaire consists of 39 questions, which are answered according to a 5-point scale (1 to 5), and it is divided in three domains: physical, psychosocial, and communication. As their names indicate, these domains correspond to some very important aspects of health-related quality of life, that is, physical, mental, emotional, family, communicational, and social functioning [340]. The Greek version of SAQoL is validated on post-stroke patients with or without aphasia [335] and the available data were used only as indications about the quality of life of our patients. The post-stroke population achieved a mean overall score of 3.1/5 (SD = 0.82), a score of 3.2 (SD = 1.09) for the physical domain, a score of 2.9/5 (SD = 0.87) for the psychosocial domain, and a score of 3.3/5 (SD = 1.07) for the communication domain. As the authors of the Greek adaptation suggest, the interview format was employed when patients suffered from receptive aphasia.

During the first year of the current doctoral research, various other tests were used experimentally. The Mini Mental State Examination (MMSE) [247], the Montreal Evaluation of Communication (MEC) [325], and the Mount Wilga high level language test [341] were all used at some point. The last two (MEC and Mount Wilga) were translated into Greek and used informally for the assessment of two right hemisphere patients. However, since they were not standardized in Greek healthy population, their use was discontinued.

Intraoperative and perioperative assessment tools

The intraoperative (and perioperative) assessments of the left hemisphere patients were conducted with GLAABS [342], which is described in detail in Chapter 3. As already has been discussed, this test was developed during the first years of this doctoral dissertation, therefore, until it was completed the patients were assessed with preliminary versions. The right hemisphere patients were assessed with a combination of tasks deriving from GLAABS test and tasks from an experimental test which was developed during the current research (Appendix A).

The speech language therapist used a semi-structured conversation elicitation technique to engage patients in a discussion about their work, family, hobbies, as well as the current events in order to assess their *conversational discourse* abilities. These very important elements of human communication "enable the transmission of information from one speaker to another in a conversational, procedural or narrative form" [325]. Simultaneously, the examiner was assessing patients' expressive and receptive language, and particularly their pragmatic, lexical-semantic, and prosodic abilities, in a natural linguistic context (as natural as it may be intraoperatively). Furthermore, the examiner took great care to avoid issues that could have negative connotations (such as accidents, illnesses, or deaths of relatives) or create strong emotional burden on patients during the awake craniotomy [69]. This for some cases included persons or objects that were associated with excessively positive emotions (e.g., children). Nevertheless, in all perioperative examinations, the speech language therapist discussed and pre-decided together with patients these "neutral" themes that were used to produce spontaneous speech at the awake stage.

The clinico-anatomical correlations we took into consideration in order to conduct the intraoperative language mapping are based on the neurolinguistic model proposed by De Witte et al. [79], and they can be found in Chapter 3 (section 1.2). This comprehensive model is based mainly on results provided by direct electrical stimulation studies and incorporates the majority of brain areas involved in comprehension and production of speech and language. However, these functional-anatomical relations were not always relevant to our cases, as several patients were suffering from lesions in different brain areas, not included in the aforementioned model. In the next paragraphs I will describe these areas and the associated functions, and I will propose specific tasks based on evidence provided by contemporary studies (Table 4.5).

Table 4.5
Additional clinico-anatomical correlations.

Brain area	**Speech-language function**	**GLAABS tasks**	
		time-limited (mapping)	tasks without time limit
Temporal pole	lexical retrieval	object & verb naming, semantic association	semantic judgment, verbal fluency (semantic)
Insula	speech praxis (articulation)	motor planning/diadochokinesis), word repetition	sentence completion (sentence)
Dorsolateral PFC	language switching (biling.), syntax, naming	semantic odd-image out (verbal stimuli), object & verb naming	grammatical judgment, verbal fluency (semantic & action)
Orbitofrontal Cortex	affective prosody, semantics	naming of emotions[a], semantic odd-image out	affective prosody judgment[b]
Occipital lobe	reading processing, semantics	semantic odd-word out, object naming	paragraph reading[c]
Frontal aslant tract	fluency (speech), syntax, morphology	verb generation, sentence completion (words), verb naming	verbal (action) fluency, sentence completion (sentences), syntactic judgment

Leg.: *GLAABS* = Greek Language Assessment for Awake Brain Surgery, *PFC* = Prefrontal Cortex

The **temporal pole** is located on the anterior part of the temporal lobe and it has been described as the "semantic hub" [343]. This area plays a major role in lexical retrieval [344], therefore *naming* (verb and object), *verb generation*, and *semantic association* are very important tasks.

Another area is the **insular cortex**, which shares reciprocal functional and structural connections with language, motor, limbic, and sensory areas [345]. Neuroimaging studies have showed that the insula is involved in several aspects of comprehension and production of speech and language (for review see Oh et al. [346]). However, the most important function supported by insula, according to lesion and fMRI studies [34,347], is the motor control of speech production (speech praxis). Therefore, tasks focusing on articulation (such as *motor planning/verbal diadochokinesis*, and *word repetition*) can be very helpful to language mapping.

It has been supported that the **dorsolateral prefrontal cortex** (DLPFC) mainly involves higher cognitive functions, such as executive functions and working memory [348-350]. Given that these two functions have an impact on human communication, DLPFC is involved in various aspects of comprehension and production of language. Particularly, neuroimaging studies have showed that the DLPFC is involved in language switching in bilinguals [351,352], sentence comprehension [353] and sentence production [354]. By using transcranial direct current stimulation, studies have demonstrated that DLPFC is involved in word retrieval process and affects the performance of naming tasks [355,356]. On the other hand, with respect to comprehension, DLPFC is involved in cases wherein working memory is required for syntactic processing [356] and cognitive control is needed for interpretation of ambiguous or non-literal structures (e.g., garden-path sentences or idioms) [357,358]. According to the evidence presented above, *semantic odd-image out (verbal stimuli)*, *object naming*, or *verb naming* tasks are appropriate for language mapping, while *syntactic judgment*, *semantic fluency*, or *action (verb) fluency* tasks can be very helpful during the resection process.

The **orbitofrontal cortex** (OFC) comprises the ventralmost regions of the prefrontal cortex and it is mainly known for its involvement in decision making and executive functions [359]. Regarding language, the bilateral orbitofrontal cortices have been linked with processing of affective (emotional) prosody [360], while a DES study [112] reported that disruption of the left (dominant) OFC induced consistently semantic paraphasias in brain tumor patients. Thus, emotional judgment tasks (e.g., *emotion naming* and *affective prosody judgment* tasks; Appendix A) and tasks that require semantic processing (such as *semantic-odd image out* task), may be very useful in intraoperative mapping.

It is known that the **occipital lobe** hosts the primary visual (striate) cortex and supports processing of visual stimuli. With regards to language, the occipital lobe is considered part of the “ventral semantic stream” which is involved in “transforming” sounds into meaning [361]. According to a view which is supported by a large body of studies (see Dehaene et al. [362] for a review) the occipito-temporal cortex (OTC) supports the visual word form system (VWFS), also known as the “orthographic input lexicon” [363]. This area is responsible for the visual identification of words [364] and lesions affecting visual word form area may cause pure alexia [365,366]. However, this view has been questioned by Price et al. [363] who argue that there is not enough evidence for that claim. Despite the ongoing debate about its exact function, it is undeniable that the left OTC (also known as mid-fusiform area) is part of a larger network that is involved in reading processing [363] (see also Fiez et al. [367] and Price [368]). Therefore, reading and object recognizing tasks (such as *object naming*, and *semantic odd-word out*) are useful tools for intraoperative mapping.

An important subcortical structure that is not covered by the neurolinguistic model proposed by De Witte et al. [79] is the **frontal aslant tract** (FAT). It is a white matter tract that connects the most posterior part of the inferior frontal gyrus (also known as “Broca’s area”) with the supplementary and pre-supplementary motor areas in the medial superior frontal gyrus, which has only recently been described in humans [369]. Regarding its function, it has been argued that the FAT is involved in several aspects of production and comprehension of language (and speech), in sign language, in executive functions, and finally in motor planning and coordination [370]. Moreover, Dick et al. [370] proposed a hemispheric specialization wherein the left FAT is involved in language and speech, while the right FAT in visuospatial domain. Although the exact functions of the left FAT (lFAT) are still under investigation, it has been supported that it is heavily involved in syntax [371], morphology [372], and speech initiation, fluency and stuttering [218,373,374]. The aforementioned recent discoveries indicate that the *verb generation*, *sentence completion (words)*, and *verb naming* tasks are appropriate for the intraoperative language mapping process. On the other hand, during the resection procedure, in which timed tasks are not required, the *action (verb) fluency*, *sentence completion (sentences)*, and *syntactic judgment* tasks are better suited.

Assessment procedures

An overview of the language assessment procedures used in awake craniotomy context, which are reported by various neurosurgical teams around the world is provided in Chapter 2 (1.3.2. The administration procedure). The specific procedures we followed in our protocol, with respect to all assessment stages, are briefly described in Chapter 3 (4.1 Clinical application of GLAABS). In this section, I will describe aspects of the protocol that have not been discussed in detail in previous chapters. It should be noted in some early cases there were some minor variations on the protocol.

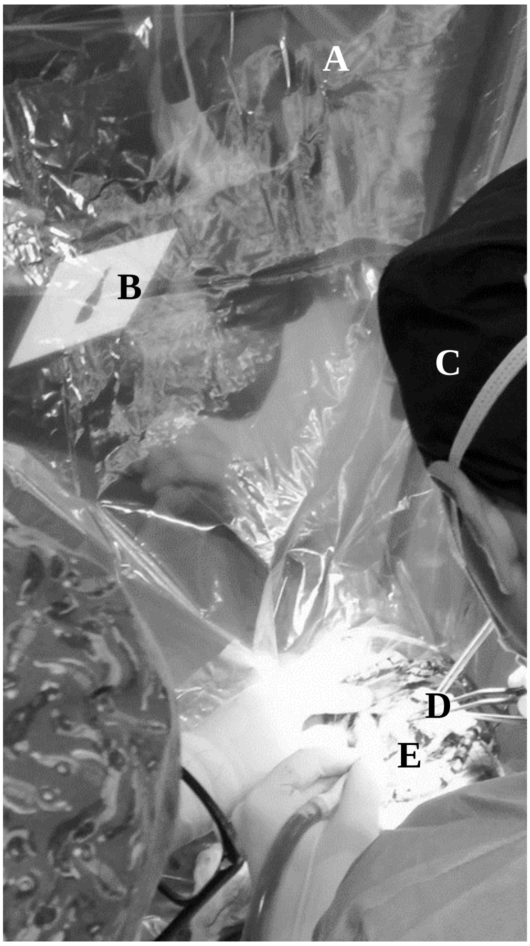
Initially, the neurosurgical team, led by the head of our department, decided which patients were candidates for awake craniotomy according to their physical and psychological status, the neuroimaging results, and the presence of any comorbidity. Then, the language specialist (the author of the current dissertation) conducted a detailed preoperative assessment of patient's speech, language, and cognitive skills, and reported the results back to the operating neurosurgeon. The duration of this assessment was approximately two hours for each patient. Candidates with normal results according to tests' normative data, who were willing and capable of cooperating at the later stages, were considered "good candidates". Patients who were unable to meet the requirements were considered "bad candidates" and their participation in awake craniotomy was re-evaluated by the team. All the preoperative assessments took place in our department, approximately one month prior to surgery.

According to awake craniotomy protocol of our clinic, all patients had to go through neuroimaging examination from the neuroradiology department of our hospital. However, some patients came to our department having already been examined by another institution. In these cases, if the MRI scans were inadequate, old, or not containing the appropriate sequences, a new MRI scan was performed in the Department of Radiology of the General University Hospital of Larisa.

Every patient that was scheduled for awake craniotomy underwent the perioperative assessment. This session took place two or three days before the operation in our clinic, and according to our protocol it was performed with GLAABS (or with the preliminary versions for some cases). The assessment was conducted with the same tasks that were planned to be used intraoperatively. In all cases the full version of GLAABS was administered once, and one more time only the tasks selected for the intraoperative stage. This procedure was usually conducted in two separate sessions that lasted approximately one hour each.

The day of the operation, the speech language therapist (the author of this dissertation) was present in the operating theatre from a very early stage, even before the patient was transferred to the operating room. After the team was ensured that the patient was in a comfortable position and his or her airway was not restricted, the anesthesiologist administered the first anesthesia and then intubated the patient. The awakening procedure started after dural infiltration and subsequent exposure of the cortex by the neurosurgeon. The anesthesiologist was responsible to extubate the patient and help him or her regain an acceptable level of consciousness. The intraoperative assessment initiated after the patient had established adequate eye contact and could effectively communicate. Various orientational and biographical questions (e.g., "what's your name?" or "where are we now?") assisted the patient to regain full consciousness. The next action was to begin the administration of the automatized speech tasks that helped the operating neurosurgeon set the appropriate electrical current of the stimulation probe (typically starting at 1mA). After adjusting the electrical current, the main assessment began by administering the pre-selected tasks (Picture 4.1, next page), and did not end until the neurosurgeon concluded mapping and resection procedures and the patient returned to general anesthesia. In order to assess the conversational discourse abilities, the speech language therapist elicited spontaneous speech with methods which was described in previous section in this chapter (2.2.2. Assessment tools). The intraoperative assessment including language mapping and tissue removal processes lasted on average 90 minutes.

Picture 4.1
Assessment during language mapping process.



Leg.: *A* = examiner (speech-language therapist), *B* = stimuli (pictures via tablet), *C* = neurosurgeon, *D* = cavitron ultrasonic surgical aspirator, CUSA), *E* = patient's exposed cortex

The postoperative assessment took place in two phases. The first one was conducted two days after the operation, during the "acute stage", and the second one four weeks later. During the former (acute) phase, the patient was evaluated informally by the language specialist who examined patient's basic communicative abilities, mainly through conversational discourse. More, specifically, the examiner was evaluating the following domains of communication: eye contact, comprehension (following orders), and verbal response (Table 4.6).

Detailed speech and language assessment was avoided in this phase as the results could be misleading due to several early postsurgical phenomena (e.g., oedema, confusion and disorientation from the anesthesia). The follow-up assessment was conducted four weeks later, with the same tests as in the preoperative assessment, in order to check if the surgery affected speech or language. The predictors of long-term functional outcome that were considered by our team, are those proposed by Brown et al. [110] and include patient and

Table 4.6
Key-functions assessed in the informal speech language evaluation during the acute postsurgical phase.

Eye Contact	Comprehension	Verbal Response
maintain eye contact	following 2 steps orders	with sentences
only when addressed	only 1 step	with words
no eye contact	no response	no response

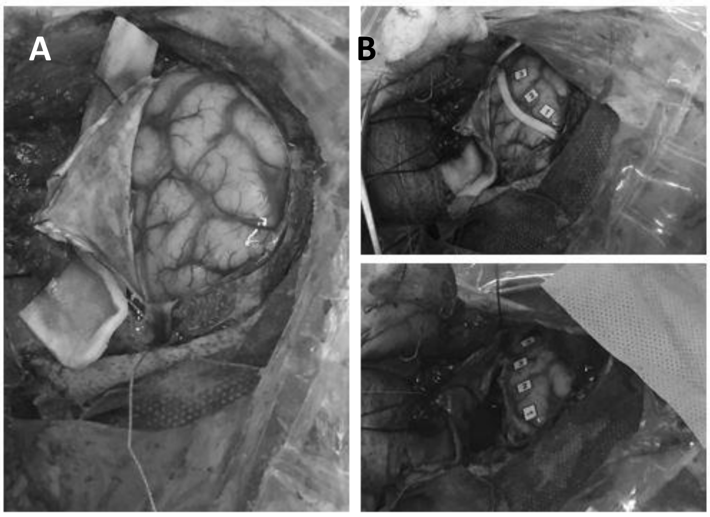
tumor characteristics, surgical details, and newly acquired postoperative deficits (even in acute stage). The data acquired from all the stages of the protocol were recorded in special forms, and then they were stored in excel spreadsheets separately for every patient.

Statistics

In this chapter I use a narrative approach to describe the language profiles of cases, and statistical analyses only where is absolutely necessary. All statistics were conducted with SPSS 17.0. I used the Kruskal-Wallis test for the non-normally distributed data and one-way ANOVA for the normally distributed ones. The Tukey's test was used as a parametric post-hoc test, while for non-parametric I used the Mann-Whitney U test. Distribution and homogeneity of variances were checked with Shapiro-Wilk and Levene's tests respectively.

Surgery technical details

Regarding the surgical details of the operations, as a standard, the operating neurosurgeon used bipolar stimulation probe for cortical mapping and monopolar for subcortical (Picture 4.2). The neurosurgeon adjusted the appropriate electrical current on every patient, typically when the automatized speech tasks were performed. Typically, the stimulation began at 1mA and it was increased until consistent disruption of language occurred (rarely above 4.5mA). This was followed by extensive cortical tumor resection using cavitron ultrasonic surgical aspirator (CUSA) and subchorionic microsurgery, in cases which were necessary. Subcortical mapping with electrical stimulation was performed again, which typically was altered with the subcortical resection. When the neurosurgeon concluded the resection, the anesthesiologist sedated and then intubated again the patient. In some cases, the neurosurgeon removed additional residual pathological tissue after the patient had returned to general anesthesia. Finally, thorough hemostasis was performed, the operated area was washed out, and the neurosurgeons performed closure of the surgical wound in anatomical layers.



Picture 4.2
Three different stages of awake craniotomy.

Leg.: *A* = after the exposure of the cortex, *B* = after language mapping, *C* = during resection

4.3. Results

In this section I will present the language profiles of all the patients that underwent awake craniotomy in our institution (Table 4.7). The case reports will focus on language and clinico-anatomical relations. Unless it is specified differently, all patients' native language is Greek. As "error" is defined any non-sufficient speech or language response produced by a patient. I further specify the type of the error according to the definitions provided in the Introduction section of this chapter. The types of errors were handwritten in special forms by the examiner.

Table 4.7
Details of the 22 awake craniotomies performed in our institution.

Case	**Type of lesion**	**Hemi-sphere**	**Lesion location**	**Initial location[a]**	**Intra-op Test**	**Histopathology (fast-track if n/a)**	**Extent of resection[b] (%)**
P2	BT	left	TPJ	postCG	pGLAABS	metastasis	subtotal (n/a)
P3	BT	left	preCG	-	pGLAABS	glioma II-III	subtotal (85)
P4	BT	left	IFG[c]	-	pGLAABS	glioblastoma	total
P5[d]	BT	left	PFC	-	pGLAABS	oligoastrocytoma grade III	total
P7	BT	left	IC	-	pGLAABS	low-grade glioma	total
P8	BT	left	LV[e]	M-SC	pGLAABS	low-grade glioma	partial (60)
P9	BT	left	TPJ	-	pGLAABS	low-grade glioma	partial (50)
P11	BT	left	IFG	-	GLAABS	low-grade glioma	subtotal (90)
P12	BT	left	IFG[f]	-	GLAABS	low-grade glioma	subtotal (85)
P13	BT	left	SFG[g]	-	GLAABS	glioblastoma	subtotal (85)
P16	BT	left	OFC	OFC	GLAABS	low-grade glioma	total
P17	BT	left	ITG	-	GLAABS	unknown	partial (80)
P18	BT	right	Claust	STG	GLAABS	astrocytoma grade II-III	partial (80)
P20	BT	left	preCG	-	GLAABS	low-grade glioma	subtotal (85)
P5[d]	BT	left	DLPFC	PFC	GLAABS	oligoastrocytoma grade III	subtotal (90)
P21	BT	right	IFG	APSC	GLAABS	low-grade glioma	subtotal (85)
P22	E	left	TPo	-	GLAABS	-	-
P23	BT	left	IFG[h]	-	GLAABS	glioma with increa-sed inflammatory cells	subtotal (85)
P25	AVM	right	MFG	-	GLAABS	-	-
P26	BT	right	preCG	-	GLAABS	inflammatory le-sion w/o malig-nant features	partial (5)[i]
P27	BT	left	SFG	-	GLAABS	low-grade glioma	subtotal (97)
P30	AVM	left	STG	-	GLAABS	-	-

The surgeries are listed in chronological order. Leg.: *BT* = brain tumor, *E* = epilepsy, *AVM* = arteriovenous malformation, *n/a* = not available, w/o = without, *GLAABS* = Greek Language Assessment for Awake Brain Surgery, *pGLAABS* = preliminary version of GLAABS, *TPJ* = temporoparietal junction, *preCG* = precentral gyrus, *postCG* = postcentral gyrus, *IFG* = inferior frontal gyrus, *PFC* = prefrontal cortex, *IC* = insular cortex, *LV* = lateral ventricle, *SFG* = superior frontal gyrus, *OFC* = orbitofrontal gyrus, *ITG* = inferior temporal gyrus, *Claust* = Claustrum, *DLPFC* = dorsolateral PFC, *TPo* = temporal pole, *MFG* = middle frontal gyrus, *STG* = superior temporal gyrus, *M-SC* = motor-sensory cortex, *APSC* = anterior perisylvian cortex.

[a] Available only for second surgeries

[b] Estimations of the neurosurgeon, not verified volumetrically (total = 100%, subtotal 99-85%, partial < 85%)

[c] Tumor was extending to middle frontal gyrus

[d] Patient P5 underwent awake craniotomy two times.

[e] via the parietal lobe (old resection)

[f] Tumor was extending to insular cortex

[g] Tumor was also encroaching postcentral gyrus

[h] Another foci was located to basal ganglia although this particular awake craniotomy involved only the IFG lesion

[I] Only a sample for biopsy was taken

Patient P2

Patient P2 is a 35-year-old, right-handed male having 16 years of education that was surgically treated by our team for a second time, after recurrence of a metastatic tumor in the left temporoparietal junction. The initial space-occupying lesion was a metastatic brain tumor located on the postcentral gyrus (parietal lobe) that originated from testicular cancer and treated with awake brain surgery 5 months ago.

The first operation induced to the patient a moderate language deficit as it was observed from the preoperative speech and language assessment. Particularly, the patient scored 35/45 cued and uncued responses on BNT while his errors included mostly phonemic paraphasias and anomias. This score is below average but slightly above the cut-off score (5%ile: 33). The assessment with SAQoL-39g revealed that his quality of life was affected by the first operation that took place 6 months ago as he scored 3.8/5 on physical, 4.3/5 on psychosocial, and 4.1/5 on communication scales. According to BDAE severity scale his symptoms were moderate (score: 3).

During perioperative session, the patient was evaluated once with the entire GLAABS test, and once more with a series of lesion-appropriate tasks that were planned for the intraoperative assessment. In word repetition task the patient scored 73.6%, in motor planning 44.4%, in object naming 65%, in semantic odd-image out 48%, in semantic association 38.5%, in sentence completion (sentences) 69.2%, in phonological odd word out 32%, in semantic odd-word out 48%, and in verb generation task the patient scored 74%. Although, GLAABS was not yet standardized and these scores cannot be compared to normal population, it is evident that phonology and semantics were the most affected language domains. All stimuli (e.g., images or sentences) that were not answered flawlessly or on time, were considered errors, and were excluded from further stages.

During intraoperative assessment, and particularly during cortical mapping process, the patient was assessed with *object naming* and *word repetition* since the mapped area was close to the posterior superior temporal sulcus, which supports the phonological network. Moreover, for the subcortical mapping process, *word repetition* was employed again in order to identify the posterior part of the arcuate fascicle. The resection process was conducted with *semantic odd-image out*, *semantic association*, and *sentence completion (sentences),* while his conversational discourse abilities were evaluated following the method described in section 2.2.2 in this chapter. The patient produced numerous errors during mapping and resection procedures. Specifically, during *word repetition* the patient produced several phonemic paraphasias, while during *object naming*, he produced more anomias and speech arrests than phonemic paraphasias. These errors are compatible with the operated areas as the temporoparietal junction and particularly the posterior part of superior temporal sulcus supports the phonological network, whilst the posterior part of superior temporal gyrus is involved in naming.

Postoperative data are available only for the acute phase, as the patient returned to his hometown several days after the surgery. During this informal and brief assessment, the patient was able to maintain eye contact, follow commands, and respond verbally, although he produced several anomias and phonemic paraphasias.

Patient P3

A 59-year-old, right-handed female visited a local hospital after she began feeling headaches and dizziness. Neuroimaging examination with MRI showed a large infiltrative tumor, presenting regional contrast enhancement, which was located on the left frontal lobe and particularly on the precentral gyrus.

The preoperative evaluation of speech and language was conducted with EHI, SAQoL-39g, BNT, Verbal Fluency (based on Kosmidis et al. [260]), and BDAE. Interestingly most of the results were normal or close to normal. Particularly, EHI revealed pure right handedness (100%), and SAQoL-39g a minor decline to patient's quality of life due to the tumor occurrence (overall score: 4.4/5), especially on physical (4.4/5), and psychosocial (4.3/5) domains. However, the functionality of her communication abilities was not affected whatsoever (5/5). Boston naming test (score 42/45), verbal fluency test, and BDAE did not reveal any deficit in speech and language. Regarding the latter test (BDAE), patient's mean percentile in all components was close to the 90th percentile.

Perioperatively, the patient was assessed once with the full version of preliminary GLAABS, and one more time with the tasks planned for the intraoperative stage. In most tasks patient's responses were excellent, and she achieved maximum scores. The only tasks in which she produced errors were the *phonological odd-word out* (92%), *semantic association* (80,8%), *motor planning* (55,5%), and *object naming* (78%). As in all cases, the stimuli that were not perfectly answered were excluded from next stages.

In order to map the precentral sulcus and the corticospinal tract, patient P3 was assessed with *object naming* and *word repetition* tasks, while both sentence completion tasks (with words and with sentences), as well as semi-structured conversational discourse evaluation were employed during the resection process. Patient's errors were only limited in the object naming task and were mostly anomias. The results of fast-track biopsy reported that the tumor was a grade II glioma with malignant (grade III) features. Finally, the estimated extent of resection was approximately 85%.

Postoperatively, the patient was assessed only during the acute stage and she was able to communicate effectively with the examiner. Specifically, she was able to maintain eye contact, follow commands, and respond verbally with sentences.

Patient P4

Patient P4 is a 38-year-old, right-handed male that presented a focal epileptic seizure exhibited with severe (but transient) aphasia, 5 months prior to the preoperative speech-language evaluation. Consecutive neuroimaging examination revealed a large fast-growing, infiltrative space-occupying lesion, located on the left (dominant) hemisphere. The tumor which was located on the inferior frontal gyrus (extending to middle frontal gyrus) was presenting necrotic features and contrast enhancement. A biopsy was performed by another institution several months before his admission to our clinic, and the histopathological diagnosis was glioblastoma multiform (GBM).

The preoperative language assessment was not conducted with the exact materials defined by our protocol, as patient's hometown was far away (Athens, Greece) and the operation was scheduled just three days after his admission to our institution. The MoCA test was used as a brief cognitive screening test and the preliminary version of GLAABS as the main language test, since the perioperative session was incorporated into the preoperative. The results from MoCA were within normal (29/30). On the other hand, the patient produced several errors in GLAABS tasks and particularly in *verb naming* (76.6%), in *object naming* (79%), in *sentence completion with words* (80%), and in *motor planning* (66.6%). Most of the errors were anomias, while in *sentence completion with words* the patient produced three grammar errors. However, GLAABS had not yet been standardized and these scores could not be compared to the normal population.

During the intraoperative stage, *verb naming*, *verb generation,* and *word repetition* were selected in order to map the inferior and middle frontal gyri, while for subcortical mapping (of the arcuate fascicle) the *word repetition* task was preferred. However, the appropriate administration of the aforementioned tasks was not possible, as the patient after the "awakening" phase, never regained his preoperative communication skills and suffered from severe aphasia. Particularly, as soon as the patient was awaken, and before the beginning of mapping process, patient P4 exhibited severe perseveration errors and he could only produce a pseudoword ([δif'goni]). Even though that symptom resolved after 15 minutes, he was still producing numerous perseveration errors and neologisms (jargon). Due to that, mapping procedure was conducted only with *object naming*, while during the resection of the tumor, the examiner assessed only verbal fluency and conversational discourse. Fast-track biopsy verified the histopathological results which led to a total resection of the tumor.

Postoperative assessment was conducted only in acute phase. The patient was able to maintain eye contact, and his comprehension abilities were adequate to follow orders, but not a conversation. Contrarily, his verbal response was severely affected by the surgery as he could respond verbally only by "yes", "no" and "okay". After personal communication with the family the examiner was informed that the patient was receiving speech-language therapy and his early symptoms were decreasing.

Patient P5

Patient P5 is a 39-year-old, right-handed female, with 12 years of education that was operated by our clinic for brain tumor removal three times in total. The first surgery was performed under general anesthesia, but the last two were awake craniotomies and were performed during the present dissertation. The first surgery that was executed in 2012 with general anesthesia and aimed to remove the initial space-occupying lesion, which was located on the prefrontal cortex of the left hemisphere. Subsequent histopathology examination showed that the tumor was a grade III oligoastrocytoma.

First awake craniotomy

In 2017 an MRI scan after a seizure revealed that the tumor, located on the prefrontal cortex, had regrown and the patient underwent awake craniotomy to remove it.

As in patient P4, due to time limitations, patient P5 was assessed preoperatively only with a preliminary version of GLAABS while the perioperative session was incorporated into the preoperative. The patient performed well enough in all GLAABS tasks and her symptoms were very mild (BDAE severity scale: 5). Most of patient's errors were anomias and occurred in *object naming* (81%), *motor planning* (77.7%), and *grammaticality judgment* (88.6%) tasks.

As soon as patient P5 regained consciousness, and before the initiation of mapping procedure, the patient exhibited severe dysarthria (spastic) and jargon speech, which became milder 10 minutes later. During cortical mapping, the patient was assessed with *verb naming* and *object naming*, whilst the *sentence completion (words)* task was used for the subcortical. For resection process, the tasks that were employed were *verb naming*, *word repetition*, and *sentence completion (sentences)*. As this procedure was progressing subcortically and the patient was evaluated with the conversational discourse method, she began experiencing apraxic errors. Despite the fact that the patient occasionally reported headaches, she was very cooperative, and the neurosurgeons managed to perform a total resection of the lesion.

In the acute postsurgical phase, the patient could communicate effectively and demonstrated only mild symptoms. Specifically, she was able to maintain eye contact, follow commands, and respond verbally with words (acute score: 5). Another postoperative assessment in the form of a follow-up session was conducted before her second awake craniotomy. However, since that session took place approximately 10 months later (instead of one month) the results cannot be compared with those of other patients. During that session, patient P5 was assessed with BDAE and her performance was within normal limits in all major components (more details in next subsection). The only errors she produced concerned verbal and non-verbal diadochokinesis and a few errors in repetition of words.

Second awake craniotomy

Patient P5 underwent awake craniotomy for a second time in 2019 after the results of an MRI scan that showed a tumor regrowth on the dorsolateral prefrontal cortex (anterior part of the middle frontal gyrus).

The patient submitted to our hospital a day before surgery, thus the preoperative assessment took place only with BDAE. Her performance was close to 90th percentile in *auditory comprehension*, *reading*, and *writing* and close to 60th percentile in *speech production* and *repetition*. According to patient's profile in BDAE, she presented a very mild anomic aphasia (BDAE severity scale score: 5). The only tasks in which she performed below normal were the non-verbal diadochokinesis (score: 9/12, 10%ile: 10/12) and the repetition of words (score: 9/10, 10%ile: 10/10), while in verbal diadochokinesis she scored equal to the 10th percentile (score: 13/14).

The perioperative session took place the same day as the preoperative (one day before the surgery) and the examiner administered only the tasks from GLAABS that were selected for the intraoperative assessment, that is, *semantic odd-word out*, *semantic odd word out (auditory stimuli), semantic odd image out, verb naming, objects naming, semantic judgment, sentence completion (sentences),* and *verbal fluency (semantic)*. The patient performed within normal limits in all tasks except *sentence completion with words* and *object naming*, in which she scored below the cut-off scores.

During language mapping, the patient was assessed with the *verb naming* task to map the anterior part of middle frontal gyrus and the *semantic odd-word out* task to map the inferior fronto-occipital fasciculus. During resection process, the patient was evaluated with *semantic odd-image out*, *semantic judgment*, *sentence completion (sentences)*, and *verbal fluency (semantic)* tasks, as well as with conversational discourse. After the patient regained consciousness, assessment began with automatized sequences (counting 0-10, days), mostly to help the neurosurgeon set the appropriate electrical current of the stimulation probe. During this task, the patient produced three speech arrests and one perseveration error, while in language mapping process she produced mostly semantic paraphasias, anomias and neologisms. Her connected speech (during resection) was evaluated with *semantic completion (sentences)* and conversational discourse and did not exhibit severe deficits, except a small quantity of perseveration errors and speech arrests. The neurosurgeons managed to identify several areas related to speech and language and to remove approximately 90% of the tumor. The awake stage lasted 80 minutes and the operation was very well tolerated by the patient.

The postoperative evaluation was performed only in the acute phase, with informal material. Patient's communication abilities were fully functional, as she could maintain eye contact, follow orders, and respond verbally with words and sentences.

Patient P7

Patient P7 is a 44-year-old, right-handed, late bilingual female (L1: Bulgarian, L2: Greek), having 12 years of education. Although she was a fluent speaker of Greek, it was not her first language and did not receive formal education in Greece (she was living in Greece the past 15 years). The onset of symptoms was approximately four years ago, when she started to experience severe headaches. After a neuroimaging examination with MRI she was diagnosed with a brain tumor, but she did not proceed to surgery. A more recent brain MRI scan revealed a non-enhancing space-occupying lesion which was located on the insular cortex of the left (dominant) hemisphere. As she reported she never had speech or language difficulties since the first diagnosis.

The preoperative assessment included the following tests: EHI, SAQoL-39g, and BDAE. The handedness inventory revealed pure right-handedness (100%), and the SAQoL-39g no impact of the disease on quality of life (overall score: 5/5). In BDAE, the patient exhibited low scores in *reading* and *writing* components (mean percentiles close to 60^{th} and 20^{th} respectively), although they were not pathological. The reason behind this finding may lie in her (late) bilingualism status and the fact that she did not receive formal education in Greek language. On the other hand, her *speech production* also presented low scores (mean percentile below the 50^{th}), and her speech profile was matching with apraxia of speech, although the symptoms were very mild (BDAE severity scale score: 5). The subtests in which the patient scored the lowest were the non-verbal diadochokinesis (score: 8/12, 10%ile: 10/12), the verbal diadochokinesis (score: 11/14, 10%ile: 13/14), and the automatized sequences (score: 7/8, 10%ile: 8/8).

Perioperatively, P7 underperformed in every task of the preliminary version of GLAABS as she did not achieve max score in any. The average hit-rate was 81.4% and the most dominant error type was anomia, followed by apraxic/articulation. However, GLAABS had not yet been standardized and these scores could not be compared to the normal population. Also, it was not clear in which cases the errors were true anomias or lack of knowledge for the particular language (Greek). As in every case, the incorrectly answered stimuli were removed from the intraoperative plan.

The selected tasks for the intraoperative assessment were *motor planning* and *object naming*. The former task (motor planning) was administered during the mapping process while the latter (object naming) was employed in both, mapping and resection processes. The patient produced one articulation error during the *motor planning* task, whilst during object naming, she produced four semantic paraphasias and six anomias. The awake stage concluded in approximately 60 minutes during which the patient was generally very cooperative. The results of the fast-track biopsy reported that the tumor was a low-grade glioma and the neurosurgeons managed to perform a total resection.

The postoperative evaluation was performed only in the acute phase, with informal material. Her communication abilities were functional, as she could maintain eye contact, follow orders, and respond verbally with words and sentences.

Patient P8

A 32-year-old male, with 16 years of education was operated 10 years ago by our institution to surgically treat a low-grade glioma located on the left motor-sensory cortex. This procedure caused an impairment in right upper extremity and the patient, who initially was a pure right-hander, gradually started to use the left hand and became ambidextrous. The neuroimaging results revealed a tumor recurrence in the left lateral ventricle.

The preoperative assessment of speech and language was conducted with EHI, BNT, SAQoL-39g, and BDAE. The Edinburgh Handedness Inventory confirmed patient's anecdotal report regarding handedness and revealed that he was a mixed right-hander (58%). However, this switch in handedness took place after the first surgery. With respect to the quality of life, SAQoL-39g scores revealed that it was generally unaffected by the tumor recurrence (overall score: 4.8/5). Speech and language were also not affected by the tumor, as he scored within normal range in all components, while in *writing* he performed the lowest scores (mean percentile below the 50^{th}). The patient also exhibited difficulties in the non-verbal diadochokinesis task from *speech production* component of BDAE (score: 9/12, 10%ile: 10/12).

A preliminary version of GLAABS was used for the perioperative and intraoperative assessments. Regarding the former, the patient performed very well and produced only a few errors. The task with the most errors was interestingly the *semantic association* task, in which the patient responded correctly in only 80% of the stimuli.

The operating neurosurgeon performed only subcortical mapping. For this procedure, the *word repetition* and *motor planning* tasks were selected, while for the resection the examiner used *object naming* and *phonological judgment* tasks. The patient cooperated adequately, and the neurosurgeons managed to partially remove the 60% of the tumor.

Again, as in every other patient previously presented, the postoperative assessment was limited in acute stage. From the brief informal examination, it was observed that the patient could communicate normally with the examiner and the nursing personnel of our clinic. His communication abilities were fully functional, as he could maintain eye contact, follow orders, and respond verbally with words.

Patient P9

Patient P9 is a 31-year-old, right-handed female, with 14 years of education, that was hospitalized after a seizure. Neuroimaging examination with MRI revealed a large space-occupying lesion in the temporoparietal junction.

Preoperatively, the patient was assessed with EHI, BNT, SAQoL-39g, and BDAE. The handedness inventory showed that P9 was a mixed right-hander (79%), while SAQoL-39g revealed that her quality of life was mildly affected by the tumor (overall score: 4.7/5) and the most affected domains was the psychosocial (4.6/5) and the communication (4.6/5). Her speech and language skills were very functional although the patient demonstrated mild anomic aphasia (severity score: 4) according to BDAE. Naming which was specifically tested with BNT verified this finding as she produced 44/45 cued and uncued responses but the uncued responses were only 38. The most affected component in BDAE was *speech production* with a mean percentile score below the 30th. She also exhibited difficulties in comprehension above word-level, as her performance in "comprehension of complex ideational material" and "comprehension of paragraphs by reading" subtests was considerably low (scores: 6/12 & 7/10, 10%iles: 9/12 & 8/10 respectively).

The perioperative assessment was conducted with a preliminary version of GLAABS and the patient had no particular difficulties to respond to the tasks, except in *semantic association* (80%), *sentence completion with words* (84%), and *object naming* (89%). Errors were mostly anomias, although the patient produced several agrammatic errors too.

The intraoperative assessment was not conducted according to the plan as the patient could not cooperate adequately. It should be noted that this was the last case which the patient was assessed intraoperatively by another clinician (a psychologist from the same institution). The only task that was administered was the object naming task which was used to map the temporoparietal junction. During the awake stage, the patient was complaining about headache and dizziness, and she was interrupting constantly the assessment procedure. Eventually, she managed to respond to 32 stimuli but only 23 were correct, the rest were errors (mainly anomias and phonological paraphasias). The awake stage was continued for approximately 30 minutes and the examiner also assessed verbal communication abilities through conversational discourse.

The postoperative evaluation in the acute phase showed that the patient was able to maintain eye contact, but she had great difficulty following instructions (especially complex ones), and her verbal responses were limited to single words.

Patient P11

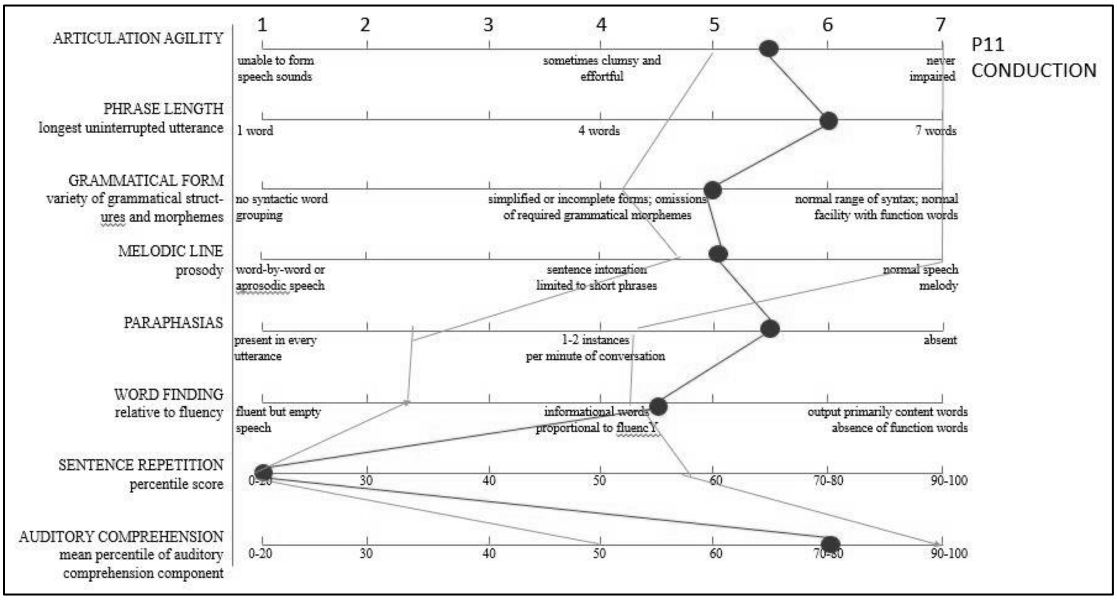
A thirty-eight-year-old, right-handed female with 12 years of education was referred to our clinic after a seizure and hospitalization in a neighboring city. The neuroimaging examination was performed with MRI and the results revealed a large primary space-occupying lesion on the left inferior frontal gyrus.

Preoperatively, the patient was evaluated with EHI, BNT, SAQoL-39g and BDAE. The examination with EHI revealed that the patient was a mixed right-hander (90%), while the SAQoL-39g questionnaire indicated minor impact of the tumor on patient's quality of life (overall score: 4.7/5). Her performance on speech and language tests was generally within normal range. Particularly, the patient scored 43/45 on BNT, while in BDAE her mean percentiles in all components were above the 60th. The lowest scores were performed in the following subtests: non-verbal diadochokinesis (score: 7/12, 10%ile: 10/12), semantic fluency (score: 13/41, 10%ile: 15/41), complex ideational material (score: 7/12, 10%ile: 9/12), and comprehension of paragraphs (score: 7/10, 10%ile: 8/10).

Perioperatively the patient was assessed with the final, standardized form of GLAABS and performed within normal range in all tasks except *word repetition, verb naming*, and *motor planning*, in which her scores were below the cut-off scores. Moreover, in *semantic association* and *object naming* tasks her scores were normal, but close to the cut-off scores. Patient P11 produced various types of errors but no type was more prominent than the others.

For the awake stage, the *verb naming* and *motor planning* tasks were selected to map the inferior frontal gyrus, while the arcuate fascicle was identified with the *word repetition* task. During the resection of the tumor, the patient was constantly evaluated with *sentence completion (sentences), semantic odd-word out, object naming*, and *action fluency* tasks, as well as conversational discourse. The patient cooperated adequately, and several areas associated to speech and language were identified and preserved through positive mapping

Figure 4.2
Postoperative speech and language characteristics of patient P11 according to BDAE's rating scale profile.



(speech arrests and anomias). The duration of the awake stage was 1 hour and 45 minutes and as it approached to the end, patient's errors (mainly anomias and perseveration errors) increased.

The assessment at the acute postoperative stage, revealed that the patient could communicate adequately, and she was able to maintain eye contact, respond verbally, and follow orders. The follow-up assessment took place one month later, with the same tests as in the preoperative session (BNT, SAQoL-39g, BDAE). The results signified a small decline in her quality of life, as the overall score on SAQoL-39g dropped from 4.7 to 4.3. Furthermore, patient's performance on BDAE and BNT tests indicated the presence of a mild (BDAE severity scale: 4) conduction aphasia (Figure 4.2, previous page).

Patient P12

Patient P12 is a 26-year-old, right-handed male, with 12 years of education. After suffering a seizure and being hospitalized, the patient went through neuroimaging examination. The results of the MRI revealed a tumor in the left hemisphere and particularly in the left inferior frontal gyrus which was extending to the insular cortex.

