In Cerebral Asymmetries (Eds. Corballis & Papagno) - Chapter 6

Oncology - Brain Asymmetries

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Abstract

Brain tumours, which are classified as rare diseases, primarily include glioblastoma, with an annual occurrence of 300,000 cases. Unfortunately, this condition leads to the loss of 241,000 lives each year, highlighting its devastating nature. However, recent advancements in diagnosis and treatment have significantly improved the management and care of brain tumours. In this chapter, we will first provide an overview of the common types of primary brain tumours (gliomas and meningiomas). We will then delve into techniques for identifying and mapping tumours that impact language processing, utilizing both non-invasive and invasive methods. Lastly, we will discuss the effects of surgery on language and cognitive functions. The focus of this chapter is on tumours affecting language processing in the brain and the application of diffusion-weighted tractography to map the white matter language system.

Keywords: Brain tumour, anatomy, language, cognition, white matter, tractography, MRI, fMRI, (awake) surgery

1. Incidence, prevalence and prognosis of brain tumours

1.1. Primary brain tumours

A brain tumour 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 concentrates on primary (as opposed to metastatic) brain tumours, which start in the brain (glioma) or its surrounding tissues (meninges).

1.2. Types of brain tumours

Gliomas and meningiomas are the prevailing forms of brain tumours found in humans. Among them, malignant gliomas stand out as the most aggressive and fatal. Conversely, while meningiomas are typically benign, they often reappear following surgical intervention. These tumours differ with regard to their origin and their effect on surrounding brain areas, however, both tumour types can affect brain areas that are involved in sensori-motor, language (the so-called 'eloquent areas') and other higher cognitive functions. These tumours can be further dichotomised into low-grade, grade I or II, and high-grade, grade III or IV according to the World Health Organisation (WHO); (Louis et al., 2016; Louis et al., 2021). This distinction is based on the cell type a tumour originates from and is determined by histology. Low-grade brain tumours have relatively slow growth rates whereas high-grade brain tumours have a more aggressive evolution. Early diagnosis is linked to better survival times ((NCIN), 2013).

Gliomas are intra-axial tumours, which means that they lie within the brain tissue (brain parenchyma). These infiltrating tumours originate from glial cells, which are brain cells that support and protect neurons. Gliomas are the most frequently occurring primary brain tumours with approximately 1,000 new diagnoses (incidence) of adult gliomas every year in the Netherlands only, of which 20% are low-grade (Ho et al., 2014). Worldwide, more than 250,000 new cases of primary brain tumours are diagnosed every year of which 77% are gliomas (Kyle M. 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 tumours in adults, eventually progress to higher grades of malignancy (WHO grades III and IV; high-grade glioma - HGG) within 5 to 10 years approximately (Hervey-Jumper and Berger, 2016). For LGGs residing in eloquent areas (i.e. inferior frontal gyrus, posterior temporal cortex), 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 avoids irreversible neurologic and cognitive damage (De Witt Hamer et al., 2012; Duffau et al., 2002; Thiebaut de Schotten et al., 2005) (see section 6.1 for more details). HGGs (otherwise referred to as anaplastic astrocytoma or oligodendroglioma, mixed anaplastic oligoastrocytoma, glioblastoma) are very aggressive tumours with poor prognosis. Amongst them, glioblastoma has the most devastating prognosis with 12-15 months 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 at the age of 50-60 years (Preusser et al., 2011).

More recently, several molecular markers have been identified as important for 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 (IDH1/2) mutations: IDH mutations are commonly observed in gliomas and are associated with a better prognosis. Gliomas with IDH1 and 2 mutations tend to have a more favorable outcome compared to those without these mutations, 2) 1p/19q codeletion: 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 tumour aggressiveness. The assessment of these markers, along with other clinical and histopathologic factors, can be of aid in predicting the prognosis and guiding treatment decisions for patients with gliomas. Traditionally, surgical removal of glioblastoma is performed under general anesthesia with the goal of achieving a maximal safe resection (see section 7.1 for more discussion).

Meningiomas are extra-axial tumours, which means that they lie outside the brain parenchyma. These tumours 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 tumours, 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). However, many meningiomas are asymptomatic and remain undiagnosed, that is 20-30 years or more, (Wiemels et al., 2010). Therefore, the overall meningioma incidence is presumably at least twice as high (Larjavaara, Haapasalo, Sankila, Helen, & Auvinen, 2008). Symptomatic meningiomas are usually discovered between the 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 tumour. Possible symptoms include epileptic seizures (temporal location), disturbed vision (occipital location), sensori-motor 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 sensory-motor 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 five-year and ten-year overall survival rates were 93.5% and 83.4%, respectively (Wang et al., 2016).

2. Brain tumours and differences

2.1 Sex differences

The dissimilarities observed between men and women with regards to glioblastomas are 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 tumours were diagnosed in men, while women accounted for 45%. In contrast, during the same period, around 36% of non-malignant brain tumours were found in men, with women comprising 64% ((Gould, 2018), see Figure 1. Not only do the rates of occurrence of tumours 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 determines 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 tumour 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 either. However, a recent retrospective cohort study demonstrated that male sex was an independent risk factor for worse outcomes as opposed to female sex in addition to 1p19q co-deletion status with better overall survival and next intervention free survival (Tewari et al., 2022). According to the Central Brain Tumour Registry of the United States (CBTRUS - CBTRUS, 2013 - 2017) and a population based study in California, meningioma is more commonly found in female sex and was at higher risk for especially between the ages of 27-37 years (Cote et al., 2022).

