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Stimulation-based language mapping in context of speech fluency and language deficits: Towards patient- and deficit-tailored mapping paradigms

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to my parents

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1 Introduction

The ability to produce and comprehend language enables communication, social and cultural interaction, and participation. It is a complex, multifaceted process of integrating phonetic, phonological, lexical, semantic, morpho-syntactic, pragmatic and non-verbal information.

Therefore, it requires a vast, complex cortical and subcortical network, and a finely tuned and synchronized interplay of multiple neuronal processes (Duffau, 2016; Friederici, 2017; Tremblay et al., 2011). For instance, even the naming of just a single object is reliant on picture recognition, concept and lemma retrieval, phonetic-phonological encoding as well as articulation (Indefrey, 2011; Indefrey & Levelt, 2004; Jodzio et al., 2023). Hence, even during object naming alone, a large and distributed network is activated to perform the task.

However, tumors growing within or in proximity to this distributed language network can cause severe speech or language impairments which profoundly impact the well-being and quality of life of individuals and their next of kin. Preserving language function by identifying and localizing functional necessary areas is a key objective in the neurosurgical treatment of patients with language eloquent brain tumors.

Already in the beginning of the 19th century, a direct relationship between distinct skull regions and specific functions was proposed by Franz Joseph Gall (Levelt, 2013). In 1861, the French surgeon Paul Broca provided first empirical evidence for a cortical language hub within the left inferior frontal gyrus (IFG) (Broca, 1861). The autopsy results of his famous patient Mr. Leborgne, who presented with a severe language production deficit, showed a lesion within the left IFG which thereafter was frequently referred to as “Broca’s area”. Shortly after, in 1874, Carl Wernicke related comprehension deficits which he termed “sensory aphasia” to lesions within left temporal lobe (Wernicke, 1874). This region was subsequently called “Wernicke’s area”. He, moreover, proposed a direct link between Broca’s and Wernicke’s area. Later versions of this model modified by Lichtheim (1885) and Geschwind (1965, 1972) were the foundation of many language models which are still being published and thought today. Whilst Wernicke proposed two subcortical pathways connecting Broca’s and Wernicke’s area (Wernicke, 1874), the classic Geschwind model only assumed a single white matter connection, which is known as the arcuate fasciculus (Geschwind, 1972).

Since the first case of Broca, advancing the understanding of the underlying, neural basis of language function and studying how lesions cause aphasia have been tightly interlinked. This motivated an era of studies to advance the understanding of how brain lesions give rise to heterogeneous language deficits observed clinically and of the neural basis of language function. Primarily focused on single or serial case studies and post-mortem brain analyses, discussions about the presumed language centers within Broca's and Wernicke's area and about opposing localistic and holistic viewpoints followed (Levelt, 2013).

Substantial technical advancements and diverse physical, medical and physiological discoveries in the 20th century, allowed to visualize and study (non-)invasively the functional brain in-vivo (Raichle, 2006). Based on numerous lesion and functional neuroimaging studies, the original models were increasingly challenged and modified.

Consequently, more current models focus on the complex, highly connected subcortical language network and its cortical hubs, while proposing a "dual stream" model, dividing different language tracts (Figure 1) into a "ventral" and "dorsal" system relevant for distinct language processing steps (Friederici, 2017; Hickok & Poeppel, 2004; Hickok & Poeppel, 2016; Rauschecker & Scott, 2009). Nowadays, it is widely established that language requires a highly complex network and aphasia is the result of a network lesion rather than a restricted cortical one as proposed by the classic models (Dronkers et al., 2007; Duffau, 2016; Duffau et al., 2014).

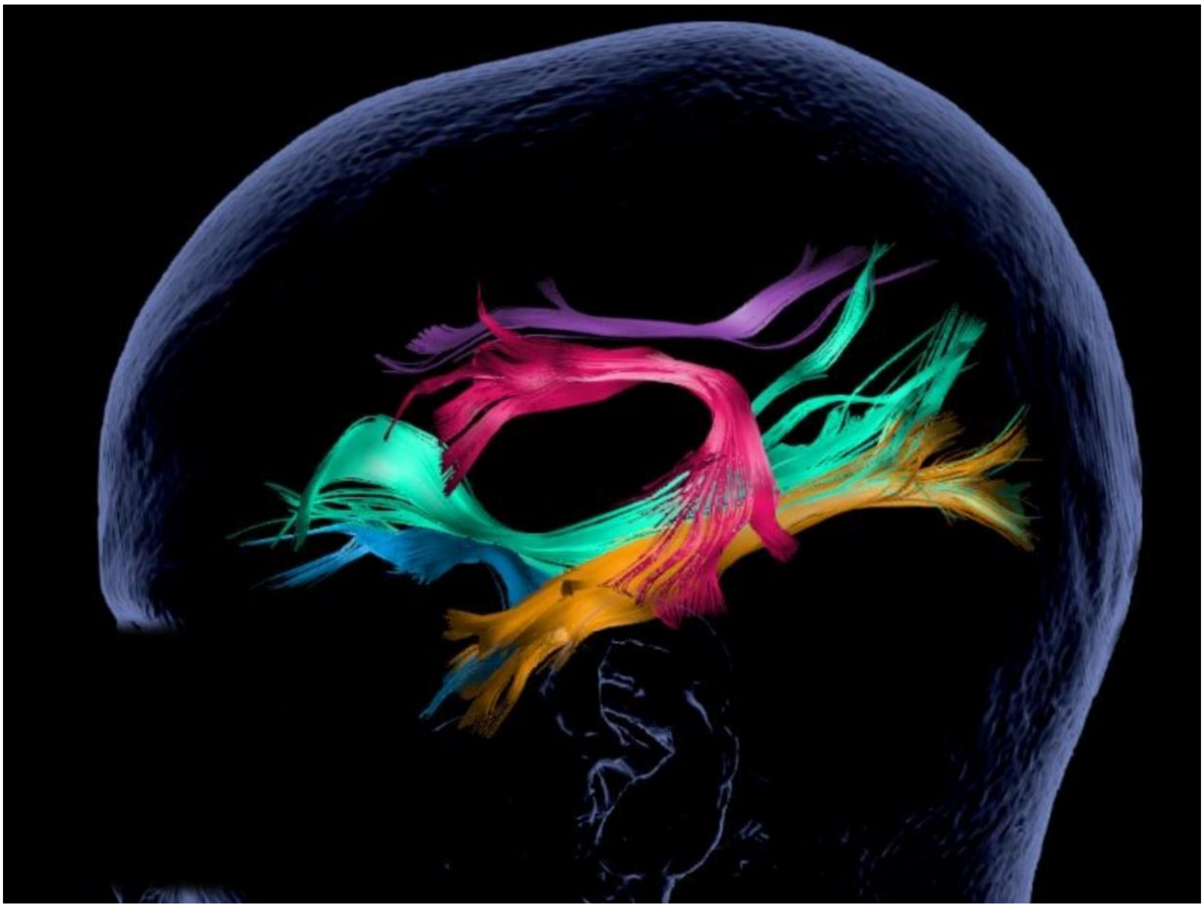


Figure 1: Overview of classic left-hemispheric language tracts. Dorsal language pathways: fasciculus arcuatus (AF, pink) and superior longitudinal fascicle (SLF, purple); ventral pathways: inferior fronto occipital fasciculus (IFOF, green), inferior longitudinal fasciculus (ILF, orange), uncinate fasciculus (UF, blue). Tractography was created with Brainlab Elements (Brainlab AG, Germany).

These findings and models are used as a theoretical basis to plan and guide neurosurgery in order to balance the preservation of functionality and the extent of resection, and, thus, substantially enhance prognosis, survival rates and quality of life (Brown et al., 2016; Chang et al., 2015; Gogos et al., 2020; Hervey-Jumper & Berger, 2016; Mandonnet et al., 2010).

Still, even nowadays no consensus about the complex cortical and subcortical network components and their role for language processing exists (Binder, 2017; Catani et al., 2005; Dick & Tremblay, 2012; Friederici, 2015; Tremblay & Dick, 2016). Moreover, in context of lesions such as brain tumors or stroke, the brain has the potential to reorganize and reallocate function to other brain areas up to a certain extent (Briganti et al., 2012; Cirillo et al., 2019; Deverdun et al., 2020; Duffau, 2020; Fisicaro et al., 2016; Hartwigsen & Saur, 2019; Ille et al., 2019; Ius et al., 2011; Nieberlein et al., 2023; Rösler et al., 2014; Saur & Hartwigsen, 2012; Stockert et al., 2020). Nevertheless, the exact mechanisms remain poorly understood. Ample neurocognitive, neuropsychologic, neurolinguistic, neuroimaging and neurosurgical research is focused on understanding the underlying mechanisms giving rise to aphasia and potential compensational and rehabilitative processes. Thus, it is vital to individually localize language function in neurosurgical patients and to understand the role and impact of pre-existing speech or language deficits on functional localization. At the same time, techniques, and methods for localizing eloquent network components need to be adapted to the demands and capabilities of patients.

1.1 Language mapping in neurosurgery

The most direct and invasive method to identify necessary areas is the administration of direct electrical stimulation (DES) over presumably eloquent brain areas whilst patients perform language tasks intraoperatively during awake craniotomies. In the late 19th and beginning of 20th century animal experiments demonstrated the excitability of the cortex and how this could be related to heterogeneous functions (Ferrier, 1886; Fritsch & Hitzig, 1870; Grünbaum & Sherrington, 1902; Leyton & Sherrington, 1917). Building on these findings, DES was first used to relate motor function and muscular contractions to cortical areas in humans at the end of the 19th century (Bartholow, 1874; Horsley, 1909). Advancements in anesthesiology enabled surgery and intraoperative testing whilst patients were awake (Cushing, 1909). This was first employed for the mapping of somatosensory function (Cushing, 1909) and subsequently extended to the localization of speech and language function (Penfield & Erickson, 1941; Penfield & Rasmussen, 1950; Penfield & Roberts, 1959). DES was originally used to study epileptic foci, however, soon it was integrated into neurosurgical resections of tumors in eloquent areas (Ojemann et al., 1989; Penfield & Roberts, 1959).

Nowadays, awake DES-based language mappings are considered the gold standard to maximize and balance oncological and functional outcome (De Witt Hamer et al., 2012). By relating a stimulated cortical site to stimulation-induced interferences of language task performance, language function can be causally linked to a specific brain area. Hence, language-relevant and non-relevant cortical sites can be differentiated to define the surgical approach or margins of the resection and to minimize surgery-related language deficits. However, this is a highly invasive method, requiring a large, interdisciplinary and highly specialized team, increasing cost and staff effort and potentially the risk of epileptic seizures as well as the psychological strain for patients (Nossek et al., 2013; Roca et al., 2020; Talacchi, Santini, Casagrande, et al., 2013).

Thus, more and more alternative non-invasive preoperative methods to visualize and identify areas, which need to be preserved during craniotomy, have been integrated into the clinical workflow. With technological and methodological advances, a broad spectrum of non-invasive neuroimaging and -modulation techniques have become available for preoperative language mapping. A popular method is task-based functional magnetic resonance imaging (fMRI) which investigates regional blood flow changes revealing task-specific activation of cortical areas (Wise & Price, 2006). By showing task-induced brain metabolism changes as indicated by an altered cerebral blood flow and (de-)oxyhemoglobin concentration, assessed with the blood oxygen level-dependent (BOLD) contrast, fMRI can show areas activated during a specific task (Glover, 2011; Ogawa, Lee, Kay, et al., 1990; Ogawa, Lee, Nayak, et al., 1990; Raichle, 2009). However, since brain tumors can alter blood volume, flow and oxygenation within (peri-) tumoral areas, the BOLD signal can be confounded in neurosurgical patients (Pak et al., 2017). These neurovascular alterations have been linked to reduced BOLD contrast within (peri-)lesional areas across different tumor entities (Holodny et al., 2000; Pak et al., 2017; Pillai & Zaca, 2011; Schreiber et al., 2000; Ulmer et al., 2003; Zaca et al., 2014). Thus, an absence of increased or even a decreased BOLD signal within peri-tumoral areas does not necessarily suggest that this area is not associated with a specific function. Hence, fMRI may be prone to false negative mapping results within eloquent areas considered for a surgical removal during neurosurgical treatment of brain tumors. Inadequate functional maps of eloquent (peri-)tumoral areas may profoundly impact the surgical approach and the preservation of functionality. Moreover, a lack of concordance between localizing functional and non-functional language hubs with fMRI and DES was corroborated (Giussani et al., 2010). What is even more, unlike DES-based language mapping, fMRI does not indicate which areas are necessary for a specific function. Since neurosurgery is highly reliant on identifying necessary cortical network hubs and subcortical network components to preserve, causal inference methods linking neuroanatomy and functionality are increasingly integrated into presurgical routine. Lesion and brain stimulation studies are the methods which thus far offer the closest causality estimate (Siddiqi et al., 2022).

Non-invasive transcranial magnetic stimulation (TMS) offers a similar mapping approach as the gold standard without requiring a craniotomy. Based on Faraday’s principle of electromagnetic induction (Faraday, 1832), a rapidly changing electric current within a wire coil induces a rapidly fluctuating magnetic field perpendicular to the plane of the coil (Barker et al., 1985). This magnetic field passes unimpededly through the scalp and skull and induces a transient secondary current within the brain (Figure 2A). If the intensity of the latter is sufficient, neurons of the target region can be depolarized, triggering action potentials (Hannula & Ilmoniemi, 2017). Depending on the region and type of stimulation, inhibitory or excitatory effects can be observed (Castrillon et al., 2020; Klomjai et al., 2015; Rossini et al., 2015). Similar to DES, TMS was first used for eliciting motor responses prior to expanding its application to language mappings (Barker et al., 1985; Epstein, 1998; Epstein et al., 1996; Jennum et al., 1994; Pascual-Leone et al., 1991). Since the introduction of navigated TMS (nTMS, Ettinger et al., 1998), the position of the coil can be stereotactically guided by individual three-dimensional reconstructions of structural magnetic resonance images (Figure 2A) to target specific cortical areas accurately for each individual (Comeau, 2014).

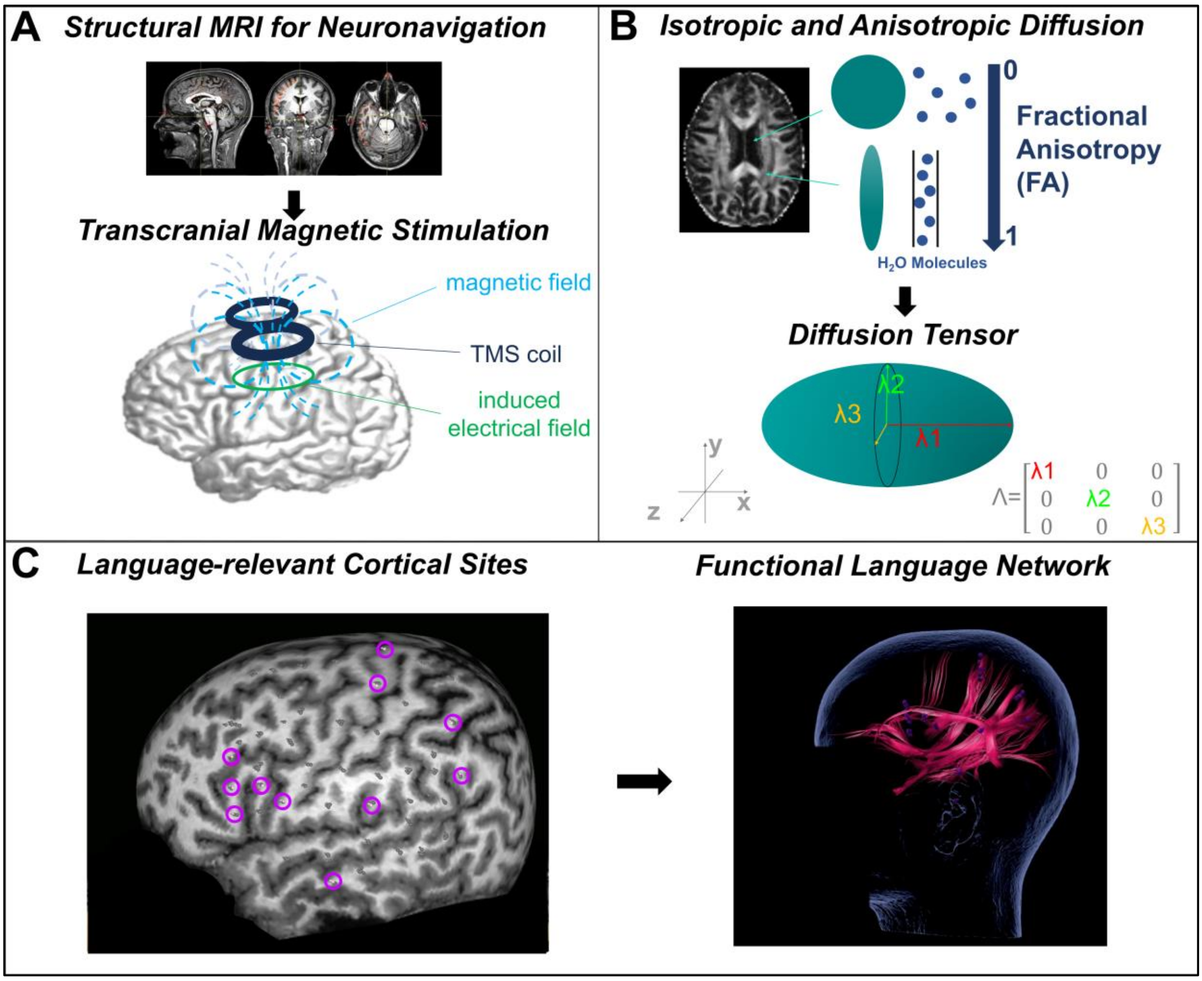


Figure 2: Principle of navigated transcranial magnetic stimulation (A) and diffusion tensor imaging (B) as well as the result of a combined nTMS-based language mapping with subsequent DTI-based tractography of the language network on the basis of the nTMS results (C).

Despite the lack of understanding the cellular processes (Cullen & Young, 2016; Müller-Dahlhaus & Vlachos, 2013), a wealth of literature shows that nTMS can be used to identify cortical language hubs. Similar to DES-based language mapping, repetitive nTMS can be used to relate transient language network disruptions, which result in hearable language mistakes during task performance, to a specific anatomical cortical area (Mäkelä & Laakso, 2017). Therefore, this safe and well-tolerated stimulation method (Rossi et al., 2021; Rossi et al., 2009; Tarapore et al., 2016) is increasingly used to guide surgical planning and resection, to support the preservation of language function and to stratify the risk of a post-surgical worsening in language function (Ille et al., 2021; Ille, Sollmann, et al., 2016; Picht, 2014; Sollmann, Zhang, Fratini, et al., 2020; Tarapore et al., 2013).

Another magnetic resonance imaging method, called diffusion tensor imaging (DTI), allows to visualize and analyze the subcortical language network, qualitatively as well as quantitatively. Diffusion weighted imaging methods can depict random motion of water molecules within a voxel, i.e., Brownian motion (Cercignani & Horsfield, 2001; de Figueiredo et al., 2011; Stejskal & Tanner, 1965). The diffusion of molecules perpendicular to white matter fiber bundle direction is restricted (Assaf & Pasternak, 2008). This anisotropic diffusion can be modelled with a diffusion tensor (Figure 2B) and quantitative microstructural properties can be derived (Mori & Zhang, 2006; Mukherjee et al., 2008). The latter comprises the degree of anisotropic diffusion (fractional anisotropy, FA) as well as the mean, axial and radial displacement of molecules (Curran et al., 2016; Winston, 2012).Thus, DTI allows to noninvasively study white matter connections in vivo and to reconstruct specific tracts or networks. While anatomical regions of interest can be used to show specific or multiple language tracts, the language-relevant cortical sites identified with nTMS can act as cortical seed regions to identify the functionally relevant subcortical language network (Negwer, Ille, et al., 2017; Negwer, Sollmann, et al., 2017; Raffa et al., 2017; Sollmann, Kubitscheck, et al., 2016; Sollmann, Negwer, et al., 2016; Sollmann, Zhang, Schramm, et al., 2020). Therefore, by combining multiple neuroimaging, i.e. structural MRI and DTI, and a neurostimulation method, an individual, three-dimensional functional map of the cortical and subcortical language network can be derived (Figure 2C).

Still, the localization of language-relevant sites with nTMS is dependent on the task, the nTMS-examiner and the stimulation protocol (Hauck et al., 2015; Sollmann, Fuss-Ruppenthal, et al., 2018; Sollmann et al., 2013). What is even more, nTMS-based language mapping has a high detection-concordance for cortical sites irrelevant for a specific language task, yet limited detection-concordance for language-relevant points compared to the gold standard, DES-based mappings (Ille, Sollmann, Hauck, Maurer, Tanigawa, Obermueller, Negwer, Droese, Zimmer, et al., 2015; Krieg et al., 2014; Picht et al., 2013; Tarapore et al., 2013). Moreover, the presence of preexisting language deficits, which are frequently observed in patients with language eloquent brain tumors prior to a surgery, additionally decrease reliability of language mappings (Kram, Neu, Ohlerth, et al., 2023; Schwarzer et al., 2018).

1.2 Acquired language disorders

Aphasia, an acquired language impairment, impacts the whole language system, i.e., language production and comprehension as well as reading and writing. Impairments are expressed in heterogenous symptoms and combinations and can affect different linguistic components. The latter comprises phonetic-phonological (sound-level), morphological (word-construction), lexico-semantic (meaning), syntactic (grammar and sentence structure) and pragmatic (discourse- and context-dependent meaning) levels (Bara et al., 2016; Davis, 2016; Idsardi & Monahan, 2016; Pylkkänen, 2016; Sprouse & Hornstein, 2016).

Moreover, aphasia occurs in a vast severity range, spanning from very mild deficits to a complete loss of communication abilities. Based on the original work of Broca and Wernicke, many still divide the substantial spectrum of aphasic symptoms in, e.g., “Broca”, “Wernicke”; “transcortical motor”, “transcortical sensory”, “conduction” and “global” aphasic syndromes (Sheppard & Sebastian, 2021). However, even in Wernicke’s early detailed case descriptions (Wernicke, 1874), a large proportion of patients presented with a mixture of symptoms. In line with neuroimaging findings showing that the original model building on the famous cases of Broca and Wernicke is outdated nowadays (Tremblay & Dick, 2016), the original syndrome-centric division does not adequately describe the vast spectrum observed in clinical routine. Since the classic syndromes are neither pathophysiologically nor anatomically well-differentiated and the expression and combination of deficits varies considerably, many advocate nowadays for an individualized, deficit-centered approach accounting for inter-individual variability (Kasselimis et al., 2017).

Irrespective of the classification and large heterogeneity of aphasic symptoms, acquired language disorders are one of the most prevalent impairments in brain tumor patients with a reported occurrence of 20.0 to 39.0% (IJzerman-Korevaar et al., 2018; Koekkoek et al., 2014; Peeters et al., 2020; Posti et al., 2015). Heterogeneous tumor entities and locations elicit receptive and expressive language deficits (Banerjee et al., 2015). Moreover, following tumor resections new or worsened language deficits are reported in up to 40.2% (Coget et al., 2018). Whilst these are primarily transient in nature, up to 6-18% persist even several months following the surgery (Ilmberger et al., 2008; Zetterling et al., 2020). A large amount of research is still focused on understanding the cause of permanent surgery-induced worsening and identifying preoperative risk factors to prevent permanent language deterioration (Caverzasi et al., 2016; Ilmberger et al., 2008; Sollmann, Zhang, Fratini, et al., 2020; Tuncer et al., 2021). Typically, in more aggressive, higher-grade tumors and towards the final life-phase, aphasia seems to be more frequent and more severely pronounced (Koekkoek et al., 2014). Hence, aphasia profoundly impacts the daily life, participation, and quality of life in brain tumor patients.

1.3 Speech (fluency) disorders

Next to the complex language network and functions, additional premotor and motor processes are required to prepare, coordinate, plan, program, initiate, execute, and control respiration, phonation and articulation required for speech motor production (Duffy, 2016; Enderby, 2013). It is presumed that around 100 striated and visceral muscles are recruited for the execution of speech movement (Kent, 2000). Multiple cortical sensorimotor areas as well as the basal-ganglia, thalamus, cerebellum and the pyramidal system are involved in these respiratory, laryngeal, pharyngeal and orofacial speech motor processes (Tremblay et al., 2016).

Similar to the broad spectrum of speech motor processes, different and heterogeneous acquired or developmental speech (fluency) disorders can manifest. One of the most prevalent neurologic communication disorders across acquired lesions and neurodegenerative disorders is dysarthria (Ackermann et al., 2018). This motor speech disorder caused by impaired neuromuscular control expresses in altered respiratory, phonatory, articulatory or prosodic speech processes which impact the quality and intelligibility of a patient’s speech (Enderby, 2013). Additionally, lesions can cause impaired planning and programming of speech movement, which results in a multitude of articulatory mistakes, limited intelligibility and increased effort during speaking (Ziegler & Staiger, 2016). This type of disorder is called apraxia of speech and needs to be differentiated thoroughly from aphasic and dysarthric impairments.

Moreover, impaired (pre-)motor processes can also cause disturbances in the flow of speech giving rise to repetitions of multiple phonemes or syllables, prolonged sounds or (in-)audible pauses - called blocks - which frequently result in tension within the speech system and may impact intelligibility (Bloodstein et al., 2021; Craig-McQuaide et al., 2014). Frequently, these symptoms lead to the loss of control over the patient’s own speech flow and occur rather unpredictably and randomly during different speaking situations. Developmental stuttering, manifesting during childhood, is the most common form of this speech fluency disorder with a prevalence of 1% (Yairi & Ambrose, 2013). Albeit ample research associated cortical or subcortical alterations with developmental stuttering, the underlying mechanisms still remain poorly understood (Etchell et al., 2018). Moreover, primarily case studies demonstrated that brain lesions such as stroke, traumatic brain injury or brain tumors can induce acquired neurogenic stuttering, which symptoms occur even more unpredictably and randomly (Cruz et al., 2018; Heuer et al., 1996; Junuzovic-Zunic et al., 2021; Logan, 2022; Lundgren et al., 2010; Peters & Turner, 2013).

1.4 Objectives of this dissertation

Whilst the preservation of (residual) functionality is a key objective, pre-existing speech and language disorders are common in language-eloquent brain tumors and their impact on the language mapping and its results need to be carefully considered.

Nonetheless, no study yet evaluated whether pre-existing stuttering, which manifests highly unpredictably and randomly, impacts language mappings. Thus, the aim of the first study was to assess the impact of pre-existing developmental or acquired neurogenic stuttering on mapping analysis as well as the number and type of stuttering symptoms mistaken as stimulation-induced language interferences (Kram, Neu, Schröder, et al., 2023). This study was published as a journal article in: Heliyon; volume 9; authors: Kram L., Neu B., Schröder A., Meyer B., Krieg S.M. & Ille S.; title: *Improving specificity of stimulation-based language mapping in stuttering glioma patients: A mixed methods serial case study*; e21984; copyright Elsevier B.V. (2023). The first sub-part of this study was a post-hoc analysis of nTMS-based language mappings to assess the prevalence of stuttering in a monocentric cohort of consecutive language-eloquent brain tumor patients as identified by a trained speech and language therapist. Moreover, all patients who stuttered were additionally analyzed by two nTMS operators with varying degree of experience in mapping analyses since an experience-dependent effect on the differentiation-ability between stuttering and stimulation-induced language errors was expected. Within the second sub-part of this study, prospective awake cases were closely monitored to thoroughly evaluate the impact of pre-existing stuttering on intraoperative DES-based language mapping reliability.

Severe forms of pre-existing speech and language deficits can not only impact reliability but also the feasibility of stimulation-based mappings. In order to perform language tasks during stimulation, accurate and reliable task performance is required to subsequently relate a language interference to a stimulated cortical area. Thus, severe aphasia is a frequently reported contraindication for stimulation-based pre- and intraoperative language mappings (Al-Adli et al., 2023; Hervey-Jumper & Berger, 2016; Morshed et al., 2021; Picht et al., 2006; Picht et al., 2013). Most of the available tasks for stimulation-based language mappings are reliant on overt responses by the patient (Alarcon et al., 2019; Bello et al., 2007; De Witte et al., 2015; Fernandez Coello et al., 2013; Hauck et al., 2015; Krieg et al., 2017; Martin-Monzon et al., 2022; Rofes et al., 2015; Talacchi, Santini, Casartelli, et al., 2013; Tarapore et al., 2013). However, as aforementioned, aphasia can impact different modalities and aspects of language. Therefore, in patients with severely impaired language production, comprehension skills may be well preserved. As a consequence, the second study aimed for developing a new covert language comprehension task suitable for patients with severe expressive aphasia thus far precluded from stimulation-based language mapping (Kram et al., 2024). This study was published as a journal article in: Cortex; volume 171; authors: Kram L., Ohlerth A.-K., Ille S., Meyer B. & Krieg S.M.; title: *CompreTAP: Feasibility and Reliability of a New Language Comprehension Mapping Task via Preoperative Navigated Transcranial Magnetic Stimulation*; pages: 347-369; copyright Elsevier Ltd. (2024). This comprehension-based mapping setup was piloted in six severely expressive aphasic brain tumor patients and fifteen healthy controls to ascertain its feasibility. Additionally, the analysis agreement of the mapping outcome and identification of covert comprehension errors induced by stimulation was evaluated between a neurolinguist and a trained speech and language therapist, both highly experienced in analyzing classic nTMS-based language mappings.

2 Materials and methods

2.1 Ethics approval

The local ethics committee of the Institutional Review Board of Technical University Munich approved both studies (Ethics committee registration number: 192/18). Moreover, the guidelines of the Declaration of Helsinki were followed throughout. All patients and healthy participants provided full written informed consent prior to the nTMS-based language mappings.

2.2 Study 1: Impact of stuttering on language mapping specificity

The first part of this study (Kram, Neu, Schröder, et al., 2023) constituted a post-hoc analysis of a prospectively enrolled, consecutive cohort of patients undergoing preoperative nTMS-based language production mapping with subsequent resection between May 2018 and January 2021. The second part was a prospective analysis of all subsequent patients who underwent preoperative nTMS-based and intraoperative DES-based language mapping between January 2021 and December 2022.

2.2.1 Patient selection

All patients considered for this analysis needed to be at least 18 years old and present without contraindication for magnetic resonance imaging or nTMS such as cochlear implants or pacemakers. Moreover, only patients who stuttered were included for this project to ascertain the impact of this preexisting speech fluency disorder on language mappings. These deficits were classified by the author of this thesis, a certified speech and language therapist (SLT) with extensive experience in the diagnosis and treatment of stuttering, a more detailed description of the language mapping process and functional assessment is provided in point 2.2.3 and point 2.2.4. The Edinburgh Handedness Inventory (Oldfield, 1971) was used to test handedness.

2.2.2 Magnetic resonance imaging for neuronavigation

Magnetic resonance imaging (MRI) was performed on a 3-Tesla Achieva dStream or Ingenia scanner (Philips Healthcare, Best, The Netherlands) during the pre-surgical clinical routine by the department of Neuroradiology of Klinikum rechts der Isar (Krieg et al., 2016; Sollmann, Kelm, et al., 2018; Sollmann, Negwer, et al., 2016). The standard image acquisition protocol for neurosurgical patients contains a three-dimensional contrast-enhanced T1-weighted turbo echo sequence (repetition time (TR)/ echo time (TE): 9/4 ms, 1 mm^3 isovoxel covering the whole head).

2.2.3 Classic preoperative nTMS-based language production mapping

The Nexstim eXimia NBS system (version 5.1) and the NEXSPEECH® module (version 2.0.1) were used for nTMS-based language mapping (Nexstim Plc., Helsinki, Finland). The setup of this stimulation system for language mappings is depicted in Figure 3.

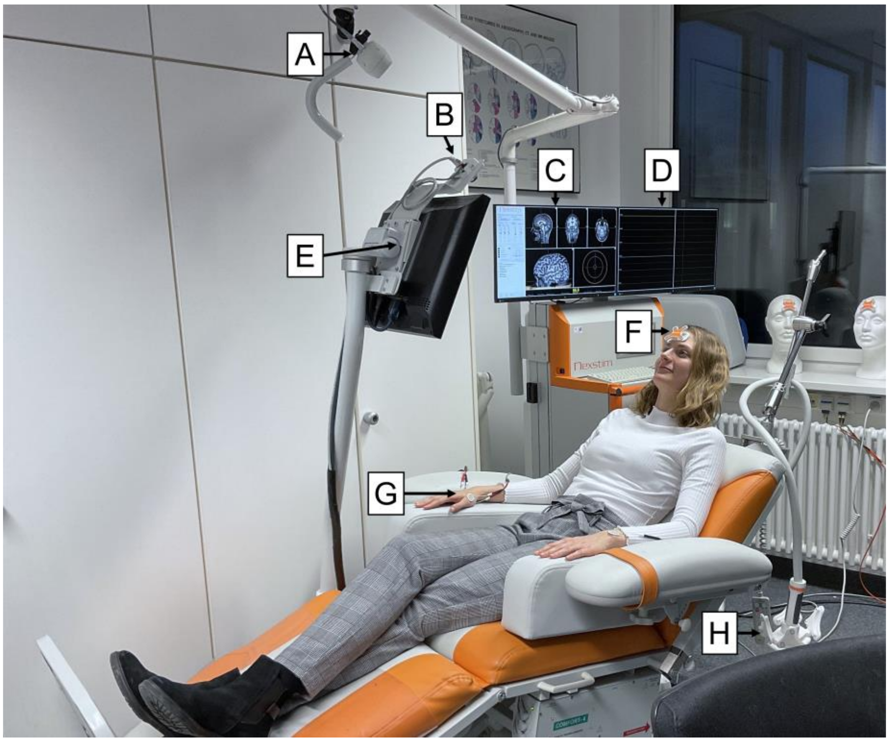


Figure 3: Setup of the nTMS system (Nexstim eXimia NBS system, version 5.1) for language mapping. Principal components comprise the stereotactic tracking device (A), the video camera for recording patient's language performance (B), two screens for displaying the 3D reconstruction of patients' MRI, neuronavigation, controlling settings, stimulation and task presentation as well as recording motor evoked potentials (C, D), a screen for displaying the pictures of the object naming task (E), head tracker for neuronavigation (F), surface electrodes to record motor evoked potentials (G), and the stimulation coil (H).

All patients underwent a routine language mapping workflow which has repeatedly been described (Krieg et al., 2017; Krieg et al., 2016). Figure 4 provides a schematic overview of the described routine language production workflow. The structural MRI sequence in a Digital Imaging and Communications in Medicine (DICOM) format was transferred to the nTMS-device. Automatically calculated individual three-dimensional head models (Figure 3C) were subsequently co-registered to the patient's skull based on anatomical landmarks (Figure 3C,F; Figure 4). A stereotactic infrared tracking device was used for neuronavigation (Figure 3A; Polaris Vicra®, NDI, Waterloo, Ontario), the reconstructed MRI displayed at a depth of 20 to 25 mm below the scalp. An electric-field navigation TMS system was used to determine the location, orientation and magnitude of the stimulation applied, as this enables to define and analyze stimulation targets accurately (Hannula & Ilmoniemi, 2017). This method demonstrated advantageous accuracy compared to classic line-navigated approaches (Sollmann, Goblirsch-Kolb, et al., 2016).