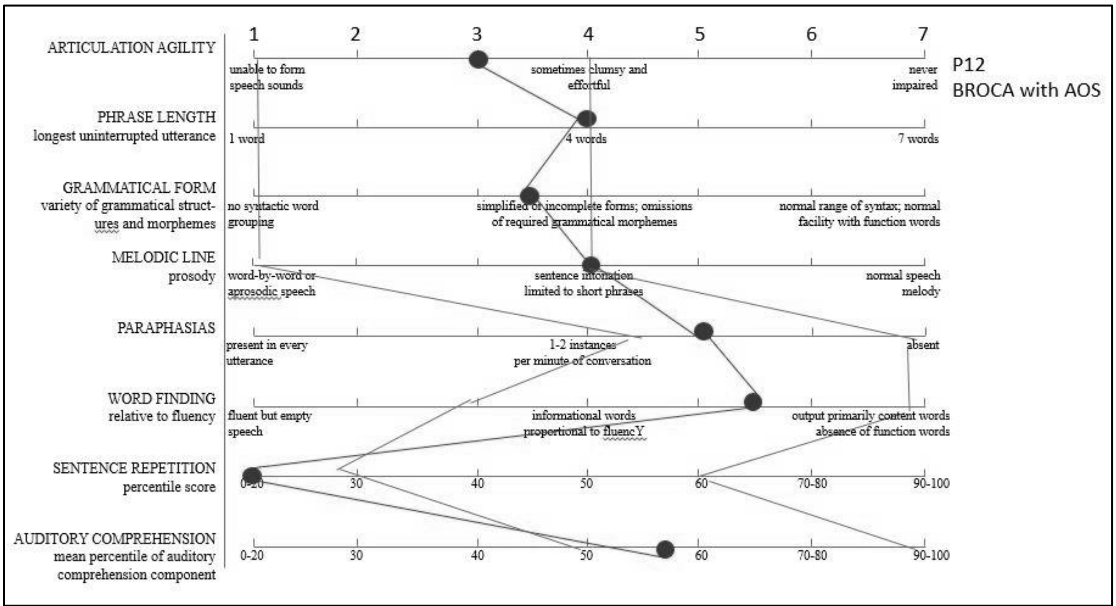
During preoperative assessment and particularly at the history taking, the patient reported that he was experiencing "difficulties to explain his thoughts" (due to syntactic errors). Also, the examiner noticed a slow rate of speech, which according to the patient it was present since his childhood. However, the produced words were calculated to be 160 per minute in connected speech, which is considered within normal limits [375]. Therefore, this finding was considered part of his idiolect and not a tumor-related symptom. The standardized tests used in this session included EHI, BNT, SAQoL-39g and BDAE. Examination with EHI revealed that the patient was a pure right-hander (100%), while SAQoL-39g indicated almost no effect of the tumor occurrence on patient's quality of life (overall score: 4.8/5), with the exception of the psychosocial domain (score: 4.5/5). His performance on speech and language tests revealed a very mild conduction aphasia (BDAE severity scale: 5). Particularly, the patient scored 44/45 on BNT, while the mean percentile in almost every component of BDAE was above the 50th. The only exception was the *repetition*, in which the mean percentile score was below the 40th. The specific subtests in which the patient presented pathological scores are the non-verbal diadochokinesis (score: 8/12, 10%ile: 10/12), the verbal diadochokinesis (score: 10/14, 10%ile: 13/14), and the repetition of sentences (score: 13/16, 10%ile: 16/16). Finally, although patient's speech was fluent, it was slightly agrammatic since in (oral and written) description of "cookie jar" picture, he omitted several functional words.

Perioperatively, the patient was assessed with the final, standardized form of GLAABS and performed within normal range in the vast majority of tasks except *motor planning* and *word repetition*, in which his performance was pathological. It should be noted that in *semantic odd-image out* and *semantic odd-word out* his performance was normal, but the scores were close to the cut-off scores. Patient P12 produced various types of errors (e.g., phonemic paraphasias, syntactic errors, anomias) and no type was more prominent than the others.

Regarding the awake stage, the *verb (action) naming* and *object naming* tasks were selected to map the inferior frontal gyrus and the insular cortex, while the *motor planning* task was preferred for the superior longitudinal fascicle. During resection process, the language specialist evaluated patient's speech and language with *object naming*, *sentence completion (words)*, *word repetition*, *sentence completion (sentences)*, and *action fluency* tasks, as well as with the previously described conversational discourse method. Patient's cooperation was excellent and through positive mapping (mainly speech arrests) the operating neurosurgeon managed to identify and preserve several eloquent areas. The duration of the awake stage was 1 hour and 5 minutes and as it was approaching to the end, patient's errors (mainly morphosyntactic errors, spastic dysarthria, and phonemic paraphasias) increased.

During the acute postoperative stage, the patient could communicate adequately as he could maintain eye contact, respond verbally with single words, and follow orders. However, his speech was characterized by apraxic errors and spastic dysarthria. The follow-up assessment took place one month later in our clinic, with the same tests as in the preoperative (BNT, SAQoL-39g, BDAE). Compared to the preoperative results, the postoperative evaluation indicated a small decline in his quality of life (overall score: 4.4/5) and particularly in psychosocial domain (score: 3.8/5). Regarding language, patient's fluency was disturbed, and his comprehension was better preserved than his speech production. Specifically, on

Figure 4.3
Postoperative speech and language characteristics of patient P12 according to BDAE's rating scale profile.



BDAE's *auditory comprehension* component patient's mean percentile was close to the 60th, on *reading* and *writing* above the 80th, whilst the lowest mean percentiles were achieved in *speech production* (45) and *repetition* (1.67). The subtests relative to speech production with the lowest scores were the two diadochokinesis tasks (scores: 8/12 and 10/14, 10%iles: 10/12 and 10/14 respectively), the reciting/melody/rhythm (score: 4/6, 10%ile: 6/6), the verbal fluency (score: 15/41, 10%ile: 15/41), the repetition of words (score: 8/10, 10%ile: 10/10), and finally, the two sentence repetition subtests (high probability score: 7/8, 10%ile: 8/8; low probability score: 7/8, 10%ile: 8/8). The result from BDAE and BNT tests indicated the presence of Broca's aphasia (Figure 4.3, previous page) accompanied with mild apraxia of speech. However, the symptoms were mild as the patient scored 4 in the severity scale from BDAE, for both disorders.

Patient P13

Patient P13 is a forty-year-old, right-handed male, with 12 years of education. After suffering a seizure and being hospitalized, he went through neuroimaging examination. The MRI brain scan revealed a multifocal primary brain tumor in the left (dominant) hemisphere, encroaching the superior frontal gyrus and the motor-sensory cortex (mostly the postcentral gyrus).

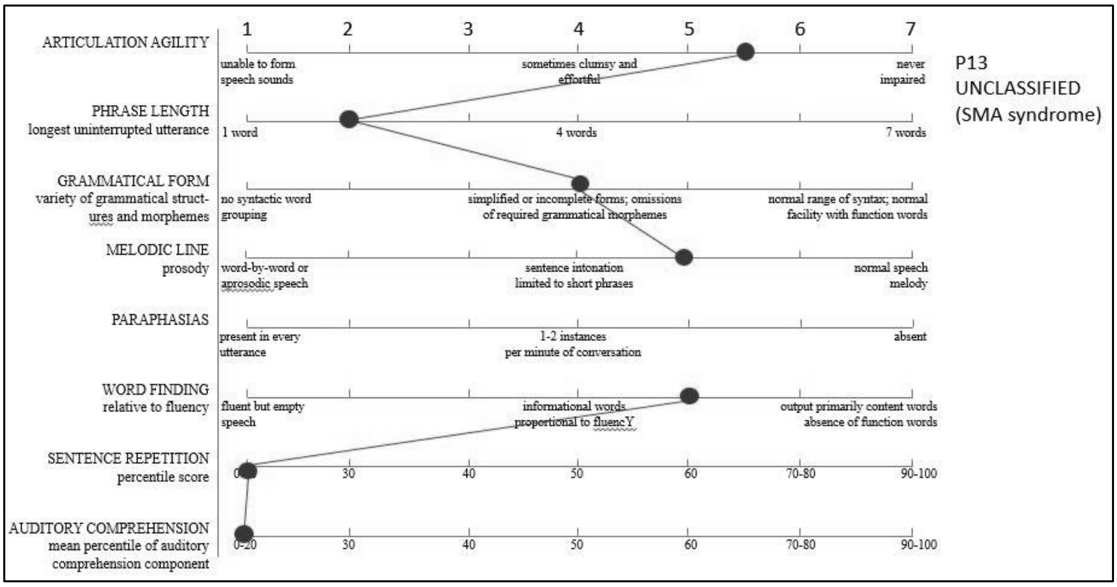
The standardized tests used in the preoperative evaluation included EHI, BNT, SAQoL-39g and BDAE. Examination with EHI revealed that the patient was a pure right-hander (100%), while SAQoL-39g indicated almost no impact of the tumor occurrence on patient's quality of life (overall score: 4.9/5). His performance on speech and language tests did not reveal any deficit. In BNT the patient scored 45/45 cued and uncued responses, while his uncued score was 44/45. Regarding BDAE, the mean percentiles of all components was above the 80th, whilst pathological scores were observed only in a few subtests in *writing*. In particular, the patient presented pathological scores in writing mechanics (score: 4/5, 10%ile: 5/5) and sentence dictation (score: 9/12, 10%ile: 10/12) subtests, while the score in narrative writing subtest was equal to the 10th percentile. Finally, it should be noted that the patient presented a particular speech pattern (accent) as he was using the Epirus dialect (North-Western Greece). Lexical differences from standard Greek were taken into consideration and variations in naming of objects or actions were recorded in perioperative session.

The perioperative session took place two weeks after, and patient's language abilities got worse. This session was conducted with the final, standardized form of GLAABS and patient P13 performed within normal range in most tasks, except *phonological odd-word out*, *semantic odd-word out*, *sentence completion with words*, *grammaticality judgment*, *phonological judgment,* and *semantic association*. The most prominent error that he produced was anomia.

Inside the operating theatre, during awake stage, the *object naming* task from GLAABS was employed for cortical mapping, while *word repetition* was used to identify the corticospinal tract. During resection process, the patient was evaluated with *sentence completion (words), verb (action) naming, sentence completion (sentences), verbal fluency (phonological)*, and *syntactic judgment* tasks, as well as with conversational discourse. Patient's cooperation was excellent and from mapping procedure we managed to identify several eloquent areas associated with speech and language, mainly through positive mapping (speech arrests and anomias). The duration of the awake stage lasted 1 hour and as it was approaching to the end, patient's comprehension slightly decreased. However, the patient was very cooperative and tolerated the awake stage very well. The fast-track biopsy results reported that the tumor was a glioblastoma, whilst the extent of the resection was estimated to be 85%.

During acute postoperative stage, the patient presented SMA syndrome accompanied by significant reduction of spontaneous speech, as previously described in the literature [376-378]. Moreover, he could maintain eye contact and follow 2-step orders, but his verbal response was severely impaired, as he was lacking language initiation and he could produce single words only after cueing by the examiner. The follow-up assessment took place one month later, in our clinic, with the same tests as in preoperative (BNT, SAQoL-39g, BDAE). Compared to preoperative, the post-op results indicated a small decline in his quality of life (overall score: 4.6/5), and a greater decline in speech and language abilities (according to BDAE and BNT). Patient's score in BNT cued and uncued responses was within normal range (42/45) and although his fluency had been improved since the acute postoperative evaluation, he was still non-fluent. The mean percentiles in *speech production*, *repetition* and *reading components* were close to the 30th, whilst in *auditory comprehension* and *writing* below the 10th. Patient P13 scored above or equal to the 10th percentile only in 9 out of 28 BDAE subtests, and particularly in word discrimination, body-part identification both diadochokinesis tasks, automatized sequences, repetition of words, symbol discrimination, word recognition, and comprehension of paragraphs. In *writing* component, he was not able to score within normal range in any subtest. The reason behind this result lies in a mild paresis in his right hand that he developed after surgery. Compared to the immediate postoperative evaluation, his clinical picture had been improved and many of the acute symptoms had been resolved. However, several signs of SMA syndrome were still present and the patient had disturbed speech initiation. For instance, although his cued responses in BNT were within normal limits (42/45), the uncued responses (30/45) were below the cut-off score (31/45). Also, during the description of the "cookie jar" picture of BDAE, which lasted almost 4 times more than his preoperative performance, the patient was producing speech only after cueing by examiner (e.g., with questions, or phonemic cues). Interestingly, his articulation had not been disturbed, as he produced only a few phonemic paraphasias and no exclusively speech related errors. Although traditionally, the SMA syndrome has been associated with transcortical motor aphasia [377], patient's P13 speech profile in BDAE did not match with any particular type of aphasia (Figure 4.4). In summary, his symptoms were considered severe (BDAE severity scale: 2) and qualitatively very close to those reported by Masdeu et al. [378] for SMA syndrome (i.e., initial mutism evolved to fluent speech, short sentences, normal grammatical abilities, severe impairment of writing, frustration related to language tasks).

Figure 4.4
Postoperative speech and language characteristics of patient P13 according to BDAE's rating scale profile.



Patient P16

A 44-year-old, right-handed male, with 12 years of education was operated 5 years ago by another institution to treat a low-grade glioma located on left prefrontal cortex. After a seizure, the patient went through neuroimaging examination with MRI, and the results revealed a tumor regrowth in the left orbitofrontal cortex.

During preoperative assessment and particularly during history taking, the patient reported that he had recently been suffering from inconsistent speech errors and anomias, as well as disturbance of short-memory. The assessment of speech and language was conducted with EHI, BNT, SAQoL-39g, and BDAE. Edinburgh Handedness Inventory showed that the patient was a pure right-hander (100%), while SAQoL-39g revealed a significant decrease in his quality of life (overall score: 4.1/5) and particularly in psychosocial domain (score: 2.9/5). Speech and language were not significantly affected by the first operation and the tumor recurrence, and the patient exhibited a very mild aphasia (BDAE severity scale score: 5). Scores were within normal limits in BNT (43/45) although he scored 38 uncued responses. In BDAE the patient performed above the 60th percentile in *auditory comprehension*, *repetition*, and *reading*, and close to the 50th in *speech production* and *writing*. Interestingly, his performance in comprehension of complex-ideational material (score: 8/12) and narrative writing (score: 3/5) subtests was impaired (10%iles: 9/12 and 4/5 respectively). He also exhibited signs of agrammatism (omission of functional words, small and unconnected sentences), especially in the description of "cookie jar", although he was generally fluent. With respect to self-reported speech and language deficits, the patient indeed produced anomias, but his articulation was within normal limits in every aspect. Finally, regarding the type of the aphasia, although patient's results in BDAE exhibit characteristics of Broca's aphasia (namely agrammatic speech), his speech rating profile did not match this or any other type.

The perioperative session took place four weeks later and was conducted with the final, standardized form of GLAABS. The patient performed within normal range in the majority of tasks except *semantic odd-image out*, *verb (action) naming*, *sentence completion with words, object naming, semantic odd-image out,* and *word repetition*, in which he scored below the cut-off scores. The semantic type was the most prominent type of paraphasia.

Inside the operating theatre, during awake stage the language specialist used *semantic odd-image out* and *verb (action) naming* tasks to assist the mapping of orbitofrontal cortex, and the *semantic association* task for subcortical mapping. During the resection process patient P16 was assessed with *sentence completion (words), sentence completion (sentences), verbal fluency (semantic), syntactic judgment* and *verb generation* tasks, as well as with conversational discourse. Patient's cooperation was excellent and from mapping procedure we managed to identify two cortical areas associated with speech and language, mainly through positive mapping (one speech arrest and one semantic paraphasia). The awake stage was concluded after 45 minutes and as the resection was approaching to the end, patient's answers in the *verb generation* task became abstract and general (e.g., stimulus: kitchen, response: "we can do a lot of things with that"). However, his cooperation during the awake stage was excellent and the neurosurgeons managed to perform a total resection.

During acute postoperative stage, patient's communication was adequate, and he could maintain eye contact, follow orders, and respond verbally with words and sentences. The follow-up assessment took place one month later in our clinic, with the same tests as in the preoperative (BNT, SAQoL-39g, BDAE). Assessment initiated with BNT, in which the patient performed within normal range (43/45) and resumed with SAQoL-39g. During the latter, which consists of 39 questions, the patient claimed fatigue after 29 responses and the assessment was terminated. Thus, the tests results cannot be conclusive. In order to informally evaluate patient's speech and language functions above word level (e.g., syntax, phrase prosody, pragmatic skills) the examiner used conversational discourse and found that patient's communication abilities were fully functional.

Patient P17

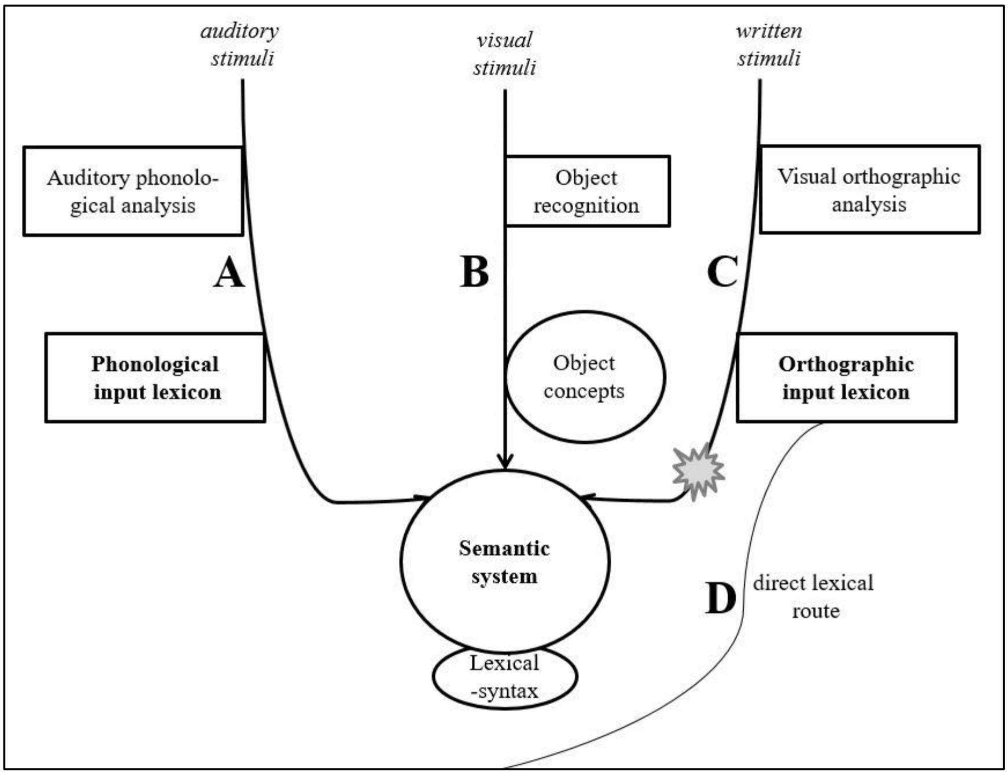
A 32-year-old, Greek speaking, right-handed male, with 12 years of education, was hospitalized in our clinic after having an epileptic seizure associated with loss of consciousness while at work. He reported mild difficulties with short-term memory in the days following the seizure and exhibited episodes of aggressive behavior during his hospitalization. A brain MRI study revealed a non-enhancing, hyperintense on T2 weighted image lesion located in the left (dominant) middle-posterior inferior temporal gyrus. Frozen-section biopsy during surgery indicated low-grade glioma but subsequent histopathology analysis excluded malignancy, without being able to exclude a tuberculoma although PCR was negative for mycobecterium.

The preoperative assessment was conducted with EHI, BNT, SAQoL-39g, MoCA, and BDAE. The handedness questionnaire revealed that the patient was purely (100%) right-handed, while his quality of life was not affected by the tumor (overall score: 4,8/5 in SAQoL-39g). Speech, language, and cognition was not significantly affected by the tumor as he scored 43/45 in BNT, and 25/30 in MoCA, which is close to the cut-off score for mild cognitive impairment. In BDAE he scored within normal limits in all components and the mean percentiles were above the 60th, although in written comprehension of paragraphs subtest his performance was marginally pathological (score: 8/10, 10%ile: 8/10).

As in all cases, the perioperative session aimed to ran through the pre-selected tasks, exclude stimuli that were not flawlessly answered, and prepare patient for the "awake" procedure. The entire GLAABS test was administered once and the patient performed within normal range in all tasks (except *verb naming*). Then a set of tasks were administered again, in order to assess semantic processing, semantic-phonological interface, mental lexicon, and comprehension or written language. The patient performed excellent in all tasks.

The cortical language mapping identified four (n = 4) distinct language areas, which were preserved by the operating neurosurgeon. During intraoperative mapping and resection of the cortex (posterior inferior temporal gyrus) the patient produced inconsistent speech/language errors in *semantic association* and *object naming* tasks. The inferior longitudinal fascicle was identified with the *semantic odd-word out* and *phonological odd-word out* tasks. During resection process the patient was evaluated with *semantic judgment, phonological judgment, verbal fluency (semantic),* and *sentence completion (sentence)* tasks. An interesting finding from language mapping process is that during the administration of *semantic odd-word out* task, in which the patient is asked to choose the semantically non-matching written word, the stimulation of the inferior longitudinal fascicle induced severe paralexias, which resulted in complete (but transient) mutism. Lexico-semantic processing of written language is heavily involved in this task, since the semantic features of the given words have to be analyzed and compared in order to find which words belong to the same semantic category. According to the cognitive model for single word processing (Figure 3.1, Chapter 3), one has to access the semantic system through visual-written route (Figure 4.5, "C" route), in order to appropriately respond in this task. Contrary to written stimuli, the patient did not experience difficulties to respond when the same task was given orally (Figure 3, "A" route) or the *semantic odd-image out* task was given visually, via visual-object input route (Figure 3, "B" route). The above analysis indicates that the pathway disruption was occurring somewhere along the orthographic-semantic route, and particularly at the orthographic input lexicon. However, patient P17 did not produce any errors when the examiner administered the *phonological odd-word out* task (with written words), which also requires access to the orthographic input lexicon but uses the direct lexical route (Figure 3, "D" route). Taking all these data into consideration, it is evident that the functional disruption was not occurring in the orthographic input lexicon per se, but in accessing the semantic system. This finding is in line with evidence regarding the involvement of the ILF in reading and semantic processing [125,140,379-383]. The operation was very well tolerated by the patient which was awake and fully cooperative for 75 minutes allowing neurosurgeons to perform a partial resection extending to 80% (neurosurgeon's estimation).

Figure 4.5
Modified graphical representation of cognitive neuropsychological model for single word processing as described in Whitworth et al. (2014) and Rofes et al. (2018).



The patient was evaluated informally two days after the operation, and he exhibited mild linguistic deficits as he produced some inconsistent anomias and semantic paraphasias during conversational discourse. The follow-up assessment was conducted four weeks later and did not reveal any impairment in speech, language, or cognition as the patient scored in all the administered tests similar to the preoperative assessment (SAQoL 39g: 4,9/5, MoCA: 26/30, BNT: 42/45, BDAE-reading paragraphs: 9/9,3). The mild deficits he demonstrated preoperatively in reading comprehension they had disappeared in his follow-up evaluation.

Patient P18

A 44 years of age, right-handed female, with 12 years of education was operated 9 years ago by our clinic to treat an astrocytoma grade II which was located on her right (non-dominant) hemisphere and particularly on the superior temporal gyrus. The first brain surgery caused left hemiparesis and a very mild dysarthria. Few days before the preoperative assessment and after a scheduled annual neuroimaging examination with MRI, it was observed that the tumor had regrown and was encroaching the area between the claustrum and the inferior temporal horn.

During history taking the patient reported excessive sleepiness, which was also maintained postoperatively. The preoperative assessment of cognition, speech, and language was conducted with EHI, MoCA, BNT, SAQoL-39g, and BDAE. The Edinburgh Handedness Inventory showed that the patient was a pure right-hander (100%), while SAQoL-39g revealed decreased quality of life (overall score: 3.7/5) particularly regarding the physical (score: 3.5/5) and psychosocial domains (score: 3.4/5). A brief cognitive evaluation with MoCA showed a mild cognitive impairment as she scored 23/30 which is below the cut-off score (25/30). Patient's speech and language abilities were not significantly affected by the first surgery or the tumor recurrence. In BNT, she scored 44/45 cued and uncued responses, which is considered normal (uncued responses 41/45). In BDAE the patient performed within normal limits and the mean percentiles were above the 70^{th} in all components, except *speech production* in which the mean percentile was close to the 50^{th}. The subtests that presented the lowest scores were the verbal (score: 10/14, 10%ile: 13/14) and non-verbal diadochokinesis (score: 6/12, 10%ile: 10/12) from *speech production* component, and the visual symbol discrimination from *reading* (score: 7/8, 10%ile: 8/8). Interestingly, the patient underperformed in narrative writing also, as she scored 4/5 which is equal to the 10th percentile. To sum up, although her language abilities were generally normal, her speech was disturbed as she exhibited very mild dysarthria (due to left hemiparesis) and apraxia of speech (BDAE severity scale: 5)

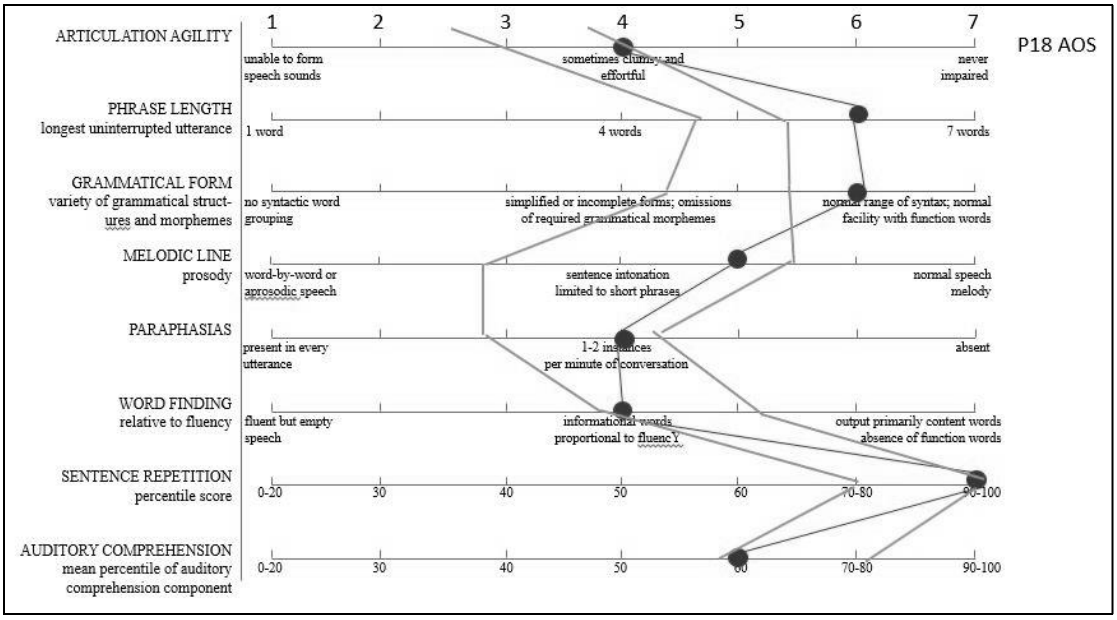
The perioperative session was conducted with a combination of tasks from GLAABS and eRHT, an experimental test developed for right (non-dominant) hemisphere awake brain surgeries (see Appendix A for details). All tasks were administered twice on two different perioperative sessions. The selection of tasks included *word repetition*, *phonological odd-word out*, *motor planning*, *sentence completion (sentences)*, and *object naming* from GLAABS, and *distant semantics*, *production of emotional prosody, naming of emotions, attention–consciousness,* and *verbal fluency without constraint* from eRHT. The patient performed above 90% in all eRHT tasks except *distant semantics.* Regarding the GLAABS tasks, the patient performed within normal only in *object naming* and *sentence completion with sentences*, while in *phonological odd-word out, motor planning*, and *repetition of words* her performance was pathological. Patient's P18 errors included apraxic errors, phonological paraphasias, and anomias.

In order to assist language mapping, the examiner used the *attention-consciousness, motor planning* and *object naming* tasks. On the other hand, during resection, the patient was evaluated with *sentence completion with sentences, distant semantics (odd word out), production of emotional prosody, naming of emotions,* and *verbal fluency without constraint* tasks, as well as with conversational discourse. As soon as the patient started to regain consciousness, she experienced dysarthria, inability to maintain eye contact, constant loss of consciousness, apraxia of speech (inconsistent errors), and flat prosody. These symptoms got milder after the first 20 minutes, but eventually, after 70 minutes of awake stage, they became worse. However, patient's cooperation was adequate enough to cooperate for 80 minutes and by mapping procedure we managed to identify several eloquent areas associated to speech, mainly through positive mapping (apraxia errors). Fast-track biopsy results indicated a grade III glioma, while the neurosurgeons managed to perform a partial resection (estimated EOR: 80%)

During the acute postoperative stage, the patient was assessed informally. She exhibited severe drowsiness and saliva drooling while, with respect to speech and language, she presented only mild symptoms, such as anomias and inconsistent speech errors. Otherwise, her communication was functional, as she could maintain eye contact, follow orders, and respond verbally with words. The follow-up assessment was conducted with the same tests as in the preoperative phase (BNT, SAQoL-39g, MoCA, and BDAE). Compared to preoperative assessment, her quality of life remained unchanged (SAQoL-39g overall score: 3.6/5). Regarding her cognitive abilities, the results of MoCA are not representative of her cognitive abilities (score: 5/30) as the patient complained about mental fatigue and aborted it during the second subscale. On the other hand, her speech and language functions (according to BNT and BDAE) remained generally unaffected, as in BNT she scored within normal range (score: 42/45) and in BDAE she presented similar to the preoperative session results.

Although postoperatively, she scored slightly better in the diadochokinesis subtests, her performance was still pathological (non-verbal score: 10/12; verbal score: 11/14). Furthermore, she scored below normal in comprehension of paragraphs reading (score: 7/10), while in narrative writing, even though the score was unchanged (score: 4/5), her description was slightly agrammatic and had low mean length of utterance (MLU). The errors she produced during the assessment include mostly anomias, paralexias, and inconsistent (apraxic) errors. Although patient's P18 speech profile in BDAE did not match any particular aphasia, her inconsistent errors and pathological performance in diadochokinesis tasks indicated a mild apraxia of speech. Indeed, her speech profile in BDAE (Figure 4.5) was very close to literature reports regarding AOS [384,385]. Regarding the severity, patient's early symptoms were mild (BDAE severity scale: 4), as she exhibited a small but obvious loss of fluency without limiting her communication abilities. It should be mentioned also that the patient exhibited left visual neglect, egocentric type, as she had difficulties to respond to stimuli in one half of her visual field (unless she was pointed to it).

Figure 4.5
Postoperative speech and language characteristics of patient P18 according to BDAE's rating scale profile.



Patient P20

Patient P20 is a 41-year-old, right-handed female, with 12 years of education. Her symptoms started with headaches that gradually got worse. Neuroimaging examination with MRI revealed a space-occupying lesion in the left (dominant) hemisphere, encroaching the precentral gyrus (motor cortex) and extending to the posterior part of the superior frontal gyrus.

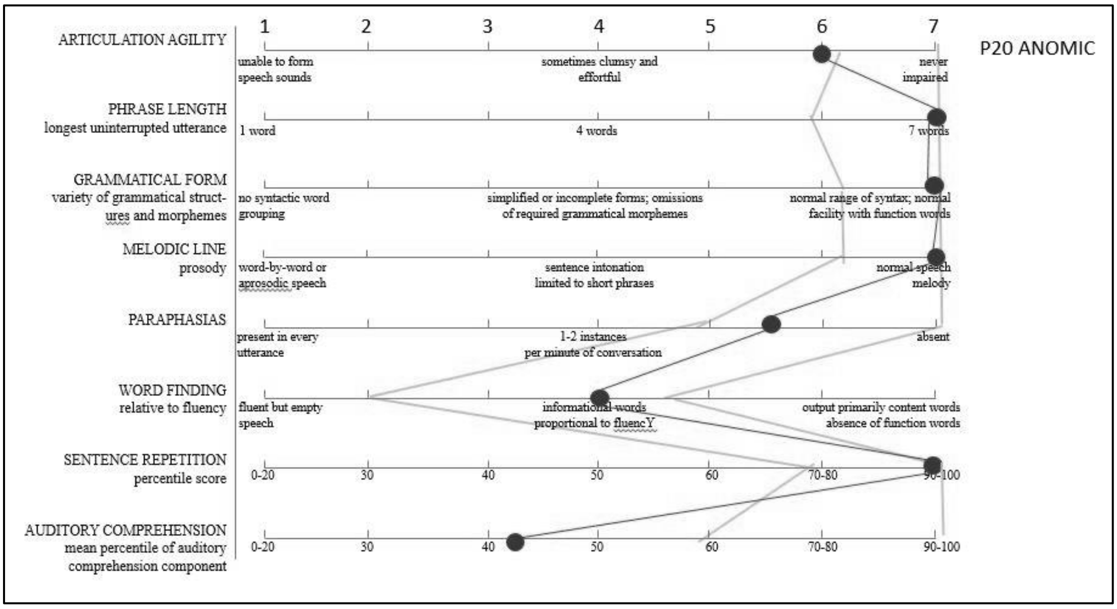
During history taking the patient reported mild dysarthria and an unrelated with the tumor (developmental) articulation disturbance regarding tongue-thrusted /s/. The preoperative assessment of cognition, speech and language was conducted with EHI, MoCA, BNT, SAQoL-39g, and BDAE. The handedness questionnaire showed that the patient was a pure right-hander (100%) while SAQoL-39g revealed no effect of the tumor on her quality of life (overall score: 4.9/5). The brief cognitive evaluation with MoCA showed that the tumor was affecting patient's cognitive abilities, as her score (24/30) was below the cut-off score for mild cognitive impairment. The assessment of patient's speech and language abilities revealed a very mild anomic aphasia (BDAE severity scale: 5). In BNT she scored within normal limits with regards to the cued and uncued responses (41/45), albeit she produced only 33 uncued responses. In BDAE, patient's mean percentile in most components was above the 70^{th}, except *speech production*, in which the mean percentile was close to the 40^{th}. The subtests with the lowest scores were the non-verbal (score: 10/12, 10%ile: 10/12) and verbal diadochokinesis (score: 12/14, 10%ile: 13/14), the recitation/singing/rhythm (score: 4/6, 10%ile: 6/6), and the visual symbol discrimination (score: 6/10, 10%ile: 10/10).

The perioperative session took place four weeks later and two days before surgery. The assessment was conducted with the final, standardized form of GLAABS, and the patient performed within normal range all tasks except *repetition of words.* A small difference in performance was observed in three tasks that were administered with two different ways (*phonological odd-word out:* orally and written, *semantic odd-image out:* orally and visually, *sentence completion:* orally and written). The patient performed better when the stimuli were given orally (96.93%) compared to written or visual administration (90.73%).

For the awake assessment, the *sentence completion with words (written stimuli)* and *object naming* tasks were selected in order to perform cortical mapping, while the *motor planning* task to identify the corticospinal tract. During the resection process, patient P20 was assessed with *semantic odd-word out*, *semantic odd-image out*, *verbal fluency (phonological)*, *syntactic judgment*, and *sentence completion (sentences)* tasks, as well as with conversational discourse. After the patient regained consciousness, the assessment started with automatized speech (counting 0-10, letter and day reciting) mostly to help the neurosurgeon to set the appropriate electrical current of the stimulation probe. During this task the patient produced only a small number of speech arrests, while during language mapping she produced mostly speech arrests and a small number of semantic paraphasias. Her connected speech which was evaluated with *semantic completion with sentences* task and conversational discourse did not exhibit severe deficits during resection, except a small quantity of semantic errors, perseveration errors, and speech arrests. The awake stage was concluded in 80 minutes during which the patient was very cooperative. After 50 minutes and while the resection process was ongoing, the patient started exhibiting signs of SMA syndrome which gradually got worsen. Also, the patient experienced four seizures (two focal, two grand mal) during the awake stage which were treated by applying cold water in the cortical surface. Fast-track biopsy results indicated a low-grade glioma and the neurosurgeons managed to perform a subtotal resection (estimated EOR: 85%).

At the acute postoperative stage, the patient was assessed informally. Her communication abilities were functional, as she could maintain eye contact, follow orders, and respond verbally with words. However, in terms of mobility, she exhibited severe paresis of the right lower extremity and a moderate one on her right upper extremity. The patient was hospitalized in a rehabilitation center for 25 days, wherein, she received therapy and she was re-evaluated by our institution about a month after the surgery. The follow-up assessment was conducted with the same tests, as in the preoperative phase (BNT, SAQoL-39g, MoCA, and BDAE). Her score in quality of life questionnaire slightly decreased (SAQoL-39g overall score: 4.3/5), whilst the physical score was the most affected from the surgery (physical score: 4.4/5). Patient's performance in MoCA test noted a significant decrease (score: 19/30) and most of the errors were associated with visuospatial skills, executive functions, and attention. Her speech and language abilities (according to BNT and BDAE) exhibited similar clinical picture as in preoperative assessment, although her symptoms slightly increased. In BNT she scored within normal limits (score: 44/45), and interestingly her score was marginally better compared to the preoperative. On the other hand, in BDAE's *auditory comprehension* component she had difficulties to locate and point to the given stimulus (auditory discrimination score: 67/72, 10%ile: 69/72), and also to execute 4-5 steps orders (following commands score: 12/15, 10%ile: 15/15). In the *speech production* component, the verbal diadochokinesis score was equal to the 10th percentile, while the reciting/signing/rhythm score pathological (score: 4/6, 10%ile: 6/6). In the *repetition* component, the repetition of words and the repetition of sentences scores were also both

Figure 4.6
Postoperative speech and language characteristics of patient P20 according to BDAE's rating scale profile.



pathological (words score: 9/10, 10%ile: 10/10; low probability sentences score: 7/8, 10%ile: 8/8). In the *reading* component, the patient scored below normal in discrimination of symbols (score: 8/10, 10%ile: 10/10) and in word-picture matching (score: 9/10, 10%ile: 10/10) and finally, in *writing* component, her narrative writing score was equal to the 10th percentile (score: 4/5) while the writing mechanisms score was pathological (score: 4/5, 10%ile: 5/5). Summing up, the results from BDAE and MoCA showed that most of the errors were associated with visual processing (visuospatial skills, recognition of objects and symbols), executive functions, attention, and movement. Moreover, patient's language deficits were mild as the handicap was minimally discernible (BDAE severity scale: 5), while her aphasia type was very close to the anomic type (Figure 4.6, previous page).

Patient P21

A 39-year-old, right-handed male, having 12 years of education was operated 7 years ago by another institution to surgically remove a low-grade glioma which was located on the right (non-dominant) anterior perisylvian cortex. After a scheduled annual neuroimaging examination with MRI a tumor regrowth was observed, located on the inferior frontal gyrus, and the patient was referred to our clinic for awake craniotomy.

During history taking the patient reported that since his first surgery an eye floater was present in his left eye. The preoperative assessment of speech and language was conducted with the standard in our clinic tests (EHI, MoCA, BNT, SAQoL-39g, BDAE) as well as with Mount Wilga test, which includes tasks that aim to right hemisphere language functions. Edinburgh Handedness Inventory showed that the patient was a pure right-hander (100%), while SAQoL-39g revealed that his quality of life was unaffected by the first surgery or the tumor recurrence (overall score: 4.9/5). Brief cognitive assessment with MoCA revealed a mild cognitive impairment as he scored 24/30 which is below the cut-off score for mild cognitive impairment. All of his errors in MoCA were associated with visuospatial abilities and short-term memory. Speech and language were generally unaffected by the first surgery and tumor recurrence. Scores were within normal limits in BNT (44/45 cued and uncued responses), while in BDAE the patient performed within normal range in almost all of the components and tasks (mean percentile of all components > 70^{th}). The subtests with the lowest scores were the comprehension of paragraphs by reading (score: 8/10), which was equal to the 10th percentile, and the symbol discrimination (score: 9/10, 10%ile: 10/10), which was mildly impaired. In Mount Wilga test, the patient underperformed in semantic processing, memory, and calculus (normative data are not available for Greek population).

The perioperative session was conducted with a combination of tasks from GLAABS and eRHT, an experimental test created for awake brain surgeries concerning the right hemisphere (see Appendix A for details). All tasks were administered twice on two different perioperative sessions. The selection of tasks included *word repetition, phonological odd-word out, motor planning, sentence completion with sentences,* and *object naming* from GLAABS, and *distant semantics (odd word out), production of emotional prosody, naming of emotions, attention–consciousness,* and *verbal fluency without constraint* from eRHT. The patient responded correctly in 90% of the stimuli in all tasks except *distant semantics* (77.7%), and most of his errors were associated with apraxia of speech.

During intraoperative assessment the examiner used *object naming, production of emotional prosody,* and *word repetition* tasks for the mapping process. During resection process, patient P21 was assessed with *distant semantics (odd word out), naming of emotions, sentence completion (sentences),* as well as with conversational discourse. The process of regaining consciousness lasted more than the usual (approximately 15 minutes more), during which the patient was very disoriented. The mapping procedure elicited mostly semantic errors while the speech related errors were fewer at start, but gradually increased. The awake stage lasted for 80 minutes in total, and as the resection process was approaching to the end, patient's speech suffered severe dysarthria. Fast-track biopsy results indicated a low-grade glioma and the neurosurgeons managed to perform a subtotal resection (estimated EOR: 85%)

During the acute postoperative stage, the patient was assessed informally. He exhibited saliva drooling and mild dysarthria, while, with respect to language, he did not present any symptom. His communication was functional, as he could maintain eye contact, follow orders, and respond verbally with words. The follow-up assessment was conducted with the same tests as in the preoperative (BNT, SAQoL-39g, MoCA, and BDAE). Compared to preoperative assessment, his quality of life (SAQoL-39g overall score: 4.8/5) and cognitive abilities (MoCA score: 25/30) remained virtually unchanged, albeit the latter was now equal and not lower than the cut-off score. Speech and language performance (according to BNT and BDAE) was excellent as his results were within normal range (mean percentiles in all BDAE components > 70^{th}).

Patient P22

Patient P22 was the youngest (18 y.o.) and the first patient in our institution that underwent awake craniotomy to treat medically intractable epilepsy with amygdalohippocampectomy. As it will be discussed in the next paragraph, this case presented many challenges due to patient's multilingual status, and his general neuropsychological profile. The patient discontinued his formal education at the age of 13 and while he had completed only 6 grades of primary school, due to frequent seizures that did not respond to medication. The neuroimaging examination with MRI revealed sclerosis in the mesial temporal lobe.

Patient P22 was very cooperative during the preoperative assessment which took place three days before the scheduled surgery. His tests results indicated severe cognitive and language impairment, which may be due to a combination of sclerosis of the temporal lobe, lack of education, and his multilingual status. The later does always indicate deficit in language, however, from history taking, it was evident that Greek language had not acquired properly. The patient reported that his parents (L1: Bulgarian for father and L1: Romanian for mother) were not proficient in the Greek language, which they used to communicate with him. The formal preoperative assessment of cognition, speech, and language was conducted with the standard in our clinic tests (EHI, MoCA, BNT, SAQoL-39g, BDAE). Edinburgh Handedness Inventory showed that the patient was a pure right-hander (100%), while SAQoL-39g revealed that the epilepsy had affected his quality of life (overall score: 3.9/5) and mostly his psychosocial aspects (score: 3.4/5). Brief cognitive assessment with MoCA revealed a cognitive impairment as he scored 13/30 which is extremely low. Speech and language were also impaired as he scored 29/45 in BNT, while in BDAE almost all subtests and components were pathological. Specifically, the following subtests were found to be impaired (below the 10th percentile): a) *auditory comprehension:* body part identification, commands, complex-ideational material, b) *speech production*: reciting/singing/rhythm, responsive naming, verbal fluency, c) *repetition*: repetition of sentences (high and low probability), d) *reading*: symbol discrimination, sentence reading, comprehension of paragraphs (aborted), and e) *writing*: writing mechanisms, narrative writing. An interpretation of the above results is that although patient P22 was non-fluent, his *speech production* (mean percentile: 35) was better than *auditory comprehension* (mean percentile: 25), which was adequate only in word level. With respect to written language, his writing skills (*writing* mean percentile: 35) were worse than reading (*reading* mean percentile: 45). Reading was slow, effortful, and characterized by severe paralexias, while writing was severely impaired above word-level. Regarding the severity of the symptoms, they were moderate (BDAE severity scale: 3), while the type of the aphasia did not match with a specific type.

The perioperative assessment was incorporated into the preoperative and was conducted with GLAABS the day prior to surgery. Taking into account his underperformance in GLAABS, the signs of mental fatigue, and the severe cognitive and linguistic deficits that was described in previous paragraph, it was decided by the team to keep the intraoperative mapping time limited (below 30 minutes), to avoid tasks that demand reading processing, and finally to select only "easy" tasks associated with temporal pole functions. Additionally, the examiner with the assistance of the patient, prepared a Bulgarian version of the object naming task. The set of tasks comprised mostly of semantic tasks: *semantic odd-image out, naming of verbs, naming of objects (Greek), naming of objects (Bulgarian), semantic association (auditory stimuli), verb generation, sentence completion (sentences)*, and *verbal fluency (semantic)*. It should be mentioned that patient's performance was pathological for *semantic* *odd-image out, object naming*, and *semantic association* tasks, whist in *verbal fluency* the patient produced 29 words, which is just above the 10th percentile (10%ile: 26 [260]).