2.2 Hemispheric differences

Neuroscience studies have recently identified that cognitive functions are much better understood for the left hemisphere than the right (Talozzi et al., 2023; Thiebaut de Schotten et al., 2020). This discrepancy is mainly due to language processing being obviously impaired with left hemisphere lesions. Left hemisphere lesions that impact on language processing likely interfere with articulation, comprehension, and semantic access while right hemisphere lesions impact prosody, intonation, and emotional affect. Impairments in the suprasegmental language functions of the right hemisphere have psychological impacts on patients (e.g. monotonous speech) but interfere less with their daily life. As such, cognitive testing has focused on the left hemisphere. Consequently, tumours considered 'eloquent' are typically left hemisphere tumours. In a study of 489 tumour patients, there were no significant differences observed between the hemispheres across major tumour types. However, LGG and meningioma tended to occur slightly more frequently on the left side, although not significantly. Conversely, HGG exhibited a non-significant tendency to occur more often on the right side (Inskip et al., 2003).

2.3 Lobar differences

A statistical review of primary brain tumours diagnosed in the United States in 2008-2012 revealed that brain tumours are inhomogeneously distributed across the brain (Figure 1A). The majority of tumours (26%) are located in the frontal lobe, followed by temporal lobe tumours (19%), parietal tumours (12%), and cerebellar tumours (5%). While the brainstem (4%), occipital lobes (2%) and ventricular tumours (2%) are less common. The remaining 30% are in other regions (Gould, 2018), see Figure 1.

[insert Figure 1 about here]

3 Techniques to identify tumours affecting the language system

3.1. Non-invasive structural and functional techniques

Non-invasive techniques offer a valuable means to map the altered brain anatomy resulting from the presence of a tumour. These techniques can be used to assess both structural changes, functional alterations and plasticity. The non-invasive nature of these techniques means they are applied externally, typically without the need for 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 pathological changes (T2-weighted scans), and to explore the connectivity of the brain (diffusion-weighted scans). However, structural MRI alone is insufficient to precisely delineate the tumour margin when it infiltrates the surrounding tissue. 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 allows for estimation of the tumour's impact on brain connections, which can be infiltrated or displaced. Consequently, diffusion-weighted imaging is often employed for estimating and visualizing the brain's connections using white matter tractography, particularly in the context of presurgical planning. Personalized tractography is crucial for patients since brain tumours can displace, disrupt, and infiltrate white matter, altering the expected trajectory compared to healthy brain atlases (Figure 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 (Figure 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 per voxel, thereby underrepresenting the complexity of the connectional anatomy in many regions. Due to the alterations caused by the lesion, manual dissections of the white matter are recommended over atlas-based tools (Figure 2A).

For preprocessing diffusion-weighted imaging data for tractography, the specific steps depend on the acquisition quality but typically involve motion and eddy current corrections (Figure 2B). It is highly recommended to perform susceptibility distortion corrections and research data should also undergo denoising and correction for Gibbs ringing (Kellner et al., 2016; Perrone et al., 2015). 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 (Figure 2C). Advanced algorithms based on High Angular Resolution Diffusion Imaging (HARDI) offer improved resolution of fiber crossings and can visualize lateral projections resembling post-mortem dissections (Dell'Acqua et al., 2013; Dell'Acqua and Tournier, 2019). However, these algorithms are more susceptible to false positive reconstructions and require comprehensive anatomical knowledge. In the case of tumours affecting language functions, tractography can selectively visualize the language network using these techniques (for detailed information, see Forkel (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 Figure 2D. Another recent review, identified, however, that there is no one tract one function association and suggests that language is a spatio-temporally dynamic process in the brain going beyond the arcuate fasciculus (Forkel et al., 2022). The current anatomical understanding of the connectional language system includes seven pathways dichotomised into a dorsal and ventral stream. However, an intriguing question arises regarding the bilateral nature of these networks, considering that language is typically described as a unilateral function (Figure 3).

[insert Figure 2 about here]

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On the functional side two sequences can be acquired using MRI scanning, namely task-based functional MRI (fMRI) and non-task based resting state functional imaging (rs-fMRI). fMRI is the most commonly used non-invasive imaging technique to map brain functions. The word-verb association task and finger tapping are often used to localize linguistic and motor functions, respectively. In the neurosurgical setting, fMRI contributes to determining dominance for these functions and predicting risk factors. In addition, fMRI can be easily repeated in the postoperative period to study brain plasticity (Young et al., 2010). However, fMRI has a number of shortcomings. First, fMRI cannot discriminate between the activated 'essential' and 'compensable' regions. Second, motion-related artifacts decrease the reliability of fMRI findings. Finally, the activation zones may vary depending on the paradigm chosen, the statistical method and the underlying neurologic disorder. Third, 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 language-relevant cortex is limited as revealed by comparison with DES (see below section 3 Invasive techniques) during awake surgery. 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 non-invasive neurophysiological technique that stimulates brain regions by means of an electromagnetic coil. Single-pulse nTMS is used as an activation tool to map the motor cortex while repetitive nTMS has an inhibitory effect. That is, 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 experienced as painful in the temporal regions due to stimulation of the facial nerves. For the mapping of the motor functions, good correlations between nTMS and DES were found (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 setting (Picht et al., 2013; Sollmann et al., 2020; Tarapore et al., 2013) 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 the identification of language functions. For example, nTMS has a significantly higher correlation with intraoperative DES and better sensitivity and specificity (exceeding 99% and 83% resp.) (Muir et al., 2022). This indicates that TMS can consistently identify critical language sites that match DES better 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 non-invasive technique directly measures brain signals in real-time by electrodes affixed to the scalp. These signals are amplified, digitalised, 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), which combines a high temporal resolution and a relatively high spatial resolution. However, EEG has the advantage of being less expensive and more widely available than MEG. Moreover, EEG is frequently used in clinical settings when brain dysfunction or epileptic seizures are suspected.