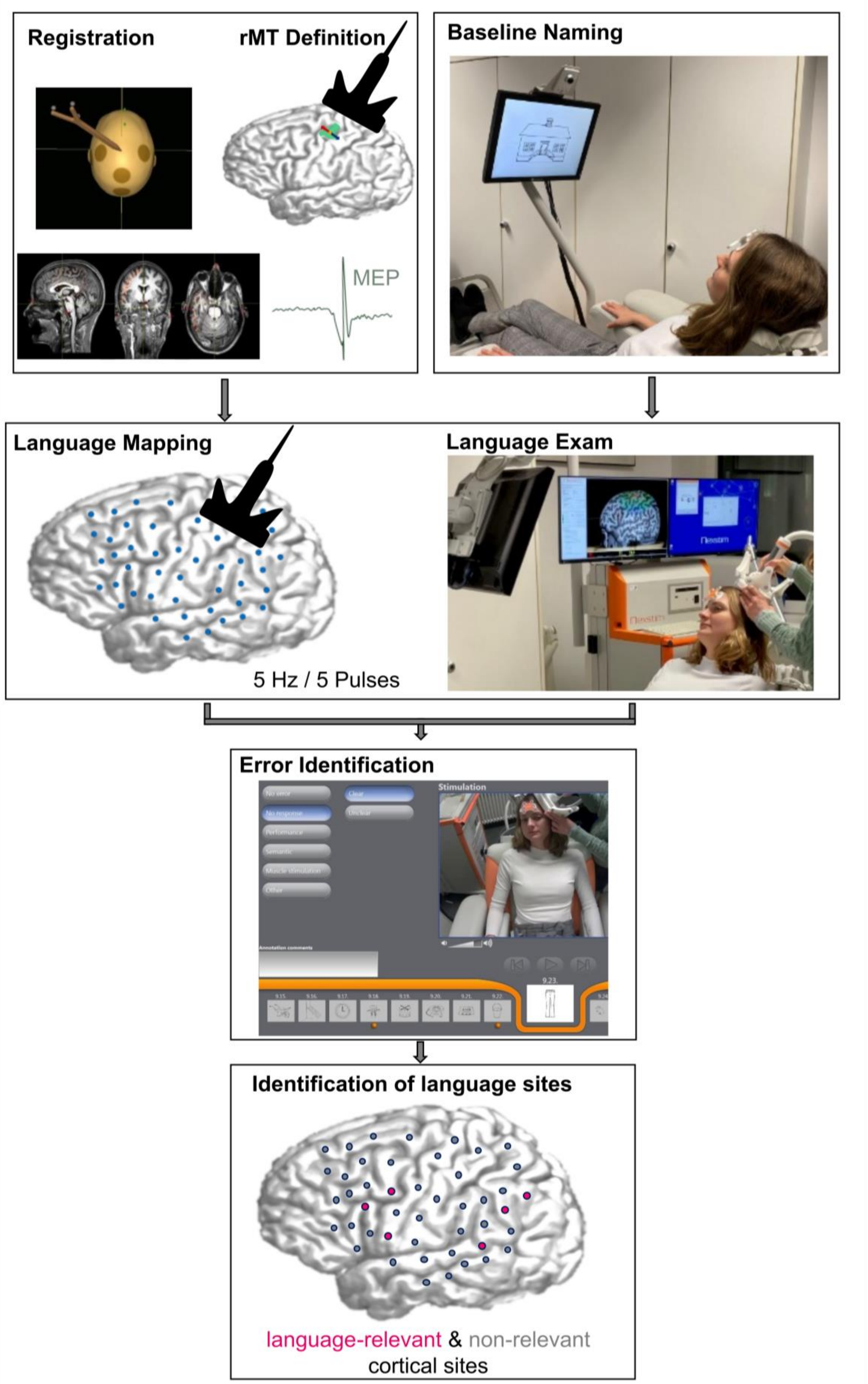
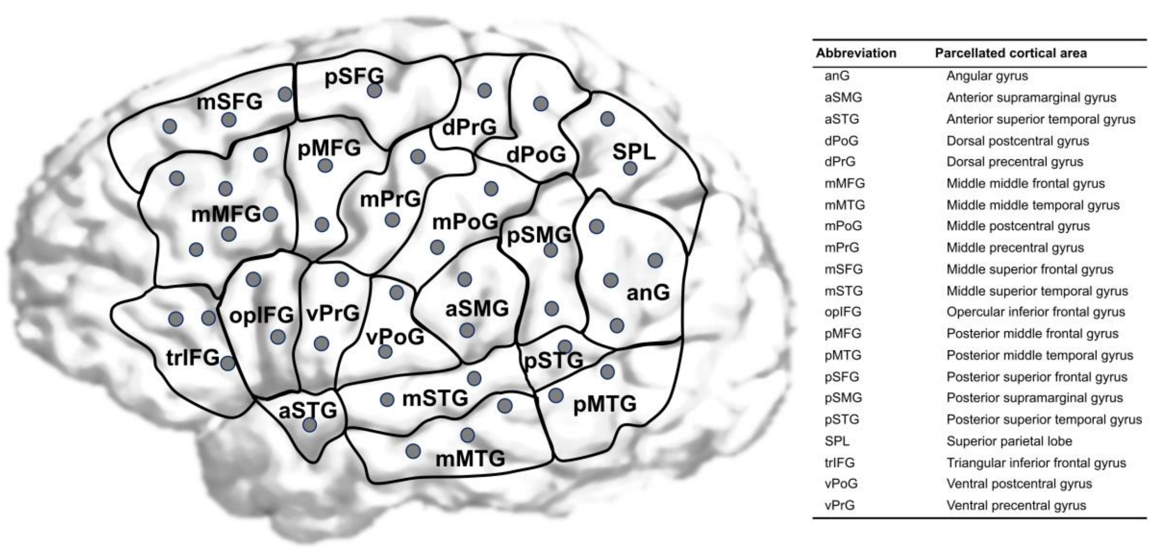


Figure 4: Schematic overview of the nTMS-based stimulation protocol, pictures showing the setup of the eXimia NBS system and the NEXSPEECH® module (Nexstim Plc., Helsinki, Finland).

Subsequently the individual lowest necessary stimulation intensity of the left hemisphere which was still able to elicit a motor evoked response (MEP), a stimulation-induced muscular contraction within abductor pollicis brevis or abductor digiti minimi, was identified (Figure 3D,G; Figure 4). The definition of this resting motor threshold (rMT) followed a standard protocol (Krieg et al., 2017; Krieg et al., 2012; Krieg et al., 2013; Picht et al., 2012; Sollmann, Tanigawa, et al., 2017). This included a motor mapping of the upper extremity, the identification of the individual most excitable cortical site at which stimulation evoked the highest MEP amplitude, and a maximum likelihood algorithm which is integrated into the Nexstim system to determine individual rMT value – the percentage of the system's maximum intensity output (Awiszus, 2003; Rossini et al., 2015; Sollmann, Tanigawa, et al., 2017).

As a next step, the patient's language performance during the task in use was examined. The most commonly employed task for preoperative nTMS-based language mapping is object naming (Jeltema et al., 2021; Krieg et al., 2017; Lioumis et al., 2012; Tarapore et al., 2013). The object naming task implemented in this study comprised 80 black-and-white drawings of common objects which were shown on a separate screen positioned in the field of view of the patient (Figure 3E; Figure 4). Prior to stimulation application patients were asked to name all items in two baseline trials in random order. This allowed to identify a subset of items each patient could name reproducibly and reliably (Krieg et al., 2016), all other items were deleted. All objects were shown with an inter-picture interval of 2,500 ms and a display time of 700 ms. If needed, these durations could be increased to a certain extent.

During the following stimulation exam, the items still included after the baseline trials were presented in randomized order time-locked to nTMS pulse application. Five repetitive nTMS pulses were applied with a figure-of-eight coil (Figure 3H) at a frequency of 5 Hz and with an intensity of 100-110% of the rMT as well as a picture-to-trigger interval of 0 ms (Kram, Neu, Schröder, et al., 2023; Krieg et al., 2017; Krieg et al., 2016; Sollmann, Kelm, et al., 2018). Stimulation targets were defined prior to the exam based on the cortical parcellation system described by Corina et al. (2005). Each of the 46 left-hemispheric target sites spread across frontal, parietal and temporal lobes (Figure 5) was stimulated three times (Kram, Neu, Schröder, et al., 2023). The stimulation coil was moved manually by the nTMS operator, the coil was positioned with an anterior-posterior orientation. Video- and audio-recordings of the baseline trials and the stimulation exam (Figure 3B) were automatically saved for subsequent mapping analysis (Lioumis et al., 2012; Tarapore et al., 2013).



Abbreviation	Parcellated cortical area
anG	Angular gyrus
aSMG	Anterior supramarginal gyrus
aSTG	Anterior superior temporal gyrus
dPoG	Dorsal postcentral gyrus
dPrG	Dorsal precentral gyrus
mMFG	Middle middle frontal gyrus
mMTG	Middle middle temporal gyrus
mPoG	Middle postcentral gyrus
mPrG	Middle precentral gyrus
mSFG	Middle superior frontal gyrus
mSTG	Middle superior temporal gyrus
opIFG	Opercular inferior frontal gyrus
pMFG	Posterior middle frontal gyrus
pMTG	Posterior middle temporal gyrus
pSFG	Posterior superior frontal gyrus
pSMG	Posterior supramarginal gyrus
pSTG	Posterior superior temporal gyrus
SPL	Superior parietal lobe
trIFG	Triangular inferior frontal gyrus
vPoG	Ventral postcentral gyrus
vPrG	Ventral precentral gyrus

Figure 5: Overview of cortically parcellated areas based on Corina et al. (2005), the distribution of the 46 left-hemispheric stimulation targets and the names of each parcellated area.

2.2.4 Speech status

The German guidelines for speech fluency disorders state that more than three percent of syllables need to be dysfluent in a representative speech sample to be classified as having a developmental persistent stutter (Neumann et al., 2016). No number is provided for acquired neurogenic stuttering. Due to the post-hoc nature of the first part of this study, the speech fluency analysis could only be based on the available video recordings (Kram, Neu, Schröder, et al., 2023). Thus, the SLT used the first object naming baseline of each patient to thoroughly examine stuttering occurrence and rate in all enrolled patients (Kram, Neu, Schröder, et al., 2023).

The following core stuttering symptoms were differentiated (Bloodstein et al., 2021): phoneme or syllable repetitions, prolongations and (non-)silent blocks. Exact definitions and examples are provided in Table 1. All of these core symptoms may be accompanied by secondary stuttering symptoms such as increased speech effort or heightened speaking rate, coping strategies (e.g., throat clearing, filler words, grimacing). While these secondary symptoms are typically more pronounced in developmental stuttering patients, neurogenic acquired and developmental stuttering are both frequently accompanied by tension within the speech system. In the second part of this study, the same differentiation criteria was applied (Kram, Neu, Schröder, et al., 2023). Still, patients could also be included if they presented with a pre-diagnosed persistent developmental stuttering.

Table 1. Differentiation criteria for core stuttering symptoms and stimulation-induced errors.

	symptom/ error category	definition	example
Core stuttering symptoms*	repetitions	phoneme or syllable repetitions but not whole word repetitions	“*↫b-b-b↫bucket”*
	prolongations	Stretching of phonemes	prolonged [l] in “*l:eave”*
	(non-)silent blocks	speech initiation impaired, fixed vocalization postures resulting in silent or non-silent paused in speech flow	inability to initiate the *“c”* in *“≠cat”* e.g. signaled by a fixed open mouth position without any vocalization
Stimulation-induced error categories	no response	no naming, no presence of stuttering symptoms such as blocks, e.g. caused by word finding difficulties	*“…”*
	phonological paraphasia	Omitted, substituted, inserted or transpositioned phonemes	*“teleon”, “felephone”, “tlelephone”, “phonetele”* for target item *“telephone”*
	semantic paraphasia	response semantically related to target item	*“rollerblades”* for *“skateboard”*
	circumlocution	multi-word response describing target item	*“to fill up”* for *“funnel”*
	neologisms	newly created non-words unrelated to target item following phonotactic properties of a language (Moses et al., 2004)	*“carrycarry”* for *“bag”*
	performance errors	motor speech errors in form of dysarthric, apraxic or non-pathological speech fluency symptoms (e.g. whole or multiple word repetitions, phrase repetitions, (filled) pauses)	
	hesitations	delayed naming onset	

** Note: The transcriptions of the exemplary core stuttering symptoms follow standard code formats for transcribing (dys-)fluencies (Bernstein Ratner & MacWhinney, 2018; MacWhinney, 2000).*

2.2.5 nTMS-based language mapping analysis

Within the NexSpeech Analyzer® (version 2.0.1) module of the nTMS system in use (Nexstim Plc., Helsinki, Finland), all video recordings could be analyzed thoroughly after the mapping (Figure 4). Errors induced by stimulation were identified in relation to the individual baseline performance and marked within the NexSpeech analyzer (Figure 4). All identified errors were divided into seven error categories based on previously described criteria (Corina et al., 2010; Krieg et al., 2016; Lioumis et al., 2012). An overview of these categories and examples is provided in Table 1.

Previous studies rarely associated non-pathological speech fluency symptoms with the pre- or intraoperative stimulation of a cortical or subcortical site. Still, the definitions and differentiation criteria reported vary considerably. For instance, some defined first syllable or word-initial repetitions as stuttering prompted by stimulation (Corina et al., 2010; Corrivetti et al., 2019) while a single study described stimulation-induced speech disruptions consistent with core stuttering symptoms (Kemerdere et al., 2016). However, these non-pathological speech fluency symptoms prompted by stimulation are not associated with any tension, speech effort or secondary symptoms which allows a clear distinction between stimulation-induced non-pathological speech fluency and stuttering symptoms.

Each stimulation exam of the patients who stuttered was analyzed during clinical routine by a highly experienced nTMS operator (120-480 language mappings, depending on the time point the mapping was conducted) and additionally retrospectively by a less experienced one (around 100 language mappings) (Kram, Neu, Schröder, et al., 2023). All error- and non-error-tagged items were matched back to the stimulation target on the three-dimensional brain model within the NBS software based on the specific ID during the stimulation exam. All error-tagged cortical sites were defined as language-positive cortical sites, all remaining as language-negative (Figure 4). Finally, we compared the identified supposedly stimulation-induced language errors as assigned by the nTMS operators to stuttering symptoms marked by the SLT to ascertain the impact of experience on differentiating stuttering and stimulation-induced errors (Kram, Neu, Schröder, et al., 2023).

2.2.6 Intraoperative DES-based language mapping

The results of the clinical preoperative language mapping in combination with subsequent diffusion tensor imaging tractography produced by the highly experienced nTMS operator were uploaded to the neuronavigation system (Brainlab AG, Germany) and used for neuronavigation during the awake language mapping. Similar to the preoperative setup, a stereotactic camera was used to track the patient’s brain, surgical tools and a navigation pointer. The patient’s head was fixed in a Mayfield clamp and co-registered to the preoperative MRI and language mapping results. The intraoperative awake language mapping with DES followed a commonly employed asleep-awake-asleep protocol (Deras et al., 2012; Hervey-Jumper et al., 2015; Ille et al., 2021). A bipolar stimulation electrode was used to apply a stimulation output of 4,000 ms at a frequency of 50 Hz and continuous intensity of 4 mA on the cortex (Inomed Medizintechnik, Emmendingen, Germany) (Kram, Neu, Schröder, et al., 2023).

During cortical mapping an object naming task was performed by the patients. As opposed to the preoperative setup, a lead in phrase in form of “This is a…” was implemented to differentiate speech arrest. The highly experienced nTMS operator who analyzed the preoperative language mapping tested intraoperative language performance (Kram, Neu, Schröder, et al., 2023). Here, a timely and direct identification of any stimulation-induced error needed to be made on the spot to identify cortically relevant language regions. Two out of three stimulations per site needed to be linked to an error in order to be marked as language-relevant (Ojemann et al., 1989). For subsequent subcortical mapping a monopolar electrode was used while the patient's spontaneous speech was monitored. In the second part of this study, audio-recordings were made of the naming and the subsequent spontaneous speech exam to allow for thorough analyses of patient's performance and stuttering rate by the SLT (Kram, Neu, Schröder, et al., 2023). Moreover, the SLT was present in all awake surgeries of patients who stuttered in the second part of this study to closely monitor the speech status throughout the procedure, applying the same differentiation criteria as described in Table 1 (Kram, Neu, Schröder, et al., 2023).

In order to simulate the instant and direct nature of differentiating speech symptoms from stimulation-induced language disruptions of the awake setting, Kram, Neu, Schröder, et al. (2023) carried out an additional analysis for the first study part: Here, the respective video recordings were watched by the SLT on an external computer once, without any option to stop or re-watch video segments. The interval between the initial and this simulated analysis comprised at least half a year. This analysis allowed to investigate whether an ad-hoc differentiation, similar to the awake setting, is feasible.

2.2.7 Statistical analysis

R3.6.3 (R Core Team, 2020) was used for all statistical analyses, a p value of $p<0.05$ considered as statistically significant. Since only very few patients who stuttered were present in the current cohort, predominantly descriptive statistical analyses were performed (Kram, Neu, Schröder, et al., 2023). The similarity and agreement on stuttering symptoms classified as stimulation-induced or no language error between nTMS operators was examined with Cohen's kappa, a kappa close to 1 was regarded as almost perfect agreement (Gamer et al., 2019; Landis & Koch, 1977).

2.3 Study 2: Preoperative language comprehension mapping

This was a prospective, monocentric, serial case study of six patients and 15 healthy controls who underwent preoperative nTMS-based language comprehension mapping between July 2021 and June 2023 (Kram et al., 2024).

2.3.1 Patient population and healthy controls

All patients included needed to show severely impaired language production, as indicated by an inability to perform the classic overt production tasks such as object naming (section 2.3.2). Additionally, patients and healthy subjects needed to be at least 18 years old and German native speakers to be considered for enrollment. Further inclusion criteria comprised the absence of contraindications for MRI or nTMS. Healthy controls could not present with any history of neurological or psychological disease. Again, handedness was examined with the Edinburgh Handedness Inventory (Oldfield, 1971).

2.3.2 Language status

Again, the author of this thesis, a trained SLT, assessed the language status in all patients (Kram et al., 2024). The severity of expressive deficits was ascertained on the basis of patients' performance in the classic object naming task described in section 2.2.3. While the baseline naming allows to define a subset of items each patient can produce correctly and reliably to be used during stimulation, a thorough analysis of the performance in the object naming task prior to any stimulation application can reveal a lot about the patients impaired and preserved expressive language abilities. Tasks such as the employed object naming task are commonly included in standardized language assessment tools such as the Aachener Aphasie Test (AAT, Huber et al., 1983). Based on this task, the following aphasic symptoms can be differentiated: automated language elements such as perseverations or phrases, semantic or phonological paraphasias, conduit d'approche, conduit d'écart, semantic or phonological neologisms and word finding difficulties. Based on the expression of each symptom type, severity and combination of different symptoms, the overall expressive aphasia severity was rated by the SLT on a Likert-Scale from 0 to 5 (Kram et al., 2024). This severity attribution is a modified and extended version of an AAT-based rating used in previous publications (Ille, Kulchytska, et al., 2016; Ille et al., 2021; Picht et al., 2013). This modification allows for a more detailed differentiation between severity levels as diagnostical tools like the AAT typically do not differentiate minimal from no aphasia and, thus, may not adequately represent the broad severity spectrum present in clinical routine. Severity was defined as follows:

(0) No deficit
(1) Minimal expressive deficit: e.g. sporadic word finding difficulties, daily communication unaffected, only occasionally object naming difficulties
(2) Light expressive symptoms: small impact on daily communication, only few object naming items affected by aphasia
(3) Moderate expressive aphasic symptoms: affecting but not restricting daily communication, moderate number of items can be named
(4) Severe expressive aphasia: significant impact on daily communication, still simple communicative tasks executable, very few objects can be named
(5) Extremely severe expressive aphasia: daily communication not viable, none of the objects named adequately

2.3.3 MRI acquisition and language eloquence definition

The same routine MRI protocol as described in section 2.2.2 was run by the Department of Neuroradiology, for healthy controls without contrast enhancement. Additionally, for each patient a Diffusion Tensor Imaging Sequence with 32 diffusion directions was acquired (TR/ TE: 5000/78 ms, b-values: 0 and 1000 s/mm^2, spatial resolution: 2 x 2 x 2 mm^3).

Based on the structural cortical and subcortical imaging as well as the presence or absence of preexisting aphasia either caused by the tumor/ a previous resection or a focal seizure, the language eloquence of each patient was defined. This method attributes a language eloquence level from 0 (low) to 9 (high) and is based on a standardized, systematic cortical, subcortical and clinical language eloquence classification (Ille et al., 2021).

2.3.4 nTMS-based CompreTAP language mapping

The aim of this study was to develop a Comprehension TAsk for Perioperative mapping (CompreTAP) not only suitable for patients with preexisting aphasia but also fitting the time-restricted and time-locked presentation mode during nTMS examination. Consequently, a thorough literature review of existing comprehension tests included in diagnostical tools and neuroscientific research of the time course of auditory comprehension was conducted.

Diagnostical instruments such as the AAT or the Western Aphasia Battery (Huber et al., 1983; Kertesz, 2007) test auditory language comprehension on single word and sentence level. The AAT, for instance, shows sets of four picture stimuli out of which a target item read by an SLT needs to be identified via pointing to the correct target image. Moreover, semantically or phonologically related distractor items are incorporated within these tools. However, to fit the time restraints, no distractor items were included in our task.

In order to comprehend language auditorily, different complex linguistic processes are carried out. It requires to categorize and discriminate acoustic-phonetic information, activate different lexical representations, process semantic information and, if sentences are presented, additional phrase structure building, morphosyntactic processes, and syntactic as well as semantic integration (Friederici, 2017). A vast amount of neuroscientific research revealed that all of these processes are performed within less than 1000 ms after auditory stimulus onset (Bornkessel et al., 2005; Eckstein & Friederici, 2006; Friederici, 2002, 2011, 2012; Friederici, 2017; Getz & Toscano, 2021; Hagoort et al., 2004). Thus, timing-restraints do allow single word and sentence comprehension tasks. Still, it may be more difficult for patients with aphasia to perform these more complex sentence tasks. Hence, for this study, a single word auditory comprehension task was developed (Kram et al., 2024).

Kram et al. (2024) extracted 62 picture stimuli from the “Verb And Noun Test for Peri-Operative testing (VAN-POP)” (Ohlerth et al., 2020). The objects were balanced in word frequency, acquisition age, and number of syllables. For the CompreTAP task, these items were randomly assembled in 28 different sub-sets of four, without the incorporation of any additional distractor or masker items. On average, each item occurred 3.94 times, each sub-set was used on average twice. None of the same sub-sets were shown with identical item position. These images were depicted on a computer screen. Onset-aligned to each picture presentation, a non-synthesized pre-recording of the target item was played automatically via the same software. The pre-recordings had an average duration of 1.0 s, with a range of 0.5 to 1.6 s. Patients were asked to select the corresponding target item via button press. Thus, no overt responses were required which allowed to perform this task in patients whose preexisting expressive aphasia precludes any overt tasks. The background of the item sets shown via the screen was color-coded and matched in position to four colored buttons (Figure 6). Since the left hand, ipsilateral to the subsequently stimulated left hemisphere, was used, hand motor difficulties caused by stimulation were minimized. Big-Point buttons (TTS, Nottinghamshire, UK) were utilized which can give out a recorded response once a button is pressed. The respective color label (red, blue, green, yellow) was recorded in advance. This was used during nTMS application to monitor the performance and attention of patients carefully and to support a post-hoc analysis of reaction times.

The same routine workflow as during classic overt nTMS-based language mappings described in section 2.2.3 was conducted with the Nexstim eXimia NBS system (version 5.1) and the NEXSPEECH® module (version 2.0.1; Nexstim Plc., Helsinki, Finland). To cover the auditory stimulation presentation and all subsequent comprehension processes, stimulation was applied for 2.0 s (10 pulses, 5 Hz,110% of rMT) stimulating each of the 46 target items three times (Kram et al., 2024). That these stimulation parameters allow nTMS-based mapping of language and cognitive functions, and are safe and well-tolerated was shown in previous studies (Maurer et al., 2017; Maurer et al., 2016; Sollmann, Fuss-Ruppenthal, et al., 2018; Tarapore et al., 2013; Tarapore et al., 2016). The inter-stimulus interval and picture presentation duration were set to 4 s. The camera of the nTMS device recorded the auditory item presentation and button response as well as the hand movement during button-press for subsequent analysis. A schematic overview of the CompreTAP mapping paradigm is provided in Figure 6.

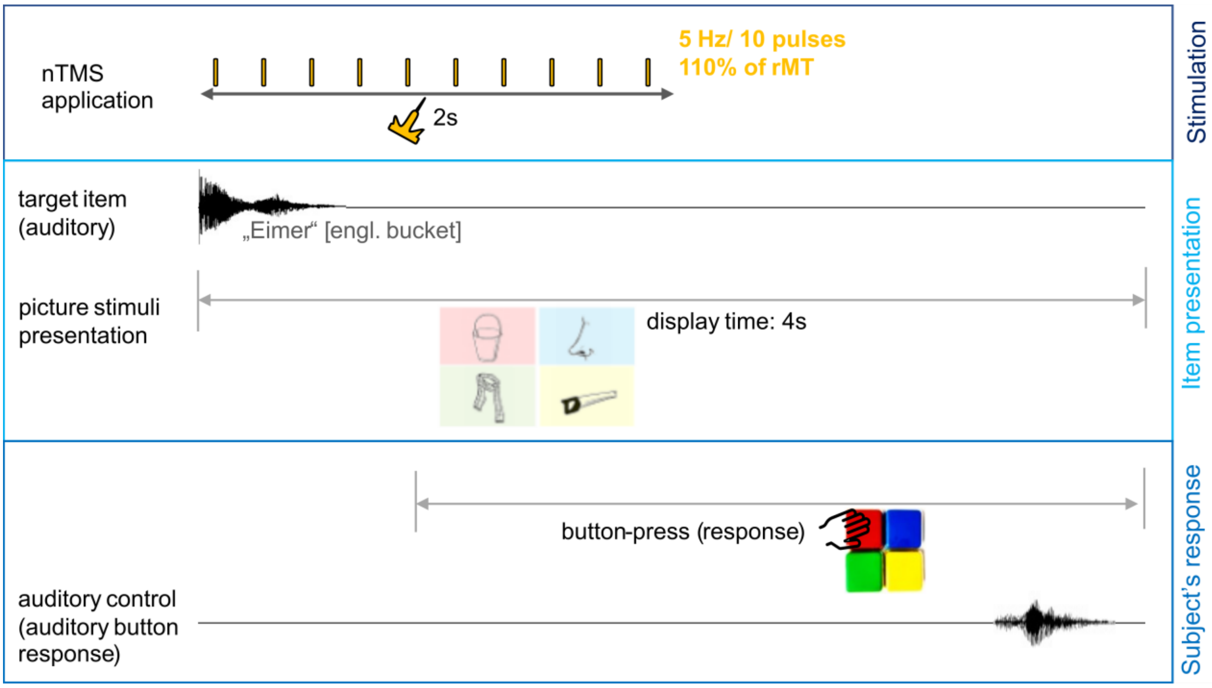


Figure 6: Schematic overview of the comprehension mapping setup and timing of stimulation application, auditory target, and picture item presentation as well as subject’s responses and auditory output elicited by button pressing.

2.3.5 Mapping analysis & identification of cortical comprehension sites

Stimulation-induced language errors were identified in the video-recordings by two language specialists: a neurolinguist (more than 200 language mappings) and the SLT (around 100 mappings) blinded to the stimulation site, both with excessive language mapping experience in classic naming protocols (Kram et al., 2024). All deviant button pressing response behavior was marked such as no, hesitant, or incorrect responses within the analysis software integrated into the nTMS system (NEXSPEECH® module version 2.0.1, Nexstim Plc., Helsinki, Finland). All error-tagged items were finally matched back to the cortical site at which stimulation was applied to mark comprehension-positive and -negative cortical sites (Kram et al., 2024). Error rates of 21 cortically parcellated regions (Figure 5) based on the system proposed by Corina et al. (2005) were calculated as the relative amount of comprehension-positive out of all applied stimulations. For this part, only the analysis of the SLT was considered. The results were exported in DICOM format to be used as seeds for subsequent nTMS-based tractography (Negwer, Ille, et al., 2017; Sollmann, Kubitscheck, et al., 2016; Sollmann, Zhang, Fratini, et al., 2020).

Additionally, recordings of the noise caused by the stimulator and the isolated auditory item presentation were made; the recording device was positioned with a 3 cm distance to the nTMS coil or the PC-screen (Kram et al., 2024). For this, exemplary 20 pulses of different stimulation intensities covering the whole range of patient’s or subject’s individual intensity settings and 10 exemplary items were taken to evaluate the impact of noise on subject’s ability to differentiate auditorily presented target items from the stimulator’s noise. Mean intensity values in dB were subsequently obtained with Praat version 6.3.04 (Boersma & Weenink, 2023).

2.3.6 Reaction-time analysis of delays induced by nTMS

Since it is known that hesitations are the most subjective and least reliable error category to identify in classic naming-based nTMS language mappings (Krieg et al., 2016; Ohlerth et al., 2021), additional objective reaction time analyses were performed and compared to the initial subjective video-based analysis of the SLT (Kram et al., 2024). All video recordings of the stimulation exam in .asf format were transferred to an external computer. The python-module MoviePy version 1.0.3 (Zulko, 2020) was used to extract the respective audio track in .wav. On the basis of the procedure described by Schramm et al. (2020), Praat version 6.3.04 (Boersma & Weenink, 2023) was used to measure the duration between auditory target stimulus onset and onset of the recorded color label prompted by a button press (Figure 7).

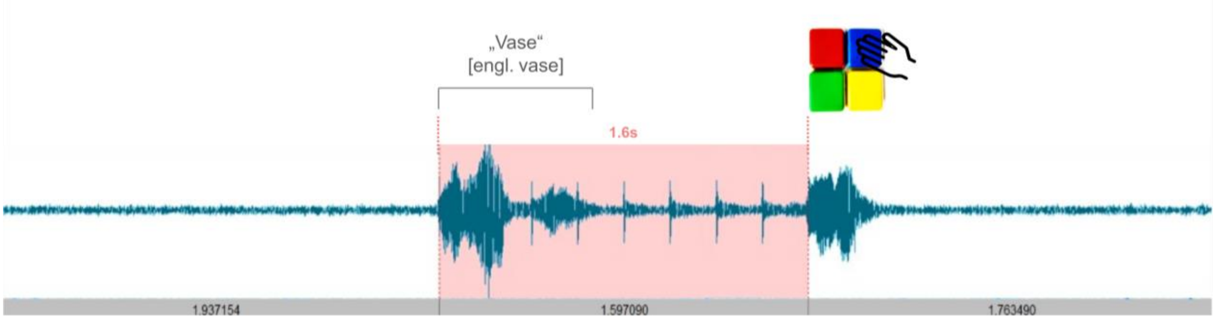


Figure 7: Measurement of reaction times. Extract of the Praat interface showing the auditory signal of an exemplary item (vase), the pre-recorded color label elicited by subsequent button press (color: blue) and the stimulation pulses applied.

Kram et al. (2024) excluded all items at which any error type apart from hesitations were identified by the SLT from the following analysis. We defined response delays as response times which exceeded the individual mean per subject by more than two standard deviations. To account for intra-subject variation during the course of the stimulation examination, all items which were identified by the SLT as hesitant ones, and the last five errorless preceding items were analyzed separately.

2.3.7 DTI-based tractography

All DTI-tractography analyses were performed with the surgical neuronavigation server Brainlab Elements, version 3.2.0.281 (Brainlab AG, Germany). The positive comprehension-sites were aligned and fused with the T1-weighted gradient echo sequence and the DTI sequences for each patient individually (Kram et al., 2024). Eddy current correction was applied.

For the DTI-based tractography a deterministic tractography algorithm implemented into Brainlab Elements (Brainlab AG, Germany) was used. All of the language positive spots were used as seed regions for tractography of the individual whole left-hemispheric language comprehension network. The minimum fiber length was set to 100 mm following a standard protocol and the minimum FA to 0.1-0.15 depending on optimal individual visualizability of most language tracts (Negwer, Ille, et al., 2017; Sollmann, Zhang, Schramm, et al., 2020). The final results were used for neuronavigation and functionally-guided surgical planning and surgical tumor removal if none of the classic tasks were feasible to allow for a preservation of the functional language network (Kram et al., 2024).

2.3.8 Statistical analysis

All statistical analyses were conducted with R (R Core Team, 2020), all p-values smaller than 0.05 were thought of as statistically significant. Inter-rater reliability was analyzed with Cohen's kappa, a kappa of 1 taken as almost perfect (Gamer et al., 2019; Landis & Koch, 1977). Moreover, Bangdiwala's agreement chart was used to compare the inter-rater agreement between the categorical data graphically (Bangdiwala, 1988; Bangdiwala & Shankar, 2013). In addition, the agreement of hesitant responses identification between the SLT and the response time analysis conducted within Praat was compared with Cohen's kappa. Due to the small sample size of the patient group, no group-wise comparisons were feasible. Thus, only descriptive analyses of the error rate distribution were performed (Kram et al., 2024).

3 Results

In the following, only the key findings of each study will be presented followed by a short description of the author's own contributions to each study. All results and figures presented within this result section stem from the respective publication (Kram, Neu, Schröder, et al., 2023; Kram et al., 2024). For a detailed description of the studies, comprehensive results and the contributions of the author of this thesis see Appendix 11.1 and 11.2.

3.1 Improving specificity of stimulation-based language mapping in stuttering glioma patients: a mixed methods serial case study

3.1.1 Key findings

The first study performed by Kram, Neu, Schröder, et al. (2023) showed a clear impact of stuttering symptoms on the reliability and consistency of identified stimulation-induced language errors and, thus, also on the cortical sites considered language-relevant. Although the six patients included across both study parts showed varying stuttering rates ($\text{Mean}_{\text{stuttering rate}}$=10.7%, range: 0.7-34.4%), for each of the six patients 29.4% up to 100.0% of all stuttering symptoms were misclassified as stimulation-induced language disruptions (Figure 8). Since on average 9.5 stuttering symptoms occurred during stimulation (range: 2-17), the occurrence of stuttering symptoms was not item dependent. A moderate concordance between both raters was shown by the authors for the (mis-)classification of blocks and prolongations (both $K \geq 0.5$, $p=0.02$), yet not for repetitions. The stimulation-induced error categories both operators assigned stuttering symptoms to varied considerably (Figure 9). In addition, the less experienced operator assigned most of the misclassified stuttering symptoms to the category "other" showing a certain degree of uncertainty and the recognition of these errors as distinct from classic stimulation-induced disruptions. Nevertheless, the less experienced operator misclassified a higher percentage of the speech fluency symptoms as stimulation-induced disruptions ($\text{Mean}_{\text{high experience}}$=48.5%, $\text{Mean}_{\text{less experience}}$=64.8%).

Moreover, the sites at which stuttering symptoms occurred spread randomly over the entire left hemisphere (Figure 8). Kram, Neu, Schröder, et al. (2023) could not identify a systematic association of stuttering symptoms with the cortical endpoints of frontal aslant tract (IFG, SFG), aSMG and pSMG. The respective rate of stuttering symptoms during stimulation of any of these cortical sites out of all speech fluency symptoms was lower than 15%, supporting that these symptoms were not induced by stimulation (Kram, Neu, Schröder, et al., 2023). Since, moreover, these stuttering symptoms were all accompanied by tension, speech effort or secondary symptoms, a clear differentiation from any stimulation-induced language disruptions and stuttering was feasible across all patients (Kram, Neu, Schröder, et al., 2023).