Patient's cooperation during awake stage was not optimal. The process of regaining consciousness lasted more than the usual (approximately 20 minutes more) during which the patient was very disoriented and was complaining about severe pain. The assessment lasted for 25 minutes in total and it was initiated with automated speech, biographical questions and counting (0-21). Language mapping was conducted with *object naming* task in Greek which was the only task administered from the pre-selected set. The resection process continued with the patient under general anesthesia due to his poor cooperation. During assessment, the patient produced 2 speech arrests (during 0-21 counting) and a semantic paraphasia during the *object naming* task. Only the Greek version of *object naming* task was administered as the patient did not respond in Bulgarian.

The postoperative evaluation was performed only in acute phase, with BNT and conversational discourse. The patient could maintain eye contact, follow orders, and respond verbally with words. Surprisingly, his performance in BNT improved (36/45 cued and uncued responses) and contrary to preoperative score, it was above the cut-off score to be considered pathological.

Patient P23

Patient P23 is a 50-year-old, right-handed male, having 12 years of education, who suffered a seizure at home while working in his garden. The neuroimaging examination with MRI revealed an infiltrative space-occupying lesion on the left (dominant) inferior frontal lobe. Additional lesions were observed subcortically, close to the basal ganglia. However, these lesions were not addressed in this operation, as it was planned to be treated with radiosurgery (gamma knife).

The preoperative assessment was conducted with EHI, BNT, SAQoL-39g, MoCA, and BDAE. The handedness questionnaire revealed that the patient was purely (100%) right-handed, while his quality of life was not affected by the tumor (overall score: 4,8/5 in SAQoL-39g). Cognition and particularly memory (delayed recall) was impaired (MoCA score: 22/30). Speech and language were unaffected by the tumor as he scored 43/45 in BNT and most components in BDAE were within normal range. Particularly, *auditory comprehension, repetition, reading* and *writing* mean percentiles were above the 70^{th}, while *speech production* close to 50^{th}. The subtests with the lowest scores were the responsive naming (score: 28/30, 10%ile: 30/30), verbal fluency (score: 10/41, 10%ile: 15/41), and symbol discrimination (score: 9/10, 10%ile: 10/10).

The perioperative session was conducted two days before the surgery with the final, standardized form of GLAABS. The patient performed within normal limits in the vast majority of the tasks except *sentence completion with words, semantic odd-image out,* and *semantic association,* in which he scored below the cut-off score.

Inside the operating theatre, the intraoperative assessment was conducted with *verb (action) naming* and *motor planning* tasks in order to assist the cortical mapping, while the *word repetition* task was employed to identify the arcuate fascicle. During resection process patient P23 was assessed with *verb generation, sentence completion (words), object naming, sentence completion (sentences),* as well as with conversational discourse. After the patient had regained his consciousness, the assessment started with automatized speech (counting 0-10, letter and day reciting) mostly to help the neurosurgeon set the appropriate electrical current of the stimulation probe. During this task the patient produced only a small number of phonemic paraphasias and speech arrests, while language mapping process induced mostly phonemic paraphasias, a few semantic paraphasias and apraxic errors. During resection of the tumor his connected speech gradually exhibited signs of impairment as his errors were increasing. His symptoms started with phonemic paraphasias and continued with perseveration errors, omission of functional words and low mean length of utterance. As the awake stage was approaching to the end, the severity of the symptoms gradually worsen and the patient had great difficulties in finding and recalling the correct verb, his grammatical errors increased, and the length of his utterances decreased to single word. It should be noted that the last task (sentence completion with words) was aborted after 5 stimuli as the patient could not respond. The awake stage was concluded in 75 minutes during which the patient was generally very cooperative. Fast-track biopsy reported that the tumor was a glioma with increased inflammatory cells and the neurosurgeons managed to perform a subtotal resection (EOR: 85%).

The postoperative evaluation was performed only in the acute phase and the patient could maintain eye contact, follow orders, and respond verbally with words and phrases.

Patient P25

Patient P25 is a 36-year-old, late bilingual, right-handed female, with 16 years of education. Two months before her attendance to our institution, the patient had presented a seizure that led to hospitalization and caused spastic dysarthria and left hemiparesis which recovered after therapy. The patient reported that, four months before that incident, she was feeling numbness in her left upper extremity. A brain MRI study revealed an intracranial arteriovenous malformation Spetzler-Martin grade 3, located deeply in the right (non-dominant) frontal lobe, underneath the posterior part of the middle frontal gyrus (premotor cortex).

Preoperative assessment was conducted with EHI, BNT, SAQoL-39g, MoCA, and BDAE. The handedness questionnaire revealed that the patient was purely (100%) right-handed, while her quality of life generally was not affected by the tumor (overall score: 4,5/5 in SAQoL-39g), although the score in psychosocial subscale is considered low (score: 4.2/5). Speech, language, and cognition was also unaffected by the lesion as she scored 40/45 in BNT, and 27/30 in MoCA which scores were within normal range. In BDAE she scored within normal limits in all major components (*auditory comprehension, speech production, repetition, reading, writing* mean percentiles > 70^{th}), although diadochokinesis was mildly impaired (non-verbal score: 10/12, 10%ile: 10/12; verbal score: 12/14, 10%ile: 13/14). As it was previously mentioned, patient P25 was a bilingual born in Bulgaria and moved to Greece at the age of 18; therefore, L1 is Bulgarian and L2 Greek. The assessment was conducted in Greek and until that point the collected data did not indicate any significant impact of her bilingual status to the performance on tests.

As in all cases, the perioperative session aimed to ran through the pre-selected tasks, exclude stimuli that were not flawlessly answered, and prepare the patient for the "awake" procedure. The perioperative session was conducted with a combination of tasks from GLAABS and eRHT, an experimental test created for right hemisphere awake brain surgeries. All tasks were administered twice, once in each session. The selection of tasks included *word repetition*, *motor planning*, *phonological odd-word out*, *sentence completion (sentences), sentence completion (words), verbal fluency (phonological),* and *object naming* from GLAABS, and *idioms, distant semantics, production of emotional prosody, naming of emotions*, *attention–consciousness* from eRHT. In several GLAABS's tasks (*repetition of words*, *object naming,* and *verbal fluency*) the patient performed below the cut-off score, which, in most cases, was due to her bilingual status. Most errors were concerning lack of knowledge for a particular lemma in Greek (n = 15), as the patient could produce the corresponding Bulgarian word. The articulation errors were fewer. Finally, it should be mentioned that the examiner (with the patient's assistance) prepared a Bulgarian version of the object naming task. A similar task it was used in a previous case (P22).

Inside the operating theatre, the language specialist selected the *object naming* (Greek, Bulgarian) task in order to perform cortical mapping, and *motor planning* for the subcortical (corticospinal tract). During resection process patient P25 was assessed with *word repetition, idioms, sentence completion (words), sentence completion (sentences), production of emotional prosody, naming of emotions, attention-consciousness,* and *distant semantics,* as well as with conversational discourse. After patient regained consciousness the assessment started with automatized speech (counting 0-10, day and month reciting) mostly to help the neurosurgeon to set the appropriate electrical current of the stimulation probe. During this task the patient experienced transient dysarthria due to oral administration of local anesthetic (lidocaine spray) to deal with coughing. The mapping process induced phonemic paraphasias, and anomias in Greek but not in the Bulgarian version of *object naming* task. Also, during mapping, the patient experienced a focal seizure (mouth), without disturbance of level of consciousness. The seizure was induced by a cortical stimulation with bipolar stimulation probe on 4mA and dealt with appliance of cold water on the cortex. The examiner was also occasionally assessing the movement of left extremities, especially during mapping. During the resection and clipping procedure, the patient cooperated well and produced a small number of articulation errors in word repetition and production of emotional prosody tasks. The *object naming* (Greek) task, due to time limitations, was not administered in its entirety during mapping process. The administration of the remaining stimuli took place towards to the end of the resection procedure during which the patient presented some interesting errors. In several images showing single objects, the patient answered with plural instead of singular. It is not clear whether they are grammatical errors or simply related to the point of view of the stimuli which may have caused a type of temporary diplopia. The awake stage concluded in 60 minutes.

The postoperative evaluation was performed only in the acute phase, informally, and the patient could maintain eye contact, follow orders, and respond verbally with words and phrases.

Patient P26

Patient P26 is a 32-year-old, Greek speaking, left-handed male, with 16 years of education that suffered a grand mal seizure while sleeping. A few days later, the patient suffered a second seizure which was focal (left hand). A brain MRI study revealed an intraparenchymal space-occupying lesion located on the right hemisphere and particularly on the motor cortex (precentral gyrus). The patient reported that after the seizures he exhibited aggressive behavior and symptoms associated with pragmatics. Also, he reported that occasionally he was experiencing numbness in the upper and low extremities.

The preoperative assessment was conducted with EHI, BNT, SAQoL-39g, MoCA, and BDAE. The handedness questionnaire (EHI) revealed that the patient was a mixed (67%) left-hander, while his quality of life was not significantly affected by the tumor (overall score: 4,7/5 in SAQoL-39g). Speech, language, and cognition were also unaffected by the lesion and the patient scored 42/45 in BNT, and 29/30 in MoCA (both within normal range). His performance in BDAE did not indicate any presurgical deficit and his mean percentiles in all components were within normal limits (lowest mean percentile on repetition). The subtests with the lowest scores were the two diadochokinesis tasks (non-verbal: 9/12, 10%ile: 10/12; verbal: 11/14, 10%ile: 13/14), the repetition of words (score: 9/10, 10%ile: 10/10), and the repetition of low probability sentences (score: 7/8; 10%ile: 8/8). The fact that patient P26 was ambidextrous (leaning to left-hand) and the lesion was located in his right hemisphere posed additional challenges in this case. From the pioneering study of Rasmussen et al. [386] it is known that the 70% of left-handers or ambidextrous individuals have as dominant the left hemisphere, the 15% the right hemisphere, while in the rest 15% the dominance is shared by both hemispheres. The tests results indicated deficit in speech production, and specifically in speech praxis (verbal motor planning) and repetition which typically are associated with the dominant hemisphere. The former (praxis) is associated with the frontal lobe, while the latter (repetition) with the arcuate fascicle.

Since it was plausible the right hemisphere to be involved in speech and language more than the typical, GLAABS and eRHT were fully administered in perioperative assessment. The evaluation which took place in two different sessions, showed that the patient performed within normal limits in GLAABS (except object naming which was marginally pathological), while the average score in eRHT tasks was above 90%. However, it was observed that patient's performance in GLAABS (mean success rate = 98.23%, SD = 0.029) was better compared to eRHT (mean success rate = 92.76%, SD = 0.080). The fact that the eRHT evaluates language functions of the non-dominant hemisphere and the lesion was located on the right hemisphere offered more evidence that his language dominance was not fully on the left hemisphere. Additionally, as the lesion was located close to the motor cortex, we incorporated two hand-motor tasks into *motor planning* and *object naming* tasks in order to distinguish between anomias and speech arrests. While the patient was responding to the first task (*motor planning*), he was finger-counting, whilst during the second task (*object naming*), he was fist clenching in every stimulus response. If patient's verbal response was disrupted but his hand was still moving, this would mean that the error was linguistic in nature (i.e., anomia). If patient's response was impaired in both motor and verbal levels, this would mean speech arrest.

Inside the operating theatre, the language specialist selected the *object naming* and *motor planning* tasks as well as motor tasks for the upper extremity (finger-counting and fist clenching) in order to perform the cortical mapping. The patient regained consciousness very fast and the assessment started with automatized speech (counting 0-10, day and month reciting) to set the appropriate electrical current of the stimulation probe. During this task the patient produced no errors, while the positive mapping process induced only one semantic paraphasia. The neurosurgeon identified the left-hand cortical area through this process, which was consistently inducing disruption in hand movement every time it was stimulated. During the resection process the continuous evaluation was conducted with *sentence completion (sentences)* task, conversational discourse, and the aforementioned motor tasks of the left hand. Patient's hand movement was severely disrupted after the resection of a small portion of the tumor and it was decided to avoid further resection of the lesion. The awake stage was concluded in 60 minutes during which the patient was generally very cooperative. Fast-track biopsy reported that the tumor was an inflammatory lesion without malignant features. The resected pathological tissue was limited to a sample for biopsy, so the extent of resection was approximately 5%.

The postoperative evaluation was performed only in the acute phase and the patient communication abilities were optimal as he could maintain eye contact, follow orders, and respond verbally with words and phrases. Regarding his hand movement, the patient exhibited a mild monoparesis of the left hand which resolved two weeks later.

Patient P27

Case P27 is a 40-year-old, right-handed female, with 14 years of education. Several weeks prior to her attendance in our institution, she suffered an absence seizure which caused loss of consciousness and disruption of speech. She reported that before the incidence she occasionally was experiencing mild anomias and numbness, and after the seizure transient “speech difficulties”. A brain MRI study revealed a large infiltrative space-occupying lesion, located on the left (dominant) frontal lobe, specifically on the superior frontal gyrus which was extending to the posterior part of the middle frontal gyrus.

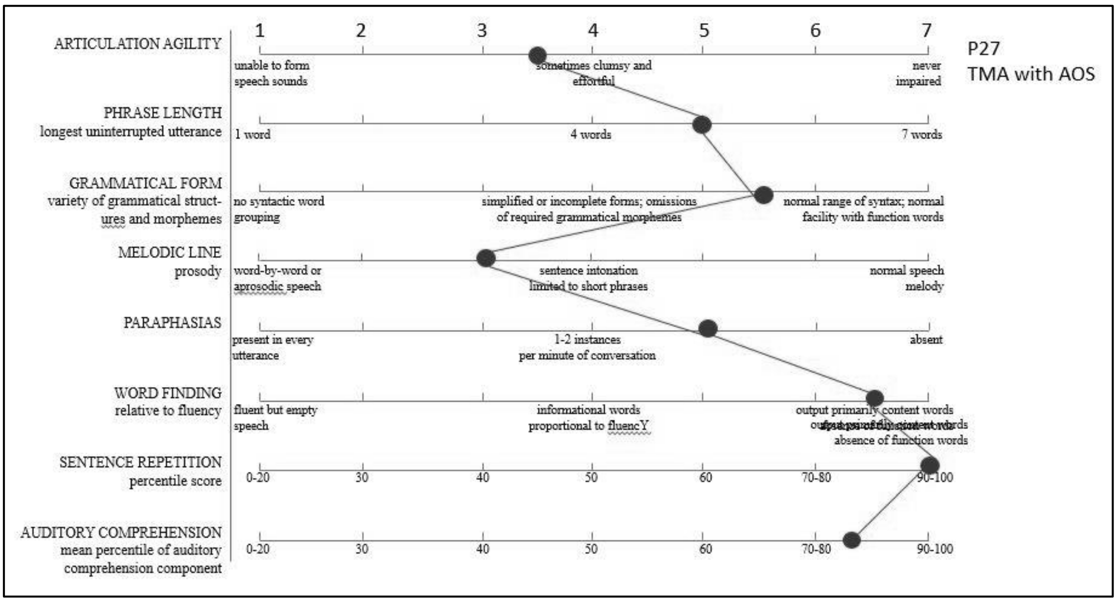
The preoperative assessment was conducted with EHI, BNT, SAQoL-39g, MoCA, and BDAE. Handedness questionnaire revealed that the patient was a pure (100%) right-hander. The quality of life questionnaire (SAQoL-39g) showed that the psychosocial aspects of her daily life were severely impaired (psychosocial score: 2.3/5) contrary to physical and communication (scores on both domains: 5/5). Speech, language, and cognition was also unaffected by the lesion as she scored 44/45 in BNT, and 29/30 in MoCA which scores were within normal range. In BDAE she scored within normal limits in all components, and the mean percentiles were all above the 80^{th}.

Due to COVID-19 pandemic and the restrictions imposed, the perioperative session was not performed, two days before the surgery, at the clinic (according to the protocol). Instead, the patient was evaluated on the same day, two hours before the operation with a set of seven tasks which all were answered perfectly.

During intraoperative assessment, the examiner used the *object naming* task for the cortical mapping process and continued to use this task also for the resection (since the patient could not respond to *sentence completion with words* task). Subcortically, mapping process which aimed to identify the frontal aslant tract was conducted with the *verb (action) naming*, while during resection patient P27 was assessed with *word repetition, syntactic judgment*, and *object naming* tasks, as well as with conversational discourse. Motor skills of right upper and lower extremities were also assessed during mapping and occasionally during the resection. After the patient regained her consciousness, the assessment started with biographical questions and evaluation of automatized speech (counting 0-10, letters and months reciting). In the course of this procedure, in which the neurosurgeon sets the appropriate electrical current of the stimulation probe, the patient produced perseveration errors, phonemic paraphasias, neologisms (jargon speech), and agrammatic errors. After the patient was fully oriented and conscious, the mapping process started. The errors she produced in this stage were phonemic paraphasias, anomias, and circumlocutions (e.g., image: "fly" response: "moves the wings to the air"). During resection, her connected speech was gradually exhibiting signs of impairment as her errors (phonemic paraphasias, and grammatical errors) were increasing. As the awake stage was approaching to the end, the severity of symptoms gradually worsened. The patient experienced increased agrammatism combined with decreased mean length of utterance, flat prosody, and emotional instability. Symptoms ultimately led to mutism and answering only after cueing. The awake stage was concluded in 70 minutes and except the last 20 minutes the patient was cooperative. The fast-track biopsy reported that the tumor was a low-grade glioma and the neurosurgeons managed to perform a subtotal resection (EOR: 95-98%).

At the acute postoperative stage, the patient was assessed with an informal evaluation of her communication abilities and BNT. Her communication was functional, as she could maintain eye contact, follow orders, and respond verbally with words. Moreover, her performance on BNT was optimal as she produced 43/45 cued and uncued responses although she was non-fluent and her speech was impaired (apraxia of speech, flat prosody, slow rate of speech). Finally, the patient exhibited right hemiparesis which was more evident in her upper extremity. The results of the follow-up assessment (four week later) indicated a similar but improved clinical picture. The assessment was conducted with the same tests as in the preoperative assessment (BNT, SAQoL-39g, MoCA, and BDAE). Her quality of life slightly decreased (SAQoL-39g overall score: 3.4/5) with comparison to the preoperative score (overall score: 3.9/5). However, the psychosocial aspects of her life which were the most defected preoperatively, slightly increased (3/5 instead of 2.3/5). The patient could not perform adequately in MoCA test and the results cannot be interpreted precisely. Apart from the errors related to attention, the patient had great difficulties in the visuospatial subscales. The reason behind this finding can be found in the deficits of the right-hand movement that were still affecting her. Speech and language were tested with BNT and BDAE. In BNT she scored within normal range (43/45) while the results of BDAE showed that patient's fluency had been restored, although not completely. Moreover, her mean percentiles in *auditory comprehension*, *repetition*, and *reading* components, were above the 70th, while in *speech production* it was below the 50th. The subtests with the lowest scores were the two diadochokinesis tasks (verbal: 6/12, 10%ile: 10/12; non-verbal: 7/14, 10%ile: 13/14), rhythm/melody/reciting (score: 4/6, 10%ile: 6/6), visual symbol discrimination (score: 9/10, 10%ile: 10/10), and verbal fluency (score: 11/41. 10%ile: 15/41). The results from writing component cannot be conclusive due to her right monoparesis. According to her BDAE speech profile rating scale, patient P27 exhibited a moderate (severity scale: 3) transcortical motor aphasia (Figure 4.7) accompanied by a moderate apraxia of speech. It is worth mentioning that apart from the very common symptoms of apraxia of speech (namely inconsistent speech errors), the patient exhibited disturbed prosody, disturbed production of melody, hyperarticulation, and severely low rate of speech (approximately 50 words/minute, normal >150 words/minute [370]). The last two symptoms may be the result of her attempts to overcome the deficiency in verbal motor planning that lies underneath apraxia of speech.

Figure 4.7
Postoperative speech and language characteristics of patient P27 according to BDAE's rating scale profile.



Patient P30

Patient P30 is a 39-year-old, right-handed male, with 12 years of education. The presenting symptoms were dizziness and headaches while the patient was working, although he did not seek medical attention immediately. He reported that he experienced severe auditory comprehension difficulties, tinnitus, and also that he could get annoyed and confused by the environmental sounds. The brain MRI study revealed a large intraparenchymal hemorrhage and an arteriovenous malformation, located on the left (dominant) superior temporal gyrus, close to the temporoparietal junction.

The preoperative assessment was conducted with EHI, BNT, SAQoL-39g, MoCA, and BDAE. The handedness questionnaire (EHI) showed that the patient was purely (100%) right-handed. The SAQoL-39g revealed that his quality of life (overall score: 4.1/5) and particularly the aspects associated with the communication were affected by the hemorrhage (score: 3.6/5). Speech, language, and cognition were also affected by the lesion as he scored

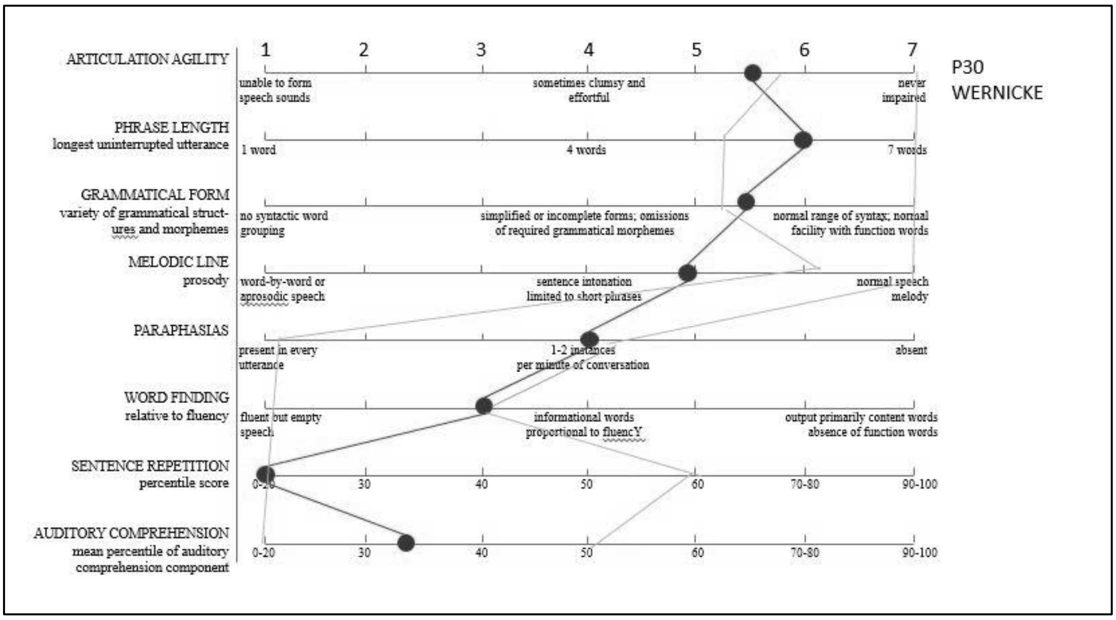
34/45 cued and uncued responses in BNT which is marginally pathological, and 21/30 in MoCA which is an indication of mild cognitive impairment. In BDAE he performed above the 60th percentile on average, in *speech production*, *reading*, and *writing* components. On the other hand, in *auditory comprehension* and *repetition* components the mean percentiles were below the 40th, while the former was the most affected (mean percentile 6.25). The only subtest that was within normal limits in *auditory comprehension* was the word discrimination, the rest were severely impaired. In *repetition* he scored 7/8 in high probability sentences (10%ile: 8/8) and 3/8 in low (10%ile: 8/8), while word level was normal (score: 10/10). Finally, the comprehension of paragraphs in *reading* component was also impaired as he scored 7/10 (10%ile: 8/10). Patient's speech and language characteristics indicated Wernicke's aphasia with moderate severity of symptoms (BDAE severity scale: 3).

The perioperative session was conducted approximately five months after the preoperative, and 3 days before surgery. The aim of this session, as in all perioperative sessions, was to run through the intraoperative tasks and exclude those which were not flawlessly answered. This session was conducted with GLAABS and the following tasks were selected for the intraoperative stage: *word repetition, motor planning, phonological odd-word out (visual and auditory), sentence completion (sentences), sentence completion with words (visual and auditory), object naming*, and *verb generation*. It should be noted that the previous day the patient was assessed with the full version of GLAABS in order to verify his language status, as due to some special conditions, too much time had passed since the preoperative examination. The patient failed to score above the cut-off scores in *repetition of words, object naming, sentence completion with words (visual and auditory stimuli), phonological judgment, naming of verbs* and *grammaticality judgment*. Interestingly, in three tasks (*semantic odd image out, phonological odd word out,* and *semantic association*) patient's performance was pathological when the stimuli were given orally but normal when the stimuli were given visually (with written language or pictures). Most errors were anomias, semantic paraphasias and agrammatic errors.

As for the intraoperative assessment, and particularly for the language mapping procedure, the *phonological odd-word out (visual)* task was selected to assist cortical mapping, while *word repetition* task for the subcortical (arcuate fascicle). However, the intraoperative assessment was not performed properly as the patient presented a grand mal seizure exactly the moment he began to regain consciousness. Despite the persistent efforts of the team (anesthesiologist, speech language therapist, and the neurosurgeon) to wake him up, the patient could not fully regain consciousness, he had no communication, no consistent eye contact, and did not respond to commands. Due to that, 90 minutes later, the team decided to sedate the patient again and continue the operation under general anesthesia. The cause of this complication probably lies to the epileptic seizure as it is known that after grand mal seizures there is intense lethargy (postictal sleep).

The acute postoperative stage informal assessment revealed that the patient could maintain eye contact, but he experienced difficulties to follow orders and respond with more than one word. In the follow-up assessment (four weeks later), he showed similar clinical picture as the preoperative, as he was experiencing difficulties in auditory comprehension and phonological processing, as well as in word recalling. However, it should be emphasized that the symptoms were considerably milder. His performance in SAQoL-39g (overall score: 4.1/5), MoCA (score: 24/30), and BNT (score: 35/45) was slightly better compared to the preoperative, albeit the latter scores (MoCA and BNT) were still marginally pathological. Regarding BDAE, the patient scored better in 18 out of 28 subtests and the most difficulties were observed in auditory comprehension. Moreover, the repetition of low frequency sentences (score: 2/8, 10%ile: 8/8) and the recitation/melody/rhythm (score: 5/6, 10%ile: 6/6) subtests were also severely impaired. According to his BDAE speech profile rating scale, the patient exhibited a moderate aphasia (severity scale: 3), which is close to the Wernicke's pattern (Figure 4.8). It is remarkable that although patient P30 exhibited immediately after the surgery a severe impairment in comprehension (and production) of speech and language, one month later he had rapidly recovered to a very functional level of communication. This is also evident from the score he achieved in the corresponding domain of the SAQoL-39g (communication score: 4.5), which measures the functionality of patient's communication abilities in every-day life.

Figure 4.8
Postoperative speech and language characteristics of patient P30 according to BDAE's rating scale profile.



Summary of cases' results

Table 4.8 (next page) provides an overview of preoperative assessments results. According to EHI, most of our patients (*n* = 13) were pure right handers, three (*n* = 3) were mixed right handers, and one (*n* = 1) was mixed left hander (EHI was not administered on 4 right-handed patients). The mean score of BNT was 41.3 (*SD* = 4.339) which is above the cut-off score for language impairment in Greek healthy population. On the other hand, the average preoperative score on MoCA was 24.5 (*SD* = 3.804), which is marginally below the cut-off score (25/30). Concerning SAQoL-39g, the results revealed that our patients scored close to maximum (5/5) in most subscales, except the psychosocial one. Particularly, our patients scored on average 4.7 (*SD* = 0.463) on physical domain, 4.2 (*SD* = 0.712) on psychosocial, and 4.8 (0.385) on communication. In BDAE the pathological population generally scored within normal limits, even though some scores are close to or below the 10^{th} percentile which is the cut-off score. Fluency was calculated by qualitative criteria according to authors of the Greek adaptation [333], and patients were classified as fluent or non-fluent.

Table 4.8
Summary of preoperative neuropsychological results.

Case	Hemi-sphere	Lesion location	EHI (%)	BNT (1-45)	MoCA (1-30)	SAQoL-39g Ph (1-5)	Ps (1-5)	Co (1-5)	BDAE – mean percentiles of components Fluency	AComp	Speech	Repet	Read	Writ	Deficit Type	Severity
P2	left	TPJ	(self-reported)	35	-	3.8	4.3	4.1	-	-	-	-	-	-	-	3
P3	left	preCG	pure R (100)	42	-	4.4	4.3	5	yes	100	90	100	87,14	87,14	*n/ap*	*n/ap*
P4	left	IFG	(self-reported)	-	29	-	-	-	-	-	-	-	-	-	-	*n/ap*
P5[a]	left	PFC	(self-reported)	-	-	-	-	-	-	-	-	-	-	-	-	5
P5[a]	left	DLPFC	(self-reported)	-	-	-	-	-	-	100	56,43	66,67	92,86	87,14	Anomic aphasia	5
P7	left	IC	(self-reported)	-	-	5	5	5	yes	76,25	41,43	100	60,00	21,14	Apraxia of speech	4
P8	left	LV	mixed R (58)	45	-	4.9	4.6	4.9	yes	80	70,71	100	87,14	34,14	*n/ap*	*n/ap*
P9	left	TPJ	mixed R (78)	44	-	5	4.6	4.6	yes	75	28,57	100	72,14	73,57	Anomic aphasia	4
P11	left	IFG	mixed R (90)	43	-	4.8	4.5	4.9	yes	76,25	59,29	100	62,86	87	*n/ap*	*n/ap*
P12	left	IFG	pure R (100)	44	-	5	4.5	5	yes	82,5	60,71	38,33	100	75,71	Conduction aphas.	5
P13	left	SFG	pure R (100)	45	-	5	4.9	5	yes	82,5	84,29	100	100	48,57	*n/ap*	*n/ap*
P16	left	OFC	pure R (100)	43	-	5	2.9	4.6	yes	76,25	53,57	100	78,57	49,29	Agrammatic	5
P17	left	ITG	pure R (100)	43	25	5	4.6	5	yes	100	90	100	87,14	87,14	*n/ap*	*n/ap*
P18	right	Claust	pure R (100)	44	23	3.5	3.4	5	yes	82,5	54,29	100	80	75,71	Apraxia of speech	5
P20	left	preCG	pure R (100)	41	24	5	4.7	5	yes	80	42,86	100	78,57	87,14	Anomic aphasia	5
P21	right	IFG	pure R (100)	44	24	5	4.7	5	yes	90	87,14	100	73,57	87,14	*n/ap*	*n/ap*
P22	left	TPo	pure R (100)	29	17	4.3	3.4	4.4	no	25	35,00	38,33	45,00	35,43	Uncl (mixed)	3
P23	left	IFG	pure R (100)	42	22	5	4.6	5	yes	82,5	47,86	100	73,57	75,57	*n/ap*	*n/ap*
P25	right	MFG	pure R (100)	40	27	4.6	4.2	5	yes	77,5	67,86	100	92,86	72,86	*n/ap*	*n/ap*
P26	right	preCG	mixed L (67)	42	29	4.9	4.5	5	yes	77,5	70,00	35,00	92,86	87,14	*n/ap*	*n/ap*
P27	left	SFG	pure R (100)	44	29	5	2.3	5	yes	90	74,29	100	100	87,14	*n/ap*	*n/ap*
P30	left	STG	pure R (100)	34	21	4.1	4.3	3.6	yes	6,25	90	36,67	73,57	62,86	Wernicke's aphas.	3
n=22			*Mean*	*41.3*	*24.5*	*4.7*	*4.2*	*4.8*		*76.84*	*63.38*	*85.00*	*80.94*	*69.57*		*4.3*
			SD	*4.339*	*3.804*	*0.463*	*0.712*	*0.385*		*23.309*	*19.403*	*26.539*	*14.797*	*21.431*		*0.905*

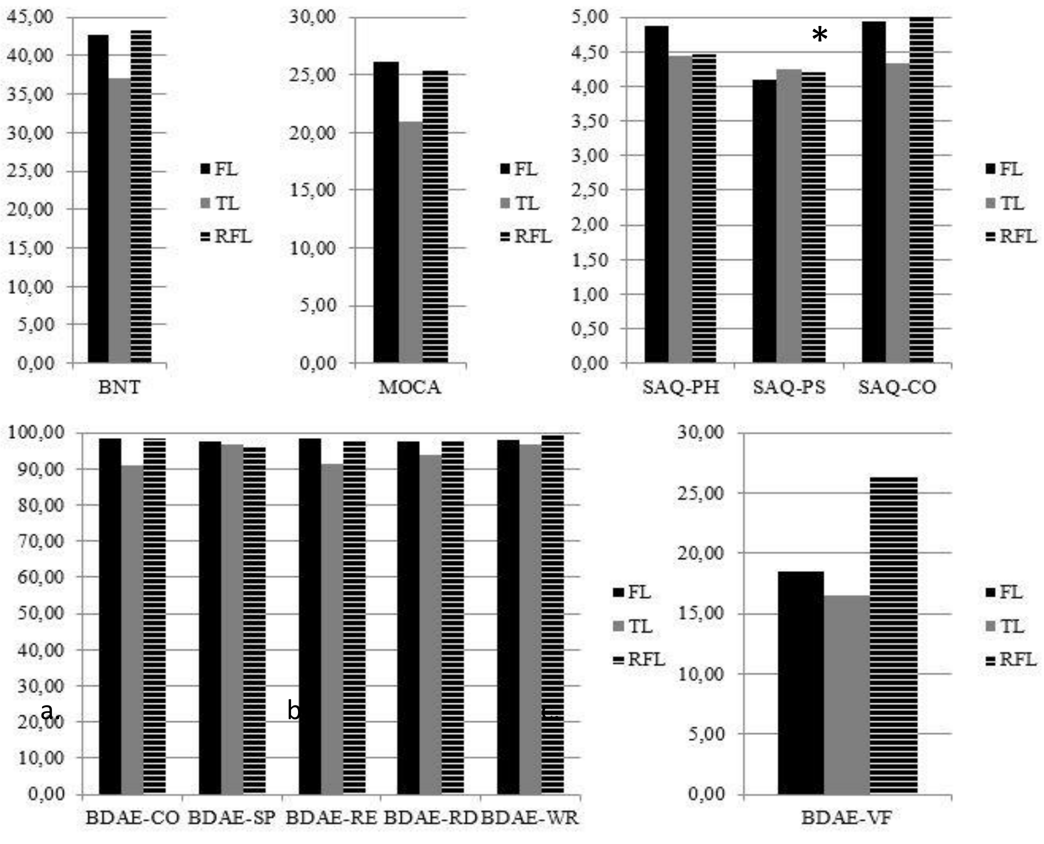
Leg.: *EHI* = Edinburgh Handedness Inventory, *BNT* = Boston Naming Test, *MoCA* = Montreal Cognitive Assessment, *SAQoL-39g* = Stroke and Aphasia quality of Life, *Ph* = physical domain, *Ps* = psychosocial domain, *Co* = communication domain, *BDAE* = Boston Diagnostic Aphasia Examination, *AComp* = auditory comprehension, *Speech* = speech production, *Repet* = repetition, *Read* = reading, *Writ* = writing, *AOS* = apraxia of speech, *Uncl* = unclassified, *n/ap* = not applicable (patient had no observable handicap in comprehension or production of language), *TPJ* = temporoparietal junction, *preCG* = precentral gyrus, *IFG* = inferior frontal gyrus, *PFC* = prefrontal cortex, *DLPFC* = dorsolateral PFC, *IC* = insular cortex, *LV* = lateral ventricle, *SFG* = superior frontal gyrus, *OFC* = orbitofrontal gyrus, *ITG* = inferior temporal gyrus, *Claust* = Claustrum, *TPo* = temporal pole, *MFG* = middle frontal gyrus, *STG* = superior temporal gyrus, *SD* = standard deviation

[a] Patient P5 underwent awake craniotomy twice and the second operation was performed two years after the first one to remove a tumor regrowth.

In *auditory comprehension* component the mean percentile was 76.84 (*SD* = 23.309), *speech production* 63.38 (*SD* = 19.403), *repetition* 85 (*SD* = 26.539), *reading* 80.94 (*SD* = 14.797), and *writing* 69.57 (*SD* = 21.431). According to BDAE's severity rating scale, patients who presented speech and language deficits before the operations had mild symptoms (*M* = 4.3, *SD* = 0.905). However, there were several patients that did not exhibit any observable handicap in production or comprehension of language.

The preoperative neuropsychological outcomes were investigated in order to locate differences among patients. Since the presented series of cases is too heterogeneous in terms of demographic variables, underlying pathologies, and areas of brain lesions, the patients were divided into three anatomical groups: a) patients with lesions on the frontal lobe (*n* = 11), b) patients with lesions on the temporal lobe (*n* = 5), and c) patients with lesions on the frontal lobe of the right hemisphere (*n* = 3). Two patients (*n* = 2) with lesions on areas that do not match any of these groups (one lesion on insular cortex and one tumor on lateral ventricle) were excluded. Also, patient's P5 first preoperative assessment was excluded as it

Figure 4.9
Graphical representations of the preoperative differences between the three subgroups of patients.



Leg.: *FL* = frontal lobe, *TL* = temporal lobe, *RFL* = right frontal lobe, *BNT* = Boston Naming Test, *MoCA* = Montreal Cognitive Assessment, *SAQ-PH* = SAQoL-39g physical domain, *SAQ-PS* = SAQoL-39g psychosocial domain, *SAQ-CO* = SAQoL-39g communication domain, *BDAE-CO* = BDAE comprehension component, *BDAE-SP* = BDAE speech production component, *BDAE-RE* = BDAE repetition component, *BDAE-RD* = BDAE reading component, *BDAE-WR* = BDAE writing component, *BDAE-VF* = BDAE verbal fluency subtest was performed only with a preliminary version of GLAABS. With respect to BDAE, the raw scores of the five components were transformed into hit-rates (percentages, not percentiles) according to the following formula:

$$raw\ score / maximum\ score \times 100 =$$

In verbal fluency there is no maximum score; therefore, the scores were calculated separately as raw numbers (*n*). As illustrated in graphs provided in Figure 4.9 (previous page), it is evident that patients with lesions located on the temporal lobe performed worse on every test and subtest compared to frontal lobe patients. The only exception on this trend is the psychosocial domain of SAQoL-39g, in which the frontal lobe patients scored marginally lower than the temporal patients (Figure 4.9.c). Patients with lesions to the right frontal lobe performed similarly compared to the left frontal lobe patients, except the physical domain of SAQoL-39g, in which right hemisphere patients scored lower (Figure 4.9.c), and the verbal fluency subtest of BDAE, in which the right hemisphere patients performed higher than both the left hemisphere subgroups (i.e., frontal and temporal lobe patients; Figure 4.9.e).

Most of the differences presented above (Figure 4.9) are not statistically significant. Two exceptions are the verbal fluency subtest of BDAE ($F = 4.818$, $p = 0.026$), in which right frontal lobe patients produced significantly more words compared to left frontal and left

Table 4.9
Differences among the three subgroups.

	Shapiro-Wilk	Levene	Kruskal-Wallis		ANOVA	
	p	*p*	$x^2(2)$	*p*	*F*	*p*
BNT	<0.001	-	2.915	0.233	-	-
MoCA	0.404	0.985	-	-	2.329	0.160
SAQoL-39g						
Physical	<0.001	-	2.452	0.293	-	-
Psychosocial	0.002	-	0.072	0.965	-	-
Communication	<0.001	-	**7.987**	**0.018***	-	-
BDAE						
Aud. Comprehension	<0.001	-	2.596	0.273	-	-
Speech production	0.231	0.001	-	-	0.485	0.625
Verbal fluency	0.547	0.370	-	-	**4.818**	**0.026***
Repetition	<0.001	-	1.911	0.385	-	-
Reading	0.014	-	4.059	0.131	-	-
Writing	0.002	-	2.383	0.304	-	-

Post-Hoc testing		Mean	SD	Median		Mann-Whitney *z*	*p*	Tukey *p*
SAQoL-39g								
Communication	FL	4.94	0.133	5	FL-TL	**-2.440**	**0.015***	-
	TL	4.34	0.527	4.4	FL-RFL	-0.853	0.394	-
	RFL	5	0.000	5	TL-RFL	**-1.906**	**0.057**	-
BDAE								
Verbal Fluency	FL	18.5	4.625	20	FL-TL	-	-	0.727
	TL	16.5	4.933	17	FL-RFL	-	-	**0.042***
	RFL	26.3	1.528	26	TL-RFL	-	-	**0.028***

Leg.: *BNT* = Boston Naming Test, *MoCA* = Montreal Cognitive Assessment, *BDAE* = Boston Diagnostic Aphasia Examination, *SAQoL-39g* = Stroke and Aphasia quality of Life, *FL* = frontal lobe patients, *TL* = temporal lobe patients, *RFL* = right frontal lobe patients, *=marginally significant (p≤0,10), **=significant (p≤0,05), ***=highly significant (p≤0,01) temporal patients (p = 0.042 and 0.028, respectively), and the communication domain of SAQoL-39g ($\chi^2(2)$ = 7.987, p = 0.018), wherein the temporal lobe group scored significantly lower than the other two subgroups (left frontal, p = 0.015; right frontal, p = 0.057). The results from the statistical analysis are illustrated on Table 4.9 (previous page).

As previously mentioned, the perioperative assessments mainly worked as preparatory sessions, aiming to "cleanse" the pre-selected tasks from unwanted stimuli, and not diagnose specific disorders. However, in most cases the full version of GLAABS was administered at least once, in order to obtain data for its validity. For this purpose, I examined the data from nine patients (P5b, P7, P9, P12, P16, P18, P20, P22, P30) that were preoperatively diagnosed with language disorders according to BDAE. The convergent validity was calculated by correlating GLAABS with two language predictors (BDAE and BNT), while one non-language predictor (psychosocial domain, SAQoL-39g) was used for discriminant validity. In order to achieve more accurate results three fluency tasks were removed from GLAABS and one from BDAE, and the scores from the rest tasks/subtests were transformed into hit-rates ranging from 0 to 1.00. The results (Table 4.10) showed that the GLAABS test was significantly correlated with both language predictors, namely BDAE (R = 0.928, p < 0.001) and BNT (R = 0.902, p = 0.006), but not with the non-language predictor (R = 0.134, p = 0.752). These findings suggest that GLAABS can be considered as validated in oncological population.

Table 4.10
Summary of the convergent and discriminant validity measurements.

		GLAABS	BDAE	BNT	SAQOL_PS
GLAABS	R		0.928	0.902	0.134
	p		**<0.001****	**0.006****	0.752
BDAE	R	0.928		0.890	0.111
	p	**<0.001****		**0.007****	0.793
BNT	R	0.902	0.890		0.161
	p	**0.006****	**0.007****		0.730
SAQOL_PS	R	0.134	0.111	0.161	
	p	0.752	0.793	0.730	

Convergent validity was calculated by correlating GLAABS test with BDAE and BNT (language predictors). The fluency tasks (three for GLAABS, one for BDAE) were excluded, and scores were transformed into hit-rates. The discriminant validity was calculated with the psychosocial domain of SAQoL-39g (non-language predictor). The results showed significant correlation of GLAABS with the two language predictors, while the correlation with the non-language predictor was not significant. Leg.: *GLAABS* = Greek Language Assessment for Awake Brain Surgery, *BDAE* = Boston Diagnostic Aphasia Examination, *BNT* = Boston Naming Test, *SAQoL_PS* = psychosocial domain of Stroke Aphasia Quality of Life (Greek version), *=marginally significant (p≤0,10), **=significant (p≤0,05), ***=highly significant (p≤0,01)

The next table (Table 4.11, next page) summarizes the results from the intraoperative assessments that were presented previously in cases' reports. The postoperative results are summarized in Table 4.12 in the subsequent page, however extended discussion will take place in the next chapter (Chapter 5).

Table 4.11
Summary of intraoperative speech and language findings.