3.2. 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 discovered language areas in the brain via various verbal paraphasias that were very widely distributed. Based on this data, he proposed that dynamic connections exist within a cortical network that are able to compensate for the damaged 'classic' linguistic areas “Broca’s and Wernicke’s area” in the left hemisphere (Penfield and Roberts, 1959) (for a critical evaluation of the terminology see (Dulyan and Forkel, submitted). 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 found 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 tumour aiming to minimize damage to the connective tissue. Neurosurgeon Hugues Duffau combined these methods and developed an entire field of "modern neurosurgical research". He discovered, among others, that apart from cortical language areas, it is extremely important to also 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 ventral tracts such as the inferior fronto-occipital fasciculus, the inferior longitudinal fasciculus (IFOF) and the uncinate fasciculus were described to play a role in language (Chang et al., 2015; Duffau, 2014)(Chang et al., 2015, Duffau, 2014). Although the role of the IFOF for language is still disputed (Schmahmann and Pandya, 2007). An exciting and very 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 greatly 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). Motor mapping may optionally be performed under local anesthesia (using evoked potentials), while linguistic, cognitive, visual and spatial mapping is generally performed using an asleep-awake-asleep procedure. Cortical stimulation is usually performed with a bipolar stimulator generating biphasic and rectangular pulses of 1 millisecond each time. Frequencies from 50 to 60 Hz are used by default and the intensity is progressively increased from 1 to 10 mA in 0.5 mA increments. A stimulus time of 1 or 2 seconds is sufficient to elicit a motor response, while the inhibition of language requires 3 to 4 seconds. Subcortical stimulation is done in a similar way (stimulus time may be extended to 6 seconds) to identify functional subcortical pathways (Berger and Ojemann, 1992; Ojemann et al., 1989; Talacchi et al., 2013a; Talacchi et al., 2013b)

Based on the location of the tumour 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), but 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 (non-linguistic) cognitive tasks for right-hemispheric functions, such as visuo-spatial and social cognitive functions in order to prevent f.i. unilateral neglect or deficits in facial emotion recognition, prosody, empathy and theory of mind (Lemée et al., 2018) (see section 6.1 for 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 Figure 4).

[insert Figure 4 about here]

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 appears to be possible. Its high sensitivity explains why DES is used to validate non-invasive mapping techniques such as fMRI, TMS, white matter networks (Mandonnet et al., 2010). Furthermore, DES is able 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 tumour 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). In particular, intraoperative findings were found to have prognostic value for the level or presence of postoperative aphasia. For instance, intraoperative language decline observed with The Pyramids and Palm Tree Test (PPTT) appeared to be a marker for improved postoperative (Kappen et al., 2022b)language performance (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 for 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 section 4.3 Supplementary Motor Area syndrome for more details). Besides the monitoring of sensori-motor, language and cognitive functions, awake surgery teams are exploring the potential of other skills relevant for the patients' 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, 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 relevance of mapping music.

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). In combination with advances in tractography, a new anatomy of language has emerged over the past three decades (Figure 5).

[insert Figure 5 about here]

Apart from DES, other direct techniques for the detection of functional boundaries are under development. A promising method is functional Ultrasound (fUS) (Deffieux et al., 2018; Imbault et al., 2017; Soloukey et al., 2019). Functional ultrasound is a mobile neuro-imaging technique with unprecedented spatiotemporal resolution. This technique allows 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 the application of this technique during conventional awake surgery with motor, language and visual tasks in a total of 10 glioma patients. fUS was able to detect functional areas also defined with DES, but also deep inside the brain. They were able to image (real-time) tumour 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).

4 Language and cognitive profiles in brain tumour patients

4.1 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 a LGG (i.e. 5 mm p/y) which allows for neuroplasticity and reorganization of language functions (Desmurget et al., 2007; Mandonnet et al., 2003).

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, 2001b), the Aachener Aphasia Test (AAT) (Huber et al., 1984) or the Comprehensive Aphasia Test (Swinburn, 2005). These tests are not always sensitive for mild language deficits (Brownsett et al., 2019; Davie et al., 2009; Satoer et al., 2012). In addition, despite the often absent objectified aphasia, LGG patients do report language complaints (Brownsett et al., 2019; Mooijman et al., 2022; Satoer et al., 2012) 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. In order to detect the generally mild language impairments in these patients on different linguistic levels, spontaneous speech analyses can be applied (see also section 4.6). 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 4 subtests: 1) repetition (words, non-words 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, both accuracy and reaction time in milliseconds are recorded. See Table 1 for examples.

[insert Table 1 about here]

Case illustrations showed the sensitivity and clinical application of DIMA in a glioma and a meningioma patient before surgery. A preliminary analysis at group level showed that preoperatively, patients deviated on DIMA sentence repetition and DIMA sentence completion. As expected, HGG patients performed worse than LGG patients, in particular on word, non-word, and sentence repetition tasks, which is probably attributed to more aggressive tumour growth (Mooijman et al., 2021). There was no difference in language scores when comparing patients with left to right hemispheric tumour localisation. 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 tumours performed worse on the BNT and Letter Fluency compared to right-hemispheric tumour 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 tumour location (see also Brownsett et al. (2019); Davie et al. (2009)). 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 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, non-linguistic 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 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 tumour location. It should also be noted that the ideal testing time should consist of no more than 45 minutes (Klein, 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, B/A (Papagno et al., 2012; Satoer et al., 2016; van Loon et al., 2015). Sensitive cognitive screeners (via tablet/computer) with limited administration time duration have been proposed by several research groups (e.g. de Sain et al. (2023); Rijnen et al. (2020). Van Kessel et al. van Kessel et al. (2021) indicated that preoperative memory deficits, which were revealed with their neuropsychological 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 neuropsychological tests, can be translated into "real-world" functions and activities (Noll et al., 2018).

