Handbook of Clinical Neurology, Vol. 208 (3rd series)
Cerebral Asymmetries
C. Papagno and P. Corballis, Editors
https://doi.org/10.1016/B978-0-443-15646-5.00041-5

Chapter 5

Oncology: Brain asymmetries in language-relevant brain tumors

DJAINA SATOER[1*], LILIT DULYAN[2,3], AND STEPHANIE FORKEL[2,3,4]

[1]*Department of Neurosurgery, Erasmus MC University Medical Center Rotterdam, The Netherlands*

[2]*Donders Institute for Brain Cognition Behaviour, Radboud University, Nijmegen, The Netherlands*

[3]*Brain Connectivity and Behaviour Laboratory, Sorbonne Universities, Paris, France*

[4]*Centre for Neuroimaging Sciences, Department of Neuroimaging, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom*

Abstract

Brain tumors are classified as rare diseases, with an annual occurrence of 300,000 cases and account for an annual loss of 241,000 lives, highlighting their devastating nature. Recent advancements in diagnosis and treatment have significantly improved the management and care of brain tumors. This chapter provides an overview of the common types of primary brain tumors affecting language functions—gliomas and meningiomas. Techniques for identifying and mapping critical language areas, including the white matter language system, such as awake brain tumor surgery and diffusion-weighted tractography, are pivotal for understanding language localization and informing personalized treatment approaches. Numerous studies have demonstrated that gliomas in the dominant hemisphere can lead to (often subtle) impairments across various cognitive domains, with a particular emphasis on language. Recently, increased attention has been directed toward (nonverbal) cognitive deficits in patients with gliomas in the nondominant hemisphere, as well as cognitive outcomes in patients with meningiomas, a group historically overlooked. A patient-tailored approach to language and cognitive functions across the pre-, intra-, and post-operative phases is mandatory for brain tumor patients to preserve quality of life. Continued follow-up studies, in conjunction with advanced imaging techniques, are crucial for understanding the brain's potential for neuroplasticity and optimizing patient outcomes.

INCIDENCE, PREVALENCE, AND PROGNOSIS OF BRAIN TUMORS

Types of brain tumors

A brain tumor is characterized by an accumulation of abnormal cells that proliferate, resulting in a growing mass of tissue infiltrating into or pressing on healthy brain tissue. This chapter focuses on primary (as opposed to metastatic) brain tumors, which originate in the brain (gliomas) or its surrounding tissues (meninges).

Gliomas and meningiomas are the prevailing types of brain tumors in humans. Among them, malignant gliomas are the most aggressive and with fatal variation. Conversely, meningiomas are typically benign but often reappear following surgical intervention. These tumors differ concerning their origin and their effects on surrounding brain areas. However, both tumor types can affect brain areas that are involved in sensorimotor language [often referred to as "eloquent areas," although this is dependent on the neurosurgeon's definition of "functional" tissue; see Rammeloo et al., 2023 for a systematic review on the assessment of eloquence in neurosurgery], and other higher cognitive functions. These tumors can be further dichotomized into low-grade, grade I or II, and high-grade, grade III or IV, according to the World Health Organization (WHO) (Louis et al., 2016, 2021). This distinction is based on the cell type a tumor originates from and is determined by histology. Low-grade brain tumors have relatively slow growth rates, whereas high-grade brain tumors have a more aggressive evolution (see later the molecular features). Early diagnosis is linked to longer survival times (NCIN, 2013).

Gliomas are intra-axial tumors within the brain tissue (brain parenchyma). These infiltrating tumors originate from glial

---

*Correspondence to: Djaina Satoer, Department of Neurosurgery, Erasmus MC University Medical Center Rotterdam, The Netherlands. Tel: +31-650008179, E-mail: d.satoer@erasmusmc.nl

cells. Gliomas are the most frequently occurring primary brain tumors with approximately 1000 new diagnoses (incidence) of adult gliomas every year in the Netherlands alone, of which 20% are low grade (Ho et al., 2014). Worldwide, more than 250,000 new cases of primary brain tumors are diagnosed every year, of which 77% are gliomas (Walsh and Hiroko Ohgaki, 2016). Furthermore, low-grade gliomas (LGG) affect relatively young individuals resulting in a mean age at diagnosis of 42 years (Ho et al., 2014). LGGs are usually discovered rather late when a patient develops overt symptoms, such as epileptic seizures, which is the most frequent symptom (58% according to a Danish Neuro-Oncology Registry (Rasmussen et al., 2017), mild language, and/or other cognitive impairments (43%), or headaches (35%). However, it may take many years before symptoms of an LGG become apparent because of its slow growth rate with a diameter expansion of approximately 4 mm/year (Mandonnet et al., 2003). This slow growth pattern offers the brain time to slowly adjust and compensate by enhancing neuroplasticity leading to functional and/or structural reorganization. LGGs, which tend to be WHO grade II tumors in adults, eventually progress to higher grades of malignancy (WHO grades III and IV; high-grade glioma—HGG) within approximately 5–10 years (Hervey-Jumper and Berger, 2016). For LGGs residing in language relevant areas, the gold standard treatment is considered to be a maximal resection with the help of direct electrical stimulation (DES) during awake surgery. Using a personalized and direct approach to mapping the language-relevant network in each patient minimizes the damaging of functional tissue, which would otherwise have resulted in irreversible neurologic and cognitive damage (Duffau et al., 2002; Thiebaut de Schotten et al., 2005; De Witt Hamer et al., 2012) (see Gliomas (awake surgery) section for more details). HGGs (otherwise referred to as anaplastic astrocytoma or oligodendroglioma, glioblastoma) are very aggressive tumors with an unfavorable prognosis. Among them, glioblastoma has the most devastating prognosis with 12–15 months survival time after diagnosis (Stupp et al., 2005), whereas the anaplastic and mixed type are less aggressive (WHO grade III). Due to their faster growth rate, neurologic deficits are common in this patient group and if they affect language systems, patients present with (moderate to severe) aphasia. Although HGGs may develop at all ages, they typically occur between 50 and 60 years of age (Preusser et al., 2011).

More recently, several molecular markers have been identified to aid prognosis in gliomas (Cohen and Colman, 2015; Louis et al., 2021; Rudà et al., 2022). Some of the key markers are the following: (1) Isocitrate dehydrogenase 1 and 2 and wild-type (IDH1/2) mutations: IDH mutations are commonly observed in gliomas with IDH1 and 2 mutations and tend to have a more favorable outcome compared to IDH-wild type and to those without these mutations; (2) 1p/19q co-deletion: co-deletion of chromosome arms 1p and 19q is commonly observed in oligodendrogliomas, a subtype of glioma. This genetic alteration is associated with a better response to chemotherapy and longer overall survival; (3) O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation: MGMT is a DNA repair enzyme that can affect the response of gliomas to alkylating chemotherapy agents, such as temozolomide. Promoter methylation of the MGMT gene is associated with improved response to chemotherapy and a better prognosis; (4) Telomerase reverse transcriptase (TERT) promoter mutations: TERT promoter mutations are frequently found in gliomas and have been associated with a worse prognosis. They are more common in HGGs and are associated with increased tumor aggressiveness. The assessment of these markers, along with other clinical and histopathologic factors, can be of help in the prognosis and guidance for treatment decisions. Traditionally, surgical removal of glioblastomas is performed under general anesthesia with the goal of achieving a maximal safe resection (see Glioma (awake procedure) section for more discussion).

Meningiomas are extra-axial tumors, which means that they lie outside the brain parenchyma. These tumors arise from the meninges, which are the protective membranes surrounding the brain (i.e., dura mater, dura, and arachnoid). Even though meningiomas generally do not infiltrate brain tissue, they can compress adjacent brain areas and displace white matter (Piper et al., 2016). Meningiomas represent approximately one-third of all primary brain tumors, of which 90% are classified as WHO low-grade I, which is considered benign (Whittle et al., 2004; Wiemels et al., 2010). Approximately 500 adults with a symptomatic meningioma are diagnosed every year in the Netherlands (the Netherlands Cancer Registry, https://iknl.nl/en/ncr). However, many meningiomas are asymptomatic and remain undiagnosed for many years if not decades (Wiemels et al., 2010). Therefore, the overall meningioma incidence is presumably at least twice as high (Larjavaara et al., 2008). Symptomatic meningiomas are usually diagnosed between the ages of 40–70 years (Radhakrishnan et al., 1995). They can manifest through a wide range of symptoms, depending on size and location of the tumor. Possible symptoms include epileptic seizures (typically located in the temporal lobe), disturbed vision (occipital location), sensorimotor dysfunction (fronto-parietal location), cognitive decline, headaches, and other signs of increased intracranial pressure (Whittle et al., 2004). A significant number of meningiomas are discovered incidentally during brain scanning for other purposes (Whittle et al., 2004). Due to its extra-axial location, meningioma surgery is performed under general anesthesia without waking the patients up for language or sensorimotor testing. About 90% of meningiomas are benign (WHO grade I), 5%–7% are atypical (WHO grade II), and 1%–3% are considered anaplastic or malignant (WHO grade III) (Louis et al., 2007). Grade I meningioma patients have a relatively long life expectancy: more than half of the patients survive the first 20 years after surgery (van Alkemade et al., 2012). For grade II and III meningiomas, the 5-year and 10-year overall survival rates were 93.5% and 83.4%, respectively (Wang et al., 2016).

BRAIN TUMORS AND DIFFERENCES

Sex differences

Sex differences are observed between men and women with regard to glioblastomas (GBMs), primarily confined to incidence rates and outcomes. Our understanding of sex differences in GBM at the level of disease phenotype and genetic/molecular factors remains limited. Between 2008 and 2012 in the United States, approximately 55% of malignant brain tumors were diagnosed in men, while women accounted for 45%. In contrast, during the same period, around 36% of non-malignant brain tumors were observed in men, with women accounting for 64% (Gould, 2018) (see Fig. 5.1). Not only do the rates of occurrence of tumors vary but also the side effects differ between the sexes. For example, women tend to have more inflammation while men tend to have more edema as sex is linked to macrophage content and inflammatory gene expression in glioblastomas (Ochocka et al., 2023). These differences have partly been attributed to hormones affecting the microenvironment of a tumor whereby estrogens seemed to have a protective impact, while increased androgen receptor expression and elevated testosterone levels had a negative impact on GBM (Carrano et al., 2021). In LGG, sex-based differences have not been investigated thoroughly. However, a recent retrospective cohort study demonstrated that male sex was an independent risk factor for unfavorable outcomes as opposed to female sex. In addition, 1p19q co-deletion status is beneficial for overall survival and “next intervention free survival,” which was defined as “any treatment subsequent to adjuvant or salvage therapy or death” (Tewari et al., 2022). According to the Central Brain Tumor Registry of the United States (CBTRUS-CBTRUS, 2013–2017) and a population-based study in California, meningioma is more commonly observed in women and the risk was elevated between the ages of 27 and 37 years (Cote et al., 2022).

Cognitive difference with left- and right-hemispheric tumors

Neuroscience studies have recently identified that cognitive functions are much better understood for the left hemisphere (LH) than the right hemisphere (RH) (Thiebaut de Schotten et al., 2020; Talozzi et al., 2023). This discrepancy is mainly due to language processing being obviously impaired with left hemisphere lesions and most neuropsychologic assessments being language-based. Looking at the impact of LH and RH tumors, evidence suggests that patients with left-hemispheric GBMs have a worse prognosis compared to right GBMs. This observation was related to the shorter progression time with a faster functional decline possibly due to a more conservative surgical approach leaving more tumor tissue behind (Coluccia et al., 2018). Left-hemisphere lesions that impact

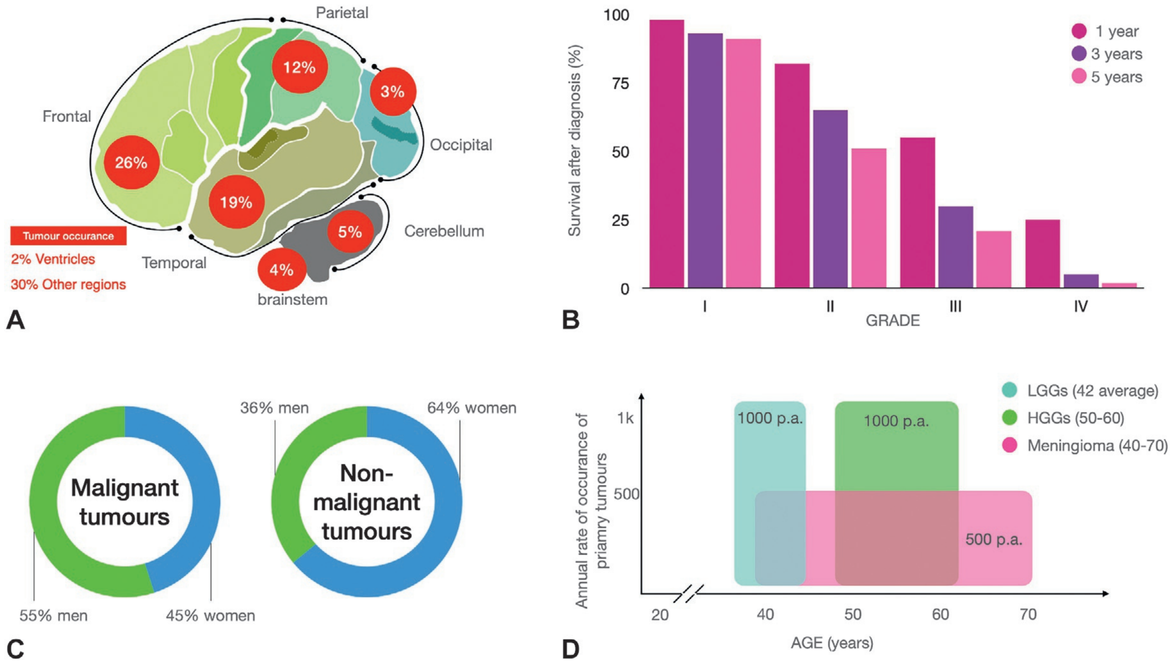

Fig. 5.1. Tumor statistics. Tumor occurrence per lobe (A), survival rate after diagnosis stratified by grading (B), mind the gap—sex differences in malignant vs nonmalignant tumors (C), and the age ranges associated with the occurrence of primary tumors (D). This figure is an original based on the data available from Gould J (2018). Breaking down the epidemiology of brain cancer. Nature 561: S40–S41.

language processing likely interfere with articulation, comprehension, syntactic sentence formation, and semantic access while right-hemisphere lesions tend to affect prosody, intonation, and emotional affect (Durfee et al., 2021; Sheppard et al., 2022). Impairments in the suprasegmental language functions of the right hemisphere have psychologic impacts on patients (e.g., monotonous speech) but interfere less with their daily life as patients are understood by others and can understand language. As such, cognitive testing has focused on left-hemisphere language functions. Consequently, tumors considered "eloquent" are typically left-hemisphere tumors, which can be closely linked to the definition of language and language in the brain. In a study of 489 tumor patients, no significant differences were observed between the hemispheres for the major tumor types. That said, LGGs and meningiomas had a tendency to occur slightly more frequently on the left side, albeit not significantly. Conversely, HGG exhibited a nonsignificant tendency to occur more often on the right side (Inskip et al., 2003).