	Case	Mapping cortical tasks	subcortical tasks	errors	Resection tasks	errors
1	P2	obj naming, repetition	repetition	phon paraphasias, anomias, speech arrests	semantic odd-image out, semantic association, sentence completion (s)	anomias, sem paraphasias
2	P3	obj naming	repetition	anomias, sem paraphasias	sentence completion (s)	anomias
3	P4	verb naming, verb generation	repetition	perseverations, speech arrests	fluency (animals, /s/, verbs),	phon paraphasias, anomias
4	P5[a]	verb naming, obj naming	sentence completion (w)	speech arrests, dysarthria, neologisms, sem parapha sias	verb naming, repetition, sentence completion (s)	sem paraphasias, apraxia
5	P5[a]	verb naming	semantic odd-word out	speech arrests, perseverations, sem paraphasias anomias, neologisms	semantic odd-image out, semantic judgment, sentence completion (s) verbal fluency (sem)	anomias, perseverations
6	P7	motor planning	object naming	apraxia error, anomias	obj naming	sem paraphasias, anomias
7	P8	obj naming	motor planning, repetition	anomias, speech arrests	phonological judgement, obj naming	(no errors)
8	P9	obj naming	-	phon paraphasias, speech arrests	-	phon paraphasias, anomias
9	P11	verb naming, motor planning	repetition	speech arrests	sentence completion (s), semantic odd-word out, object naming, action fluency (verbs)	perseverations,.anomias
10	P12	verb & obj naming	motor planning	speech arrests	object naming, repetition, sentence completion (w), sentence completion (s), action fluency (verbs)	agrammatic errors, dysarthria phon paraphasias
11	P13	obj naming	repetition	speech arrests, perseveretions	verb naming, sentence completion (w), sentence completion (s), verbal fluency (phon), grammaticality judgement	sem paraphasias, anomias, comprehension errors
12	P16	semantic odd-image out, verb naming	semantic association	speech arrest, sem paraphasia	sentence completion (w), sentence completion (s), verbal fluency (sem), grammaticality judgement, verb generation	anomias, circumlocutions
13	P17	semantic association, obj naming	semantic odd-word out, phonological odd-word out	anomias, sem paraphaias, paralexias	semantic judgement, phonological judgement, verbal fluency (sem), sentence completion (sem)	sem paraphasias, anomias
14	P18	attention-consciousness, motor planning	object naming	dysarthria, loss of consciousness, apraxia	sentence completion (s), distant semantics, production of emotional	apraxia, aprosodia

					prosody, emotions naming, verbal fluency without constraint	
15	P20	sentence completion (w), obj naming	motor planning	speech arrests	semantic odd-word out, semantic odd-image out, verbal fluency (phon), grammaticality judgment, sentence completion (s)	speech arrests, sem paraphasias
16	P21	production of emotional prosody, obj naming	repetition	sem paraphasias, articulation errors	distant semantics, emotions naming, sentence completion (s)	dysarthria, articulation errors
17	P22	obj naming	-	speech arrests, sem paraphasias	-	-
18	P23	verb naming, motor planning	repetition	phon paraphasias, speech arrest, apraxia	verb generation, sentence completion (s), obj naming, sentence completion (w)	phon paraphasias, perseverations, agrammatism, low MLU
19	P25	obj naming (el, bg),	motor planning	phon paraphasias, anomias (in bg, normal)	repetition, idioms, sentence comple-, tion (w), sentence completion (s), production of emotional prosody, emotions naming, attention-consciousness, distant semantics	phon paraphasias
20	P26	motor planning[b], obj naming	-	sem paraphasia	sentence completion (s)	(no errors)
21	P27	obj naming, sentence completion (w)	verb naming	phon paraphasias, neologisms, agrammatism, circumlocutions, speech arrests, perseverations	obj naming, repetition, grammaticality judgement	phon paraphasias, agrammatism low MLU, aprosodia, lack of speech initiation
22	P30	phonological odd-word out (visual)	word repetition	*(inability to retain consciousness, intraoperative assessment was not performed properly)*		

The mapping errors column includes also errors produced during the automatized tasks, while those produced during conversational discourse evaluation are incorporated in the resection errors.
Leg.: *phon* = phonemic, *sem* = semantic, *obj* = object, *el* = Greek (language), *bg* = Bulgarian, *MLU* = mean length of utterance, *(w)* = words, *(s)* = sentence
[a] Patient P5 underwent awake craniotomy twice and the second operation was performed two years after the first one to remove a tumor regrowth.
[b] Motor tasks for the left hand were administered simultaneously with speech tasks. These tasks helped neurosurgeons identify left hand motor area. See section 3.1.19 for details.

Table 4.12
Summary of the postoperative speech and language findings.

Case	**Hemi-sphere**	**Lesion location**	**BNT**	**MoCA**	**SAQoL-39g**			**BDAE – mean percentile of components**						**Deficit**	
			(1-45)	(1-30)	Ph (1-5)	Ps (1-5)	Co (1-5)	Flu	AComp	Speech	Repet	Read	Writ	Type	Severity
P2	L	TPJ	-	-	-	-	-	-	-	-	-	-	-	-	-
P3	L	preCG	-	-	-	-	-	-	-	-	-	-	-	-	-
P4	L	IFG	-	-	-	-	-	-	-	-	-	-	-	-	-
P5[a]	L	PFC	-	-	-	-	-	-	-	-	-	-	-	-	-
P5[b]	L	DLPFC	-	-	-	-	-	-	-	-	-	-	-	-	-
P7	L	IC	-	-	-	-	-	-	-	-	-	-	-	-	-
P8	L	LV	-	-	-	-	-	-	-	-	-	-	-	-	-
P9	L	TPJ	-	-	-	-	-	-	-	-	-	-	-	-	-
P11	L	IFG	43	-	4.4	4.1	4.4	yes	77,5	59,29	68,33	82,86	100	Conduction aphas.	4
P12	L	IFG	42	-	5	3,8	4,4	no	57,5	45	1,67	87,14	88,57	Broca's, AOS	4
P13	L	SFG	42	-	4,8	4,7	4,1	no	6,25	31,43	35	30	0	SMA syndrome	2
P16	L	OFC	43	-	-	-	-	-	-	-	-	-	-	-	-
P17	L	ITG	42	26	5	4,8	5	yes	90	80,71	100	64,29	63,57	n/ap	n/ap
P18	R	Claust	44	-	3,3	3,4	4,9	yes	60	53,57	100	76,43	54,29	AOS	4
P20	L	preCG	44	19	4,4	4,6	5	yes	41,25	62,86	35	50,71	75	Anomic aphasia	5
P21	R	IFG	44	25	5	4,6	5	yes	90	85,71	100	78,57	100	n/ap	n/ap
P22	L	TPo	36	-	-	-	-	-	-	-	-	-	-	-	-
P23	L	IFG	-	-	-	-	-	-	-	-	-	-	-	-	-
P25	R	MFG	-	-	-	-	-	-	-	-	-	-	-	-	-
P26	R	preCG	-	-	-	-	-	-	-	-	-	-	-	-	-
P27	L	SFG	43	20	3,5	3	3,9	no	82,5	43,57	100	76,43	0	TMA, AOS	3
P30	L	STG	35	24	4,5	4	4,5	yes	31,25	65,71	66,67	74,29	88,57	Wernicke's	3
n=22		*Mean*	*41.6*	*22.8*	*4.4*	*4.1*	*4.6*		*59,58*	*58,65*	*67,41*	*68,97*	*63,33*		*3.6*
		SD	*3.139*	*3.114*	*0.638*	*0.627*	*0.418*		*28,906*	*17,563*	*36,525*	*18,127*	*39,056*		*0.976*

Leg.: *BNT* = Boston Naming Test, *BDAE* = Boston Diagnostic Aphasia Examination, *MoCA* = Montreal Cognitive Assessment, *SAQoL-39g* = Stroke and Aphasia quality of Life, *Ph* = physical domain, *Ps* = psychosocial domain, *Co* = communication domain, *Flu* = fluency, *AComp* = auditory comprehension, *Speech* = speech production, *Repet* = repetition, *Read* = reading, *Writ* = writing, *n/ap* = not applicable (patient had no observable handicap in comprehension or production of language), *TPJ* = temporoparietal junction, *preCG* = precentral gyrus, *IFG* = inferior frontal gyrus, *PFC* = prefrontal cortex, *DLPFC* = dorsolateral PFC, *IC* = insular cortex, *LV* = lateral ventricle, *SFG* = superior frontal gyrus, *OFC* = orbitofrontal gyrus, *ITG* = inferior temporal gyrus, *Claust* = Claustrum, *TPo* = temporal pole, *MFG* = middle frontal gyrus, *STG* = superior temporal gyrus, *SD* = standard deviation
[a] Patient P5 underwent awake craniotomy twice and the second operation was performed two years after the first one to remove a tumor regrowth.

The calculation of mean extent of resection (EOR) was based on seventeen (n = 17) surgeries and found to be 85.71% (SD = 13.660). The eliminated awake craniotomies include three non-brain tumor patients (P22, P25, P30), one patient (P2) for whom the exact EOR is unknown, and one patient (P26) in which only a sample for biopsy was extracted. Moreover, more than half of our brain tumor patients received a total or subtotal tumor resection (64%), as the neurosurgeons managed to perform total resection in 23% of our sample, while subtotal was possible on the 41%. However, it should be stressed that these results are only indicative as they are extracted by the neurosurgeons' estimations and they are not verified volumetrically.

4.4. Discussion

This section will discuss some interesting findings drawn from the described cases. First, I will review the performance of our sample on the preoperative tests, and then I will address the differences that were found between the three anatomical subgroups. Furthermore, a special reference will be made to the application of cognitive neuropsychological models for language in awake craniotomy context, and this chapter will conclude with the discussion of some noteworthy intraoperative findings.

Generally, the results from preoperative assessments indicated mild or very mild symptoms for patients that had impairments in language, cognition, and quality of life. Specifically for speech and language, none of the patients that presented impairments in comprehension or production levels suffered from severe symptoms according to BDAE's severity rating scale, and the deficits of our sample can be characterized as mild (M = 4.3, SD = 0.905). More details for each patient are provided in section 3 of this chapter (Results). With the exception of psychosocial domain, the average scores on SAQoL-39g are close to maximum (physical 4.8, psychosocial 4.2, communication 4.7), and well above the corresponding scores achieved by Greek post-stroke patients (physical 3.18, psychosocial 2.92, communication 3.33 [335]). The psychosocial domain, which was the lowest domain in our sample, measures thinking, personality, mood changes, as well as family and social functioning. Concerning cognition, it is interesting that the average score on MoCA was found to be 24.5 (SD = 3.804), which is just below the cut-off score for mild cognitive impairment (25/30) for the Greek healthy population [285]. The fact that this score is derived from assessments performed before surgeries indicates that tumor occurrence (or recurrence for some cases) may have affected the cognitive abilities of our patients.

In order to investigate further the preoperative findings, our sample was divided into three (unequal) subgroups according to anatomical areas of their lesions and particularly, according to the affected lobe. As it is demonstrated in Results of the current chapter, the patients with right (non-dominant) frontal lobe lesions produced significantly more words on verbal fluency subtest of BDAE, compared to the two left hemisphere groups (frontal and temporal). This finding is in accordance with numerous reports in literature regarding the sensitivity of verbal fluency in dominant hemisphere damage (for a review, see Henry et al. [387]). Significant differences were also observed in SAQoL-39g communication domain, according to which the left temporal lobe patients scored significantly lower compared to the left frontal and the right frontal lobe patients. This finding indicates that our temporal lobe patients experienced more difficulties related to communication in their every-day lives as they were less functional than the patients with tumors in the other brain areas.

Direct comparison with postoperative results is not possible mainly due to two reasons: a) not all patients took the follow-up assessments, thus the groups will be very unequal and heterogeneous, and b) pathologies and lesion locations are too indifferent within this sample. Nevertheless, in the next chapter (Chapter 5) I will attempt to statistically analyze a selection of patients that pose the highest homogeneity.

Utilization of cognitive neuropsychological models for language in awake craniotomies

The studies exploring the applications of cognitive neuropsychological models for language (Figure 3.1, Chapter 3) in awake craniotomy context are scarce and limited to retrospective interpretations of mapping results [253]. The case reports of patients P30 and P17 presented in the previous section demonstrate two different perspectives on how to use these models. Patient's P30 case report focuses on perioperative stage and on task selection process, while patient's P17 case report, focuses on awake stage and on optimization of the assessment. Nevertheless, both methods share a common aim, that is, to provide better postsurgical outcomes for patients and more generally, to provide evidence regarding brain and language relations.

According to preoperative assessment, patient P30 (AVM, posterior STG) exhibited moderate Wernicke's aphasia and suffered from impairment in auditory comprehension, especially above word-level. This was also evident during perioperative session which was conducted with GLAABS. The language specialist utilized the variety of tasks and presentation methods available in this test, in order to assess different input routes and cognitive processes. The results showed a difference in performance between auditory and written/visual input routes. Specifically, the patient answered flawlessly (score: 100%) when the administration of the *phonological odd word-out* task was conducted visually with written words, but experienced great difficulties to respond to the same task (score: 21.7%) when the stimuli were given orally. The same pattern, but in a smaller degree, was observed in *semantic odd-image out* (auditory score: 80%; visual score: 96%), in *sentence completion* *with words* (auditory score: 71,4%; written score: 81%), and in *semantic association* (auditory score: 73.7%, written score: 78.9%). Concerning the three judgment tasks that also use the auditory input route and require adequate comprehension, patient's score was normal in *semantic judgment*, marginal in *grammaticality judgment*, and pathological in *phonological judgment*, which engages the phonological encoding process. These findings are in accordance with the traditional neurolinguistic literature that suggests heavy involvement of the posterior superior temporal gyrus and the superior temporal sulcus in phonology and auditory processing of language [388]. This was a valuable procedure that helped the language specialist to avoid tasks which could compromise the results of intraoperative language mapping, for instance the auditory version of *phonological odd-word* out task.

On the other hand, the case of patient P17 (brain tumor, posterior ITG) provides an illustrative example of the use of cognitive neuropsychological models inside the operating theatre, in order to optimize the intraoperative assessment. Again, as in the previous case, by using different tasks and stimuli administration methods, the language specialist managed to assess various routes and processes, and consecutively isolate the one that was disrupted by stimulation (i.e., access to the semantic system via the orthographic input lexicon). The results from this procedure (see section 4.3. "Patient P17" for more details) provide evidence regarding dissociation between orthographic semantic and auditory lexical-semantic routes, and dissociation between orthographic semantic and direct lexical routes. Also, adds in the pre-existing evidence regarding the critical role of the inferior longitudinal fascicle in semantic processing of written words, and therefore in the comprehension process of written language [125,140,379-383].

Other noteworthy findings

In the following paragraphs, I will discuss various interesting findings from our cases and focus on peri- and intraoperative outcomes as measured by GLAABS. Nonetheless, the discussion will not be limited to speech and language.

Comprehension impairments, which are common within patients with temporal lesions, were not observed only in patients P30 and P17 discussed above. Patients P9 (brain tumor, TPJ) and P22 (epilepsy, TPo) also showed in their peri- and intraoperative assessments some degree of impairment in comprehension of oral or written language. Disturbances in language production level are also not uncommon in temporal lesions. Intraoperatively, it was observed that patients P2, P9, and P22 all suffering from temporal lesions produced several language errors. The first two patients (P2 and P9; brain tumors, TPJ) produced mainly phonemic paraphasias while patient P22 (epilepsy, TPo) mostly semantic paraphasias. These findings are in line with studies suggesting involvement of the temporoparietal junction in phonology [388] and the temporal pole in semantic processing [343,344]. Furthermore, patients P9 and

P22 that were both operated for temporal lesions, during the awake stage they complained about severe headaches and dizziness, which led to very poor cooperation. Patient P30 (AVM, posterior STG) also exhibited poor cooperation, as he suffered a grand mal seizure exactly when he was returning to a conscious state. It is suspected that this seizure caused a severe lethargy (postictal sleep), even though the neurosurgeons encountered the seizure with cold water appliance in the cortical area.

Headaches were also reported by patient P5 (brain tumor, superior PFC) who additionally exhibited severe spastic dysarthria and jargon speech at the early awake phase. A similar symptom (severe spastic dysarthria) began to manifest as the awake stage of patient P21 (brain tumor, right IFG) was approaching the end, and the resection procedure was advancing subcortically. It should be mentioned that during the acute postoperative phase the patient exhibited mild dysarthria and saliva drooling, although both symptoms resolved a month later.

Patients P4 (brain tumor, IFG) and P18 (brain tumor, right Claustrum) experienced similar symptoms during the "awakening" phase as both had difficulties to regain consciousness. Particularly patient P4, as soon as he regained consciousness also presented severe aphasia that was not present preoperatively. The symptoms included excessive perseveration and repetition of a pseudoword («*διφγκόνι*» [δif'goni]) and began before the stimulation process. Symptoms after 20 minutes of awake stage were milder but he continued to produce numerous perseveration errors, and neologisms. Patient P18 on the other hand, as soon as she started to regain consciousness, she experienced dysarthria, inability to maintain eye contact, difficulties to keep herself awake, constant loss of consciousness, apraxia of speech (inconsistent errors), and aprosodia, which were progressively worsening.

Patients P12 and P23 (both brain tumors, IFG) presented agrammatic speech inside the operating theatre and specifically as the awake stage was approaching the end. Particularly patient P23 presented progressively increasing symptoms of agrammatism which resulted to grammatical structure loss as the patient could only produce single words. Patient P12 presented milder symptoms intraoperatively but his difficulties were evident from the preoperative assessment, as he was omitting several functional words during oral and written description.

Patient P13 (brain tumor, SFG) and patient P20 (brain tumor, preCG) exhibited similar intraoperative symptoms during the resection process as both presented disturbed language initiation (i.e., difficulties to initiate an utterance unless a cue is provided).

Two patients (P16, brain tumor, OFC; P27, brain tumor, SFG) presented a similar symptom but in different stages of their awake stages. During the resection, at later stages of the awake stage, the responses of patient P16 were general accompanied by an abstract phrase. For instance, in a verb generation task the examiner presented the stimulus "kitchen" and the patient P16 responded, "we can do a lot of things with that". Patient P27 on the other hand, produced more circumlocutions during the language mapping. For example, during the object naming task, the examiner presented the image of a "butterfly" and the patient responded, "moves the wings to the air". The latter patient during the resection procedure exhibited also agrammatism, dysarthria, and aprosodia.

Finally, one more interesting finding was recorded during intraoperative assessment of patient P25 (AVM, right MFG, L1: Bulgarian, L2: Greek), and specifically during mapping procedure. Electrical stimulation of the right middle frontal gyrus induced several phonemic paraphasias and anomias in the Greek version of *object naming* task but not a single error when she was asked to respond in Bulgarian (L1). This finding is in accordance with studies that found greater right hemispheric activity during tasks related to the non-native language [389].

Concluding remarks

In this chapter I report the patients' linguistic profiles we treated with awake craniotomy in a case series design. Most of the patients suffered from brain tumors in eloquent areas and received intraoperative language mapping in order to protect these areas from resection. During intraoperative assessments which were conducted with GLAABS, our patients exhibited various types of speech or language disturbances, related to areas that the tumors were encroaching. As it happened in the case of patient P17, the use of cognitive neurolinguistic models which GLAABS is based on simultaneous assessment during mapping and resection provides a rare opportunity to further examine the clinico-anatomical correlations of brain and language. These data, although they do not come from large populations but from single patients, are still very valuable in the study of human brain as they allow us to understand the brain connectome which may vary in every individual.

Chapter 5. Group analysis

Abstract

This chapter investigates the postoperative outcomes of a group of brain tumor patients that went through intraoperative language mapping. The analysis of their data, as well as the comparison with other studies will shed light on the effectiveness of GLAABS. The sample under investigation derives from previously presented series of patients and it consists of 5 males and 3 females that were assessed in four stages (pre-, peri-, intra-, and postoperative). The results revealed that, generally, awake craniotomies did not significantly alter the language abilities of our patients. Their quality of life, on the other hand, decreased significantly although our patients' scores were considerably higher compared to Greek post-stroke patients. The mean extent of resection (~86%) was found to be similar with reports in the literature regarding awake craniotomies, and higher compared to reports for general anesthesia. With respect to the linguistic deficits, our findings agree with studies that suggest a high rate of new early deficits after awake craniotomy, which dramatically decrease after a few months, with or without therapy. Our results indicate that GLAABS is a valid assessment tool that can be used to assist the neurosurgeons achieve maximum resections without affecting permanently the language abilities of patients.

5.1. Introduction

The present chapter investigates the effectiveness of Greek Language Assessment for Awake Brain Surgery (GLAABS), by analyzing the postoperative outcome of 8 brain tumor patients of Neurosurgery Clinic of General University Hospital of Larisa. These patients comprise the most homogenous subgroup deriving from awake craniotomy sample presented in Chapter 4, for which there are data available for all assessment stages. The term "effectiveness" is used here to refer to the degree an awake craniotomy achieves maximum possible resection of a brain tumor with minimum postoperative deficits. Thus, the main goal is to examine whether our patients' language systems were affected by awake craniotomy and to further compare the postoperative outcome of our sample (i.e., extent of resection and linguistic deficit) with reports in the literature that concern not only awake craniotomies but also brain surgeries under general anesthesia.

The direct comparison between patients underwent awake craniotomy and those who went under general anesthesia is very challenging as it is difficult to perfectly match the characteristics of these two mutually exclusive populations. In other words, it is difficult to match age and grade of tumor simultaneously as younger patients with low-grade gliomas (LGGs) are typically operated with awake craniotomy, which offers better surgical outcomes.

Furthermore, some investigators suggest that it is unethical to include in general anesthesia groups patients with LGGs in eloquent areas. As our postoperative neuropsychological outcomes will be compared to similar findings reported in the literature, it is necessary to first briefly overview the results of various studies that include both main surgical methods (i.e., general anesthesia and awake craniotomy).

Extent of Resection

In awake craniotomies context, the extent of resection is a very important notion, as early maximal tumor removal increases the overall survival[11] and has a direct impact on patients' quality of life [12,390]. As Duffau [390] stresses, earlier surgeries allow more aggressive resections since tumors are still relatively small and the risk of permanent postoperative deficits is still low. In the same article, after investigation of 26 articles (case series, case reports, and reviews) reporting the volumetrically calculated extents of resection (EOR) after awake craniotomies, the author found that the EOR was ranging from 68 to 100%.

A prospective study [391] that compared two groups of brain tumor patients, with the first undergoing awake craniotomy (AC) and the second brain surgery with general anesthesia (GA), found that there was no statistical difference in the extent of resection (EOR). Specifically, they reported total resection achievement on the 47.6% of the AC patients, while the corresponding rate for the GA group was 63%. Although this result indicates larger average extent of resection for GA patients the difference is not statistically significant and it might be deceiving, given that the authors did not perform language or motor mapping with electrical stimulation, resulting in more residual tumor for the AC group.

Another prospective study, comparing general anesthesia and awake craniotomy, was performed by Sacko et al. [392]. These investigators divided the general anesthesia group into two subgroups, one that included patients with tumors in eloquent areas (GA72) and one with patients suffering from tumors in non-eloquent areas. The authors reported that total and subtotal tumor removal was possible in 37% and 45% respectively concerning the AC group, while the corresponding rates for the GA72 group were 14% (total) and 26% (subtotal). These rates suggested again larger mean of extent of resection for AC groups.

In another study, by Duffau and colleagues [112], the authors reported that in their GA group the 6% of resections were categorized as total and the 37% as subtotal, while the corresponding rates for the AC group were 25.4% for total and 50.8% for subtotal.

Eseonu et al. [393] found that total resection for perirolandic tumors was achieved in significantly more AC patients compared to patients who underwent general anesthesia. This

[11] The overall survival is estimated to be approximately 14-15 years when total resection is performed at diagnosis [390,394].

led to larger resections for the AC group (EOR: 86.3% vs 79.6%), although that difference was not statistically significant.

Gravesteijn et al. [395] found a similar result as the average extent of resection in their AC group was 81%, while for GA group the EOR was limited to 55.95%. However, it is interesting to combine this finding with the authors' reports regarding postoperative language deficits, which are included in the next section.

In a different study design, De Benedictis et al. [396] compared the same group of patients, which underwent general anesthesia and subsequently after several years underwent awake craniotomy to treat tumor recurrence. They found that a gross total resection was achieved in the 44.4% of the AC patients, while regarding the GA patients, a total tumor resection was not possible in any patient.

Finally, in a review published by Brown et al. [110], which included 8 studies that compared patients who underwent general anesthesia and awake craniotomy, the reported rate of total resections in the AC group was 41%, while the rate for GA group was 44%. This difference between the two methods is attributed by the authors to better identification of functional cortical boundaries during awake surgery. Thus, it may be that higher tumor tissue resection in the GA groups came at the price of higher functional tissue loss and neurological morbidity as well.

Postoperative neuropsychological outcome

Another important issue which is undoubtedly associated with successful and effective awake craniotomies is the postoperative neurological deficit, and in our case speech and language impairment. The postsurgical deficits can be caused by cerebral edema, vascular injury, and damage to the deep white matter tracts or areas with heavy involvement to eloquent regions [110]. It should be noted that impairments after a surgery may arise, even if critical structures are not directly damaged during the operation [397,398]. The distinction between transient and permanent deficits is important because, as it was also discussed in the 2nd chapter of the present dissertation, it is common after awake craniotomies some postsurgical symptoms to last only for a while and resolve without therapy [110]. For instance, in a large series published by Sacko et al. [392] that included 643 brain tumor patients (operated under both local and general anesthesia), the 1/3 of the patients (*n*=192) developed transient deficits, while the number of patients whose deficits became permanent was only 34 (5.3%).

According to Duffau's review [390], the most prominent presenting symptom among patients that undergo awake craniotomy is seizure, while the preoperative neurological examinations are generally normal. However, in studies that neuropsychological assessments are included, the preoperative cognitive disturbances are more frequent (20-91%). Although there is a high rate of postoperative deficits in the acute phase after awake craniotomy (on a rate of 33 to 100%), no severe permanent deficits are reported in most articles [390]. With respect to the latter claim, Duffau notes that it needs more investigation as objective postoperative neuropsychological assessments are rarely reported. A large retrospective study [399], which included 610 patients that underwent awake craniotomy, found that only 25 patients (4.1%) developed postoperative speech and/or cognitive deficits. Finally, in another large series [176], it was found that the 10.9% of patients with tumors near or within language cortex (with no preoperative deficits) had new permanent deficits 7 months after their surgery.

In a prospective study, Gupta and colleagues [391] compared brain surgery under general anesthesia and awake craniotomy (without intraoperative mapping), and measured the postoperative neurological deficits with Karnofsky Performance Status scale. They found that there was no statistical difference between AC and GA groups, and also reported that none of the patients in the AC group developed new language deficits.

Sacko et al. [392] reported that the 56% of patients that underwent awake craniotomy had no preoperative deficits. Of these patients, only the 1.7% developed permanent neurological deficits after the surgery. On the other hand, all patients from group GA72 (with lesions to eloquent areas) that had no preoperative deficits, developed new impairments. As authors note, the 7.8% these new deficits were permanent. Finally, the overall rate for permanent deficits (new or pre-existing) in the AC group was 4.6% while in GA72 it was 16%. These results led the authors to conclude that patients with supratentorial lesions in eloquent areas that underwent awake craniotomy had better neurological outcome and larger extent of resections than the patients who underwent general anesthesia. However, the authors do not specify or describe the “neurological deficits”, nor do they specify the assessment tools they used to measure them.

Duffau et al. [112] did not find significant differences between patients who underwent awake craniotomy (AC) and the ones that went under general anesthesia (GA) in preoperative speech and language symptoms. The authors reported that postoperatively the 11% of the GA group suffered severe speech and language deficits, while the rate for the AC group was only 1.6%.

Eseonu et al. [393] published a comparative study between awake craniotomy and general anesthesia, although their sample included only tumors in sensory-motor areas (perirolandic gliomas). The authors report no difference between the two groups regarding new motor, sensory, language, cognitive, or visual permanent deficits. Interestingly, concerning language, the authors reported that 4 patients (14.8%) from the AC group presented permanent language deficit without exhibiting any transient deficit (0%). On the other hand, the rate of permanent language deficit for the general anesthesia group was 6.5%.

De Benedictis et al. [396] found that the 22.2% of patients who underwent brain surgery with general anesthesia presented permanent mild aphasia. Concerning awake craniotomies, which were performed several years later, the 50% of patients presented transient worsening in language, which, in all cases, was resolved several weeks later. Specifically, the authors reported that all patients recovered to their preoperative condition and overcame their early speech difficulties, and additionally, the 33,3% of the patients saw an improvement of their quality of life (although no particular measures reported).

In their review, Brown et al. [110] stated that "the mean percentage of new neurological deficits were clearly lower in AC groups (7% in awake group compared with 23% in GA groups)" (p. 245), which is in accordance with the previously discussed findings.

Finally, in a relatively recent study [395], it was found that a preoperative language dysfunction was present in the 1/4 of their sample, including 25 patients that were operated under both methods, general anesthesia and awake craniotomy. Regarding the postoperative outcomes, they report that the 25% of AC group and the 11% of GA group developed early severe deficits including aphasia. On the other hand, the "late severe deficits" were present in the 12% of AC group and in the 5% of GA group. The authors underline that none of these differences were significant, and that the GA group showed more (new) permanent neurological deficits.

Table 5.1
Postoperative outcomes reported in the literature.

Study	**Study type**	**Extent of Resection** AC (%)	GA (%)	**Postoperative Deficits**[a] Early (transient) AC (%)	GA (%)	Late (permanent) AC (%)	GA (%)
Brown et al. [110]	review	total: 41	total: 44	-	-	7	23
De Benedictis et al. [396]	clinical	total: 44.4	total: 0	44	-	0	22.2
Duffau [390]	review	mean: 90	-	57	-	0-5	-
Duffau et al. [112]	clinical	total: 25.4	total: 6	-	-	1.6	11
Eseonu et al. [393]	clinical	mean: 86.3	mean: 79.6	0	6.5	14.8	6.5
Gravesteijna et al. [395]	clinical	mean: 81	mean: 55.9	25	11	12[c]	5
Gupta et al. [b] [391]	clinical	total: 47.6	total: 63	18.7[c]	11.7	-	-
Sacko et al. [392]	clinical	total: 37	total: 14	1.7	92	1.7	7.8
Serletis and Bernstein [399]	clinical	-	-	-	-	4.1	-
Ilmberger et al. [176]	clinical	-	-	-	-	10.9	-
Zelitzki et al. [400]	clinical	mean: 86.2[c] total: 40.9[c]	mean: 91.1 total: 41.4	43.2[c]	58.5	25[c]	34.1

Leg.: *AC* = awake craniotomy, *GA* = general anesthesia
[a] Newly acquired neuropsychological deficits, in most (but not all) cases including speech/language
[b] No intraoperative mapping with DES was performed
[c] No statistical difference between AC and GA

This chapter

The aforementioned findings (summarized in Table 5.1) indicate that there is a trend according to which in the early postoperative stages there are more neurological deficits after awake craniotomies while in the late stages the deficits are more for general anesthesia. With respect to this phenomenon, De Witt Hamer et al. [1] hypothesized that in awake craniotomies there is more tumor control and larger extent of resection, which lead to preservation of neurological functions at the cost of early transient neurological deficits.

In literature, there are various terms to characterize the postoperative neurological and neuropsychological deficits. Usually, the "early" deficits are also transient, as permanent deficits are diagnosed in the subsequent, follow-up assessments [110]. Some investigators use the term "new deficit", which refers to deficits that were not present before the operation, while others focus only on the long-term neurological outcome, regardless of whether there were similar or different deficits prior to surgery.

As discussed above, during the early assessments it is common for patients to exhibit aggravated symptoms due to various postsurgical phenomena. These deficits are typically transient and may mislead the results of an assessment. According to our protocol, patients that undergo awake craniotomy are informally assessed immediately after the operation (2-3 days after) and then again one month later by using preoperative tests. As it was observed from our experience, the four-week period between the surgery and the follow-up assessment is adequate to allow the immediate postsurgical phenomena to resolve, and provide a better clinical picture of the patient. However, as it will be discussed in Methods section, due to classification reasons the follow-up session will be considered as "early".

Given the above analysis, the following hypotheses were formed:

1. Our patients' postoperative performance in language tests will remain unaffected by awake craniotomy and will be the same as preoperative.
2. The extent of resection of our patients (named "Group PIP") will be similar to other reports in the literature about awake craniotomies, and greater than patients operated under general anesthesia.
3. The new early postoperative deficits of our patients will be similar to other reports in the literature about awake craniotomies, and higher than patients operated under general anesthesia.

5.2. Methods

In this section I will demonstrate the materials and methods used in order to conclude this chapter.

Participants

The patients that comprise the sample under investigation (Group PIP, Table 5.2) were all patients of the Neurosurgery Clinic of the General University Hospital of Larisa during the period 2017-2020 and they are extracted from the larger pool of patients that was presented in the previous chapter (Chapter 4).

Table 5.2
Demographic and clinical characteristics of Group PIP patients.

	Case number	**Age**	**Gender**	**Hand-edness**	**Educa-tion**	**Patho-logy**	**Hemi-sphere**	**Histopathology (fast-track biopsy)**
1	P11	38	F	right	12	BT	L	(low-grade glioma)
2	P12	26	M	right	12	BT	L	(low-grade glioma)
3	P13	40	M	right	12	BT	L	glioblastoma
4	P17	32	M	right	12	BT	L	(low-grade glioma)
5	P18	44	F	right	12	BT	R	astrocytoma grade II-III
6	P20	41	F	right	12	BT	L	low-grade glioma
7	P21	39	F	right	12	BT	R	low-grade glioma
8	P27	40	F	right	12	BT	L	(low-grade glioma)
Gender								
	Female		5					
	Male		3					
Age								
	Range		26-44					
	Average		37.5					
	Std. Dev.		5.757					
Education (years)								
	Range		12-12					
	Average		12					
	Std. Dev.		0.000					
Lateralization								
	Right-handed		8					
	Left-handed		0					
Hemisphere of lesion								
	Hemisphere							
	left		6					
	right		2					

Leg.: *F* = female, *M* = male, *BT* = brain tumor, *L* = left hemisphere, *R* = right hemisphere

Of the 22 awake craniotomies that have been performed in 21 patients in our clinic, I selected the most homogenous group (Group PIP) that consists of five (n=5) females and three males (n=3). These patients match in terms of age (M = 37.5, SD = 5.757, $RANGE$ = 26-44), handedness (all right-handed), pathology (all brain tumors), and education (M = 12, SD = 0.000). In six (n=6) patients the tumor was located on the left hemisphere, while there are two patients in the sample with tumors in the right hemisphere. All tumors were located within or close to speech or language areas. The patients included in this group had to fulfill the following criteria:

- Patients' cognitive and linguistic skills were assessed preoperatively, perioperatively, intraoperatively, and postoperatively (acute phase and follow-up).

- Preoperative and postoperative evaluations (follow-up) were performed with the same evaluation tools.
- Patients' perioperative and intraoperative evaluations were performed with the same, final, and standardized protocol (GLAABS).
- The assessments were made by the same clinician.
- Data were appropriately collected and recorded in the same way for every case.

Statistics

In order to check the first hypothesis, I used paired sample tests to compare the preoperative neuropsychological results of Group PIP with the postoperative performances. The most common statistical tests are the *paired sample t-test*, *McNemar's test*, *Wilcoxon signed-rank test*, and the *sign test*. The first one is parametric, and it is used when there is normal distribution, while the last two tests (*Wilcoxon signed-rank* and *sign*) are non-parametric; therefore they are used when normal distribution is not assumed. In order to check the distribution of all hypotheses the *Shapiro-Wilk* test was employed, which is appropriate for small data and it is considered the best choice provided by SPSS software [401]. Homogeneity of variance assumption is not needed for paired sample tests, since the samples come from the same group. Concerning the second and third hypotheses, the *Mann-Whitney U* test was used to compare the extent of resection and neuropsychological outcomes between Group PIP and results from the literature.

Procedures and outcome measures

The tests and procedures used in our protocol have been described in detail in previous chapters of this dissertation (Chapter 3 and Chapter 4). Briefly, all the assessments were performed with valid and standardized assessment tools that have been reported in similar studies and they are widely used in speech, language, and cognitive disorders assessment. All patients were evaluated four times: a) preoperatively, one month prior to surgery (with EHI, BNT, BDAE, MoCA, and SAQoL-39g), b) perioperatively, two days before operation (with GLAABS), c) intraoperatively (with GLAABS), and d) postoperatively in two phases, two days and one month after (informally for the acute and with BNT, BDAE, MoCA, and SAQoL-39g for the follow-up sessions). The results of MoCA test are not included in the analysis, as it was administered only to five patients (P17, P18, P20, P21, and P27).

In order to check the second hypothesis, I will calculate the mean extent of resection in order to compare it with the reports from literature. The extent of resection is derived by neurosurgeons' estimations; thus, the percentages are only indicative and are not verified volumetrically. The term *partial* is used to characterize resections below 84%, the term *subtotal* for resections between 85 and 99%, and the term *total* for the cases where the absolute 100% was achieved.

Regarding neuropsychological postoperative outcomes (third hypothesis), our results will be classified according to De Witt Hamer et al. [1] classification system, in which the deficits are categorized according to severity ("severe" and "less severe") and timing of assessment ("early" and "late"). The deficits observed within the first three months are considered *early*, while the deficits observed three months after surgery are considered *late*. With respect to our data, only the early deficits are relevant as in all cases the follow-up assessments took place one month after the surgeries. With respect to severity, De Witt Hamer et al. [1] state that if the postoperative symptoms involve "muscle strength grade 1 to 3 on the Medical Research Council Scale, aphasia or severe dysphasia, hemianopia, or a vegetative state" (p. 2) are considered *severe*, whilst "all other neurologic deficits […] including grade 4 monoparesis, isolated central facial palsy or other cranial nerve deficit, dysnomia, somatosensory syndrome, or parietal syndrome" (p.2) are considered *less severe*. Concerning speech and language deficits, the authors make a distinction which essentially incorporates moderate and severe aphasias in the *severe* status, while more mild aphasias, such as mild anomia (or "dysnomia" as it they call it), and speech disorders caused by peripheral damage (e.g., dysarthria) are classified as *less severe*. In this chapter, in order to follow an objective and consistent method of classification, the severity of diagnosed aphasia (any type), dysarthria (any type), or apraxia of speech is determined according to BDAE's severity scale[12] where: 1 = extremely severe, 2 = severe, 3 = moderate, 4 = mild, 5 = extremely mild. In other words, speech and language disorders scored with 0 to 3 are considered *severe*, while scores 4 to 5 *less severe*.

5.3. Results

In most cases the presenting symptom of Group PIP patients was a seizure (grand mal or absence), while the preoperative neuropsychological results were generally close to normal (see Chapter 4, section 3: Results, for a detailed description). Regarding the first hypothesis, the preoperative and postoperative neuropsychological results of Group PIP were compared with paired statistical tests. After checking the normality assumptions with Shapiro-Wilk test, it was revealed that, several variables were normally distributed. However, all pairwise comparisons were conducted with non-parametric tests (*Wilcoxon sign-rank* test and *sign test*), which are generally considered safer choices when it comes to small groups [402]. Furthermore, limited samples may pass incorrectly the normality assumption testing, as they have little power to reject the null hypothesis [401]. The Wilcoxon signed rank test has a

[12] For details, see Chapter 4, section 2.2.1 (Preoperative and postoperative assessment tools).

symmetry assumption, which was checked with mean/median ratio (< 0.50), and also visually, by observing the corresponding boxplots. The variables that met the symmetry assumption were analyzed with *Wilcoxon signed-rank* test, while the rest with *sign* test. Finally, the *McNemar* test was selected for one dependent variable (fluency, BDAE) as it is better suited for categorical/nominal variables.

Almost all subtests of **BDAE** (Table 5.3) show no significant difference between preoperative and postoperative results. The only exception is the verbal fluency subtest from the *speech production* component that shows a postoperative decrease (pre-op: M = 21, SD = 5.425; post-op: M = 15.63, SD = 6.675), which is statistically significant (p = 0.041).

Table 5.3
Comparison of the preoperative and postoperative performances on BDAE.

Component	**Subtest**	**Preoperative**			**Postoperative**			**Sign Test**
		Mean	SD	Median	Mean	SD	Median	*p*
Auditory comprehension	Body-part identification	20	0.000	20	19.88	0.354	20	-
	Commands	15	0.000	15	14.12	1.642	15	0.500
	Complex-ldeational material	10.37	1.598	10.5	9.87	1.126	10	0.219
Speech production	Non-verb diadochokinesis	9.5	2.268	10	9.25	2.053	10	1.000
	Verbal diadochokinesis	12.75	1.832	14	12	2.563	13	1.000
	Automatized sequences	7.63	0.744	8	7.88	0.354	8	-
	Recitation, melody, rhythm	16.75	0.707	14	13	1.069	13	0.250
	Naming (visual confrontation)	114	0.000	114	113.63	1.061	114	-
Repetition	Word repetition	10	0.000	10	9.63	0.744	10	0.500
	Sentence repetition (high-probability)	7.88	0.354	8	7.75	0.463	8	-
	Sentence repetition (low-probability)	7.75	0.707	8	7.5	0.535	7.50	0.625
Reading	Word recognition	7.88	0.354	8	8	0.000	8	-
	Comprehension or oral spelling	7.88	0.354	8	7.13	1.356	7.5	0.250
	Reading (words)	30	0.000	30	28.88	2.232	30	0.500
	Reading (sentences)	10	0.000	10	9.5	1.069	10	0.500
	Word-picture matching	10	0.000	10	9.63	0.744	10	0.500
Writing	Writing mechanics	4.88	0.354	5	3.75	1.832	4.5	0.125
	Serial writing	45	0.000	45	37.38	16.106	45	0.500
	Basic encoding skills	15	0.000	15	12.63	5.290	15	0.500
	Words to dictation	9.88	0.354	10	7.63	4.138	10	0.625
	Written confrontation naming	10	0.000	10	7.63	4.138	10	0.250
	Sentences to dictation	11.63	1.061	12	9.13	4.794	11.5	0.125
	Narrative writing	4.62	0.518	5	3.25	2.053	4	0.125
Component	**Subtest**	**Preoperative**		**Postoperative**		**Wilcoxon S-R**		
		Mean	SD	Mean	SD	*Z*	*p*	
Auditory comprehension	Word discrimination	71.75	0.707	70.38	1.923	**-1.890**	**0.059**	
Speech production	Responsive naming	29.75	0.463	29.5	1.069	-0.378	0.705	
	Verbal fluency (semantic)	21	5.425	15.63	6.675	**-2.043**	**0.041***	
Reading	Symbol discrimination	9.25	1.389	9.63	0.744	-1.134	0.257	
	Comprehension of paragraphs	8.88	1.126	8.62	0.916	-0.649	0.516	
Component	**Subtest**	**Preoperative**		**Postoperative**		**McNemar's Test**		
		Fluent	Non	Fluent	Non	*p*		
Speech production	Fluency	8	0	5	3	0.250		

*=marginally significant ($p \leq 0,10$), **=significant ($p \leq 0,05$), ***=highly significant ($p \leq 0,01$)

Moreover, the word discrimination subtest from *auditory comprehension* component also shows a small decrease postoperatively, although this difference is marginal but not statistically significant ($p = 0.059$).

Regarding **BNT** (Table 5.4), the preoperative ($M = 43.5$, $SD = 1.195$) and postoperative results ($M = 43$, $SD = 0.926$) exhibit a small difference which is not statistically significant ($p = 0.414$).

Table 5.4
Comparison of the preoperative and postoperative performances on BNT.

Test	**Function tested**	**Preoperative**			**Postoperative**			**Wilcoxon S-R**	
		Mean	SD	Median	Mean	SD	Median	Z	*p*
BNT	Naming	43.5	1.195	44	43	0.926	43	-0.816	0.414

*=marginally significant ($p \leq 0,10$), **=significant ($p \leq 0,05$), ***=highly significant ($p \leq 0,01$)

As it is illustrated in Table 5.5, the overall score of **SAQoL-39g** questionnaire decreased significantly ($p = 0.024$). Specifically, the *physical* (pre-op: $M = 4.79$, $SD = 0.525$; post-op: $M = 4.43$, $SD = 0.682$), and the *communication* subscales (pre-op: $M = 4.99$, $SD = 0.035$; post-op: $M = 4.59$, $SD = 0.445$) demonstrated a marginal, but significant, decrease in scores (p=0.042 and p=0.043 respectively). On the other hand, the difference between the preoperative results of the *psychosocial* subscale ($M = 4.20$, $SD = 0.893$) and the postoperative ($M = 4.13$, $SD = 0.669$) is not significant (p=0.497).

Table 5.5
Comparison of the preoperative and postoperative performances on SAQoL-39g.