4.2 Meningiomas

As opposed to gliomas, less research has been done related to cognitive functioning in meningioma patients. It is only for about the last decade that mostly non-linguistic cognitive functions were looked into in this patient group. As these tumours do not infiltrate in eloquent brain areas, they were considered more or less "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 the domains of (working) memory, attention and executive functioning before surgery. More recent studies have also 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 (Bommakanti et al., 2016; Hendrix et al., 2017; Liouta et al., 2016; Tucha et al., 2003). Some studies in contrasts reported intact performance (Butts et al., 2017; van Nieuwenhuizen et al., 2013). 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 taken into account.

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 tumour and treatment characteristics (localisation, tumour 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 they 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 in 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 tumours (gliomas and metastatic tumours), while correcting for tumour size and surrounding edema. The difference between tumour types is presumably due to the fact that meningiomas are not infiltrative but only cause mass effect on surrounding brain tissue, especially on subcortical tissue, and that white matter pathways "only" tend to be displaced but intact. Therefore, meningiomas cause probably minimal or no white-matter injury, hence, only minimal or no delta activity. However, a functional connectivity analysis showed that a greater small worldness was related to worse language performance (Wolthuis et al., 2021).

4.3. Supplementary Motor Area Syndrome and spontaneous speech

The Supplementary Motor Area (SMA) is a dorsomedial prefrontal region in which 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). 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 despite the fact that a patient with a transcortical motor aphasia is barely able to 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 to the supplementary motor area (SMA) (Krainik et al., 2003; Naeser and Hayward, 1978)(Krainik et al., 2003; Naeser & Hayward, 1978). or "dynamic aphasia" (Luria, 1968). Dynamic aphasia resembles transcortical motor aphasia, apart from the fact that the patient does not <u>initiate</u> to communicate (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 has to be selected (Robinson et al., 1998). The underlying mechanism of dynamic aphasia has been associated with a language specific impairment or with a more general impairment of the 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 (Jehna et al., 2017; Thomson et al., 1998). 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 versus 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., 2018; Satoer, 2021; Satoer et al., 2014a).

The frequent occurrence of this transient syndrome underlines the relevance of monitoring spontaneous speech (in context) as this it 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 even deteriorated in the long run after surgery. A subsequent study by Rofes et al. (2018) partially confirmed these findings and 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 who described a postoperative dynamic aphasia in a patient with a left frontal meningioma involving Brodmann area 45 followed by full recovery within two weeks (Robinson et al., 1998). Finally, spontaneous speech is the most ecological 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.

5. Anatomical and Functional Alterations

5.1 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.

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 tumour can compress and displace a segment of the corticospinal tract (CST) towards the medial wall. However, this alteration only affects the immediate vicinity of the tumour, resulting in a change in the overall trajectory of that specific portion of the CST (Figure 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, tumours can indirectly impact white matter through their pathologic cascade, such as the presence of edema around a tumour, which temporarily compromises the white matter and may cause transient clinical symptoms. For example, a tumour 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).

Tumours 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 (Figure 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 post-surgical consequences (Cochereau et al., 2020; Dragoy et al., 2020; Duffau et al., 2008; Kemerdere et al., 2016; Leclercq et al., 2010; Mirchandani et al., 2020; Sollmann et al., 2020; Thiebaut de Schotten et al., 2005).

[insert Figure 6 about here]

5.2 Functional connectivity alterations due to tumour lesions

Intracranial tumours 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 which may also be indicative of brain dysfunction in wakeful restful conditions. In brain tumour patients, both increased slow-wave activity and deviant functional connectivity compared to healthy participants have been observed (Baayen et al., 2003; Bartolomei et al., 2006a; Bartolomei et al., 2006b).

Characteristics of slow-wave activity and functional connectivity network may also be a marker of language or cognitive dysfunction. 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 (Nicolo et al., 2015; Szelies et al., 2002). In brain tumour patients, Bosma et al. (2009) demonstrated a relation between functional connectivity networks and cognitive impairments. Wolthuis et al. Wolthuis et al. (2022) also showed with EEG that LGG patients had increased slow-wave activity compared to healthy individuals, before (and one year after surgery). Increased preoperative slow-wave activity was associated with the presence of language impairment and with poor language performance in specific language domains. Slow-wave activity before surgery was also related to word retrieval after surgery.

As for functional connectivity, no differences were observed 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 (in particular word retrieval, semantics and writing) and hub presence. Preoperative better average clustering (local connectivity) and global integration were predictive of worse outcome on language function one year after surgery. However, these results have to be interpreted with caution as small numbers of patients were included and both patients with and without language impairments collapsed. Investigation of FC in specific brain areas (in larger -specified- groups) may provide further insights into language impairments in brain tumour patients.

6. Cortical and subcortical areas: functions and tasks

6.1. 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 (Collée et al., 2023; Papagno et al., 2011). 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 neuro-oncologic patients. However, based on the literature and clinical studies, several schemas and proposals have been made (De Witte et al., 2015; Fernández Coello et al., 2013; Collée et al., 2023), see a selection below in Tables 2 and 3.

[insert Table 2 about here]

[insert Table 3 about here]

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, semantic and phonologic errors in both the left and right hemisphere. (for review see Collée et al. (2023).