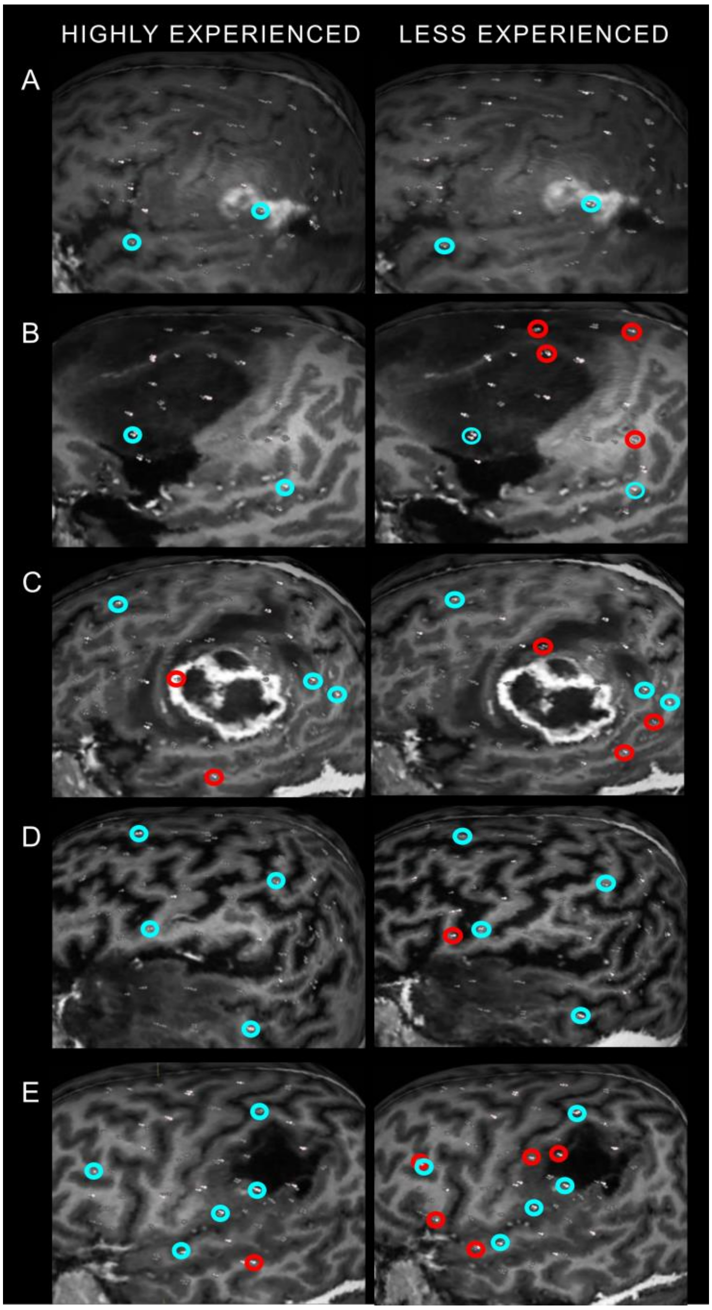


Figure 8: Comparison of stuttering symptoms classified as stimulation-induced language errors and consequently falsely considered as language-relevant cortical sites for the highly and the less experienced nTMS operator across P1-6 (P1: A, P2: B, P3: C, P4: D, P5: E). Stuttering symptoms misassigned by both nTMS raters indicated by a blue outline and stuttering symptoms misassigned by only one of the nTMS raters highlighted by a red outline. Figure taken from Kram, Neu, Schröder, et al. (2023, p.7).

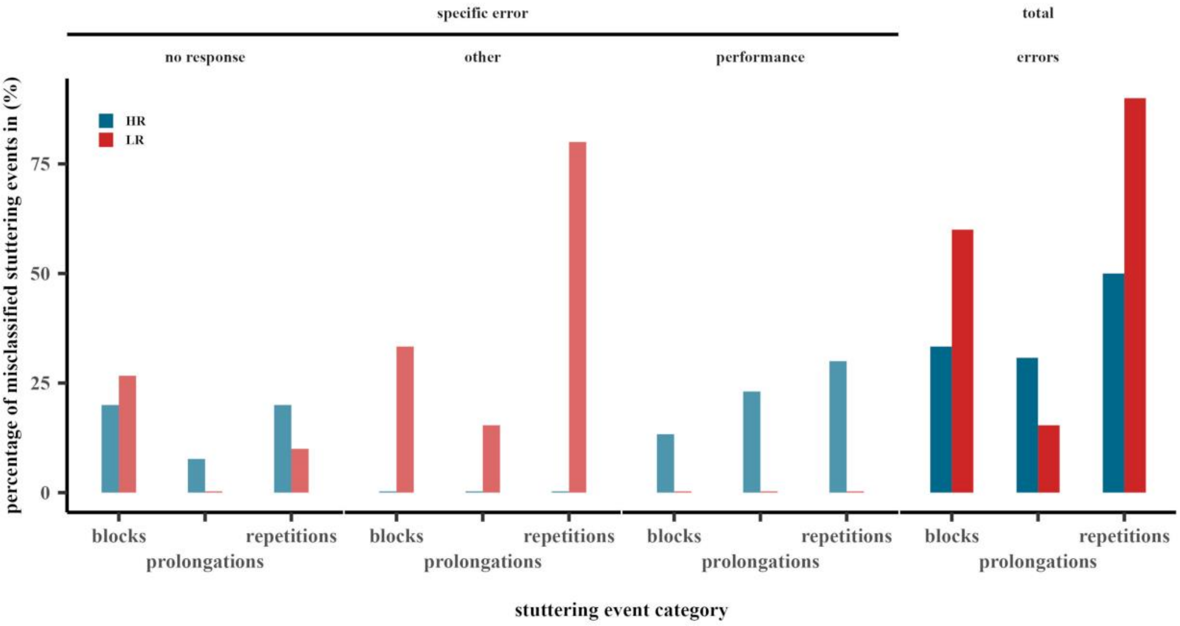


Figure 9: Overview of stuttering symptom types (blocks, prolongations, repetitions) misclassified as any stimulation-induced language disruption (total errors) as well as stratified across the respective stimulation-induced language error category (no response, other, performance) they were assigned to by the highly (blue) and the less experienced nTMS rater (red). Figure taken from Kram, Neu, Schröder, et al. (2023, p.8).

Additionally, 83.2% of the stuttering symptoms occurring during the nTMS examination were also identified by the SLT in the simulated awake analysis (Kram, Neu, Schröder, et al., 2023). While Kram, Neu, Schröder, et al. (2023) observed a dependency on stuttering severity, across all patients at least 72.7% of stuttering symptoms could be identified promptly by the SLT. Similarly, an instant identification of stuttering symptoms was feasible during the awake DES-based language mapping in a single patient with persistent developmental stuttering. This was subsequently confirmed by the post-hoc analysis of the respective audio recording. Furthermore, the same experienced rater misclassified both non-silent blocks as shown by impaired speech initiation, tension within the speech system, fixed vocalization pattern and pressed vocalization during the naming-based cortical awake mapping. Since neither stuttering symptoms nor proper stimulation-induced disruptions manifested during stimulation directly in the tumor area, these two symptoms did not directly impact the surgical approach in this case. Moreover, during the spontaneous speech examination and subcortical resection, the stuttering rate continuously increased from 1.5% up to 3.1%. Due to this in combination with focal seizures, the awake testing had to be stopped after 18 minutes.

3.1.2 Own contribution

As the speech and language therapist involved in this study, I screened the video recordings of the baseline and stimulation examination of 211 patients for stuttering symptoms. After identifying patients who presented with a stutter, I performed thorough analyses of the stimulation examination and the simulated intraoperative analysis. This entailed a particular detailed differentiation and identification of all stuttering symptoms manifesting prior to and during nTMS stimulation. For the second study part, I was additionally involved in the prospective recruitment of patients, screening for stuttering, and intraoperative monitoring of stuttering symptoms as well as post-hoc analysis of all available audio- and video recordings. I carried out all statistical analyses, created the figures, performed the literature research and wrote the initial draft of the manuscript. Moreover, I revised the manuscript according to the co-authors' remarks as well as the reviewers' comments while the manuscript was under review in Heliyon. All steps were performed under supervision of Prof. Krieg and Dr. Ille.

3.2 CompreTAP: Feasibility and Reliability of a New Language Comprehension Mapping Task via Preoperative Navigated Transcranial Magnetic Stimulation

3.2.1 Key findings

Across healthy subjects and patients, the auditory single word comprehension mapping setup was feasible. During the two baseline trials before stimulation application, controls were able to correctly select 100.0% and patients on average 62.8% (standard deviation: ±21.6%) of the auditory target items correctly via button press in the study carried out by Kram et al. (2024). Deviant response behavior prompted by nTMS was differentiable into four categories by both raters: no selection of any item (no response), hesitant or delayed button press (hesitation), indecisive hand motion toward different buttons not matching the target item in color with a final push of the correct button (searching behavior) and pushing a button not corresponding to the target item (selection of wrong target item). Moreover, the mean noise of the nTMS system (57.3 dB) did not exceed the mean intensity of exemplary items (73.4 dB).

Kram et al. (2024) were able to identify deviant response behavior with a substantial inter-rater reliability for patients and controls (K=0.7, p<0.001). A closer analysis of error category specific inter-rater agreement revealed at least a substantial reliability for all categories except hesitations in patients and for searching behavior and selection of wrong target items for controls. A fair agreement was verified for no responses in healthy subjects, the agreement for hesitations was limited in patients and controls. The separate analysis of reaction times indicated additionally only a slight agreement between the SLT and objective response time measurements across both groups (both K=0.1, p<0.001). Out of 66 hesitations classified by the SLT in total, only 15 were attributed based on a seemingly delayed response while all other hesitations were accompanied or indicated solely by hesitant hand motions such as faltering or reluctant movements before a button press. Additionally, 73.3% of these 15 hesitations, identified solely based on seemingly delayed responses, exceeded the response time of the last five errorless items by more than two standard deviations.

Descriptive results showed a higher error rate in patients (18.3% ± 4.8%) than controls (9.9% ± 4.6%) (Kram et al., 2024). At single case level, the distribution of error rates across frontal, parietal and temporal cortical sites varied considerably for controls (Figure 10) and patients (Figure 11). At group level, however, common cortical language hubs were shown to be comprehension-relevant (Figure 12). Particularly, high error rates across all categories were found within IFG, vPrG, STG, MTG, pSMG and AnG (Figure 12).

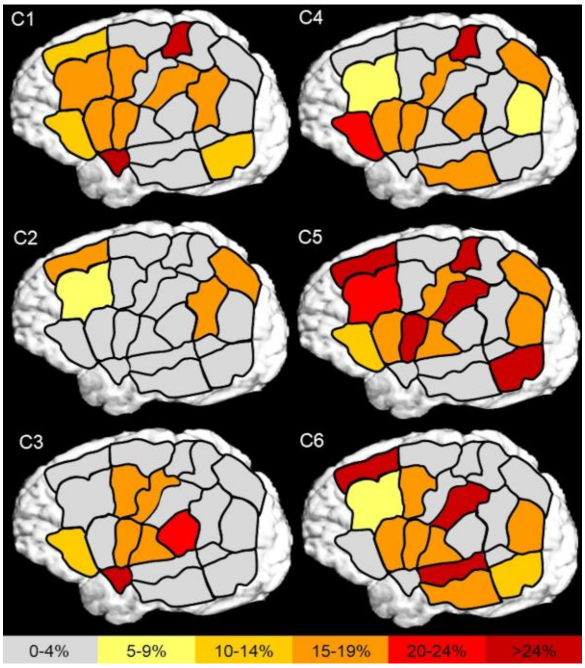


Figure 10: Individual mean error rates for the 21 cortically parcellated areas across the first six healthy subjects C1-6. Figure taken from Kram et al. (2024, p.353).

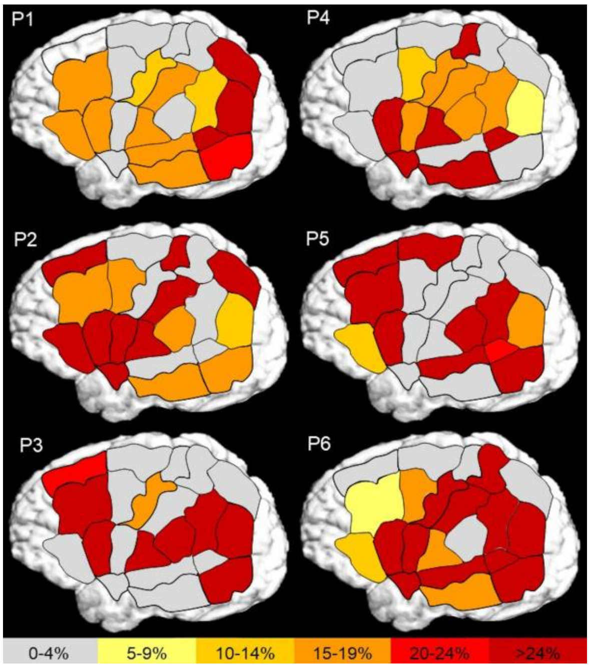


Figure 11: Individual mean error rates for the 21 cortically parcellated areas across the six patients P1-6. Figure taken from Kram et al. (2024, p. 355).

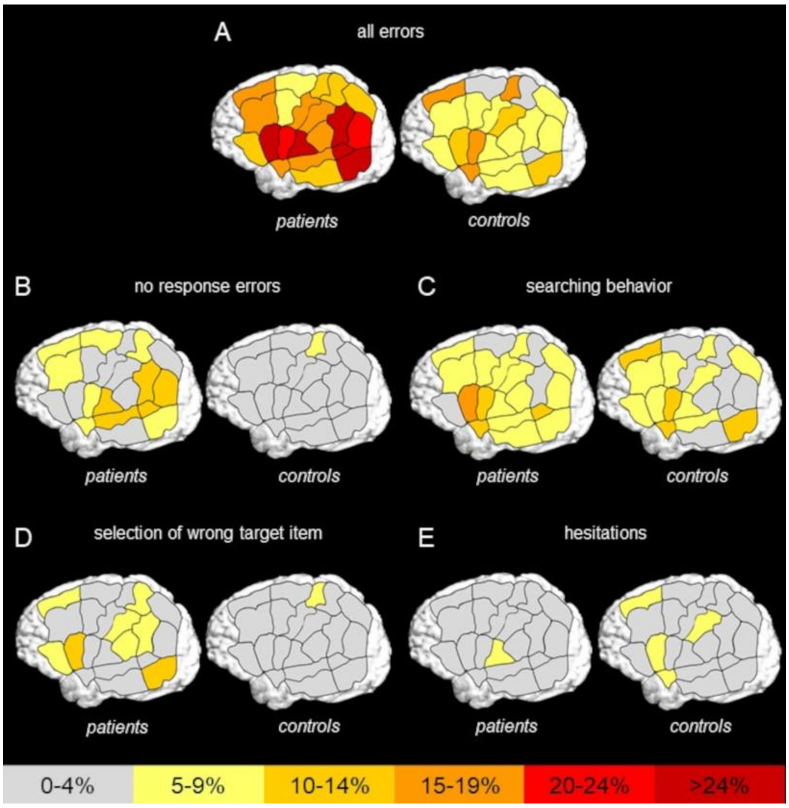


Figure 12: Comparison of the mean error rates for the 21 cortically parcellated areas between patients and controls across all language error categories (A) and for each specific category (B-E). Figure taken from Kram et al. (2024, p. 357)

Moreover, since this task was the only feasible one in five out of the six patients, the comprehension mapping results were used in 83.3% of the current patient cohort to inform functional tractographies used for surgical planning and removal (Figure 13). Out of these five cases, only a single patient showed transient worsening postoperatively, for none of the patients any long-term deterioration in language functionality was reported (Kram et al., 2024).

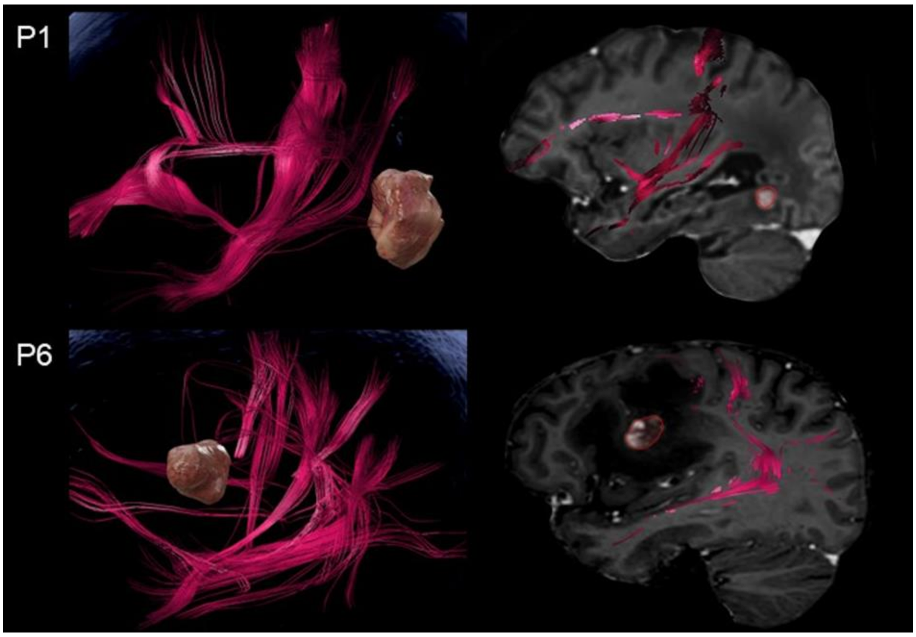


Figure 13: Reconstruction of the functional left-hemispheric language network (pink) for two illustrative patient cases (P1 and P6), glioblastoma highlighted in brown (left) or outlined in red (right). Figure taken from Kram et al. (2024, p. 356).

3.2.2 Own contribution

For this second study, I constructed the task, recruited patients and healthy subjects in collaboration with the neurolinguist Dr. Ohlerth. I carried out the majority of the mappings, performed one of the two stimulation examination analyses by identifying and categorizing stimulation-induced language comprehension errors which was necessary for inter-rater comparisons. Moreover, I ran all statistical analyses, created all figures, and supported the creation of clinical tractographies. I, furthermore, performed the additional analysis of reaction times and comparisons of the intensity of auditory item stimuli with the noise of the stimulation system. I performed the initial and the final literature research, wrote the initial draft of the manuscript, and revised it according to the co-authors’ remarks and reviewer comments provided during the review process in Cortex. All steps were carried out under supervision of Prof. Krieg.

4 Discussion

Stimulation-based language mapping offers an individual insight into the unique, vast and largely distributed language network and, thus, substantially aids the preservation of functionality in patients with language eloquent brain tumors. Whilst the benefit of such mappings is widely supported across studies and centers (De Witt Hamer et al., 2012; Ille et al., 2021; Mandonnet et al., 2010; Picht, 2014; Raffa et al., 2019; Tarapore et al., 2013), these methods thus far are primarily available for patients with very well-preserved abilities. This, however, excludes a large proportion of patients who already present with pre-existing speech or language disorders. Still, particularly patients who show language impairments prior to a resection, harbor language eloquent tumors and, hence, may benefit substantially from reliable language mappings. Consequently, mapping protocols and techniques need to be adjusted to the needs of these patients to allow for a preservation of residual abilities. As opposed to the gold standard, DES during awake surgeries, the more relaxed and adjustable preoperative setting of nTMS-based language mappings may be more adaptable to the individual needs and capabilities of patients. Thus, the two publications included in this thesis set out to evaluate the impact of speech and language disorders on feasibility and reliability of stimulation-based language mappings as well as new approaches and paradigms to improve these mappings and, consequently, the preservation of functionality in context of both disorders (Kram, Neu, Schröder, et al., 2023; Kram et al., 2024). In the following, the results of the two studies described in detail above will be summarized, discussed and finally combined to draw a synthesized conclusion about the implications of pre-existing aphasia or speech (fluency) impairments, and possibilities to tailor language mapping procedures to patients and their deficits in order to support the preservation of functionality.

4.1 Language production mapping in patients with speech (fluency) disorders

Stimulation-based language mappings are reliant on linking an error during language task performance to the stimulation of a cortical site. The most common and well-known language task in use for pre- and intraoperative stimulation-based mapping, respectively, is object naming (Jeltema et al., 2021; Martin-Monzon et al., 2022; Natalizi et al., 2022). Hence, the most commonly classified error categories comprise clear language mistakes such as semantic or phonological paraphasia, clear speech motor disruptions such as articulatory deviations, or no and hesitant responses which are not clearly assignable to a specific language or speech process (Corina et al., 2010; Lioumis et al., 2012). Whilst stimulation can elicit any of these deviations from accurate naming responses, it is well known that speech disorders such as dysarthria and pre-existing language disorders such as aphasia need to be differentiated to allow for reliable interpretation of results. Some, for instance, stated the need to distinguish dysarthria from stimulation-induced language arrest during DES-based stimulation by closely monitoring any orofacial or pharyngeal muscular contractions which may impact speech production (Gogos et al., 2020; Hervey-Jumper et al., 2015; Sanai et al., 2008; Talacchi, Santini, Casartelli, et al., 2013). However, while the differentiation of a specific dysarthric symptom, which may potentially manifest during intraoperative language mapping, is frequently described, no detailed evaluations or reports exist about the impact of pre-existing dysarthria which can decrease communicative abilities and intelligibility of patients. Consequently, severe forms of dysarthria may be a contraindication for stimulation-based language mappings similar to severe forms of aphasia (Hervey-Jumper & Berger, 2016; Morshed et al., 2021). Still, if intelligibility is not impaired, pre-existing dysarthria may be easily differentiable from stimulation-induced language network disruptions as the respiratory, phonatory and articulatory symptoms of this speech motor disorder persistently present during speech production irrespective of items, tasks, or stimulation application.

Unlike dysarthria, the speech fluency disorder stuttering manifests a lot more unpredictably, uncontrollably, and randomly. The symptom expression of developmental stuttering shows to be more coherent than the acquired form as it is dependent on linguistic complexity and the language task and seems to manifest at the initial position in a word or phrase (Lundgren et al., 2010). Still, developmental and acquired neurogenic stuttering present with similar dysfluency symptoms. This makes a differentiation between these types of fluency disorders merely on the basis of symptom presentation difficult (Logan, 2022). The only diagnostical differentiation criteria agreed upon across studies, is the new manifestation of these stuttering symptoms following an acquired brain lesion which indicates an acquired stuttering (Cruz et al., 2018). Hence, due to the post-hoc nature of the present study, no differentiation between acquired and developmental stuttering was possible (Kram, Neu, Schröder, et al., 2023).

While stuttering is only rarely described in neurosurgical patients (Helm et al., 1980; Peters & Turner, 2013), the prevalence of stuttering across the entire life-span is estimated to be 0.72% while the lifetime incidence is assumed to be 5-10% (Yairi & Ambrose, 2013). The results of the present study indicate a prevalence of 4.85% of patients who stutter out of a sample of 103 glioma patients (Kram, Neu, Schröder, et al., 2023). Consequently, stuttering was present in neurosurgical patients – whether acquired or developmental. All of the patients who stuttered included by Kram, Neu, Schröder, et al. (2023) showed a clear symptom pattern, distinct to other speech and language disorders: multiple repetitions of phonemes or syllables, prolongations and silent as well as non-silent pauses in the speech flow, all accompanied by tensed or fixed muscular activation within the pharyngeal or orofacial speech system. Despite this clear symptom pattern, this speech fluency disorder remained unrecognized during presurgical clinical routine. Since stuttering is not a frequently diagnosed disorder across brain tumor patients, it may be that a lack of thorough training in diagnosis and differentiation of speech (fluency) disorders may lead to an oversight of this pathology in neurosurgical patients. This may explain the shortage of reports on acquired stuttering following brain tumors as opposed to other neurological lesion types (Cruz et al., 2018; Logan, 2022).

Across the stuttering glioma patients, stuttering manifested even prior to stimulation application in up to 34.41% of all syllables produced (Kram, Neu, Schröder, et al., 2023). As naming accuracy determines the subset of items used during subsequent stimulation application, this may have substantially decreased the number of available items (Kram, Neu, Schröder, et al., 2023). Moreover, it is likely that the items which were excluded due to a stuttering symptom may have been produced fluently during the next time presented. To qualify patients for stimulation-based language mappings, frequently strict cut-off criteria are applied, such as the correct naming of at least 75% of items (Hervey-Jumper & Berger, 2016). Thus, moderate or severe stuttering rates may even preclude stuttering patients completely from these language mappings, even if their language abilities would allow for adequate task performance.

Irrespective of the baseline stratification, stuttering symptoms manifested up to 17 times during the stimulation examination (Kram, Neu, Schröder, et al., 2023). This demonstrates that the occurrence of stuttering was not item-dependent and symptoms occurred randomly regardless of the exclusion of items during baseline. Some studies reported to induce non-pathological speech fluency errors during stimulation of anterior and posterior supramarginal gyrus or the frontal aslant tract (Corina et al., 2010; Kemerdere et al., 2016). Still, clearly identifiable symptoms of pre-existing stuttering could not be causally related to the stimulation of a specific cortical site. This underlines the necessity to carefully differentiate symptoms caused by the pre-existing speech fluency disorder from stimulation-induced language network disruptions, to increase the number of items available during subsequent testing and improve the reliability and consistency of the language-relevant sites identified during stimulation mapping.

In addition, 60.0% of the stuttering patients in the first post-hoc study part subsequently underwent an awake surgery (Kram, Neu, Schröder, et al., 2023). Stuttering frequency and severity are known to accumulate in rate in particularly stressful situations (Sander & Osborne, 2019; Tichenor & Yaruss, 2021). Thus, it is very likely that these symptoms are also present or even more pronounced across all stuttering patients during awake DES-based language mappings which may increase the psychological strain for patients (Mofatteh et al., 2023). Case 6 demonstrated that her stuttering manifested uncontrollably during the DES-based naming and subsequent spontaneous speech examination during the resection of the tumor (Kram, Neu, Schröder, et al., 2023). Consequently, the presence and misclassification of stuttering may substantially affect the areas identified as relevant during the DES-based craniotomy, and in turn the extent of resection.

4.2 Language comprehension mapping in patients with expressive aphasia

Whilst the first study was focused on improving the reliability of classic stimulation-based language production mapping in patients with pre-existing speech (fluency) disorders (Kram, Neu, Schröder, et al., 2023), the second study developed and evaluated a new testing paradigm for patients with severely impaired language production but preserved language comprehension (Kram et al., 2024). Aphasia is known to substantially increase the number of errors during the stimulation examination (Schwarzer et al., 2018). A meta-analysis indicated that severe aphasia is one of the most widely accepted deficit-based contraindications for DES-based mapping during awake surgeries (Fiore et al., 2022). Still, exact numbers on the prevalence of patients whose aphasia severity prohibited any stimulation-based language mapping are scarcely reported. Moreover, many centers limit awake surgeries to low-grade gliomas. The reason for this may comprise better preserved language functionality in low-grade glioma patients due to the brain's potential to functionally reorganize as a response to the slow tumor progression (Bertani et al., 2009; Duffau, 2006). Still, studies also support the benefit and the feasibility of awake surgeries in high-grade tumors, primarily in cases with mild to moderate aphasia (Clavreul et al., 2021). A single study piloted patient-tailored intraoperative language tasks adjusted in complexity to severe aphasia of glioblastoma patients (Donders-Kamphuis et al., 2023). The preliminary results of this study demonstrated the feasibility of DES-based language mapping even in five cases with severe preoperative aphasia if patient-tailored approaches are employed. Kram, Neu, Ohlerth, et al. (2023), moreover, showed a higher susceptibility of linguistically more complex items to errors during nTMS-based language mappings across moderately and severely expressive aphasic patients. Thus, an adjustment of the complexity of items used for pre- and intraoperative stimulation-based language mappings to the individual capabilities of patients with preoperative language deficit may increase feasibility and reliability of mappings and in turn substantially support the preservation of functionality during surgery.

At the same time, seven of the 96 patients reported by Kram, Neu, Ohlerth, et al. (2023) were unable to perform any classic preoperative nTMS-based language production mapping due to extremely severe expressive aphasia. Additionally, Picht et al. (2006) reported that 22.5% of patients considered for awake craniotomy could not undergo DES-based mapping due to severe aphasia. Since expressive deficits are one of the most frequent and well-known aphasic symptoms (Fridriksson et al., 2015), alternative test paradigms are required to allow patients with language production deficits to undergo stimulation-based mappings.

As the results of Kram et al. (2024) show, applying a language comprehension test for nTMS-based language mapping, which eliminates the need for overt responses, was feasible in six severely aphasic patients whose language production abilities were insufficient for classic expressive test paradigms. Moreover, the preliminary results of this pilot study suggest that CompreTAP-based language tractographies can support the preservation of residual functionality. Across the five patients, for whom these functional tractographies were used for neuronavigation during surgery, only one patient showed a transient worsening, all other patients did not show any signs of language deterioration. Since transient deficits are commonly reported following tumor removal, these results provide first indications for the utility of this mapping setup.

To the best of the author's knowledge, this is the first non-overt comprehension setup for nTMS-based language mapping in adult glioma patients. Since stimulation over a cortically relevant area prompts a hearable error during a language task, primarily overt tasks such as object or action naming, repetition and reading are performed (De Witte et al., 2015; Hauck et al., 2015; Krieg et al., 2017; Ohlerth et al., 2020; Rofes et al., 2015; Talacchi, Santini, Casartelli, et al., 2013). A recent meta-analysis showed that comprehension-based mapping studies still only make up 5% of 149 awake language mapping studies (Fiore et al., 2022). Moreover, most of these receptive test paradigms require overt responses by the patients (Alarcon et al., 2019; De Witte et al., 2015; Fernandez Coello et al., 2013).

Few studies thus far reported pointing-based comprehension setups. For instance, Rejnö-Habte Selassie et al. (2020) were the first to pilot a nTMS-based non-overt sentence comprehension mapping in three pediatric patients. Moreover, Roux et al. (2015) performed a complex visual association task reliant on pointing-based responses during DES-based language mapping. Due to the visual presentation mode, the latter task does not allow to examine acoustic and phonological categorization which comprise crucial auditory comprehension processing steps (Friederici, 2012). At the same time, sentence comprehension tasks increase the linguistic complexity as additional semantic, morpho-syntactic and prosodic processes are needed to perform the task (Friederici, 2002). Still, many of the processes required for single word are also necessary for sentence comprehension (Friederici, 2017). Moreover, a recent lesion-symptom and connectome study in stroke patients linked overlapping cortical and subcortical comprehension areas to single word and sentence comprehension (Matchin et al., 2022). Thus, a single word auditory comprehension setup – which fits the time-restricted presentation mode required for online nTMS-based language mapping and the linguistic capabilities of aphasic patients – may be sufficient for stimulation-based language mapping. However, whether sentence and word comprehension primarily rely on the same or on distinct temporal areas remains highly controversial (Matchin et al., 2023; Mesulam et al., 2023; Mesulam et al., 2015). Subsequent studies may employ a sentence comprehension paradigm next to the single word setup presented within this thesis to evaluate the cortical basis of different language comprehension processes systematically.

The results of the study performed by Kram et al. (2024) related distributed left-hemispheric cortical sites to single word comprehension even in healthy subjects. The distribution of stimulation-induced error rates demonstrated that commonly known language areas such as the inferior or posterior middle frontal gyrus as well as middle and superior temporal areas are associated with language comprehension at group level (Figure 12). Even at case level, a large proportion of patients (Figure 11) and controls (Figure 10) showed a high expression of no responses and searching behavior within superior and middle temporal areas. The middle and posterior superior temporal gyrus have been associated with comprehension since the initial reports of the classic “Wernicke’s” area (Binder, 2017). Moreover, current research linked the anterior superior and posterior middle temporal gyrus to comprehension processes (DeWitt & Rauschecker, 2013; Turken & Dronkers, 2011). At the same time, the present study causally related wide-spread frontal and parietal areas to word comprehension with high error rates in the inferior frontal and ventral precentral gyrus across patients and controls (Kram et al., 2024). This is in line with more recent reports of an involvement of historically presumed language production sites in language comprehension (Klaus & Hartwigsen, 2019). Overall, the individual language maps of the first six illustrative healthy control cases (Figure 10) and of the six patients (Figure 11) revealed a high inter-subject variability. Hence, localizing and identifying language-relevant areas within each individual is paramount to support the preservation of language function during craniotomies of language-eloquent brain tumors.

4.3 Role of trained and experienced specialists

Since stimulation-based language mappings rely on detecting an error prompted by stimulation application of a specific cortical site, the mapping results are highly dependent on a consistent and reliable identification of stimulation-induced disruptions of task performance. Therefore, this thesis investigated whether trained and experienced specialists may improve the consistent differentiation of stimulation-prompted errors in task performance from symptoms of pre-existing speech disorders (Kram, Neu, Schröder, et al., 2023) and whether these specialists can reliably identify errors during the new button press setup (Kram et al., 2024).

The results of the first study show that across nTMS examiners a large proportion of stuttering symptoms were classified as stimulation-induced language disruptions (Kram, Neu, Schröder, et al., 2023). This substantially increased inconsistency in the mapping analysis, decreasing reliability and specificity. Thus far, the application and interpretation of nTMS-based language mapping results highly depend on a very high negative predictive value in comparison to the gold standard, DES-based language mapping (Ille, Sollmann, Hauck, Maurer, Tanigawa, Obermueller, Negwer, Droese, Boeckh-Behrens, et al., 2015; Picht et al., 2013; Tarapore et al., 2013). Thus, the adequate identification of non-relevant language sites and the minimization of false positive sites is crucial for a reliable mapping and subsequently the preservation of functionality.

Albeit the overall language mapping experience decreased the percentage of all stuttering symptoms misclassified, individual prior knowledge or a different professional background seemed to affect the proportion of symptoms misclassified per stuttering symptom type (Kram, Neu, Schröder, et al., 2023). The highly experienced examiner classified more prolongations whilst the less experienced examiner classified more pauses and repetitions as stimulation-induced language disruptions (Kram, Neu, Schröder, et al., 2023). Additionally, the type of stimulation-induced error category both examiners attributed stuttering symptoms to, varied. Still, no response was the only stimulation-induced error category both examiners misassigned stuttering symptoms to, even if this is typically considered the most reliable and crucial error category in stimulation-based language mappings (Ille, Sollmann, Hauck, Maurer, Tanigawa, Obermueller, Negwer, Droese, Boeckh-Behrens, et al., 2015; Sollmann et al., 2013). Thus, speech fluency symptoms substantially decreased the reliability and specificity if analyzed by examiners untrained in stuttering diagnostics.

At the same time, the results of the second study conducted by Kram et al. (2024) supported a high inter-rater agreement for the comprehension-based language mapping results analyzed by two experienced specialists with a background in language science and trained in nTMS mappings. As opposed to the classic language production mapping, the analysis of the CompreTAP setup required the identification of deviant button press behavior. Particularly, selection of wrong target items, searching behavior and no responses were consistently identifiable for patients. While for healthy controls the former two categories also showed a high concordance, the agreement for the few no responses was only fair. Since a large proportion of no responses classified by the SLT were rated as hesitations by the neurolinguist, this discrepancy may be attributable to the co-occurrence of both deviant response behaviors. Despite the overall high agreement for classifying deviant and non-deviant responses across the described error categories, the identification of hesitant response behavior across patients and controls was least reliable. Up to date no system-integrated solutions for measuring response times are readily available within the nTMS system in use. Thus, identifying hesitant or delayed responses during nTMS-based language mapping relies on subjective estimates during the offline video analysis which follows the nTMS mapping. As the added objective reaction time analysis within a third-party program revealed, there was only a slight agreement between delayed responses identified as reaction times exceeding two standard deviation of each subject’s individual response time mean and the subjective hesitation classification by the SLT. Still, the SLT assigned just over a fifth of hesitant responses due to visible response delays, whilst hesitant, halting, or indecisive hand motions preceding a button press were the primary cause for classifying hesitations. Since an intra-subject variability in reaction times throughout the course of the nTMS examination is well established (Sollmann, Ille, et al., 2017), it was additionally evaluated whether items at which the SLT classified a delayed responses exceeded the mean of the last five errorless preceding items by more than two standard deviations. This reaction time analysis considering intra-subject variability revealed a high accordance for controls and perfect agreement for patients (Kram et al., 2024).

While the video-based analysis is required to identify the wealth of errors induced by stimulation, integrating objective reaction time analyses based on intra-subject specific cut-off criteria may enhance the reliable identification of delayed responses and enhance the certainty of examiners during error classification. However, the implementation of this approach in clinical routine would require a reaction time analysis integrated into the nTMS system as the present analysis within a third-party program increased analysis duration on average by 53 minutes for controls and 79 minutes for patients (Kram et al., 2024).

Alternatively, machine learning approaches may also support a more objective classification of errors induced by stimulation in the long run. For this, an extensive data set would be required which provides sufficient data on errors induced by stimulation, symptoms arising from pre-existing speech and language disorders and different dialects and languages as well as a thorough analysis by trained specialists if supervised approaches are applied. Since speech and language disorders express in highly variable and complex forms, it is assumed that a combined approach of an integrated data driven machine learning based analysis and a trained analyzer may substantially support the reliable analysis of language mappings in this patient cohort. Still, even without this objective analysis, the experienced specialists were able to identify stimulation-induced deviant response behavior with high inter-rater reliability.