Test	**Domain**	**Preoperative**			**Postoperative**			**Wilcoxon S-R**	
		Mean	SD	Median	Mean	SD	Median	Z	*p*
SAQoL -39g	Physical	4.79	0.525	5	4.43	0.682	4.6	-2.032	0.042*
	Psychosocial	4.20	0.893	4.55	4.13	0.669	4.35	-0.680	0.497
	Communication	4.99	0.035	5	4.59	0.445	4.65	-2.023	0.043*
	Overall	4.58	0.486	4.8	4.29	0.536	4.35	-2.254	0.024*

*=marginally significant ($p \leq 0,10$), **=significant ($p \leq 0,05$), ***=highly significant ($p \leq 0,01$)

The results of **MoCA** test (presented in Table 5.6, next page) are not included in the analysis as the assessment was administered only to five patients (P17, P18, P20, P21, and P27). Preoperatively, two patients (P17 and P27) scored within normal limits, whereas the other three patients scored below the cut-off score for mild cognitive impairment (below 25/30). The postsurgical results of MoCA, on the other hand, remained generally similar as again two patients exhibited normal scores and three pathological. Specifically, one patient (P17) kept his score within normal limits, one patient (P21) improved his score above the cut-off score for mild cognitive impairment, two patients (P18 and P20) remained pathological pre- and postsurgically, while one patient (P27) performed normal preoperatively and pathological postoperatively. It should be stressed that the postoperative scores for patients P18, P20, P27 are not representative since these patients had physical deficit that prevented them to adequately participate in assessment procedure (see the Table 5.6 caption for details).

Table 5.6
Comparison of the preoperative and postoperative performances on MoCA.

Test	Case	Preoperative (score)	Postoperative (score)
MoCA	P11	-	-
	P12	-	-
	P13	-	-
	P17	Normal (25)	Normal (26)
	P18	Pathological (23)	Pathological[a] (5)
	P20	Pathological (24)	Pathological[b] (19)
	P21	Pathological (24)	Normal (26)
	P27	Normal (29)	Pathological[c] (20)

[a] Complained about mental fatigue and aborted the assessment during the second subscale
[b] Although the deficit in the dominant upper extremity played a role in her low score patient also underperformed in attention and naming fields (visuospatial: 1/5, naming: 1/3, attention: 3/6)
[c] Unable to properly fill the visuospatial fields due to monoparesis of the dominant hand

Table 5.7 illustrates the postoperative outcome of Group PIP (extent of resection and linguistic deficits) that will be compared with other brain tumor patients that went under general anesthesia or awake craniotomy. The mean estimated extent of resection of Group PIP is 85.88% (*SD* = 5.515), which is very close to the mean EOR of all our patients that went through awake craniotomy for tumor resection in our clinic (*M* = 85.71%, *SD* = 13.660).

Table 5.7
Postoperative outcomes of the awake craniotomies.

	Case number	Hemi-sphere	Tumor location	Present. sympt.	EOR[a] (%)	Early post-op deficit
1	P11	L	IFG	seizure	subtotal (90)	Deficit (less severe)
2	P12	L	IFG[b]	seizure, agrammatism (S-R)	subtotal (85)	Deficit (less severe)
3	P13	L	SFG[c]	seizure	subtotal (85)	Deficit (severe)
4	P17	L	ITG	seizure, mild memory loss (S-R)	partial (80)	No deficit
5	P18	R	Claust	(unknown)[d]	partial (80)	No new deficit[e]
6	P20	L	preCG	headaches	subtotal (85)	Deficit (less severe)
7	P21	R	IFG	(unknown)[d]	subtotal (85)	No deficit
8	P27	L	SFG	absence seizure	subtotal (97)	Deficit (severe)

Leg.: *L* = left, *R* = right, *IFG* = inferior frontal gyrus, *SFG* = superior frontal gyrus, *ITG* = inferior temporal gyrus, *Claust* = claustrum, *preCG* = precentral gyrus, *S-R* = self-reported
[a] Estimations of the neurosurgeon, not verified volumetrically (total = 100%, subtotal 99-85%, partial < 84%)
[b] Tumor was extending to insular cortex
[c] Multifocal tumor, it was also encroaching postcentral gyrus
[d] Patients P18 and P21 were operated again in the past, and the tumor recurrence was observed in a scheduled MRI scan
[e] Patient P18 exhibited the same deficits as preoperatively. They are not considered newly acquired

It should be noted that there is no significant difference between the mean EOR of Group PIP with the corresponding EOR reported in the studies of Table 5.1[13]. Specifically, there is no

[13] The clinical studies in Table 5.1 that were also included in the two reviews [110,390] were excluded from the final calculation of EOR, in order to avoid duplicates.

significant difference between our patients and patients from other studies that underwent awake craniotomy ([393,395,400] and studies included in Duffau [390]) (*M* = 88.48%, *SD* = 8.433; *p* = 0.117), or general anesthesia [393,395,400] (*M* = 74.53%, *SD* = 17.691; *p* = 0.295).

Furthermore, six of our patients exhibited deficits in early phase, whilst two patients presented normal speech and language results (Table 5.7). Five (out of six) patients developed new deficits, whereas in one patient (P18) the speech impairment was pre-existing and got worsen immediately after surgery. However, one month later her symptoms returned to preoperative (mild) level; therefore, this deficit is not considered “new”. In two cases (P13 and P27) the symptoms were considered *severe*, as they exhibited aphasia equal or below 3 in BDAE severity scale. On the other hand, in three cases (P11, P12, and P20) the postsurgical symptoms were *less severe*, as they presented mild or very mild aphasia (above 4 in severity scale). Although patient P20 exhibited right hemiparesis involving mostly the lower extremity, the deficit was not severe (grade 4 on Medical Research Council Scale). Compared to the results reported in literature, and presented in Introduction[14], there is no statistically significant difference between new early deficits of Group PIP (*M* = 62.5%) with other patients that underwent awake craniotomy [391,392,393,395,396,400,403-410] (*M* = 41.9, *SD* = 32.169; *p* = 0.422) or brain surgery under general anaesthesia [391,392,393,395,400] (*M* = 35.9, *SD* = 37.842; *p* = 0.380). Table 5.8 demonstrates the qualitative perspective of the postoperative neurological deficits with a focus on speech and language. Detailed descriptions of language profiles of these patients have been already presented in previous chapter (4.3).

Table 5.8
Postoperative speech and language deficits.

	P11	**P12**	**P13**	**P17**
New speech or language deficit	Yes	Yes	Yes	No
Aphasia presence	Yes	Yes	Yes	No
type of aphasia	Conduction	Broca	Unclassified[a]	-
severity (1-5)	4	4	2	-
AOS presence	No	Yes	No	No
severity (1-5)	-	4	-	-
Other new neurological deficits	No	No	No	No
	P18	**P20**	**P21**	**P27**
New speech or language deficit	No	Yes	No	Yes
Aphasia presence	No	Yes	No	Yes
type of aphasia	-	Anomic	-	Transcortical motor
severity (1-5)	-	5	-	3
AOS presence	Yes	No	No	Yes
severity (1-5)	4	-	-	3
Other new neurological deficits	Left visual neglect (egocentric)	Right hemiparesis (mostly lower extremity)	No	Aprosodia, left monoparesis (hand)

[a] Speech and language symptoms similar to SMA syndrome, as described in the literature [376-378]

[14]The related studies are described in sections “Extent of Resection” and “Postoperative neuropsychological outcome” (current chapter), and also presented in Table 5.1. However, some of the studies [403-410] that I took into consideration in order to calculate the average rate of new early deficits, were extracted from Duffau’s review [390] but they are not included in Table 5.1.

5.4. Discussion

This chapter analyzes the postoperative outcome of a relatively small and homogenous group of brain tumor patients and compares the results with other outcomes reported in the literature.

Regarding the preoperative neuropsychological status of our group, the most prominent presenting symptom was seizure, while all patients were generally functional with respect to their communication abilities. Specifically, the preoperative performances on BNT and most of BDAE subtests were above the 10th percentile (see Chapter 4 for details). One exception is patient P18, who had previously undergone brain surgery with extraoperative mapping, and this was her second operation. Her first operation caused speech deficits, which were still noticeable (i.e., very mild apraxia and spastic dysarthria). With respect to quality of life, our group scored an overall score of 4.58 (SD = 0.486) in SAQoL-39g, which is close to maximum, and considerably higher (SD > 1.5) than the overall score reported by Efstratiadou et al. [335] for Greek post-stoke patients (M = 3.1, SD = 0.82). Interestingly, these two populations present a similar pattern in the individual domains, as in both the highest score is observed in communication domain, the second highest in physical domain, while the psychosocial domain exhibits the lowest score. Finally, regarding the cognitive abilities, which were measured with MoCA test, the results are not available for all patients. Of the five patients that was administered presurgically, three patients scored close to, but lower than 25/30, which is the cut-off score for cognitive impairment. The above findings are in accordance with studies that have conducted detailed neuropsychological examinations and observed preoperative cognitive deficits (regardless of severity) in 20 to 91% of the patients (see Duffau [390] for a review). However, rarely these deficits are severe, as severe linguistic or cognitive impairments are counter-indications for awake craniotomy.

In order to examine if the awake craniotomy affected the speech and language abilities of Group PIP, we statistically compared the preoperative with the postoperative results in BDAE and BNT. Most of the scores achieved postsurgically by our patients in BDAE and BNT were close to normal according to the normative data. The mean percentiles of the five BDAE components were between the 50th and the 70th percentile (*auditory comprehension*: 60, *speech production*: 59, *repetition*: 67, *reading*: 69, *writing*: 63). This finding suggest that the presented postsurgical deficits were generally mild. The subtests that exhibited mean or median scores below normal at postoperative stage were the verbal diadochokinesis, repetition of low probability sentences, writing mechanics, narrative writing, and symbol discrimination. Interestingly, our statistical analysis did not reveal statistically significant differences between the pre- and postoperative results of our speech and language tests (BNT and BDAE). The only exception can be found in the verbal fluency subtest of BDAE, in which our patients performed significantly worse after the awake craniotomy (p = 0.041). The above findings indicate that the first hypothesis was confirmed as the awake craniotomies did not affect the speech and language abilities of patients and our team managed with the assist of GLAABS to keep the postoperative deficits at minimum.

With respect to the quality of life, measured with SAQoL-39g, the postoperative results follow a different trend. Compared to the preoperative findings, the overall quality of life of Group PIP decreased significantly (p = 0.024). Specifically, the patients scored significantly lower in physical (p = 0.042) and communication domains (p = 0.043), while the difference on psychosocial domain was not statistically significant. The reason behind this finding may lie on the fact that their psychosocial score was already low at preoperative stage. According to this rationale, the disease (brain tumor) had already from its onset affected the psychosocial aspects of our patients' quality of life. Albeit there are no normative data for SAQoL-39g concerning Greek healthy population, the postsurgical overall quality of life score of Group PIP (M = 4.29/5, SD = 0.536) is significantly higher (> 1SD) than the corresponding score of Greek post-stroke population (M = 3.1/5, SD = 0.82). Regarding the results of MoCA they were excluded from the analysis as the test was not administered in all Group PIP patients.

The mean extent of resection that was achieved in Group PIP is estimated to be ~86%, although this value is not volumetrically verified. Nevertheless, it is similar to the mean extent of resection reported in the literature for awake craniotomy, which is approximately 90% and ranges from 68 to 100% [390,393,395]. Also, it is considerably higher than several reports regarding brain surgery under general anesthesia [393,395], although this difference is not statistically significant. The aforementioned findings indicate that the second hypothesis is confirmed although verification by volumetry is needed.

The permanent postoperative neuropsychological deficits and in our case, speech and language deficits, are a far more complex issue. What makes challenging the direct comparison of reported outcomes between different studies is the heterogeneity in tests and methods that every study uses to classify the results. It is evident that the more in depth a study examines the postoperative neuropsychological status of its patients, the more likely is to detect deficits [390]. Furthermore, the methods according to which the reported deficits are classified into transient, permanent, early, late, mild, and severe vary substantially across studies. We chose the classification system proposed by De Witt Hamer et al. [1] which is widely used, although it does not perfectly match the timings of our postoperative assessments. According to that method, all deficits that were observed during our follow-up sessions were considered *early* as they took place one month postsurgically. Finally, speech and language disorders with a score between 0-3 in BDAE severity scale are considered *severe* while scores 4 and 5 denote *less severe* deficits (more details in section 2.3 Procedures and outcome measures, this Chapter). With regards to the third hypothesis, direct comparisons with general anesthesia patients are even more challenging as in addition to the aforementioned obstacles, there is a great variation in the reported rates of deficits (6.5-92%). Moreover, the reported extent of resection is typically smaller under general anesthesia, due to less tumor control, which leads to decreased early neurological deficits compared to awake craniotomy [1].

Our results revealed that five patients of Group PIP (62.5%) developed new early postoperative speech and language deficits. Of these patients, three developed *severe* and two *less severe* deficits. It is evident that Group PIP exhibited higher rate of deficits (62.5%) compared to the rates after general anesthesia reported by Gravesteijna et al. [395] and Gupta et al. [391], but lower compared to 92% reported by Sacko et al. [392], or 100% reported by several studies cited in Duffau's review [390] and come from awake craniotomy studies. With respect to early deficits after awake craniotomy, our results are close to De Benedictis et al. [396], Zelitzki et al. [400], Teixidor et al. [403], Santini et al. [405], Racine et al. [408]. Furthermore, our results agree with the findings by Duffau [390], wherein a higher rate of new early deficits after awake craniotomies is reported (33-100%), as well as with Thomas et al. [111] who reported that more than 80% of their patients developed some form of aphasia. To sum up, although Group PIP presented similar rate of new early language deficits compared to other awake craniotomy patients, and higher compared to patients that have undergone general anesthesia, none of these differences are statistically significant; therefore, the third hypothesis is confirmed. This trend (i.e., more early deficits in AC than in GA) is a known phenomenon that have been reported by other similar studies [1,110,390].

Concluding remarks

The findings reported in this chapter suggest that at least two of our hypotheses (first and third) are confirmed. Therefore, the use of GLAABS can assist in preserving the speech and language functions of patients undergoing awake craniotomy. Regarding the extent of resection (second hypothesis), although our results confirmed it, verification with volumetry method is required in order to draw safer conclusion. The aforementioned findings support the use of GLAABS in awake craniotomies in order to assist the neurosurgical team achieve greater resections without compromising the neuropsychological function of the patient postsurgically. However, further research with a larger and more homogenous group of patients is needed in order to draw safer conclusions.

Chapter 6. General Discussion

The present dissertation aimed to investigate the different methods of language assessment in awake craniotomy setting and develop a valid assessment tool. Meticulous analysis of the collected data allowed also a detailed description of patients' language profiles. This process was crucial in order to detect flaws in the procedure as well as to find evidence for test's validity and effectiveness.

The first introductory chapter (Chapter 1) provides an overview of tumor-related language disorders, which is a relatively unexplored field for clinicians associated to speech and language, such as speech-language pathologists and clinical linguists. Although the main focus of the current dissertation and subsequently of the first chapter was brain tumors, I also discussed other pathologies, such as medically intractable epilepsy and arteriovenous malformations. Based on literature [25,31,35] I argue that the neuroplastic mechanisms involved in brain tumors and brain tumor surgery play a major role on how the language related symptoms manifest. The study of these mechanisms can offer a better understanding on the exact role of neuroplasticity on tumor-related language disorders, as well as on the impact it has on intraoperative mapping and therapy intervention.

In the second chapter I explored the literature through a scoping review in order to review the different methods of intraoperative language assessment used by different neurosurgical teams, as well as to identify and analyze the standardized language tests used in that setting. The scoping review found only three tests that met the criteria established in this chapter, and revealed that only a few teams use standardized methods and assessment tools developed or modified properly for awake craniotomy. The most common practice used by numerous neurosurgical teams is the employment of an object naming task accompanied by automatized tasks during electrical current optimization. The three critically reviewed tests [79,183,235] showed some advantages and disadvantages. The Italian test (ECCO and VISC) [183] is developed with the most rigorous methodology, while DuLIP [79] provides a detailed neurolinguistic model and offers numerous tasks that can cover a wide range in language functions and processes, and subsequently anatomical areas. According to analysis presented in the discussion of Chapter 2, larger tests, such as the latter, that cover a wide range of language processes and functions may lead to higher sensitivity and reduced postoperative deficits, at the cost of increased administration time. However, as authors of DuLIP note, no more than two or three tasks on average are proposed for each cortical or subcortical structure, therefore it is reasonable to presume that the duration of the mapping process will not greatly differ from the other two tests. Based on the analysis provided in Chapter 2, I argue that comprehensive perioperative sessions can diminish Type I errors while accurate correlations between tasks, functions, and neuroanatomy will keep Type II error rate low.

Nevertheless, this is a challenging task considering the neuroplastic mechanisms involved in brain tumors, thus closer collaboration between researchers, clinicians, neurosurgeons and the other specialties involved in intraoperative language mapping is very important in order to develop more accurate and efficient assessment methods.

The third chapter describes the process of developing and norming a language test, specialized for intraoperative use. The analyses of the normative data revealed only a few main effects and interactions of demographic variables on the test scores. Regarding age, even though the results indicate light impact of age on GLAABS scores, according to which older participants tend to perform slightly worse than younger ones, in terms of statistical significance this is true only for four tasks. Gender and education depended variables posed significant effects on *phonological judgment* and *action fluency* tasks respectively. Although, these differences seem to have little impact on the cut-off scores, I suggest that in tasks in which significant differences among groups were found, specific cut-off scores should be considered. The main limitation of the work presented in Chapter 3 is associated with the sample size, as a bigger sample could increase the accuracy of the standard scores estimation. However, the fact that GLAABS is also criterion-referenced in addition to norm-referenced somehow mitigates this limitation. It should be noted that 80 additional participants were involved in various experiments during the development of the test and stimuli norming procedures, but they cannot be included in the final normative sample. Regarding its usability outside awake craniotomy setting first the sensitivity and specificity of GLAABS need to be calculated in order to accurately identify pathology in speech and language, although this process is very challenging.

The fourth chapter is a case series study, in which I described a series of patients that underwent awake craniotomy and intraoperative language assessment with GLAABS, and outlined their language profiles. Furthermore, I provided evidence regarding the convergent and discriminant validity of GLAABS. Most of the patients included in this chapter suffered from brain tumors in eloquent areas, while all went through intraoperative language mapping. Analysis of preoperative assessments revealed that patients exhibited only very mild symptoms related to tumor growth. I further divided the sample into three subgroups according to affected lobe, in order to detect differences in tests scores. Patients with right (non-dominant) frontal lobe lesions produced significantly more words on verbal fluency subtest of BDAE, compared to the two left hemisphere groups (frontal and temporal). This result highlights the sensitivity of verbal fluency tasks in damage of the dominant hemisphere [387]. Significant differences were also observed in SAQoL-39g communication domain, according to which the left temporal lobe patients scored significantly lower compared to left frontal and right frontal lobe patients. This finding indicates that our temporal lobe patients experienced more difficulties related to communication in their every-day lives as they were less functional than patients with tumors in the other brain areas. During the intraoperative assessments, patients exhibited various types of speech or language disturbances, which in most cases they were related to the anatomic areas of tumors. As it is demonstrated by the case reports of patients P17 and P30, the employment of the cognitive neurolinguistic models adopted by GLAABS during the intraoperative assessment provides a rare opportunity to further examine the clinico-anatomical correlations of brain and language.

In the fifth chapter I investigated the effectiveness of GLAABS and presented the postoperative outcomes of a group of brain tumor patients that went through intraoperative language mapping in a single institution (General University Hospital of Larisa, Department of Neurosurgery). The analyses showed that patients' postoperative performances in speech and language tests did not differ significantly from the preoperative in almost all subtests. Regarding the quality of life, our patients showed a significant decrease in physical and communicational functionality after the operations, although these scores were considerably higher than the corresponding scores of Greek post-stroke patients. These findings suggest that the awake craniotomies did not have a significant impact on patients' language systems and quality of life. Our sample exhibited similar rate of new early postoperative language deficits compared to other awake craniotomy patients [396,400,403,405,408], and higher compared to patients that have undergone general anesthesia [391,393,395]. These results are extensively discussed in Chapter 5 (introduction and discussion). The extent of resection was found to be similar to other awake craniotomy studies [390,393,395,400], and higher than studies reporting results for general anesthesia [393,395,400], whilst verification with volumetry method is required in order to draw safer conclusions. The aforementioned findings support the use of GLAABS in awake craniotomies in order to assist the neurosurgeons achieve greater resections without compromising the postsurgical neuropsychological functions of patients.

References

[1] De Witt Hamer PC, Robles SG, Zwinderman AH, Duffau H, Berger MS. Impact of intraoperative stimulation brain mapping on glioma surgery outcome: a meta-analysis. J Clin Oncol. 2012 Jul 10;30(20):2559-65. doi: 10.1200/JCO.2011.38.4818.

[2] Duffau H, Peggy Gatignol ST, Mandonnet E, Capelle L, Taillandier L. Intraoperative subcortical stimulation mapping of language pathways in a consecutive series of 115 patients with Grade II glioma in the left dominant hemisphere. J Neurosurg. 2008 Sep;109(3):461-71. doi: 10.3171/JNS/2008/109/9/0461.

[3] De Witte E, Mariën P. The neurolinguistic approach to awake surgery reviewed. Clin Neurol Neurosurg. 2013 Feb;115(2):127-45. doi: 10.1016/j.clineuro.2012.09.015.

[4] Mandonnet E, Winkler PA, Duffau H. Direct electrical stimulation as an input gate into brain functional networks: principles, advantages and limitations. Acta Neurochir (Wien). 2010 Feb;152(2):185-93. doi: 10.1007/s00701-009-0469-0.

[5] Ojemann G, Ojemann J, Lettich E, Berger M. Cortical language localization in left, dominant hemisphere. An electrical stimulation mapping investigation in 117 patients. 1989. J Neurosurg. 2008 Feb;108(2):411-21. doi: 10.3171/JNS/2008/108/2/0411.

[6] Barker FG 2nd, Amin-Hanjani S. Changing neurosurgical workload in the United States, 1988-2001: craniotomy other than trauma in adults. Neurosurgery. 2004 Sep;55(3):506-17; discussion 517-8. doi: 10.1227/01.neu.0000134284.47965.71.

[7] Anderson SW, Damasio H, Tranel D. Neuropsychological impairments associated with lesions caused by tumor or stroke. Arch Neurol. 1990 Apr;47(4):397-405. doi: 10.1001/archneur.1990.00530040039017.

[8] McNeill KA. Epidemiology of Brain Tumors. Neurol Clin. 2016 Nov;34(4):981-998. doi: 10.1016/j.ncl.2016.06.014.

[9] Iacoangeli M, Roselli R, Prezioso A, Scerrati M, Rossi GF. Staging of supratentorial hemispheric glioma using tumour extension, histopathological grade and extent of surgical resection. Br J Surg. 1993 Sep;80(9):1130-3. doi: 10.1002/bjs.1800800920.

[10] Vecht CJ, Avezaat CJ, van Putten WL, Eijkenboom WM, Stefanko SZ. The influence of the extent of surgery on the neurological function and survival in malignant glioma. A retrospective analysis in 243 patients. J Neurol Neurosurg Psychiatry. 1990 Jun;53(6):466-71. doi: 10.1136/jnnp.53.6.466.

[11] Claus EB, Black PM. Survival rates and patterns of care for patients diagnosed with supratentorial low-grade gliomas: data from the SEER program, 1973-2001. Cancer. 2006 Mar 15;106(6):1358-63. doi: 10.1002/cncr.21733.

[12] Sanai N, Berger MS. Glioma extent of resection and its impact on patient outcome. Neurosurgery. 2008 Apr;62(4):753-64; discussion 264-6. doi: 10.1227/01.neu.0000318159.21731.cf.

[13] Partovi S, Jacobi B, Rapps N, Zipp L, Karimi S, Rengier F, Lyo JK, Stippich C. Clinical standardized fMRI reveals altered language lateralization in patients with brain tumor. AJNR Am J Neuroradiol. 2012 Dec;33(11):2151-7. doi: 10.3174/ajnr.A3137.

[14] Jessen KR. Glial cells. Int J Biochem Cell Biol. 2004 Oct;36(10):1861-7. doi: 10.1016/j.biocel.2004.02.023.

[15] Banan R, Hartmann C. The new WHO 2016 classification of brain tumors-what neurosurgeons need to know. Acta Neurochir (Wien). 2017 Mar;159(3):403-418. doi: 10.1007/s00701-016-3062-3.

[16] Davis ME. Epidemiology and Overview of Gliomas. Semin Oncol Nurs. 2018 Dec;34(5):420-429. doi: 10.1016/j.soncn.2018.10.001.

[17] Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, Ohgaki H, Wiestler OD, Kleihues P, Ellison DW. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol. 2016 Jun;131(6):803-20. doi: 10.1007/s00401-016-1545-1.

[18] Walker DG, Kaye AH. Low grade glial neoplasms. J Clin Neurosci. 2003 Jan;10(1):1-13. doi: 10.1016/s0967-5868(02)00261-8.

[19] Mandonnet E, Delattre JY, Tanguy ML, Swanson KR, Carpentier AF, Duffau H, Cornu P, Van Effenterre R, Alvord EC Jr, Capelle L. Continuous growth of mean tumor diameter in a subset of grade II gliomas. Ann Neurol. 2003 Apr;53(4):524-8. doi: 10.1002/ana.10528.

[20] Mandonnet E, Capelle L, Duffau H. Extension of paralimbic low grade gliomas: toward an anatomical classification based on white matter invasion patterns. J Neurooncol. 2006 Jun;78(2):179-85. doi: 10.1007/s11060-005-9084-y.

[21] Wessels PH, Weber WE, Raven G, Ramaekers FC, Hopman AH, Twijnstra A. Supratentorial grade II astrocytoma: biological features and clinical course. Lancet Neurol. 2003 Jul;2(7):395-403. doi: 10.1016/s1474-4422(03)00434-4.

[22] Wesseling P, Capper D. WHO 2016 Classification of gliomas. Neuropathol Appl Neurobiol. 2018 Feb;44(2):139-150. doi: 10.1111/nan.12432.

[23] Claes A, Idema AJ, Wesseling P. Diffuse glioma growth: a guerilla war. Acta Neuropathol. 2007 Nov;114(5):443-58. doi: 10.1007/s00401-007-0293-7.

[24] Ostrom QT, Gittleman H, Liao P, Rouse C, Chen Y, Dowling J, Wolinsky Y, Kruchko C, Barnholtz-Sloan J. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2007-2011. Neuro Oncol. 2014 Oct;16 Suppl 4(Suppl 4):iv1-63. doi: 10.1093/neuonc/nou223.

[25] Duffau H. Brain plasticity and tumors. Adv Tech Stand Neurosurg. 2008;33:3-33. doi: 10.1007/978-3-211-72283-1_1. PMID: 18383811.

[26] Duffau H, Capelle L, Denvil D, Sichez N, Gatignol P, Taillandier L, Lopes M, Mitchell MC, Roche S, Muller JC, Bitar A, Sichez JP, van Effenterre R. Usefulness of intraoperative electrical subcortical mapping during surgery for low-grade gliomas located within eloquent brain regions: functional results in a consecutive series of 103 patients. J Neurosurg. 2003 Apr;98(4):764-78. doi: 10.3171/jns.2003.98.4.0764.

[27] Taphoorn MJ, Klein M. Cognitive deficits in adult patients with brain tumours. Lancet Neurol. 2004 Mar;3(3):159-68. doi: 10.1016/S1474-4422(04)00680-5.

[28] Teixidor P, Gatignol P, Leroy M, Masuet-Aumatell C, Capelle L, Duffau H. Assessment of verbal working memory before and after surgery for low-grade glioma. J Neurooncol. 2007 Feb;81(3):305-13. doi: 10.1007/s11060-006-9233-y.

[29] Papagno C, Casarotti A, Comi A, Gallucci M, Riva M, Bello L. Measuring clinical outcomes in neuro-oncology. A battery to evaluate low-grade gliomas (LGG). J Neurooncol. 2012 Jun;108(2):269-75. doi: 10.1007/s11060-012-0824-5.

[30] Ojemann JG, Miller JW, Silbergeld DL. Preserved function in brain invaded by tumor. Neurosurgery. 1996 Aug;39(2):253-8; discussion 258-9. doi: 10.1097/00006123-199608000-00003.

[31] Ganslandt O, Buchfelder M, Hastreiter P, Grummich P, Fahlbusch R, Nimsky C. Magnetic source imaging supports clinical decision making in glioma patients. Clin Neurol Neurosurg. 2004 Dec;107(1):20-6. doi: 10.1016/j.clineuro.2004.02.027.

[32] Meyer PT, Sturz L, Schreckenberger M, Spetzger U, Meyer GF, Setani KS, Sabri O, Buell U. Preoperative mapping of cortical language areas in adult brain tumour patients using PET and individual non-normalised SPM analyses. Eur J Nucl Med Mol Imaging. 2003 Jul;30(7):951-60. doi: 10.1007/s00259-003-1186-1.

[33] Heiss WD, Thiel A, Kessler J, Herholz K. Disturbance and recovery of language function: correlates in PET activation studies. Neuroimage. 2003 Nov;20 Suppl 1:S42-9. doi: 10.1016/j.neuroimage.2003.09.005.

[34] Duffau H, Bauchet L, Lehéricy S, Capelle L. Functional compensation of the left dominant insula for language. Neuroreport. 2001 Jul 20;12(10):2159-63. doi: 10.1097/00001756-200107200-00023.

[35] Thiel A, Herholz K, Koyuncu A, Ghaemi M, Kracht LW, Habedank B, Heiss WD. Plasticity of language networks in patients with brain tumors: a positron emission tomography activation study. Ann Neurol. 2001 Nov;50(5):620-9. doi: 10.1002/ana.1253.

[36] Holodny AI, Schulder M, Ybasco A, Liu WC. Translocation of Broca's area to the contralateral hemisphere as the result of the growth of a left inferior frontal glioma. J

Comput Assist Tomogr. 2002 Nov-Dec;26(6):941-3. doi: 10.1097/00004728-200211000-00014.

[37] Petrovich NM, Holodny AI, Brennan CW, Gutin PH. Isolated translocation of Wernicke's area to the right hemisphere in a 62-year-man with a temporo-parietal glioma. AJNR Am J Neuroradiol. 2004 Jan;25(1):130-3.

[38] Thiel A, Habedank B, Winhuisen L, Herholz K, Kessler J, Haupt WF, Heiss WD. Essential language function of the right hemisphere in brain tumor patients. Ann Neurol. 2005 Jan;57(1):128-31. doi: 10.1002/ana.20342.

[39] Herholz K, Heiss WD. Functional imaging correlates of recovery after stroke in humans. J Cereb Blood Flow Metab. 2000 Dec;20(12):1619-31. doi: 10.1097/00004647-200012000-00001.

[40] Rosen HJ, Petersen SE, Linenweber MR, Snyder AZ, White DA, Chapman L, Dromerick AW, Fiez JA, Corbetta MD. Neural correlates of recovery from aphasia after damage to left inferior frontal cortex. Neurology. 2000 Dec 26;55(12):1883-94. doi: 10.1212/wnl.55.12.1883.

[41] Weiller C. Imaging recovery from stroke. Exp Brain Res. 1998 Nov;123(1-2):13-7. doi: 10.1007/s002210050539.

[42] Selnes OA. Recovery from aphasia: activating the "right" hemisphere. Ann Neurol. 1999 Apr;45(4):419-20.

[43] Duffau H, Capelle L. Récupération fonctionnelle à la suite de lésions de l'aire somato-sensorielle primaire. Etude des mécanismes de compensation [Functional recuperation following lesions of the primary somatosensory fields. Study of compensatory mechanisms]. Neurochirurgie. 2001 Dec;47(6):557-63. French.

[44] Papathanasiou I, Coppens P, Davidson B. Aphasia and related neurogenic communication disorders: basic concepts, management, and efficacy. In: Papathanasiou I, Coppens P, editors. Aphasia and related neurogenic communication disorders. 2nd ed. Burlington (MA): Jones and Bartlett Publishers; 2017. p. 3-14.

[45] Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, Greenlund K, Daniels S, Nichol G, Tomaselli GF, Arnett DK, Fonarow GC, Ho PM, Lauer MS, Masoudi FA, Robertson RM, Roger V, Schwamm LH, Sorlie P, Yancy CW, Rosamond WD; American Heart Association Strategic Planning Task Force and Statistics Committee. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. Circulation. 2010 Feb 2;121(4):586-613. doi: 10.1161/CIRCULATIONAHA.109.192703.

[46] American Cancer Society. Cancer facts and figures 2005. Atlanta (GA): American Cancer Society; 2005.

[47] Haglund MM, Berger MS, Shamseldin M, Lettich E, Ojemann GA. Cortical localization of temporal lobe language sites in patients with gliomas. Neurosurgery. 1994 Apr;34(4):567-76; discussion 576. doi: 10.1227/00006123-199404000-00001.

[48] Miceli G, Caltagirone C, Gainotti G, Masullo C, Silveri MC, Villa G. Influence of age, sex, literacy and pathologic lesion on incidence, severity and type of aphasia. Acta Neurol Scand. 1981 Nov;64(5):370-82. doi: 10.1111/j.1600-0404.1981.tb04416.x.

[49] Tandon P, Mahapatra AK, Khosla A. Operations on gliomas involving speech centres. Acta Neurochir Suppl (Wien). 1993;56:67-71. doi: 10.1007/978-3-7091-9239-9_11.

[50] Berthier ML. Poststroke aphasia: epidemiology, pathophysiology and treatment. Drugs Aging. 2005;22(2):163-82. doi: 10.2165/00002512-200522020-00006. PMID: 15733022.

[51] Armstrong DJ, Horner J, Fedor KH, Massey EW. Aphasia associated with intracerebral neoplasms. In: Brookshire R, editor. Clinical Aphasiology: Proceedings of the Conference 14; 1984 May 20-24; Seabrook Island, SC. Minneapolis (MN): BRK Publishers; c1984. p. 85-93.

[52] Thomson AM, Taylor R, Fraser D, Whittle IR. Stereotactic biopsy of nonpolar tumors in the dominant hemisphere: a prospective study of effects on language functions. J Neurosurg. 1997 Jun;86(6):923-6. doi: 10.3171/jns.1997.86.6.0923. PMID: 9171169.

[53] Kazner M. Early symptoms of aphasia with brain tumours. J Nerv Ment Dis. 1942 Jun;95(6):702-20.

[54] Whittle IR, Pringle AM, Taylor R. Effects of resective surgery for left-sided intracranial tumours on language function: a prospective study. Lancet. 1998 Apr 4;351(9108):1014-8. doi: 10.1016/S0140-6736(97)08295-0.

[55] Haas J, Vogt G, Schiemann M, Patzold U. Aphasia and non-verbal intelligence in brain tumour patients. J Neurol. 1982;227(4):209-18. doi: 10.1007/BF00313388.

[56] Greenblatt SH. Alexia without agraphia or hemianopsia. Anatomical analysis of an autopsied case. Brain. 1973 Jun;96(2):307-16. doi: 10.1093/brain/96.2.307.

[57] Fincham RW, Nibbelink DW, Aschenbrener CA. Alexia with left homonymous hemianopia without agraphia. A case report with autopsy findings. Neurology. 1975 Dec;25(12):1164-8. doi: 10.1212/wnl.25.12.1164. PMID: 1238959.

[58] Davie GL, Hutcheson KA, Barringer DA, Weinbers JS, Lewin JS. Aphasia in patients after brain tumour resection. Aphasiology. 2009 Sep;23(9):1196–1206. doi: 10.1080/02687030802436900

[59] Miceli G, Capasso R, Monti A, Santini B, Talacchi A. Language testing in brain tumor patients. J Neurooncol. 2012 Jun;108(2):247-52. doi: 10.1007/s11060-012-0810-y.

[60] Papagno C, Gallucci M, Casarotti A, Castellano A, Falini A, Fava E, Giussani C, Carrabba G, Bello L, Caramazza A. Connectivity constraints on cortical reorganization

of neural circuits involved in object naming. Neuroimage. 2011 Apr 1;55(3):1306-13. doi: 10.1016/j.neuroimage.2011.01.005.

[61] Cohadon F. Indications for surgery in the management of gliomas. Adv Tech Stand Neurosurg. 1990;17:189-234. doi: 10.1007/978-3-7091-6925-4_6.

[62] Kauhanen ML, Korpelainen JT, Hiltunen P, Määttä R, Mononen H, Brusin E, Sotaniemi KA, Myllylä VV. Aphasia, depression, and non-verbal cognitive impairment in ischaemic stroke. Cerebrovasc Dis. 2000 Nov-Dec;10(6):455-61. doi: 10.1159/000016107.

[63] Kertesz A, Sheppard A. The epidemiology of aphasic and cognitive impairment in stroke: age, sex, aphasia type and laterality differences. Brain. 1981 Mar;104(Pt 1):117-28. doi: 10.1093/brain/104.1.117.

[64] Pashek GV, Holland AL. Evolution of aphasia in the first year post-onset. Cortex. 1988 Sep;24(3):411-23. doi: 10.1016/s0010-9452(88)80004-2.

[65] Pedersen PM, Vinter K, Olsen TS. Aphasia after stroke: type, severity and prognosis. The Copenhagen aphasia study. Cerebrovasc Dis. 2004;17(1):35-43. doi: 10.1159/000073896.

[66] Giovagnoli AR. Crossed aphasia. Report of a rare case in a glioblastoma patient. Ital J Neurol Sci. 1993 May;14(4):329-32. doi: 10.1007/BF02339301.

[67] Vassal M, Le Bars E, Moritz-Gasser S, Menjot N, Duffau H. Crossed aphasia elicited by intraoperative cortical and subcortical stimulation in awake patients. J Neurosurg. 2010 Dec;113(6):1251-8. doi: 10.3171/2010.6.JNS10719.

[68] Zammar SG, Specht CS, Zacharia BE. Crossed Aphasia as a Manifestation of Glioblastoma. Cureus. 2018 Feb 27;10(2):e2239. doi: 10.7759/cureus.2239.

[69] Robert E. Linguistic procedure in “awake neurosurgery”. Stem-, Spraak- en Taalpathologie. 2005 Mar;13(1):54-64.

[70] Meyer FB, Bates LM, Goerss SJ, Friedman JA, Windschitl WL, Duffy JR, Perkins WJ, O'Neill BP. Awake craniotomy for aggressive resection of primary gliomas located in eloquent brain. Mayo Clin Proc. 2001 Jul;76(7):677-87. doi: 10.4065/76.7.677.

[71] Catani M, Thiebaut de Schotten M. A diffusion tensor imaging tractography atlas for virtual in vivo dissections. Cortex. 2008 Sep;44(8):1105-32. doi: 10.1016/j.cortex.2008.05.004.

[72] Hickok G. Computational neuroanatomy of speech production. Nat Rev Neurosci. 2012 Jan 5;13(2):135-45. doi: 10.1038/nrn3158.

[73] Jääskeläinen J, Randell T. Awake craniotomy in glioma surgery. Acta Neurochir Suppl. 2003;88:31-5. doi: 10.1007/978-3-7091-6090-9_6.

[74] World Health Organization. International Classification of Functioning, Disability and Health (ICF). Geneva (Switzerland): World Health Organization; 2001.

[75] Taphoorn MJB. Quality of Life in Low-Grade Gliomas. In: Duffau H, editor. Diffuse Low-Grade Gliomas in Adults. London (UK): Springer; 2013. p. 205-17. doi: 10.1007/978-1-4471-2213-5_14.

[76] Simmons-Mackie N, Kagan A. Application of the ICF in aphasia. Semin Speech Lang. 2007 Nov;28(4):244-53. doi: 10.1055/s-2007-986521.

[77] Efficace F, Bottomley A. Health related quality of life assessment methodology and reported outcomes in randomised controlled trials of primary brain cancer patients. Eur J Cancer. 2002 Sep;38(14):1824-31. doi: 10.1016/s0959-8049(02)00173-9.

[78] Ali FS, Hussain MR, Gutiérrez C, Demireva P, Ballester LY, Zhu JJ, Blanco A, Esquenazi Y. Cognitive disability in adult patients with brain tumors. Cancer Treat Rev. 2018 Apr;65:33-40. doi: 10.1016/j.ctrv.2018.02.007.

[79] De Witte E, Satoer D, Robert E, Colle H, Verheyen S, Visch-Brink E, Mariën P. The Dutch Linguistic Intraoperative Protocol: a valid linguistic approach to awake brain surgery. Brain Lang. 2015 Jan;140:35-48. doi: 10.1016/j.bandl.2014.10.011.

[80] Coomans MB, Dirven L, Taphoorn MJB. Quality of Life and Cognition. In: Tonn JC, Reardon D, Rutka J, Westphal M, editors. Oncology of CNS Tumors. Cham (Switzerland): Springer; 2019. p. 769-86. doi: 10.1007/978-3-030-04152-6_43

[81] Meyers CA, Smith JA, Bezjak A, Mehta MP, Liebmann J, Illidge T, Kunkler I, Caudrelier JM, Eisenberg PD, Meerwaldt J, Siemers R, Carrie C, Gaspar LE, Curran W, Phan SC, Miller RA, Renschler MF. Neurocognitive function and progression in patients with brain metastases treated with whole-brain radiation and motexafin gadolinium: results of a randomized phase III trial. J Clin Oncol. 2004 Jan 1;22(1):157-65. doi: 10.1200/JCO.2004.05.128. PMID: 14701778.

[82] Tucha O, Smely C, Preier M, Lange KW. Cognitive deficits before treatment among patients with brain tumors. Neurosurgery. 2000 Aug;47(2):324-33; discussion 333-4. doi: 10.1097/00006123-200008000-00011.

[83] Wefel JS, Noll KR, Scheurer ME. Neurocognitive functioning and genetic variation in patients with primary brain tumours. Lancet Oncol. 2016 Mar;17(3):e97-e108. doi: 10.1016/S1470-2045(15)00380-0.

[84] Satoer D, Vork J, Visch-Brink E, Smits M, Dirven C, Vincent A. Cognitive functioning early after surgery of gliomas in eloquent areas. J Neurosurg. 2012 Nov;117(5):831-8. doi: 10.3171/2012.7.JNS12263. Epub 2012 Aug 31. PMID: 22937930.

[85] Meskal I, Gehring K, Rutten GJ, Sitskoorn MM. Cognitive functioning in meningioma patients: a systematic review. J Neurooncol. 2016 Jun;128(2):195-205. doi: 10.1007/s11060-016-2115-z.

[86] Crossen JR, Garwood D, Glatstein E, Neuwelt EA. Neurobehavioral sequelae of cranial irradiation in adults: a review of radiation-induced encephalopathy. J Clin Oncol. 1994 Mar;12(3):627-42. doi: 10.1200/JCO.1994.12.3.627.

[87] Habets EJ, Kloet A, Walchenbach R, Vecht CJ, Klein M, Taphoorn MJ. Tumour and surgery effects on cognitive functioning in high-grade glioma patients. Acta Neurochir (Wien). 2014 Aug;156(8):1451-9. doi: 10.1007/s00701-014-2115-8.

[88] Schagen SB, Wefel JS. Chemotherapy-related changes in cognitive functioning. EJC Suppl. 2013 Sep;11(2):225-32. doi: 10.1016/j.ejcsup.2013.07.007.

[89] Wefel JS, Kayl AE, Meyers CA. Neuropsychological dysfunction associated with cancer and cancer therapies: a conceptual review of an emerging target. Br J Cancer. 2004 May 4;90(9):1691-6. doi: 10.1038/sj.bjc.6601772.

[90] Alarcón G, Bird Pedersen M, Juárez-Torrejón N, Martín-López D, Ughratdar I, Selway RP, Valentín A. The Single Word Auditory Comprehension (SWAC) test: A simple method to identify receptive language areas with electrical stimulation. Epilepsy Behav. 2019 Jan;90:266-272. doi: 10.1016/j.yebeh.2018.10.022.

[91] Corina DP, Gibson EK, Martin R, Poliakov A, Brinkley J, Ojemann GA. Dissociation of action and object naming: evidence from cortical stimulation mapping. Hum Brain Mapp. 2005 Jan;24(1):1-10. doi: 10.1002/hbm.20063.

[92] Serafini S, Clyde M, Tolson M, Haglund MM. Multimodality word-finding distinctions in cortical stimulation mapping. Neurosurgery. 2013 Jul;73(1):36-47; discussion 47. doi: 10.1227/01.neu.0000429861.42394.d8.

[93] Gabarrós A, Young WL, McDermott MW, Lawton MT. Language and motor mapping during resection of brain arteriovenous malformations: indications, feasibility, and utility. Neurosurgery. 2011 Mar;68(3):744-52. doi: 10.1227/NEU.0b013e318207a9a7. PMID: 21311300.

[94] Gamble AJ, Schaffer SG, Nardi DJ, Chalif DJ, Katz J, Dehdashti AR. Awake Craniotomy in Arteriovenous Malformation Surgery: The Usefulness of Cortical and Subcortical Mapping of Language Function in Selected Patients. World Neurosurg. 2015 Nov;84(5):1394-401. doi: 10.1016/j.wneu.2015.06.059.