6.2. Meningiomas

As opposed to gliomas, in meningioma patients it is not so clear yet whether there is a relation between tumour 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) radiological follow-up allows us to gain more knowledge about the effects of a meningioma and its location on cognition.

Mixed findings of localisation were found on cognition ranging from; 1) no signs at all (Tucha et al., 2003; Meskal et al., 2016; Steinvorth et al., 2003), 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 frontobasal location (Tucha et al., 2003). A recent large lesion symptom mapping study showed that patients with tumour location 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 non-significant observation showed that the majority of patients with an anterior (frontal) meningioma did not have a language impairment, whereas the majority of patients with a posterior (parietal/parieto-occipital) meningioma did have a language impairment before surgery. Cipolotti et al. (2015) comparable deviating cognitive scores in low-grade glioma and meningioma patients with frontal lesion location. In a three-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 tumour location. Left-hemispheric meningioma patients were worse in verbal tests than right-hemispheric patients. In sum, due to this great variety, it seems that even in non-infiltrating tumours functional neuroplasticity takes place.

7. Effect of surgery on language / cognitive functions

7.1. Glioma (awake procedure)

To goal of awake surgery is to preserve neurologic outcome and obtain larger extent of resections. Risk factors for postoperative language impairment are preoperative aphasia, non-frontal tumour location, intraoperative complications, and language-positive stimulation sites within the tumour (Ilmberger et al., 2008). Over the last two decades the research field tapping onto 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 eventually fully recovered within three months (e.g. (Duffau et al., 2002; Sanai et al., 2008; Whittle et al., 2003). Further comprehensive neuropsychological examinations revealed that while there is a temporary decline in language functions shortly after surgery (between three and six months), language performance tends to improve over time. Nevertheless, certain tests, such as category fluency, continued to show impairment even one year after the surgery (Satoer et al., 2014b; Satoer et al., 2016) Additionally, Satoer and colleagues (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 detect surgical effects than standard tests: all phonologic DIMA subtests captured short-term decline (pre -three months postoperatively), in line with earlier evidence for the value of (non-)word repetition (Mooijman et al., 2021; Sierpowska et al., 2017). 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. Short-term postoperative decline affected verbal fluency as well. Only the localisation of left-hemispheric tumours 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 the 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.

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; van Kessel et al., 2021). Furthermore, severe aphasia is regarded as an exclusion criterion (Bonifazi et al., 2020; Dziedzic and Bernstein, 2014; Zigiotto et al., 2020) as it challenges intraoperative monitoring and defining a functional boundary. However, there seems to be a trend towards 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; Gerritsen et al., 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 language pathologist / clinical linguist. More standardized intraoperative tasks for severe aphasia are needed for this population and a revised version of DuLIP (De Witte et al., 2015) with standardized tasks designed especially for patients with severe aphasia is in preparation.

7.2. 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 three and twelve months after surgery with a neuropsychological assessment. Seven cognitive domains were tested: Verbal Memory, Visual Memory, Processing Speed, Psychomotor Speed, Reaction Time, Complex Attention, and Cognitive Flexibility. At 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 three months after surgery and on three out of seven domains one 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 (Bommakanti et al., 2016; Campanella et al., 2015; Hendrix et al., 2017; Tucha et al., 2003). 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.

8. Conclusion

This chapter delved into 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 tumour patients. It is without doubt that these tumours can have a profound impact on language and cognitive processes, which highlights the significance for early detection and treatment in order to preserve patients' quality of life. The presence and severity of functional impairment can be influenced by several factors such as tumour type (e.g. intra or axial location, slow or fast tumour growth) and lesion location (e.g. hemisphere, lobe and white matter connections) which in turn may affect the potential of neuroplasticity.

The emergence of both non-invasive neuroimaging techniques, such as fMRI and tractography, and invasive awake brain surgery have revolutionized our ability to map and monitor brain tumours. These methods provided valuable insights in understanding the neurobiology of language and revealed high inter-individual variability. In the last decade, a patient-tailored approach for language and cognitive tests takes into account demographic and clinical variables and has been shown to be inevitable in neuro-oncological 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 tumour. Addressing this intricate labyrinth of factors contributing to language and cognitive impairments in brain tumour 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.

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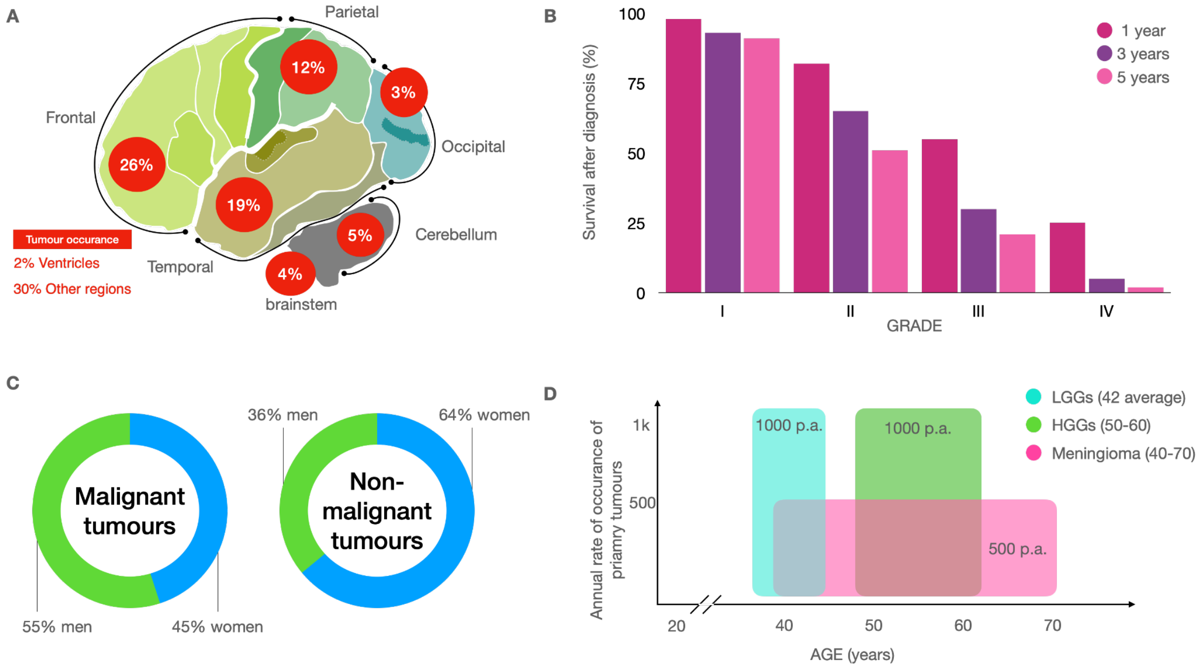