Consequently, both studies demonstrate the need for skilled specialists trained in speech and language diagnostics and experienced in mapping analysis to improve reliability and specificity of language mappings in patients with pre-existing impairments. This is in line with recommendations for intraoperative awake language testing and standardly employed in large centers (Bertani et al., 2009; Fernandez Coello et al., 2013; Hervey-Jumper et al., 2015; Kelm et al., 2017; National Institute for Health and Care Excellence (NICE), 2018; O'Neill et al., 2020).

4.4 Patient- and deficit-tailored mapping paradigms

Since a large proportion of patients with language eloquent brain tumors present with pre-existing speech or language impairments (IJzerman-Korevaar et al., 2018; Koekkoek et al., 2014; Peeters et al., 2020; Posti et al., 2015), it is crucial to develop tasks and analysis procedures that substantially enhance feasibility and reliability to support the preservation of residual language functionality. The first study indicated that symptoms of speech fluency disorders, even if they manifest randomly and unpredictably, can be carefully differentiated by trained and experienced specialists such as a speech therapist (Kram, Neu, Schröder, et al., 2023). Hence, in this context improved analysis procedures, training of nTMS examiners, employing trained specialists or repeated testing of a cortical site if a random stuttering symptom manifested may improve specificity. Overall, if the speech disorder expresses in mild to moderate degrees, symptoms need to be distinguished but neither the complexity nor the language task need to be adjusted. At the same time, in patients with very severe expressions of speech (fluency) disorders, expressive language mapping paradigms may not be feasible. For instance, in cases with severe dysarthria intelligibility can be reduced to such an extent that the speech output may not be reliably analyzable by the examiner. Simultaneously, in cases with very severe stuttering rates and highly prolonged disruptions in the speech flow, patients may not be able to produce items sufficiently during the time restricted presentation mode. Thus, in these cases alternative language testing paradigms such as the CompreTAP setup presented in the second study (Kram et al., 2024) may provide suitable alternatives. Since, however, none of the patients in the presented cohort showed such severe forms of stuttering, this needs to be evaluated in subsequent studies.

Moreover, as the second study showed, language disorders may require adaptions of tests to fit the residual abilities of patients (Kram et al., 2024). By circumventing the need for verbal responses, the CompreTAP-based mapping allowed for the first time to test and localize language comprehension with nTMS-based language mapping in brain tumor patients with severely impaired language production yet sufficiently preserved comprehension (Kram et al., 2024). Hence, these results underline the necessity to not only select tasks based on lesion location as it is frequently proposed (De Witte et al., 2015; Fernandez Coello et al., 2013), but also consider the individual language profile. Moreover, due to functional reorganization, a specific language function may not necessarily still be allocated to the specific area as would be expected based on healthy data. It is assumed that a specific function is only persisting within the lesion area during the very early stages of left-hemispheric tumor growth (Nieberlein et al. 2023). During progression, the same function may be reorganized to perilesional, extended left-hemispheric or even right-hemispheric homologous areas (Nieberlein et al. 2023). Since the underlying mechanism remain poorly understood and differential effects based on tumor location or volume and its aggressiveness have been proposed (Ille et al., 2019; Pasquini et al., 2023; Southwell et al., 2016; Yuan et al., 2020), the lesion location alone may not be a very suitable indicator for task selection.

The impaired language function may provide some indication as to which language function the lesion area may contribute, and this function may be worthwhile to map. Still, if the impairment is too severe, alternative language tasks are required to at least derive a map of the residual functions and subsequently preserve these during craniotomy. Hence, developing tasks adjusted in linguistic complexity and modality to patients' language abilities is paramount to support the preservation of functionality in aphasic brain tumor patients.

4.5 Limitations and perspectives

The studies presented advanced the understanding of pre-existing speech fluency disorders and the role of trained specialists during stimulation-based language mappings as well as developed and employed patient- and capability-tailored testing paradigms. Still, some limitations and ways to address these in subsequent studies need to be discussed.

Building on the serial cases presented within both studies, larger sample sizes are required in subsequent studies to allow generalizable conclusions. Since acquired stuttering, however, is only rarely described in brain tumor patients (Cruz et al., 2018; Helm et al., 1980; Peters & Turner, 2013) and the prevalence of persistent developmental stuttering in brain tumor patients remains unknown, the presented sample size of six already considerably exceeds previous publications. Moreover, the prevalence of patients with very severe expressive aphasia in language eloquent brain tumor patients is not systematically reported. Studies showed that less than 5.0% up to 22.5% patients present with an aphasia severity that precludes naming-based language mappings (Picht et al., 2006; Sanai et al., 2008). Still, this may not necessarily comprise extremely severe expressive deficits precluding any overt task. Therefore, the second pilot study with six patients with extremely severe expressive aphasia already provided important implications which need to be extended in future studies. Moreover, this task may also be suitable for comparing the neural basis of language production and comprehension in healthy and patient cohorts within subsequent potentially longitudinal studies to shed some light on the exact role and interplay of different network components and potential reorganization mechanisms for different language modalities.

Additionally, neither of the studies presented used standardized testing batteries for assessing the severity and symptom expression of the respective deficit. A thorough standardized testing and diagnosis of individual strengths and difficulties may enable to tailor the subsequent task selection for language mapping to each individual in a more systematic way.

While the mapping of the primary motor area via the elicitation of motor evoked potentials is well established across centers, nTMS-based language mapping is still at a very early stage. Heterogeneous language tasks are emerging, existing ones adapted and advanced to picture the complexity of the language network, linguistic levels and modalities (Hauck et al., 2015; Ohlerth et al., 2020). The predominantly applied language task to date is object naming next to action naming or verb generation (Hauck et al., 2015; Natalizi et al., 2022). The auditory single word comprehension mapping proposed in the second study of this thesis was the first paradigm which allowed comprehension mapping with nTMS in adult brain tumor patients (Kram et al., 2024). Within future studies it may be worthwhile to integrate additional reading and writing tasks into the preoperative nTMS language mapping setup. Whilst reading tasks are easily integrable into the rapid presentation mode (Hauck et al., 2015), writing tasks may be more complex and cumbersome to integrate. However, writing of short sentences during nTMS-based mappings of the supplementary motor area were shown to be feasible (Engelhardt et al., 2023; Schramm et al., 2019). By improving tasks and mapping paradigms for nTMS-based language mappings, we may not only increase reliability and feasibility for individual patients but may also come a step closer to understanding the complexity of the distributed and highly interconnected language network.

What is even more, the button press setup presented may not only be suitable for testing language comprehension, but may also be adjusted to map neurocognitive functions. For instance, the colored button setup may allow to perform an adjusted non-verbal version of the Stroop task (Stroop, 1935). The Stroop task has been integrated into awake surgeries to localize and preserve executive functions (Puglisi et al., 2018; Wager et al., 2013). Since the button press setup does not require overt responses and the hand which is ipsilateral to the stimulated hemisphere can be used, stimulation-induced deviant response behavior could be linked to cognitive interference rather than disruptions of language production or hand motion. Thus, this setup may allow to delineate different language and cognitive functions and advance our understanding of the underlying mechanisms substantially.

5 Summary

5.1 English

Stimulation-based language mappings rely on causally relating disruptions in task performance to the stimulation of a specific cortical site. This becomes challenging in brain tumor patients with preexisting language or speech (fluency) impairments. Depending on the expressed disorder severity, the specificity, reliability or even feasibility of stimulation-based language mappings is significantly affected. Since a large proportion of patients present with preoperative deficits, it is paramount to improve mapping paradigms supporting the preservation of functionality during resections and enhancing the patients' quality of life.

The first study systematically evaluated the impact of preexisting stuttering, expressed in distinctive uncontrollably and randomly manifesting disruptions in the speech flow, on the reliability and specificity of pre- and intraoperative stimulation-based language mapping (Kram, Neu, Schröder, et al., 2023). The core findings showed that examiners without prior training in diagnosing stuttering misclassified many of these stuttering symptoms as stimulation-induced language disruptions and the respective stimulation site as language-relevant. This underlines the necessity of trained specialists for consistent, specific, and reliable language mappings in glioma patients who stutter.

The second study developed a new non-overt comprehension mapping paradigm based on button press responses to enable stimulation-based language mapping in patients with severe expressive aphasia thus far precluded from these mappings (Kram et al., 2024). This mapping setup was feasible in six patients and in 15 healthy controls. With high inter-rater reliability cortical language comprehension-relevant sites, especially in superior and middle temporal as well as inferior frontal areas were identified.

Taken together, both studies demonstrated the direct impact of language and speech (fluency) disorders on the feasibility and results of stimulation-based language mappings. Consequently, thoroughly differentiating speech (fluency) and aphasic symptoms from stimulation-induced disruptions in task performance by trained and experienced specialists, as well as employing tasks adjusted to the patient's language capabilities, is crucial for reliable and specific language mappings. This may substantially support the preservation of language functionality while advancing the understanding of cortical and subcortical language network components in patients with language and speech disorders.

5.2 German

Stimulationsbasierte Sprachkartierungen stellen einen kausalen Zusammenhang zwischen transientem Sprachfehler und der Stimulation eines bestimmten kortikalen Areals her. Dies ist jedoch bei Hirntumorpatientinnen und -patienten mit vorbestehenden Sprach-, Sprech- oder Redeflussstörungen herausfordernd. Abhängig vom Störungsschweregrad ist die Spezifität, Zuverlässigkeit oder sogar die Durchführbarkeit stimulationsbasierter Sprachkartierungen erheblich eingeschränkt. Da ein großer Anteil der Betroffenen bereits präoperativ Defizite aufweist, müssen die Kartierungsverfahren verbessert werden, um die Funktionalität während Resektionen zu erhalten und die Lebensqualität maßgeblich zu verbessern.

Die erste Studie untersuchte systematisch den Einfluss präoperativen Stotterns, welches sich in charakteristischen unkontrollierbaren und zufällig auftretenden Unterbrechungen im Redefluss äußert, auf die Reliabilität und Spezifität prä- und intraoperativer stimulationsbasierter Sprachkartierungen (Kram, Neu, Schröder, et al., 2023). Die zentralen Ergebnisse zeigten, dass Auswertende, welche unerfahren in der Diagnose von Stottern waren, viele der Stottersymptome fälschlicherweise als stimulationsinduzierte Sprachfehler und somit die entsprechenden Stimulationsareale als sprachrelevant einstuften. Deshalb braucht es für eine konsistente, spezifische und zuverlässige Sprachkartierung bei stotternden Gliompatientinnen und -patienten geschulte Spezialistinnen und Spezialisten.

Die zweite Studie entwickelte ein neues Paradigma für Sprachverständniskartierungen, welches auf nicht-verbalen Antworten via Tastendruck basierte (Kram et al., 2024). Dies zielte darauf ab, stimulationsbasierte Sprachkartierungen bei Patientinnen und Patienten mit ausgeprägter expressiver Aphasie zuzulassen, welche bisher von solchen Kartierungen ausgeschlossen waren. Dieses Kartierungs-Setup war bei sechs Patientinnen und Patienten und 15 gesunden Kontrollpersonen möglich. Mit hoher Inter-Rater-Reliabilität wurden für das Sprachverständnis relevante Areale identifiziert, insbesondere in superioren und medialen temporalen sowie in inferioren frontalen Arealen.

Zusammenfassend demonstrieren beide Studien den direkten Einfluss von Sprach-, Sprech- und Redeflussstörungen auf die Durchführbarkeit und Ergebnisse stimulationsbasierter Sprachkartierungen. Daher ist für zuverlässige und spezifische Sprachkartierungen eine sorgfältige Differenzierung zwischen Symptomen vorbestehender Störungen und stimulationsinduzierten Fehlern in der Testdurchführung in enger Zusammenarbeit mit geschulten und erfahrenen Expertinnen und Experten sowie die Verwendung von Testparadigmen, welche an die residualen Sprachfähigkeiten angepasst sind, entscheidend. Dies kann den Erhalt der Sprachfunktionalität wesentlich unterstützen und gleichzeitig das Verständnis über kortikale und subkortikale Sprachnetzwerk-Komponenten bei Patientinnen und Patienten mit Sprach- und Sprechstörungen maßgeblich verbessern.

6 References

Ackermann, H. et al. (2018). Neurogene Sprechstörungen (Dysarthrien), S1-Leitlinie [Neurogenic speech disorders (dysarthrias), S1 guideline]. In Deutsche Gesellschaft für Neurologie (Ed.), *Leitlinien für Diagnostik und Therapie in der Neurologie [guidelines for diagnosis and therapy in neurology]*. www.dgn.org/leitlinien (accessed on 26.04.2023)

Al-Adli, N. N., Young, J. S., Sibih, Y. E., & Berger, M. S. (2023). Technical Aspects of Motor and Language Mapping in Glioma Patients. *Cancers 15*(7), 2173. https://doi.org/10.3390/cancers15072173

Alarcon, G., Bird Pedersen, M., Juarez-Torrejon, N., Martin-Lopez, D., Ughratdar, I., Selway, R. P., & Valentin, A. (2019). The Single Word Auditory Comprehension (SWAC) test: A simple method to identify receptive language areas with electrical stimulation. *Epilepsy Behav*, *90*, 266-272. https://doi.org/10.1016/j.yebeh.2018.10.022

Assaf, Y., & Pasternak, O. (2008). Diffusion tensor imaging (DTI)-based white matter mapping in brain research: a review. *J Mol Neurosci*, *34*(1), 51-61. https://doi.org/10.1007/s12031-007-0029-0

Awiszus, F. (2003). TMS and threshold hunting. *Suppl Clin Neurophysiol*, *56*, 13-23. https://doi.org/10.1016/s1567-424x(09)70205-3

Banerjee, P., Leu, K., Harris, R. J., Cloughesy, T. F., Lai, A., Nghiemphu, P. L., Pope, W. B., Bookheimer, S. Y., & Ellingson, B. M. (2015). Association between lesion location and language function in adult glioma using voxel-based lesion-symptom mapping. *Neuroimage Clin*, *9*, 617-624. https://doi.org/10.1016/j.nicl.2015.10.010

Bangdiwala, S. I. (1988). *The Agreement Chart*. The University of North Carolina.

Bangdiwala, S. I., & Shankar, V. (2013). The agreement chart. *BMC Med Res Methodol*, *13*, 97. https://doi.org/10.1186/1471-2288-13-97

Bara, B. G., Enrici, I., & Adenzato, M. (2016). At the Core of Pragmatics. In G. Hickok & S. L. Small (Eds.), *Neurobiology of Language* (pp. 675-685). Academic Press, Elsevier. https://doi.org/10.1016/b978-0-12-407794-2.00054-7

Barker, A. T., Jalinous, R., & Freeston, I. L. (1985). Non-invasive magnetic stimulation of human motor cortex. *Lancet*, *325*(8437), 1106-1107. https://doi.org/https://doi.org/10.1016/S0140-6736(85)92413-4

Bartholow, R. (1874). Art. I.— Experimental Investigations into the Functions of the Human Brain. *Am J Med Sci*, *66*(134), 305-313.

Bello, L., Gallucci, M., Fava, M., Carrabba, G., Giussani, C., Acerbi, F., Baratta, P., Songa, V., Conte, V., Branca, V., Stocchetti, N., Papagno, C., & Gaini, S. M. (2007). Intraoperative subcortical language tract mapping guides surgical removal of gliomas involving speech areas. *Neurosurgery*, *60*(1), 67-82. https://doi.org/10.1227/01.NEU.0000249206.58601.DE

Bernstein Ratner, N., & MacWhinney, B. (2018). Fluency Bank: A new resource for fluency research and practice. *J Fluency Disord*, *56*, 69-80. https://doi.org/10.1016/j.jfludis.2018.03.002

Bertani, G., Fava, E., Casaceli, G., Carrabba, G., Casarotti, A., Papagno, C., Castellano, A., Falini, A., Gaini, S. M., & Bello, L. (2009). Intraoperative mapping and monitoring of brain functions for the resection of low-grade gliomas: Technical considerations. *Neurosurg Focus*, *27*(4), E4. https://doi.org/10.3171/2009.8.FOCUS09137

Binder, J. R. (2017). Current Controversies on Wernicke's Area and its Role in Language. *Curr Neurol Neurosci Rep*, *17*(8), 58. https://doi.org/10.1007/s11910-017-0764-8

Bloodstein, O., Ratner, N. B., & Brundage, S. B. (2021). *A Handbook on Stuttering.* (7th ed.). Plural Publishing, Inc.

Boersma, P., & Weenink, D. (2023). Praat: doing phonetics by computer [Computer program]. Version 6.3.04. *retrieved 24 January 2023 from* http://www.praat.org/.

Bornkessel, I., Zysset, S., Friederici, A. D., von Cramon, D. Y., & Schlesewsky, M. (2005). Who did what to whom? The neural basis of argument hierarchies during language comprehension. *NeuroImage*, *26*(1), 221-233. https://doi.org/10.1016/j.neuroimage.2005.01.032

Briganti, C., Sestieri, C., Mattei, P. A., Esposito, R., Galzio, R. J., Tartaro, A., Romani, G. L., & Caulo, M. (2012). Reorganization of functional connectivity of the language network in patients with brain gliomas. *AJNR Am. J. Neuroradiol.*, *33*(10), 1983-1990. https://doi.org/10.3174/ajnr.A3064

Broca, P. (1861). Perte de la parole: ramollissement chronique et destruction partielle du lobe anterieur gauche du cerveau [Loss of speech: chronic softening and partial destruction of the left anterior lobe of the brain]. *Bulletins de la Societe d'anthropologie*, *1re serie*(2), 235–238.

Brown, T. J., Brennan, M. C., Li, M., Church, E. W., Brandmeir, N. J., Rakszawski, K. L., Patel, A. S., Rizk, E. B., Suki, D., Sawaya, R., & Glantz, M. (2016). Association of the Extent of Resection With Survival in Glioblastoma: A Systematic Review and Meta-analysis. *JAMA Oncol*, *2*(11), 1460-1469. https://doi.org/10.1001/jamaoncol.2016.1373

Castrillon, G., Sollmann, N., Kurcyus, K., Razi, A., Krieg, S. M., & Riedl, V. (2020). The physiological effects of noninvasive brain stimulation fundamentally differ across the human cortex. *Sci Adv*, *6*(5), eaay2739. https://doi.org/10.1126/sciadv.aay2739

Catani, M., Jones, D. K., & Ffytche, D. H. (2005). Perisylvian language networks of the human brain. *Ann Neurol*, *57*(1), 8-16. https://doi.org/10.1002/ana.20319

Caverzasi, E., Hervey-Jumper, S. L., Jordan, K. M., Lobach, I. V., Li, J., Panara, V., Racine, C. A., Sankaranarayanan, V., Amirbekian, B., Papinutto, N., Berger, M. S., & Henry, R. G. (2016). Identifying preoperative language tracts and predicting postoperative functional recovery using HARDI q-ball fiber tractography in patients with gliomas. *J Neurosurg*, *125*(1), 33-45. https://doi.org/10.3171/2015.6.JNS142203

Cercignani, M., & Horsfield, M. A. (2001). The physical basis of diffusion-weighted MRI. *J Neurol Sci*, *186*, 11-14. https://doi.org/https://doi.org/10.1016/S0022-510X(01)00486-5

Chang, E. F., Raygor, K. P., & Berger, M. S. (2015). Contemporary model of language organization: An overview for neurosurgeons. *J Neurosurg*, *122*(2), 250-261. https://doi.org/10.3171/2014.10.JNS132647

Cirillo, S., Caulo, M., Pieri, V., Falini, A., & Castellano, A. (2019). Role of Functional Imaging Techniques to Assess Motor and Language Cortical Plasticity in Glioma Patients: A Systematic Review. *Neural Plast*, *2019*, 4056436. https://doi.org/10.1155/2019/4056436

Clavreul, A., Aubin, G., Delion, M., Lemee, J. M., Ter Minassian, A., & Menei, P. (2021). What effects does awake craniotomy have on functional and survival outcomes for glioblastoma patients? *J Neurooncol*, *151*(2), 113-121. https://doi.org/10.1007/s11060-020-03666-7

Coget, A., Deverdun, J., Bonafé, A., van Dokkum, L., Duffau, H., Molino, F., Le Bars, E., & de Champfleur, N. M. (2018). Transient immediate postoperative homotopic functional disconnectivity in low-grade glioma patients. *NeuroImage: Clinical*, *18*, 656-662. https://doi.org/10.1016/j.nicl.2018.02.023

Comeau, R. (2014). Neuronavigation for Transcranial Magnetic Stimulation. In A. Rotenberg, J. C. Horvath, & A. Pascual-Leone (Eds.), *Transcranial Magnetic Stimulation* (pp. 31-56). Humana Press, Springer. https://doi.org/10.1007/978-1-4939-0879-0

Corina, D. P., Gibson, E. K., Martin, R., Poliakov, A., Brinkley, J., & Ojemann, G. A. (2005). Dissociation of action and object naming: evidence from cortical stimulation mapping. *Hum Brain Mapp*, *24*(1), 1-10. https://doi.org/10.1002/hbm.20063

Corina, D. P., Loudermilk, B. C., Detwiler, L., Martin, R. F., Brinkley, J. F., & Ojemann, G. (2010). Analysis of naming errors during cortical stimulation mapping: implications for models of language representation. *Brain Lang*, *115*(2), 101-112. https://doi.org/10.1016/j.bandl.2010.04.001

Corrivetti, F., de Schotten, M. T., Poisson, I., Froelich, S., Descoteaux, M., Rheault, F., & Mandonnet, E. (2019). Dissociating motor-speech from lexico-semantic systems in the left frontal lobe: insight from a series of 17 awake intraoperative mappings in glioma patients. *Brain Struct Funct*, *224*(3), 1151-1165. https://doi.org/10.1007/s00429-019-01827-7

Craig-McQuaide, A., Akram, H., Zrinzo, L., & Tripoliti, E. (2014). A review of brain circuitries involved in stuttering. *Front Hum Neurosci*, *8*, 884. https://doi.org/10.3389/fnhum.2014.00884

Cruz, C., Amorim, H., Beca, G., & Nunes, R. (2018). Neurogenic stuttering: a review of the literature. Tartamudez neurogena: revision de la bibliografia. *Rev Neurol*, *66*(2), 59-64. https://doi.org/10.33588/rn.6602.2017151

Cullen, C. L., & Young, K. M. (2016). How Does Transcranial Magnetic Stimulation Influence Glial Cells in the Central Nervous System? *Front Neural Circuits*, *10*, 26. https://doi.org/10.3389/fncir.2016.00026

Curran, K. M., Emsell, L., & Leemans, A. (2016). Quantitative DTI Measures. In W. Van Hecke, L. Emsell, & S. Sunaert (Eds.), *Diffusion Tensor Imaging: A Practical Handbook* (pp. 65-87). Springer. https://doi.org/10.1007/978-1-4939-3118-7_5

Cushing, H. (1909). A note upon the faradic stimulation of the postcentral gyrus in conscious patients. *Brain*, *32*, 44-53. https://doi.org/https://doi.org/10.1093/brain/32.1.44

Davis, M. H. (2016). The Neurobiology of Lexical Access. In G. Hickok & S. L. Small (Eds.), *Neurobiology of Language* (pp. 541-555). Academic Press, Elsevier. https://doi.org/10.1016/b978-0-12-407794-2.00044-4

de Figueiredo, E. H., Borgonovi, A. F., & Doring, T. M. (2011). Basic concepts of MR imaging, diffusion MR imaging, and diffusion tensor imaging. *Magn Reson Imaging Clin N Am*, *19*(1), 1-22. https://doi.org/10.1016/j.mric.2010.10.005

De Witt Hamer, P. C., Robles, S. G., Zwinderman, A. H., Duffau, H., & Berger, M. S. (2012). Impact of intraoperative stimulation brain mapping on glioma surgery outcome: A meta-analysis. *J Clin Oncol*, *30*(20), 2559–2565. https://doi.org/10.1200/JCO.2011.38.4818

De Witte, E., Satoer, D., Robert, E., Colle, H., Verheyen, S., Visch-Brink, E., & Marien, P. (2015). The Dutch Linguistic Intraoperative Protocol: a valid linguistic approach to awake brain surgery. *Brain Lang*, *140*, 35-48. https://doi.org/10.1016/j.bandl.2014.10.011

Deras, P., Moulinie, G., Maldonado, I. L., Moritz-Gasser, S., Duffau, H., & Bertram, L. (2012). Intermittent general anesthesia with controlled ventilation for asleep-awake-asleep brain surgery: a prospective series of 140 gliomas in eloquent areas. *Neurosurgery*, *71*(4), 764-771. https://doi.org/10.1227/NEU.0b013e3182647ab8

Deverdun, J., van Dokkum, L. E. H., Le Bars, E., Herbet, G., Mura, T., D'agata, B., Picot, M. C., Menjot, N., Molino, F., Duffau, H., & Moritz Gasser, S. (2020). Language reorganization after resection of low-grade gliomas: an fMRI task based connectivity study. *Brain Imaging Behav*, *14*(5), 1779-1791. https://doi.org/10.1007/s11682-019-00114-7

DeWitt, I., & Rauschecker, J. P. (2013). Wernicke's Area Revisited: Parallel Streams and Word Processing. *Brain Lang*, *127*(2), 181-191. https://doi.org/10.1016/j.bandl.2013.09.014

Dick, A. S., & Tremblay, P. (2012). Beyond the arcuate fasciculus: Consensus and controversy in the connectional anatomy of language. *Brain*, *135*(12), 3529-3550. https://doi.org/10.1093/brain/aws222

Donders-Kamphuis, M., Vincent, A., Schouten, J., Smits, M., Docter-Kerkhof, C., Dirven, C., Kloet, A., Nandoe Tewarie, R., & Satoer, D. (2023). Feasibility of awake brain surgery in glioblastoma patients with severe aphasia: Five case illustrations. *Aphasiology*, *37*(12), 1944-1963. https://doi.org/10.1080/02687038.2022.2137773

Dronkers, N. F., Plaisant, O., Iba-Zizen, M. T., & Cabanis, E. A. (2007). Paul Broca's historic cases: high resolution MR imaging of the brains of Leborgne and Lelong. *Brain*, *130*(5), 1432-1441. https://doi.org/10.1093/brain/awm042

Duffau, H. (2006). New concepts in surgery of WHO grade II gliomas: Functional brain mapping, connectionism and plasticity - A review. *J Neuro-Oncol*, *79*(1), 77-115. https://doi.org/10.1007/s11060-005-9109-6

Duffau, H. (2016). White Matter Pathways in the Human. In G. Hickok & S. L. Small (Eds.), *Neurobiology of Language* (pp. 129-137). Academic Press, Elsevier. https://doi.org/10.1016/b978-0-12-407794-2.00011-0

Duffau, H. (2020). Functional mapping before and after low-grade glioma surgery: A new way to decipher various spatiotemporal patterns of individual neuroplastic potential in brain tumor patients. *Cancers*, *12*(9), 2611. https://doi.org/10.3390/cancers12092611

Duffau, H., Moritz-Gasser, S., & Mandonnet, E. (2014). A re-examination of neural basis of language processing: Proposal of a dynamic hodotopical model from data provided by brain stimulation mapping during picture naming. *Brain Lang*, *131*, 1-10. https://doi.org/10.1016/j.bandl.2013.05.011

Duffy, J. R. (2016). Functional speech disorders: clinical manifestations, diagnosis, and management. In M. Hallett, J. Stone, & A. Carson (Eds.), *Handbook of Clinical Neurology* (Vol. 139, pp. 379-388). Elsevier. https://doi.org/10.1016/B978-0-12-801772-2.00033-3

Eckstein, K., & Friederici, A. D. (2006). It's early: event-related potential evidence for initial interaction of syntax and prosody in speech comprehension. *J Cogn Neurosci*, *18*(10), 1696-1711. https://doi.org/10.1162/jocn.2006.18.10.1696

Enderby, P. (2013). Disorders of communication: dysarthria. In M. P. Barnes & D. C. Good (Eds.), *Handbook of Clinical Neurology* (Vol. 110, pp. 273-281). Elsevier B.V. https://doi.org/10.1016/B978-0-444-52901-5.00022-8

Engelhardt, M., Kern, G., Karhu, J., & Picht, T. (2023). Protocol for mapping of the supplementary motor area using repetitive navigated transcranial magnetic stimulation. *Front Neurosci*, *17*, 1185483. https://doi.org/10.3389/fnins.2023.1185483

Epstein, C. M. (1998). Transcranial magnetic stimulation: language function. *J Clin Neurophysiol*, *15*(4), 325-332. https://doi.org/10.1097/00004691-199807000-00004

Epstein, C. M., Lah, J. J., Meador, K., Weissman, J. D., Gaitan, L. E., & Dihenia, B. (1996). Optimum stimulus parameters for lateralized suppression of speech with magnetic brain stimulation. *Neurology*, *47*(6), 1590-1593. https://doi.org/10.1212/wnl.47.6.1590

Etchell, A. C., Civier, O., Ballard, K. J., & Sowman, P. F. (2018). A systematic literature review of neuroimaging research on developmental stuttering between 1995 and 2016. *J Fluency Disord*, *55*, 6-45. https://doi.org/10.1016/j.jfludis.2017.03.007

Ettinger, G. J., Leventon, M. E., Grimson, W. E. L., Kikinis, R., Gugino, L., Cote, W., Sprung, L., Aglio, L., Shenton, M. E., Potts, G., Hernandez, V. L., & Alexander, E. (1998). Experimentation with transcranial magnetic stimulation system for functional brain mapping. *Med. Image Anal*, *2*(2), 133-142. https://doi.org/10.1016/S1361-8415(98)80008-X

Faraday, M. (1832). Experimental researches in electricity. *Phil. Trans. R. Soc. Lond.*, *122*, 125–162. https://doi.org/https://doi.org/10.1098/rstl.1832.0006

Fernandez Coello, A., Moritz-Gasser, S., Martino, J., Martinoni, M., Matsuda, R., & Duffau, H. (2013). Selection of intraoperative tasks for awake mapping based on relationships between tumor location and functional networks. *J Neurosurg*, *119*(6), 1380-1394. https://doi.org/10.3171/2013.6.JNS122470

Ferrier, D. (1886). *The functions of the brain* (2 ed.). Smith, Elder. https://doi.org/https://doi.org/10.1037/12860-000

Fiore, G., Abete-Fornara, G., Forgione, A., Tariciotti, L., Pluderi, M., Borsa, S., Bana, C., Cogiamanian, F., Vergari, M., Conte, V., Caroli, M., Locatelli, M., & Bertani, G. A. (2022). Indication and eligibility of glioma patients for awake surgery: A scoping review by a multidisciplinary perspective. *Front Oncol*, *12*, 951246. https://doi.org/10.3389/fonc.2022.951246

Fisicaro, R. A., Jost, E., Shaw, K., Brennan, N. P., Peck, K. K., & Holodny, A. I. (2016). Cortical Plasticity in the Setting of Brain Tumors. *Top Magn Reson Imaging*, *25*(1), 25-30. https://doi.org/10.1097/RMR.0000000000000077

Fridriksson, J., Fillmore, P., Guo, D., & Rorden, C. (2015). Chronic Broca's Aphasia Is Caused by Damage to Broca's and Wernicke's Areas. *Cereb Cortex*, *25*(12), 4689-4696. https://doi.org/10.1093/cercor/bhu152

Friederici, A. D. (2002). Towards a neural basis of auditory sentence processing. *Trends Cogn Sci 6*(2), 78-84. https://doi.org/10.1016/s1364-6613(00)01839-8

Friederici, A. D. (2011). The brain basis of language processing: from structure to function. *Physiol Rev*, *91*(4), 1357-1392. https://doi.org/10.1152/physrev.00006.2011

Friederici, A. D. (2012). The cortical language circuit: from auditory perception to sentence comprehension. *Trends Cogn Sci*, *16*(5), 262-268. https://doi.org/10.1016/j.tics.2012.04.001

Friederici, A. D. (2015). White-matter pathways for speech and language processing. In M. J. Aminoff, F. Boller, & D. F. Swaab (Eds.), *Handbook of Clinical Neurology: The Human Auditory System Fundamental Organization and Clinical Disorders* (1 ed., Vol. 129, pp. 177-186). Elsevier B.V. https://doi.org/10.1016/B978-0-444-62630-1.00010-X

Friederici, A. D. (2017). *Language in our Brain: The Origins of a uniquely human capacity*. MIT Press.

Fritsch, G., & Hitzig, E. (1870). Über die elektrische Erregbarkeit des Grosshirns [About the electrical excitability of the cerebrum]. *Arch Anat Physiol Wissenschaftl Med*, *37*, 300-332.

Gamer, M., Lemon, J., & Singh, I. F. P. (2019). *irr: Various Coefficients of Interrater Reliability and Agreement. R package version 0.84.1*. https://CRAN.R-project.org/package=irr

Geschwind, N. (1965). Disconnexion syndromes in animals and man. I. *Brain*, *88*(2), 237-294. https://doi.org/10.1093/brain/88.2.237

Geschwind, N. (1972). Language and the brain. *Sci Am*, *226*(4), 76-83. https://doi.org/10.1038/scientificamerican0472-76

Getz, L. M., & Toscano, J. C. (2021). The time-course of speech perception revealed by temporally-sensitive neural measures. *Wiley Interdiscip Rev Cogn Sci*, *12*(2), e1541. https://doi.org/10.1002/wcs.1541

Giussani, C., Roux, F. E., Ojemann, J., Sganzerla, E. P., Pirillo, D., & Papagno, C. (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*(1), 113-120. https://doi.org/10.1227/01.NEU.0000360392.15450.C9

Glover, G. H. (2011). Overview of functional magnetic resonance imaging. *Neurosurg Clin N Am*, *22*(2), 133-139. https://doi.org/10.1016/j.nec.2010.11.001

Gogos, A. J., Young, J. S., Morshed, R. A., Hervey-Jumper, S. L., & Berger, M. S. (2020). Awake glioma surgery: technical evolution and nuances. *J Neurooncol*, *147*(3), 515-524. https://doi.org/10.1007/s11060-020-03482-z

Grünbaum, A. S. F., & Sherrington, C. S. (1902). Observations on the physiology of the cerebral cortex of some of the higher apes. *Proc R Soc Lond*, *69*(451-458), 206–209. https://doi.org/https://doi.org/10.1098/rspl.1901.0100

Hagoort, P., Hald, L., Bastiaansen, M., & Petersson, K. M. (2004). Integration of word meaning and world knowledge in language comprehension. *Science*, *304*(5669), 438-441. https://doi.org/10.1126/science.1095455

Hannula, H., & Ilmoniemi, R. J. (2017). Basic Principles of Navigated TMS. In S. M. Krieg (Ed.), *Navigated Transcranial Magnetic Stimulation in Neurosurgery* (pp. 3-30). Springer.

Hartwigsen, G., & Saur, D. (2019). Neuroimaging of stroke recovery from aphasia - Insights into plasticity of the human language network. *NeuroImage*, *190*, 14-31. https://doi.org/10.1016/j.neuroimage.2017.11.056

Hauck, T., Tanigawa, N., Probst, M., Wohlschlaeger, A., Ille, S., Sollmann, N., Maurer, S., Zimmer, C., Ringel, F., Meyer, B., & Krieg, S. M. (2015). Task type affects location of language-positive cortical regions by repetitive navigated transcranial magnetic stimulation mapping. *PLoS ONE*, *10*(4), e0125298. https://doi.org/10.1371/journal.pone.0125298

Helm, N. A., Butler, R. B., & Canter, G. J. (1980). Neurogenic Acquired Stuttering. *J Fluency Disord*, *5*(3), 269-279. https://doi.org/10.1016/0094-730X(80)90032-7

Hervey-Jumper, S. L., & Berger, M. S. (2016). Maximizing safe resection of low- and high-grade glioma. *J Neuro-Oncol*, *130*(2), 269-282. https://doi.org/10.1007/s11060-016-2110-4

Hervey-Jumper, S. L., Li, J., Lau, D., Molinaro, A. M., Perry, D. W., Meng, L., & Berger, M. S. (2015). Awake craniotomy to maximize glioma resection: Methods and technical nuances over a 27-year period. *J Neurosurg*, *123*(2), 325-339. https://doi.org/10.3171/2014.10.JNS141520

Heuer, R. J., Sataloff, R. T., Mandel, S., & Travers, N. (1996). Neurogenic stuttering: further corroboration of site of lesion *Ear Nose Throat J*, *75*(3), 161-168.