[95] Lawton MT, Rutledge WC, Kim H, Stapf C, Whitehead KJ, Li DY, Krings T, terBrugge K, Kondziolka D, Morgan MK, Moon K, Spetzler RF. Brain arteriovenous malformations. Nat Rev Dis Primers. 2015 May 28;1:15008. doi: 10.1038/nrdp.2015.8. PMID: 27188382.

[96] Crawford PM, West CR, Shaw MD, Chadwick DW. Cerebral arteriovenous malformations and epilepsy: factors in the development of epilepsy. Epilepsia. 1986 May-Jun;27(3):270-5. doi: 10.1111/j.1528-1157.1986.tb03539.x.

[97] Ondra SL, Troupp H, George ED, Schwab K. The natural history of symptomatic arteriovenous malformations of the brain: a 24-year follow-up assessment. J Neurosurg. 1990 Sep;73(3):387-91. doi: 10.3171/jns.1990.73.3.0387.

[98] Englot DJ, Young WL, Han SJ, McCulloch CE, Chang EF, Lawton MT. Seizure predictors and control after microsurgical resection of supratentorial arteriovenous malformations in 440 patients. Neurosurgery. 2012 Sep;71(3):572-80; discussion 580. doi: 10.1227/NEU.0b013e31825ea3ba.

[99] de Souza Coelho D, de Oliveira Santos BF, da Costa MDS, Silva GS, Cavalheiro S, Santos FH, Chaddad-Neto F. Cognitive performance in patients with cerebral arteriovenous malformation. J Neurosurg. 2019 Aug 1:1-8. doi: 10.3171/2018.12.JNS181883.

[100] Surbeck W, Hildebrandt G, Duffau H. The evolution of brain surgery on awake patients. Acta Neurochir (Wien). 2015 Jan;157(1):77-84. doi: 10.1007/s00701-014-2249-8.

[101] Georgiadis I, Kapsalaki EZ, Fountas KN. Temporal lobe resective surgery for medically intractable epilepsy: a review of complications and side effects. Epilepsy Res Treat. 2013;2013:752195. doi: 10.1155/2013/752195.

[102] Wiebe S, Blume WT, Girvin JP, Eliasziw M; Effectiveness and Efficiency of Surgery for Temporal Lobe Epilepsy Study Group. A randomized, controlled trial of surgery for temporal-lobe epilepsy. N Engl J Med. 2001 Aug 2;345(5):311-8. doi: 10.1056/NEJM200108023450501.

[103] Schuele SU, Lüders HO. Intractable epilepsy: management and therapeutic alternatives. Lancet Neurol. 2008 Jun;7(6):514-24. doi: 10.1016/S1474-4422(08)70108-X.

[104] Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, Moshé SL, Perucca E, Wiebe S, French J. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia. 2010 Jun;51(6):1069-77. doi: 10.1111/j.1528-1167.2009.02397.x. Erratum in: Epilepsia. 2010 Sep;51(9):1922.

[105] Salanova V, Markand O, Worth R. Temporal lobe epilepsy surgery: outcome, complications, and late mortality rate in 215 patients. Epilepsia. 2002 Feb;43(2):170-4. doi: 10.1046/j.1528-1157.2002.33800.x.

[106] Tanriverdi T, Ajlan A, Poulin N, Olivier A. Morbidity in epilepsy surgery: an experience based on 2449 epilepsy surgery procedures from a single institution. J Neurosurg. 2009 Jun;110(6):1111-23. doi: 10.3171/2009.8.JNS08338.

[107] Hamberger MJ. Cortical language mapping in epilepsy: a critical review. Neuropsychol Rev. 2007 Dec;17(4):477-89. doi: 10.1007/s11065-007-9046-6. Epub 2007 Nov 16. PMID: 18004662.

[108] Sommer B, Grummich P, Coras R, Kasper BS, Blumcke I, Hamer HM, Stefan H, Buchfelder M, Roessler K. Integration of functional neuronavigation and intraoperative MRI in surgery for drug-resistant extratemporal epilepsy close to eloquent brain areas. Neurosurg Focus. 2013 Apr;34(4):E4. doi: 10.3171/2013.2.FOCUS12397.

[109] Zhang X, Zhang G, Yu T, Ni D, Cai L, Qiao L, Du W, Li Y. Surgical treatment for epilepsy involving language cortices: a combined process of electrical cortical stimulation mapping and intra-operative continuous language assessment. Seizure. 2013 Nov;22(9):780-6. doi: 10.1016/j.seizure.2013.06.006.

[110] Brown T, Shah AH, Bregy A, Shah NH, Thambuswamy M, Barbarite E, Fuhrman T, Komotar RJ. Awake craniotomy for brain tumor resection: the rule rather than the exception? J Neurosurg Anesthesiol. 2013 Jul;25(3):240-7. doi: 10.1097/ANA.0b013e318290c230.

[111] Thomas R, O'Connor AM, Ashley S. Speech and language disorders in patients with high grade glioma and its influence on prognosis. J Neurooncol. 1995;23(3):265-70. doi: 10.1007/BF01059960.

[112] Duffau H, Lopes M, Arthuis F, Bitar A, Sichez JP, Van Effenterre R, Capelle L. Contribution of intraoperative electrical stimulations in surgery of low grade gliomas: a comparative study between two series without (1985-96) and with (1996-2003) functional mapping in the same institution. J Neurol Neurosurg Psychiatry. 2005 Jun;76(6):845-51. doi: 10.1136/jnnp.2004.048520.

[113] Duffau H. Surgery of low-grade gliomas: towards a 'functional neurooncology'. Curr Opin Oncol. 2009 Nov;21(6):543-9. doi: 10.1097/CCO.0b013e3283305996.

[114] Duffau H, Moritz-Gasser S, Gatignol P. Functional outcome after language mapping for insular World Health Organization Grade II gliomas in the dominant hemisphere: experience with 24 patients. Neurosurg Focus. 2009 Aug;27(2):E7. doi: 10.3171/2009.5.FOCUS0938.

[115] Spena G, Nava A, Cassini F, Pepoli A, Bruno M, D'Agata F, Cauda F, Sacco K, Duca S, Barletta L, Versari P. Preoperative and intraoperative brain mapping for the resection of eloquent-area tumors. A prospective analysis of methodology, correlation, and usefulness based on clinical outcomes. Acta Neurochir (Wien). 2010 Nov;152(11):1835-46. doi: 10.1007/s00701-010-0764-9.

[116] Tonn JC. Awake craniotomy for monitoring of language function: benefits and limits. Acta Neurochir (Wien). 2007 Dec;149(12):1197-8. doi: 10.1007/s00701-007-1368-x.

[117] Claus EB, Black PM. Survival rates and patterns of care for patients diagnosed with supratentorial low-grade gliomas: data from the SEER program, 1973-2001. Cancer. 2006 Mar 15;106(6):1358-63. doi: 10.1002/cncr.21733. PMID: 16470608.

[118] Zanin E, Riva M, Bambini V, Cappa SF, Magrassi L, Moro A. The contribution of surgical brain mapping to the understanding of the anatomo-functional basis of syntax: A critical review. Neurol Sci. 2017 Sep;38(9):1579-1589. doi: 10.1007/s10072-017-3016-4.

[119] Berger MS, Ojemann GA. Intraoperative brain mapping techniques in neuro-oncology. Stereotact Funct Neurosurg. 1992;58(1-4):153-61. doi: 10.1159/000098989.

[120] Duffau H. Brain mapping: from neural basis of cognition to surgical applications. Duffau H, editor. New York: Springer Wien; 2011.

[121] Bertani G, Fava E, Casaceli G, Carrabba G, Casarotti A, Papagno C, Castellano A, Falini A, Gaini SM, Bello L. Intraoperative mapping and monitoring of brain functions for the resection of low-grade gliomas: technical considerations. Neurosurg Focus. 2009 Oct;27(4):E4. doi: 10.3171/2009.8.FOCUS09137.

[122] Grossman R, Nossek E, Sitt R, Hayat D, Shahar T, Barzilai O, Gonen T, Korn A, Sela G, Ram Z. Outcome of elderly patients undergoing awake-craniotomy for tumor resection. Ann Surg Oncol. 2013 May;20(5):1722-8. doi: 10.1245/s10434-012-2748-x.

[123] Pallud J, Dezamis E. Functional and oncological outcomes following awake surgical resection using intraoperative cortico-subcortical functional mapping for supratentorial gliomas located in eloquent areas. Neurochirurgie. 2017 Jun;63(3):208-218. doi: 10.1016/j.neuchi.2016.08.003.

[124] Zemmoura I, Herbet G, Moritz-Gasser S, Duffau H. New insights into the neural network mediating reading processes provided by cortico-subcortical electrical mapping. Hum Brain Mapp. 2015 Jun;36(6):2215-30. doi: 10.1002/hbm.22766.

[125] Bello L, Gallucci M, Fava M, Carrabba G, Giussani C, Acerbi F, Baratta P, Songa V, Conte V, Branca V, Stocchetti N, Papagno C, Gaini SM. Intraoperative subcortical language tract mapping guides surgical removal of gliomas involving speech areas. Neurosurgery. 2007 Jan;60(1):67-80; discussion 80-2. doi: 10.1227/01.NEU.0000249206.58601.DE.

[126] Duffau H, Capelle L, Sichez N, Denvil D, Lopes M, Sichez JP, Bitar A, Fohanno D. Intraoperative mapping of the subcortical language pathways using direct stimulations. An anatomo-functional study. Brain. 2002 Jan;125(Pt 1):199-214. doi: 10.1093/brain/awf016.

[127] Hulou MM, Cote DJ, Olubiyi OI, Smith TR, Chiocca EA, Johnson MD. Awake right hemisphere brain surgery. J Clin Neurosci. 2015 Dec;22(12):1921-7. doi: 10.1016/j.jocn.2015.06.009.

[128] Vilasboas T, Herbet G, Duffau H. Challenging the Myth of Right Nondominant Hemisphere: Lessons from Corticosubcortical Stimulation Mapping in Awake Surgery

and Surgical Implications. World Neurosurg. 2017 Jul;103:449-456. doi: 10.1016/j.wneu.2017.04.021.

[129] Hervey-Jumper SL, Li J, Lau D, Molinaro AM, Perry DW, Meng L, Berger MS. Awake craniotomy to maximize glioma resection: methods and technical nuances over a 27-year period. J Neurosurg. 2015 Aug;123(2):325-39. doi: 10.3171/2014.10.JNS141520.

[130] Kanno A, Mikuni N. Evaluation of Language Function under Awake Craniotomy. Neurol Med Chir (Tokyo). 2015;55(5):367-73. doi: 10.2176/nmc.ra.2014-0395.

[131] Kemerdere R, de Champfleur NM, Deverdun J, Cochereau J, Moritz-Gasser S, Herbet G, Duffau H. Role of the left frontal aslant tract in stuttering: a brain stimulation and tractographic study. J Neurol. 2016 Jan;263(1):157-67. doi: 10.1007/s00415-015-7949-3.

[132] Schapiro R, Ferson D, Prabhu SS, Tummula S, Wefel J, Rao G. A technique for mapping cortical areas associated with speech arrest. Stereotact Funct Neurosurg. 2012;90(2):118-23. doi: 10.1159/000335500.

[133] Herbet G, Moritz-Gasser S. Beyond Language: Mapping Cognition and Emotion. Neurosurg Clin N Am. 2019 Jan;30(1):75-83. doi: 10.1016/j.nec.2018.08.004.

[134] Mazerand E, Le Renard M, Hue S, Lemée JM, Klinger E, Menei P. Intraoperative Subcortical Electrical Mapping of the Optic Tract in Awake Surgery Using a Virtual Reality Headset. World Neurosurg. 2017 Jan;97:424-430. doi: 10.1016/j.wneu.2016.10.031.

[135] Ruis C. Monitoring cognition during awake brain surgery in adults: A systematic review. J Clin Exp Neuropsychol. 2018 Dec;40(10):1081-1104. doi: 10.1080/13803395.2018.1469602.

[136] Riva M, Casarotti A, Comi A, Pessina F, Bello L. Brain and Music: An Intraoperative Stimulation Mapping Study of a Professional Opera Singer. World Neurosurg. 2016 Sep;93:486.e13-8. doi: 10.1016/j.wneu.2016.06.130.

[137] Becker J, Jehna M, Steinmann E, Mehdorn HM, Synowitz M, Hartwigsen G. The sensory-motor profile awake-A new tool for pre-, intra-, and postoperative assessment of sensory-motor function. Clin Neurol Neurosurg. 2016 Aug;147:39-45. doi: 10.1016/j.clineuro.2016.05.022.

[138] Lucas TH 2nd, McKhann GM 2nd, Ojemann GA. Functional separation of languages in the bilingual brain: a comparison of electrical stimulation language mapping in 25 bilingual patients and 117 monolingual control patients. J Neurosurg. 2004 Sep;101(3):449-57. doi: 10.3171/jns.2004.101.3.0449.

[139] Roux FE, Lubrano V, Lauwers-Cances V, Trémoulet M, Mascott CR, Démonet JF. Intra-operative mapping of cortical areas involved in reading in mono- and bilingual patients. Brain. 2004 Aug;127(Pt 8):1796-810. doi: 10.1093/brain/awh204.

[140] Sierpowska J, Gabarrós A, Fernández-Coello A, Camins À, Castañer S, Juncadella M, François C, Rodríguez-Fornells A. White-matter pathways and semantic processing: intrasurgical and lesion-symptom mapping evidence. Neuroimage Clin. 2019;22:101704. doi: 10.1016/j.nicl.2019.101704.

[141] Kayama T; Guidelines committee of the Japan awake surgery conference. The guidelines for awake craniotomy guidelines committee of the Japan awake surgery conference. Neurol Med Chir (Tokyo). 2012;52(3):119-41. doi: 10.2176/nmc.52.119.

[142] Lohkamp LN, Mottolese C, Szathmari A, Huguet L, Beuriat PA, Christofori I, Desmurget M, Di Rocco F. Awake brain surgery in children-review of the literature and state-of-the-art. Childs Nerv Syst. 2019 Nov;35(11):2071-2077. doi: 10.1007/s00381-019-04279-w.

[143] Trevisi G, Roujeau T, Duffau H. Awake surgery for hemispheric low-grade gliomas: oncological, functional and methodological differences between pediatric and adult populations. Childs Nerv Syst. 2016 Oct;32(10):1861-74. doi: 10.1007/s00381-016-3069-3.

[144] Patil CG, Veeravagu A, Lad SP, Boakye M. Craniotomy for resection of meningioma in the elderly: a multicentre, prospective analysis from the National Surgical Quality Improvement Program. J Neurol Neurosurg Psychiatry. 2010 May;81(5):502-5. doi: 10.1136/jnnp.2009.185074.

[145] Balogun JA, Khan OH, Taylor M, Dirks P, Der T, Carter Snead Iii O, Weiss S, Ochi A, Drake J, Rutka JT. Pediatric awake craniotomy and intra-operative stimulation mapping. J Clin Neurosci. 2014 Nov;21(11):1891-4. doi: 10.1016/j.jocn.2014.07.013.

[146] Delion M, Terminassian A, Lehousse T, Aubin G, Malka J, N'Guyen S, Mercier P, Menei P. Specificities of Awake Craniotomy and Brain Mapping in Children for Resection of Supratentorial Tumors in the Language Area. World Neurosurg. 2015 Dec;84(6):1645-52. doi: 10.1016/j.wneu.2015.06.073. Epub 2015 Jul 9. PMID: 26164190.

[147] Young RJ, Brennan N, Fraser JF, Brennan C. Advanced imaging in brain tumor surgery. Neuroimaging Clin N Am. 2010 Aug;20(3):311-35. doi: 10.1016/j.nic.2010.04.011.

[148] Fountas KN, Kapsalaki EZ, Gotsis SD, Kapsalakis JZ, Smisson HF 3rd, Johnston KW, Robinson JS Jr, Papadakis N. In vivo proton magnetic resonance spectroscopy of brain tumors. Stereotact Funct Neurosurg. 2000;74(2):83-94. doi: 10.1159/000056467.

[149] Tsolaki E, Kousi E, Svolos P, Kapsalaki E, Theodorou K, Kappas C, Tsougos I. Clinical decision support systems for brain tumor characterization using advanced magnetic resonance imaging techniques. World J Radiol. 2014 Apr 28;6(4):72-81. doi: 10.4329/wjr.v6.i4.72.

[150] Jung J, Lavrador JP, Patel S, Giamouriadis A, Lam J, Bhangoo R, Ashkan K, Vergani F. First United Kingdom Experience of Navigated Transcranial Magnetic Stimulation in Preoperative Mapping of Brain Tumors. World Neurosurg. 2019 Feb;122:e1578-e1587. doi: 10.1016/j.wneu.2018.11.114.

[151] Mäkelä JP, Forss N, Jääskeläinen J, Kirveskari E, Korvenoja A, Paetau R. Magnetoencephalography in neurosurgery. Neurosurgery. 2006 Sep;59(3):493-510; discussion 510-1. doi: 10.1227/01.NEU.0000232762.63508.11.

[152] Castillo EM, Simos PG, Wheless JW, Baumgartner JE, Breier JI, Billingsley RL, Sarkari S, Fitzgerald ME, Papanicolaou AC. Integrating sensory and motor mapping in a comprehensive MEG protocol: clinical validity and replicability. Neuroimage. 2004 Mar;21(3):973-83. doi: 10.1016/j.neuroimage.2003.10.020.

[153] Kamada K, Houkin K, Takeuchi F, Ishii N, Ikeda J, Sawamura Y, Kuriki S, Kawaguchi H, Iwasaki Y. Visualization of the eloquent motor system by integration of MEG, functional, and anisotropic diffusion-weighted MRI in functional neuronavigation. Surg Neurol. 2003 May;59(5):352-61; discussion 361-2. doi: 10.1016/s0090-3019(03)00018-1.

[154] Korvenoja A, Kirveskari E, Aronen HJ, Avikainen S, Brander A, Huttunen J, Ilmoniemi RJ, Jääskeläinen JE, Kovala T, Mäkelä JP, Salli E, Seppä M. Sensorimotor cortex localization: comparison of magnetoencephalography, functional MR imaging, and intraoperative cortical mapping. Radiology. 2006 Oct;241(1):213-22. doi: 10.1148/radiol.2411050796.

[155] Hyder R, Kamel N, Boon TT, Reza F. Mapping of language brain areas in patients with brain tumors. Annu Int Conf IEEE Eng Med Biol Soc. 2015 Aug;2015:626-9. doi: 10.1109/EMBC.2015.7318440.

[156] Traut T, Sardesh N, Bulubas L, Findlay A, Honma SM, Mizuiri D, Berger MS, Hinkley LB, Nagarajan SS, Tarapore PE. MEG imaging of recurrent gliomas reveals functional plasticity of hemispheric language specialization. Hum Brain Mapp. 2019 Mar;40(4):1082-1092. doi: 10.1002/hbm.24430.

[157] Zimmermann M, Rössler K, Kaltenhäuser M, Grummich P, Brandner N, Buchfelder M, Dörfler A, Kölble K, Stadlbauer A. Comparative fMRI and MEG localization of cortical sensorimotor function: Bimodal mapping supports motor area reorganization in glioma patients. PLoS One. 2019 Mar 7;14(3):e0213371. doi: 10.1371/journal.pone.0213371.

[158] Bizzi A. Presurgical mapping of verbal language in brain tumors with functional MR imaging and MR tractography. Neuroimaging Clin N Am. 2009 Nov;19(4):573-96. doi: 10.1016/j.nic.2009.08.010.

[159] Hirsch J, Ruge MI, Kim KH, Correa DD, Victor JD, Relkin NR, Labar DR, Krol G, Bilsky MH, Souweidane MM, DeAngelis LM, Gutin PH. An integrated functional magnetic resonance imaging procedure for preoperative mapping of cortical areas associated with tactile, motor, language, and visual functions. Neurosurgery. 2000 Sep;47(3):711-21; discussion 721-2. doi: 10.1097/00006123-200009000-00037.

[160] Kuchcinski G, Mellerio C, Pallud J, Dezamis E, Turc G, Rigaux-Viodé O, Malherbe C, Roca P, Leclerc X, Varlet P, Chrétien F, Devaux B, Meder JF, Oppenheim C. Three-tesla functional MR language mapping: comparison with direct cortical stimulation in gliomas. Neurology. 2015 Feb 10;84(6):560-8. doi: 10.1212/WNL.0000000000001226.

[161] Stippich C, Rapps N, Dreyhaupt J, Durst A, Kress B, Nennig E, Tronnier VM, Sartor K. Localizing and lateralizing language in patients with brain tumors: feasibility of routine preoperative functional MR imaging in 81 consecutive patients. Radiology. 2007 Jun;243(3):828-36. doi: 10.1148/radiol.2433060068.

[162] Giussani C, Roux FE, Ojemann J, Sganzerla EP, Pirillo D, Papagno C. Is preoperative functional magnetic resonance imaging reliable for language areas mapping in brain tumor surgery? Review of language functional magnetic resonance imaging and direct cortical stimulation correlation studies. Neurosurgery. 2010 Jan;66(1):113-20. doi: 10.1227/01.NEU.0000360392.15450.C9.

[163] Duffau H. Contribution of cortical and subcortical electrostimulation in brain glioma surgery: methodological and functional considerations. Neurophysiol Clin. 2007 Dec;37(6):373-82. doi: 10.1016/j.neucli.2007.09.003.

[164] Mandonnet E, Sarubbo S, Duffau H. Proposal of an optimized strategy for intraoperative testing of speech and language during awake mapping. Neurosurg Rev. 2017 Jan;40(1):29-35. doi: 10.1007/s10143-016-0723-x.

[165] Meyer FB, Bates LM, Goerss SJ, Friedman JA, Windschitl WL, Duffy JR, Perkins WJ, O'Neill BP. Awake craniotomy for aggressive resection of primary gliomas located in eloquent brain. Mayo Clin Proc. 2001 Jul;76(7):677-87. doi: 10.4065/76.7.677.

[166] Trimble G, McStravick C, Farling P, Megaw K, McKinstry S, Smyth G, Law G, Courtney H, Quigley G, Flannery T. Awake craniotomy for glioma resection: Technical aspects and initial results in a single institution. Br J Neurosurg. 2015;29(6):836-42. doi: 10.3109/02688697.2015.1054354.

[167] Wager M, Du Boisgueheneuc F, Pluchon C, Bouyer C, Stal V, Bataille B, Guillevin CM, Gil R. Intraoperative monitoring of an aspect of executive functions: administration of the Stroop test in 9 adult patients during awake surgery for resection

of frontal glioma. Neurosurgery. 2013 Jun;72(2 Suppl Operative):ons169-80; discussion ons180-1. doi: 10.1227/NEU.0b013e31827bf1d6.

[168] Rofes A, Spena G, Talacchi A, Santini B, Miozzo A, Miceli G. Mapping nouns and finite verbs in left hemisphere tumors: a direct electrical stimulation study. Neurocase. 2017 Apr;23(2):105-113. doi: 10.1080/13554794.2017.1307418.

[169] De Witte E, Satoer D, Visch-Brink E, Mariën P. Letter to the editor regarding Bilotta et al. 2014 Diagnostic work up for language testing in patients undergoing awake craniotomy for brain lesions in language areas. Br J Neurosurg. 2015;29(4):606-7. doi: 10.3109/02688697.2015.1071335.

[170] Rofes A, Mandonnet E, Godden J, Baron MH, Colle H, Darlix A, de Aguiar V, Duffau H, Herbet G, Klein M, Lubrano V, Martino J, Mathew R, Miceli G, Moritz-Gasser S, Pallud J, Papagno C, Rech F, Robert E, Rutten GJ, Santarius T, Satoer D, Sierpowska J, Smits A, Skrap M, Spena G, Visch E, De Witte E, Zetterling M, Wager M. Survey on current cognitive practices within the European Low-Grade Glioma Network: towards a European assessment protocol. Acta Neurochir (Wien). 2017 Jul;159(7):1167-1178. doi: 10.1007/s00701-017-3192-2.

[171] Herbet G, Rigaux-Viodé O, Moritz-Gasser S. Peri- and intraoperative cognitive and language assessment for surgical resection in brain eloquent structures. Neurochirurgie. 2017 Jun;63(3):135-141. doi: 10.1016/j.neuchi.2016.10.011.

[172] Rofes A, Spena G, Miozzo A, Fontanella MM, Miceli G. Advantages and disadvantages of intraoperative language tasks in awake surgery: a three-task approach for prefrontal tumors. J Neurosurg Sci. 2015 Dec;59(4):337-49.

[173] Borius PY, Giussani C, Draper L, Roux FE. Sentence translation in proficient bilinguals: a direct electrostimulation brain mapping. Cortex. 2012 May;48(5):614-22. doi: 10.1016/j.cortex.2011.01.011.

[174] De Witte E, Van Hecke W, Dua G, De Surgeloose D, Moens M, Mariën P. Atypical cerebral language dominance in a right-handed patient: An anatomoclinical study. Clin Neurol Neurosurg. 2014 Feb;117:12-21. doi: 10.1016/j.clineuro.2013.11.014.

[175] Sierpowska J, Gabarrós A, Ripollés P, Juncadella M, Castañer S, Camins Á, Plans G, Rodríguez-Fornells A. Intraoperative electrical stimulation of language switching in two bilingual patients. Neuropsychologia. 2013 Nov;51(13):2882-92. doi: 10.1016/j.neuropsychologia.2013.09.003.

[176] Ilmberger J, Ruge M, Kreth FW, Briegel J, Reulen HJ, Tonn JC. Intraoperative mapping of language functions: a longitudinal neurolinguistic analysis. J Neurosurg. 2008 Oct;109(4):583-92. doi: 10.3171/JNS/2008/109/10/0583.

[177] Bilotta F, Stazi E, Delfini R, Rosa G. Language testing during awake "anesthesia" in a bilingual patient with brain lesion adjacent to Wernicke's area. Anesth Analg. 2011

Apr;112(4):938-9. doi: 10.1213/ANE.0b013e31820bd1a4. Epub 2011 Feb 2. PMID: 21288971.

[178] Fujii M, Maesawa S, Motomura K, Futamura M, Hayashi Y, Koba I, Wakabayashi T. Intraoperative subcortical mapping of a language-associated deep frontal tract connecting the superior frontal gyrus to Broca's area in the dominant hemisphere of patients with glioma. J Neurosurg. 2015 Jun;122(6):1390-6. doi: 10.3171/2014.10.JNS14945.

[179] Lubrano V, Draper L, Roux FE. What makes surgical tumor resection feasible in Broca's area? Insights into intraoperative brain mapping. Neurosurgery. 2010 May;66(5):868-75; discussion 875. doi: 10.1227/01.NEU.0000368442.92290.04.

[180] Moritz-Gasser S, Herbet G, Duffau H. Mapping the connectivity underlying multimodal (verbal and non-verbal) semantic processing: a brain electrostimulation study. Neuropsychologia. 2013 Aug;51(10):1814-22. doi: 10.1016/j.neuropsychologia.2013.06.007.

[181] Costello TG. Awake craniotomy and multilingualism: language testing during anaesthesia for awake craniotomy in a bilingual patient. J Clin Neurosci. 2014 Aug;21(8):1469-70. doi: 10.1016/j.jocn.2013.11.053.

[182] Tomasino B, Marin D, Canderan C, Maieron M, Budai R, Fabbro F, Skrap M. Involuntary switching into the native language induced by electrocortical stimulation of the superior temporal gyrus: a multimodal mapping study. Neuropsychologia. 2014 Sep;62:87-100. doi: 10.1016/j.neuropsychologia.2014.07.011.

[183] Rofes A, de Aguiar V, Miceli G. A minimal standardization setting for language mapping tests: an Italian example. Neurol Sci. 2015 Jul;36(7):1113-9. doi: 10.1007/s10072-015-2192-3.

[184] Ries SK, Piai V, Perry D, Griffin S, Jordan K, Henry R, Knight RT, Berger MS. Roles of ventral versus dorsal pathways in language production: An awake language mapping study. Brain Lang. 2019 Apr;191:17-27. doi: 10.1016/j.bandl.2019.01.001.

[185] Rofes A, Miceli G. Language mapping with verbs and sentences in awake surgery: a review. Neuropsychol Rev. 2014 Jun;24(2):185-99. doi: 10.1007/s11065-014-9258-5.

[186] Goebel S, Nabavi A, Schubert S, Mehdorn HM. Patient perception of combined awake brain tumor surgery and intraoperative 1.5-T magnetic resonance imaging: the Kiel experience. Neurosurgery. 2010 Sep;67(3):594-600; discussion 600. doi: 10.1227/01.NEU.0000374870.46963.BB.

[187] Meskelevicius D, Schäfer A, Weber JK, Hegmann L, Haddad L, Kamp MA, Mainzer B, Rapp M, Steiger HJ, Sabel M. Determination of optimal time window for cortical mapping in awake craniotomy: assessment of intraoperative reaction speed. Neurosurg Rev. 2020 Apr;43(2):633-642. doi: 10.1007/s10143-019-01094-4.

[188] Wahab SS, Grundy PL, Weidmann C. Patient experience and satisfaction with awake craniotomy for brain tumours. Br J Neurosurg. 2011 Oct;25(5):606-13. doi: 10.3109/02688697.2011.568642.

[189] Turkstra LS, Coelho C, Ylvisaker M. The use of standardized tests for individuals with cognitive-communication disorders. Semin Speech Lang. 2005 Nov;26(4):215-22. doi: 10.1055/s-2005-922101.

[190] Glaser R, Nitko J. Measurement in learning and instruction. In: Thorndike RL, editor. Educational measurement. 2nd ed. Washington (DC): American Council on Education; 1971. p. 625-70.

[191] Anastasi A, Urbina S. Psychological testing. Upper Saddle River (NJ): Prentice Hall; 1997

[192] Polczynska MM. New tests for language mapping with intraoperative electrical stimulation of the brain to preserve language in individuals with tumors and epilepsy: A preliminary follow-up study. Poznań Stud Contemp Linguist. 2009 Jun;45(2):261-79. doi: 10.2478/v10010-009-0015-5

[193] Duffau H. Mapping the connectome in awake surgery for gliomas: an update. J Neurosurg Sci. 2017 Dec;61(6):612-630. doi: 10.23736/S0390-5616.17.04017-6. Epub 2017 Mar 6. PMID: 28263047.

[194] Arksey H, O'Malley L. Scoping studies: towards a methodological framework. Int J Soc Res Methodol. 2005; 8(1):19-32. doi: 10.1080/1364557032000119616

[195] Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, Moher D, Peters MDJ, Horsley T, Weeks L, Hempel S, Akl EA, Chang C, McGowan J, Stewart L, Hartling L, Aldcroft A, Wilson MG, Garritty C, Lewin S, Godfrey CM, Macdonald MT, Langlois EV, Soares-Weiser K, Moriarty J, Clifford T, Tunçalp Ö, Straus SE. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. Ann Intern Med. 2018 Oct 2;169(7):467-473. doi: 10.7326/M18-0850.

[196] Tricco AC, Lillie E, Zarin W, O'Brien K, Colquhoun H, Kastner M, Levac D, Ng C, Sharpe JP, Wilson K, Kenny M, Warren R, Wilson C, Stelfox HT, Straus SE. A scoping review on the conduct and reporting of scoping reviews. BMC Med Res Methodol. 2016 Feb 9;16:15. doi: 10.1186/s12874-016-0116-4.

[197] Kilbride RD. Intraoperative functional cortical mapping of language. J Clin Neurophysiol. 2013 Dec;30(6):591-6. doi: 10.1097/01.wnp.0000436900.48243.9f.

[198] Saito T, Tamura M, Muragaki Y, Maruyama T, Kubota Y, Fukuchi S, Nitta M, Chernov M, Okamoto S, Sugiyama K, Kurisu K, Sakai KL, Okada Y, Iseki H. Intraoperative cortico-cortical evoked potentials for the evaluation of language function during brain tumor resection: initial experience with 13 cases. J Neurosurg. 2014 Oct;121(4):827-38. doi: 10.3171/2014.4.JNS131195.

[199] Ille S, Sollmann N, Hauck T, Maurer S, Tanigawa N, Obermueller T, Negwer C, Droese D, Zimmer C, Meyer B, Ringel F, Krieg SM. Combined noninvasive language mapping by navigated transcranial magnetic stimulation and functional MRI and its comparison with direct cortical stimulation. J Neurosurg. 2015 Jul;123(1):212-25. doi: 10.3171/2014.9.JNS14929.

[200] Bilotta F, Stazi E, Titi L, Lalli D, Delfini R, Santoro A, Rosa G. Diagnostic work up for language testing in patients undergoing awake craniotomy for brain lesions in language areas. Br J Neurosurg. 2014 Jun;28(3):363-7. doi: 10.3109/02688697.2013.854313.

[201] Motomura K, Chalise L, Ohka F, Aoki K, Tanahashi K, Hirano M, Nishikawa T, Yamaguchi J, Shimizu H, Wakabayashi T, Natsume A. Neurocognitive and functional outcomes in patients with diffuse frontal lower-grade gliomas undergoing intraoperative awake brain mapping. J Neurosurg. 2019 May 17:1-9. doi: 10.3171/2019.3.JNS19211.

[202] Sobottka SB, Bredow J, Beuthien-Baumann B, Reiss G, Schackert G, Steinmeier R. Comparison of functional brain PET images and intraoperative brain-mapping data using image-guided surgery. Comput Aided Surg. 2002;7(6):317-25. doi: 10.1002/igs.10060.

[203] Picht T, Kombos T, Gramm HJ, Brock M, Suess O. Multimodal protocol for awake craniotomy in language cortex tumour surgery. Acta Neurochir (Wien). 2006 Feb;148(2):127-37; discussion 137-8. doi: 10.1007/s00701-005-0706-0.

[204] Leal RTM, Barcellos BM, Landeiro JA. Technical Aspects of Awake Craniotomy with Mapping for Brain Tumors in a Limited Resource Setting. World Neurosurg. 2018 May;113:67-72. doi: 10.1016/j.wneu.2018.02.013.

[205] Skrap M, Marin D, Ius T, Fabbro F, Tomasino B. Brain mapping: a novel intraoperative neuropsychological approach. J Neurosurg. 2016 Oct;125(4):877-887. doi: 10.3171/2015.10.JNS15740.

[206] Whittle IR, Borthwick S, Haq N. Brain dysfunction following 'awake' craniotomy, brain mapping and resection of glioma. Br J Neurosurg. 2003 Apr;17(2):130-7. doi: 10.1080/0268869031000108873.

[207] Ott C, Kerscher C, Luerding R, Doenitz C, Hoehne J, Zech N, Seemann M, Schlaier J, Brawanski A. The impact of sedation on brain mapping: a prospective, interdisciplinary, clinical trial. Neurosurgery. 2014 Aug;75(2):117-23; discussion 123; quiz 123. doi: 10.1227/NEU.0000000000000359. PMID: 24691469.

[208] Low D, Ng I, Ng WH. Awake craniotomy under local anaesthesia and monitored conscious sedation for resection of brain tumours in eloquent cortex--outcomes in 20 patients. Ann Acad Med Singap. 2007 May;36(5):326-31.

[209] Kim SS, McCutcheon IE, Suki D, Weinberg JS, Sawaya R, Lang FF, Ferson D, Heimberger AB, DeMonte F, Prabhu SS. Awake craniotomy for brain tumors near eloquent cortex: correlation of intraoperative cortical mapping with neurological outcomes in 309 consecutive patients. Neurosurgery. 2009 May;64(5):836-45; discussion 345-6. doi: 10.1227/01.NEU.0000342405.80881.81.

[210] Bello L, Acerbi F, Giussani C, Baratta P, Taccone P, Songa V, Fava M, Stocchetti N, Papagno C, Gaini SM. Intraoperative language localization in multilingual patients with gliomas. Neurosurgery. 2006 Jul;59(1):115-25; discussion 115-25. doi: 10.1227/01.NEU.0000219241.92246.FB. PMID: 16823307.

[211] Gonen T, Sela G, Yanakee R, Ram Z, Grossman R. Surgery-Independent Language Function Decline in Patients Undergoing Awake Craniotomy. World Neurosurg. 2017 Mar;99:674-679. doi: 10.1016/j.wneu.2016.12.081. Epub 2016 Dec 27. PMID: 28034812.

[212] Gil-Robles S, Carvallo A, Jimenez Mdel M, Gomez Caicoya A, Martinez R, Ruiz-Ocaña C, Duffau H. Double dissociation between visual recognition and picture naming: a study of the visual language connectivity using tractography and brain stimulation. Neurosurgery. 2013 Apr;72(4):678-86. doi: 10.1227/NEU.0b013e318282a361.

[213] Gil Robles S, Gatignol P, Capelle L, Mitchell MC, Duffau H. The role of dominant striatum in language: a study using intraoperative electrical stimulations. J Neurol Neurosurg Psychiatry. 2005 Jul;76(7):940-6. doi: 10.1136/jnnp.2004.045948.

[214] Spena G, Costi E, Panciani PP, Roca E, Migliorati K, Fontanella MM. Acute functional reactivation of the language network during awake intraoperative brain mapping. Neurocase. 2015;21(3):403-7. doi: 10.1080/13554794.2014.910306.

[215] Sarubbo S, Le Bars E, Moritz-Gasser S, Duffau H. Complete recovery after surgical resection of left Wernicke's area in awake patient: a brain stimulation and functional MRI study. Neurosurg Rev. 2012 Apr;35(2):287-92; discussion 292. doi: 10.1007/s10143-011-0351-4.

[216] Sakurada K, Sato S, Sonoda Y, Kokubo Y, Saito S, Kayama T. Surgical resection of tumors located in subcortex of language area. Acta Neurochir (Wien). 2007 Feb;149(2):123-9; discussion 129-30. doi: 10.1007/s00701-006-0857-7.

[217] Krieg SM, Schnurbus L, Shiban E, Droese D, Obermueller T, Buchmann N, Gempt J, Meyer B, Ringel F. Surgery of highly eloquent gliomas primarily assessed as non-resectable: risks and benefits in a cohort study. BMC Cancer. 2013 Feb 2;13:51. doi: 10.1186/1471-2407-13-51.

[218] Kinoshita M, de Champfleur NM, Deverdun J, Moritz-Gasser S, Herbet G, Duffau H. Role of fronto-striatal tract and frontal aslant tract in movement and speech: an axonal

mapping study. Brain Struct Funct. 2015 Nov;220(6):3399-412. doi: 10.1007/s00429-014-0863-0.

[219] Vidorreta JG, Garcia R, Moritz-Gasser S, Duffau H. Double dissociation between syntactic gender and picture naming processing: a brain stimulation mapping study. Hum Brain Mapp. 2011 Mar;32(3):331-40. doi: 10.1002/hbm.21026. PMID: 21319264; PMCID: PMC6869915.

[220] Polczynska MM, Benjamin CF, Japardi K, Frew A, Bookheimer SY. Language system organization in a quadrilingual with a brain tumor: Implications for understanding of the language network. Neuropsychologia. 2016 Jun;86:167-75. doi: 10.1016/j.neuropsychologia.2016.04.030.

[221] Roux FE, Trémoulet M. Organization of language areas in bilingual patients: a cortical stimulation study. J Neurosurg. 2002 Oct;97(4):857-64. doi: 10.3171/jns.2002.97.4.0857.

[222] Corina DP, Loudermilk BC, Detwiler L, Martin RF, Brinkley JF, Ojemann G. Analysis of naming errors during cortical stimulation mapping: implications for models of language representation. Brain Lang. 2010 Nov;115(2):101-12. doi: 10.1016/j.bandl.2010.04.001.

[223] Eisner W, Reulen HJ, Ilmberger J, Swozil U, Bise K. Intraoperative mapping of eloquent brain areas. Front Radiat Ther Oncol. 1999;33:28-36. doi: 10.1159/000061244.

[224] Kin H, Ishikawa E, Takano S, Ayuzawa S, Matsushita A, Muragaki Y, Aiyama H, Sakamoto N, Yamamoto T, Matsumura A. Language areas involving the inferior temporal cortex on intraoperative mapping in a bilingual patient with glioblastoma. Neurol Med Chir (Tokyo). 2013;53(4):256-8. doi: 10.2176/nmc.53.256.

[225] Spena G, Garbossa D, Panciani PP, Griva F, Fontanella MM. Purely subcortical tumors in eloquent areas: awake surgery and cortical and subcortical electrical stimulation (CSES) ensure safe and effective surgery. Clin Neurol Neurosurg. 2013 Sep;115(9):1595-601. doi: 10.1016/j.clineuro.2013.02.006.

[226] De Witte E, Satoer D, Colle H, Robert E, Visch-Brink E, Mariën P. Subcortical language and non-language mapping in awake brain surgery: the use of multimodal tests. Acta Neurochir (Wien). 2015 Apr;157(4):577-88. doi: 10.1007/s00701-014-2317-0.

[227] Martino J, Gomez E, de Lucas EM, Mato D, Vázquez-Bourgon J. Intraoperative Identification and Preservation of Verbal Memory in Diffuse Gliomas: A Matched-Pair Cohort Study. Neurosurgery. 2018 Dec 1;83(6):1209-1218. doi: 10.1093/neuros/nyx617.

[228] Chang WH, Pei YC, Wei KC, Chao YP, Chen MH, Yeh HA, Jaw FS, Chen PY. Intraoperative linguistic performance during awake brain surgery predicts postoperative linguistic deficits. J Neurooncol. 2018 Aug;139(1):215-223. doi: 10.1007/s11060-018-2863-z.

[229] Krieg SM, Sollmann N, Hauck T, Ille S, Meyer B, Ringel F. Repeated mapping of cortical language sites by preoperative navigated transcranial magnetic stimulation compared to repeated intraoperative DCS mapping in awake craniotomy. BMC Neurosci. 2014 Jan 30;15:20. doi: 10.1186/1471-2202-15-20.

[230] Papagno C, Comi A, Riva M, Bizzi A, Vernice M, Casarotti A, Fava E, Bello L. Mapping the brain network of the phonological loop. Hum Brain Mapp. 2017 Jun;38(6):3011-3024. doi: 10.1002/hbm.23569.

[231] Lubrano V, Roux FE, Démonet JF. Writing-specific sites in frontal areas: a cortical stimulation study. J Neurosurg. 2004 Nov;101(5):787-98. doi: 10.3171/jns.2004.101.5.0787.

[232] Chang EF, Kurteff G, Wilson SM. Selective Interference with Syntactic Encoding during Sentence Production by Direct Electrocortical Stimulation of the Inferior Frontal Gyrus. J Cogn Neurosci. 2018 Mar;30(3):411-420. doi: 10.1162/jocn_a_01215.

[233] De Witte E, Mariën P. Non-organic language deficits following awake brain surgery: a case report. Clin Neurol Neurosurg. 2015 Mar;130:11-3. doi: 10.1016/j.clineuro.2014.12.012.

[234] Faulkner JW, Wilshire CE, Parker AJ, Cunningham K. An evaluation of language in brain tumor patients using a new cognitively motivated testing protocol. Neuropsychology. 2017 Sep;31(6):648-665. doi: 10.1037/neu0000374. Epub 2017 Apr 6. PMID: 28383971.

[235] Dragoy O, Chrabaszcz A, Tolkacheva V, Buklina S. Russian Intraoperative Naming Test: A standardized tool to map noun and verb production during awake neurosurgeries. Russ J of Cogn Sci. 2016 Dec;3(4): 4-25.

[236] Bastiaanse R, Bosje M, Visch-Brink EG. PALPA: Nederlandse versie. Hove (UK): Lawrence; 1995.

[237] Visch-Brink E, Vandenborre D, De Smet HJ, Mariën P. Comprehensive Aphasia Test-Nederlandse bewerking-Handleiding. The Netherlands: Pearson; 2014.

[238] Mariën P, Mampaey E, Vervaet A, Saerens J, De Deyn PP. Normative data for the Boston naming test in native Dutch-speaking Belgian elderly. Brain Lang. 1998 Dec;65(3):447-67. doi: 10.1006/brln.1998.2000.

[239] Metz-Lutz MN. [Standardization of an oral naming test: control of the effects of age, sex and educational level in normal adult subjects]. Rev Neuropsychol, 1991;1:73-95. French.

[240] Howard D, Patterson K. The pyramids and Palm Trees Test: A test of semantic access from words and pictures. Bury St Edmunds (UK): Thames Valley Test Company; 1992.

[241] Shewan CM, Kertesz A. Reliability and validity characteristics of the Western Aphasia Battery (WAB). J Speech Hear Disord. 1980 Aug;45(3):308-24. doi: 10.1044/jshd.4503.308. PMID: 7412225.

[242] Beland R, Lecours AR. The MT-86b aphasia battery: A subset of normative data in relation to age and level of school education. Aphasiology. 1990;4(5):439-62. doi: 10.1080/02687039008248786

[243] Willmes K. An approach to analyzing a single subject's scores obtained in a standardized test with application to the Aachen Aphasia Test (AAT). J Clin Exp Neuropsychol. 1985 Aug;7(4):331-52. doi: 10.1080/01688638508401268.