Figure 1. Tumour statistics. Tumour occurrence per lobe (A), survival rate after diagnosis stratified by grading (B), mind the gap - sex differences in malignant vs non-malignant tumours (C), and the age ranges associated with the occurrence of primary tumours (D). This *Figure is an original based on the data available from Breaking down the epidemiology of brain cancer by Julie Gould, 2018, Nature 561, S40-S41 (2018), doi:* https://doi.org/10.1038/d41586-0dan *18-06704-7* [Gould, 2018]()

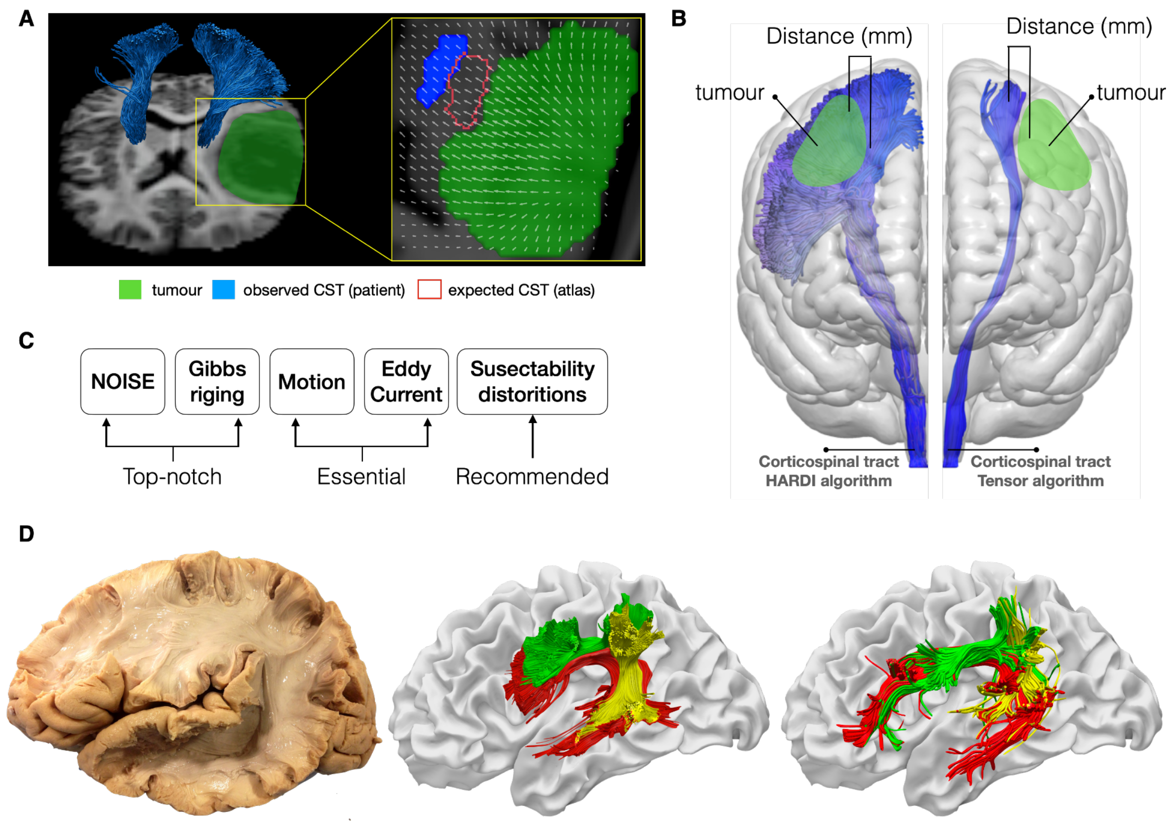

Figure 2. Technical considerations in tractography reconstructions for brain tumours. Panel (A) emphasizes the limitations of atlas-based approaches due to white matter displacement. Panel (B) underscores the impact of algorithm selection on reconstruction reliability. Panel (C) presents the recommended pre-processing 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). *Panel A and B are modified from Dissecting White Matter Pathways: A neuroanatomical approach. Forkel SJ, Bortolami C, Dulyan L, Barrett RLC, Beyh A. In Handbook of Diffusion MRI Tractography (Eds Leemands/ Dell'Acqua), in press. Reused and modified with permission from my co-authors. C-D is an original by the authors.*