Hickok, G., & Poeppel, D. (2004). Dorsal and ventral streams: a framework for understanding aspects of the functional anatomy of language. *Cognition*, *92*(1-2), 67-99. https://doi.org/10.1016/j.cognition.2003.10.011

Hickok, G., & Poeppel, D. (2016). Neural Basis of Speech Perception. In G. Hickok & S. L. Small (Eds.), *Neurobiology of Language* (pp. 299-310). Academic Press, Elsevier. https://doi.org/10.1016/b978-0-12-407794-2.00025-0

Holodny, A. I., Schulder, M., Liu, W. C., Wolko, J., Maldjian, J. A., & Kalnin, A. J. (2000). The effect of brain tumors on BOLD functional MR Imaging activation in the adjacent motor cortex: implications for image-guided neurosurgery. *AJNR Am J Neuroradiol*, *21*(8), 1415-1422.

Horsley, V. (1909). The Linacre Lecture on the function of the so-called motor area of the brain. *Br Med J 2*(2533), 121-132.

Huber, W., Poeck, K., & Springer, L. (1983). *Aachener Aphasietest (AAT)*. Hogrefe.

Idsardi, W. J., & Monahan, P. J. (2016). Phonology. In G. Hickok & S. L. Small (Eds.), *Neurobiology of Language* (pp. 141-151). Academic Press, Elsevier. https://doi.org/10.1016/b978-0-12-407794-2.00012-2

IJzerman-Korevaar, M., Snijders, T. J., de Graeff, A., Teunissen, S., & de Vos, F. Y. F. (2018). Prevalence of symptoms in glioma patients throughout the disease trajectory: a systematic review. *J Neurooncol*, *140*(3), 485-496. https://doi.org/10.1007/s11060-018-03015-9

Ille, S., Engel, L., Albers, L., Schroeder, A., Kelm, A., Meyer, B., & Krieg, S. M. (2019). Functional reorganization of cortical language function in glioma patients-a preliminary study. *Front Oncol*, *9*, 446. https://doi.org/10.3389/fonc.2019.00446

Ille, S., Kulchytska, N., Sollmann, N., Wittig, R., Beurskens, E., Butenschoen, V. M., Ringel, F., Vajkoczy, P., Meyer, B., Picht, T., & Krieg, S. M. (2016). Hemispheric language dominance measured by repetitive navigated transcranial magnetic stimulation and postoperative course of language function in brain tumor patients. *Neuropsychologia*, *91*, 50-60. https://doi.org/10.1016/j.neuropsychologia.2016.07.025

Ille, S., Schroeder, A., Albers, L., Kelm, A., Droese, D., Meyer, B., & Krieg, S. M. (2021). Non-invasive mapping for effective preoperative guidance to approach highly language-eloquent gliomas—a large scale comparative cohort study using a new classification for language eloquence. *Cancers*, *13*(2), 207. https://doi.org/10.3390/cancers13020207

Ille, S., Sollmann, N., Butenschoen, V. M., Meyer, B., Ringel, F., & Krieg, S. M. (2016). Resection of highly language-eloquent brain lesions based purely on rTMS language mapping without awake surgery. *Acta Neurochir*, *158*(12), 2265-2275. https://doi.org/10.1007/s00701-016-2968-0

Ille, S., Sollmann, N., Hauck, T., Maurer, S., Tanigawa, N., Obermueller, T., Negwer, C., Droese, D., Boeckh-Behrens, T., Meyer, B., Ringel, F., & Krieg, S. M. (2015). Impairment of preoperative language mapping by lesion location: a functional magnetic resonance imaging, navigated transcranial magnetic stimulation, and direct cortical stimulation study. *J Neurosurg*, *123*(2), 314-324. https://doi.org/10.3171/2014.10.JNS141582

Ille, S., Sollmann, N., Hauck, T., Maurer, S., Tanigawa, N., Obermueller, T., Negwer, C., Droese, D., Zimmer, C., Meyer, B., Ringel, F., & Krieg, S. M. (2015). Combined noninvasive language mapping by navigated transcranial magnetic stimulation and functional MRI and its comparison with direct cortical stimulation. *J Neurosurg*, *123*(1), 212-225. https://doi.org/10.3171/2014.9.JNS14929

Ilmberger, J., Ruge, M., Kreth, F. W., Briegel, J., Reulen, H. J., & Tonn, J. C. (2008). Intraoperative mapping of language functions: a longitudinal neurolinguistic analysis. *J Neurosurg*, *109*(4), 583-592. https://doi.org/10.3171/JNS/2008/109/10/0583

Indefrey, P. (2011). The spatial and temporal signatures of word production components: A critical update. *Front Psychol*, *2*, 1-16. https://doi.org/10.3389/fpsyg.2011.00255

Indefrey, P., & Levelt, W. J. M. (2004). The spatial and temporal signatures of word production components. *Cognition*, *92*(1-2), 101-144. https://doi.org/10.1016/j.cognition.2002.06.001

Ius, T., Angelini, E., Thiebaut de Schotten, M., Mandonnet, E., & Duffau, H. (2011). Evidence for potentials and limitations of brain plasticity using an atlas of functional resectability of WHO grade II gliomas: Towards a "minimal common brain". *NeuroImage*, *56*(3), 992-1000. https://doi.org/10.1016/j.neuroimage.2011.03.022

Jeltema, H. R., Ohlerth, A. K., de Wit, A., Wagemakers, M., Rofes, A., Bastiaanse, R., & Drost, G. (2021). Comparing navigated transcranial magnetic stimulation mapping and "gold standard" direct cortical stimulation mapping in neurosurgery: a systematic review. *Neurosurg Rev*, *44*(4), 1903-1920. https://doi.org/10.1007/s10143-020-01397-x

Jennum, P., Friberg, L., Fuglsang-Frederiksen, A., & Dam, M. (1994). Speech localization using repetitive transcranial magnetic stimulation. *Neurology*, *44*(2), 269-273. https://doi.org/10.1212/wnl.44.2.269

Jodzio, A., Piai, V., Verhagen, L., Cameron, I., & Indefrey, P. (2023). Validity of chronometric TMS for probing the time-course of word production: a modified replication. *Cereb Cortex*(12), 7816–7829. https://doi.org/10.1093/cercor/bhad081

Junuzovic-Zunic, L., Sinanovic, O., & Majic, B. (2021). Neurogenic Stuttering: Etiology, Symptomatology, and Treatment. *Med Arch*, *75*(6), 456-461. https://doi.org/10.5455/medarh.2021.75.456-461

Kasselimis, D. S., Simos, P. G., Peppas, C., Evdokimidis, I., & Potagas, C. (2017). The unbridged gap between clinical diagnosis and contemporary research on aphasia: A short discussion on the validity and clinical utility of taxonomic categories. *Brain Lang*, *164*, 63-67. https://doi.org/10.1016/j.bandl.2016.10.005

Kelm, A., Sollmann, N., Ille, S., Meyer, B., Ringel, F., & Krieg, S. M. (2017). Resection of Gliomas with and without Neuropsychological Support during Awake Craniotomy-Effects on Surgery and Clinical Outcome. *Front Oncol*, *7*, 176. https://doi.org/10.3389/fonc.2017.00176

Kemerdere, R., de Champfleur, N. M., Deverdun, J., Cochereau, J., Moritz-Gasser, S., Herbet, G., & Duffau, H. (2016). Role of the left frontal aslant tract in stuttering: a brain stimulation and tractographic study. *J Neurol*, *263*(1), 157-167. https://doi.org/10.1007/s00415-015-7949-3

Kent, R. D. (2000). Research on speech motor control and its disorders: a review and prospective. *J Commun Disord*, *33*(5), 391-428. https://doi.org/10.1016/s0021-9924(00)00023-x

Kertesz, A. (2007). *WAB-R : Western Aphasia Battery-Revised*. The Psychological Corporation.

Klaus, J., & Hartwigsen, G. (2019). Dissociating semantic and phonological contributions of the left inferior frontal gyrus to language production. *Hum Brain Mapp*, *40*(11), 3279-3287. https://doi.org/10.1002/hbm.24597

Klomjai, W., Katz, R., & Lackmy-Vallee, A. (2015). Basic principles of transcranial magnetic stimulation (TMS) and repetitive TMS (rTMS). *Ann Phys Rehabil Med*, *58*(4), 208-213. https://doi.org/10.1016/j.rehab.2015.05.005

Koekkoek, J. A., Dirven, L., Sizoo, E. M., Pasman, H. R., Heimans, J. J., Postma, T. J., Deliens, L., Grant, R., McNamara, S., Stockhammer, G., Medicus, E., Taphoorn, M. J., & Reijneveld, J. C. (2014). Symptoms and medication management in the end of life phase of high-grade glioma patients. *J Neurooncol*, *120*(3), 589-595. https://doi.org/10.1007/s11060-014-1591-2

Kram, L., Neu, B., Ohlerth, A. K., Schroeder, A., Meyer, B., Krieg, S. M., & Ille, S. (2023). The impact of linguistic complexity on feasibility and reliability of language mapping in aphasic glioma patients [Manuscript submitted for publication].

Kram, L., Neu, B., Schröder, A., Meyer, B., Krieg, S. M., & Ille, S. (2023). Improving specificity of stimulation-based language mapping in stuttering glioma patients: a mixed methods serial case study. *Heliyon*, *9*(11), e21984. https://doi.org/10.1016/j.heliyon.2023.e21984

Kram, L., Ohlerth, A. K., Ille, S., Meyer, B., & Krieg, S. M. (2024). CompreTAP: Feasibility and Reliability of a New Language Comprehension Mapping Task via Preoperative Navigated Transcranial Magnetic Stimulation. *Cortex*, *171*, 347-369. https://doi.org/10.1016/j.cortex.2023.09.023

Krieg, S. M., Lioumis, P., Mäkelä, J. P., Wilenius, J., Karhu, J., Hannula, H., Savolainen, P., Lucas, C. W., Seidel, K., Laakso, A., Islam, M., Vaalto, S., Lehtinen, H., Vitikainen, A. M., Tarapore, P. E., & Picht, T. (2017). Protocol for motor and language mapping by navigated TMS in patients and healthy volunteers; workshop report. *Acta Neurochir*, *159*(7), 1187-1195. https://doi.org/10.1007/s00701-017-3187-z

Krieg, S. M., Shiban, E., Buchmann, N., Gempt, J., Foerschler, A., Meyer, B., & Ringel, F. (2012). Utility of presurgical navigated transcranial magnetic brain stimulation for the resection of tumors in eloquent motor areas: Clinical article. *J Neurosurg*, *116*(5), 994-1001. https://doi.org/10.3171/2011.12.JNS111524

Krieg, S. M., Shiban, E., Buchmann, N., Meyer, B., & Ringel, F. (2013). Presurgical navigated transcranial magnetic brain stimulation for recurrent gliomas in motor eloquent areas. *Clin Neurophysiol*, *124*(3), 522-527. https://doi.org/10.1016/j.clinph.2012.08.011

Krieg, S. M., Sollmann, N., Tanigawa, N., Foerschler, A., Meyer, B., & Ringel, F. (2016). Cortical distribution of speech and language errors investigated by visual object naming and navigated transcranial magnetic stimulation. *Brain Struct Funct*, *221*(4), 2259-2286. https://doi.org/10.1007/s00429-015-1042-7

Krieg, S. M., Tarapore, P. E., Picht, T., Tanigawa, N., Houde, J., Sollmann, N., Meyer, B., Vajkoczy, P., Berger, M. S., Ringel, F., & Nagarajan, S. (2014). Optimal timing of pulse onset for language mapping with navigated repetitive transcranial magnetic stimulation. *NeuroImage*, *100*, 219-236. https://doi.org/10.1016/j.neuroimage.2014.06.016

Landis, J. R., & Koch, G. G. (1977). The Measurement of Observer Agreement for Categorical Data. *Biometrics*, *33*(1), 159-174. https://doi.org/10.2307/2529310

Levelt, W. J. M. (2013). *A history of Psycholinguistics: The Pre-Chomskyan Era*. Oxford University Press. https://doi.org/https://doi.org/10.1093/acprof:oso/9780199653669.001.0001

Leyton, A. S. F., & Sherrington, C. S. (1917). Observations on the Excitable Cortex of the Chimpanzee, Orang-Utan, and Gorilla. *Quarterly Journal of Experimental Physiology*, *11*(2), 135-222. https://doi.org/10.1113/expphysiol.1917.sp000240

Lichtheim, L. (1885). On Aphasia. *Brain*, *7*(4), 433-484. https://doi.org/ https://doi.org/10.1093/brain/7.4.433

Lioumis, P., Zhdanov, A., Mäkelä, N., Lehtinen, H., Wilenius, J., Neuvonen, T., Hannula, H., Deletis, V., Picht, T., & Mäkelä, J. P. (2012). A novel approach for documenting naming errors induced by navigated transcranial magnetic stimulation. *J Neurosci Methods*, *204*(2), 349-354. https://doi.org/10.1016/j.jneumeth.2011.11.003

Logan, K. J. (2022). Acquired Stuttering. In K. J. Logan (Ed.), *Fluency Disorders: Stuttering, Cluttering, and Related Fleuncy Problems, Second Edition* (2nd ed., pp. 211-225). Plural Publishing, Inc.

Lundgren, K., Helm-Estabrooks, N., & Klein, R. (2010). Stuttering Following Acquired Brain Damage: A Review of the Literature. *J Neurolinguistics*, *23*(5), 447-454. https://doi.org/10.1016/j.jneuroling.2009.08.008

MacWhinney, B. (2000). *The CHILDES Project: Tools for Analyzing Talk.* (3rd ed.). Mahwah, NJ: Lawrence Erlbaum Associates. https://doi.org/10.21415/3mhn-0z89

Mäkelä, J. P., & Laakso, A. (2017). nTMS Language Mapping: Basic Principles and Clinical Use. In S. M. Krieg (Ed.), *Navigated Transcranial Magnetic Stimulation in Neurosurgery* (pp. 131-150). Springer. https://doi.org/10.1007/978-3-319-54918-7

Mandonnet, E., Winkler, P. A., & Duffau, H. (2010). Direct electrical stimulation as an input gate into brain functional networks: Principles, advantages and limitations. *Acta Neurochir*, *152*(2), 185-193. https://doi.org/10.1007/s00701-009-0469-0

Martin-Monzon, I., Rivero Ballagas, Y., & Arias-Sanchez, S. (2022). Language mapping: A systematic review of protocols that evaluate linguistic functions in awake surgery. *Appl Neuropsychol Adult*, *29*(4), 845-854. https://doi.org/10.1080/23279095.2020.1776287

Matchin, W., den Ouden, D.-B., Hickok, G., Hillis, A. E., Bonilha, L., & Fridriksson, J. (2022). The Wernicke conundrum revisited: evidence from connectome-based lesionsymptom mapping in post-stroke aphasia. *Brain*, *145*(11), 3916-3930. https://doi.org/10.1093/brain/awac219

Matchin, W., Ouden, D. D., Hickok, G., Hillis, A. E., Bonilha, L., & Fridriksson, J. (2023). Reply: The Wernicke conundrum is misinterpreted. *Brain*, *146*(4), e23-e24. https://doi.org/10.1093/brain/awac483

Maurer, S., Giglhuber, K., Sollmann, N., Kelm, A., Ille, S., Hauck, T., Tanigawa, N., Ringel, F., Boeckh-Behrens, T., Meyer, B., & Krieg, S. M. (2017). Non-invasive Mapping of Face Processing by Navigated Transcranial Magnetic Stimulation. *Front Hum Neurosci*, *11*, 4. https://doi.org/10.3389/fnhum.2017.00004

Maurer, S., Tanigawa, N., Sollmann, N., Hauck, T., Ille, S., Boeckh-Behrens, T., Meyer, B., & Krieg, S. M. (2016). Non-invasive mapping of calculation function by repetitive navigated transcranial magnetic stimulation. *Brain Struct Funct*, *221*(8), 3927-3947. https://doi.org/10.1007/s00429-015-1136-2

Mesulam, M., Thompson, C., Weintraub, S., & Rogalski, E. (2023). The Wernicke conundrum is misinterpreted. *Brain*, *146*(4), e21-e22. https://doi.org/10.1093/brain/awac482

Mesulam, M. M., Thompson, C. K., Weintraub, S., & Rogalski, E. J. (2015). The Wernicke conundrum and the anatomy of language comprehension in primary progressive aphasia. *Brain*, *138*(8), 2423-2437. https://doi.org/10.1093/brain/awv154

Mofatteh, M., Mashayekhi, M. S., Arfaie, S., Chen, Y., Hendi, K., Kwan, A. T. H., Honarvar, F., Solgi, A., Liao, X., & Ashkan, K. (2023). Stress, Anxiety, and Depression Associated With Awake Craniotomy: A Systematic Review. *Neurosurgery*, *92*(2), 225-240. https://doi.org/10.1227/neu.0000000000002224

Mori, S., & Zhang, J. (2006). Principles of diffusion tensor imaging and its applications to basic neuroscience research. *Neuron*, *51*(5), 527-539. https://doi.org/10.1016/j.neuron.2006.08.012

Morshed, R. A., Young, J. S., Lee, A. T., Berger, M. S., & Hervey-Jumper, S. L. (2021). Clinical Pearls and Methods for Intraoperative Awake Language Mapping. *Neurosurgery*, *89*(2), 143-153. https://doi.org/10.1093/neuros/nyaa440

Moses, M. S., Nickels, L. A., & Sheard, C. (2004). Disentangling the web: neologistic perseverative errors in jargon aphasia. *Neurocase*, *10*(6), 452-461. https://doi.org/10.1080/13554790490894057

Mukherjee, P., Berman, J. I., Chung, S. W., Hess, C. P., & Henry, R. G. (2008). Diffusion tensor MR imaging and fiber tractography: theoretic underpinnings. *AJNR Am J Neuroradiol*, *29*(4), 632-641. https://doi.org/10.3174/ajnr.A1051

Müller-Dahlhaus, F., & Vlachos, A. (2013). Unraveling the cellular and molecular mechanisms of repetitive magnetic stimulation. *Front Mol Neurosci*, *6*, 50. https://doi.org/10.3389/fnmol.2013.00050

Natalizi, F., Piras, F., Vecchio, D., Spalletta, G., & Piras, F. (2022). Preoperative Navigated Transcranial Magnetic Stimulation: New Insight for Brain Tumor-Related Language Mapping. *J Pers Med*, *12*(10), 1589. https://doi.org/10.3390/jpm12101589

National Institute for Health and Care Excellence (NICE). (2018). Brain tumours (primary) and brain metastases in adults. NICE guidelines. Retrieved 3 January 2022 from https://www.nice.org.uk/guidance/ng99.

Negwer, C., Ille, S., Hauck, T., Sollmann, N., Maurer, S., Kirschke, J. S., Ringel, F., Meyer, B., & Krieg, S. M. (2017). Visualization of subcortical language pathways by diffusion tensor imaging fiber tracking based on rTMS language mapping. *Brain Imaging Behav*, *11*(3), 899-914. https://doi.org/10.1007/s11682-016-9563-0

Negwer, C., Sollmann, N., Ille, S., Hauck, T., Maurer, S., Kirschke, J. S., Ringel, F., Meyer, B., & Krieg, S. M. (2017). Language pathway tracking: comparing nTMS-based DTI fiber tracking with a cubic ROIs-based protocol. *J Neurosurg*, *126*(3), 1006-1014. https://doi.org/10.3171/2016.2.JNS152382

Neumann, K., Euler, H. A., Bosshardt, H. G., Cook, S., Sandrieser, P., Schneider, P., Sommer, M., Thum, G., & * (Hrsg.: Deutsche Gesellschaft für Phoniatrie und Pädaudiologie). (2016). Pathogenese, Diagnostik und Behandlung von Redeflussstörungen. Evidenz- und konsensbasierte S3-Leitlinie [Pathogenesis, diagnostic and treatment of speech fluency disorders. Evidence- and consensus-based S3-guidelines], AWMF-Registernummer 049-013, Version 1. 2016; http://www.awmf.org/leitlinien/detail/ll/049-013.html. Gelesen am 01.09.2016 *im Auftrag der Leitliniengruppe.

Nieberlein, L., Rampp, S., Gussew, A., Prell, J., & Hartwigsen, G. (2023). Reorganization and Plasticity of the Language Network in Patients with Cerebral Gliomas. *Neuroimage Clin*, *37*, 103326. https://doi.org/10.1016/j.nicl.2023.103326

Nossek, E., Matot, I., Shahar, T., Barzilai, O., Rapoport, Y., Gonen, T., Sela, G., Grossman, R., Korn, A., Hayat, D., & Ram, Z. (2013). Intraoperative seizures during awake craniotomy: incidence and consequences: analysis of 477 patients. *Neurosurgery*, *73*(1), 135-140. https://doi.org/10.1227/01.neu.0000429847.91707.97

O'Neill, M., Henderson, M., Duffy, O. M., & Kernohan, W. G. (2020). The emerging contribution of speech and language therapists in awake craniotomy: a national survey of their roles, practices and perceptions. *Int J Lang Commun Disord*, *55*(1), 149-162. https://doi.org/10.1111/1460-6984.12510

Ogawa, S., Lee, T. M., Kay, A. R., & Tank, D. W. (1990). Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proc. Natl. Acad. Sci. USA*, *87*(24), 9868-9872. https://doi.org/10.1073/pnas.87.24.9868

Ogawa, S., Lee, T. M., Nayak, A. S., & Glynn, P. (1990). Oxygenation-sensitive contrast in magnetic resonance image of rodent brain at high magnetic fields. *Magn Reson Med*, *14*(1), 68-78. https://doi.org/10.1002/mrm.1910140108

Ohlerth, A.-K., Bastiaanse, R., Negwer, C., Sollmann, N., Schramm, S., Schröder, A., & Krieg, S. M. (2021). Bihemispheric Navigated Transcranial Magnetic Stimulation Mapping for Action Naming Compared to Object Naming in Sentence Context. *Brain Sci*, *11*(9), 1190. https://doi.org/10.3390/brainsci11091190

Ohlerth, A. K., Valentin, A., Vergani, F., Ashkan, K., & Bastiaanse, R. (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*(2), 397-406. https://doi.org/10.1007/s00701-019-04159-x

Ojemann, G., Ojemann, J., Lettich, E., & Berger, M. (1989). Cortical language localization in left, dominant hemisphere. An electrical stimulation mapping investigation in 117 patients. *J Neurosurg*, *71*(3), 316-326. https://doi.org/10.3171/jns.1989.71.3.0316

Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychol*, *9*(1), 97-113. https://doi.org/10.1016/0028-3932(71)90067-4

Pak, R. W., Hadjiabadi, D. H., Senarathna, J., Agarwal, S., Thakor, N. V., Pillai, J. J., & Pathak, A. P. (2017). Implications of neurovascular uncoupling in functional magnetic resonance imaging (fMRI) of brain tumors. *J Cereb Blood Flow Metab*, *37*(11), 3475-3487. https://doi.org/10.1177/0271678X17707398

Pascual-Leone, A., Gates, J. R., & Dhuna, A. (1991). Induction of speech arrest and counting errors with rapid-rate transcranial magnetic stimulation. *Neurology*, *41*(5), 697-702. https://doi.org/10.1212/wnl.41.5.697

Pasquini, L., Yildirim, O., Silveira, P., Tamer, C., Napolitano, A., Lucignani, M., Jenabi, M., Peck, K. K., & Holodny, A. (2023). Effect of tumor genetics, pathology, and location on fMRI of language reorganization in brain tumor patients. *Eur Radiol*, *33*, 6069–6078. https://doi.org/10.1007/s00330-023-09610-3

Peeters, M. C. M., Dirven, L., Koekkoek, J. A. F., Gortmaker, E. G., Fritz, L., Vos, M. J., & Taphoorn, M. J. B. (2020). Prediagnostic symptoms and signs of adult glioma: the patients' view. *J Neurooncol*, *146*(2), 293-301. https://doi.org/10.1007/s11060-019-03373-y

Penfield, W., & Erickson, T. C. (1941). *Epilepsy and cerebral localization*. Charles C. Thomas.

Penfield, W., & Rasmussen, T. (1950). *The cerebral cortex of man: A clinical study of localization of function*. The Macmillan Company.

Penfield, W., & Roberts, L. (1959). *Speech and Brain Mechanisms*. Princton University Press. https://doi.org/http://www.jstor.org/stable/j.ctt7ztt6j

Peters, K. B., & Turner, S. (2013). Acquired stuttering due to recurrent anaplastic astrocytoma. *BMJ Case Rep*. https://doi.org/10.1136/bcr-2013-009562

Picht, T. (2014). Current and potential utility of transcranial magnetic stimulation in the diagnostics before brain tumor surgery. *CNS Oncol*, *3*(4), 299-310. https://doi.org/10.2217/cns.14.25

Picht, T., Kombos, T., Gramm, H. J., Brock, M., & Suess, O. (2006). Multimodal protocol for awake craniotomy in language cortex tumour surgery. *Acta Neurochir*, *148*(2), 127-138. https://doi.org/10.1007/s00701-005-0706-0

Picht, T., Krieg, S. M., Sollmann, N., Rösler, J., Niraula, B., Neuvonen, T., Savolainen, P., Lioumis, P., Mäkelä, J. P., Deletis, V., Meyer, B., Vajkoczy, P., & Ringel, F. (2013). A comparison of language mapping by preoperative navigated transcranial magnetic stimulation and direct cortical stimulation during awake surgery. *Neurosurg*, *72*(5), 808-819. https://doi.org/10.1227/NEU.0b013e3182889e01

Picht, T., Schulz, J., Hanna, M., Schmidt, S., Suess, O., & Vajkoczy, P. (2012). Assessment of the influence of navigated transcranial magnetic stimulation on surgical planning for tumors in or near the motor cortex. *Neurosurgery*, *70*(5), 1248-1256; discussion 1256-1247. https://doi.org/10.1227/NEU.0b013e318243881e

Pillai, J. J., & Zaca, D. (2011). Clinical utility of cerebrovascular reactivity mapping in patients with low grade gliomas. *World J Clin Oncol*, *2*(12), 397-403. https://doi.org/10.5306/wjco.v2.i12.397

Posti, J. P., Bori, M., Kauko, T., Sankinen, M., Nordberg, J., Rahi, M., Frantzen, J., Vuorinen, V., & Sipila, J. O. (2015). Presenting symptoms of glioma in adults. *Acta Neurol Scand*, *131*(2), 88-93. https://doi.org/10.1111/ane.12285

Puglisi, G., Sciortino, T., Rossi, M., Leonetti, A., Fornia, L., Conti Nibali, M., Casarotti, A., Pessina, F., Riva, M., Cerri, G., & Bello, L. (2018). Preserving executive functions in nondominant frontal lobe glioma surgery: an intraoperative tool. *J Neurosurg*, *131*(2), 474-480. https://doi.org/10.3171/2018.4.JNS18393

Pylkkänen, L. (2016). Composition of Complex Meaning. In G. Hickok & S. L. Small (Eds.), *Neurobiology of Language* (pp. 621-631). Academic Press, Elsevier. https://doi.org/10.1016/b978-0-12-407794-2.00050-x

R Core Team. (2020). *R: A language and environment for statistical computing*. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/

Raffa, G., Conti, A., Scibilia, A., Sindorio, C., Quattropani, M. C., Visocchi, M., Germano, A., & Tomasello, F. (2017). Functional Reconstruction of Motor and Language Pathways Based on Navigated Transcranial Magnetic Stimulation and DTI Fiber Tracking for the Preoperative Planning of Low Grade Glioma Surgery: A New Tool for Preservation and Restoration of Eloquent Networks. *Acta Neurochir Suppl*, *124*, 251-261. https://doi.org/10.1007/978-3-319-39546-3_37

Raffa, G., Quattropani, M. C., & Germanò, A. (2019). When imaging meets neurophysiology: The value of navigated transcranial magnetic stimulation for preoperative neurophysiological mapping prior to brain tumor surgery. *Neurosurg Focus*, *47*(6), E10. https://doi.org/10.3171/2019.9.FOCUS19640

Raichle, M. E. (2006). Functional Neuroimaging: A Historical and Physiological Perspective. In R. Cabeza & A. Kingstone (Eds.), *Handbook of Functional Neuroimaging of Cognition* (2 ed., pp. 3-20). Boston Review. https://doi.org/https://doi-org.eaccess.tum.edu/10.7551/mitpress/3420.003.0003

Raichle, M. E. (2009). A brief history of human brain mapping. *Trends Neurosci*, *32*(2), 118-126. https://doi.org/10.1016/j.tins.2008.11.001

Rauschecker, J. P., & Scott, S. K. (2009). Maps and streams in the auditory cortex: nonhuman primates illuminate human speech processing. *Nat Neurosci*, *12*(6), 718-724. https://doi.org/10.1038/nn.2331

Rejnö-Habte Selassie, G., Pegenius, G., Karlsson, T., Viggedal, G., Hallböök, T., & Elam, M. (2020). Cortical mapping of receptive language processing in children using navigated transcranial magnetic stimulation. *Epilepsy Behav*, *103*(Pt A), 106836. https://doi.org/10.1016/j.yebeh.2019.106836

Roca, E., Pallud, J., Guerrini, F., Panciani, P. P., Fontanella, M., & Spena, G. (2020). Stimulation-related intraoperative seizures during awake surgery: a review of available evidences. *Neurosurg Rev*, *43*(1), 87-93. https://doi.org/10.1007/s10143-019-01214-0

Rofes, A., Spena, G., Miozzo, A., Fontanella, M. M., & Miceli, G. (2015). Advantages and disadvantages of intraoperative language tasks in awake surgery: a three-task approach for prefrontal tumors *J Neurosurg Sci*, *59*(4), 337-349.

Rösler, J., Niraula, B., Strack, V., Zdunczyk, A., Schilt, S., Savolainen, P., Lioumis, P., Mäkelä, J., Vajkoczy, P., Frey, D., & Picht, T. (2014). Language mapping in healthy volunteers and brain tumor patients with a novel navigated TMS system: Evidence of tumor-induced plasticity. *Clin Neurophysiol*, *125*(3), 526-536. https://doi.org/10.1016/j.clinph.2013.08.015

Rossi, S., Antal, A., Bestmann, S., Bikson, M., Brewer, C., Brockmoller, J., Carpenter, L. L., Cincotta, M., Chen, R., Daskalakis, J. D., Di Lazzaro, V., Fox, M. D., George, M. S., Gilbert, D., Kimiskidis, V. K., Koch, G., Ilmoniemi, R. J., Lefaucheur, J. P., Leocani, L., . . . basis of this article began with a Consensus Statement from the IFCN Workshop on "Present Future of TMS Safety: Ethical Guidelines" Siena October 17-20 2018 updating through April 2020. (2021). Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: Expert Guidelines. *Clin Neurophysiol*, *132*(1), 269-306. https://doi.org/10.1016/j.clinph.2020.10.003

Rossi, S., Hallett, M., Rossini, P. M., Pascual-Leone, A., & Safety of TMS Consensus Group. (2009). Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol*, *120*(12), 2008-2039. https://doi.org/10.1016/j.clinph.2009.08.016

Rossini, P. M., Burke, D., Chen, R., Cohen, L. G., Daskalakis, Z., Di Iorio, R., Di Lazzaro, V., Ferreri, F., Fitzgerald, P. B., George, M. S., Hallett, M., Lefaucheur, J. P., Langguth, B., Matsumoto, H., Miniussi, C., Nitsche, M. A., Pascual-Leone, A., Paulus, W., Rossi, S., . . . Ziemann, U. (2015). Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: Basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee. *Clin Neurophysiol*, *126*(6), 1071-1107. https://doi.org/10.1016/j.clinph.2015.02.001

Roux, F. E., Miskin, K., Durand, J. B., Sacko, O., Rehault, E., Tanova, R., & Demonet, J. F. (2015). Electrostimulation mapping of comprehension of auditory and visual words. *Cortex*, *71*, 398-408. https://doi.org/10.1016/j.cortex.2015.07.001

Sanai, N., Mirzadeh, Z., & Berger, M. S. (2008). Functional Outcome after Language Mapping for Glioma Resection. *N Engl J Med*, *358*(1), 18-27. https://doi.org/10.1056/nejmoa067819

Sander, R. W., & Osborne, C. A. (2019). Stuttering: Understanding and Treating a Common Disability. *Am Fam Physician*, *100*(9), 556-560.

Saur, D., & Hartwigsen, G. (2012). Neurobiology of language recovery after stroke: Lessons from neuroimaging studies. *Archives of Physical Medicine and Rehabilitation*, *93*(1 SUPPL.), S15-S25. https://doi.org/10.1016/j.apmr.2011.03.036

Schramm, S., Albers, L., Ille, S., Schroder, A., Meyer, B., Sollmann, N., & Krieg, S. M. (2019). Navigated transcranial magnetic stimulation of the supplementary motor cortex disrupts fine motor skills in healthy adults. *Sci Rep*, *9*(1), 17744. https://doi.org/10.1038/s41598-019-54302-y

Schramm, S., Tanigawa, N., Tussis, L., Meyer, B., Sollmann, N., & Krieg, S. M. (2020). Capturing multiple interaction effects in L1 and L2 object-naming reaction times in healthy bilinguals: a mixed-effects multiple regression analysis. *BMC Neurosci*, *21*(1), 3. https://doi.org/10.1186/s12868-020-0549-x

Schreiber, A., Hubbe, U., Ziyeh, S., & Hennig, J. (2000). The Influence of Gliomas and Nonglial Space-occupying Lesions on Blood-oxygen-level–dependent Contrast Enhancement. *AJNR Am J Neuroradiol 21*(6), 1055–1063.