[244] Wechsler D. Wechsler Adult Intelligence Scale 3rd edition (WAIS-III). San Antonio (TX): The Psychological Corporation; 1997

[245] Miceli G, Laudanna A, Burani C, Capasso R. [Battery for evaluation of aphasic deficits]. Roma (Italy): CEPSAG; 1994. Italian.

[246] Snodgrass JG, Vanderwart M. A standardized set of 260 pictures: norms for name agreement, image agreement, familiarity, and visual complexity. J Exp Psychol Hum Learn. 1980 Mar;6(2):174-215. doi: 10.1037//0278-7393.6.2.174.

[247] Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975 Nov;12(3):189-98. doi: 10.1016/0022-3956(75)90026-6.

[248] Chen S, Bates E. The dissociation between nouns and verbs in Broca's and Wernicke's aphasia: Findings from Chinese. Aphasiology. 1998;12(1):5-36. doi: 10.1016/0093-934x(91)90153-r

[249] Damasio AR, Tranel D. Nouns and verbs are retrieved with differently distributed neural systems. Proc Natl Acad Sci U S A. 1993 Jun 1;90(11):4957-60. doi: 10.1073/pnas.90.11.4957.

[250] Shapiro K, Caramazza A. Grammatical processing of nouns and verbs in left frontal cortex? Neuropsychologia. 2003;41(9):1189-98. doi: 10.1016/s0028-3932(03)00037-x.

[251] Gatignol P, Duffau H, Capelle L, Plaza M. Naming performance in two bilinguals with frontal vs. temporal glioma. Neurocase. 2009 Dec;15(6):466-77. doi: 10.1080/13554790902950434.

[252] Brennan NP, Peck KK, Holodny A. Language Mapping Using fMRI and Direct Cortical Stimulation for Brain Tumor Surgery: The Good, the Bad, and the Questionable. Top Magn Reson Imaging. 2016 Feb;25(1):1-10. doi: 10.1097/RMR.0000000000000074.

[253] Rofes A, Mandonnet E, de Aguiar V, Rapp B, Tsapkini K, Miceli G. Language processing from the perspective of electrical stimulation mapping. Cogn Neuropsychol. 2019 May-Jun;36(3-4):117-139. doi: 10.1080/02643294.2018.1485636.

[254] Whitworth A, Webster J, Howard D. A cognitive neuropsychological approach to assessment and intervention in aphasia: A clinician's guide. Hove (UK): Psychology Press; 2014

[255] Morton J, Patterson KE. A new attempt at an interpretation, or an attempt at a new inter-pretation. In: Coltheart M, Patterson KE, Marshall JC, editors. Deep dyslexia. London (UK): Routledge & Kegan Paul; 1980. p. 91-118.

[256] Garrett MF. Levels of processing in sentence production. In: Butterworth B, editor. Language production. Vol. 1: Speech and talk. London (UK): Academic Press; 1980. p. 176-220.

[257] Bock JK, Levelt WJ. Language production. Grammatical encoding. In: Gernsbacher MA, editor. Handbook of Psycholinguistics. San Diego (CA): Academic Press; 1994. p. 945-84.

[258] Rofes A. Verbs and nouns in awake neurosurgery: needs and answers [dissertation]. [Trento]: University of Trento; 2015.

[259] Alvarez JA, Emory E. Executive function and the frontal lobes: a meta-analytic review. Neuropsychol Rev. 2006 Mar;16(1):17-42. doi: 10.1007/s11065-006-9002-x.

[260] Kosmidis MH, Vlahou CH, Panagiotaki P, Kiosseoglou G. The verbal fluency task in the Greek population: normative data, and clustering and switching strategies. J Int Neuropsychol Soc. 2004 Mar;10(2):164-72. doi: 10.1017/S1355617704102014.

[261] Moret-Tatay C, Perea M. Do serifs provide an advantage in the recognition of written words?. J Cogn Psychol. 2011;23(5):619-24.

[262] Rossion B, Pourtois G. Revisiting Snodgrass and Vanderwart's object pictorial set: the role of surface detail in basic-level object recognition. Perception. 2004;33(2):217-36. doi: 10.1068/p5117.

[263] Papathanasiou I, Garitou M, Gavrilaki P, Griva A, Doulami A, Kyritsis I, Tomara P, Malefaki S. The psychometric properties of the Snodgrass and Vanderwart pictures in Greek normal and aphasic population. Paper presented at: International Aphasia Rehabilitation Conference; 2006 Jan 4-6; Sheffield, UK.

[264] Cohen G, Burke DM. Memory for proper names: a review. Memory. 1993 Dec;1(4):249-63. doi: 10.1080/09658219308258237.

[265] Lubrano V, Filleron T, Démonet JF, Roux FE. Anatomical correlates for category-specific naming of objects and actions: a brain stimulation mapping study. Hum Brain Mapp. 2014 Feb;35(2):429-43. doi: 10.1002/hbm.22189.

[266] Ojemann G, Mateer C. Human language cortex: localization of memory, syntax, and sequential motor-phoneme identification systems. Science. 1979 Sep 28;205(4413):1401-3. doi: 10.1126/science.472757. PMID: 472757.

[267] Kyparissiadis A, van Heuven WJ, Pitchford NJ, Ledgeway T. GreekLex 2: A comprehensive lexical database with part-of-speech, syllabic, phonological, and stress information. PLoS One. 2017 Feb 23;12(2):e0172493. doi: 10.1371/journal.pone.0172493.

[268] Pierce JE, Cotton S, Perry A. Alternating and sequential motion rates in older adults. Int J Lang Commun Disord. 2013 May-Jun;48(3):257-64. doi: 10.1111/1460-6984.12001.

[269] Schwartz MF, Saffran EM, Marin OS. The word order problem in agrammatism. I. Comprehension. Brain Lang. 1980 Jul;10(2):249-62. doi: 10.1016/0093-934x(80)90055-3.

[270] van Heuven WJ, Mandera P, Keuleers E, Brysbaert M. SUBTLEX-UK: a new and improved word frequency database for British English. Q J Exp Psychol (Hove). 2014;67(6):1176-90. doi: 10.1080/17470218.2013.850521.

[271] Rosch E, Mervis CB, Gray WD, Johnson DM, Boyes-Braem P. Basic objects in natural categories. Cogn Psychol. 1976;8(3):382-439.

[272] Goutsos D. The corpus of Greek texts: A reference corpus for Modern Greek. Corpora. 2010;5(1):29-44.

[273] Donderi DC. An information theory analysis of visual complexity and dissimilarity. Perception. 2006;35(6):823-35. doi: 10.1068/p5249.

[274] Kurland J, Reber A, Stokes P. Beyond picture naming: norms and patient data for a verb-generation task. Am J Speech Lang Pathol. 2014 May;23(2):S259-70. doi: 10.1044/2014_AJSLP-13-0094.

[275] Thompson-Schill SL, D'Esposito M, Aguirre GK, Farah MJ. Role of left inferior prefrontal cortex in retrieval of semantic knowledge: a reevaluation. Proc Natl Acad Sci U S A. 1997 Dec 23;94(26):14792-7. doi: 10.1073/pnas.94.26.14792.

[276] Bernthal JE, Bankson NW, Flipsen P. Articulation and Phonological Disorders: Speech Sound Disorders in Children. Boston (MA): Pearson; 2017.

[277] PAL: Panhellenic Association of Logopaedics. [Assessment of phonetic and phonological development]. Athens (Greece): PAL; 1995. Greek.

[278] Roussou A, Tsimpli IM. On Greek VSO again!. J Linguist. 2006;42(2):317-354.

[279] Kim M, Thompson CK. Semantic anomaly judgement in individuals with probable Alzheimer's disease. Aphasiology. 2003 Dec;17(12):1103-1113. doi: 10.1080/02687030344000391.

[280] Protopapas A, Cheimariou S, Economou A, Kakavoulia M, Varlokosta S. Functional categories related to verb inflection are not differentially impaired in Greek aphasia. Lang Cogn. 2016;8(1):124-141.

[281] Varlokosta S, Valeonti N, Kakavoulia M, Lazaridou M, Economou A, Protopapas A. The breakdown of functional categories in Greek aphasia: Evidence from agreement, tense, and aspect. Aphasiology. 2006;20(8):723-743.

[282] Stavrakaki S, Kouvava S. Functional categories in agrammatism: evidence from Greek. Brain Lang. 2003 Jul;86(1):129-41. doi: 10.1016/s0093-934x(02)00541-2.

[283] Benton AL, Hamsher K, Sivan AB. Controlled oral word association test (COWAT). Multilingual Aphasia Examination, 3rd ed. Iowa City (IA): AJA Associates; 1983.

[284] Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia. 1971 Mar;9(1):97-113. doi: 10.1016/0028-3932(71)90067-4.

[285] Konstantopoulos K, Vogazianos P, Doskas T. Normative Data of the Montreal Cognitive Assessment in the Greek Population and Parkinsonian Dementia. Arch Clin Neuropsychol. 2016 May;31(3):246-53. doi: 10.1093/arclin/acw002. Epub 2016 Feb 17. PMID: 26891720.

[286] Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005 Apr;53(4):695-9. doi: 10.1111/j.1532-5415.2005.53221.x. Erratum in: J Am Geriatr Soc. 2019 Sep;67(9):1991.

[287] World Medical Association General Assembly. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. J Int Bioethique. 2004 Mar;15(1):124-9.

[288] R Core Team. R: A language and environment for statistical computing. Vienna (Austria): R Foundation for Statistical Computing; 2014.

[289] Palmer BW, Boone KB, Lesser IM, Wohl MA. Base rates of "impaired" neuropsychological test performance among healthy older adults. Arch Clin Neuropsychol. 1998 Aug;13(6):503-11.

[290] Benton A, Van Allen M, Hamsher K, Levin H. Test of facial recognition manual. Iowa City (IA): Benton Laboratory of Neuropsychology; 1978.

[291] Orsini DL, Van Gorp WG, Boone KB. The neuropsychology casebook. New York (NY): Springer Verlag; 1988

[292] Friberg JC. Considerations for test selection: How do validity and reliability impact diagnostic decisions? Child Lang Teach Ther. 2010;26(1):77-92. doi: 10.1177/0265659009349972

[293] Ingraham LJ, Aiken CB. An empirical approach to determining criteria for abnormality in test batteries with multiple measures. Neuropsychology. 1996;10(1):120-124.

[294] Simos PG, Kaselimis D, Mouzaki A. Age, gender, and education effects on vocabulary measures in Greek. Aphasiology.2011;25(4):475-491.

[295] Crawford JR, Howell DC. Comparing an individual's test score against norms derived from small samples. Clin Neuropsychol. 1998;12(4):482-86.

[296] Mitrushina M, Boone KN, Razani J, D'Elia LF. Handbook of Normative Data for Neuropsychological Assessment. New York (NY): Oxford University Press; 2005.

[297] Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. Control Clin Trials. 1989 Dec;10(4):407-15. doi: 10.1016/0197-2456(89)90005-6.

[298] Potagas C, Kaselimis DS, Evdokimidis I. Elements of Neurology Essential for Understanding the Aphasias. In: Papathanasiou I, Coppens P, editors. Aphasia and related neurogenic communication disorders. 2nd ed. Burlington (MA): Jones and Bartlett Publishers; 2017. p. 23-48.

[299] Dell GS, Schwartz MF, Martin N, Saffran EM, Gagnon DA. Lexical access in aphasic and nonaphasic speakers. Psychol Rev. 1997 Oct;104(4):801-38. doi: 10.1037/0033-295x.104.4.801.

[300] Basso A. Aphasia and its Therapy. Oxford (UK): Oxford University Press; 2003.

[301] Miceli G, Silveri C, Nocentini U, and Caramazza A. Patterns of dissociation in comprehension and production of nouns verb. Aphasiology. 1988;29(3-4):351–358.

[302] Miceli G, Silveri MC, Villa G, Caramazza A. On the basis for the agrammatic's difficulty in producing main verbs. Cortex. 1984 Jun;20(2):207-20. doi: 10.1016/s0010-9452(84)80038-6.

[303] Kemmerer D. Cognitive Neuroscience of Language. New York (NY): Psychology Press; 2015

[304] Joanette Y, Keller E, Lecours AR. Sequences of phonemic approximations in aphasia. Brain Lang. 1980 Sep;11(1):30-44. doi: 10.1016/0093-934x(80)90107-8. PMID: 7427723.

[305] Kohn SE. The nature of the phonological disorder in conduction aphasia. Brain Lang. 1984 Sep;23(1):97-115. doi: 10.1016/0093-934x(84)90009-9. PMID: 6478196.

[306] Schuell H. Paraphasia and paralexia. J Speech Disord. 1950 Dec;15(4):291-306. doi: 10.1044/jshd.1504.291. PMID: 14804686.

[307] Polelle D. Paralexia. In: Kreutzer JS, DeLuca J, Caplan B, editors. Encyclopedia of Clinical Neuropsychology. New York (NY): Springer; 2011. p. 1855. doi: 10.1007/978-0-387-79948-3_906.

[308] Marshall JC, Newcombe F. Patterns of paralexia: a psycholinguistic approach. J Psycholinguist Res. 1973 Jul;2(3):175-99. doi: 10.1007/BF01067101.

[309] Sandson J, Albert ML. Varieties of perseveration. Neuropsychologia. 1984;22(6):715-32. doi: 10.1016/0028-3932(84)90098-8.

[310] Martin N, Roach A, Brecher A, Lowery J. Lexical retrieval mechanisms underlying whole-word perseveration errors in anomic aphasia. Aphasiology. 1998;12(4-5):319-333.

[311] Kent RD. The MIT encyclopedia of communication disorders. Cambridge (MA): The MIT Press; 2004.

[312] Goodglass H, Kaplan E. Boston Diagnostic Aphasia Examination. Philadelphia (PA): Lea & Febiger; 1972.

[313] Grodzinsky Y. The syntactic characterization of agrammatism. Cognition. 1984 Mar;16(2):99-120. doi: 10.1016/0010-0277(84)90001-5.

[314] Penfield W, Welch K. The supplementary motor area of the cerebral cortex; a clinical and experimental study. AMA Arch Neurol Psychiatry. 1951 Sep;66(3):289-317. doi: 10.1001/archneurpsyc.1951.02320090038004.

[315] Darley FL, Aronson AE, Brown JR. Motor Speech Disorders 1st ed. Philadelphia (PA): Saunders; 1975.

[316] Ogar J, Slama H, Dronkers N, Amici S, Gorno-Tempini ML. Apraxia of speech: an overview. Neurocase. 2005 Dec;11(6):427-32. doi: 10.1080/13554790500263529.

[317] Wertz RT, LaPointe LL, Rosenbek JC. Apraxia of speech: The disorder and its management. New York (NY): Grune and Stratton; 1984.

[318] Duffy J. Motor speech disorders: substrates, differential diagnosis, and management 2nd ed. St. Louis (MO): Elsevier Mosby; 2005.

[319] Yorkston KM, Beukelman DR. Ataxic dysarthria: treatment sequences based on intelligibility and prosodic considerations. J Speech Hear Disord. 1981 Nov;46(4):398-404. doi: 10.1044/jshd.4604.398.

[320] Ferré P, Ska B, Lajoie C, Bleau A, Joanette Y. Clinical Focus on Prosodic, Discursive and Pragmatic Treatment for Right Hemisphere Damaged Adults: What's Right? Rehabil Res Pract. 2011;2011:131820. doi: 10.1155/2011/131820.

[321] Meyer M, Alter K, Friederici AD, Lohmann G, von Cramon DY. FMRI reveals brain regions mediating slow prosodic modulations in spoken sentences. Hum Brain Mapp. 2002 Oct;17(2):73-88. doi: 10.1002/hbm.10042.

[322] Leon SA, Rodriguez DA. Aprosodia and its treatment. Perspect Neurophysiol Neurogenic Speech Lang Disord. 2008;18(2):66–72.

[323] Gussenhoven C, Bruce G. Word prosody and intonation. In: van der Hulst H, editor. Empirical approaches to language typology (EALT). Berlin (Germany): De Gruyter Mouton; 1999. p. 233-72.

[324] ‘t Hart J, Collier R, Cohen A. A Perceptual Study of Intonation: An Experimental-Phonetic Approach to Speech Melody. Cambridge (UK): Cambridge University Press; 1990.

[325] Joanette Y, Ska B, Côté H. Protocole MEC – Protocole Montreál d’Évaluation de la Communication [MEC Protocol – Montreal Protocol for the Evaluation of Communication]. Montreal (Canada): Ortho Édition; 2004. French.

[326] Pell MD. Fundamental frequency encoding of linguistic and emotional prosody by right hemisphere-damaged speakers. Brain Lang. 1999 Sep;69(2):161-92. doi: 10.1006/brln.1999.2065. PMID: 10447989.

[327] Blonder LX, Pickering JE, Heath RL, Smith CD, Butler SM. Prosodic characteristics of speech pre-and post-right hemisphere stroke. Brain Lang. 1995;51(2):318-335.

[328] Gibbs RW Jr. Speakers' intuitions and pragmatic theory. Cognition. 1999 Jan 1;69(3):355-9. doi: 10.1016/s0010-0277(98)00071-7. PMID: 10193052.

[329] Champagne-Lavau M, Joanette Y. Pragmatics , theory of mind and executive functions after a right-hemisphere lesion: Different patterns of deficits. J Neurolinguist. 2009;22:2–5. doi:10.1016/j.jneuroling.2009.02.002

[330] Kooistra B, Dijkman B, Einhorn TA, Bhandari M. How to design a good case series. J Bone Joint Surg Am. 2009 May;91 Suppl 3:21-6. doi: 10.2106/JBJS.H.01573.

[331] Mathes T, Pieper D. Clarifying the distinction between case series and cohort studies in systematic reviews of comparative studies: potential impact on body of evidence and workload. BMC Med Res Methodol. 2017 Jul 17;17(1):107. doi: 10.1186/s12874-017-0391-8.

[332] Schwartz MF, Dell GS. Case series investigations in cognitive neuropsychology. Cogn Neuropsychol. 2010 Sep;27(6):477-94. doi: 10.1080/02643294.2011.574111.

[333] Papathanasiou I, Papadimitriou D, Gavrilou V, Mihou A. Psihometrika dedomena tis diagnostikis dokimasias tis Vostonis gia tin afasia se igii plithismo enilikon: o rolos tis ilikias ke tou filou [Normative data for the Boston Diagnostic Aphasia Battery in Greek: gender and age effects]. Psixologia. 2008;15(4), 398-410. Greek.

[334] Kounti F, Tsolaki M, Eleftheriou M, Agogiatou C, Karagiozi K, Bakoglidou E. Administration of Montreal Cognitive Assessment (MoCA) test in Greek elderly, patients with mild cognitive impairment and patients with dementia. Poster session presented at: 9th European Conference on psychological assessment (ECPA9). European association of psychological assessment; 2007 May 3-6; Thessaloniki (Greece).

[335] Efstratiadou EA, Chelas EN, Ignatiou M, Christaki V, Papathanasiou I, Hilari K. Quality of life after stroke: evaluation of the Greek SAQOL-39g. Folia Phoniatr Logop. 2012;64(4):179-86. doi: 10.1159/000340014.

[336] Kartsona A, Hilari K. Quality of life in aphasia: Greek adaptation of the stroke and aphasia quality of life scale - 39 item (SAQOL-39). Eura Medicophys. 2007 Mar;43(1):27-35.

[337] Zhang Y. Online tool for handedness assessment [Internet]. Minneapolis (MN): University of Minnesota, Zhang Lab in SLHS; 2014. Available from: http://zhanglab.wikidot.com/handedness

[338] Kaplan E, Goodglass H, Weintraub S. Boston Naming Test. Philadelphia (PA): Lea & Febiger; 1983.

[339] Hilari K, Byng S, Lamping DL, Smith SC. Stroke and Aphasia Quality of Life Scale-39 (SAQOL-39): evaluation of acceptability, reliability, and validity. Stroke. 2003 Aug;34(8):1944-50. doi: 10.1161/01.STR.0000081987.46660.ED.

[340] Hays RD, Anderson R, Revicki D. Psychometric considerations in evaluating health-related quality of life measures. Qual Life Res. 1993 Dec;2(6):441-9. doi: 10.1007/BF00422218.

[341] Simpson F, Christie J, Clark W, Mortensen L. Mount Wilga high level language test. 20th Anniversary Revised Edition 1. Sydney (Australia): Mount Wilga Rehabilitation Centre, Speech Pathology Department; 2006.

[342] Papatzalas C, Fountas K, Brotis A, Kapsalaki E, Papathanasiou I. The Greek linguistic assessment for awake brain surgery: development process and normative data. Clin Linguist Phon. 2021 May 4;35(5):458-488. doi: 10.1080/02699206.2020.1792997. Epub 2020 Jul 15.

[343] Patterson K, Nestor PJ, Rogers TT. Where do you know what you know? The representation of semantic knowledge in the human brain. Nat Rev Neurosci. 2007 Dec;8(12):976-87. doi: 10.1038/nrn2277.

[344] Tsapkini K, Frangakis CE, Hillis AE. The function of the left anterior temporal pole: evidence from acute stroke and infarct volume. Brain. 2011 Oct;134(Pt 10):3094-105. doi: 10.1093/brain/awr050.

[345] Augustine JR. Circuitry and functional aspects of the insular lobe in primates including humans. Brain Res Brain Res Rev. 1996 Oct;22(3):229-44. doi: 10.1016/s0165-0173(96)00011-2.

[346] Oh A, Duerden EG, Pang EW. The role of the insula in speech and language processing. Brain Lang. 2014 Aug;135:96-103. doi: 10.1016/j.bandl.2014.06.003.

[347] Dronkers NF. A new brain region for coordinating speech articulation. Nature. 1996 Nov 14;384(6605):159-61. doi: 10.1038/384159a0.

[348] D'Esposito M, Detre JA, Alsop DC, Shin RK, Atlas S, Grossman M. The neural basis of the central executive system of working memory. Nature. 1995 Nov 16;378(6554):279-81. doi: 10.1038/378279a0.

[349] Nejati V, Salehinejad MA, Nitsche MA. Interaction of the Left Dorsolateral Prefrontal Cortex (l-DLPFC) and Right Orbitofrontal Cortex (OFC) in Hot and Cold Executive Functions: Evidence from Transcranial Direct Current Stimulation (tDCS). Neuroscience. 2018 Jan 15;369:109-123. doi: 10.1016/j.neuroscience.2017.10.042.

[350] Wagner AD, Maril A, Bjork RA, Schacter DL. Prefrontal contributions to executive control: fMRI evidence for functional distinctions within lateral Prefrontal cortex. Neuroimage. 2001 Dec;14(6):1337-47. doi: 10.1006/nimg.2001.0936.

[351] Hernandez AE, Martinez A, Kohnert K. In search of the language switch: An fMRI study of picture naming in Spanish-English bilinguals. Brain Lang. 2000 Jul;73(3):421-31. doi: 10.1006/brln.1999.2278.

[352] Price CJ, Green DW, von Studnitz R. A functional imaging study of translation and language switching. Brain. 1999 Dec;122 (Pt 12):2221-35. doi: 10.1093/brain/122.12.2221.

[353] Hsu NS, Jaeggi SM, Novick JM. A common neural hub resolves syntactic and non-syntactic conflict through cooperation with task-specific networks. Brain Lang. 2017 Mar;166:63-77. doi: 10.1016/j.bandl.2016.12.006.

[354] Humphreys GF, Gennari SP. Competitive mechanisms in sentence processing: common and distinct production and reading comprehension networks linked to the prefrontal cortex. Neuroimage. 2014 Jan 1;84:354-66. doi: 10.1016/j.neuroimage.2013.08.059.

[355] Fertonani A, Rosini S, Cotelli M, Rossini PM, Miniussi C. Naming facilitation induced by transcranial direct current stimulation. Behav Brain Res. 2010 Apr 2;208(2):311-8. doi: 10.1016/j.bbr.2009.10.030.

[356] Klaus J, Schutter DJLG. The Role of Left Dorsolateral Prefrontal Cortex in Language Processing. Neuroscience. 2018 May 1;377:197-205. doi: 10.1016/j.neuroscience.2018.03.002.

[357] Hussey EK, Ward N, Christianson K, Kramer AF. Language and Memory Improvements following tDCS of Left Lateral Prefrontal Cortex. PLoS One. 2015 Nov 3;10(11):e0141417. doi: 10.1371/journal.pone.0141417.

[358] Sela T, Ivry RB, Lavidor M. Prefrontal control during a semantic decision task that involves idiom comprehension: a transcranial direct current stimulation study. Neuropsychologia. 2012 Jul;50(9):2271-80. doi: 10.1016/j.neuropsychologia.2012.05.031.

[359] Zald DH, Kim, SW. The orbitofrontal cortex. In: Salloway SP, Malloy PF, Duffy JD, editors. The frontal lobes and neuropsychiatric illness. Washington (DC): American Psychiatric Publishing, Inc; 2001. p. 33-69

[360] Wildgruber D, Ethofer T, Grandjean D, Kreifelts B. A cerebral network model of speech prosody comprehension. Int H Speech Lang Pathol. 2009;11(4):277-281.

[361] Hickok G, Poeppel D. Dorsal and ventral streams: a framework for understanding aspects of the functional anatomy of language. Cognition. 2004 May-Jun;92(1-2):67-99. doi: 10.1016/j.cognition.2003.10.011.

[362] Dehaene S, Cohen L. The unique role of the visual word form area in reading. Trends Cogn Sci. 2011 Jun;15(6):254-62. doi: 10.1016/j.tics.2011.04.003.

[363] Price CJ, Devlin JT. The myth of the visual word form area. Neuroimage. 2003 Jul;19(3):473-81. doi: 10.1016/s1053-8119(03)00084-3.

[364] Eden GF, Olulade OA, Evans TM, Krafnick AJ, Alkire DR. Imaging studies of reading and reading disability. In: Toga AW, editor. Brain Mapping: An Encyclopedic Reference. Volume 3. Amsterdam (The Netherlands): Academic Press; 2015. p. 571-78.

[365] Cohen L, Dehaene S, Naccache L, Lehéricy S, Dehaene-Lambertz G, Hénaff MA, Michel F. The visual word form area: spatial and temporal characterization of an initial stage of reading in normal subjects and posterior split-brain patients. Brain. 2000 Feb;123 (Pt 2):291-307. doi: 10.1093/brain/123.2.291.

[366] McCandliss BD, Cohen L, Dehaene S. The visual word form area: expertise for reading in the fusiform gyrus. Trends Cogn Sci. 2003 Jul;7(7):293-299. doi: 10.1016/s1364-6613(03)00134-7.

[367] Fiez JA, Petersen SE. Neuroimaging studies of word reading. Proc Natl Acad Sci U S A. 1998 Feb 3;95(3):914-21. doi: 10.1073/pnas.95.3.914.

[368] Price CJ. The anatomy of language: contributions from functional neuroimaging. J Anat. 2000 Oct;197 Pt 3(Pt 3):335-59. doi: 10.1046/j.1469-7580.2000.19730335.x.

[369] Catani M, Dell'acqua F, Vergani F, Malik F, Hodge H, Roy P, Valabregue R, Thiebaut de Schotten M. Short frontal lobe connections of the human brain. Cortex. 2012 Feb;48(2):273-91. doi: 10.1016/j.cortex.2011.12.001.

[370] Dick AS, Garic D, Graziano P, Tremblay P. The frontal aslant tract (FAT) and its role in speech, language and executive function. Cortex. 2019 Feb;111:148-163. doi: 10.1016/j.cortex.2018.10.015.

[371] Chernoff BL, Sims MH, Smith SO, Pilcher WH, Mahon BZ. Direct electrical stimulation of the left frontal aslant tract disrupts sentence planning without affecting articulation. Cogn Neuropsychol. 2019 May-Jun;36(3-4):178-192. doi: 10.1080/02643294.2019.1619544.

[372] Sierpowska J, Gabarrós A, Fernandez-Coello A, Camins À, Castañer S, Juncadella M, de Diego-Balaguer R, Rodríguez-Fornells A. Morphological derivation overflow as a result of disruption of the left frontal aslant white matter tract. Brain Lang. 2015 Mar;142:54-64. doi: 10.1016/j.bandl.2015.01.005.

[373] Kronfeld-Duenias V, Amir O, Ezrati-Vinacour R, Civier O, Ben-Shachar M. The frontal aslant tract underlies speech fluency in persistent developmental stuttering. Brain Struct Funct. 2016 Jan;221(1):365-81. doi: 10.1007/s00429-014-0912-8.

[374] Dragoy O, Zyryanov A, Bronov O, Gordeyeva E, Gronskaya N, Kryuchkova O, Klyuev E, Kopachev D, Medyanik I, Mishnyakova L, Pedyash N, Pronin I, Reutov A, Sitnikov A, Stupina E, Yashin K, Zhirnova V, Zuev A. Functional linguistic specificity of the left frontal aslant tract for spontaneous speech fluency: Evidence from intraoperative language mapping. Brain Lang. 2020 Sep;208:104836. doi: 10.1016/j.bandl.2020.104836.

[375] Tauroza S, Allison D. Speech rates in british english. Appl Linguist. 1990;11(1):90-105.

[376] Abel TJ, Buckley RT, Morton RP, Gabikian P, Silbergeld DL. Recurrent Supplementary Motor Area Syndrome Following Repeat Brain Tumor Resection Involving Supplementary Motor Cortex. Neurosurgery. 2015 Sep;11 Suppl 3(0 3):447-55; discussion 456. doi: 10.1227/NEU.0000000000000847.

[377] Krainik A, Lehéricy S, Duffau H, Capelle L, Chainay H, Cornu P, Cohen L, Boch AL, Mangin JF, Le Bihan D, Marsault C. Postoperative speech disorder after medial frontal surgery: role of the supplementary motor area. Neurology. 2003 Feb 25;60(4):587-94. doi: 10.1212/01.wnl.0000048206.07837.59.

[378] Masdeu JC, Schoene WC, Funkenstein H. Aphasia following infarction of the left supplementary motor area: a clinicopathologic study. Neurology. 1978 Dec;28(12):1220-3. doi: 10.1212/wnl.28.12.1220.

[379] Nikki Arrington C, Kulesz PA, Juranek J, Cirino PT, Fletcher JM. White matter microstructure integrity in relation to reading proficiency☆. Brain Lang. 2017 Nov;174:103-111. doi: 10.1016/j.bandl.2017.08.002.

[380] Ben-Shachar M, Dougherty RF, Wandell BA. White matter pathways in reading. Curr Opin Neurobiol. 2007 Apr;17(2):258-70. doi: 10.1016/j.conb.2007.03.006.

[381] Herbet G, Moritz-Gasser S, Lemaitre AL, Almairac F, Duffau H. Functional compensation of the left inferior longitudinal fasciculus for picture naming. Cogn Neuropsychol. 2019 May-Jun;36(3-4):140-157. doi: 10.1080/02643294.2018.1477749.

[382] Horowitz-Kraus T, Wang Y, Plante E, Holland SK. Involvement of the right hemisphere in reading comprehension: a DTI study. Brain Res. 2014 Sep 25;1582:34-44. doi: 10.1016/j.brainres.2014.05.034.

[383] Mandonnet E, Nouet A, Gatignol P, Capelle L, Duffau H. Does the left inferior longitudinal fasciculus play a role in language? A brain stimulation study. Brain. 2007 Mar;130(Pt 3):623-9. doi: 10.1093/brain/awl361.

[384] Hart RP, Beach WA, Taylor JR. A case of progressive apraxia of speech and non-fluent aphasia. Aphasiology. 1997;11(1):73-82.

[385] Peach RK, Tonkovich JD. Phonemic characteristics of apraxia of speech resulting from subcortical hemorrhage. J Commun Disord. 2004 Jan-Feb;37(1):77-90. doi: 10.1016/j.jcomdis.2003.08.001.

[386] Rasmussen T, Milner B. The role of early left-brain injury in determining lateralization of cerebral speech functions. Ann N Y Acad Sci. 1977 Sep 30;299:355-69. doi: 10.1111/j.1749-6632.1977.tb41921.x.

[387] Henry JD, Crawford JR. A meta-analytic review of verbal fluency performance following focal cortical lesions. Neuropsychology. 2004 Apr;18(2):284-95. doi: 10.1037/0894-4105.18.2.284.

[388] Buchsbaum BR, Hickok G, Humphries C. Role of left posterior superior temporal gyrus in phonological processing for speech perception and production. Cogn Sci. 2001;25(5):663-78.

[389] Leonard MK, Brown TT, Travis KE, Gharapetian L, Hagler DJ Jr, Dale AM, Elman JL, Halgren E. Spatiotemporal dynamics of bilingual word processing. Neuroimage. 2010 Feb 15;49(4):3286-94. doi: 10.1016/j.neuroimage.2009.12.009.

[390] Duffau H. Is non-awake surgery for supratentorial adult low-grade glioma treatment still feasible? Neurosurg Rev. 2018 Jan;41(1):133-139. doi: 10.1007/s10143-017-0918-9.

[391] Gupta DK, Chandra PS, Ojha BK, Sharma BS, Mahapatra AK, Mehta VS. Awake craniotomy versus surgery under general anesthesia for resection of intrinsic lesions of eloquent cortex--a prospective randomised study. Clin Neurol Neurosurg. 2007 May;109(4):335-43. doi: 10.1016/j.clineuro.2007.01.008.

[392] Sacko O, Lauwers-Cances V, Brauge D, Sesay M, Brenner A, Roux FE. Awake craniotomy vs surgery under general anesthesia for resection of supratentorial lesions. Neurosurgery. 2011 May;68(5):1192-8; discussion 1198-9. doi: 10.1227/NEU.0b013e31820c02a3.

[393] Eseonu CI, Rincon-Torroella J, ReFaey K, Lee YM, Nangiana J, Vivas-Buitrago T, Quiñones-Hinojosa A. Awake Craniotomy vs Craniotomy Under General Anesthesia

for Perirolandic Gliomas: Evaluating Perioperative Complications and Extent of Resection. Neurosurgery. 2017 Sep 1;81(3):481-489. doi: 10.1093/neuros/nyx023.

[394] Jakola AS, Skjulsvik AJ, Myrmel KS, Sjåvik K, Unsgård G, Torp SH, Aaberg K, Berg T, Dai HY, Johnsen K, Kloster R, Solheim O. Surgical resection versus watchful waiting in low-grade gliomas. Ann Oncol. 2017 Aug 1;28(8):1942-1948. doi: 10.1093/annonc/mdx230.

[395] Gravesteijn BY, Keizer ME, Vincent AJPE, Schouten JW, Stolker RJ, Klimek M. Awake craniotomy versus craniotomy under general anesthesia for the surgical treatment of insular glioma: choices and outcomes. Neurol Res. 2018 Feb;40(2):87-96. doi: 10.1080/01616412.2017.1402147.

[396] De Benedictis A, Moritz-Gasser S, Duffau H. Awake mapping optimizes the extent of resection for low-grade gliomas in eloquent areas. Neurosurgery. 2010 Jun;66(6):1074-84; discussion 1084. doi: 10.1227/01.NEU.0000369514.74284.78.

[397] Berger MS. Lesions in functional ("eloquent") cortex and subcortical white matter. Clin Neurosurg. 1994;41:444-63.

[398] Walsh AR, Ojemann GA. Anterior temporal lobectomy for epilepsy. Clin Neurosurg. 1992;38:535-47.

[399] Serletis D, Bernstein M. Prospective study of awake craniotomy used routinely and nonselectively for supratentorial tumors. J Neurosurg. 2007 Jul;107(1):1-6. doi: 10.3171/JNS-07/07/0001.

[400] Zelitzki R, Korn A, Arial E, Ben-Harosh C, Ram Z, Grossman R. Comparison of Motor Outcome in Patients Undergoing Awake vs General Anesthesia Surgery for Brain Tumors Located Within or Adjacent to the Motor Pathways. Neurosurgery. 2019 Sep 1;85(3):E470-E476. doi: 10.1093/neuros/nyz007.

[401] Ghasemi A, Zahediasl S. Normality tests for statistical analysis: a guide for non-statisticians. Int J Endocrinol Metab. 2012 Spring;10(2):486-9. doi: 10.5812/ijem.3505.

[402] Krithikadatta J. Normal distribution. J Conserv Dent. 2014 Jan;17(1):96-7. doi: 10.4103/0972-0707.124171.

[403] Teixidor P, Gatignol P, Leroy M, Masuet-Aumatell C, Capelle L, Duffau H. Assessment of verbal working memory before and after surgery for low-grade glioma. J Neurooncol. 2007 Feb;81(3):305-13. doi: 10.1007/s11060-006-9233-y.

[404] Benzagmout M, Gatignol P, Duffau H. Resection of World Health Organization Grade II gliomas involving Broca's area: methodological and functional considerations. Neurosurgery. 2007 Oct;61(4):741-52; discussion 752-3. doi: 10.1227/01.NEU.0000298902.69473.77.

[405] Santini B, Talacchi A, Squintani G, Casagrande F, Capasso R, Miceli G. Cognitive outcome after awake surgery for tumors in language areas. J Neurooncol. 2012 Jun;108(2):319-26. doi: 10.1007/s11060-012-0817-4.

[406] Chan-Seng E, Moritz-Gasser S, Duffau H. Awake mapping for low-grade gliomas involving the left sagittal stratum: anatomofunctional and surgical considerations. J Neurosurg. 2014 May;120(5):1069-77. doi: 10.3171/2014.1.JNS132015.

[407] Lima GL, Duffau H. Is there a risk of seizures in "preventive" awake surgery for incidental diffuse low-grade gliomas? J Neurosurg. 2015 Jun;122(6):1397-405. doi: 10.3171/2014.9.JNS141396.

[408] Racine CA, Li J, Molinaro AM, Butowski N, Berger MS. Neurocognitive Function in Newly Diagnosed Low-grade Glioma Patients Undergoing Surgical Resection With Awake Mapping Techniques. Neurosurgery. 2015 Sep;77(3):371-9; discussion 379. doi: 10.1227/NEU.0000000000000779.

[409] Cochereau J, Herbet G, Duffau H. Patients with incidental WHO grade II glioma frequently suffer from neuropsychological disturbances. Acta Neurochir (Wien). 2016 Feb;158(2):305-12. doi: 10.1007/s00701-015-2674-3.

[410] Mandonnet E, De Witt Hamer P, Poisson I, Whittle I, Bernat AL, Bresson D, Madadaki C, Bouazza S, Ursu R, Carpentier AF, George B, Froelich S. Initial experience using awake surgery for glioma: oncological, functional, and employment outcomes in a consecutive series of 25 cases. Neurosurgery. 2015 Apr;76(4):382-9; discussion 389. doi: 10.1227/NEU.0000000000000644.

[411] Lindell AK. In your right mind: right hemisphere contributions to language processing and production. Neuropsychol Rev. 2006 Sep;16(3):131-48. doi: 10.1007/s11065-006-9011-9.

[412] Eisenson J. Language dysfunctions associated with right brain damage. Amer Speech Hear Assoc, 1959;1:107.

[413] Curtiss S, Schaeffer J. Syntactic development in children with hemispherectomy: the I-, D-, and C-systems. Brain Lang. 2005 Aug;94(2):147-66. doi: 10.1016/j.bandl.2004.12.004.

[414] Joanette Y, Goulet P. Word-naming in right-brain-damaged subjects. In: Chiarello C, editor. Right hemisphere contributions to lexical semantics. Berlin, Heidelberg (Germany): Springer; 1988. p. 1-18.

[415] Abusamra V, Côté H, Joanette Y, Ferreres A. Communication impairments in patients with right hemisphere damage. Life Span Disabil. 2009;12(1):67-82.

[416] Buchanan TW, Lutz K, Mirzazade S, Specht K, Shah NJ, Zilles K, Jäncke L. Recognition of emotional prosody and verbal components of spoken language: an

fMRI study. Brain Res Cogn Brain Res. 2000 Jun;9(3):227-38. doi: 10.1016/s0926-6410(99)00060-9.
[417] Bernard F, Lemée JM, Ter Minassian A, Menei P. Right hemisphere cognitive functions: from clinical and anatomic bases to brain mapping during awake craniotomy part I: clinical and functional anatomy. World Neurosurg. 2018;118:348-359.
[418] Herbet G, Moritz-Gasser S, Duffau H. Direct evidence for the contributive role of the right inferior fronto-occipital fasciculus in non-verbal semantic cognition. Brain Struct Funct. 2017;222(4):1597-1610.
[419] Kleber B, Friberg A, Zeitouni A, Zatorre R. Experience-dependent modulation of right anterior insula and sensorimotor regions as a function of noise-masked auditory feedback in singers and nonsingers. NeuroImage. 2017 Feb 15;147:97-110. doi: 10.1016/j.neuroimage.2016.11.059.
[420] Lester BD, Dassonville P. The role of the right superior parietal lobule in processing visual context for the establishment of the egocentric reference frame. J Cogn Neurosci. 2014;26(10):2201-2209.
[421] Mayer J, Wildgruber D, Riecker A, Dogil G, Ackermann H, Grodd W. Prosody production and perception: converging evidence from fMRI studies. In: International Speech Communication Association, editor. Proceedings of International Conference Speech Prosody 2002; 2002 Apr 11-13; Aix-en-Provence (France): ISCA; 2002. p. 487-490. Available from: https://www.isca-speech.org/archive/sp2002/papers/sp02_487.pdf
[422] Riecker A, Ackermann H, Wildgruber D, Dogil G, Grodd W. Opposite hemispheric lateralization effects during speaking and singing at motor cortex, insula and cerebellum. Neuroreport. 2000;11(9):1997-2000.
[423] Stoeckel MC, Weder B, Binkofski F, Choi HJ, Amunts K, Pieperhoff P, Shah NJ, Seitz RJ. Left and right superior parietal lobule in tactile object discrimination. Euro J Neurosci. 2004;19(4):1067-1072.
[424] Uddin LQ, Nomi JS, Hébert-Seropian B, Ghaziri J, Boucher O. Structure and Function of the Human Insula. J Clin Neurophysiol. 2017 Jul;34(4):300-306. doi: 10.1097/WNP.0000000000000377.
[425] Whitehead JC, Armony JL. Singing in the brain: Neural representation of music and voice as revealed by fMRI. Hum Brain Mapp. 2018 Dec;39(12):4913-4924. doi: 10.1002/hbm.24333.
[426] Wildgruber D, Hertrich I, Ackermann H, Riecker A, Grodd, W. Processing of linguistic and affective aspects of speech intonation evaluated by fMRI. NeuroImage. 2001 Jun;13(6 Suppl):627.

Appendices

Appendix A. Experimental Right Hemisphere Test

It is widely accepted that the language related brain functions are supported mainly -but not exclusively- by the dominant hemisphere [325,411]. According to the groundbreaking study of Rasmussen et al. [386], in most cases the dominant hemisphere is the left one (i.e., 95% of the right-handed and 70% of the left-handed). The last 50 years various studies have associated the right hemisphere to metalinguistic and pragmatic skills (e.g., non-literal meaning, speech acts), second language acquisition, lexical-semantics, prosody, discourse, and sign language [320,412-416].

In awake craniotomy context, there are several studies reporting right hemisphere patients undergoing awake brain surgery, but to our knowledge, none of them have addressed the specific language functions supported by the non-dominant hemisphere. An exception is the article published by Polczynska [192], who proposed a series of highly specialized tasks, although they were not tested inside the operating theatre.

The experimental test that was used on our right hemisphere patients consists of 9 tasks and most of them were based on the aforementionef article [192]. Table A.1 demonstrates the clinico-anatomical correlations, based on Bernard et al. [417], Herbet et al. [418], Kleber et al. [419], Lester et al. [420], Lindell [411], Mayer et al. [421], Riecker et al. [422], Stoeckel et al. [423], Uddin et al. [424], Whitehead et al. [425], and Wildgruber et al. [426], while Table A.2 and Figure A.1 briefly present the tasks that comprise the experimental right hemisphere test.

Table A.1
Right hemisphere brain areas and their corresponding speech and language functions.