The linguistic competency of each hemisphere is also relevant when looking at recovery after surgery. Different patterns of recovery in language and other cognitive functions have been associated with several neuronal adaptations. For example, Nieberlein et al. (2023) performed an extensive systematic review and described four different types of neural (language) reorganization in gliomas: (1) persisting (language) functions within the tumor, (2) perilesional reorganization, (3) reorganization in a distributed network of the affected hemisphere, (4) contralesional reorganization (i.e., RH in the case of LH dominant hemisphere), which is also associated by tumor grade. In addition, it is noted that specific tumor locations have different magnitudes for potential of reorganization. Nevertheless, right-hemispheric reorganization seems to occur rather late in the course of the disease, when interhemispheric plasticity (e.g., perilesional or via reorganization in a distributed network) is already utilized. Another aspect that has not been studied extensively to date is how gliomas affect language-related activity within the cerebellum. The cerebellum is known to show a crossed activation pattern with the contralateral cerebral hemisphere during language processing. However, there is some evidence for a crossed activation pattern in glioma patients (Méndez Orellana et al., 2015; Cho et al., 2018; Zhang et al., 2018). With the increasing interest in cerebellar contributions to cognition, future research ought to explore this aspect further. In the next section, we will parcellate the hemispheres into separate lobes.

Lobar differences

The frontal and temporal lobes in the left hemisphere are undeniably crucial for language functioning. However, a debate continues regarding, which frontal/temporal structures (Tremblay and Dick, 2016) and which additional structures in other lobes should be included in the language network. While the parietal and anterior temporal lobe also play roles in language processes, they are not always incorporated into models that focus exclusively on syntactic processing. Similarly, as discussed earlier, this uncertainty extends to the role of the entire right hemisphere. A statistical review of primary brain tumors diagnosed in the United States in 2008–2012 revealed that brain tumors are inhomogeneously distributed across the brain (Fig. 5.1A). Most tumors (26%) are in the frontal lobe, followed by temporal lobe tumors (19%), parietal tumors (12%), and cerebellar tumors (5%) while the brainstem (4%), occipital lobes (2%), and ventricular tumors (2%) are less common. The remaining 30% are in other regions (Gould, 2018) (see Fig. 5.1).

TECHNIQUES TO IDENTIFY TUMORS AFFECTING THE LANGUAGE SYSTEM

Noninvasive structural and functional techniques

Noninvasive techniques offer a valuable means to map the altered brain anatomy resulting from the presence of a tumor. These techniques can assess structural changes, functional alterations, and plasticity changes. The noninvasive nature of these techniques means they are applied externally, typically without medication administration, except in cases where patients have a low tolerance for confined spaces (e.g., claustrophobia).

Structural techniques primarily rely on magnetic resonance imaging (MRI) methods to investigate the cortical and subcortical structures (T1-weighted scans), to identify pathologic changes (T2-weighted scans) and to explore the connectivity of the brain (diffusion-weighted scans). However, structural MRI alone is insufficient to delineate the tumor margin precisely. Additionally, classical structural MRI sequences do not fully capture the impact on white matter architecture and individual pathways (Forkel and Catani, 2018). Diffusion-weighted imaging estimates the tumor's effect on brain connections, which can be infiltrated or displaced. Consequently, diffusion-weighted imaging often assesses and visualizes the brain's connections using white matter tractography, particularly in presurgical planning. Personalized tractography is crucial for patients since brain tumors can displace, disrupt, and infiltrate white matter, altering the expected trajectory compared to healthy brain atlases (Fig. 5.1A).

Given the importance of preserving subcortical pathways for optimal outcomes, tractography is increasingly used in the preoperative evaluation of awake surgery (Desmurget and Sirigu, 2015). However, there exists a disparity between the advances in research and the clinically FDA-approved algorithm for fiber reconstruction (Fig. 5.2C). While the neuroimaging community relies on high angular resolution diffusion imaging (HARDI) techniques, which can partially overcome fiber crossings (~90% of the brain) and track through edema, clinical applications often still employ tensor-based tractography, which reconstructs only one fiber orientation

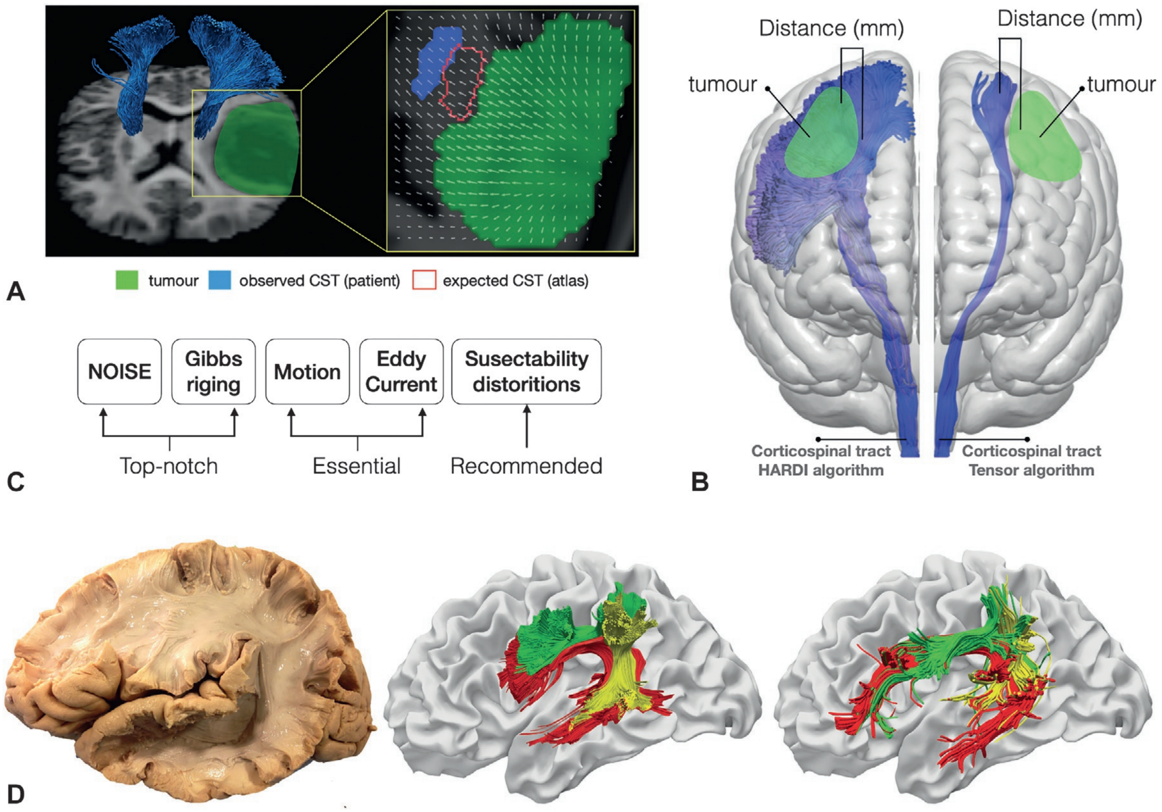

Fig. 5.2. Technical considerations in tractography reconstructions for brain tumors. Panel (A) emphasizes the limitations of atlas-based approaches due to white matter displacement. Panel (B) underscores the impact of algorithm selection on reconstruction reliability. Panel (C) presents the recommended preprocessing pipeline for tractography. Finally, panel (D) showcases the comparison between different techniques for visualizing the arcuate fasciculus using Klingler dissection (*left*, diffusion tensor imaging (DTI, *middle*) and spherical deconvolution (SD, *right*). Panels (A) and (B) are modified from Forkel SJ, Bortolami C, Dulyan L, et al. (in press). Dissecting white matter pathways: a neuroanatomical approach. In: Leemands A and Dell'Acqua F. (Eds). Handbook of Diffusion MRI Tractography. Reused and modified with permission from my coauthors. (DWI methods) Panels (C) and (D) are original.

per voxel, thereby underrepresenting the complexity of the connectional anatomy [for a review see Beyh et al., 2024]. Due to the alterations caused by the lesion, manual dissections of the white matter are recommended over atlas-based tools (Fig. 5.2A).

The steps for preprocessing diffusion-weighted imaging data for tractography depend on the acquisition quality but typically involve motion and eddy current corrections (Fig. 5.2B). It is highly recommended that susceptibility distortion corrections be performed, and research data should also undergo denoising and correction for Gibbs ringing where the data quality is sufficient (Perrone et al., 2015; Kellner et al., 2016). The choice of processing parameters and tracking algorithms directly influences the reconstruction of white matter. Traditional tensor-based algorithms, such as DTI, cannot resolve crossing fibers, leading to false positive and false negative reconstructions of the anatomy (Fig. 5.2C). Advanced algorithms based on high angular resolution diffusion imaging (HARDI) offer an improved resolution of fiber crossings and can visualize lateral projections that have been demonstrated using postmortem dissections (Dell'Acqua et al., 2013; Dell'Acqua and Tournier, 2019). However, these algorithms are more susceptible to false positive reconstructions and require comprehensive anatomic knowledge. In the case of tumors affecting language functions, tractography can selectively visualize the language network using these techniques [for detailed information, see Beyh et al., 2024, Ohlerth et al., in press]. A recent review has highlighted the variability observed in the cortical terminations of the arcuate fasciculus in the temporal lobe (Giampiccolo and Duffau, 2022) (see Fig. 5.2D). However, another recent review identified no one tract-one function association and suggests that language is a spatiotemporally dynamic process in the brain beyond the arcuate fasciculus (Forkel et al., 2022). The current anatomic understanding of the connectional language system includes seven pathways dichotomized into a dorsal and ventral stream depending on whether they arch above or below the lateral fissure. However, an intriguing

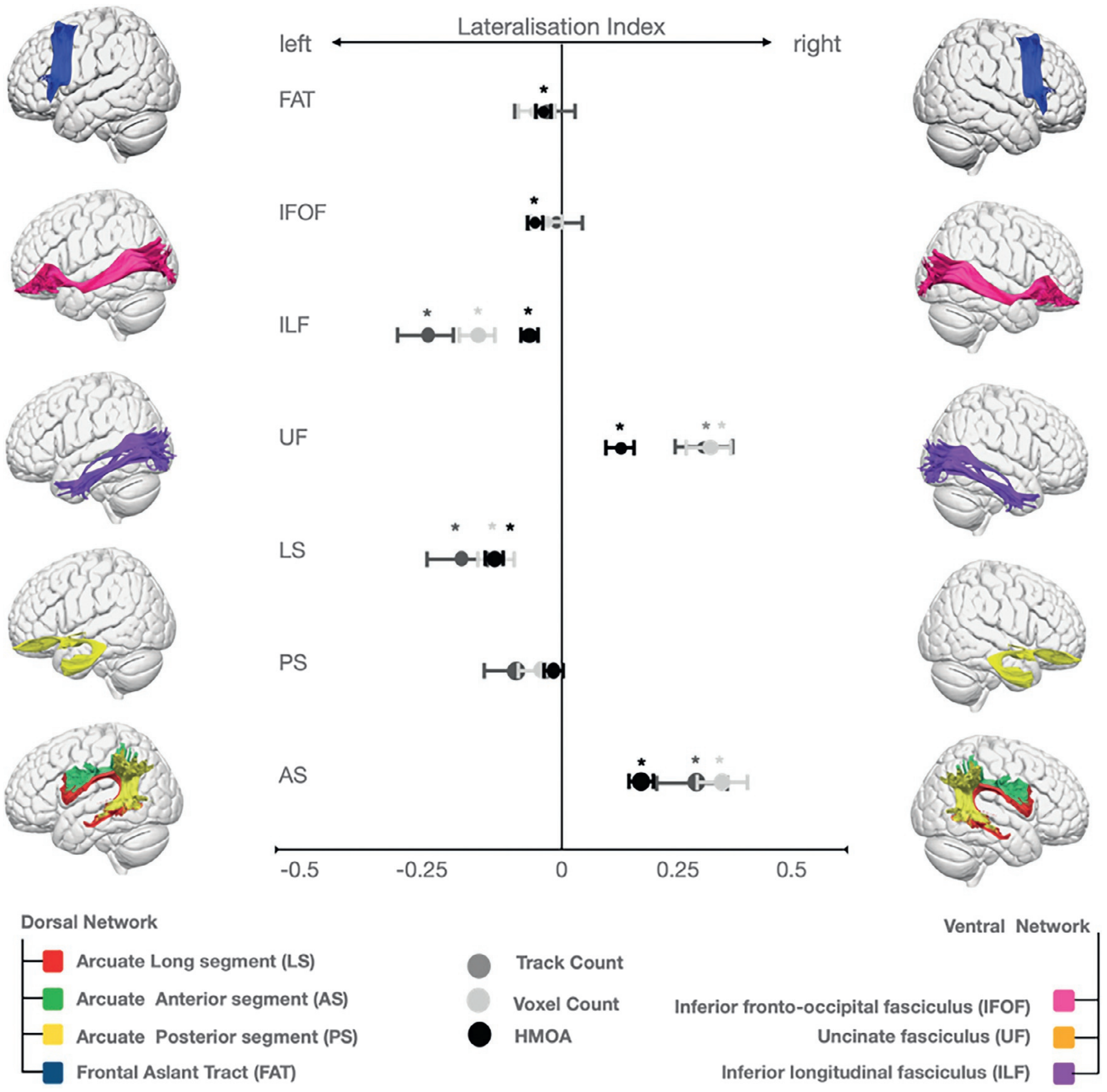

Fig. 5.3. White matter network asymmetry in the dorsal and ventral networks associated with language. Data shown are from the Human Connectome Project 7T data set (www.humanconnectome.com) and are available preprocessed from www.bcblab.com; HMOA: Hinderance Modulated Orientational Anisotropy. See Chapter 2 in this volume (Dulyan et al., 2025) for the asymmetry pattern of all white matter connections. This is an original figure.

question arises regarding the bilateral nature of these networks, considering that language is typically described as a unilateral function (Fig. 5.3).