Schwarzer, V., Bährend, I., Rosenstock, T., Dreyer, F. R., Vajkoczy, P., & Picht, T. (2018). Aphasia and cognitive impairment decrease the reliability of rnTMS language mapping. *Acta Neurochir*, *160*(2), 343-356. https://doi.org/10.1007/s00701-017-3397-4

Sheppard, S. M., & Sebastian, R. (2021). Diagnosing and managing post-stroke aphasia. *Expert Rev Neurother*, *21*(2), 221-234. https://doi.org/10.1080/14737175.2020.1855976

Siddiqi, S. H., Kording, K. P., Parvizi, J., & Fox, M. D. (2022). Causal mapping of human brain function. *Nat Rev Neurosci*, *23*(6), 361-375. https://doi.org/10.1038/s41583-022-00583-8

Sollmann, N., Fuss-Ruppenthal, S., Zimmer, C., Meyer, B., & Krieg, S. M. (2018). Investigating stimulation protocols for language mapping by repetitive navigated transcranial magnetic stimulation. *Front Behav Neurosci*, *12*, 197. https://doi.org/10.3389/fnbeh.2018.00197

Sollmann, N., Goblirsch-Kolb, M. F., Ille, S., Butenschoen, V. M., Boeckh-Behrens, T., Meyer, B., Ringel, F., & Krieg, S. M. (2016). Comparison between electric-field-navigated and line-navigated TMS for cortical motor mapping in patients with brain tumors. *Acta Neurochir*, *158*(12), 2277-2289. https://doi.org/10.1007/s00701-016-2970-6

Sollmann, N., Hauck, T., Hapfelmeier, A., Meyer, B., Ringel, F., & Krieg, S. M. (2013). Intra- and interobserver variability of language mapping by navigated transcranial magnetic brain stimulation. *BMC Neurosci*, *14*, 150. https://doi.org/10.1186/1471-2202-14-150

Sollmann, N., Ille, S., Negwer, C., Boeckh-Behrens, T., Ringel, F., Meyer, B., & Krieg, S. M. (2017). Cortical time course of object naming investigated by repetitive navigated transcranial magnetic stimulation. *Brain Imaging Behav*, *11*(4), 1192-1206. https://doi.org/10.1007/s11682-016-9574-x

Sollmann, N., Kelm, A., Ille, S., Schroder, A., Zimmer, C., Ringel, F., Meyer, B., & Krieg, S. M. (2018). Setup presentation and clinical outcome analysis of treating highly language-eloquent gliomas via preoperative navigated transcranial magnetic stimulation and tractography. *Neurosurg Focus*, *44*(6), E2. https://doi.org/10.3171/2018.3.FOCUS1838

Sollmann, N., Kubitscheck, A., Maurer, S., Ille, S., Hauck, T., Kirschke, J. S., Ringel, F., Meyer, B., & Krieg, S. M. (2016). Preoperative language mapping by repetitive navigated transcranial magnetic stimulation and diffusion tensor imaging fiber tracking and their comparison to intraoperative stimulation. *Neuroradiology*, *58*(8), 807-818. https://doi.org/10.1007/s00234-016-1685-y

Sollmann, N., Negwer, C., Ille, S., Maurer, S., Hauck, T., Kirschke, J. S., Ringel, F., Meyer, B., & Krieg, S. M. (2016). Feasibility of nTMS-based DTI fiber tracking of language pathways in neurosurgical patients using a fractional anisotropy threshold. *J Neurosci Methods*, *267*, 45-54. https://doi.org/10.1016/j.jneumeth.2016.04.002

Sollmann, N., Tanigawa, N., Bulubas, L., Sabih, J., Zimmer, C., Ringel, F., Meyer, B., & Krieg, S. M. (2017). Clinical Factors Underlying the Inter-individual Variability of the Resting Motor Threshold in Navigated Transcranial Magnetic Stimulation Motor Mapping. *Brain Topogr*, *30*(1), 98-121. https://doi.org/10.1007/s10548-016-0536-9

Sollmann, N., Zhang, H., Fratini, A., Wildschuetz, N., Ille, S., Schroder, A., Zimmer, C., Meyer, B., & Krieg, S. M. (2020). Risk Assessment by Presurgical Tractography Using Navigated TMS Maps in Patients with Highly Motor- or Language-Eloquent Brain Tumors. *Cancers*, *12*(5), 1264. https://doi.org/10.3390/cancers12051264

Sollmann, N., Zhang, H., Schramm, S., Ille, S., Negwer, C., Kreiser, K., Meyer, B., & Krieg, S. M. (2020). Function-specific Tractography of Language Pathways Based on nTMS Mapping in Patients with Supratentorial Lesions. *Clin Neuroradiol*, *30*(1), 123-135. https://doi.org/10.1007/s00062-018-0749-2

Southwell, D. G., Hervey-Jumper, S. L., Perry, D. W., & Berger, M. S. (2016). Intraoperative mapping during repeat awake craniotomy reveals the functional plasticity of adult cortex. *J Neurosurg*, *124*(5), 1460-1469. https://doi.org/10.3171/2015.5.JNS142833

Sprouse, J., & Hornstein, N. (2016). Syntax and the Cognitive Neuroscience of Syntactic Structure Building. In G. Hickok & S. L. Small (Eds.), *Neurobiology of Language* (pp. 165-174). Academic Press, Elsevier. https://doi.org/10.1016/b978-0-12-407794-2.00014-6

Stejskal, E. O., & Tanner, J. E. (1965). Spin Diffusion Measurements: Spin Echoes in the Presence of a Time‐Dependent Field Gradient. *J Chem Phys*, *42*(1), 288-292. https://doi.org/10.1063/1.1695690

Stockert, A., Wawrzyniak, M., Klingbeil, J., Wrede, K., Kümmerer, D., Hartwigsen, G., Kaller, C. P., Weiller, C., & Saur, D. (2020). Dynamics of language reorganization after left temporo-parietal and frontal stroke. *Brain*, *143*(3), 844-861. https://doi.org/10.1093/brain/awaa023

Stroop, J. R. (1935). Studies of interference in serial verbal reactions. *J Exp Psychol*, *18*(6), 643–662. https://doi.org/10.1037/h0054651

Talacchi, A., Santini, B., Casagrande, F., Alessandrini, F., Zoccatelli, G., & Squintani, G. M. (2013). Awake surgery between art and science. Part I: clinical and operative settings. *Funct Neurol*, *28*(3), 205-221. https://doi.org/10.11138/FNeur/2013.28.3.205

Talacchi, A., Santini, B., Casartelli, M., Monti, A., Capasso, R., & Miceli, G. (2013). Awake surgery between art and science. Part II: language and cognitive mapping. *Funct Neurol*, *28*(3), 223-239. https://doi.org/10.11138/FNeur/2013.28.3.223

Tarapore, P. E., Findlay, A. M., Honma, S. M., Mizuiri, D., Houde, J. F., Berger, M. S., & Nagarajan, S. S. (2013). Language mapping with navigated repetitive TMS: Proof of technique and validation. *NeuroImage*, *82*, 260-272. https://doi.org/10.1016/j.neuroimage.2013.05.018

Tarapore, P. E., Picht, T., Bulubas, L., Shin, Y., Kulchytska, N., Meyer, B., Berger, M. S., Nagarajan, S. S., & Krieg, S. M. (2016). Safety and tolerability of navigated TMS for preoperative mapping in neurosurgical patients. *Clin Neurophysiol*, *127*(3), 1895-1900. https://doi.org/10.1016/j.clinph.2015.11.042

Tichenor, S. E., & Yaruss, J. S. (2021). Variability of Stuttering: Behavior and Impact. *Am J Speech Lang Pathol*, *30*(1), 75-88. https://doi.org/10.1044/2020_AJSLP-20-00112

Tremblay, P., Deschamps, I., & Gracco, V. L. (2016). Neurobiology of Speech Production. In G. Hickok & S. L. Small (Eds.), *Neurobiology of Language* (pp. 741-750). Academic Press, Elsevier. https://doi.org/10.1016/b978-0-12-407794-2.00059-6

Tremblay, P., & Dick, A. S. (2016). Broca and Wernicke are dead, or moving past the classic model of language neurobiology. *Brain Lang*, *162*, 60-71. https://doi.org/10.1016/j.bandl.2016.08.004

Tremblay, P., Dick, A. S., & Small, S. L. (2011). New insights into the neurobiology of language from functional brain imaging. In H. Duffau (Ed.), *Brain Mapping: From Neural Basis of Cognition to Surgical Applications* (pp. 131-143). SpringerWienNewYork.

Tuncer, M. S., Salvati, L. F., Grittner, U., Hardt, J., Schilling, R., Bährend, I., Silva, L. L., Fekonja, L. S., Faust, K., Vajkoczy, P., Rosenstock, T., & Picht, T. (2021). Towards a tractography-based risk stratification model for language area associated gliomas. *NeuroImage: Clinical*, *29*, 102541. https://doi.org/10.1016/j.nicl.2020.102541

Turken, A. U., & Dronkers, N. F. (2011). The neural architecture of the language comprehension network: converging evidence from lesion and connectivity analyses. *Front Syst Neurosci*, *5*. https://doi.org/10.3389/fnsys.2011.00001

Ulmer, J. L., Krouwer, H. G., Mueller, W. M., Ugurel, M. S., Kocak, M., & Mark, L. P. (2003). Pseudo-reorganization of language cortical function at fMRI Imaging: A consequence of tumor-induced neurovascular uncoupling. *AJNR Am J Neuroradiol*, *24*(2), 213-217.

Wager, M., Du Boisgueheneuc, F., Pluchon, C., Bouyer, C., Stal, V., Bataille, B., Guillevin, C. M., & Gil, R. (2013). Intraoperative monitoring of an aspect of executive functions: administration of the Stroop test in 9 adult patients during awake surgery for resection of frontal glioma. *Oper Neurosurg*, *72*, ons169-181. https://doi.org/10.1227/NEU.0b013e31827bf1d6

Wernicke, C. (1874). *Der aphasische Symptomencomplex. Eine psychologische Studie auf anatomischer Basis [The aphasic symptom-complex: a psychological study on an anatomical basis]*. Breslau: Max Cohn & Weigert.

Winston, G. P. (2012). The physical and biological basis of quantitative parameters derived from diffusion MRI. *Quant Imaging Med Surg*, *2*(4), 254-265. https://doi.org/10.3978/j.issn.2223-4292.2012.12.05

Wise, R. J. S., & Price, C. J. (2006). Functional Neuroimaging of Language. In R. Cabeza & A. Kingstone (Eds.), *Handbook of Functional Neuroimaging of Cognition* (2 ed., pp. 191–227). Boston Review. https://doi.org/https://doi-org.eaccess.tum.edu/10.7551/mitpress/3420.001.0001

Yairi, E., & Ambrose, N. (2013). Epidemiology of stuttering: 21st century advances. *J Fluency Disord*, *38*(2), 66-87. https://doi.org/10.1016/j.jfludis.2012.11.002

Yuan, B., Zhang, N., Yan, J., Cheng, J., Lu, J., & Wu, J. (2020). Tumor grade-related language and control network reorganization in patients with left cerebral glioma. *Cortex*, *129*, 141-157. https://doi.org/10.1016/j.cortex.2020.04.015

Zaca, D., Jovicich, J., Nadar, S. R., Voyvodic, J. T., & Pillai, J. J. (2014). Cerebrovascular reactivity mapping in patients with low grade gliomas undergoing presurgical sensorimotor mapping with BOLD fMRI. *J Magn Reson Imaging*, *40*(2), 383-390. https://doi.org/10.1002/jmri.24406

Zetterling, M., Elf, K., Semnic, R., Latini, F., & Engstrom, E. R. (2020). Time course of neurological deficits after surgery for primary brain tumours. *Acta Neurochir 162*(12), 3005-3018. https://doi.org/10.1007/s00701-020-04425-3

Ziegler, W., & Staiger, A. (2016). Motor Speech Impairments. In G. Hickok & S. L. Small (Eds.), *Neurobiology of Language* (pp. 985-994). Academic Press, Elsevier. https://doi.org/10.1016/b978-0-12-407794-2.00078-x

Zulko. (2020). *MoviePy [Python module for video editing]* (Vol. Accessed on 19th May 2023). https://github.com/Zulko/moviepy.

7 Abbreviations

AAT	Aachener Aphasietest
AF	Fasciculus Arcuatus
anG	Gyrus angularis
aSMG	anterior Supramarginal Gyrus
aSTG	anterior Superior Temporal Gyrus
BOLD	Blood Oxygen Level-Dependent
CompreTAP	Comprehension TAsk for Perioperative mapping
DES	Direct Electrical Stimulation
dPoG	dorsal Postcentral Gyrus
dPrG	dorsal Precentral Gyrus
DICOM	Digital Imaging and Communications in Medicine
DTI	Diffusion Tensor Imaging
FA	Fractional Anisotropy
fMRI	functional Magnetic Resonance Imaging
IFG	Inferior Frontal Gyrus
IFOF	Inferior Fronto Occipital Fasciculus
ILF	Inferior Longitudinal Fasciculus
MEP	Motor Evoked Potential
mMFG	middle Middle Frontal Gyrus
mMTG	middle Middle Temporal Gyrus
mPoG	middle Postcentral Gyrus
mPrG	middle Precentral Gyrus
MRI	Magnetic Resonance Imaging
mSFG	middle Superior Frontal Gyrus
mSTG	middle Superior Temporal Gyrus
nTMS	navigated Transcranial Magnetic Stimulation
opIFG	opercular Inferior Frontal Gyrus
pMFG	posterior Middle Frontal Gyrus
pMTG	posterior Middle Temporal Gyrus
pSFG	posterior Superior Frontal Gyrus
pSMG	posterior Supramarginal Gyrus
pSTG	posterior Superior Temporal Gyrus
rMT	resting Motor Threshold

SLF	Superior Longitudinal Fasciculus
SLT	Speech and Language Therapist
SPL	Superior Parietal Lobe
TE	Echo Time
TMS	Transcranial Magnetic Stimulation
TR	Repetition Time
trIFG	triangular Inferior Frontal Gyrus
UF	Uncinate Fasciuculus
VAN-POP	Verb And Noun Test for Peri-Operative testing (VAN-POP)
vPoG	ventral Postcentral Gyrus
vPrG	ventral Precentral Gyrus

Units

cm	centimeter
dB	decibel
Hz	Hertz
mA	milliampere
mm	millimeter
mm^2	square millimeter
mm^3	cubic millimeter
ms	millisecond(s)
s	second(s)

8 List of Figures and Tables

8.1 Figures

8.2 Tables

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10 Publications

10.1 Original articles

Kram, L., Neu, B., Schröder, A., Meyer, B., Krieg, S. M., & Ille, S. (2023). Improving specificity of stimulation-based language mapping in stuttering glioma patients: a mixed methods serial case study. *Heliyon*, 9(11), e21984. https://doi.org/https://doi.org/10.1016/j.heliyon.2023.e21984

Kram, L., Ohlerth, A. K., Ille, S., Meyer, B., & Krieg, S. M. (2024). CompreTAP: Feasibility and Reliability of a New Language Comprehension Mapping Task via Preoperative Navigated Transcranial Magnetic Stimulation. *Cortex*, 171, 347-369. https://doi.org/10.1016/j.cortex.2023.09.023

Kram, L., Neu, B., Ohlerth, A. K., Schroeder, A., Meyer, B., Krieg, S. M., & Ille, S. (2023). The impact of linguistic complexity on feasibility and reliability of language mapping in aphasic glioma patients [Manuscript submitted for publication].

Kram, L., Neu, B. Schroeder, A., Wiestler, B., Meyer, B., Krieg, S.M., & Ille, S. (2023). Towards a Systematic Grading for the Selection of Patients to Undergo Awake Surgery: Identifying Suitable Predictor Variables [Manuscript submitted for publication].

Kram, L., Schroeder, A., Meyer, B., Krieg, S.M., & Ille, S. (2024). Function-guided differences of arcuate fascicle and inferior fronto-occipital fascicle tractography as diagnostic indicators for surgical risk stratification [in press].

10.2 Published abstracts

Kram, L., Ille, S., Meyer, B., & Krieg, S. M. (2021). Developing a standardized grading for awake surgeries based on preoperative language abilities and language eloquence classification. *Brain and Spine*, 1, Supplement 2: 100489. https://doi.org/10.1016/j.bas.2021.100489 (oral presentation at EANS 2021 Virtual Congress 04/10/2021).

Kram, L., Ille, S., Meyer, B., & Krieg, S. M. (2022). Quantifying functionally relevant subcortical differences in arcuate and inferior fronto-occipital fasciculus between language-eloquent brain tumor patients with no, transient and permanent aphasia. *Brain and Spine*, 2, Supplement 2: 101492. https://doi.org/10.1016/j.bas.2022.101492 (poster presentation at EANS 2022 Congress, Belgrade, Serbia, 19/10/2022).

Kram, L., Neu, B., Schröder, A., Meyer, B., Krieg, S. M., & Ille, S. (2023). Linguistic Factors Impacting Reliability of Classic Navigated Transcranial Magnetic Stimulation (nTMS)-based Language Mapping in Glioma Patients with Non-fluent Aphasia. *Brain and Spine*, 3, 101970. https://doi.org/https://doi.org/10.1016/j.bas.2023.101970 (oral presentation at EANS 2023 Congress, Barcelona, Spain, 27/09/2023).

Kram, L., Ohlerth, A. K., Ille, S., Jacob, S. N., Meyer, B., & Krieg, S. M. (2022). Stimulation-based language mapping in patients with severe expressive aphasia and healthy controls: piloting a new comprehension-related task. *Brain and Spine*, 2, Supplement 2: 101253. https://doi.org/10.1016/j.bas.2022.101253 (oral presentation at EANS 2022 Congress, Belgrade, Serbia, 19/10/2022).

Kram, L., Ohlerth, A.-K., Meyer, B., Krieg, S. M., & Ille, S. (2023). Functionally Relevant Left-hemispheric Cortical and Subcortical Correlates of Receptive Aphasia in High Grade Glioma Patients. Brain and Spine, 3, 102112. https://doi.org/https://doi.org/10.1016/j.bas.2023.102112 (poster presentation at EANS 2023 Congress, Barcelona, Spain, 25/09/2023).

Ohlerth, A. K., Bastiaanse, R., **Kram, L.**, Neu, B., Meyer, B., & Krieg, S. M. (2022). Benefit of verb over standard noun naming task to reveal cortical language areas in preoperative language mapping under navigated Transcranial Magnetic Stimulation. Brain and Spine, 2, Supplement 2: 101517. https://doi.org/10.1016/j.bas.2022.101517

10.3 Invited talks/ lectures

Kram, L. (2023, June 19). *Neurowissenschaftliche Sprachforschung & Neurostimulations-basierte Sprachkartierungen [engl.: Neuroscientific language research & neurostimulation-based language mapping].* Guest Lecture at Department of Linguistics of Paris Lodron University Salzburg, Austria.

Kram, L., Ohlerth, A. K., Neu, B., Schröder, A., Ille, S., Meyer, B., & Krieg, S. M. (2022, December 16). *Mapping language comprehension and production in neurosurgical patients with severe language deficits*. Oral presentation at 12th International Symposium on nTMS in Neurosurgery and Neuromodulation, Berlin, Germany.

10.4 Oral presentations

Kram, L., Neu, B., Schröder, A., Meyer, B., Krieg, S. M., & Ille, S. (2023, June 26). *Impact of item complexity and word frequency on language mapping reliability in aphasic glioma patients* [Conference presentation]. Oral presentation at 74th annual conference of the German Society of Neurosurgery, Stuttgart, Germany.

Kram, L., Ohlerth, A. K., Meyer, B., Krieg, S. M., & Ille, S. (2023, June 26). *Crucial cortical comprehension sites in high-grade glioma patients with receptive aphasia* [Conference presentation]. Oral presentation at 74th annual conference of the German Society of Neurosurgery, Stuttgart, Germany.

Kram, L., Ohlerth, A. K., Ille, S., Meyer, B., & Krieg, S. M. (2023, February 4). *Mapping of cortical language comprehension-related sites in highgrade glioma patients with receptive aphasia* [Symposium presentation]. Short oral presentation at the Bridging Neurosciences and Neurosurgery: New Frontiers in Intraoperative Neurophysiology, Verona, Italy.

Kram, L., Ille, S., Meyer, B., & Krieg, S. M. (2022, June 1). *Developing a standardized grading for intraoperative language mapping based on preoperative language abilities and language eloquence classification* [Conference presentation]. Oral presentation at 73th annual conference of the German Society of Neurosurgery, Cologne, Germany.

Kram, L., Neu, B., Schröder, A., Meyer, B., Krieg, S.M., & Ille, S. (2022, May 31). *Misidentification of involuntary and unpredictably manifesting speech motor symptoms as language-relevant during stimulation-based language mapping in glioma patients who stutter* [Conference presentation]. Oral presentation at 73th annual conference of the German Society of Neurosurgery, Cologne, Germany.

Kram, L., Ohlerth, A.K., Ille, S., Jacob, S.N., Meyer, B., & Krieg, S.M. (2022, May 30). *Feasibility of nTMS-based language comprehension mapping in brain tumour patients with severe expressive aphasia – a case series* [Conference presentation]. Oral presentation at 73th annual conference of the German Society of Neurosurgery, Cologne, Germany.

Zhang, H.*, **Kram, L.***, Ille, S., Schröder, A., Meyer, B., & Krieg, S.M. (2021, September 30) *Sprach-involvierte superiore kortikale Endpunkte des Frontal Aslant Tracts identifiziert mittels präoperativer navigierter transkranieller Magnetstimulation korrelieren mit Aphasien bei Hirntumorpatienten [engl.: Language-involved superior cortical endpoints of the frontal aslant tracts as identified with preoperative nacigated transcranial magnetic stimulation correlate with aphasia in brain tumor patients*; conference presentation]. Oral presentation at 1st convention week of the sections of the Society of Neurosurgery, Göttingen, Germany. **authors contributed equally*

10.5 Virtual posters

Kram, L., Neu, B., Schröder, A., Meyer, B., Krieg, S. M., & Ille, S. (2022, October). *The role of experienced specialists in the analysis of stimulation-based language mappings in stuttering glioma patients: improving the specificity of nTMS-based language mapping* [Virtual poster exhibited at conference]. Virtual e poster at EANS 2022 Congress, Belgrade, Serbia.

Kram, L., Stassen, N., Min, A., Meyer, B., Ille, S., & Krieg, S. M. (2023, September). *Efficacy and safety of direct cortical language mapping with 4 mA stimulation intensity: a single-center serial case study* [Virtual poster exhibited at conference]. Virtual e poster at EANS 2023 Congress, Barcelona, Spain.

11 Appendix: Original Articles

1. Kram, L., Neu, B., Schröder, A., Meyer, B., Krieg, S. M., & Ille, S. (2023). Improving specificity of stimulation-based language mapping in stuttering glioma patients: a mixed methods serial case study. *Heliyon*, 9(11), e21984. https://doi.org/https://doi.org/10.1016/j.heliyon.2023.e21984
2. Kram, L., Ohlerth, A. K., Ille, S., Meyer, B., & Krieg, S. M. (2024). CompreTAP: Feasibility and Reliability of a New Language Comprehension Mapping Task via Preoperative Navigated Transcranial Magnetic Stimulation. *Cortex*, 171, 347-369. https://doi.org/10.1016/j.cortex.2023.09.023

11.1 Improving specificity of stimulation-based language mapping in stuttering glioma patients: a mixed methods serial case study.

11.1.1 Summary of this publication and own contributions to this study

The first publication included and presented in this thesis ascertained the impact of the speech fluency disorder stuttering on the consistency and specificity of stimulation-based language mappings and ways to improve the reliability of mapping results in context of preexisting speech (fluency) disorders (Kram, Neu, Schröder, et al., 2023).

The first part of the study conducted by Kram, Neu, Schröder, et al. (2023) comprised a post-hoc analysis of all patients who underwent nTMS-based language mappings between May 2018 and January 2021. Since stuttering distinct and characteristic disruptions in the speech flow are typically diagnosed and treated by trained and certified speech and language therapists (SLTs), all the video recordings of the baseline and stimulation examinations of 211 patients were screened for stuttering by me, a certified SLT. On this basis, I identified five patients who presented with a stutter and thoroughly identified stuttering symptoms during baseline testing and stimulation examination and differentiated these from stimulation-induced language disruptions. Moreover, this analysis was compared to the analysis of two nTMS examiners with varying degrees of experience. Since this was a post-hoc analysis and no video recordings of intraoperative awake language mappings were available for these six patients, I performed an additional simulated intraoperative analysis. This allowed to obtain first implications about whether stuttering can be differentiated instantly during the DES-based language mappings by trained specialists. During the second part of this study, I screened all prospective patient cases, who underwent nTMS- and DES-based language mapping between January 2021 and December 2022, for preexisting stuttering. A single case presented with preexisting developmental stuttering. Thus, next to the routine nTMS- and DES-based analysis performed by a highly experienced examiner without training in stuttering diagnosis, I closely monitored and differentiated all stuttering symptoms during pre- and intraoperative stimulation-based language mappings as well as in available video- and audio-recordings. I carried out all statistical analyses, created the figures, performed the literature research and wrote the initial draft of the manuscript. Moreover, I revised the manuscript according to the co-authors' remarks as well as the reviewers' comments while it was under review in Heliyon. All steps were performed under supervision of Prof. Krieg and Dr. Ille.

All of these analyses revealed that stuttering symptoms were frequently mistaken as stimulation-induced language disruptions and the respective stimulation sites consequently mistaken as language-relevant cortical sites by the two nTMS examiners (Kram, Neu, Schröder, et al., 2023). Moreover, the level of experience both nTMS examiners had in language mapping analysis seemed to impact the type and number of stuttering symptoms mistaken as stimulation-induced language disruptions (Kram, Neu, Schröder, et al., 2023). Hence, these speech fluency symptoms decreased the reliability and specificity of the language mapping outcome. Moreover, these results underline the necessity of either training examiners in the diagnosis and differentiation of symptoms caused by preexisting speech disorders or the benefit of relying on trained specialists. This may considerably improve the mapping outcome and, thus, support the preservation of functionality in brain tumor patients with preexisting stuttering.

11.1.2 Publication

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Improving specificity of stimulation-based language mapping in stuttering glioma patients: A mixed methods serial case study

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ABSTRACT

Objective: Stimulation-based language mapping relies on identifying stimulation-induced language disruptions, which preexisting speech disorders affecting the laryngeal and orofacial speech system can confound. This study ascertained the effects of preexisting stuttering on pre- and intraoperative language mapping to improve the reliability and specificity of established language mapping protocols in the context of speech fluency disorders.
Method: Differentiation-ability of a speech therapist and two experienced nrTMS examiners between stuttering symptoms and stimulation-induced language errors during preoperative mappings were retrospectively compared (05/2018-01/2021). Subsequently, the impact of stuttering on intraoperative mappings was evaluated in all prospective patients (01/2021-12/2022).
Results: In the first part, 4.85 % of 103 glioma patients stuttered. While both examiners had a significant agreement for misclassifying pauses in speech flow and prolongations ($K \geq 0.50$, $p \leq 0.02$, respectively), less experience resulted in more misclassified stuttering symptoms. In one awake surgery case within the second part, stuttering decreased the reliability of intraoperative language mapping.
Comparison with Existing Method(s): By thoroughly differentiating speech fluency symptoms from stimulation-induced disruptions, the reliability and proportion of stuttering symptoms falsely attributed to stimulation-induced language network disruptions can be improved. This may increase the consistency and specificity of language mapping results in stuttering glioma patients.
Conclusions: Preexisting stuttering negatively impacted language mapping specificity. Thus, surgical planning and the functional outcome may benefit substantially from thoroughly differentiating speech fluency symptoms from stimulation-induced disruptions by trained specialists.

1. Introduction

Preserving language function whilst aiming for the greatest possible extent of resection is the principal objective in the

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Abbreviations: nrTMS, navigated repetitive transcranial magnetic stimulation; DES, direct electrical stimulation.

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neurosurgical treatment of language eloquent brain tumors [1,2]. Depending on tumor location, this requires a thorough pre- and intraoperative mapping of language function. Stimulation-based approaches are the gold standard for intraoperative language monitoring [3]. However, not every patient is eligible for awake craniotomies with direct electrical stimulation (DES) [4,5]. Navigated repetitive transcranial magnetic stimulation (nrTMS), a non-invasive preoperative stimulation technique combining anatomical information of magnetic resonance imaging (MRI) with correlates of neural language function, repeatedly demonstrated its effectivity and reliability for presurgical planning and risk stratification [6–10]. Both stimulation methods temporarily interrupt the language network, causing so-called "virtual lesions" [11] while the patient performs language tasks. These interruptions result in audible and identifiable language errors, such as paraphasia or speech arrest [6,12]. Consequently, language mapping is highly dependent on identifying a causal link between stimulation of a specific area and produced language mistake.

However, analyzing these errors becomes challenging if a patient presents with preexisting speech or language impairments. During our clinical presurgical routine, we realized that a certain kind of speech fluency impairment, called stuttering, is prone to cause errors being misidentified as stimulation-induced language errors. However, they stem from involuntary, unpredictable, and random speech fluency symptoms. Persistent developmental or acquired neurogenic stuttering are speech fluency disorders resulting from impaired (pre-)motor processes [13]. Stuttering symptoms are commonly classified into multiple repetitions of phonemes or syllables, prolongations, and (in-)audible pauses, called blocks [14]. These frequently cause tension within the articulatory, phonatory, or respiratory speech system [15]. Particularly blocks may be challenging to differentiate from stimulation-induced errors by the untrained eye, resulting in an inability to initiate any or specific sounds. Still, they are typically caused by visible and hearable closures within the laryngeal and orofacial system, thus showing a differentiable symptom pattern. The most common form of this speech fluency disorder emerges during childhood, with a prevalence of roughly 1 % [16]. Moreover, predominantly case studies link an acquired, neurogenic form to neurodegenerative diseases, stroke, or traumatic brain injuries and rarely to brain tumors [17–20].

While the prevalence of stuttering in brain tumor patients – whether acquired or persistent developmental – is unknown, these involuntary, random, and unpredictable disturbances could occur at any time point before or during language mappings, potentially impacting mapping analysis and interpretation. Thus, the primary objective of the present study was to assess the influence of stuttering on the consistency, specificity, and reliability of stimulation-based language mappings.

We hypothesized that stuttering results in false positive language-relevant points if analyzed by examiners without any prior training in the diagnosis and symptom classification of stuttering compared to the evaluation of a speech therapist, experienced in stuttering diagnostics and language mapping evaluation. We first performed a post hoc analysis of preoperative stimulation-based language mappings. The therapist differentiated all stuttering symptoms manifesting during the nrTMS examination from proper stimulation-induced language errors. To provide first implications for the impact of individual experience levels a nrTMS operator has in analyzing language mappings, we compared the stuttering-related language mapping results of a high to a less experienced nrTMS operator.

To evaluate the impact on awake surgeries more directly, we compared the differentiation-ability during awake DES-based language mapping between an experienced examiner routinely performing awake surgery testing and a speech therapist within a prospective case study. Thus, the present study allows to draw first conclusions about the impact of preexisting stuttering on the specificity of pre- and intraoperative stimulation-based language mappings and of the role of experienced, specialized, and trained examiners for consistent and reliable mapping analyses in stuttering glioma patients.

2. Material and methods

Ethics Approval

This study was approved by our local ethics committee (registration number: 192/18) and was conducted in accordance with the declaration of Helsinki. Prior to the respective nrTMS language mapping, each patient provided written informed consent.

2.1. Patient cohort

The first part of this study comprised a post hoc analysis of prospectively enrolled patients receiving preoperative nrTMS-based language mapping within our neurosurgical department between May 2018 and January 2021. We included patients at least 18 years of age who presented with no nrTMS exclusion criteria (e.g., cochlear implants or cardiac pacemakers). Handedness was tested with the Edinburgh Handedness Inventory [21].

In the second part, a speech therapist closely monitored all patients undergoing preoperative nrTMS-based language mapping with additional awake DES-based surgery between January 2021 and December 2022 prospectively for a preexisting speech fluency disorder to examine the impact of stuttering symptoms on intraoperative, awake language mapping.

2.2. MR image acquisition

This study followed a standardized MRI protocol described in previous publications to derive structural MR images for neuronavigation on a 3T-MRI scanner (Achieva dStream or Ingenia; Philips Healthcare, Best, Netherlands) in combination with an 8- or 32-channel phased-array head coil [9,22]. The sequence comprised at least three-dimensional T1-weighted gradient echo sequences with and without the application of an intravenous contrast agent. This anatomical imaging sequence was subsequently transferred to the nrTMS system for neuronavigation.

2.3. *Preoperative nrTMS language mapping*

Our highly experienced nrTMS operator conducted and analyzed all preoperative nrTMS language mappings during the presurgical routine. Language mappings were performed with the Nexstim eXimia NBS system version 4.3 or 5.1.1 with a NEXSPEECH® module (Nexstim Plc, Helsinki, Finland) following an established standardized mapping protocol [23]. Contrast-enhanced T1-weighted images were used for anatomical co-registration. Before stimulation, each patient performed an 80-item object naming task with black-and-white drawings twice. The items used are balanced for the age of acquisition, word frequency, and syllable length. The baseline without the nrTMS application familiarized patients with the task and simultaneously allowed the exclusion of any objects a patient could not name promptly and adequately. This step is required to relate all following errors during nrTMS application to the stimulation of a specific cortical area. Subsequently, the same task was performed with the correctly named items while nrTMS was applied.

Each of the previously described 46 target points [4], covering frontal, parietal, and temporal cortical sites, was stimulated three times. Items were typically presented with an inter-picture interval of 2500 ms and a picture presentation duration of 700 ms. These durations could be extended to patients' capabilities to a certain extent if required. The respective stimulation intensity applied was defined as 100–110 % of the individual resting motor threshold, i.e., the minimum intensity needed to elicit a motor-evoked response in the abductor pollicis brevis. Stimulation was applied with 5 Hz/5 pulses triggered by each picture stimulus onset.

2.4. *Speech status*

A certified speech and language therapist (L.K.) with extensive experience in diagnosing and treating stuttering analyzed the first baseline of each patient retrospectively to evaluate individual speech status and identify patients who stutter. Patients were defined as having a stutter based on the German guidelines for speech fluency disorders [24]. While no definite number exists for acquired neurogenic stuttering, for developmental stuttering, more than 3 % of syllables of a representative speech sample need to be stuttered [24]. The present analysis considered the following stuttering symptom categories: phoneme or syllable repetitions, prolongations, and (non-)silent blocks. Due to the retrospective nature of this analysis, only baseline recordings could be used to identify patients with >3 % stuttered syllables. In the second part of this study, the same cut-off values were used for undiagnosed stuttering. Alternatively, patients were included if they had pre-diagnosed stuttering. Furthermore, the speech therapist analyzed each stimulation exam to differentiate typical preexisting stuttering symptoms [15] from frequently described stimulation-induced language disruptions [6,25,26]. Across stimulation-based language mapping studies, stimulation-induced stuttering is only rarely described. Subcortical DES-based stimulation has been linked to stuttering-like symptoms, while especially cortical stimulation is sparsely reported to induce a stutter. At the same time, studies frequently do not describe a detailed symptom pattern to differentiate stimulation-induced stuttering from other speech errors elicited by stimulation. For instance, some authors defined stuttering as one of the dysarthric or apraxic speech errors prompted by stimulation and expressed primarily as word-initial repetitions [25]. Whilst some related only first syllable repetitions to stimulation prompted speech disruptions [27], a single study reported symptoms consistent with neurogenic stuttering, such as repetitions, prolongations, and blockages without co-occurring orofacial symptoms [28]. Thus, symptoms consistent with persistent developmental stuttering are more clearly differentiable as secondary symptoms are frequently observable next to the core symptoms of repetitions, prolongations, and pauses in speech flow. The former can express in heterogeneous forms such as increased speech effort, enhanced speaking rate, coping strategies such as clearing the throat, introducing filler words, grimacing, sudden and jerky head movement, loss of fixation, or frequent eye blinking. Moreover, tension within the articulatory, phonatory, or respiratory speech system frequently accompanies persistent developmental and neurogenic acquired stuttering. Hence, it is feasible to differentiate symptoms arising from preexisting stuttering from stuttering-like symptoms induced by stimulation, such as repetitions without any secondary behavior, tension, or increased speech effort. Overall, a need to classify error types and provide detailed descriptions across studies becomes obvious. While stuttering-like symptoms may be reported in other stimulation-based language mapping studies, it is not consistently defined, which complicates the differentiation of persistent developmental and neurogenic stuttering from stimulation-induced disruptions of the speech flow.

The present study applied the following differentiation criteria.

2.4.1. *Stuttering symptoms*

The following three core stuttering symptoms [15] were classified if patients showed any secondary behavior, tension within the speech system, or observable speech effort:

- *Repetition* of phonemes or syllables such as "*↫c-c-c↫cat*"
- *Prolongation*, e.g., a prolonged [l] in "*l:adder*"
- *(non-)silent blocks* impacting the initiation of speech, indicated by fixed vocalization postures or tension within laryngeal or orofacial speech-related systems, e.g., a block during the initiation of "*≠guitar*"

2.4.2. *Stimulation-induced language errors*

- *No responses:* lack of naming response, e.g., caused by anomia, not accompanied by any stuttering symptom.
- *Phonological or semantic paraphasias:* phonological substitutions, omissions, insertions, or substitution of a semantically related target item.

- *Performance errors:* articulatory errors such as dysarthric or apraxic ones.
- *Stuttering-like errors:* phoneme, syllable, or whole word repetitions, pauses in the speech flow without additional secondary, tense, or effortful behavior.
- *Hesitations*: delayed responses.

2.5. nrTMS data analysis

The identification of language-positive, i.e., language-relevant, points comprised the post hoc identification of stimulation sites at which language errors arose during the nrTMS application. For this, nrTMS operators identified language errors in video recordings of the respective stimulation exam. The following error categories were classified: no response, performance error, semantic and phonological paraphasia, hesitation, and neologism [6,25], as well as others if not assignable. All error and non-error-tagged items had an individual ID predefined by the software. Thus, these were finally matched back to the stimulation target of the nrTMS session to identify all language-relevant and non-relevant cortical stimulation sites.