Brain area	**Functions relative to speech and language**	**Tasks of eRHT** timed	not timed
Insular cortex	Intonation (and melody), interoception attention	Affective prosody (production), attention task	Singing
Inferior frontal gyrus	Prosody production (affective), paralinguistic features (eg, gestures), linguistic prosody (judgment)	Affective prosody (production), naming of emotions, non-literal language, linguistic prosody judgment	Conversational discourse, verbal fluency, singing
Superior temporal gyrus	Prosody comprehension (affective), auditory processing, pitch perception	Word repetition, affective prosody (comprehension), distant semantics, non-literal language	Semantic judgment, verbal fluency
Superior parietal lobule	Visual object recognition, imagery	Attention task, object naming	Object naming
Pre- & postcentral gyrus	Motor-sensory areas of the left side	Word repetition, object naming, motor planing	Conversational discourse, object naming
Inferior fronto-occipital fascicle	Non-verbal semantic cognition	Semantic odd-image out	Conversational discourse

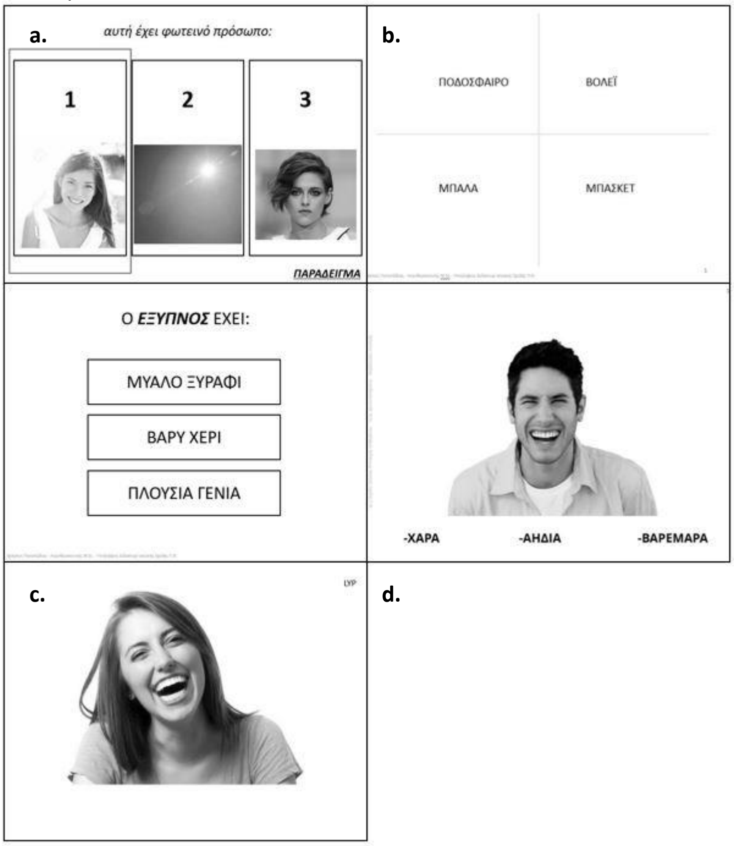
Other speech and language related functions related to the right hemisphere are: production of automatized speech, humor comprehension, narrative comprehension and production, distant semantics, naming of concrete words.

Table A.2
Description of the tasks comprising the protocol used in right hemisphere patients.

Task	Description	Stimuli
Comprehension of metaphors	The patient has to choose the correct image (out of three) that matches with the given metaphor (Fig. A.1.a)	Vis, Writ, Or
Distant semantics	The patient is asked to read the word that does not match with the other three semantically related words. The target word usually belongs to a subordinate category (Fig. A.1.b)	Writ
Non-literal language (production)	The patient has to read the metaphorical phrase that best describes the given word (Fig. A.1.c)	Writ / Or
Affective prosody judgment	The patient has to answer (with yes or no) if the orally given phrase matches the emotion-representing image (Fig. A.1.d)	Vis, Or
Affective prosody production	The patient is asked to produce the orally given phrase with three different emotions (happy, sad, angry). Phrases are semantically neutral and match in terms of pragmatics with all three emotions (e.g., "It will be very hot in July")	Or
Linguistic prosody judgment	The patient is asked to answer if the orally given phrase is a statement, a question, or an order	Or
Word repetition[a]	The patient has to repeat the orally given word	Or
Naming of emotions	The patient is asked to name the correct emotion, which is illustrated in the visually presented image (Fig. A.1.e)	Vis, Writ
Object naming[a]	The patient is asked to name the visually presented object.	Vis
Attention task	The patient has to choose the image that correctly fits to the pattern	Vis
Semantic odd-image out[a]	The patient has to choose the semantically non-matching image	Vis / Or
Motor planning[a]	The patient is asked to produce five times a sequence of syllables	Or

[a] Task deriving from GLAABS

Figure A.1
Examples of eRHT tasks



Appendix B. Supplementary data

Effects of demographic variables

		Main effect			Interaction		
		AG	**GE**	**ED**	**AG*GE**	**AG*ED**	**ED*GE**
Word repetition	*F*	-	-	-	-	-	-
	p	n/s	n/s	n/s	n/s	n/s	n/s
Motor planning	*F*	-	-	-	-	-	-
	p	n/s	n/s	n/s	n/s	n/s	n/s
Phon. odd-word out	*F*	2,839	-	-	-	-	-
	p	0,044**	n/s	n/s	n/s	n/s	n/s
Semantic odd-word out	*F*	-	-	-	-	-	-
	p	n/s	n/s	n/s	n/s	n/s	n/s
Semantic odd-image out	*F*	-	-	-	2,312	-	-
	p	n/s	n/s	n/s	0,083*	n/s	n/s
Verb naming	*F*	-	-	-	2,434	-	-
	p	n/s	n/s	n/s	0,072*	n/s	n/s
Object naming	*F*	-	-	-	-	-	-
	p	n/s	n/s	n/s	n/s	n/s	n/s
Semantic association	*F*	3,829		-	-	-	-
	p	0,013**	0,066*	n/s	n/s	n/s	n/s
Sentence completion w	*F*	-	-	-	-	-	-
	p	n/s	n/s	n/s	n/s	n/s	n/s
Verb generation	*F*	-	-	-	-	-	-
	p	n/s	n/s	n/s	n/s	n/s	n/s
Sentence completion s	*F*	-	-	-	-	-	-
	p	n/s	n/s	n/s	n/s	n/s	n/s
Phonological judgment	*F*	-	14,215	3,769	-	-	4,632
	p	n/s	0,001***	0,056*	n/s	n/s	0,035**
Semantic judgment	*F*	-	-	-	-	-	-
	p	n/s	n/s	n/s	n/s	n/s	n/s
Grammaticality judgment	*F*	3,434	-	-	-	-	-
	p	0,021**	n/s	n/s	n/s	n/s	n/s
Action fluency (verbs)	*F*	-	-	9,170	-	-	-
	p	n/s	n/s	0,003***	n/s	n/s	n/s

Table 1 title: Summary of effects and interactions of demographic variables.
Table 1 description: Leg.: *AG*=age group, *GE*=gender, *ED*=education, *n/s*=not significant
Table 1 footnotes: *=marginally significant ($p \leq 0{,}10$), **=significant ($p \leq 0{,}05$), ***=highly significant ($p \leq 0{,}01$)

Differences between demographic groups

	Females (*n*=40)				Males (*n*=40)				M-W	
	Mean	**Median**	**SD**	**SE**	**Mean**	**Median**	**SD**	**SE**	***U***	***p***
Word repetition	60,00	60,00	0,000	0,0000	60,00	60,00	0,000	0,0000	n/a	n/a
Motor planning	5,97	6,00	0,158	0,0250	6,00	6,00	0,000	0,0000	780	0,330
Phonological odd-word out	22,63	23,00	1,055	0,1667	22,77	23,00	0,480	0,0758	792	0,912
Semantic odd-word out	19,65	20,00	0,864	0,1366	19,63	20,00	0,586	0,0926	714	0,282
Semantic odd-image	24,60	25,00	0,672	0,1062	24,80	25,00	0,464	0,0734	679	0,124
Verb naming	37,35	38,00	0,975	0,1542	37,17	37,50	1,130	0,1786	728	0,442
Object naming	108,35	109,00	1,099	0,1738	108,38	109,00	0,868	0,1372	799	0,996
Semantic association	18,13	18,00	1,181	0,1867	18,50	19,00	0,599	0,0947	677	0,192
Sentence completion (word)	20,52	21,00	0,640	0,1012	20,65	21,00	0,533	0,0844	729	0,418
Verb generation	13,80	14,00	1,363	0,2154	13,88	14,00	1,202	0,1901	800	1,000
Sentence completion (sentence)	4,63	4,40	1,186	0,1876	4,46	4,00	1,495	0,2364	638	0,119
Phonological judgment	20,95	21,00	0,221	0,0349	20,63	21,00	0,490	0,0775	540	<0 ,001***
Semantic judgment	23,00	23,00	0,000	0,000	22,95	23,00	0,221	0,0349	760	0,160
Grammaticali ty	19,68	20,00	0,526	0,0831	19,57	20,00	0,844	0,1334	778	0,788
Action fluency	25,57	25,00	6,097	0,9640	27,68	27,50	7,141	1,1291	643	0,131

Table 2 title: Differences in performance between females and males.
Table 2 description: Leg.: *M-W*=Mann-Whitney U test, *n/a*=data not available due to constant results
Table 2 footnotes: *=marginally significant ($p \leq 0,10$), **=significant ($p \leq 0,05$), ***=highly significant ($p \leq 0,01$)

Tasks	Cut-off score (2%ile)	10%ile	25%ile	50%ile	75%ile	100%ile
Word repetition	60,0	60,0	60,0	60,0	60,0	60,0
Motor planning	6,0	6,0	6,0	6,0	6,0	6,0
Phonological odd-word out	21,0	22,0	23,0	23,0	23,0	23,0
Semantic odd-word out	18,0	19,0	19,0	20,0	20,0	20,0
Semantic odd-image out	23,0	24,0	25,0	25,0	25,0	25,0
Verb naming	33,0	35,1	37,0	37,5	38,0	38,0
Object naming	106,0	107,0	108,0	109,0	109,0	109,0
Semantic association	17,0	18,0	18,0	19,0	19,0	19,0
Sentence completion (word)	19,0	20,0	20,0	21,0	21,0	21,0
Verb generation	9,0	13,0	13,0	14,0	15,0	15,0
Sentence completion (sentences)	2,7	3,1	3,3	4,0	5,2	8,7
Phonological judgment	20,0	20,0	20,0	21,0	21,0	21,0
Semantic judgment	22,0	23,0	23,0	23,0	23,0	23,0
Grammaticality judgment	17,0	18,0	20,0	20,0	20,0	20,0
Action fluency (verbs)	15,0	18,1	21,3	27,5	31,5	47,0

Table 3 title: Cut-off scores, 10%ile and quartiles for male participants.

Tasks	Cut-off score (2%ile)	10%ile	25%ile	50%ile	75%ile	100%ile
Word repetition	60,0	60,0	60,0	60,0	60,0	60,0
Motor planning	5,0	6,0	6,0	6,0	6,0	6,0
Phonological odd-word out	17,0	22,0	23,0	23,0	23,0	23,0
Semantic odd-word out	16,0	19,0	20,0	20,0	20,0	20,0
Semantic odd-image out	22,0	24,0	24,0	25,0	25,0	25,0
Verb naming	34,0	36,0	37,0	38,0	38,0	38,0
Object naming	103,0	108,0	108,0	109,0	109,0	109,0
Semantic association	14,0	17,0	18,0	18,0	19,0	19,0
Sentence completion (word)	19,0	20,0	20,0	21,0	21,0	21,0
Verb generation	9,0	12,0	13,0	14,0	15,0	15,0
Sentence completion (sentences)	2,5	3,6	3,9	4,4	5,2	8,9
Phonological judgment	20,0	21,0	21,0	21,0	21,0	21,0
Semantic judgment	23,0	23,0	23,0	23,0	23,0	23,0
Grammaticality judgment	18,0	19,0	19,0	20,0	20,0	20,0
Action fluency (verbs)	14,0	18,1	22,0	25,0	29,0	46,0

Table 4 title: Cut-off scores, 10%ile and quartiles for female participants.

	-12 (*n*=40)				+12 (*n*=40)				M-W	
	Mean	**Median**	**SD**	**SE**	**Mean**	**Median**	**SD**	**SE**	***U***	***p***
Word repetition	60,00	60,00	0,000	0,0000	60,00	60,00	0,000	0,0000	n/a	n/a
Motor planning	6,00	6,00	0,000	0,000	5,98	6,00	0,158	0,025	780	0,317
Phonological odd-word out	22,60	23,00	1,057	0,167	22,80	23,00	0,464	0,073	754	0,520
Semantic odd-word out	19,55	20,00	0,714	0,113	19,73	20,00	0,751	0,119	665	0,090*
Semantic odd-image out	24,78	25,00	0,480	0,076	24,62	25,00	0,667	0,106	718	0,292
Verb naming	37,10	38,00	1,215	0,192	37,43	38,00	0,844	0,133	710	0,334
Object naming	108,43	109,00	0,813	0,129	108,30	109,00	1,137	0,180	770	0,745
Semantic association	18,40	19,00	0,709	0,112	18,23	18,00	1,143	0,181	770	0,745
Sentence completion (word)	20,58	21,00	0,549	0,087	20,60	21,00	0,632	0,100	758	0,628
Verb generation	13,80	14,00	1,244	0,197	13,88	14,00	1,324	0,209	747	0,590
Sentence completion (sentences)	4,365	4,200	1,1544	0,1825	4,728	4,150	1,5030	0,2376	729	0,491
Phonological judgment	20,70	21,00	0,464	0,073	20,88	21,00	0,335	0,053	660	0,057*
Semantic judgment	22,97	23,00	0,158	0,025	22,97	23,00	0,158	0,025	800	1,000
Grammaticalit y	19,53	20,00	0,784	0,124	19,73	20,00	0,599	0,095	698	0,491
Action fluency	24,45	24,50	5,198	0,822	28,80	28,00	7,328	1,159	504	0,004***

Table 5 title: Differences in performance between participants with 12 or bellow years of education and or more than 12.
Table 5 description: Leg.: *M-W*=Mann-Whitney U test, *n/a*=data not available due to constant results
Table 5 footnotes: *=marginally significant ($p \leq 0,10$), **=significant ($p \leq 0,05$), ***=highly significant ($p \leq 0,01$)

Tasks	Cut-off score (2%ile)	10%ile	25%ile	50%ile	75%ile	100%ile
Word repetition	60,0	60,0	60,0	60,0	60,0	60,0
Motor planning	5,0	6,0	6,0	6,0	6,0	6,0
Phonological odd-word out	21,0	22,0	23,0	23,0	23,0	23,0
Semantic odd-word out	16,0	19,0	20,0	20,0	20,0	20,0
Semantic odd-image out	22,0	24,0	24,0	25,0	25,0	25,0
Verb naming	34,0	36,1	37,0	38,0	38,0	38,0
Object naming	103,0	107,0	108,0	109,0	109,0	109,0
Semantic association	14,0	17,1	18,0	18,0	19,0	19,0
Sentence completion (word)	19,0	20,0	20,0	21,0	21,0	21,0
Verb generation	9,0	12,1	13,0	14,0	15,0	15,0
Sentence completion (sentences)	2,5	3,2	3,7	4,2	5,7	8,9
Phonological judgment	20,0	20,0	21,0	21,0	21,0	21,0
Semantic judgment	22,0	23,0	23,0	23,0	23,0	23,0
Grammaticality judgment	18,0	19,0	20,0	20,0	20,0	20,0
Action fluency (verbs)	14,0	19,2	25,0	28,0	32,8	47,0

Table 6 title: Cut-off scores, 10%ile and quartiles for Education +12 group.

Tasks	Cut-off score (2%ile)	10%ile	25%ile	50%ile	75%ile	100%ile
Word repetition	60,0	60,0	60,0	60,0	60,0	60,0
Motor planning	6,0	6,0	6,0	6,0	6,0	6,0
Phonological odd-word out	17,0	22,0	23,0	23,0	23,0	23,0
Semantic odd-word out	17,0	19,0	19,0	20,0	20,0	20,0
Semantic odd-image out	23,0	24,0	25,0	25,0	25,0	25,0
Verb naming	33,0	35,0	36,3	38,0	38,0	38,0
Object naming	106,0	107,0	108,0	109,0	109,0	109,0
Semantic association	17,0	17,0	18,0	19,0	19,0	19,0
Sentence completion (word)	19,0	20,0	20,0	21,0	21,0	21,0
Verb generation	9,0	12,1	13,0	14,0	15,0	15,0
Sentence completion (sentences)	2,7	3,1	3,5	4,2	4,8	8,5
Phonological judgment	20,0	20,0	20,0	21,0	21,0	21,0
Semantic judgment	22,0	23,0	23,0	23,0	23,0	23,0
Grammaticality judgment	17,0	18,0	19,0	20,0	20,0	20,0
Action fluency (verbs)	15,0	17,1	21,0	24,5	28,8	35,0

Table 7 title: Cut-off scores, 10%ile and quartiles for Education -12 group.

Age groups	Ages	Mean	SD	SE	K-W	
					χ^2	***p***
Word repetition	**20-29**	60,00	0,000	0,0000	n/a	n/a
	30-39	60,00	0,000	0,0000		
	40-49	60,00	0,000	0,0000		
	50-60	60,00	0,000	0,0000		
Motor planning	**20-29**	6,00	0,000	0,0000	3,000	0,392
	30-39	6,00	0,000	0,0000		
	40-49	5,95	0,224	0,0500		
	50-60	6,00	0,000	0,0000		
Phonological odd-word out	**20-29**	22,90	0,308	0,0688	9,531	0,023**
	30-39	22,95	0,224	0,0500		
	40-49	22,30	1,380	0,3086		
	50-60	22,65	0,671	0,1500		
Semantic odd-word out	**20-29**	19,50	0,761	0,1701	4,565	0,207
	30-39	19,90	0,308	0,0688		
	40-49	19,50	0,946	0,2115		
	50-60	19,65	0,745	0,1666		
Semantic odd-image out	**20-29**	24,65	0,813	0,1817	8,473	0,037**
	30-39	24,95	0,224	0,0500		
	40-49	24,70	0,470	0,1051		
	50-60	24,50	0,607	0,1357		
Verb naming	**20-29**	37,30	0,923	0,2065	1,320	0,724
	30-39	37,35	1,137	0,2542		
	40-49	37,45	0,759	0,1698		
	50-60	36,95	1,317	0,2945		
Object naming	**20-29**	108,20	1,361	0,3044	3,645	0,302
	30-39	108,70	0,571	0,1277		
	40-49	108,25	0,967	0,2161		
	50-60	108,30	0,865	0,1933		
Semantic association	**20-29**	18,30	1,174	0,2626	14,771	0,002***
	30-39	18,75	0,550	0,1230		
	40-49	18,40	0,598	0,1338		
	50-60	17,80	1,105	0,2471		
Sentence completion (word)	**20-29**	20,35	0,671	0,1500	4,446	0,217
	30-39	20,65	0,489	0,1094		
	40-49	20,65	0,671	0,1500		
	50-60	20,70	0,470	0,1051		
Verb generation	**20-29**	13,50	1,433	0,3204	2,312	0,510
	30-39	14,15	0,875	0,1957		
	40-49	13,90	1,252	0,2800		
	50-60	13,80	1,473	0,3293		
Sentence completion (sentences)	**20-29**	4,92	1,497	0,3347	3,709	0,295
	30-39	4,16	0,914	0,2044		
	40-49	4,55	1,414	0,3161		
	50-60	4,55	1,458	0,3259		
Phonological judgment	**20-29**	20,85	0,366	0,0819	0,811	0,847
	30-39	20,80	0,410	0,0918		

	40-49	20,75	0,444	0,0993		
	50-60	20,75	0,444	0,0993		
Semantic judgment	**20-29**	22,95	0,224	0,0500	2,026	0,567
	30-39	23,00	0,000	0,0000		
	40-49	23,00	0,000	0,0000		
	50-60	22,95	0,224	0,0500		
Grammaticality judgment	**20-29**	19,80	0,410	0,0918	9,305	0,025**
	30-39	19,90	0,308	0,0688		
	40-49	19,50	0,946	0,2115		
	50-60	19,30	0,801	0,1792		
Action fluency	**20-29**	28,60	7,514	1,6802	2,499	0,475
	30-39	26,60	7,029	1,5718		
	40-49	26,60	7,163	1,6016		
	50-60	24,70	4,520	1,0107		

Table 8 title: Differences in performance between age groups.
Table 8 description: Leg.: *K-W*=Kruskal-Wallis, *n/a*=data not available due to constant results
Table 8 footnotes:*=marginally significant ($p\leq0,10$), **=significant ($p\leq0,05$), ***=highly significant ($p\leq0,01$)

	Ages	**Age groups**	**D-S-C-F**
Phonological odd-word	20-29 and 40-49	1 – 3	0,026**
	30-39 and 40-49	2 – 3	0,008***
Semantic odd-image out	30-39 and 40-49	2 – 3	0,040**
	30-39 and 50-60	2 – 4	0,004***
Semantic association	30-39 and 40-49	2 – 3	0,034**
	20-29 and 50-60	1 – 4	0,028**
	30-39 and 50-60	2 – 4	0,001***
	40-49 and 50-60	3 – 4	0,036**
Grammaticality judgment	20-29 and 50-60	1 – 4	0,029**
	30-39 and 50-60	2 – 4	0,005***

Table 9 title: Post-hoc results between age groups.
Table 9 description: Leg.: D-S-C-F=Dwass-Steel-Critchlow-Fligner,
Table 9 footnotes: *=marginally significant ($p\leq0,10$), **=significant ($p\leq0,05$), ***=highly significant ($p\leq0,01$)

Tasks	Cut-off score (2%ile)	10%ile	25%ile	50%ile	75%ile	100%ile
Word repetition	60,0	60,0	60,0	60,0	60,0	60,0
Motor planning	6,0	6,0	6,0	6,0	6,0	6,0
Phonological odd-word out	22,0	22,1	23,0	23,0	23,0	23,0
Semantic odd-word out	18,0	18,0	19,0	20,0	20,0	20,0
Semantic odd-image out	22,0	23,1	25,0	25,0	25,0	25,0
Verb naming	35,0	36,0	37,0	38,0	38,0	38,0
Object naming	103,0	107,1	108,0	108,5	109,0	109,0
Semantic association	14,0	17,1	18,0	19,0	19,0	19,0
Sentence completion (word)	19,0	19,1	20,0	20,0	21,0	21,0
Verb generation	9,0	12,0	13,0	14,0	14,0	15,0
Sentence completion (sentences)	2,7	3,1	4,1	4,7	5,3	8,7
Phonological judgment	20,0	20,0	21,0	21,0	21,0	21,0
Semantic judgment	22,0	23,0	23,0	23,0	23,0	23,0
Grammaticality judgment	19,0	19,0	20,0	20,0	20,0	20,0
Action fluency (verbs)	14,0	21,1	24,3	27,5	31,5	47,0

Table 10 title: Cut-off scores, 10%ile and quartiles for 20-29 age group.

Tasks	Cut-off score (2%ile)	10%ile	25%ile	50%ile	75%ile	100%ile
Word repetition	60,0	60,0	60,0	60,0	60,0	60,0
Motor planning	6,0	6,0	6,0	6,0	6,0	6,0
Phonological odd-word out	22,0	23,0	23,0	23,0	23,0	23,0
Semantic odd-word out	19,0	19,1	20,0	20,0	20,0	20,0
Semantic odd-image out	24,0	25,0	25,0	25,0	25,0	25,0
Verb naming	33,0	37,0	37,0	38,0	38,0	38,0
Object naming	107,0	108,0	108,3	109,0	109,0	109,0
Semantic association	17,0	18,0	19,0	19,0	19,0	19,0
Sentence completion (word)	20,0	20,0	20,0	21,0	21,0	21,0
Verb generation	13,0	13,0	13,0	14,0	15,0	15,0
Sentence completion (sentences)	2,5	3,1	3,4	4,2	4,7	6,3
Phonological judgment	20,0	20,0	21,0	21,0	21,0	21,0
Semantic judgment	23,0	23,0	23,0	23,0	23,0	23,0
Grammaticality judgment	19,0	19,1	20,0	20,0	20,0	20,0
Action fluency (verbs)	17,0	17,2	21,3	26,0	29,0	46,0

Table 11 title: Cut-off scores, 10%ile and quartiles for 30-39 age group.

Tasks	Cut-off score (2%ile)	10%ile	25%ile	50%ile	75%ile	100%ile
Word repetition	60,0	60,0	60,0	60,0	60,0	60,0
Motor planning	5,0	6,0	6,0	6,0	6,0	6,0
Phonological odd-word out	17,0	21,1	22,0	23,0	23,0	23,0
Semantic odd-word out	16,0	19,0	19,0	20,0	20,0	20,0
Semantic odd-image out	24,0	24,0	24,0	25,0	25,0	25,0
Verb naming	36,0	36,0	37,0	38,0	38,0	38,0
Object naming	106,0	107,0	107,3	109,0	109,0	109,0
Semantic association	17,0	18,0	18,0	18,0	19,0	19,0
Sentence completion (word)	19,0	19,1	20,3	21,0	21,0	21,0
Verb generation	11,0	11,2	13,0	14,0	15,0	15,0
Sentence completion (sentences)	3,0	3,1	3,3	4,1	5,7	7,2
Phonological judgment	20,0	20,0	20,3	21,0	21,0	21,0
Semantic judgment	23,0	23,0	23,0	23,0	23,0	23,0
Grammaticality judgment	17,0	18,0	19,3	20,0	20,0	20,0
Action fluency (verbs)	15,0	17,2	21,0	25,5	33,0	43,0

Table 12 title: Cut-off scores, 10%ile and quartiles for 40-49 age group.

Tasks	Cut-off score (2%ile)	10%ile	25%ile	50%ile	75%ile	100%ile
Word repetition	60,0	60,0	60,0	60,0	60,0	60,0
Motor planning	6,0	6,0	6,0	6,0	6,0	6,0
Phonological odd-word out	21,0	21,1	22,3	23,0	23,0	23,0
Semantic odd-word out	17,0	19,0	19,3	20,0	20,0	20,0
Semantic odd-image out	23,0	24,0	24,0	25,0	25,0	25,0
Verb naming	34,0	35,0	36,0	37,5	38,0	38,0
Object naming	106,0	107,0	108,0	108,5	109,0	109,0
Semantic association	14,0	17,0	17,3	18,0	18,0	19,0
Sentence completion (word)	20,0	20,0	20,0	21,0	21,0	21,0
Verb generation	9,0	12,1	13,0	14,0	15,0	15,0
Sentence completion (sentences)	3,2	3,2	3,6	4,0	5,7	8,9
Phonological judgment	20,0	20,0	20,3	21,0	21,0	21,0
Semantic judgment	22,0	23,0	23,0	23,0	23,0	23,0
Grammaticality judgment	18,0	18,0	19,0	19,5	20,0	20,0
Action fluency (verbs)	15,0	18,0	20,3	26,0	28,8	30,0

Table 13 title: Cut-off scores, 10%ile and quartiles for 50-60 age group.

Cut-off scores and descriptive statistics for separate groups

		Age Group 20-29 (1)		Age Group 30-39 (2)		Age Group 40-49 (3)		Age Group 50-60 (4)	
		-12	+12	-12	+12	-12	+12	-12	+12
Word repetition	Mean	60	60	60	60	60	60	60	60
	Median	60	60	60	60	60	60	60	60
	SD	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000
	Range	60-60	60-60	60-60	60-60	60-60	60-60	60-60	60-60
	2%ile	60	60	60	60	60	60	60	60
Motor planning	Mean	6	6	6	6	6	5,90	6	6
	Median	6	6	6	6	6	6	6	6
	SD	0,000	0,000	0,000	0,000	0,000	0,316	0,000	0,000
	Range	6-6	6-6	6-6	6-6	6-6	5-6	6-6	6-6
	2%ile	6	6	6	6	6	5	6	6
Phonological odd-word out	Mean	22,90	22,90	23	22,90	22	22,60	22,50	22,80
	Median	23	23	23	23	22,50	23	23	23
	SD	0,316	0,316	0,000	0,316	1,826	0,699	0,850	0,422
	Range	22-23	22-23	23-23	22-23	17-23	21-23	21-23	22-23
	2%ile	22	22	23	22	17	21	21	22
Semantic odd-word out	Mean	19,30	19,70	19,90	19,90	19,60	19,40	19,40	19,90
	Median	19,50	20	20	20	20	20	20	20
	SD	0,823	0,675	0,316	0,316	0,516	1,265	0,966	0,316
	Range	18-20	18-20	19-20	19-20	19-20	16-20	17-20	19-20
	2%ile	18	18	19	19	19	16	17	19
Semantic odd-image out	Mean	24,90	24,40	25	24,90	24,80	24,60	24,40	24,60
	Median	25,00	25	25	25	25	25	24,50	25
	SD	0,315	1,075	0,000	0,316	0,422	0,516	0,699	0,516
	Range	24-25	22-25	25-25	24-25	24-25	24-25	23-25	24-25
	2%ile	24	22	25	24	24	24	23	24
Verb naming	Mean	37,10	37,50	37,10	37,60	37,60	37,30	36,60	37,30
	Median	37,50	38	37,50	38	38	37	37	38
	SD	1,101	0,707	1,524	0,516	0,843	0,675	1,265	1,337
	Range	35-38	36-38	33-38	37-38	36-38	36-38	35-38	34-38
	2%ile	35	36	33	37	36	36	35	34
Object naming	Mean	108,60	107,80	108,80	108,60	108,20	108,30	108,10	108,50
	Median	109	108	109	109	108,50	109	108,50	108,50
	SD	0,516	1,814	0,422	0,699	0,929	1,059	1,101	0,527
	Range	108-109	103-109	108-109	107-109	107-109	106-109	106-109	108-109
	2%ile	108	103	108	107	107	106	106	108
Semantic association	Mean	18,60	18	18,80	18,70	18,30	18,50	17,90	17,70
	Median	19	18	19	19	18	19	18	18
	SD	0,699	1,491	0,422	0,675	0,483	0,707	0,876	1,337
	Range	17-19	14-19	18-19	17-19	18-19	17-19	17-19	14-19
	2%ile	17	14	18	17	18	17	17	14
Sentence completion (words)	Mean	20,50	20,20	20,80	20,50	20,50	20,80	20,50	20,90
	Median	20,50	20	21	20,50	21	21	20,50	21
	SD	0,527	0,789	0,422	0,527	0,707	0,632	0,527	0,316
	Range	20-21	19-21	20-21	20-21	19-21	19-21	20-21	20-21
	2%ile	20	19	20	20	19	19	20	20
Verb generation	Mean	13,10	13,90	14,20	14,10	14,40	13,40	13,50	14,10
	Median	13,50	14	14,50	14	14,50	13,50	13	15
	SD	1,792	0,876	0,919	0,876	0,699	1,506	0,972	1,853
	Range	9-15	12-15	13-15	13-15	13-15	11-15	12-15	9-15
	2%ile	9	12	13	13	13	11	12	9
Sentence completion (sentences)	Mean	4,66	5,19	4,38	3,93	4,01	5,09	4,41	4,7
	Median	4,5	4,7	4,35	3,9	4	4,8	4,1	3,75
	SD	1,582	1,438	0,991	0,818	0,837	1,694	1,161	1,758
	Range	2,7-8,5	3,8-8,7	3,1-6,3	2,5-5,3	3-5,8	3,1-7,2	3,2-6,8	3,6-8,9
	2%ile	2,7	3,8	3,1	2,5	3	3,1	3,2	3,6
Phonological judgment	Mean	20,90	20,80	20,70	20,90	20,70	20,80	20,50	21
	Median	21	21	21	21	21	21	20,50	21
	SD	0,316	0,422	0,483	0,316	0,483	0,422	0,527	0,000
	Range	20-21	20-21	20-21	20-21	20-21	20-21	20-21	21-21
	2%ile	20	20	20	20	20	20	20	21
Semantic judgment	Mean	23	22,90	23	23	23	23	22,90	23
	Median	23	23	23	23	23	23	23	23
	SD	0,000	0,316	0,000	0,000	0,000	0,000	0,316	0,000
	Range	23-23	22-23	23-23	23-23	23-23	23-23	22-23	23-23
	2%ile	23	22	23	23	23	23	22	23

Grammaticality judgment	Mean	19,80	19,80	19,80	20	19,30	19,70	19,20	19,40
	Median	20	20	20	20	20	20	19	20
	SD	0,422	0,422	0,422	0,000	1,160	0,675	0,789	0,843
	Range	19-20	19-20	19-20	20-20	17-20	18-20	18-20	18-20
	2%ile	19	19	19	20	17	18	18	18
Action fluency (verbs)	Mean	27,20	30	23,90	29,30	24,70	28,50	22	27,40
	Median	27,50	28	23,50	28	23,50	28	22	28,50
	SD	3,736	10,044	5,859	7,334	6,219	7,849	3,830	3,502
	Range	22-34	14-47	17-35	21-46	15-34	17-43	15-26	18-30
	2%ile	22	14	17	21	15	17	15	18

Table 14 title: Cut-off scores and descriptive statistics for age and education groups.

		Age Group 20-29 (1)		Age Group 30-39 (2)		Age Group 40-49 (3)		Age Group 50-60 (4)	
		Males	**Females**	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**
Word repetition	Mean	60	60	60	60	60	60	60	60
	Median	60	60	60	60	60	60	60	60
	SD	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000
	Range	60-60	60-60	60-60	60-60	60-60	60-60	60-60	60-60
	2%ile	60	60	60	60	60	60	60	60
Motor planning	Mean	6	6	6	6	6	5,90	6	6
	Median	6	6	6	6	6	6	6	6
	SD	0,000	0,000	0,000	0,000	0,000	0,316	0,000	0,000
	Range	6-6	6-6	6-6	6-6	6-6	5-6	6-6	6-6
	2%ile	6	6	6	6	6	5	6	6
Phonological odd-word out	Mean	22,80	23	23	22,90	22,30	22,30	23	22,30
	Median	23	23	23	23	22	23	23	22,50
	SD	0,422	0,000	0,000	0,316	0,675	1,889	0,000	0,823
	Range	22-23	23-23	23-23	22-23	21-23	17-23	23-23	21-23
	2%ile	22	23	23	22	21	17	23	21
Semantic odd-word out	Mean	19,30	19,70	19,80	20	19,70	19,30	19,70	19,60
	Median	19,50	20	20,00	20	20	20	20	20
	SD	0,823	0,675	0,422	0,000	0,483	1,252	0,493	0,966
	Range	18-20	18-20	19-20	20-20	19-20	16-20	19-20	17-20
	2%ile	18	18	19	20	19	16	19	17
Semantic odd-image out	Mean	25	24,30	25	24,90	24,60	24,80	24,60	24,40
	Median	25	25	25	25	25	25	25	24
	SD	0,000	1,059	0,000	0,316	0,516	0,422	0,699	0,516
	Range	25-25	22-25	25-25	24-25	24-25	24-25	23-25	24-25
	2%ile	25	22	25	24	24	24	23	24
Verb naming	Mean	37	37,60	36,90	37,80	37,50	37,40	37,30	36,60
	Median	37	39	37	38	38	38	38	37
	SD	1,054	0,699	1,449	0,422	0,707	0,843	1,252	1,350
	Range	35-38	36-38	33-38	37-38	36-38	36-38	35-38	34-38
	2%ile	35	36	33	37	36	36	35	34
Object naming	Mean	108,40	108	108,90	108,50	108,10	108,40	108,10	108,50
	Median	108,50	108,50	109	109	108,50	109	108,50	108,50
	SD	0,699	1,826	0,316	0,707	0,994	0,966	1,101	0,527
	Range	107-109	103-109	108-109	107-109	107-109	106-109	106-109	108-109
	2%ile	107	103	108	107	107	106	106	108
Semantic association	Mean	18,60	18	18,90	18,60	18,40	18,40	18,10	17,50
	Median	19	18,50	19	19	18	18,50	18	18
	SD	0,516	1,563	0,316	0,699	0,516	0,699	0,738	1,354
	Range	18-19	14-19	18-19	17-19	18-19	17-19	17-19	14-19
	2%ile	18	14	18	17	18	17	17	14
Sentence completion (words)	Mean	20,30	20,40	20,60	20,70	20,90	20,40	20,80	20,60
	Median	20	20,50	21	21	21	21	21	21
	SD	0,675	0,699	0,516	0,483	0,316	0,843	0,422	0,516
	Range	19-21	19-21	20-21	20-21	20-21	19-21	20-21	20-21
	2%ile	19	19	20	20	20	19	20	20
Verb generation	Mean	13,20	13,80	13,90	14,40	14,40	13,40	14	13,60
	Median	14	14,00	14	15	15	14	14	14
	SD	1,687	1,135	0,876	0,843	0,843	1,430	1,054	1,838
	Range	9-15	12-15	13-15	13-15	13-15	11-15	12-15	9-15
	2%ile	9	12	13	13	13	11	12	9
Sentence completion (sentences)	Mean	5,47	4,38	3,85	4,46	4,16	4,94	4,36	4,75
	Median	5	4,5	3,9	4,45	3,4	4,5	3,9	4
	SD	1,920	0,618	0,542	1,124	1,637	1,096	1,171	1,740
	Range	2,7-8,7	3,0-5,1	3,1-4,8	2,5-6,3	3,0-7,2	3,7-7,2	3,2-6	3,6-8,9
	2%ile	2,7	3	3,1	2,5	3	3,7	3,2	3,6

Phonological judgment	Mean	20,80	20,90	20,60	21	20,50	21	20,60	20,90
	Median	21	21	21	21	20,50	21	21	21
	SD	0,422	0,316	0,516	0,000	0,527	0,000	0,516	0,316
	Range	20-21	20-21	20-21	21-21	20-21	21-21	20-21	20-21
	2%ile	20	20	20	21	20	21	20	20
Semantic judgment	Mean	22,90	23	23	23	23	23	22,90	23
	Median	23	23	23	23	23	23	23	23
	SD	0,316	0,000	0,000	0,000	0,000	0,000	0,316	0,000
	Range	22-23	23-23	23-23	23-23	23-23	23-23	22-23	23-23
	2%ile	22	23	23	23	23	23	22	23
Grammaticality judgment	Mean	19,90	19,70	20	19,80	19,20	19,80	19,20	19,40
	Median	20	20	20	20,00	20	20	20	19
	SD	0,316	0,483	0,000	0,422	1,135	0,632	1,033	0,516
	Range	19-20	19-20	20-20	19-20	17-20	18-20	18-20	19-20
	2%ile	19	19	20	19	17	18	18	19
Action fluency (verbs)	Mean	31,10	26,10	25,40	27,80	28,90	24,30	25,30	24,10
	Median	29,50	25	24,50	26,50	31	24	26,50	24,50
	SD	8,034	6,385	6,398	7,757	7,992	5,716	4,990	4,175
	Range	21-47	14-37	17-35	17-46	17-43	15-35	15-30	18-29
	2%ile	21	14	17	17	17	15	15	18

Table 15 title: Cut-off scores and descriptive statistics for age and gender groups.

Tasks	**Cut-off scores of sample**	**Cut-off scores for particular groups**
Word repetition	60	-
Motor planning	6	-
Phonological odd-word out	20	17 (40-49 age group)
Semantic odd-word out	17	-
Semantic odd-image out	23	22 (20-29 age group)
Verb naming	34	-
Object naming	105	
Semantic association	14	17 (30-39 & 40-49 age groups)
Sentence completion (word)	19	-
Verb generation	9	-
Sentence completion (sentences)	2,6	-
Phonological judgment	20	20
Semantic judgment	22	-
Grammaticality judgment	18	17 (40-49 age groups)
Action fluency (verbs)	15	14 (+12 years of education)

Table 16 title: Summary of different cut-off scores of groups that demonstrated statistically different scores.

Table 16 description: All scores are rounded since each point corresponds to one correct answer. Note that although we found significant differences in *phonological judgment* task between genders and age groups the cut-off scores remain essentially the same for all groups.

Appendix C. Dissertation related publications and awards

Journal articles

Papatzalas C, Papathanasiou I, Paschalis T, Tzerefos C, Kapsalaki E, Petsiti A, Fountas K. Left inferior longitudinal fascicle and reading: Exploring their relationship through a brain stimulation case study. Communic Dis Quart. Forthcoming 2021. (Journal's Impact Factor 0.863)

Papatzalas C, Fountas K, Kapsalaki E, Papathanasiou I. The Use of Standardized Intraoperative Language Tests in Awake Craniotomies: A Scoping Review. Neuropsychol Rev. 2021 Mar 31. doi: 10.1007/s11065-021-09492-6. Epub ahead of print. (Journal's Impact Factor 4.840)

Papatzalas C, Fountas K, Brotis A, Kapsalaki E, Papathanasiou I. The Greek linguistic assessment for awake brain surgery: development process and normative data. Clin Linguist Phon. 2021 May 4;35(5):458-488. doi: 10.1080/02699206.2020.1792997. Epub 2020 Jul 15. (Journal's Impact Factor 0.975)

Book chapters

Papatzalas C, Fountas K, Kapsalaki E, Papathanasiou I. Language Disorders in Neurosurgery. In: Coppens P, Papathanasiou I, editors. Aphasia and Related Neurogenic Communication Disorders. 3rd ed. Burlington (MA): Jones and Bartlett Publishers; 2021. p. 581-601.

Posters

Papatzalas C, Fountas K, Kapsalaki E, Papathanasiou I. The role of left inferior longitudinal fascicle in reading: evidence from a brain stimulation case study. Poster session presented at: Annual Convention of the American Speech-Language-Hearing Association; 2019 November 21-23; Orlando (FL).

Papatzalas C, Fountas K, Paschalis T, Tzerefos C, Kapsalaki E, Petsiti A, Papathanasiou I. The role of left inferior longitudinal fascicle in reading: evidence from a case study. e-Poster session presented at: Intracranial Glioma Workshop from A to Z; 2019 May 6-8; Athens (Greece).

Lectures and presentations

Papatzalas C. Λειτουργική νευροαπεικόνιση του λόγου [Greek: Functional neuroimaging of language]. [Lecture] Αρχές Ακτινολογίας & Νευροαπεικόνιση. Postgraduate program in Clinical and Experimental Neurosurgery, Department of Medicine, National and Kapodistrian University of Athens. 4th June 2021.

Papatzalas C. Advanced issues in language assessment during awake brain surgery. [Lecture, online] Language Testing during Awake Brain Surgery. Erasmus Mundus postgraduate program in Clinical Linguistics (EMCL++). Faculty of Arts, University of Groningen.

Papatzalas C. Η Αξιολόγηση των λειτουργιών του λόγου στις κρανιοτομές σε αφύπνιση [Greek: The assessment of language functions in awake craniotomies]. [Lecture] Βασικές αρχές επείγουσας νευροχειρουργικής. Department of Medicine, University of Thessaly. 8th December 2020.

Papatzalas C. Λειτουργική νευροαπεικόνιση του λόγου [Greek: Functional neuroimaging of language]. [Lecture] Αρχές Ακτινολογίας & Νευροαπεικόνιση. Postgraduate program in Clinical and Experimental Neurosurgery, Department of Medicine, National and Kapodistrian University of Athens. 11th September 2020.

Papatzalas C. Λειτουργική νευροαπεικόνιση του λόγου [Greek: Functional neuroimaging of language]. [Lecture] Κλινική και λειτουργική νευροαπεικόνιση. Department of Medicine, University of Thessaly. 2nd May 2020.

Papatzalas C. Ογκολογικές αφασίες [Greek: Tumor-related aphasia]. [Lecture] Εξειδικευμένα θέματα αφασίας. Department of Speech & Language Therapy, University of Patras. 30th April 2020.

Papatzalas C. Λειτουργική νευροαπεικόνιση του λόγου [Greek: Functional neuroimaging of language]. [Lecture] MA01 Ανατομία-εφαρμοσμένη νευροανατομία, νευροφυσιολογία και νευροαπεικόνιση. Neurorehabilitation postgraduate program, Department of Medicine, University of Thessaly. 6th April 2020.

Papatzalas C. Η Αξιολόγηση των λειτουργιών του λόγου στις κρανιοτομές σε αφύπνιση [Greek: The assessment of language functions in awake craniotomies]. [Lecture] Βασικές αρχές επείγουσας νευροχειρουργικής. Department of Medicine, University of Thessaly. 13th December 2019.

Papatzalas C. Cortical & subcortical anatomy. [Presentation] Functional anatomy workshop. Intracranial Glioma Workshop: from A to Z, Athens, Greece. 9th May 2019.

Papatzalas C. Mapping language functions. [Lecture] Clinical and functional neuroimaging. Department of Medicine, University of Thessaly. 10th April 2019.

Papatzalas C. Διάγνωση και αντιμετώπιση ασθενούς με ενδοκρανιακό όγκο [Greek: Diagnosis and treatment management of a patient with intracranial tumor]. [Lecture] Βασικές αρχές επείγουσας νευροχειρουργικής. Department of Medicine, University of Thessaly. 14th December 2018.

Papatzalas C. Ελληνικό Διεγχειρητικό Γλωσσικό Πρωτόκολλο [Greek: Greek Intraoperative Language Protocol]. [Presentation] Department of Neurosurgery, General University Hospital of Larisa. 2nd November 2018.

Grands and awards

2018-2021 Doctorate research scholarship from the Greek State Scholarship Foundation (IKY), through the act "Strengthening Human Resources Research Potential via Doctorate Research" (MIS-5000432).