On the functional side, two sequences can be acquired using MRI scanning: task-based functional MRI (fMRI) and non-task-based resting state functional imaging (rs-fMRI). fMRI is the most used noninvasive imaging technique to map brain functions. The word-verb association task and finger tapping are often used to localize linguistic and motor functions. In the neurosurgical setting, fMRI contributes to determining dominance for these functions. In addition, fMRI can be easily repeated in the postoperative period to study brain plasticity (Young et al., 2010). However, fMRI has several shortcomings. First, fMRI cannot discriminate between the activated "essential" and "compensable" regions. Second, motion-related artifacts decrease the reliability of fMRI findings. Third, the activation zones may vary depending on the paradigm chosen, the statistical method, and the underlying neurologic disorder. Fourth, the sensitivity of fMRI is limited. While fMRI has mapped the cortical language network of brain areas involved in language processing (e.g., Price, 2010), in clinical populations, its predictive power for the language-relevant cortex is limited (Kullmann, 2020) as revealed by comparison with DES (see Invasive techniques section) during awake surgery (Giussani et al., 2010). fMRI-DES match for motor mapping was estimated at approximately 71%, while the correlation for language mapping was only 66% (Bartos et al., 2009).

A technique that has proven reliable in the presurgical mapping of language functions is navigating transcranial magnetic stimulation (nTMS). nTMS is a noninvasive neurophysiologic technique that stimulates brain regions using an electromagnetic coil. Single-pulse nTMS is used as an activation tool to map the motor cortex, while repetitive nTMS has an inhibitory effect. Linguistic processes can be interrupted, leading to temporary speech errors (paraphasia) or even "speech arrest" (no speech output). This technique best approximates the effects of DES so that the patient also experiences preoperatively what a disruption of speech, such as a "speech arrest," feels like. A disadvantage is that TMS can be painful in the temporal regions due to stimulation of the facial nerves. Good correlations between nTMS and DES were reported for mapping the motor functions (Krieg et al., 2012). Localizing the language functions with nTMS, on the other hand, is complex; however, there is growing evidence with promising results for clinical neuro-oncologic settings (Picht et al., 2013; Tarapore et al., 2013; Sollmann et al., 2020) and the design of new linguistics test batteries for nTMS interventions is also in development (Ohlerth et al., 2020). Compared to fMRI, nTMS has a significantly higher sensitivity for identifying language functions. For example, nTMS correlates significantly higher with intraoperative DES and demonstrates better sensitivity and specificity (exceeding 99% and 83%, respectively) (Muir et al., 2022). This indicates that TMS can consistently identify critical language sites that match DES more reliably than fMRI-positive sites. Given the limited spatial resolution and low specificity of nTMS in posterior language regions, further research is needed before nTMS can fully replace fMRI for preoperative functional screening.

Brain activity can also be registered using electroencephalography (EEG). This noninvasive technique directly measures brain signals in real-time by electrodes affixed to the scalp. These signals are amplified, digitalized, and plotted as changes in voltage over time. EEG registration has a high temporal resolution, but its spatial resolution is low compared to structural MRI imaging. Alternatively, brain activity can be registered using magnetoencephalography (MEG), combining high temporal and relatively high spatial resolutions. However, EEG has the advantage of being less expensive and more widely available than MEG. Moreover, EEG is frequently used in clinical settings when brain dysfunction or epileptic seizures are suspected.

Finally, a recent ground-breaking and upcoming noninvasive technique concerns ultrasound stimulation, which can open the blood–brain barrier to optimize deliverance of an increased concentration of medication to a targeted brain area; see, for instance, GBM patients and patients with Alzheimer disease (Arrieta et al., 2024; Rezai et al., 2024).

Invasive techniques

Wilder Penfield (1891–1976) was the first to systematically examine language with DES in 190 patients with a brain lesion. He initially used the technique to detect motor functions and epileptic foci but also described speech and language areas in the brain by eliciting verbal paraphasias when stimulating a widely distributed surface of the brain. Based on this data, he proposed that dynamic connections exist within a cortical network that can compensate when "classic" linguistic areas "Broca's and Wernicke's area" in the left hemisphere are damaged (Penfield and Roberts, 1959) (for a critical evaluation of the terminology see (Dulyan and Forkel, 2024)). These findings were confirmed by George Ojemann in a study of 117 patients (Ojemann et al., 1989), where even more variation of critical language areas in the brain was observed in the language-dominant hemisphere.

The pioneers of white matter neurosurgery were the scholars of the Zurich school (Dziedzic et al., 2021). They paid close attention to the connectional anatomy of the brain when planning their entry routes to a tumor, aiming to minimize damage to the connective tissue. Neurosurgeon Hugues Duffau combined these methods and developed an entire "modern neurosurgical research" field. He discovered, among others, that apart from cortical language areas, it is extremely important to localize language functions at the subcortical level with DES (Duffau et al., 2002; Duffau, 2014). Not only the arcuate fasciculus (a dorsal tract) but also the frontal aslant tract (FAT, dorsal tract) and ventral tracts such as the inferior fronto-occipital fasciculus (IFOF), the inferior longitudinal fasciculus (ILF), and the uncinate fasciculus (UF) were described to play a role in language (Duffau et al., 2005; Duffau, 2014; Chang et al., 2015; Kemerdere et al., 2016). An exciting and recent development is digitally combining postmortem white matter dissections with in vivo virtual tractography-based dissections using brain dissection photogrammetry (https://bradipho.eu/). Merging diffusion tractography with photogrammetric dissection of the human brain offers a user-friendly framework to explore microdissection and tractography data within the same environment and can significantly improve neurosurgical training.

Nowadays, awake surgery with DES is the gold standard treatment for resecting LGGs in eloquent brain regions (De Witt Hamer et al., 2012). The motor mapping may optionally be performed under local anesthesia (using evoked potentials), while linguistic, cognitive, visual, and spatial mapping generally use an asleep-awake-asleep procedure. Cortical stimulation is usually performed with a bipolar stimulator generating biphasic and rectangular pulses of 1 ms each time. Frequencies from 50 to 60 Hz are used by default, and the intensity progressively increases from 1 to 10 mA in 0.5 mA increments. A stimulus time of 1 or 2 s is sufficient to elicit a motor response, while language inhibition requires 3–4 s. Subcortical stimulation is done in a similar way (stimulus time may be extended to 6 s) to identify functional subcortical pathways (Ojemann et al., 1989; Berger and Ojemann, 1992; Talacchi et al., 2013a,b).

Based on the location of the tumor and the patient's personal history (preoperative cognitive linguistic level, line of work, hobbies), a test battery is tailored to the patient's needs in the preoperative phase by a clinical linguist/speech-language therapist/neuropsychologist. The tests a patient can perform well preoperatively are selected for use during cortico-subcortical stimulation and throughout the resection. For example, an intraoperative test battery may consist of motor tasks (e.g., precentral gyrus, inferior frontal gyrus) and language tasks (e.g., perisylvian region), and also arithmetic tasks (e.g., angular gyrus), visual tasks (e.g., occipital lobe), visuospatial tasks (e.g., parietal regions), and mnestic tasks (e.g., hippocampal regions) or according to latest developments also (nonlinguistic) cognitive tasks for right-hemispheric functions, such as prosody, visuospatial and social cognitive functions to prevent unilateral neglect or deficits in facial emotion recognition, prosody, empathy, and theory of mind (Lemée et al., 2018) (see Gliomas (awake surgery) section for an elaborate discussion).

In the event of a motor response or inhibition of linguistic/cognitive/visual functions following DES, these critical areas are marked on the brain using numbered sterile tags reporting a particular type of response (see Fig. 5.4).

One of the main advantages of DES is its high sensitivity. The individual critical language zones are accurately identified, and differentiation between "essential" and "compensable" language zones is possible. Its high sensitivity explains why DES is used to validate noninvasive mapping techniques such as fMRI and TMS (Mandonnet et al., 2010). Furthermore, DES can be used to examine subcortical structures. As a result, essential subcortical connections can be detected during surgery. Since disconnection of the subcortical pathways can lead to severe neurologic deficits, cortical mapping is increasingly combined with subcortical mapping (Trinh et al., 2013). Hence, DES makes it possible to remove a tumor after identification of the functional (sub)cortical boundaries and can reduce the risk of postoperative disturbances. For this reason, DES is often associated with a good postoperative outcome and quality of life (De Witt Hamer et al., 2012). Intraoperative findings were found to have prognostic value for the level or presence of postoperative aphasia. For instance, intraoperative performance on The Pyramids and Palm Tree Test (PPTT) appeared to predict postoperative language outcomes (Chang et al., 2018), underlining the application of a semantic task intraoperatively. A recent systematic review on intraoperative language errors and outcome measures reported that the occurrence of anomia and speech initiation problems were significant predictors of postoperative acute language impairments in the context of production and spontaneous speech deficits (Collée et al., 2022), stressing the need for the administration of at least an object-naming task and the monitoring of spontaneous speech during awake surgery (see "Supplementary motor area syndrome and spontaneous speech" section for more details). Besides monitoring sensorimotor, language, and cognitive functions, awake surgery teams are exploring the potential of other skills relevant to the patient's daily life, such as mapping musical skills. A recent systematic review revealed the feasibility of mapping musical skills by asking patients to play in theater (reported so far: piano, saxophone, violin, guitar, and clarinet, e.g., violin: https://www.youtube.com/watch?v=o-oGpD_Nx5U, opera singer: https://www.youtube.com/watch?v=obiARnsKUAo&t=3s, guitar: https://youtu.be/dnzjZqgfZSc), and sing during awake surgery (Kappen et al., 2022a). They identified studies describing brain regions relevant for music production suggesting the added

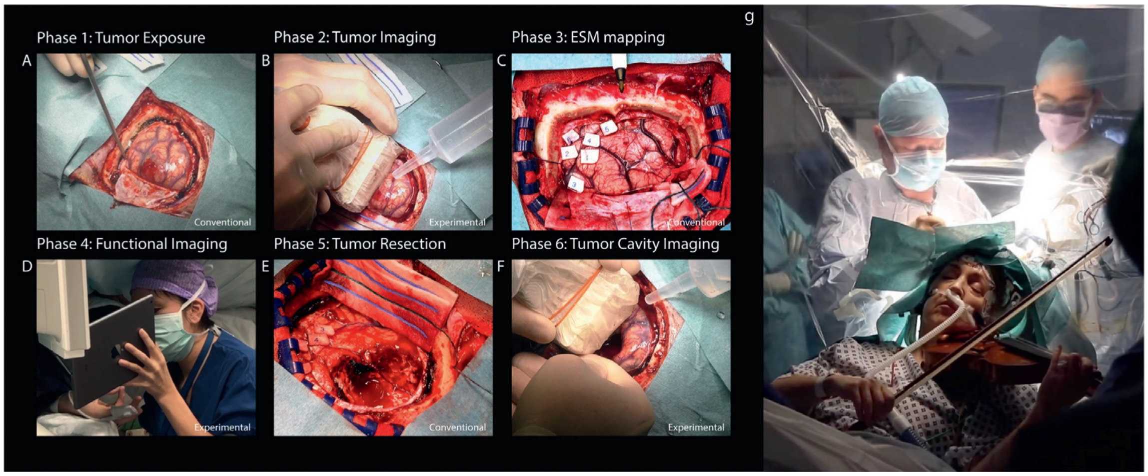

Fig. 5.4. Step-by-step principle of the direct electrical stimulation procedure in an awake patient. Panel (A–F) figure taken from Soloukey et al. (2019) during mapping in theater G) music mapping—in this case playing the violin—courtesy of Professor Ashkan and team at King's College London, video available online: https://www.youtube.com/watch?v=o-oGpD_Nx5U) and we obtained permission from the surgeons in the photograph to use it.

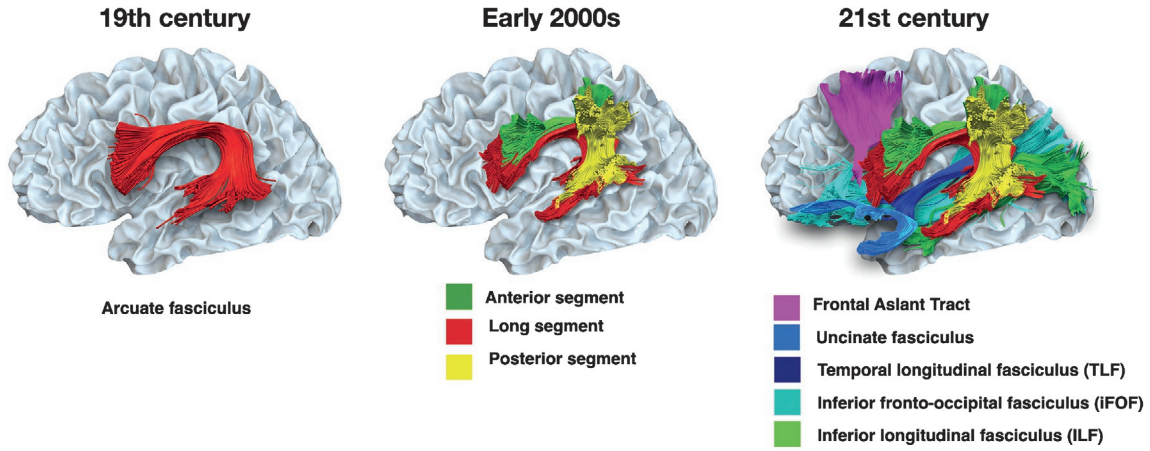

Fig. 5.5. Language network in transition. Since the discovery of the first language areas in the brain by the physician Paul Broca (1824–1880) and psychiatrist Carl Wernicke (1848–1905), knowledge about the neuronal language networks has changed considerably. Whereas in the 19th century, we assumed that there was only one fiber tract—the arcuate fasciculus, which connects the inferior frontal gyrus (i.e., "Broca" area) and the posterior temporal cortex (i.e., "Wernicke" area). In the early 2000s, there were already three connecting tracts that also rely on the inferior parietal lobe (i.e., "Geschwind's" territory, Catani et al., 2005). Today, we consider a minimum of eight pathways relevant for speech and language (three segments of the arcuate fasciculus, frontal aslant tract, uncinate fasciculus, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, and temporal longitudinal fasciculus), most of which have already been clinically validated through neurosurgical approaches, lesion studies, and DES. Modified from Catani M, Forkel SJ (2019). Diffusion imaging methods in language sciences. In: de Zubicaray GI, Schiller, NO (eds). Oxford Handbook of Neurolinguistics. Oxford University Press. S.F. is the author of the original figure.

relevance of mapping music for left- and right-hemispheric tumors. Another small patient study by the same research group found that musicality contributes to language recovery after awake surgery, underlining its relevance (Kappen et al., 2022b). They also found a trend toward a larger size of the corpus callosum in musical patients, which may have contributed to functional reorganization toward the contralateral side of the lesion. In combination with advances in tractography, a new understanding of anatomy of language has emerged over the past three decades (Fig. 5.5).