The highly experienced nrTMS operator (A.S., ~120–480 language mappings, depending on when the mapping took place) analyzed each language mapping directly post nrTMS during the clinical routine. Moreover, a less experienced nrTMS operator (B.N., ~100 language mappings) analyzed each stimulation exam of the patients who stuttered retrospectively. Since the speech therapist additionally marked all stuttering symptoms manifesting during the respective nrTMS language mapping, we could compare the subset of items at which a stuttering symptom occurred during the stimulation examination for each subject. Hence, the differentiation ability of each operator between stuttering and stimulation-induced language error was compared between the two nrTMS operators for each patient included in the first part of this study. This comparison provided insights into the impact of experience on the differentiation between stuttering-caused and stimulation-induced mistakes. To further evaluate whether the stuttering symptoms occurred systematically in cortical sites which either have been associated directly with stimulation-induced repetitions or which make up the cortical terminations of subcortical tracts previously related to stimulation-induced stuttering [25,27,28], the percentage of stuttering symptoms manifesting within the following cortical sites were additionally compared: anterior and posterior supramarginal as well as inferior and superior frontal gyrus.

2.6. Awake DES-based language mapping

Intraoperative awake language mapping followed our standard asleep-awake-asleep protocol in line with multiple recommendations [29,30]. Cortical DES-based mapping was conducted with a bipolar stimulation electrode, 4s stimulation output, frequency of 50 Hz, an intensity of 4 mA, and subcortical mapping with a monopolar stimulation electrode (Inomed Medizintechnik, Emmendingen, Germany). During cortical mapping, patients performed an object-naming task. The lead-in phrase "This is …" was used to differentiate speech arrest. The same highly experienced examiner who conducted the routine preoperative language mapping analyzed the intraoperative language mapping. Unlike the preoperative setup, any stimulation-induced language network disruptions had to be identified on the spot and linked directly to the cortical site stimulated.

During subcortical mapping, the experienced examiner and the speech therapist closely monitored patients' spontaneous speech. In the second part of this study, naming responses and spontaneous speech were audio recorded to allow a post hoc in-depth analysis of the speech and language status. During this analysis, the therapist relied on the same differentiation criteria to distinguish stimulation-induced language errors and speech fluency symptoms caused by preexisting stuttering.

Since no intraoperative recordings were available, this study could not systematically evaluate the potential impact of stuttering on the intraoperative results for the patients of the first post hoc study part. Hence, to investigate whether the differentiation of stuttering from stimulation-induced language errors by a trained specialist is feasible instantly and on the spot without the possibility to re-watch a video recording, the following analysis was performed to simulate the intraoperative analysis procedure as closely as possible: All video recordings of the respective nrTMS examination in .asf format were transferred to an external computer. Subsequently, the speech therapist analyzed and documented all stuttering symptoms while watching the video simultaneously. No possibilities of re-watching or stopping were allowed. A minimum interval of 6 months between the initial analysis within the nrTMS software and this second analysis was required to prevent learning effects.

2.7. Statistical analysis

All statistical analyses were performed with R3.6.3 [31]; a p-value less than 0.05 was considered statistically significant. Based on the small cohort size of patients who stuttered, mainly descriptive statistics were implemented. Cohen's kappa was used to compare the similarity between the assessments of the highly and the less experienced rater [32]. A kappa approaching 1 was considered almost perfect [33].

3. Results

3.1. Patient characteristics

In the first part of this study, 211 patients with a suspected primary or recurrent brain tumor, metastasis, lymphoma, meningioma, cavernoma, or arteriovenous malformations were included. The mean age of this cohort was 56.6 ± 15.2 years; 91 were female, 179 right-handed, 12 left-handed, and 12 were ambidextrous; for eight patients, no handedness was reported. 52.13 % of these patients had a histologically confirmed glioma with a mean age of 57.35 ± 14.5 years (49 female, 61 male).

The speech therapist identified five patients who stuttered, all from the subgroup of histologically confirmed glioma. Moreover, all patients who stuttered were native German speakers. While of 77 glioma patients asleep during surgery, 2.60 % stuttered, 11.54 % of 26 awake surgery glioma cases presented with a significant stutter. Seven glioma sub-group cases, whose tumors were not surgically removed, did not present a stutter.

In the second part, out of 10 subsequent patients undergoing pre- and intraoperative awake language mapping, a 37-year-old female patient presented with a developmental form of the speech fluency disorder.

Table 1 provides an overview of individual demographic and tumor characteristics and the language status, combined for both study parts, i.e., five retrospectively identified patients and one prospective stuttering case. These six left-hemispheric tumor cases had a mean age of 57.17 ± 14.66 years, and 50.00 % were female. The most significant proportion had high-grade gliomas (83.3 %), and two-thirds of tumors were located within parietal areas. All patients had at least a co-occurring light non-fluent aphasia.

3.2. Speech fluency status and preoperative language mapping results

During the baseline, patients showed, on average, 10.66 % (range: 0.68 %–34.41 %) stuttered syllables out of all syllables produced. Table 2 provides an overview of the number of stuttering symptoms during nrTMS, the most prevalent stuttering symptom types, and the percentage of stuttering symptoms classified as stimulation-induced language errors. While heterogeneous nrTMS-induced symptoms were observed, such as no or hesitant responses, and semantic or phonologic paraphasia, no stimulation-elicited stuttering-like symptoms occurred. Moreover, we evaluated whether the stuttering symptoms related to the preexisting speech fluency disorder manifested systematically in cortical sites which provide cortical endpoints of fiberpaths that were either associated with stimulation-induced stuttering or which were directly related to stuttering-like symptoms in previous studies [25,27,28]. Of the four cortical sites evaluated, the highest percentage of stuttering symptoms occurred during stimulation of the posterior supramarginal gyrus, with only 14.4 % across the six patients. During stimulation of the inferior frontal gyrus, 7.6 % of stuttering symptoms co-occurred, whilst it was just under 5.0 % during the stimulation of the superior frontal and anterior supramarginal gyrus, respectively. Across the six patients presented in the current study, stuttering symptoms occurred spontaneously, unpredictably, and unsystematically during the preoperative language mapping across heterogeneous cortical sites (see Fig. 1). Moreover, many of these misclassified stuttering symptoms were located directly within (Fig. 1A, C) or in direct proximity to the tumor area (Fig. 1D and E) as well as in one case within the edema surrounding the tumor (Fig. 1B). In the following, two exemplary cases will be presented in detail to illustrate the impact of preexisting stuttering on preoperative stimulation-based language mapping.

3.2.1. Case 2

P2 was a right-handed 49-year-old female patient with preexisting non-fluent aphasia harboring a left-hemispheric insular astrocytoma.

The baseline video analysis indicated severe aphasia and a profound stuttering rate primarily comprising blocks showing additional tense orofacial activation or fixed vocalization patterns. Facial expression and the patient's reaction revealed an increased effort during final vocalization if a stuttering symptom occurred. Of 11 stuttering symptoms during nrTMS, nearly a fifth were classified as stimulation-induced language disruptions by the highly and more than half by the less experienced rater (Fig. 1B), many close to the lesion.

3.2.2. Case 3

This female 69-year-old patient presented with preexisting dysarthria, severe aphasia, and stuttering. During baseline, 12.41 % were stuttered syllables. The most prominent stuttering symptoms were prolongations and repetitions of syllables or phonemes, indicated by increased tension and tight or pressed orofacial muscles during vocalization. Of 17 stuttering symptoms during the nrTMS stimulation exam, the less and the highly experienced rater classified a large proportion as stimulation-induced performance, no response, or uncategorized language errors.

One stuttering symptom misclassified by the highly experienced rater was located directly in the lesion area (Fig. 1C), which may

Table 1
Characteristics of six brain tumor patients who stutter[a].

case no.	age, yrs	sex	entity	WHO/ZNS grade	location	surgery type	aphasia severity[b]
P1	58	M	GBM	4	parietal	awake	2
P2	49	F	AA	3	insular	asleep	4
P3	69	F	GBM	4	parietal	awake	4
P4	78	M	GBM	4	temporal	asleep	5
P5	52	M	OD	3	parietal	awake	2
P6	37	F	A	2	frontoparietal	awake	1

(A)A = (anaplastic) astrocytoma, F = female, GBM = glioblastoma, M = male, OD = oligodendroglioma.

[a] Overview of patient-related characteristics comprising age (in years), sex, tumor entity, aphasia severity, and speech status (percentage of stuttered syllables during the baseline object naming task; number of stuttering events during the stimulation exam).

[b] 0 = no, 1 = minimal, 2 = light, 3 = moderate, 4 = major, 5 = severe aphasia.

Table 2
Overview of stuttering characteristics and misclassifications of stuttering events during preoperative language mapping[a].

case no.	% stuttered syllables baseline	n of stuttering events during nrTMS	prevalent stuttering symptom[b]	% of misclassified stuttering events during nrTMS	
				HR	LR
P1	3.18	2	R, B, P	100.00	100.00
P2	34.41	11	B, R, P	18.18	54.55
P3	12.41	17	P, R	29.41	35.29
P4	4.86	7	R, B, P	57.14	71.43
P5	8.39	16	B, R, P	37.50	62.50
P6	0.68	4	B	100.00	/

HR = highly experienced rater, LR = less experienced rater.

[a] Overview of individual stuttering characteristics, including the percentage of stuttered syllables during baseline, number of stuttering events during the preoperative nrTMS-based language mapping, the individual prevalent stuttering event type, and the percentage of stuttering events classified as stimulation-induced language error for each nrTMS operator.

[b] R= Repetition of syllables and/or phonemes, P=Prolongations, B= Block; named according to the frequency of symptom occurrence (from most to least frequent stuttering symptom).

have impacted the surgical strategy and the decision for awake surgery.

3.3. *Stuttering during awake DES-based language mapping*

During the first part of this study, the intraoperative DES-based language mapping analysis was simulated to assess the feasibility of differentiating stuttering symptoms from stimulation-induced language disruptions even during the more time-restricted and prompt error evaluation in the operating room. Hence, the speech therapist's analysis of the nrTMS mapping was based on watching the complete video only once and identifying stuttering symptoms directly. The results were compared to the initial analysis of the nrTMS mapping within the nrTMS system allowing for multiple viewings of patient's responses. Across the five patients who stuttered (P1–P5), on average, 83.2 % of stuttering symptoms identified with the classic nrTMS analysis were additionally recognizable during the simulated intraoperative analysis procedure. A lower percentage was observed for patients with a higher number of stuttering symptoms (P2: 72.7 %, P5: 75.0 %, P3: 82.4 %). However, for patients with lower stuttering severity, stuttering symptoms were more clearly differentiable even during the simulated instant analysis (percentage of stuttering symptoms identified during the simulated analysis P1: 100.0 %, P4: 85.7 %).

In-depth analyses of audio recordings of the awake language mapping could only be conducted for a single patient in the second part of this study as, due to the post hoc nature of the first study part, no recordings were available for patients 1 to 5. Therefore, in the following, only the results of the prospective case study are presented. Patient 6 presented with light expressive aphasia and a prediagnosed persistent developmental stuttering. During the nrTMS-based stimulation exam, four stuttering symptoms manifested in the form of silent and non-silent pauses caused by visible blockages of the laryngeal and facial muscles. The highly experienced rater classified all of these as stimulation-induced language errors. During the object-naming DES-based cortical awake mapping, two non-silent blocks occurred. The patient partly vocalized the initial sound, accompanied by tension and pressure resulting in a hearable disfluency. These two stuttering symptoms gave rise to a stuttering rate of 1.79 % during awake naming testing. They were already identified during the awake language mapping by the speech therapist in the operating room and subsequently confirmed by the analysis of the available audio recording. The same highly experienced specialist who performed the preoperative nrTMS mapping classified these as stimulation-induced no response language mistakes. No language-relevant sites were identified directly in the tumor area. The opercular part of the inferior frontal and the ventral pre- and postcentral gyrus comprised the predominant stimulation sites during the naming task. Both stuttering symptoms occurred during stimulation of the pre- and postcentral gyrus. Since there were only two blockages, this may be by chance, especially since they were not located directly within the identical stimulation site.

Additionally, the speech therapist closely monitored the stuttering rate during spontaneous speech production and simultaneous subcortical resection. The stuttering rate continuously increased from 1.47 % during the first to 1.63 % during the second to 3.05 % during the last third of 18 min of testing. Due to increasingly worse overall performance and the occurrence of focal seizures, the final part of the resection was conducted under anesthesia.

3.4. *Comparison between raters*

As outlined above, we descriptively compared the analysis of two different raters and compared the analysis agreement on classifying any and different stuttering symptom types as stimulation-induced language errors. Across all these brain tumor patients who stuttered during the first part of this study, the differentiation ability between stuttering symptoms and real stimulation-induced language mistakes were compared for the two nrTMS operator. All speech motor dysfluencies caused by preexisting stuttering unpredictably and uncontrollably occurred before or during the stimulation application. Since the laryngeal and orofacial speech musculature are affected, stuttering can be distinguished from stimulation-induced language errors by experienced specialists. Thus, the speech therapist identified and marked all stuttering symptoms during the nrTMS-based stimulation. The nrTMS rater analyzed the respective stimulation exams, blinded to the therapist's analysis. Subsequently, we examined whether these speech fluency disruptions

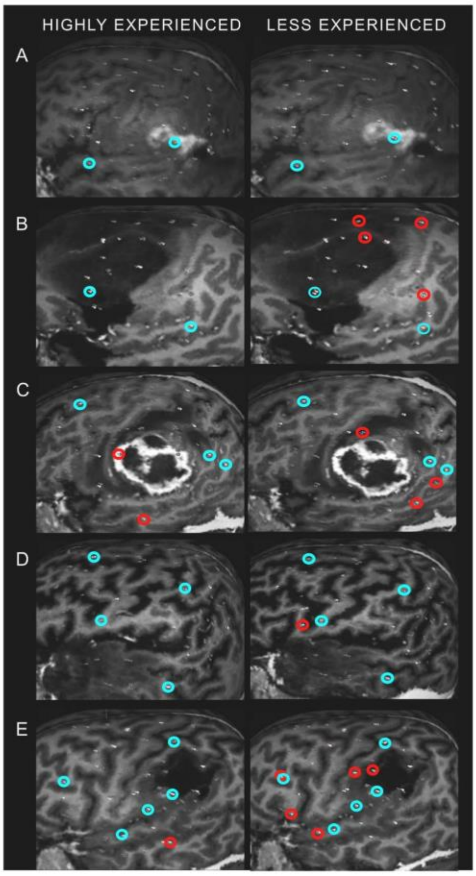

Fig. 1. Stuttering-caused misclassified language-positive stimuli. The figure shows the misclassified stuttering symptoms rated as stimulation-induced language errors by the highly experienced rater (left column) and by the less experienced rater (right column) for each patient individually (A: P1, B: P2, C: P3, D: P4, E: P5). Points misclassified by both nrTMS operators are highlighted in blue, and points misclassified exclusively by one of the operators are highlighted in red.

attributed to preexisting stuttering, as identified by the speech therapist, were mistaken as language errors elicited by stimulation. The highly experienced rater classified on average 48.45 % (range: 18.18–100.00 %) of stuttering symptoms as stimulation-induced language-relevant sites, the less experienced operator 64.75 % (range: 35.29–100.00 %), as highlighted in Fig. 1. Fig. 2 illustrates the differences across all attributed language errors and in language error category attribution for each stuttering symptom type. The highly experienced operator rated 18.87 % of all stuttering symptoms as "performance" and 16.98 % as "no response" errors. The less experienced one rated 37.74 % of all stuttering symptoms as "other" and 16.98 % as "no response". Table 3 summarizes the attributed language errors for each stuttering category ("repetitions", "prolongations", "blocks") by the highly and the less experienced rater. Separate comparisons for each stuttering type revealed that both raters had a significant, yet moderate, similarity for blocks ($K = 0.500$, $p = 0.002$) and prolongations ($K = 0.581$, $p = 0.021$) but not for repetitions ($p = 0.292$).

4. Discussion

The present study investigated the impact of the speech motor impairment stuttering on the analysis and outcome of preoperative nrTMS language mapping. By comparing the number of stuttering symptoms classified as stimulation-induced language-positive sites between nrTMS operators with different experience levels and a trained speech therapist, we demonstrated that many were misclassified as language-relevant cortical sites. Our results suggest that it is crucial to differentiate these involuntary and random motor

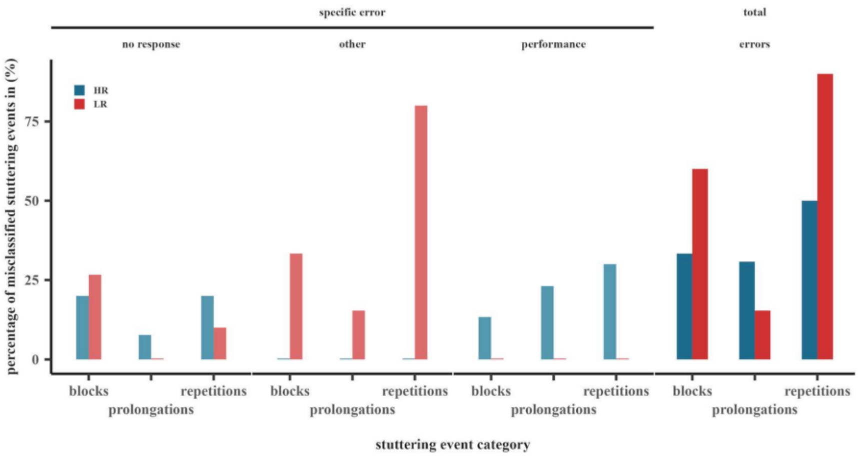

Fig. 2. Comparison of specific stuttering symptoms categories and classified language-error categories. The figure shows the percentage of misclassified stuttering symptoms across raters (red: less experienced rater LR, blue: highly experienced rater HR) across all (right column) and specific attributed language error categories (no response, other, performance) utilizing ggplot2 and ggh4x R packages for visualization [34,35][.

Table 3
Comparison of percentage of assigned language error categories to stuttering events across nrTMS operators[a].

stuttering event category	% of respectively assigned language error category							
	all error categories		performance		no response		other	
	HR	LR	HR	LR	HR	LR	HR	LR
repetitions	50.00	90.00	30.00	–	20.00	10.00	–	80.00
prolongations	30.77	15.38	23.08	–	7.69	–	–	15.38
blocks	33.33	60.00	13.33	–	20.00	26.67	–	33.33

HR = highly experienced rater, LR = less experienced rater.

[a] Overview of nrTMS operator-specific percentage of misclassified stuttering events per stuttering category (repetition, prolongation, blocks) across all attributed language error categories and for specific language error categories (performance, no response, other).

disruptions in the flow of speech from stimulation-induced temporary disruptions of the language network. In the following paragraphs, we will first consider the role of experienced and trained examiners during the analysis of stimulation-based language mappings. Subsequently, the impact of stuttering on pre- and intraoperative language mapping reliability, specificity, and consistency will be discussed.

4.1. Effect of experience on the identification of stuttering symptoms

Patients with brain tumors within the language or speech network frequently present preoperative speech and language disorders. It is well established that aphasia and dysarthria can decrease the reliability and feasibility of stimulation-based language mappings, and symptoms of these disorders need to be carefully differentiated from stimulation-induced language disruptions [30,36,37]. Aphasia affects the whole language system, language production and comprehension, and can impair any linguistic level, i.e., comprises phonetic-phonologic, lexico-semantic, morpho-syntactic, and pragmatic symptoms [38]. At the same time, speech motor and fluency disorders impact processes involved in preparing, coordinating, planning, and executing respiratory, laryngeal, phonatory, and articulatory processes needed to produce speech movements [39,40]. Although severe forms can decrease intelligibility, more moderate and light expressions of dysarthria may be easily differentiated from stimulation-induced language errors as the symptoms are consistently present throughout speech production, irrespective of task or stimulation. Compared to dysarthria, repetitions of phonemes or syllables, prolongations, and silent as well as non-silent blocks accompanied by tensed muscular activation, secondary behavior, or speech effort occur more randomly. Thus, stuttering may be more cumbersome to recognize than other speech or language disorders by untrained professionals. Still, no report exists on the necessity or difficulty of differentiating stuttering symptoms. The present results indicate that even examiners with experience in analyzing stimulation-based language mappings but untrained in stuttering diagnostics struggle with distinguishing these speech fluency symptoms from proper stimulation-induced disruptions in language production, even if stuttering patients show a distinct symptom pattern.

Moreover, as the comparison between two raters with varying experience levels showed, the nrTMS rater's experience seemed to substantially impact the number of stuttering symptoms classified as stimulation-induced language disruptions. On average, the highly experienced rater classified nearly half of all stuttering symptoms during stimulation as stimulation-induced errors across the patients who stutter. Case 1, 3, and 5, all of whom were operated awake, had language-positive sites resulting from falsely identified stuttering symptoms by the highly experienced nrTMS operator located directly in or in proximity to the lesion area (Fig. 1). As this rating was used during clinical routine, this could have promoted the decision for awake surgery. However, the decision for or against an awake surgery is typically determined based on heterogeneous factors to provide optimal care for each patient [2]. In order to be able to attribute more weight to language-positive points identified with nrTMS in or close to tumor location, a minimization of false positive points is necessary. As the present results indicate, this, among other things, depends on the differentiation of spontaneous speech motor symptoms manifesting during stimulation but not resulting from it.

Simultaneously, the less experienced nrTMS rater misclassified nearly two-thirds of all stuttering symptoms as stimulation-induced language errors across the five patients. Consequently, both raters misclassified many of these stuttering symptoms as stimulation-induced language-relevant, but fewer were rated as stimulation-induced errors by the more experienced rater. Our results suggest that the experience and expertise of the person conducting and analyzing the language mapping can reduce the amount of falsely identified speech motor symptoms.

Still, the more detailed assessment of stuttering types misclassified by both nrTMS operators indicated that not the number of mappings analyzed alone determines how well stuttering symptoms are differentiable from stimulation-induced language errors. When comparing stuttering symptoms misclassified as language systematic mistakes, the influence of individual prior knowledge about different disorders or error types became obvious. The less experienced rater classified a higher number of blocks and repetitions as language errors, and the highly experienced rater a higher number of prolongations. Whilst both raters had a significant yet moderate agreement for blocks and prolongations, no agreement was verified for repetitions of syllables or phonemes. These results highlight that irrespective of experience level, the two operators without prior training in diagnosing speech fluency disorders misclassified a considerable number of stuttering symptoms, especially for blocks and prolongations. Moreover, the only language error category both nrTMS operators misassigned the stuttering symptoms to was no response. Albeit results between nrTMS raters can vary [41], no response errors seem reproducibly identifiable and are often considered the most crucial error category in this context [41, 42]. The classification as "other" by the less experienced rater could either reflect a higher uncertainty about these stuttering-caused errors or a recognition that these differ from the typically classified language error categories [6,25].

Accordingly, the present results underline the benefit of experienced and trained specialists in analyzing preoperative language mappings, especially since the results can directly impact the stimulation sites identified as language-relevant preoperatively. This aligns with recommendations for intraoperative language testing during awake craniotomies [43]. Typically, the latter is performed in close collaboration with neuropsychologists or speech and language therapists in large centers [30,44–46].

4.2. Significance of the present study

The observed discrepancies in identifying speech fluency symptoms caused by preexisting stuttering from stimulation-induced language errors highlight the decreased reliability and specificity of language mapping results if the analysis is performed by raters untrained in stuttering diagnostics. The latter may substantially increase the amount of false positive language-relevant cortical sites in stuttering glioma patients. While preoperative nrTMS-based language mapping is increasingly integrated into neurosurgical routine [8], its biggest shortcoming remains the adequate identification of language-positive cortical sites [7,10,47,48]. During intraoperative language mapping, positive sites are typically used to localize and preserve areas critical for language function [3]. Consequently, the reliable identification of real language-relevant sites is essential. However, the current study's findings demonstrate that preexisting stuttering decreases mapping reliability and specificity as speech fluency symptoms cannot be consistently differentiated from stimulation-induced language errors by examiners who are experienced in mapping analysis yet untrained in stuttering diagnostics.

Typically, only items the patient can produce accurately and without systematic mistake are used, minimizing false positive errors caused by aphasia. Since already during baseline, a large percentage of all syllables produced were stuttered across patients, many items were excluded. At the same time, an item at which a stuttering symptom occurred once may be named correctly and fluently during the next presentation. Due to our cohort's unpredictable and random nature of stuttering symptom occurrence, they also manifested irrespective of baseline analysis during the preoperative stimulation exam.

Some studies linked cortical or subcortical stimulation to stuttering-like symptoms in brain tumor patients without preexisting speech fluency disorders. For instance, subcortical stimulation of the frontal aslant tract was related to speech fluency symptoms resembling core stuttering symptoms without the presence of any secondary symptoms typically associated with the speech fluency disorder [28]. Within the present study, only a tiny proportion of stuttering symptoms manifested simultaneously to the stimulation of the cortical endpoints of the frontal aslant tract. Moreover, since symptom patterns showed additional secondary behavior, tension, or heightened speech effort already described during the baseline prior to stimulation, these most likely were not elicited by stimulation application. Similarly, albeit a study linked stuttering-like repetitions to stimulation of the anterior and posterior supramarginal gyrus [25], the present findings could not associate stuttering-like symptoms with nrTMS application over these cortical sites. Overall, across stuttering patients stuttering symptoms arose irrespective of the stimulation site. Next to the distinct symptom pattern, this supports that these stuttering symptoms observed were not induced by stimulation application.

Moreover, stuttering was especially prominent in our awake surgery cohort. It seemed already challenging to differentiate stuttering symptoms in the preoperative setup in which nrTMS operators identify stimulation-induced language errors based on video recordings. Intraoperative language mapping, however, depends on an instant and prompt identification of language mistakes whilst the neurosurgeon applies the stimulation [12]. The simulated awake surgery analysis of instant differentiation within the first part of this study revealed that a high percentage of stuttering symptoms are promptly identifiable by the trained speech therapist if the nrTMS recording was only viewed once. Even if a higher stuttering rate seemed to decrease the percentage of promptly differentiated stuttering symptoms slightly, a minimum of 73 % of stuttering symptoms were identified for each patient. Enhancing the speech therapist's familiarity with the expression of stuttering symptoms, for instance, by performing thorough stuttering diagnostics prior to the resection, may improve the instant differentiation ability. At the same time, severe forms of stuttering may even contraindicate awake language monitoring with DES as an unreliable intraoperative patient's performance and specialist's identification of stimulation-induced language errors can directly impact the surgical approach and extent of resection. Further prospective research is required to evaluate the impact of trained and experienced specialists on the postoperative outcome, the influence of a specialist's familiarity with the individual symptom pattern, and the effect of stuttering severity on the feasibility of DES-based language mappings.

Also, as case 6, a woman with preexisting persistent developmental stuttering, showed, stuttering symptoms were present during the awake language mapping, and the rate increased during the course of surgery. Moreover, both non-silent blocks were classified as positive language-relevant sites. Since no positive cortical sites were found directly within the tumor area, these misclassified stuttering symptoms did not negatively impact the awake surgery in this case. Still, this speech motor impairment may directly affect the surgical approach in patients with higher stuttering rates. Consequently, identifying patients who stutter prior to surgery is highly important. The extent of resection and surgical outcome of these cases may benefit if the language mapping is performed with a qualified specialist experienced in stuttering diagnostics. To improve the sensitivity and reliability of language mappings, a better understanding of language errors caused by stimulation and the differentiation from errors caused by existing language and speech disorders is paramount.

4.3. Limitations and Perspectives

As indicated above, only a single awake surgery case with preexisting stuttering could be analyzed due to the lack of available intraoperative recordings for three post hoc awake cases. While this provided valuable insights into the potential influence on the gold standard, no generalizations can be drawn. For this, prospective and careful evaluations of the impact of stuttering on intraoperative DES language mapping with larger sample sizes would be necessary. Our results indicate that a differentiation between stimulation-induced language errors and stuttering symptoms based on video recordings that can repeatedly be replayed and thoroughly analyzed is already challenging preoperatively. Hence, in the time-constraint context of awake resections, requiring a prompt identification and classification of intraoperative errors, random and unpredictably manifesting speech motor errors may have an even more significant impact on the language mapping analysis.

Another critical aspect to consider is that the effects of a nrTMS operator's experience were not analyzed systematically or quantitatively. Subsequent studies could examine whether the number of mappings analyzed, the educational background, or social and environmental factors impact a rater's ability to identify stimulation-induced language errors and differentiate any preexisting language or speech (fluency) symptoms. Hence, these factors need to be recorded systematically, and the number of raters included needs to be increased in further studies. Still, the present study shows that relying on trained specialists such as speech therapists may increase reliability and consistency in analyzing patients with preexisting speech disorders. Subsequent studies are warranted to ascertain whether training nrTMS operators in differentiating speech (fluency) disorders may produce comparable results.

Additionally, identifying stuttering in patients in the first part could only be based on video recordings since no standardized stuttering diagnostics were routinely conducted. Prospective studies may benefit from a more detailed classification of stuttering symptoms, severity, and differentiation between acquired and developmental forms.

Moreover, only a small number of cases presented a stutter. This cohort of six, however, is already larger than most studies focusing on stuttering in brain tumor patients, which typically are based on single case descriptions [18,20]. Still, this number limited the statistical analysis possibilities. Further investigations could benefit from larger cohort sizes to generalize the results, especially in the context of heterogeneous brain tumors. Thus, large-scale, systematic, and multi-center studies may be required to recruit a large enough sample size, allowing for statistical comparisons, and extending the present study's findings.

5. Conclusion

The present study highlights the importance of differentiating stuttering manifesting in random and involuntary repetitions, prolongations, or blocks, from stimulation-induced disruptions of the language network during stimulation-based language mappings. The expertise of a nrTMS operator impacted the amount and type of stuttering symptoms misclassified. Across all the described cases, many stuttering symptoms were falsely classified as stimulation-induced language errors. Thus, a thorough differentiation by trained specialists may substantially increase the consistency, specificity, and reliability of language mapping in stuttering glioma patients. Due to the significant impact of this speech fluency disorder on the mapping results and interpretation, surgical planning and functional outcome may benefit considerably from an improved analysis procedure.

Data availability statement

Due to privacy restrictions of our clinical data, individual MRI and nrTMS data cannot be made publicly available. All data presented in this study are available upon reasonable request, access will be granted to named individuals in accordance with ethical procedures governing the reuse of sensitive data. Readers seeking access to the data are advised to contact the corresponding author, Prof. Dr. med. S.M. Krieg.

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CRediT authorship contribution statement

Leonie Kram: Writing – original draft, Investigation, Formal analysis, Data curation, Conceptualization. **Beate Neu:** Investigation, Formal analysis. **Axel Schröder:** Resources, Methodology, Investigation. **Bernhard Meyer:** Writing – review & editing, Supervision, Resources. **Sandro M. Krieg:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition. **Sebastian Ille:** Validation, Supervision, Resources, Project administration, Methodology.

Declaration of competing interest

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References

[1] H. Duffau, E. Mandonnet, The "onco-functional balance" in surgery for diffuse low-grade glioma: integrating the extent of resection with quality of life, Acta Neurochir. 155 (2013) 951–957, https://doi.org/10.1007/s00701-013-1653-9.
[2] S.L. Hervey-Jumper, M.S. Berger, Maximizing safe resection of low- and high-grade glioma, J. Neuro Oncol. 130 (2016) 269–282, https://doi.org/10.1007/s11060-016-2110-4.
[3] P.C. De Witt Hamer, S.G. Robles, A.H. Zwinderman, H. Duffau, M.S. Berger, Impact of intraoperative stimulation brain mapping on glioma surgery outcome: a meta-analysis, J. Clin. Oncol. 30 (2012) 2559–2565, https://doi.org/10.1200/JCO.2011.38.4818.
[4] S. Ille, N. Sollmann, V.M. Butenschoen, B. Meyer, F. Ringel, S.M. Krieg, Resection of highly language-eloquent brain lesions based purely on rTMS language mapping without awake surgery, Acta Neurochir. 158 (2016) 2265–2275, https://doi.org/10.1007/s00701-016-2968-0.
[5] N. Sanai, Z. Mirzadeh, M.S. Berger, Functional outcome after language mapping for glioma resection, N. Engl. J. Med. 358 (2008) 18–27, https://doi.org/10.1056/nejmoa067819.
[6] P. Lioumis, A. Zhdanov, N. Mäkelä, H. Lehtinen, J. Wilenius, T. Neuvonen, H. Hannula, V. Deletis, T. Picht, J.P. Mäkelä, A novel approach for documenting naming errors induced by navigated transcranial magnetic stimulation, J. Neurosci. Methods 204 (2012) 349–354, https://doi.org/10.1016/j.jneumeth.2011.11.003.
[7] T. Picht, S.M. Krieg, N. Sollmann, J. Rösler, B. Niraula, T. Neuvonen, P. Savolainen, P. Lioumis, J.P. Mäkelä, V. Deletis, et al., A comparison of language mapping by preoperative navigated transcranial magnetic stimulation and direct cortical stimulation during awake surgery, Neurosurgery (Baltim.) 72 (2013) 808–819, https://doi.org/10.1227/NEU.0b013e3182889e01.
[8] G. Raffa, M.C. Quattropani, A. Germanò, When imaging meets neurophysiology: the value of navigated transcranial magnetic stimulation for preoperative neurophysiological mapping prior to brain tumor surgery, Neurosurg. Focus 47 (2019) E10, https://doi.org/10.3171/2019.9.FOCUS19640.
[9] N. Sollmann, H. Zhang, A. Fratini, N. Wildschuetz, S. Ille, A. Schroder, C. Zimmer, B. Meyer, S.M. Krieg, Risk assessment by presurgical tractography using navigated TMS maps in patients with highly motor- or language-eloquent brain tumors, Cancers 12 (2020) 1264, https://doi.org/10.3390/cancers12051264.
[10] P.E. Tarapore, A.M. Findlay, S.M. Honma, D. Mizuiri, J.F. Houde, M.S. Berger, S.S. Nagarajan, Language mapping with navigated repetitive TMS: proof of technique and validation, Neuroimage 82 (2013) 260–272, https://doi.org/10.1016/j.neuroimage.2013.05.018.
[11] A. Pascual-Leone, D. Bartres-Faz, J.P. Keenan, Transcranial magnetic stimulation: studying the brain-behaviour relationship by induction of 'virtual lesions', Philos. Trans. R. Soc. Lond. B Biol. Sci. 354 (1999) 1229–1238, https://doi.org/10.1098/rstb.1999.0476.
[12] A. Talacchi, B. Santini, M. Casartelli, A. Monti, R. Capasso, G. Miceli, Awake surgery between art and science. Part II: language and cognitive mapping, Funct. Neurol. 28 (2013) 223–239, https://doi.org/10.11138/FNeur/2013.28.3.223.
[13] A. Craig-McQuaide, H. Akram, L. Zrinzo, E. Tripoliti, A review of brain circuitries involved in stuttering, Front. Hum. Neurosci. 8 (2014) 884, https://doi.org/10.3389/fnhum.2014.00884.
[14] A.C. Etchell, O. Civier, K.J. Ballard, P.F. Sowman, A systematic literature review of neuroimaging research on developmental stuttering between 1995 and 2016, J. Fluen. Disord. 55 (2018) 6–45, https://doi.org/10.1016/j.jfludis.2017.03.007.
[15] O. Bloodstein, N.B. Ratner, S.B. Brundage, A Handbook on Stuttering, 7 ed., Plural Publishing, Inc., San Diego, CA, 2021.
[16] E. Yairi, N. Ambrose, Epidemiology of stuttering: 21st century advances, J. Fluen. Disord. 38 (2013) 66–87, https://doi.org/10.1016/j.jfludis.2012.11.002.
[17] C. Cruz, H. Amorim, G. Beca, R. Nunes, Neurogenic stuttering: a review of the literature. Tartamudez neurogena: revision de la bibliografia, Rev Neurol 66 (2018) 59–64, https://doi.org/10.33588/rn.6602.2017151.
[18] R.J. Heuer, R.T. Sataloff, S. Mandel, N. Travers, Neurogenic stuttering: further corroboration of site of lesion, Ear Nose Throat J. 75 (1996) 161–168.
[19] K.J. Logan, Acquired stuttering, in: K.J. Logan (Ed.), Fluency Disorders: Stuttering, Cluttering, and Related Fleuncy Problems, second ed., Plural Publishing, Inc, 2022. Volume 2nd.
[20] K.B. Peters, S. Turner, Acquired stuttering due to recurrent anaplastic astrocytoma, BMJ Case Rep. (2013), https://doi.org/10.1136/bcr-2013-009562.