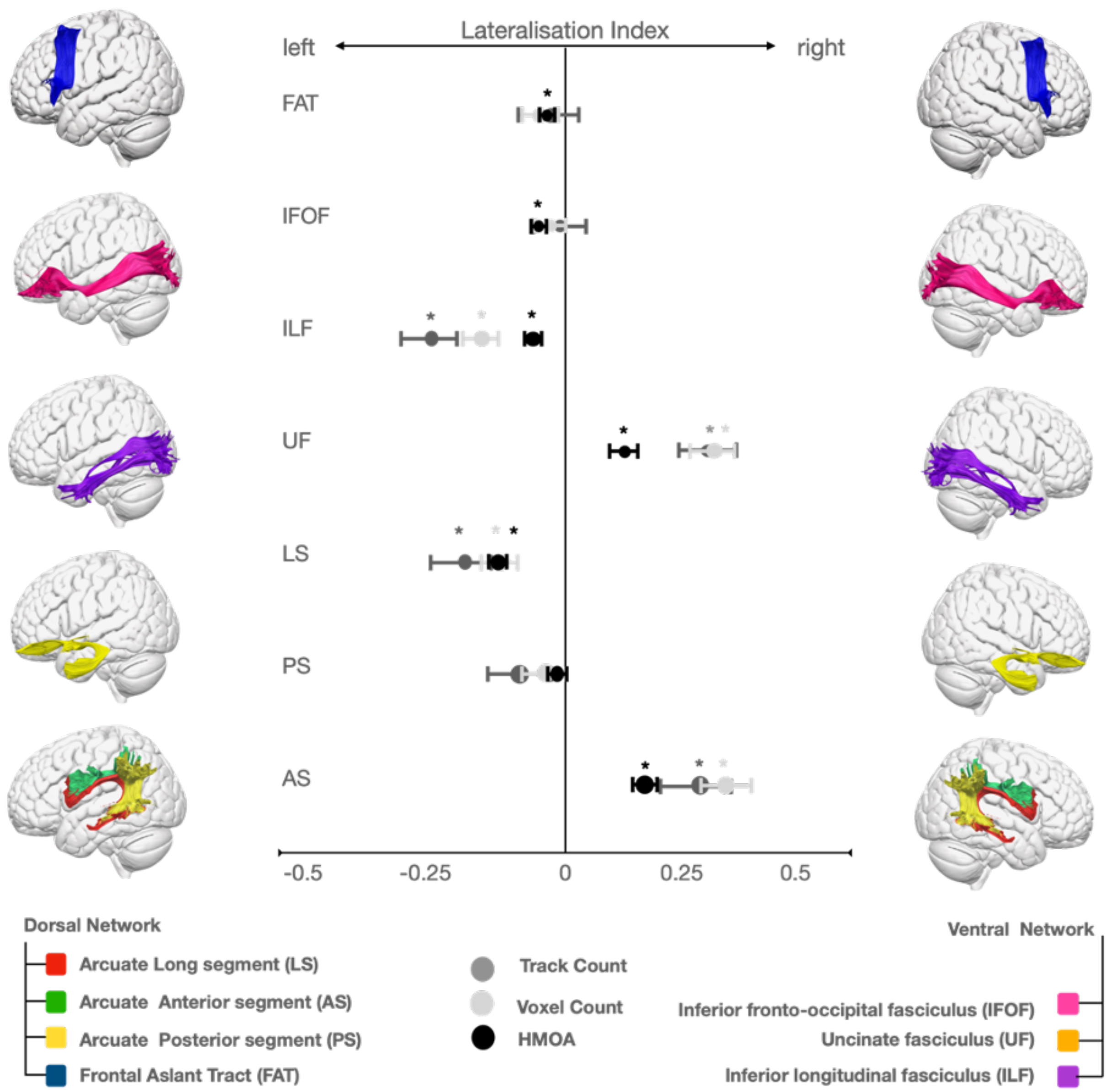

Figure 3. White matter network asymmetry in the dorsal and ventral networks associated with language. Data shown are from the Human Connectome Project 7T data set (www.humanconnectome.com) and are available preprocessed from www.bcblab.com; HMOA: Hinderance Modulated Orientational Anisotropy. See chapter X in this volume [crossreference] for the asymmetry pattern of all white matter connections. *This is an original figure.*

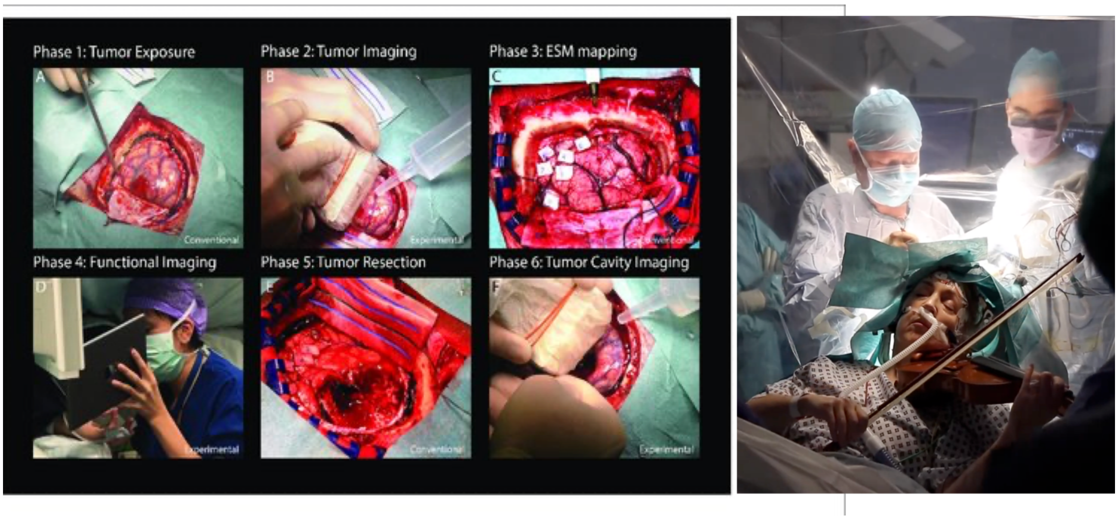

Figure 4. Step-by-step principle of the direct electrical stimulation procedure in an awake patient. *Figure taken from Soloukey et al. 2020) during music mapping - in this case playing the violin - in theater (b, courtesy of Professor Ashkan and team at King's College London, video available online: https://www.youtube.com/watch?v=o-oGpD_Nx5U) and we obtained permission from the surgeons in the photograph to use it.*