Apart from DES, other direct techniques for detecting functional boundaries are under development. A promising method is functional ultrasound (fUS) (Imbault et al., 2017; Deffieux et al., 2018; Soloukey et al., 2019). Functional ultrasound is a mobile neuroimaging technique with unprecedented spatiotemporal resolution. This technique allows the detection of small changes in blood dynamics reflecting changes in the metabolic activity of activated neurons through neurovascular coupling. Soloukey et al. (2019) showed the clinical potential of applying this technique during conventional awake surgery with motor, language, and visual tasks in 10 glioma patients. fUS could detect functional areas defined with DES and deep inside the brain. They were able to image (real-time) tumor-specific and healthy vascular characteristics (see Video 3 in Supplementary Materials of Soloukey et al. (2019) for an illustration of fUS during an awake surgery with a verbal and silent word repetition: https://www.frontiersin.org/articles/10.3389/fnins.2019.01384/full#supplementary-material).

LANGUAGE AND COGNITIVE PROFILES IN BRAIN TUMOR PATIENTS

Gliomas

Regardless of the origin of the exact neural disturbance, it is without doubt that glioma patients suffer from language and other cognitive impairments before receiving any type of treatment [for systematic reviews see: Satoer et al., 2016; van Kessel et al., 2017). Performance on tests for word retrieval was reported to be most frequently impaired before surgery (Satoer et al., 2016). However, many studies investigated a mixed group of LGG and HGG patients; language impairments in LGG patients seem less severe than those in HGG patients (Campanella et al., 2015; Noll et al., 2015). This difference is presumably due to the slow growth rate of an LGG (i.e., 5 mm p/year), which allows for neuroplasticity and reorganization of language functions (Mandonnet et al., 2003; Desmurget et al., 2007).

Most studies used "classical" aphasia tests in glioma patients that were developed for stroke patients, who typically suffer from moderate to severe language impairment, such as the Boston Diagnostic Aphasia Examination (BDAE) (Goodglass et al., 2001), the Aachener Aphasia Test (AAT), (Huber et al., 1984) or the Comprehensive Aphasia Test (Swinburn et al., 2005). These tests are not always sensitive to mild language deficits (Davie et al., 2009; Satoer et al., 2012; Brownsett et al., 2019). In addition, despite the often-absent objectified aphasia, LGG patients do report language complaints (Satoer et al., 2012; Brownsett et al., 2019;

Mooijman et al., 2022) underlining the need for suitable tests. Standardized tests that are often described to be sensitive in LGG patients are verbal fluency (category and letter) and (rapid) naming (objects and actions) and are therefore recommended in a minimal test battery to tap into the language domain [Papagno et al., 2012; see also Rofes et al. (2017) for a European survey on cognitive assessment]. However, verbal fluency and naming are limited to the word level. Spontaneous speech analyses can be applied to detect the generally mild language impairments in these patients on different linguistic levels (see also section "Supplementary motor area syndrome and spontaneous speech"). Although sensitive, this method is rather time-consuming in clinical practice. Therefore, a new linguistic test battery was developed, the Diagnostic Instrument for Mild Aphasia (DIMA; Satoer et al., 2022), with complex production and comprehension tests at the levels of phonology, semantics, and syntax derived from the Dutch Linguistic Intraoperative Protocol (DuLIP, De Witte et al., 2015). Most complex tasks and items were selected from DuLIP and new subtasks and items were added to DIMA. It consists of four subtests: (1) repetition (words, nonwords, and sentences), (2) semantic odd-picture-out (under time constraints), (3) sentence completion, and (4) sentence judgment. In the latter subtest, correct and incorrect sentences (at all linguistic levels) are randomly presented on a laptop screen, and both accuracy and reaction time in milliseconds are recorded (see, e.g., Table 5.1).

Case illustrations showed the sensitivity and clinical application of DIMA in a glioma and a meningioma patient before surgery. A preliminary analysis at the group level showed that preoperatively, patients deviated on DIMA sentence repetition and DIMA sentence completion. As expected, HGG patients performed worse than LGG patients, on word, nonword, and sentence repetition tasks, which is probably attributed to more aggressive tumor growth (Mooijman et al., 2021). There was no difference in language scores when comparing patients with left- to right-hemispheric tumor localization. As for standard language tests, LGG patients were preoperatively impaired on the Boston Naming Test (BNT), Category and Letter Fluency. In contrast, HGG patients performed worse than LGG patients on the BNT and the Token Test. Patients with left-hemispheric tumors performed worse on the BNT and Letter Fluency compared to right-hemispheric tumor patients. In sum, it seems that HGG patients tend to suffer from a more "classic" aphasia profile that is left-lateralized attested with standard instruments whereas LGG patients suffer from mild language disorders at the sentence level (production), irrespective of hemispheric tumor location (see also Davie et al., 2009; Brownsett et al., 2019), which is supported by other (neuroimaging) studies as well [see extensive review from Nieberlein et al., 2023]. In addition, as DIMA has subtests at all linguistic levels and was derived from DuLIP, it can be used to select DuLIP tasks for the intraoperative procedure [see Satoer et al., 2022 for case illustrations]. DIMA is currently digitized to an app format but also adapted and standardized to other languages (Clément et al., 2022), aiming for a more uniform international language assessment in glioma patients.

As for other cognitive functions, there is also no clear consensus about the selection of diagnostic instruments. van Loon et al. (2015) demonstrated in a systematic review that 46 different instruments were used for the evaluation of cognition in glioma patients. Similarly, as with language testing, nonlinguistic cognitive tests should also be sensitive to detect the more subtle deviations. Correa et al. (2007) suggested the use of a test battery with at least the Digit Span, Trail Making Test A/B, Brief Test of Attention, Hopkins Verbal Learning Test, the Grooved Pegboard test, and the Barona

Table 5.1

Diagnostic Instrument for mild aphasia.

Linguistic level and modality	Subtest	Example
Phonology—production	Repetition words	*Gorilla (gorilla)*
	Repetition compounds	*Ontdekkingsreiziger (explorer)*
	Repetition sentences	*De Griek ontdekte vier nietjes in de band van zijn fiets* *(The Greek discovered four staples in the tire of his bike)*
Phonology—comprehension	Sentence judgment	*De wikker gaat naar Parot* *(The wikker goes to Parot)*
Semantics—production	Semantic odd-picture-out	*Snake—dog—cat*
Semantics—comprehension	Sentence judgment	*De sigaar verveelde zich* *(The cigar was bored)*
Syntax—production	Sentence completion	*Hij viel van … (He fell off …)* *Om 5 uur … (At 5 o'clock …)*
Syntax—comprehension	Sentence judgment	*Hij gaat geschilderd op de muur* *(He goes painted on the wall)*

Index tapping into attention, executive functioning, motor function, verbal memory, and premorbid IQ estimation and quality of life. Papagno et al. (2012) suggested The Milano-Bicocca Battery (MIBIB) with tests for the domains of (language) memory, executive functions, apraxia, and spatial cognition. Other tests are to be selected according to tumor location. It should also be noted that the ideal testing time should consist of no more than 45 min (Klein and De Witt Hamer, 2011). Indeed, it appeared that LGG patients often deviate in the domains of verbal/working memory as assessed with a verbal learning test or digit span and attention/executive functions as assessed with Trail Making Test A, B, and B/A (Papagno et al., 2012; van Loon et al., 2015; Satoer et al., 2016). Sensitive cognitive screeners (via tablet/computer) with limited administration time duration have been proposed by several research groups (e.g., Rijnen et al., 2020; de Sain et al., 2023). van Kessel et al. (2021) indicated that preoperative memory deficits, which were revealed with their neuropsychologic examination, were of additional prognostic value in HGG to other well-known predictors of survival, underlining the relevance of including a memory test. Another study also demonstrated a significant predictive value of preoperative cognitive functioning with regard to functional independence in patients with glioma, providing evidence that cognitive functioning, assessed with neuropsychologic tests, can be translated into “real-world” functions and activities (Noll et al., 2018). Deficits in cognition are associated with gliomas in both the left and right hemisphere, although tasks with a verbal component are more frequently affected in patients with a glioma in the left hemisphere, in particular the left fronto-parietal network (Noll et al., 2015; Habets et al., 2019).

Meningiomas

As opposed to gliomas, less research has been done related to cognitive functioning in meningioma patients. It has only been for about the last decade that most nonlinguistic cognitive functions have been investigated in this patient group. As these tumors do not infiltrate eloquent brain areas, they were considered “harmless” to cognitive functions. However, a systematic review by Meskal et al. (2016) demonstrated that most meningioma patients suffer from one or more impaired cognitive functions in (working) memory, attention, and executive functioning before surgery. Recent studies have replicated these findings (van Nieuwenhuizen et al., 2018).

Previous studies on cognition in meningioma patients included a small number of language measures. Before surgery, performance on letter fluency (phonology) and category fluency (semantics) tests, which at least partly assess language processing (Whiteside et al., 2016), was reported to be impaired at the group and the individual level (Tucha et al., 2003; Bommakanti et al., 2016; Liouta et al., 2016; Hendrix et al., 2017). Some studies, in contrast, reported intact performance (van Nieuwenhuizen et al., 2013; Butts et al., 2017). Similarly, contradictory findings are reported for object naming tests (assessing word retrieval) and the Token Test [assessing language comprehension, presence and severity of aphasia; Campanella et al., 2015; Butts et al., 2017; Di Cristofori et al., 2018]. Word retrieval deficits were also revealed in a study including elderly patients (>70 years) with meningioma (Di Cristofori et al., 2018). However, other linguistic functions were not considered.

The first extensive neurolinguistic (longitudinal) study in a small number of patients with a meningioma in the language-dominant hemisphere (N = 10) was done by Wolthuis et al. (2021, 2022), who investigated the linguistic levels of phonology, semantics, and syntax. They revealed deficits in word retrieval, grammar, and writing compared to healthy controls. In a reading test, patients scored higher than the healthy population, as all but one patient made no errors on this test. At the individual level, four patients (40%) had a preoperative language impairment based on performance measures. No effects of preoperative tumor and treatment characteristics (localization, tumor volume, use of anti-epileptic drugs, and extent of resection) were found on the presence of a language impairment before surgery (nor on worsening of language performance). A limitation of this study was that they did not include right-sided meningiomas as a control group.

In addition to objective testing, van der Linden et al. (2020) showed the relevance of adding a subjective measure, studying patient-proxy agreement on executive functioning and the potential of performance-based measures on the level of agreement. It was remarkable that patients rated their executive functioning lower compared to what was objectively tested. They also rated themselves lower in comparison to their proxies (partner/caretaker). The subjective-objective relation and patient-proxy agreement should be investigated further in other domains of cognitive functioning. For language at the subjective level, Wolthuis (2022) administered structured interviews, and the study revealed that six meningioma patients (60%) self-reported one or more speech and/or language problems in daily life before surgery. They mentioned difficulties with word finding ($N = 6$), speaking (producing words, formulating sentences, expressing thoughts; $N = 5$), articulation ($N = 1$), reading ($N = 5$), and writing/typing ($N = 2$). No patient-proxy comparison was made. As meningiomas do not infiltrate into eloquent brain areas, the question arises as to why these patients suffer from cognitive and/or language deficits. One of the reasons could be a (long-term) disturbed brain activity pattern, such as abnormal slow-wave activity or disturbed functional networks. Increased slow-wave activity in low-grade glioma patients was associated with poorer working memory, information processing, and executive functioning (Bosma et al., 2009). Wolthuis et al. (2022) described that meningioma patients did not have preoperative abnormal slow-wave activity at the group level, as was seen in the study conducted by

Oshino et al. (2007). In their study, meningiomas were associated with less delta activity and less consistent delta source locations than intra-axial tumors (gliomas and metastatic tumors), while correcting for tumor size and surrounding edema. The difference between tumor types is presumably because meningiomas are not infiltrative but "only" cause a mass effect on surrounding brain tissue, especially subcortical tissue. The white matter pathways "only" tend to be displaced but are intact. Therefore, meningiomas probably cause minimal or no white-matter injury; hence, only minimal or no delta activity. However, a functional connectivity analysis showed that a greater small worldness (entire network configuration) was related to worse language performance (Wolthuis et al., 2021).

Supplementary motor area syndrome and spontaneous speech

The supplementary motor area (SMA) is a dorsomedial prefrontal region where gliomas often reside. Surgery in this area can result in the SMA syndrome, a well-known clinical phenomenon, which is associated with loss of initiation of motor or speech function (Laplane et al., 1977; Palmisciano et al., 2022). The SMA syndrome can occur after resection in either a left- or a right-sided glioma. However, the loss of speech initiation is more frequently observed after surgery in the left hemisphere (Palmisciano et al., 2022). Typically, the decline is at its worst in the acute phase, followed by spontaneous recovery within weeks to months after surgery. This "non-fluent" type of aphasia is classically known as transcortical aphasia. There are two forms of transcortical aphasia: the sensory form and the motor form. In sensory transcortical aphasia, language comprehension is impaired, production is fluent and contains paraphasias and/or neologisms, while the repetition of words is intact (unlike Wernicke's aphasia). In motor transcortical aphasia (spontaneous), language production is not fluent, often with intact language comprehension. Repetition of words and sentences is often intact even though a patient with transcortical motor aphasia can barely produce spontaneous spoken and written language. It is sometimes possible to elicit an appropriate target word via a carrier phrase (for example, "I cut bread with a … [knife]." The latter type is typically observed in lesions located in the supplementary motor area (SMA) (Naeser and Hayward, 1978; Krainik et al., 2003) and also known as "dynamic aphasia" (Luria and Tsvetkova, 1968). Dynamic aphasia resembles transcortical motor aphasia, apart from the patient not initiating (Ardila and Lopez, 1984). Luria described this pattern as a failure of an early stage of verbal planning, translating the "internal speech" into the linear scheme of the sentence [see also Costello and Warrington, 1989]. An alternative explanation viewed this syndrome as an inability to select a unique response in "open" situations, in which one out of many possible verbal responses or competitors must be selected (Robinson et al., 1998). The underlying mechanism of dynamic aphasia has been associated with a language-specific impairment or a more general impairment of executive functions (Esmonde et al., 1996; Robinson et al., 2006). Apart from the "classical" left-hemispheric involvement in language production, there are also studies in which spontaneous speech was affected after right-hemispheric damage (Thomson et al., 1998; Jehna et al., 2017). Intraoperative results reporting on (semi-)spontaneous speech production deficits during DES or resection have shed light on the location of this dynamic function in addition to the SMA. Dissociations were found between sentence production/generation, sentence completion, and spontaneous speech vs other isolated language tasks (Chernoff et al., 2019; Chivukula et al., 2018; Dragoy et al., 2020; Ojemann and Mateer, 1979; De Witte et al., 2015; Satoer et al., 2014a, 2018, 2021).

The frequent occurrence of this transient syndrome underlines the relevance of monitoring spontaneous speech (in context), as this can be missed when only applying isolated language tasks in the perioperative phase (e.g., object naming). In addition, the added value of a spontaneous speech analysis has been demonstrated by Satoer et al. (2013, 2018) in addition to verbal fluency and object naming. One of the most sensitive parameters in their perioperative spontaneous speech was the occurrence of incomplete sentences, which deteriorated in the long run after surgery. A subsequent study by Rofes et al. (2018) partially confirmed these findings. It argued that a spontaneous speech analysis can be of added value when there is a lack of time to administer a comprehensive neurolinguistic protocol or when the patient is too tired. To the best of our knowledge, no thorough spontaneous speech analyses have been conducted in meningioma patients, apart from one case study that described postoperative dynamic aphasia in a patient with a left frontal meningioma involving Brodmann area 45 followed by full recovery within 2 weeks (Robinson et al., 1998). Finally, spontaneous speech is the most ecologically valid way of daily conversation, hence, crucial for quality of life and should therefore be adopted as a standard measure in clinical care for LGGs.

ANATOMIC AND FUNCTIONAL ALTERATIONS

White matter dysfunctions and disconnections

Deprivation of connections in a brain region triggers dendritic and synaptic pruning, leading to the degeneration or death of neurons (Capurso et al., 1997). Consequently, both functional disconnection, characterized by impaired communication (Stephan et al., 2006), and structural disconnection occur within the affected region. This phenomenon, known as diaschisis (Carrera and Tononi, 2014), highlights the critical role of connections in maintaining the integrity and functionality of distant brain regions.

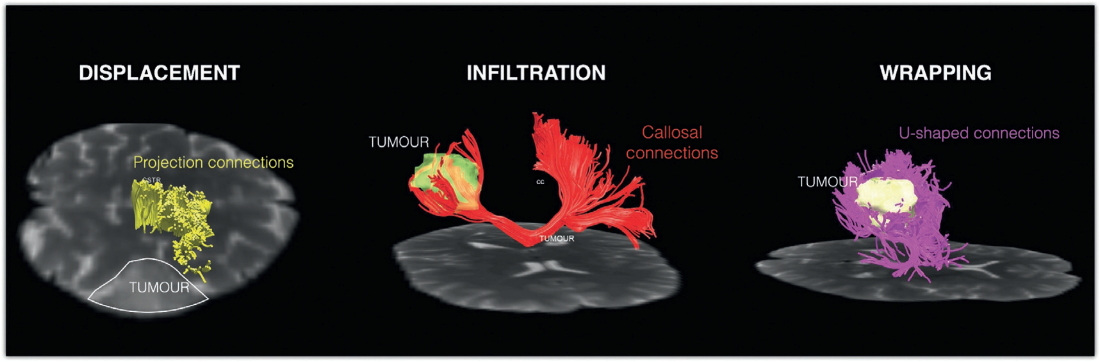

Fig. 5.6. Various impacts of tumor lesions on white matter. In the *left panel*, low-grade gliomas (LGGs) are depicted as gradually exerting pressure on the surrounding brain tissue, including the white matter, leading to displacement. The *middle panel* represents tumors infiltrating the white matter and migrating along the connective tissue. Finally, in the *right panel*, a phenomenon is observed where the white matter appears to wrap around the tumor, which could either be indicative of a pathologic process or a methodological artifact. This figure is previously unpublished data and was modified with permission from the creator, Dr. Henrietta Howells.

In the case of brain injuries caused by masses like gliomas, the mass can exert pressure on or displace neighboring white matter fibers, causing deviations from the expected anatomy in terms of shape and location. For example, a lateral frontal lobe tumor can compress and displace a corticospinal tract (CST) segment toward the medial wall. However, this alteration only affects the immediate vicinity of the tumor, resulting in a change in the overall trajectory of that specific portion of the CST (Fig. 5.6). It is important to note that these deviations are unique to each patient, and tractography is necessary to visualize the precise shape of the CST in individual cases. Additionally, tumors can indirectly impact white matter through their pathologic cascade, such as edema around a tumor, which temporarily compromises the white matter and may cause transient clinical symptoms. For example, a tumor in the motor cortex surrounded by edema can affect the arcuate fasciculus, leading to language deficits resembling Broca-like aphasia (i.e., effortful articulation, telegraphic speech).

Tumors can impact brain regions and their connections through various mechanisms. Minor displacement of white matter typically has minimal or no significant effect on structural or functional integrity (Fig. 5.6, *left*). However, if the strain on the white matter becomes too severe, it can cause structural damage and disconnection. Quantifying the extent of disconnection relies on analyzing the white matter of the healthy hemisphere, as atlas-based approaches fail to account for interindividual variability. Tractography emerges as a valuable tool in personalized diagnostics, enabling the assessment of a lesion's impact on white matter, aiding in presurgical planning, and determining postsurgical consequences (Thiebaut de Schotten et al., 2005; Duffau et al., 2008; Leclercq et al., 2010; Kemerdere et al., 2016; Cochereau et al., 2020; Dragoy et al., 2020; Mirchandani et al., 2020; Sollmann et al., 2020).

Functional connectivity alterations due to tumor lesions

Intracranial tumors can also lead to disruptions of functional connectivity, that is the extent to which brain areas can functionally interact, which can in turn cause brain dysfunctions. Increased slow-wave activity in adults is considered pathologic and may also indicate brain dysfunction in wakeful restful conditions. In brain tumor patients, increased slow-wave activity and deviant functional connectivity are observed compared to healthy participants (Baayen et al., 2003; Bartolomei et al., 2006a,b).

Characteristics of slow-wave activity and functional connectivity network may also be a language or cognitive dysfunction marker. In stroke patient groups, brain activity in the delta and theta frequency band (i.e., slow-wave activity) and functional connectivity networks were predictive of language outcome (Szelies et al., 2002; Nicolo et al., 2015). Bosma et al. (2009) demonstrated a relationship between functional connectivity networks and cognitive impairments in brain tumor patients. Wolthuis et al. (2022) also showed with EEG that LGG patients had increased slow-wave activity compared to healthy individuals before (and 1 year after surgery). Increased preoperative slow-wave activity was associated with language impairment and poor language performance in specific language domains. Slow-wave activity before surgery was also related to word retrieval after surgery.

As for functional connectivity, Wolthuis et al. (2022) did not observe differences between LGG patients and healthy participants, although hub presence (i.e., nodes with many connections and a central position in a network) and higher focal and global functional connectivity were associated with poorer language functioning (in particular with production and comprehension at the sentence level). For meningioma patients, a greater small worldness (entire network configuration) was related to worse preoperative language performance (word retrieval, semantics, and writing) and hub presence. Preoperative better average clustering (local connectivity) and global integration predicted worse outcomes on language function 1 year after surgery. However, these results must be interpreted cautiously as small numbers of patients were included, and patients with and without language impairments collapsed. Investigation into FC in specific brain areas (in larger, specified groups) may provide further insights into language impairments in brain tumor patients.

CORTICAL AND SUBCORTICAL AREAS: FUNCTIONS AND TASKS

Gliomas (awake surgery)

For a long time, only counting and/or naming pictures were used as intraoperative tasks during awake glioma surgery. However, counting is automatized language and confrontational object naming does not capture complex linguistic functions; hence, they are insufficiently sensitive to investigate critical language functions (Petrovich Brennan et al., 2007; De Witte and Mariën, 2013). Although object naming does not tap into complex linguistic functions, the relevance of this test was underlined by several studies; preoperative (subnormal) performance on an object naming task appeared to be predictive for postoperative language outcome (Ilmberger et al., 2008) and object naming appeared to be involved in large cortico-subcortical areas important for preservation (Papagno et al., 2011; Collée et al., 2023). However, by solely applying an object naming test, other linguistic functions can be missed, such as auditory language comprehension (De Witte et al., 2015).

Hence, a decade ago, for the first time an extensive standardized language test battery was developed in Dutch (DuLIP), consisting of phonologic, semantic, and syntactic language tasks [De Witte et al., 2015 and see Collée et al., 2023 for an update of DuLIP]. Ever since, adaptations of DuLIP to other languages has been applied (e.g., in Portuguese, Alves et al., 2021) and other linguistic tasks or test batteries have been developed [see Martín-Monzón et al., 2022 for a review]. There is no uniform consensus about the application of specific language/cognitive tasks in neurooncologic patients. However, based on the literature and clinical studies, several schemas and proposals have been made (Fernández Coello et al., 2013; De Witte et al., 2015; Collée et al., 2023) (see a selection later in Tables 5.2 and 5.3).

A thorough systematic review on intraoperative errors in awake surgery with 102 studies made an attempt to sketch an overview of eloquent stimulation sites. The most frequently reported errors concerned: speech arrest, anomia, dysarthria/anarthria, and semantic and phonologic errors in both the left and right hemisphere [for a review see Collée et al., 2023].

Meningiomas

As opposed to gliomas, in meningioma patients it is not so clear yet whether there is a relation between tumor location and cognitive performance. However, due to greater diagnostic imaging, an increasing number of meningiomas are found, albeit (more or less) asymptomatic. Clinical (and research-related) radiologic follow-up allows us to gain more knowledge about the effects of a meningioma and its location on cognition.

Mixed findings of localization were found on cognition ranging from: (1) no signs at all (Steinvorth et al., 2003; Tucha et al., 2003; Meskal et al., 2016), (2) better performance in patients with right-sided meningiomas in (verbal) cognitive tests (Yoshii et al., 2008; Dijkstra et al., 2009; Sleurs et al., 2022) than left-sided meningioma, and (3) more positive findings in patients with falx meningioma in comparison to convexity and fronto-basal location (Tucha et al., 2003). A recent large lesion-symptom mapping study showed that patients with tumor locations in the left middle and superior frontal gyrus were more at risk for lower performance on cognitive flexibility and complex attention, respectively (De Baene et al., 2019). As for language, a nonsignificant observation showed that the majority of patients with an anterior (frontal) meningioma did not have a language impairment. In contrast, the majority of patients with a posterior (parietal/parieto-occipital) meningioma did have a language impairment before surgery. Cipolotti et al. (2015) compared deviating cognitive scores in low-grade glioma and meningioma patients with frontal lesion location. In a 3-year follow-up study, Liouta et al. (2016) found that patients with anterior convexity meningiomas performed worse in executive functioning tests than patients with posterior tumor location. Left-hemispheric meningioma patients performed worse in verbal tests than right-hemispheric patients. In sum, due to this great variety, it seems that even in non-infiltrating tumors, functional neuroplasticity takes place.

EFFECT OF SURGERY ON LANGUAGE/ COGNITIVE FUNCTIONS

Glioma (awake procedure)

The goal of awake surgery is to preserve neurologic outcomes and obtain a larger extent of resection. Risk factors for postoperative language impairment are preoperative aphasia, non-frontal tumor location, intraoperative complications, and language-positive stimulation sites within the tumor (Ilmberger et al., 2008). Over the last two decades, the research field tapping into the effects of awake surgery on language mapping cognitive functions intraoperatively has grown exponentially.

Previously, it was believed that language and cognitive abilities declined immediately after surgery but fully recovered within 3 months (e.g., Duffau et al., 2002; Whittle et al., 2003;

Table 5.2

Overview of cortical brain regions with sensorimotor, language/cognitive functions and tasks.

Cortical level—lobe	Function	Task (example)	Hemisphere
Frontal lobe			
Precentral gyrus	Motor	Movement upper limb	L+R
Inferior frontal gyrus	Speech articulation	Counting, repetition, verbal diadochokinesis	L+R
	Word-finding	Picture naming	L
	Syntax	Action naming, verb generation	L
	Semantics	Semantic association and judgment, odd-picture/word-out	L
(+ middle frontal frontal gyrus)	Writing	Writing	L
Prefrontal areas	Executive functions, inhibition	Stroop	L+R
	Working memory	Double task	L+R
Supplementary Motor Area	Language initiation	Sentence completion, spontaneous speech	L
Parietal lobe			
Postcentral gyrus	Sensory-motor, articulatory processing, motor speech	Movements, counting, verbal diadochokinesis, repetition	L+R
	Articulation/motor processing	Verbal diadochokinesis	
Supramarginal gyrus	Word-finding	Picture naming	L
	Reading	Reading, odd-word-out	L
	Semantics	Odd-picture/word-out, semantic association, PPTT	L
	Working memory	Double task	L+R
	Visuo-spatial	Line bisection	R
	Set-shifting, inhibition	Trail Making Test	R
Angular gyrus	Arithmetics	Calculation (see also Gerstmann syndrome, e.g., Ardila, 2020))	L
	Finger recognition	Finger naming (see also Gerstman syndrome, e.g., Ardila, 2020)	L
	Reading	Reading, odd-word-out	L
	Writing	Writing	L
Superior parietal gyrus	Writing	Writing	L
Insular lobe			
	Word-finding	Picture naming	L
	Sensory-motor	Movements	L+R
	Working memory	Double task	L+R
Temporal lobe			
Superior temporal gyrus	Word-finding	Picture naming	L
	Phonologic network	Phonologic judgment	L
Inferior temporal gyrus	Semantics (verbal)	Semantic association and judgment, odd-picture-out	L
	Semantic (nonverbal)	Semantic association and judgment, odd-picture-out	R
Middle temporal gyrus	Face naming/recognition	Famous face naming	L
	Reading	Reading, odd-word-out	L
Posterior temporal areas	Visual field/recognition	Visual tasks	L+R
	Reading	Reading	L
Occipital lobe			
	Visual field/recognition	Visual tasks	L+R

Table 5.3

Overview of subcortical brain regions with sensorimotor, language/cognitive functions and tasks.