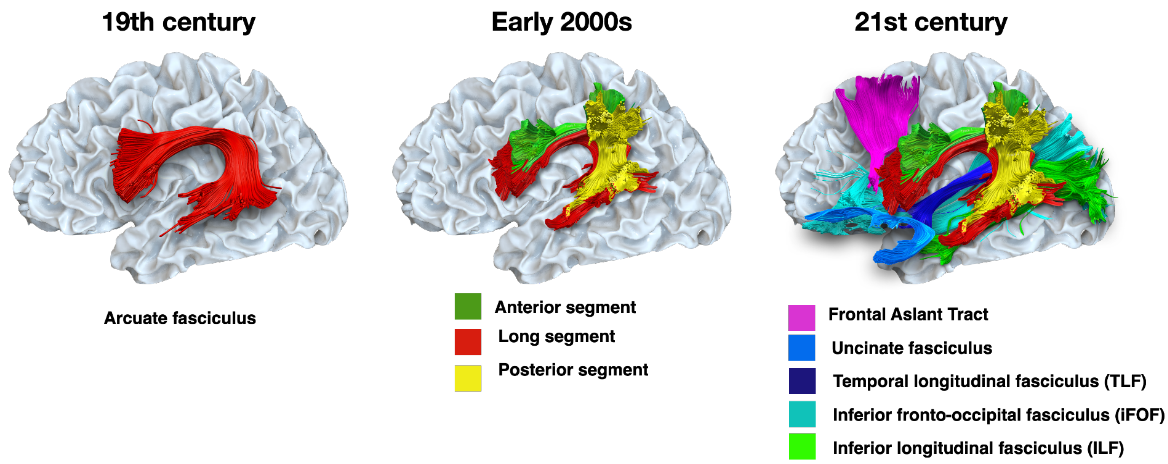

Figure 5. Language network in transition. Since the discovery of the first language areas in the brain by the physician Paul Broca (1824-1880) and psychiatrist Carl Wernicke (1848-1905), knowledge about the neuronal language networks has changed considerably. Whereas in the 19th century we assumed that 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, unicnate fasciculus, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, temporal longitudinal fasciculus), most of which have already been clinically validated through neurosurgical approaches, lesion studies and DES. *Modified from Catani M & Forkel SJ. Diffusion Imaging Methods in Language Sciences. In Oxford Handbook of Neurolinguistics (de Zubicaray & Schiller, Eds). OUP, 2019. SF is the author of the original figure.*

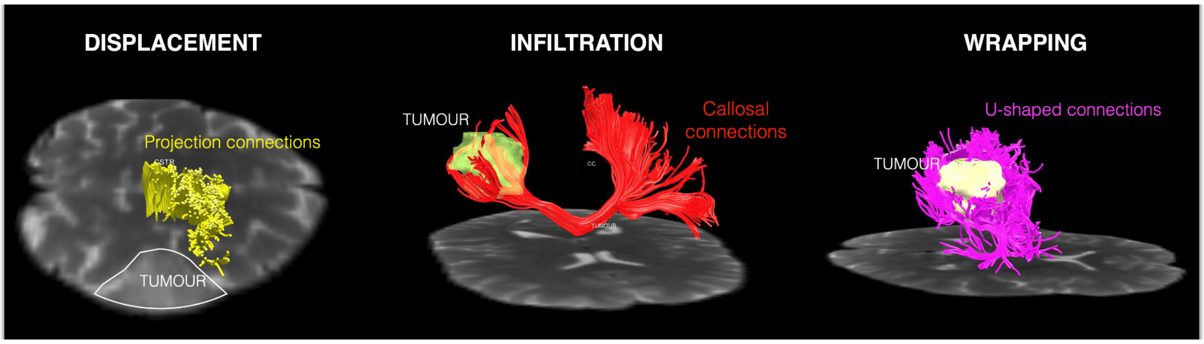

Figure 6. Various impacts of tumour lesions on white matter. In the left panel, low-grade gliomas (LGGs) are depicted as gradually exerting pressure on the surrounding brain tissue, including the white matter, leading to displacement. The middle panel represents tumours infiltrating the white matter and migrating along the connective tissue. Finally, in the right panel, a phenomenon is observed where the white matter appears to wrap around the tumour, indicating either a pathological process or a methodological artifact. *This figure is previously unpublished data and was modified with permission from the creator, Dr. Henrietta Howells.*

Table 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 Syntax - comprehension	Sentence completion Sentence judgment	*Hij viel van … (He fell off …)* *Om 5 uur … (At 5 o'clock …)* *Hij gaat geschilderd op de muur (He goes painted on the wall)*

Table 2. Overview cortical and subcortical brain regions with sensori-motor, 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 (non-verbal)	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
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	Visuo spatial	Line bisection	R
Inferior Frontal Occipital Fasciculus	Word retrieval Semantics, reading Visuo spatial	Naming Semantic judgment and association Line bisection	L L + R 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

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