Subcortical level—tracts	Function	Task	Hemisphere
Frontal Aslant Tract	Initiation of speech, motor speech	Verbal fluency, sentence completion, spontaneous speech	L+R
Corticospinal tract	Motor speech	Verbal diadochokinesis, word repetition	L+R
Arcuate fasciculus	Phonology	(Non) word repetition	L
Superior longitudinal fasciculus	Visuospatial	Line bisection	R
Inferior frontal occipital fasciculus	Word retrieval Semantics, reading	Naming	L
		Semantic judgment and association	L+R
	Visuospatial	Line bisection	R
Inferior Longitudinal Fasciculus	Reading, phonology, semantics	Reading, (non) word repetition, semantic judgment, association, object naming	L
Uncinate fasciculus	Word/proper name retrieval, semantics, phonology, face naming/recognition	Object naming/proper noun naming, semantic judgment, famous face naming, (non) word repetition	L

Sanai et al., 2008). Further comprehensive neuropsychologic examinations revealed that while there is a temporary decline in language functions shortly after surgery (between 3 and 6 months), language performance tends to improve over time. Nevertheless, certain tests, such as category fluency, showed impairment even 1 year after the surgery (Satoer et al., 2014b, 2016). Additionally, Satoer et al. (2013, 2018) found that characteristics of spontaneous speech, particularly the occurrence of incomplete sentences, worsened in the year following the surgery (see also Rofes et al., 2018). A preliminary study from the same group showed that subtests from DIMA even appeared more sensitive to detecting surgical effects than standard tests: all phonologic DIMA subtests captured short-term decline (pre- and 3 months postoperatively), in line with earlier evidence for the value of (non)word repetition (Sierpowska et al., 2017; Mooijman et al., 2021). A long-term decline was detected with DIMA sentence completion in the year after surgery, reflecting an earlier spontaneous speech analysis with incomplete sentences as a sensitive parameter. The short-term postoperative decline affected verbal fluency as well. Only the localization of left-hemispheric tumors had an impact on performance in standard language tests. HGG patients showed more significant impairments compared to LGG patients in DIMA repetition and standard tests such as the BNT and the Token Test. Therefore, it is recommended to include DIMA in the standard language evaluation of glioma patients to enable more precise counseling regarding language outcomes.

As for higher cognitive functions, Rijnen et al. (2019) investigated a large group of LGG patients, who underwent surgery (with or without DES). There was no hemispheric effect on performance compared to normative data, and cognitive impairments were identified in both groups. Verbal memory and sustained attention were more prone to postoperative deterioration in patients with LGG in the left hemisphere. Patients with DES surgery scored worse than patients without DES on tests for executive functions and verbal fluency (over time). The authors conclude that the addition of tests for higher cognitive functions to the intraoperative procedure may enhance cognitive outcome. Noll et al. (2015) showed that in patients with tumors in the left temporal lobe, a decline was most frequent in verbal learning, memory, executive functioning, and object naming. Postoperative worsening was relatively less often observed in patients with right-sided lesions, but still present on measures of processing speed, executive functioning, and verbal learning and memory. It is notable that both left- and right-hemispheric patients exhibited a postoperative decline in verbal learning and memory, yet more pronounced in the left-hemispheric patient group.

Although awake surgery is the gold standard treatment in LGGs, it is not widely accepted to be a standard treatment for HGGs, in particular glioblastoma (GBM) patients. The main reason is that this patient group suffers from more severe neurologic and cognitive deficits (Noll et al., 2015; van Kessel et al., 2017, 2021). Furthermore, severe aphasia is regarded as an exclusion criterion (Dziedzic and Bernstein, 2014; Bonifazi et al., 2020; Zigiotto et al., 2020) as it challenges intraoperative monitoring and defining a functional boundary. However, there seems to be a trend toward a higher percentage of total resection, a lower complication rate, and a longer median survival in awake versus surgery with general anesthesia (Gerritsen et al., 2019, 2022; Li et al., 2021). A recent case series showed that resection of glioblastoma patients with severe aphasia undergoing awake surgery was feasible without perioperative complications. By using a patient-tailored peri- and intraoperative language monitoring, intraoperative language deterioration was distinguished from preoperative aphasia. Postoperatively, language measures were stable or even improved (Donders-Kamphuis et al., 2022). A prospective multicenter randomized clinical trial [SAFE-trial NL7589 Gerritsen et al., 2020] is ongoing to assess the added value of awake surgery in glioblastoma patients. High expertise of a multidisciplinary awake team is mandatory including a specialized speech and language pathologist/clinical linguist. More standardized intraoperative tasks for severe aphasia are needed for this population. An extended version of DuLIP (De Witte et al., 2015) with standardized tasks designed especially for patients with severe aphasia is in preparation.

Meningioma (asleep procedure)

A systematic review by Meskal et al. (2016) reported that meningioma patients tend to improve after surgery, but impairments are still present in 44% of the patients. A large observational study by Rijnen et al. (2019) investigated meningioma (WHO grade I and II) patients preoperatively and at 3 and 12 months after surgery with a neuropsychologic assessment. Seven cognitive domains were tested: Verbal Memory, Visual Memory, Processing Speed, Psychomotor Speed, Reaction Time, Complex Attention, and Cognitive Flexibility. At the group level, impairments were found in all cognitive domains across all time points. On the individual patient level, impairments were significantly more common in meningioma patients compared with normative controls on six out of seven domains at 3 months after surgery and on three out of seven domains 1 year after surgery. Performance on Psychomotor Speed, Reaction Time, and Complex Attention was most frequently, as well as most severely, impaired. The authors postulated that patients in their study may have difficulties with the agility and adequacy of movements (related to Psychomotor Speed), may respond slowly to stimuli (related to Reaction Time), and may struggle to adapt behaviors and thoughts to new, changing, or unexpected events (related to Complex Attentions, but also to higher order executive functions) potentially harming daily activities, such as driving a car or cooking dinner. They claim that they underline the necessity to implement routine cognitive screening in meningioma patients to adequately monitor cognitive deficits in order to maximize quality of life and functional independence in home, work, and social settings. According to another study, no long-term decline was observed at the group level in executive functioning tests; instead, some of the tests showed improvement over time (Liouta et al., 2016).

Studies that included language tests in their protocol, such as object naming, verbal fluency or the Token Test found generally no effect of surgery on patients' performance (Tucha et al., 2003; Campanella et al., 2015; Bommakanti et al., 2016; Hendrix et al., 2017). It is to be debated whether these tests are sensitive enough to detect more subtle (as in LGGs) language deficits. Wolthuis et al. (2022) reported both postoperative improvement in the domains of word retrieval and syntax, whereas writing remained impaired compared to healthy population, which suggest that further research with larger groups must be conducted.

CONCLUSION

This chapter discussed the incidence, prevalence and prognosis of gliomas and meningiomas, considering their impact on language and cognitive functions while discussing the available techniques to map language in brain tumor patients. It is without doubt that these tumors can have a profound impact on language and cognitive processes, which highlights the significance for early detection and treatment to preserve patients' quality of life. The presence and severity of functional impairment can be influenced by several factors such as tumor type (e.g., intra- or axial location, slow or fast tumor growth) and lesion location (e.g., hemisphere, lobe, and white matter connections), which in turn may affect the potential of neuroplasticity. Up to now, evidence shows that patients with left-hemispheric tumors still run the highest risk for neurocognitive impairments with emphasis on language/verbal components. The added value of more sensitive (and nonlinguistic) measurements should be investigated further in patients with right-sided tumors.

The emergence of noninvasive neuroimaging techniques, such as fMRI and tractography, and invasive awake brain surgery have revolutionized our ability to map and monitor brain tumors. These methods provided valuable insights in understanding the neurobiology of language and revealed high interindividual variability. In the last decade, a patient-tailored approach for language and cognitive tests considers demographic and clinical variables and is inevitable in neuro-oncologic care.

Despite significant progress, challenges remain. Longitudinal studies with large patient cohorts are necessary to explore the temporal and dynamic evolution of linguistic and cognitive changes caused by a brain tumor. Addressing this intricate labyrinth of factors contributing to language and cognitive impairments in brain tumor patients requires a multidisciplinary and open approach. Neurosurgeons, neurologists, speech language pathologists, neuropsychologists, neuroimaging specialists, and industry partners must work together to facilitate the mapping of cognitive functions in the surgical setting to improve patients' outcomes and quality of life.

REFERENCES

Alves J, Cardoso M, Morgado M et al. (2021). Language assessment in awake brain surgery: the Portuguese adaptation of the Dutch linguistic intraoperative protocol (DuLIP). Clin Linguist Phon 35: 1113–1131.

Ardila A (2020). Gerstmann syndrome. Curr Neurol Neurosci Rep 20: 48.

Ardila A, Lopez MV (1984). Transcortical motor aphasia: one or two aphasias? Brain Lang 22: 350–353.

Arrieta VA, Gould A, Kim KS et al. (2024). Ultrasound-mediated delivery of doxorubicin to the brain results in immune modulation and improved responses to PD-1 blockade in gliomas. Nat Commun 15: 4698.

Baayen JC, de Jongh A, Stam CJ et al. (2003). Localization of slow wave activity in patients with tumor-associated epilepsy. Brain Topogr 16: 85–93.

Bartolomei F, Bosma I, Klein M et al. (2006a). Disturbed functional connectivity in brain tumor patients: evaluation by graph analysis of synchronization matrices. Clin Neurophysiol 117: 2039–2049.

Bartolomei F, Bosma I, Klein M et al. (2006b). How do brain tumors alter functional connectivity? A magnetoencephalography study. Ann Neurol 59: 128–138.

Bartos R, Jech R, Vymazal J et al. (2009). Validity of primary motor area localization with fMRI versus electric cortical stimulation: a comparative study. Acta Neurochir 151: 1071–1080.

Berger MS, Ojemann GA (1992). Intraoperative brain mapping techniques in neuro-oncology. Stereotact Funct Neurosurg 58: 153–161.

Beyh A, Ohlerth A-k, Forkel S (2024). Harnessing advanced tractography in neurosurgical practice. In: K Picht (Ed.), Navigated transcranial magnetic stimulation in neurosurgery. https://osf.io/preprints/psyarxiv/emhrn.

Bommakanti K, Somayajula S, Suvarna A et al. (2016). Pre-operative and post-operative cognitive deficits in patients with supratentorial meningiomas. Clin Neurol Neurosurg 143: 150–158.

Bonifazi S, Passamonti C, Vecchioni S et al. (2020). Cognitive and linguistic outcomes after awake craniotomy in patients with high-grade gliomas. Clin Neurol Neurosurg 198: 106089.

Bosma I, Reijneveld JC, Klein M et al. (2009). Disturbed functional brain networks and neurocognitive function in low-grade glioma patients: a graph theoretical analysis of resting-state MEG. Nonlinear Biomed Phys 3: 9.

Brownsett SLE, Ramajoo K, Copland D et al. (2019). Language deficits following dominant hemisphere tumor resection are significantly underestimated by syndrome-based aphasia assessments. Aphasiology 33: 1163–1181.

Butts AM, Weigand S, Brown PD et al. (2017). Neurocognition in individuals with incidentally-identified meningioma. J Neurooncol 134: 125–132.

Campanella F, Fabbro F, Ius T et al. (2015). Acute effects of surgery on emotion and personality of brain tumor patients: surgery impact, histological aspects, and recovery. Neuro Oncol 17: 1121–1131.

Capurso SA, Calhoun ME, Sukhov RR et al. (1997). Deafferentation causes apoptosis in cortical sensory neurons in the adult rat. J Neurosci 17: 7372–7384.

Carrano A, Juarez JJ, Incontri D et al. (2021). Sex-specific differences in glioblastoma. Cells 10.

Carrera E, Tononi G (2014). Diaschisis: past, present, future. Brain 137: 2408–2422.

Catani M, Jones DK, Ffytche DH (2005). Perisylvian language networks of the human brain. Ann Neurol 57: 8–16.

Chang EF, Raygor KP, Berger MS (2015). Contemporary model of language organization: an overview for neurosurgeons. J Neurosurg 122: 250–261.

Chang WH, Pei YC, Wei KC et al. (2018). Intraoperative linguistic performance during awake brain surgery predicts postoperative linguistic deficits. J Neurooncol 139: 215–223.

Chernoff BL, Sims MH, Smith SO et al. (2019). Direct electrical stimulation of the left frontal aslant tract disrupts sentence planning without affecting articulation. Cogn Neuropsychol 36: 178–192.

Chivukula S, Pikul BK, Black KL et al. (2018). Contralateral functional reorganization of the speech supplementary motor area following neurosurgical tumor resection. Brain Lang 183: 41–46.

Cho NS, Peck KK, Zhang Z et al. (2018). Paradoxical activation in the cerebellum during language fMRI in patients with brain tumors: possible explanations based on neurovascular uncoupling and functional reorganization. Cerebellum 17: 286–293.

Cipolotti L, Healy C, Chan E et al. (2015). The impact of different aetiologies on the cognitive performance of frontal patients. Neuropsychologia 68: 21–30.

Clément A, Perez A, Mandonnet E et al. (2022). DIMA-fr: a French adaptation and standardization of the Dutch diagnostic instrument for mild aphasia (DIMA-nl). Clin Linguist Phon 36: 954–967.

Cochereau J, Lemaitre AL, Wager M et al. (2020). Network-behavior mapping of lasting executive impairments after low-grade glioma surgery. Brain Struct Funct 225: 2415–2429.

Cohen AL, Colman H (2015). Glioma biology and molecular markers. Cancer Treat Res 163: 15–30.

Collée E, Vincent A, Dirven C et al. (2022). Speech and language errors during awake brain surgery and postoperative language outcome in glioma patients: a systematic review. Cancers (Basel) 14.

Collée E, Vincent A, Visch-Brink E et al. (2023). Localization patterns of speech and language errors during awake brain surgery: a systematic review. Neurosurg Rev 46: 38.

Coluccia D, Roth T, Marbacher S et al. (2018). Impact of laterality on surgical outcome of glioblastoma patients: a retrospective single-center study. World Neurosurg 114: e121–e128.

Correa DD, Maron L, Harder H et al. (2007). Cognitive functions in primary central nervous system lymphoma: literature review and assessment guidelines. Ann Oncol 18: 1145–1151.

Costello AL, Warrington EK (1989). Dynamic aphasia: the selective impairment of verbal planning. Cortex 25: 103–114.

Cote DJ, Wang R, Morimoto LM et al. (2022). Birth characteristics and risk of meningioma in a population-based study in California. Neurooncol Adv 4: vdac173.

Davie GL, Hutcheson KA, Barringer DA et al. (2009). Aphasia in patients after brain tumor resection. Aphasiology 23: 1196–1206.

De Baene W, Rijnen SJM, Gehring K et al. (2019). Lesion symptom mapping at the regional level in patients with a meningioma. Neuropsychology 33: 103–110.

de Sain AM, Mantione MHM, Wajer I et al. (2023). A timeline of cognitive functioning in glioma patients who undergo awake brain tumor surgery. Acta Neurochir 165: 1645–1653.

De Witt Hamer PC, Robles SG, Zwinderman AH et al. (2012). Impact of intraoperative stimulation brain mapping on glioma surgery outcome: a meta-analysis. J Clin Oncol 30: 2559–2565.

De Witte E, Mariën P (2013). The neurolinguistic approach to awake surgery reviewed. Clin Neurol Neurosurg 115: 127–145.

De Witte E, Satoer D, Robert E et al. (2015). The Dutch linguistic intraoperative protocol: a valid linguistic approach to awake brain surgery. Brain Lang 140: 35–48.

Deffieux T, Demene C, Pernot M et al. (2018). Functional ultrasound neuroimaging: a review of the preclinical and clinical state of the art. Curr Opin Neurobiol 50: 128–135.

Dell'Acqua F, Tournier JD (2019). Modelling white matter with spherical deconvolution: how and why? NMR Biomed 32: e3945.

Dell'Acqua F, Simmons A, Williams SC et al. (2013). Can spherical deconvolution provide more information than fiber orientations? Hindrance modulated orientational anisotropy, a true-tract specific index to characterize white matter diffusion. Hum Brain Mapp 34: 2464–2483.

Desmurget M, Sirigu A (2015). Revealing humans' sensorimotor functions with electrical cortical stimulation. Philos Trans R Soc Lond B Biol Sci 370: 20140207.

Desmurget M, Bonnetblanc F, Duffau H (2007). Contrasting acute and slow-growing lesions: a new door to brain plasticity. Brain 130: 898–914.

Di Cristofori A, Zarino B, Bertani G et al. (2018). Surgery in elderly patients with intracranial meningioma: neuropsychological functioning during a long term follow-up. J Neurooncol 137: 611–619.

Dijkstra M, van Nieuwenhuizen D, Stalpers LJ et al. (2009). Late neurocognitive sequelae in patients with WHO grade I meningioma. J Neurol Neurosurg Psychiatry 80: 910–915.

Donders-Kamphuis M, Vincent A, Schouten J et al. (2022). Feasibility of awake brain surgery in glioblastoma patients with severe aphasia: five case illustrations. Aphasiology 37: 1944–1963.

Dragoy O, Zyryanov A, Bronov O et al. (2020). Functional linguistic specificity of the left frontal aslant tract for spontaneous speech fluency: evidence from intraoperative language mapping. Brain Lang 208: 104836.

Duffau H (2014). The huge plastic potential of adult brain and the role of connectomics: new insights provided by serial mappings in glioma surgery. Cortex 58: 325–337.

Duffau H, Capelle L, Sichez N et al. (2002). Intraoperative mapping of the subcortical language pathways using direct stimulations. An anatomo-functional study. Brain 125: 199–214.

Duffau H, Gatignol P, Mandonnet E et al. (2005). New insights into the anatomo-functional connectivity of the semantic system: a study using cortico-subcortical electrostimulations. Brain 128: 797–810.

Duffau H, Thiebaut de Schotten M, Mandonnet E (2008). White matter functional connectivity as an additional landmark for dominant temporal lobectomy. J Neurol Neurosurg Psychiatry 79: 492–495.

Dulyan L, Forkel S (2024). The complexity of anatomical language: unravelling terminological discrepancies in the neuroanatomy of language. In: J Grafmann (Ed.), Encyclopedia of the human brain. Elsevier.

Dulyan, L., Bortolami, C. & Forkel, S.J. (2025) Asymmetries in the human brain. In: C Papagno, P Corballis (Eds.), Handbook of clinical neurology, pp. 15–36. Elsevier

Durfee AZ, Sheppard SM, Blake ML et al. (2021). Lesion loci of impaired affective prosody: a systematic review of evidence from stroke. Brain Cogn 152: 105759.

Dziedzic T, Bernstein M (2014). Awake craniotomy for brain tumor: indications, technique and benefits. Expert Rev Neurother 14: 1405–1415.

Dziedzic TA, Balasa A, Jeżewski MP et al. (2021). White matter dissection with the Klingler technique: a literature review. Brain Struct Funct 226: 13–47.

Esmonde T, Giles E, Xuereb J et al. (1996). Progressive supranuclear palsy presenting with dynamic aphasia. J Neurol Neurosurg Psychiatry 60: 403–410.

Fernández Coello A, Moritz-Gasser S, Martino J et al. (2013). Selection of intraoperative tasks for awake mapping based on relationships between tumor location and functional networks. J Neurosurg 119: 1380–1394.

Forkel SJ, Catani M (2018). Lesion mapping in acute stroke aphasia and its implications for recovery. Neuropsychologia 115: 88–100.

Forkel SJ, Labache L, Nachev P et al. (2022). Stroke disconnectome decodes reading networks. Brain Struct Funct 227: 2897–2908.

Gerritsen JKW, Viëtor CL, Rizopoulos D et al. (2019). Awake craniotomy versus craniotomy under general anesthesia without surgery adjuncts for supratentorial glioblastoma in eloquent areas: a retrospective matched case-control study. Acta Neurochir 161: 307–315.

Gerritsen JKW, Klimek M, Dirven CMF et al. (2020). The SAFE-trial: safe surgery for glioblastoma multiforme: awake craniotomy versus surgery under general anesthesia. Study protocol for a multicenter prospective randomized controlled trial. Contemp Clin Trials 88: 105876.

Gerritsen JKW, Zwarthoed RH, Kilgallon JL et al. (2022). Effect of awake craniotomy in glioblastoma in eloquent areas (GLIOMAP): a propensity score-matched analysis of an international, multicentre, cohort study. Lancet Oncol 23: 802–817.

Giampiccolo D, Duffau H (2022). Controversy over the temporal cortical terminations of the left arcuate fasciculus: a reappraisal. Brain 145: 1242–1256.

Giussani C, Roux FE, Ojemann J et al. (2010). 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 66: 113–120.

Goodglass H, Kaplan E, Barresi B (2001). Boston diagnostic aphasia examination, third edn. Lippincott Williams & Wilkins, Philadelphia, PA.

Gould J (2018). Breaking down the epidemiology of brain cancer. Nature 561: S40–S41.

Habets EJJ, Hendriks EJ, Taphoorn MJB et al. (2019). Association between tumor location and neurocognitive functioning using tumor localization maps. J Neurooncol 144: 573–582. https://doi.org/10.1007/s11060-019-03259-z. Epub 2019 Aug 13. PMID: 31410731.

Hendrix P, Hans E, Griessenauer CJ et al. (2017). Neurocognitive function surrounding the resection of frontal WHO grade I meningiomas: a prospective matched-control study. World Neurosurg 98: 203–210.

Hervey-Jumper SL, Berger MS (2016). Maximizing safe resection of low- and high-grade glioma. J Neurooncol 130: 269–282.

Ho VK, Reijneveld JC, Enting RH et al. (2014). Changing incidence and improved survival of gliomas. Eur J Cancer 50: 2309–2318.

Huber W, Poeck K, Willmes K (1984). The Aachen aphasia test. Adv Neurol 42: 291–303.

Ilmberger J, Ruge M, Kreth FW et al. (2008). Intraoperative mapping of language functions: a longitudinal neurolinguistic analysis. J Neurosurg 109: 583–592.

Imbault M, Chauvet D, Gennisson JL et al. (2017). Intraoperative functional ultrasound imaging of human brain activity. Sci Rep 7: 7304.

Inskip PD, Tarone RE, Hatch EE et al. (2003). Laterality of brain tumors. Neuroepidemiology 22: 130–138.

Jehna M, Becker J, Zaar K et al. (2017). Symmetry of the arcuate fasciculus and its impact on language performance of patients with brain tumors in the language-dominant hemisphere. J Neurosurg 127: 1407–1416.

Kappen PR, Beshay T, Vincent A et al. (2022a). The feasibility and added value of mapping music during awake craniotomy: a systematic review. Eur J Neurosci 55: 388–404.

Kappen PR, van den Brink J, Jeekel J et al. (2022b). The effect of musicality on language recovery after awake glioma surgery. Front Hum Neurosci 16: 1028897.

Kellner E, Dhital B, Kiselev VG et al. (2016). Gibbs-ringing artifact removal based on local subvoxel-shifts. Magn Reson Med 76: 1574–1581.

Kemerdere R, de Champfleur NM, Deverdun J et al. (2016). Role of the left frontal aslant tract in stuttering: a brain stimulation and tractographic study. J Neurol 263: 157–167.

Klein M, De Witt Hamer PC (2011). Neurocognitive outcome and resective brain tumor surgery in adults. In: H Duffau (Ed.), Brain mapping. From neural basis of cognition to surgical applications. Springer, Vienna.

Krainik A, Lehéricy S, Duffau H et al. (2003). Postoperative speech disorder after medial frontal surgery: role of the supplementary motor area. Neurology 60: 587–594.

Krieg SM, Shiban E, Buchmann N et al. (2012). Utility of presurgical navigated transcranial magnetic brain stimulation for the resection of tumors in eloquent motor areas. J Neurosurg 116: 994–1001.

Kullmann DM (2020). Editorial. Brain 143: 1045. https://doi.org/10.1093/brain/awaa082.

Laplane D, Talairach J, Meininger V et al. (1977). Clinical consequences of corticectomies involving the supplementary motor area in man. J Neurol Sci 34: 301–314.

Larjavaara S, Haapasalo H, Sankila R et al. (2008). Is the incidence of meningiomas underestimated? A regional survey. Br J Cancer 99: 182–184.

Leclercq D, Duffau H, Delmaire C et al. (2010). Comparison of diffusion tensor imaging tractography of language tracts and intraoperative subcortical stimulations. J Neurosurg 112: 503–511.

Lemée JM, Bernard F, Ter Minassian A et al. (2018). Right hemisphere cognitive functions: from clinical and anatomical bases to brain mapping during awake craniotomy. Part II: neuropsychological tasks and brain mapping. World Neurosurg 118: 360–367.

Li YC, Chiu HY, Lin YJ et al. (2021). The merits of awake craniotomy for glioblastoma in the left hemispheric eloquent area: one institution experience. Clin Neurol Neurosurg 200: 106343.

Liouta E, Koutsarnakis C, Liakos F et al. (2016). Effects of intracranial meningioma location, size, and surgery on neurocognitive functions: a 3-year prospective study. J Neurosurg 124: 1578–1584.

Louis DN, Ohgaki H, Wiestler OD et al. (2007). The 2007 WHO classification of tumors of the central nervous system. Acta Neuropathol 114: 97–109.

Louis DN, Perry A, Reifenberger G et al. (2016). The 2016 World Health Organization classification of tumors of the central nervous system: a summary. Acta Neuropathol 131: 803–820.

Louis DN, Perry A, Wesseling P et al. (2021). The 2021 WHO classification of tumors of the central nervous system: a summary. Neuro Oncol 23: 1231–1251.

Luria AR, Tsvetkova LS (1968). The mechanism of dynamic aphasia. Found Lang 4: 296–307.

Mandonnet E, Delattre JY, Tanguy ML et al. (2003). Continuous growth of mean tumor diameter in a subset of grade II gliomas. Ann Neurol 53: 524–528.

Mandonnet E, Winkler PA, Duffau H (2010). Direct electrical stimulation as an input gate into brain functional networks: principles, advantages and limitations. Acta Neurochir 152: 185–193.

Martín-Monzón I, Rivero Ballagas Y, Arias-Sánchez S (2022). Language mapping: a systematic review of protocols that evaluate linguistic functions in awake surgery. Appl Neuropsychol Adult 29: 845–854.

Méndez Orellana C, Visch-Brink E, Vernooij M et al. (2015). Crossed cerebrocerebellar language lateralization: an additional diagnostic feature for assessing atypical language representation in presurgical functional MR imaging. AJNR Am J Neuroradiol 36: 518–524.

Meskal I, Gehring K, Rutten GJ et al. (2016). Cognitive functioning in meningioma patients: a systematic review. J Neurooncol 128: 195–205.

Mirchandani AS, Beyh A, Lavrador JP et al. (2020). Altered corticospinal microstructure and motor cortex excitability in gliomas: an advanced tractography and transcranial magnetic stimulation study. J Neurosurg 134: 1368–1376.

Mooijman S, Vincent A, De Witte E et al. (2021). OS07.5A diagnostic instrument for mild aphasia (DIMA): sensitive and valuable addition to standard language assessment in glioma patients. Neuro Oncol 23: ii10–ii11.

Mooijman S, Bos LS, De Witte E et al. (2022). Language processing in glioma patients: speed or accuracy as a sensitive measure? Aphasiology 36: 1467–1491.

Muir M, Patel R, Traylor J et al. (2022). Validation of non-invasive language mapping modalities for eloquent tumor resection: a pilot study. Front Neurosci 16: 833073.

Naeser MA, Hayward RW (1978). Lesion localization in aphasia with cranial computed tomography and the Boston diagnostic aphasia exam. Neurology 28: 545–551.

NCIN (2013). NCIN data briefing astrocytic brain tumors: survival rates in England, UNCIN.

Nicolo P, Rizk S, Magnin C et al. (2015). Coherent neural oscillations predict future motor and language improvement after stroke. Brain 138: 3048–3060.

Nieberlein L, Rampp S, Gussew A et al. (2023). Reorganization and plasticity of the language network in patients with cerebral gliomas. Neuroimage Clin 37: 103326.

Noll KR, Sullaway C, Ziu M et al. (2015). Relationships between tumor grade and neurocognitive functioning in patients with glioma of the left temporal lobe prior to surgical resection. Neuro Oncol 17: 580–587.

Noll KR, Bradshaw ME, Weinberg JS et al. (2018). Neurocognitive functioning is associated with functional independence in newly diagnosed patients with temporal lobe glioma. Neurooncol Pract 5: 184–193.

Ochocka N, Segit P, Wojnicki K et al. (2023). Specialized functions and sexual dimorphism explain the functional diversity of the myeloid populations during glioma progression. Cell Rep 42: 111971.

Ohlerth AK, Valentin A, Vergani F et al. (2020). The verb and noun test for peri-operative testing (VAN-POP): standardized language tests for navigated transcranial magnetic stimulation and direct electrical stimulation. Acta Neurochir 162: 397–406.

Ohlerth AK, Lavrador JP, Vergani F et al. (in press). Combining nTMS and tractography for language mapping: an integrated paradigm for neurosurgical planning. In: E Picht (Ed.), Navigated transcranial magnetic stimulation in neurosurgery. Springer.

Ojemann G, Mateer C (1979). Human language cortex: localization of memory, syntax, and sequential motor-phoneme identification systems. Science 205: 1401–1403.

Ojemann G, Ojemann J, Lettich E et al. (1989). Cortical language localization in left, dominant hemisphere. An electrical stimulation mapping investigation in 117 patients. J Neurosurg 71: 316–326.

Oshino S, Kato A, Wakayama A et al. (2007). Magnetoencephalographic analysis of cortical oscillatory activity in patients with brain tumors: synthetic aperture magnetometry (SAM) functional imaging of delta band activity. Neuroimage 34: 957–964.

Palmisciano P, Haider AS, Balasubramanian K et al. (2022). Supplementary motor area syndrome after brain tumor surgery: a systematic review. World Neurosurg 165: 160–171.e162.

Papagno C, Gallucci M, Casarotti A et al. (2011). Connectivity constraints on cortical reorganization of neural circuits involved in object naming. Neuroimage 55: 1306–1313.

Papagno C, Casarotti A, Comi A et al. (2012). Measuring clinical outcomes in neuro-oncology. A battery to evaluate low-grade gliomas (LGG). J Neurooncol 108: 269–275.

Penfield W, Roberts L (1959). Speech and brain-mechanisms, Princeton University Press, Princeton, New Jersey.

Perrone D, Aelterman J, Pižurica A et al. (2015). The effect of Gibbs ringing artifacts on measures derived from diffusion MRI. Neuroimage 120: 441–455.

Petrovich Brennan NM, Whalen S, de Morales BD et al. (2007). Object naming is a more sensitive measure of speech localization than number counting: converging evidence from direct cortical stimulation and fMRI. Neuroimage 37: S100–S108.

Picht T, Krieg SM, Sollmann N et al. (2013). A comparison of language mapping by preoperative navigated transcranial magnetic stimulation and direct cortical stimulation during awake surgery. Neurosurgery 72: 808–819.

Piper RJ, Mikhael S, Wardlaw JM et al. (2016). Imaging signatures of meningioma and low-grade glioma: a diffusion tensor, magnetization transfer and quantitative longitudinal relaxation time MRI study. Magn Reson Imaging 34: 596–602.

Preusser M, de Ribaupierre S, Wöhrer A et al. (2011). Current concepts and management of glioblastoma. Ann Neurol 70: 9–21.

Price CJ (2010). The anatomy of language: a review of 100 fMRI studies published in 2009. Ann N Y Acad Sci 1191: 62–88.

Radhakrishnan K, Mokri B, Parisi JE et al. (1995). The trends in incidence of primary brain tumors in the population of Rochester, Minnesota. Ann Neurol 37: 67–73.

Rammeloo E, Schouten JW, Krikour K et al. (2023). Preoperative assessment of eloquence in neurosurgery: a systematic review. J Neurooncol 165: 413–430.

Rasmussen BK, Hansen S, Laursen RJ et al. (2017). Epidemiology of glioma: clinical characteristics, symptoms, and predictors of glioma patients grade I-IV in the Danish neuro-oncology registry. J Neurooncol 135: 571–579.

Rezai AR, D'Haese PF, Finomore V et al. (2024). Ultrasound blood-brain barrier opening and Aducanumab in Alzheimer's disease. N Engl J Med 390: 55–62.

Rijnen SJM, Meskal I, Bakker M et al. (2019). Cognitive outcomes in meningioma patients undergoing surgery: individual changes over time and predictors of late cognitive functioning. Neuro Oncol 21: 911–922.

Rijnen SJM, Meskal I, Emons WHM et al. (2020). Evaluation of normative data of a widely used computerized neuropsychological battery: applicability and effects of sociodemographic variables in a Dutch sample. Assessment 27: 373–383.

Robinson G, Blair J, Cipolotti L (1998). Dynamic aphasia: an inability to select between competing verbal responses? Brain 121: 77–89.

Robinson G, Shallice T, Cipolotti L (2006). Dynamic aphasia in progressive supranuclear palsy: a deficit in generating a fluent sequence of novel thought. Neuropsychologia 44: 1344–1360.

Rofes A, Mandonnet E, Godden J et al. (2017). Survey on current cognitive practices within the European low-grade glioma network: towards a European assessment protocol. Acta Neurochir 159: 1167–1178.

Rofes A, Talacchi A, Santini B et al. (2018). Language in individuals with left hemisphere tumors: is spontaneous speech analysis comparable to formal testing? J Clin Exp Neuropsychol 40: 722–732.

Rudà R, Capper D, Waldman AD et al. (2022). EANO - EURACAN - SNO guidelines on circumscribed astrocytic gliomas, glioneuronal, and neuronal tumors. Neuro Oncol 24: 2015–2034.

Sanai N, Mirzadeh Z, Berger MS (2008). Functional outcome after language mapping for glioma resection. N Engl J Med 358: 18–27.

Satoer D, Vork J, Visch-Brink E et al. (2012). Cognitive functioning early after surgery of gliomas in eloquent areas. J Neurosurg 117: 831–838.

Satoer D, Vincent A, Smits M et al. (2013). Spontaneous speech of patients with gliomas in eloquent areas before and early after surgery. Acta Neurochir 155: 685–692.

Satoer D, Kloet A, Vincent A et al. (2014a). Dynamic aphasia following low-grade glioma surgery near the supplementary motor area: a selective spontaneous speech deficit. Neurocase 20: 704–716.

Satoer D, Visch-Brink E, Smits M et al. (2014b). Long-term evaluation of cognition after glioma surgery in eloquent areas. J Neurooncol 116: 153–160.

Satoer D, Visch-Brink E, Dirven C et al. (2016). Glioma surgery in eloquent areas: can we preserve cognition? Acta Neurochir 158: 35–50.

Satoer D, Vincent A, Ruhaak L et al. (2018). Spontaneous speech in patients with gliomas in eloquent areas: evaluation until 1 year after surgery. Clin Neurol Neurosurg 167: 112–116.

Satoer D, De Witte E, Dragoy O (2021). Spontaneous speech. In: EHG Mandonnet (Ed.), Intraoperative mapping of cognitive networks. Which tasks for which locations. Springer, Cham.

Satoer D, De Witte E, Bulté B et al. (2022). Dutch diagnostic instrument for mild aphasia (DIMA): standardisation and a first clinical application in two brain tumor patients. Clin Linguist Phon 36: 929–953.

Sheppard SM, Stockbridge MD, Keator LM et al. (2022). The company prosodic deficits keep following right hemisphere stroke: a systematic review. J Int Neuropsychol Soc 28: 1075–1090.

Sierpowska J, Gabarrós A, Fernandez-Coello A et al. (2017). Words are not enough: nonword repetition as an indicator of arcuate fasciculus integrity during brain tumor resection. J Neurosurg 126: 435–445.

Sleurs C, Zegers CML, Compter I et al. (2022). Neurocognition in adults with intracranial tumors: does location really matter? J Neurooncol 160: 619–629.

Sollmann N, Zhang H, Fratini A et al. (2020). Risk assessment by presurgical tractography using navigated TMS maps in patients with highly motor- or language-eloquent brain tumors. Cancers (Basel) 12: 1264.

Soloukey S, Vincent A, Satoer DD et al. (2019). Functional ultrasound (fUS) during awake brain surgery: the clinical potential of intraoperative functional and vascular brain mapping. Front Neurosci 13: 1384.

Steinvorth S, Welzel G, Fuss M et al. (2003). Neuropsychological outcome after fractionated stereotactic radiotherapy (FSRT) for base of skull meningiomas: a prospective 1-year follow-up. Radiother Oncol 69: 177–182.

Stephan KE, Baldeweg T, Friston KJ (2006). Synaptic plasticity and dysconnection in schizophrenia. Biol Psychiatry 59: 929–939.

Stupp R, Mason WP, van den Bent MJ et al. (2005). Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 352: 987–996.

Swinburn K, Porter G, Howard D (2005). The Comprehensive Aphasia Test (CAT), Psychology Press, Hove, UK.

Szelies B, Mielke R, Kessler J et al. (2002). Prognostic relevance of quantitative topographical EEG in patients with poststroke aphasia. Brain Lang 82: 87–94.

Talacchi A, Santini B, Casagrande F et al. (2013a). Awake surgery between art and science. Part I: clinical and operative settings. Funct Neurol 28: 205–221.

Talacchi A, Santini B, Casartelli M et al. (2013b). Awake surgery between art and science. Part II: language and cognitive mapping. Funct Neurol 28: 223–239.

Talozzi L, Forkel SJ, Pacella V et al. (2023). Latent disconnectome prediction of long-term cognitive-behavioural symptoms in stroke. Brain 146: 1963–1978.

Tarapore PE, Findlay AM, Honma SM et al. (2013). Language mapping with navigated repetitive TMS: proof of technique and validation. Neuroimage 82: 260–272.

Tewari S, Tom MC, Park DYJ et al. (2022). Sex-specific differences in low-grade glioma presentation and outcome. Int J Radiat Oncol Biol Phys 114: 283–292.

Thiebaut de Schotten M, Urbanski M, Duffau H et al. (2005). Direct evidence for a parietal-frontal pathway subserving spatial awareness in humans. Science 309: 2226–2228.

Thiebaut de Schotten M, Foulon C, Nachev P (2020). Brain disconnections link structural connectivity with function and behaviour. Nat Commun 11: 5094.

Thomson AM, Taylor R, Whittle IR (1998). Assessment of communication impairment and the effects of resective surgery in solitary, right-sided supratentorial intracranial tumors: a prospective study. Br J Neurosurg 12: 423–429.

Tremblay P, Dick AS (2016). Broca and Wernicke are dead, or moving past the classic model of language neurobiology. Brain Lang 162: 60–71.

Trinh VT, Fahim DK, Shah K et al. (2013). Subcortical injury is an independent predictor of worsening neurological deficits following awake craniotomy procedures. Neurosurgery 72: 160–169.

Tucha O, Smely C, Preier M et al. (2003). Preoperative and postoperative cognitive functioning in patients with frontal meningiomas. J Neurosurg 98: 21–31.

van Alkemade H, de Leau M, Dieleman EM et al. (2012). Impaired survival and long-term neurological problems in benign meningioma. Neuro Oncol 14: 658–666.

van der Linden SD, Gehring K, De Baene W et al. (2020). Assessment of executive functioning in patients with meningioma and low-grade glioma: a comparison of self-report, proxy-report, and test performance. J Int Neuropsychol Soc 26: 187–196.

van Kessel E, Baumfalk AE, van Zandvoort MJE et al. (2017). Tumor-related neurocognitive dysfunction in patients with diffuse glioma: a systematic review of neurocognitive functioning prior to anti-tumor treatment. J Neurooncol 134: 9–18.

van Kessel E, Schuit E, Huenges Wajer IMC et al. (2021). Added value of cognition in the prediction of survival in low and high grade glioma. Front Neurol 12: 773908.

van Loon EM, Heijenbrok-Kal MH, van Loon WS et al. (2015). Assessment methods and prevalence of cognitive dysfunction in patients with low-grade glioma: a systematic review. J Rehabil Med 47: 481–488.

van Nieuwenhuizen D, Ambachtsheer N, Heimans JJ et al. (2013). Neurocognitive functioning and health-related quality of life in patients with radiologically suspected meningiomas. J Neurooncol 113: 433–440.

van Nieuwenhuizen D, Douw L, Klein M et al. (2018). Cognitive functioning and functional brain networks in postoperative WHO grade I meningioma patients. J Neurooncol 140: 605–613.

Walsh KM, Hiroko Ohgaki MRW (2016). Epidemiology. In: S Mitchel, MW Berger (Eds.), Handbook of clinical neurology. Elsevier.

Wang YC, Chuang CC, Wei KC et al. (2016). Long term surgical outcome and prognostic factors of atypical and malignant meningiomas. Sci Rep 6: 35743.

Whiteside DM, Kealey T, Semla M et al. (2016). Verbal fluency: language or executive function measure? Appl Neuropsychol Adult 23: 29–34.

Whittle IR, Borthwick S, Haq N (2003). Brain dysfunction following 'awake' craniotomy, brain mapping and resection of glioma. Br J Neurosurg 17: 130–137.

Whittle IR, Smith C, Navoo P et al. (2004). Meningiomas. Lancet 363: 1535–1543.

Wiemels J, Wrensch M, Claus EB (2010). Epidemiology and etiology of meningioma. J Neurooncol 99: 307–314.

Wolthuis N (2022). Language impairments and resting-state EEG in brain tumor patients: revealing connections, Doctor of Philosophy. University of Groningen, Groningen, The Netherlands.

Wolthuis N, Satoer D, Veenstra W et al. (2021). Resting-state electroencephalography functional connectivity networks relate to pre- and postoperative language functioning in low-grade glioma and meningioma patients. Front Neurosci 15: 785969.

Wolthuis N, Bosma I, Bastiaanse R et al. (2022). Distinct slow-wave activity patterns in resting-state electroencephalography and their relation to language functioning in low-grade glioma and meningioma patients. Front Hum Neurosci 16: 748128.

Yoshii Y, Tominaga D, Sugimoto K et al. (2008). Cognitive function of patients with brain tumor in pre- and postoperative stage. Surg Neurol 69: 51–61discussion 61.

Young RJ, Brennan N, Fraser JF et al. (2010). Advanced imaging in brain tumor surgery. Neuroimaging Clin N Am 20: 311–335.

Zhang N, Xia M, Qiu T et al. (2018). Reorganization of cerebro-cerebellar circuit in patients with left hemispheric gliomas involving language network: a combined structural and resting-state functional MRI study. Hum Brain Mapp 39: 4802–4819.

Zigiotto L, Annicchiarico L, Corsini F et al. (2020). Effects of supra-total resection in neurocognitive and oncological outcome of high-grade gliomas comparing asleep and awake surgery. J Neurooncol 148: 97–108.

WEB REFERENCES

https://iknl.nl/en/ncr - Netherlands Cancer Registry (NCR).

https://cbtrus.org/ - CBTRUS.

https://bradipho.eu/.

https://www.youtube.com/watch?v=o-oGpD_Nx5U.

https://www.youtube.com/watch?v=obiARnsKUAo&t=3s.

https://youtu.be/dnzjZqgfZSc.

https://www.frontiersin.org/articles/10.3389/fnins.2019.01384/full#supplementary-material.