[21] R.C. Oldfield, The assessment and analysis of handedness: the Edinburgh inventory, Neuropsychol 9 (1971) 97–113, https://doi.org/10.1016/0028-3932(71)90067-4.

[22] N. Sollmann, A. Kelm, S. Ille, A. Schroder, C. Zimmer, F. Ringel, B. Meyer, S.M. Krieg, Setup presentation and clinical outcome analysis of treating highly language-eloquent gliomas via preoperative navigated transcranial magnetic stimulation and tractography, Neurosurg. Focus 44 (2018) E2, https://doi.org/10.3171/2018.3.FOCUS1838.

[23] S.M. Krieg, P. Lioumis, J.P. Mäkelä, J. Wilenius, J. Karhu, H. Hannula, P. Savolainen, C.W. Lucas, K. Seidel, A. Laakso, et al., Protocol for motor and language mapping by navigated TMS in patients and healthy volunteers; workshop report, Acta Neurochir. 159 (2017) 1187–1195, https://doi.org/10.1007/s00701-017-3187-z.

[24] K. Neumann, H.A. Euler, H.G. Bosshardt, S. Cook, P. Sandrieser, P. Schneider, M. Sommer, G. Thum, (Hrsg.: Deutsche Gesellschaft für Phoniatrie und Pädaudiologie). Pathogenese, Diagnostik und Behandlung von Redeflussstörungen. Evidenz- und konsensbasierte S3-Leitlinie [Pathogenesis, diagnostic and treatment of speech fluency disorders. Evidence- and consensus-based S3-guidelines], AWMF-Registernummer 049-013, 2016. Version 1, http://www.awmf.org/leitlinien/detail/ll/049-013.html. Gelesen am 01.09.2016 *im Auftrag der Leitliniengruppe. 2016.

[25] D.P. Corina, B.C. Loudermilk, L. Detwiler, R.F. Martin, J.F. Brinkley, G. Ojemann, Analysis of naming errors during cortical stimulation mapping: implications for models of language representation, Brain Lang. 115 (2010) 101–112, https://doi.org/10.1016/j.bandl.2010.04.001.

[26] S.M. Krieg, N. Sollmann, N. Tanigawa, A. Foerschler, B. Meyer, F. Ringel, Cortical distribution of speech and language errors investigated by visual object naming and navigated transcranial magnetic stimulation, Brain Struct. Funct. 221 (2016) 2259–2286, https://doi.org/10.1007/s00429-015-1042-7.

[27] F. Corrivetti, M.T. de Schotten, I. Poisson, S. Froelich, M. Descoteaux, F. Rheault, E. Mandonnet, Dissociating motor-speech from lexico-semantic systems in the left frontal lobe: insight from a series of 17 awake intraoperative mappings in glioma patients, Brain Struct. Funct. 224 (2019) 1151–1165, https://doi.org/10.1007/s00429-019-01827-7.

[28] R. Kemerdere, N.M. de Champfleur, J. Deverdun, J. Cochereau, S. Moritz-Gasser, G. Herbet, H. Duffau, Role of the left frontal aslant tract in stuttering: a brain stimulation and tractographic study, J. Neurol. 263 (2016) 157–167, https://doi.org/10.1007/s00415-015-7949-3.

[29] S. Ille, A. Schroeder, L. Albers, A. Kelm, D. Droese, B. Meyer, S.M. Krieg, Non-invasive mapping for effective preoperative guidance to approach highly language-eloquent gliomas—a large scale comparative cohort study using a new classification for language eloquence, Cancers 13 (2021) 207, https://doi.org/10.3390/cancers13020207.

[30] S.L. Hervey-Jumper, J. Li, D. Lau, A.M. Molinaro, D.W. Perry, L. Meng, M.S. Berger, Awake craniotomy to maximize glioma resection: methods and technical nuances over a 27-year period, J. Neurosurg. 123 (2015) 325–339, https://doi.org/10.3171/2014.10.JNS141520.

[31] R Core Team. R. A Language and Environment for Statistical Computing, R Foundation for Statistical Computing, Vienna, Austria, 2020. https://www.R-project.org/.

[32] Gamer M., Lemon J., Singh I.F.P., Irr: Various Coefficients of Interrater Reliability and Agreement. R Package Version 0.84, 2019. https://CRAN.R-project.org/package=irr.

[33] J.R. Landis, G.G. Koch, The measurement of observer agreement for categorical data, Biometrics 33 (1977) 159–174, https://doi.org/10.2307/2529310.

[34] Tvan den Brand T., ggh4x: Hacks for 'ggplot2'. R Package Version 0.2.1, 2021. https://CRAN.R-project.org/package=ggh4x.

[35] H. Wickham. ggplot2: Elegant Graphics for Data Analysis, Springer-Verlag, New York, 2016, https://doi.org/10.1007/978-0-387-98141-3.

[36] V. Schwarzer, I. Bährend, T. Rosenstock, F.R. Dreyer, P. Vajkoczy, T. Picht, Aphasia and cognitive impairment decrease the reliability of rnTMS language mapping, Acta Neurochir. 160 (2018) 343–356, https://doi.org/10.1007/s00701-017-3397-4.

[37] A.J. Gogos, J.S. Young, R.A. Morshed, S.L. Hervey-Jumper, M.S. Berger, Awake glioma surgery: technical evolution and nuances, J. Neuro Oncol. 147 (2020) 515–524, https://doi.org/10.1007/s11060-020-03482-z.

[38] S.M. Sheppard, R. Sebastian, Diagnosing and managing post-stroke aphasia, Expert Rev. Neurother. 21 (2021) 221–234, https://doi.org/10.1080/14737175.2020.1855976.

[39] P. Enderby, Disorders of communication: dysarthria, in: 1 ed, in: M.P. Barnes, D.C. Good (Eds.), Handbook of Clinical Neurology, vol. 110, Elsevier B.V., 2013, pp. 273–281.

[40] J.R. Duffy, Functional speech disorders: clinical manifestations, diagnosis, and management, in: M. Hallett, J. Stone, A. Carson (Eds.), Handbook of Clinical Neurology, vol. 139, 2016, pp. 379–388.

[41] N. Sollmann, T. Hauck, A. Hapfelmeier, B. Meyer, F. Ringel, S.M. Krieg, Intra- and interobserver variability of language mapping by navigated transcranial magnetic brain stimulation, BMC Neurosci. 14 (2013) 150, https://doi.org/10.1186/1471-2202-14-150.

[42] S. Ille, N. Sollmann, T. Hauck, S. Maurer, N. Tanigawa, T. Obermueller, C. Negwer, D. Droese, T. Boeckh-Behrens, B. Meyer, et al., Impairment of preoperative language mapping by lesion location: a functional magnetic resonance imaging, navigated transcranial magnetic stimulation, and direct cortical stimulation study, J. Neurosurg. 123 (2015) 314–324, https://doi.org/10.3171/2014.10.JNS141582.

[43] National Institute for Health and Care Excellence (NICE). Brain tumours (primary) and brain metastases in adults. NICE guidelines (2018). https://www.nice.org.uk/guidance/ng99.2018.

[44] A. Kelm, N. Sollmann, S. Ille, B. Meyer, F. Ringel, S.M. Krieg, Resection of gliomas with and without neuropsychological support during awake craniotomy-effects on surgery and clinical outcome, Front. Oncol. 7 (2017) 176, https://doi.org/10.3389/fonc.2017.00176.

[45] M. O'Neill, M. Henderson, O.M. Duffy, W.G. Kernohan, The emerging contribution of speech and language therapists in awake craniotomy: a national survey of their roles, practices and perceptions, Int. J. Lang. Commun. Disord 55 (2020) 149–162, https://doi.org/10.1111/1460-6984.12510.

[46] A. Fernandez Coello, S. Moritz-Gasser, J. Martino, M. Martinoni, R. Matsuda, H. Duffau, Selection of intraoperative tasks for awake mapping based on relationships between tumor location and functional networks, J. Neurosurg. 119 (2013) 1380–1394, https://doi.org/10.3171/2013.6.JNS122470.

[47] I. Bährend, M.R. Muench, H. Schneider, R. Moshourab, F.R. Dreyer, P. Vajkoczy, T. Picht, K. Faust, Incidence and linguistic quality of speech errors: a comparison of preoperative transcranial magnetic stimulation and intraoperative direct cortex stimulation, J. Neurosurg. 134 (2020) 1409–1418, https://doi.org/10.3171/2020.3.JNS193085.

[48] S. Ille, N. Sollmann, T. Hauck, S. Maurer, N. Tanigawa, T. Obermueller, C. Negwer, D. Droese, C. Zimmer, B. Meyer, et al., Combined noninvasive language mapping by navigated transcranial magnetic stimulation and functional MRI and its comparison with direct cortical stimulation, J. Neurosurg. 123 (2015) 212–225, https://doi.org/10.3171/2014.9.JNS14929.

11.2 CompreTAP: Feasibility and reliability of a new language comprehension mapping task via preoperative navigated transcranial magnetic stimulation

11.2.1 Summary of this publication and own contributions to this study

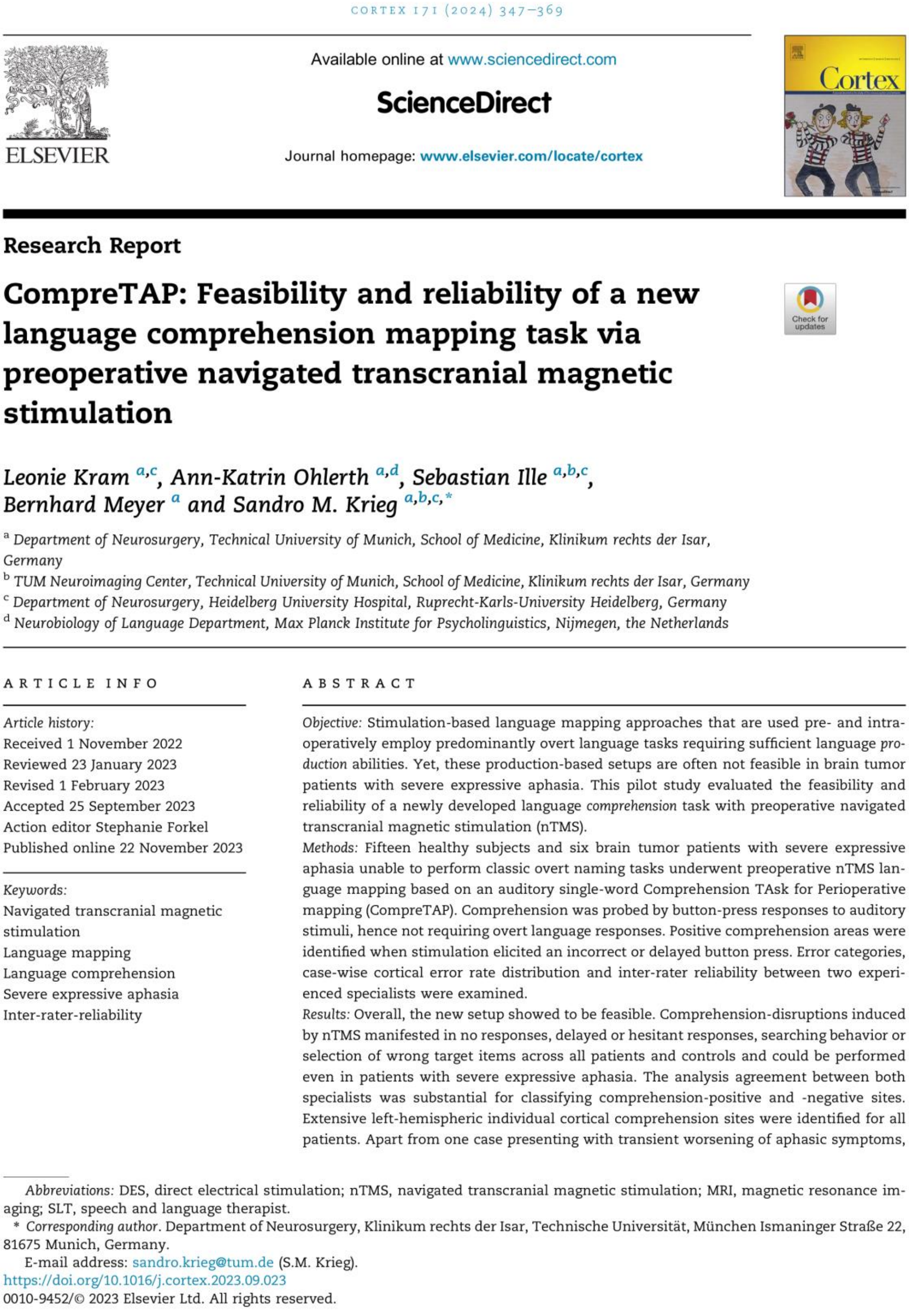
The second study incorporated into this thesis developed and tested the feasibility as well as reliability of a non-verbal single word comprehension mapping paradigm to allow stimulation-based language mappings in brain tumor patients who present with pre-existing severe expressive aphasia (Kram et al., 2024).

Patients with severe expressions of language disorders are frequently precluded from these language mapping approaches as a reliable association of stimulated cortical site and a hearable disruption in language task performance is not possible. Since stimulation-based language mappings thus far primarily use overt language tasks, sufficient language production skills are necessary, which particularly excludes patients with expressive deficits. To overcome this, Kram et al. (2024) developed a new non-verbal comprehension task based on button press instead of verbal responses for nTMS-based language mappings (CompreTAP). We performed a thorough literature review of existing comprehension diagnostical tools and neuroscientific research on the time course of auditory language comprehension to inform the stimulation protocol and timing during nTMS-based language mappings. In collaboration with Dr. Ohlerth, I constructed the language task, recruited six patients with severe expressive aphasia and 15 healthy controls to test the feasibility and reliability of the CompreTAP mapping paradigm. I carried out the majority of the mappings, performed one of the two stimulation examination analyses by identifying and categorizing stimulation-induced language comprehension errors which was necessary for inter-rater comparisons. Moreover, I ran all statistical analyses and created all figures included in the final manuscript. This analysis revealed that stimulation-induced comprehension errors as indicated by deviant response behavior during subjects' button press were identified with substantial inter-rater reliability. Moreover, I evaluated the distribution of the error rates across predefined cortically parcellated areas which revealed a high inter-rater variability for cortical comprehension sites across patients and controls at single-case level, yet at group level the association of commonly known cortical areas with language comprehension. This underlined the validity of this comprehension-based mapping setup.

I, moreover, supported the creation of clinical tractographies used for preoperative surgical planning which provided initial support for the utility of this mapping paradigm in supporting functional preservation if the results are used clinically (Kram et al., 2024).

I, furthermore, performed the additional analysis of reaction times and comparisons of the intensity of auditory item stimuli with the noise of the stimulation system. I carried out the final literature research, wrote the initial draft of the manuscript, and revised it according to the co-authors' remarks and reviewer comments provided during the review process in Cortex. All steps were carried out under supervision of Prof. Krieg.

11.2.2 Publication



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Research Report

CompreTAP: Feasibility and reliability of a new language comprehension mapping task via preoperative navigated transcranial magnetic stimulation

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ABSTRACT

Objective: Stimulation-based language mapping approaches that are used pre- and intraoperatively employ predominantly overt language tasks requiring sufficient language *production* abilities. Yet, these production-based setups are often not feasible in brain tumor patients with severe expressive aphasia. This pilot study evaluated the feasibility and reliability of a newly developed language *comprehension* task with preoperative navigated transcranial magnetic stimulation (nTMS).

Methods: Fifteen healthy subjects and six brain tumor patients with severe expressive aphasia unable to perform classic overt naming tasks underwent preoperative nTMS language mapping based on an auditory single-word Comprehension TAsk for Perioperative mapping (CompreTAP). Comprehension was probed by button-press responses to auditory stimuli, hence not requiring overt language responses. Positive comprehension areas were identified when stimulation elicited an incorrect or delayed button press. Error categories, case-wise cortical error rate distribution and inter-rater reliability between two experienced specialists were examined.

Results: Overall, the new setup showed to be feasible. Comprehension-disruptions induced by nTMS manifested in no responses, delayed or hesitant responses, searching behavior or selection of wrong target items across all patients and controls and could be performed even in patients with severe expressive aphasia. The analysis agreement between both specialists was substantial for classifying comprehension-positive and -negative sites. Extensive left-hemispheric individual cortical comprehension sites were identified for all patients. Apart from one case presenting with transient worsening of aphasic symptoms,

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Abbreviations: DES, direct electrical stimulation; nTMS, navigated transcranial magnetic stimulation; MRI, magnetic resonance imaging; SLT, speech and language therapist.

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pre-existing language deficits did not aggravate if results were used for subsequent surgical planning.

Conclusion: Employing this new comprehension-based nTMS setup allowed to identify language relevant cortical sites in all healthy subjects and severely aphasic patients who were thus far precluded from classic production-based mapping. This pilot study, moreover, provides first indications that the CompreTAP mapping results may support the preservation of residual language function if used for subsequent surgical planning.

1. Introduction

Language comprises a highly complex, interconnected neural network synchronizing numerous expressive and receptive functions (Chang et al., 2015; Friederici, 2017; Tremblay, Dick, & Small, 2011). Localizing functionally relevant areas necessary for language is one of the major objectives in the treatment of language-eloquent brain tumors in order to balance the overall survival, functional outcome and quality of life (Duffau & Mandonnet, 2013; Gogos et al., 2020; Ottenhausen, Krieg, Meyer, & Ringel, 2015). Whilst for this matter direct electrical stimulation (DES) during awake surgeries remains the gold standard, non-invasive navigated transcranial magnetic stimulation (nTMS)-based language mapping is increasingly employed preoperatively (Bährend et al., 2020; De Witt Hamer et al., 2012; Haddad et al., 2021; Ille, Sollmann, et al., 2016; Mandonnet et al., 2010; Picht et al., 2013; Szelényi et al., 2010; Tarapore et al., 2016). Both, nTMS and DES mapping allow localization of areas relevant for language function and, therefore, can guide preoperative planning and intraoperative resection, respectively.

Typically, overt *production* tasks are employed during language mapping (Hauck et al., 2015; Krieg et al., 2017; Rofes et al., 2015; Talacchi et al., 2013; Tarapore et al., 2013) as stimulation methods rely on identifying a causal link between a stimulation of a specific cortical area and the transient disruption of language function. The latter typically manifests in expressive language mistakes. However, these overt production tasks can be challenging for patients with language impairments affecting productive language abilities. Brain tumors located within language-eloquent areas can cause precisely these inabilities by affecting single or multiple stages of language (Faulkner et al., 2017; IJzerman-Korevaar et al., 2018). Expressive aphasia, one of the most widely studied and known language impairments, predominantly affects language production abilities whilst comprehension skills may be well preserved (Fridriksson et al., 2015). Studies suggest that preoperative language mapping can be confounded by distinct or severe aphasia as these impairments can lead to an increased number of errors during nTMS-based language mapping (Schwarzer et al., 2018). Especially severe manifestations of expressive aphasia can preclude patients completely from these overt production-based language mappings since patients are unable to name sufficient or any items repeatedly and correctly. Nonetheless, their comprehension skills may still be preserved enabling a comprehension-based language mapping. Fernandez Coello and colleagues stressed the importance of choosing stimulation tasks based on patient- and lesion-specific characteristics (Fernandez Coello et al., 2013). Hence, it is very important to develop tasks for patients with tumors affecting productive language skills and thereby to allow a language mapping pre- and intraoperatively in order to preserve unaffected language abilities.

More and more tasks and intraoperative testing batteries specifically target receptive functions (Alarcon et al., 2019; Bello et al., 2007; De Witte et al., 2015; Fernandez Coello et al., 2013; Gatignol et al., 2004; Martin-Monzon et al., 2022; Rofes et al., 2015; Rofes & Miceli, 2014). Yet, most of these receptive tasks still require an overt response by the patient. Only one pilot study tested the feasibility and the optimal stimulation parameters for an auditory sentence comprehension task during preoperative nTMS-based language mapping in three pediatric patients not requiring overt responses (Rejno-Habte Selassie et al., 2020). Reliable pre- and intraoperative language tasks entail the usage of items that a patient can respond to promptly and accurately during a time-restricted rapid presentation (Krieg et al., 2017; Rofes et al., 2015; Talacchi et al., 2013). However, these setups of *overt* or complex auditory comprehension tasks might be challenging for patients with expressive language impairments especially under the time-constrained conditions during language mapping.

Thus far, no study in adult patients with language-eloquent tumors and language deficits employed a receptive language test for preoperative stimulation-based language mapping. Therefore, developing a task suitable for patients with severe expressive aphasia unable to perform classic overt language mapping tasks is highly valuable. To this end, this pilot-study aims to evaluate the feasibility and reliability of a newly developed language Comprehension TAsk for Perioperative mapping (CompreTAP) in brain tumor patients with severe expressive aphasia and in healthy controls. Prior to testing this new setup in the operating room under more challenging and time-restricted conditions, this study examines its effectiveness and utility for preoperative nTMS language mapping. Since it is yet unknown in which ways comprehension-errors manifest in this new setup, we, moreover, assessed the analysis agreement of error evaluation between a neurolinguist and a trained speech and language therapist.

2. Material and methods

We report all data exclusions, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study. Since this pilot study tested the feasibility of this new comprehension task within a first small cohort, no a priori sample size calculations were performed.

2.1. *Patient and healthy subject population*

Six brain tumor patients and 15 healthy controls were prospectively included between July 2021 and June 2023. All subjects needed to be at least 18 years old, German native speakers, and present without contraindications for magnetic resonance imaging (MRI) or nTMS such as cochlear implants or cardiac pacemakers. The absence of any neurological or psychiatric history was additionally required for the inclusion of healthy controls, patients needed to present with a severe expressive aphasia. This was attributed by a trained speech and language therapist (SLT) based on the individual performance on an object naming task typically used for preoperative nTMS language mapping (Krieg et al., 2017). Aphasia severity was rated from 0 = no aphasia to 5 = very severe aphasia. This rating is a modified version of a rating based on the Aachener Aphasie Test (Huber et al., 1983) used in former publications (Ille et al., 2021; Ille, Kulchytska, et al., 2016; Picht et al., 2013). Two additional severity points were added to the scale: No deficit (0), minimal symptoms such as occasional word finding difficulties with no impact on daily communication (1), light aphasic symptoms with a small impact on daily communication (2), moderate aphasic symptoms impacting but not limiting daily communication (3), severe aphasic symptoms with a profound impact on daily communication but simple communicative tasks still possible (4), Extremely severe aphasia precluding patients from daily communication (5). This allows to differentiate aphasia severity more thoroughly, particularly light symptoms. While the Aachener Aphasie Test is very useful in identifying moderate and severe aphasia, it does not differentiate minimal aphasic symptoms from no aphasic symptoms which may not adequately reflect the wide severity spectrum observed in clinical routine. Handedness was tested with the Edinburgh Handedness Inventory (Oldfield, 1971). Moreover, standardized language eloquence levels (low: 0–2, moderate: 3–5, high: 6–9) were determined for patients' tumors based on a recently published classification system (Ille et al., 2021).

Participants provided written informed consent. The study was approved by the local ethics committee of the Institutional Review Board (reference number: 192/18S) and followed the guidelines of the Declaration of Helsinki.

No part of the study procedures or analysis plans was preregistered prior to the research being conducted. The data is stored in an institutional repository and not publicly available due to hospital legislation and medical ethical objections. All data presented in this study are available upon reasonable request, access will be granted to named individuals in accordance with ethical procedures governing the reuse of sensitive data, i.e., if the ethical committee approves and if the data sharing agreement is signed by both a demanding and providing party. Readers seeking access to the data are advised to contact the corresponding author, Prof. Dr. med. S.M. Krieg.

2.2. *MR image acquisition*

Patients and healthy controls underwent a standardized structural MRI protocol in the department of neuroradiology on a 3-T MRI scanner (Achieva dStream or Ingenia; Philips Healthcare, Best, Netherlands) with an 8- or 32-channel phased-array head coil (Sollmann et al., 2016, 2018). This comprised at least a Diffusion Tensor Imaging (DTI) sequence with 32 diffusion sensitizing gradient directions as well as a three-dimensional T1-weighted gradient echo sequence, for healthy controls without contrast agent administration and for patients with and without contrast agent, respectively. These structural scans were subsequently used for neuronavigation to individually guide nTMS-coil positioning during stimulation.

2.3. *CompreTAP task*

Since one of our primary objectives was to construct a test suitable for patients with aphasia, classic diagnostic tools for rehabilitation planning as well as symptom and severity estimation acted as an initial orientation (Huber et al., 1983; Kertesz, 2007). These aphasia diagnostic instruments typically include an auditory language comprehension section which tests single-word as well as sentence comprehension. Based on one commonly employed tool in Germany, the Aachener Aphasie Test (Huber et al., 1983), our test consists of auditorily presented target items which were simultaneously shown in sets of four picture stimuli from which the correct target item had to be selected. In contrast to these commonly used tests, we opted for presentation of items without semantically or phonologically related distractors in each set of four black-and-white drawings in order to fit the task to the time-restricted presentation mode that can be time-locked to the stimulation application. The 62 items of everyday objects and animals stem from the object naming test of "the Verb And Noun Test for Peri-Operative testing (VAN-POP)" (Ohlerth et al., 2020). Thus, word frequencies, age of acquisition, syllable lengths and livingness of objects were balanced for in our item set. Legal copyright restrictions do not permit us to publicly archive or share the full set of stimuli used in this experiment in a trusted digital repository. All items used stem from the "verb and noun test for peri-operative testing (Van-POP)", the copyright of the pictures belongs to the Rijksuniversiteit Groningen, the Netherlands. Readers seeking access to the stimuli are advised to contact the author, Dr. A.-K. Ohlerth [Ann-Katrin.Ohlerth@mpi.nl; ann.katrin.ohlerth@gmail.com]. Stimuli will be released if the declaration of usage agreement is signed, and all points of the agreement are followed closely. On the basis of these 62 items, sets of four figures were created, no additional masker figures were integrated. The items were randomly combined, while the only constraint applied was to control for phonological and semantic similarities precluding any distractor items. Each item was used on average 3.94 times for 28 different item sub-sets, which in turn each appeared on average twice. Moreover, the position of items was varied throughout, none of the item sub-sets re-appeared in identical order. All these sets were presented via PowerPoint on a computer screen together with non-synthesized pre-recordings of the target item (mean duration of prerecording: 1.0 sec, range: .5 sec–1.6 sec). The background of each of the four images on a slide were color-matched to four colored buttons and their respective position (left or right column, upper or lower row) and were placed between the participant and the computer screen. Fig. 1 shows the setup in an example item. As soon as the four images appeared on screen, participants heard the auditorily presented target word and were asked to select the matching target item by pressing the button with the corresponding color. To minimize hand motor difficulties during button press while stimulation is applied, patients were instructed to use their fingers of the left hand for pushing the button – ipsilateral to the subsequently stimulated left hemisphere. The presentation of the picture stimuli and the auditory stimulus were onset-aligned. Picture presentation lasted for 4 sec. Moreover, Big-Point recordable buttons (TTS, Nottinghamshire, UK) which are typically employed in context of alternative communication were used as these allowed to pre-record the color label of each button. Consequently, each button press elicited the corresponding pre-recorded color label of the respective button chosen. This acted as an auditory control for the nTMS operator during the analysis of the reaction times post-mapping and allowed to monitor closely patient's performance and attention to the task during the mapping.

2.4. *nTMS-based CompreTAP language mapping*

Participants underwent language mapping using the Nexstim eXimia NBS system, version 5.1 with a NEXSPEECH® module (Nexstim Plc, Helsinki, Finland). Prior to performing the comprehension task under stimulation, subjects and patients completed two baseline trials without nTMS to preclude any items that could not be identified promptly and correctly by the individual. Based on numerous neuroimaging findings demonstrating that acoustic-phonetic, lexical, morphologic as well as syntactic and semantic comprehension processes are all performed within under 1 sec after auditory stimulus onset (Bornkessel-Schlesewsky et al., 2016; Eckstein & Friederici, 2006; Friederici, 2002, 2011; Getz & Toscano, 2021; Hagoort et al., 2004), stimulation during nTMS mapping was applied for 2 sec (10 repetitive pulses) covering the entire duration of the auditory stimulus presentation and presumed comprehension processes. The inter-stimulation interval was set to 4000 msec matching the slide presentation duration. Following our standard object naming protocol, the stimulation frequency was applied at 5 Hz, the intensity set at 110% of the ipsilateral resting motor threshold (Krieg et al., 2016, 2017). The resting motor threshold is defined as the minimum necessary stimulation intensity needed for eliciting a motor evoked potential in the abductor pollicis brevis. The nTMS comprehension mapping targeted the majority of the frontal, parietal and temporal lobe of the left, tumor-hemisphere as these results were substantial for the subsequent surgical workflow. Each of 46 predetermined left-hemispheric stimulation target sites was stimulated three times with repetitive nTMS (Fig. 2, abbreviations Table 1).

"Kalender" [engl. calendar]

Fig. 1 – Exemplary item setup. Each item comprises an auditorily presented target item (calendar) and four visually presented items shown simultaneously on the computer screen with the respectively colored background matching four colored buttons.

2.5. *Identification of language comprehension positive nTMS sites*

The camera of the nTMS device was positioned in such a way that it could record the hand movement of the subject or patient reaching for the button. Moreover, the auditorily presented target item and button-press sounds were recorded on video. Two nTMS operators specialized on language and language impairments, a trained SLT (rater 1, LK) and a neurolinguist (rater 2, AKO), with extensive nTMS mapping experience of standard overt naming protocols (rater 1: ~100, rater 2: >200 language mappings), identified stimulation-induced comprehension errors based on video recordings of the stimulation exam. Videos were scanned for deviant behavior during button press compared to baseline behavior, such as delayed or incorrect responses or change of hand positioning. Blinded to the stimulation site, both raters finally marked all comprehension errors following stimulation-caused disruptions of the language network as comprehension-positive. These were then transferred to the neuronavigation system indicating specific cortical sites at which stimulation elicited a comprehension error, allowing to delineate comprehension-positive and comprehension-negative cortical sites. Error rates were defined as the number of errors divided by number of stimulations applied for each cortical region as parcellated based on Corina's cortical system (Corina et al., 2005, Fig. 2, Table 1). All error rates reported prior to inter-rater assessment were based on the analysis of rater 1.

Since the introduction of synchronous video recordings and nTMS mappings the video-based analysis became standard and is widely applied across centers in the field of pre-operative nTMS-based language and cognitive mappings (Lioumis et al., 2012). It allows to identify a wide variety of

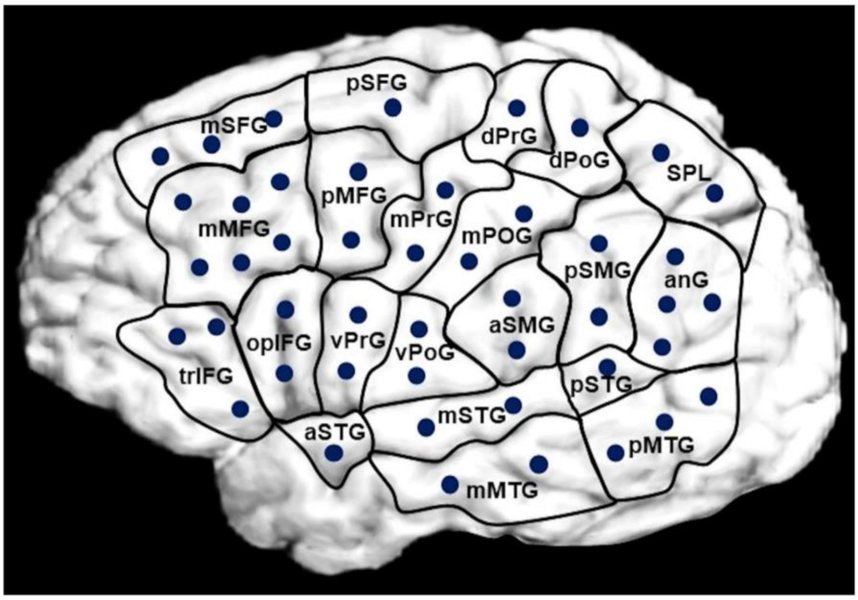

Fig. 2 – Stimulation target template. Depicted are 46 left-hemispheric targets based on cortical parcellation system (CPS) regions. See Table 1 for corresponding abbreviations of CPS regions.

Table 1 – Overview of cortically parcellated areas.

Abbreviation	Cortical anatomical area
anG	Angular gyrus
aSMG	Anterior supramarginal gyrus
aSTG	Anterior superior temporal gyrus
dPoG	Dorsal postcentral gyrus
dPrG	Dorsal precentral gyrus
mMFG	Middle middle frontal gyrus
mMTG	Middle middle temporal gyrus
mPoG	Middle postcentral gyrus
mPrG	Middle precentral gyrus
mSFG	Middle superior frontal gyrus
mSTG	Middle superior temporal gyrus
opIFG	Opercular inferior frontal gyrus
pMFG	Posterior middle frontal gyrus
pMTG	Posterior middle temporal gyrus
pSFG	Posterior superior frontal gyrus
pSMG	Posterior supramarginal gyrus
pSTG	Posterior superior temporal gyrus
SPL	Superior parietal lobe
trIFG	Triangular inferior frontal gyrus
vPoG	Ventral postcentral gyrus
vPrG	Ventral precentral gyrus

The table provides an overview of the cortical parcellations system shown in Fig. 1, based on Corina et al. (2005) and the corresponding abbreviations used.

stimulation-induced errors with a high accuracy and reliability, such as no responses or semantic and phonologic paraphasias (Lioumis et al., 2012; Sollmann et al., 2013). Still, while accounting for a large proportion of identified errors, hesitant responses are typically considered as the most subjective and least reliable error category induced by nTMS (Krieg et al., 2016; Ohlerth, Bastiaanse, Negwer, et al., 2021). The initial identification of hesitant responses by both nTMS operators was based on the video recordings, as this is thus far the standard approach in preoperative nTMS-based language mappings during clinical routine. Moreover, additional reaction time analyses were performed to ascertain the reliability and accuracy of this most subjective error category based on an approach proposed by Schramm et al. (2020). All video recordings available in .asf format were copied to an external computer to extract the audio track in .wav format. For this, the Python-module MoviePy version 1.0.3 (Zulko, 2020) was employed. Subsequently Praat version 6.3.04 (Boersma & Weenink, 2023) was used to measure the response times for each item separately. The reaction time between each auditory stimulus onset and the onset of the respective prerecorded color label elicited with each button press were measured and documented. All items at which any other error type occurred, i.e., press of the wrong target button, searching behavior or no responses were excluded. Subsequently, hesitations in reaction time were defined as all responses that exceeded two standard deviations of the mean response time per individual and compared to the analysis of rater 1. Moreover, since reaction times tend to vary over the course of the stimulation examination, the mean and standard deviation of the last five error-less items preceding the item marked as hesitant by rater 1 were examined separately.

2.6. Function-based tractography of the subcortical language network

All language-positive cortical sites were subsequently used as seeds for an individual tractography of the functional language network. DTI-based tractography was conducted with a deterministic tracking algorithm embedded into Brainlab Elements (version 3.2.0.281; Brainlab AG, Munich, Germany) following a standard protocol (Negwer et al., 2017; Sollmann et al., 2018; Sollmann, Zhang, Schramm, et al., 2020). These results were subsequently used to guide preoperative surgical planning and intraoperative resection of the tumor. Albeit the present nTMS-based tractography results allow not to draw any conclusions about the benefit of this comprehension-based functional tractography compared to other possible variants, they offer preliminary insights into the utility of this mapping setup for preserving residual language function as the combined results of comprehension-positive cortical sites and subsequent tractography were used perioperatively to support the preservation of language skills in the present cohort.

2.7. Inter-rater reliability and statistical analysis

All statistical analyses were performed with R (R Core Team, 2020). A *p*-value <.05 was considered statistically significant. To ascertain the reliability of this newly developed task, the two raters individually analyzed the video recordings of the stimulation exams. Cohen's kappa was used to compute inter-rater agreement between the two nTMS operators (Gamer et al., 2019) as well as between the analysis of hesitant responses by rater 1 and hesitations identified with the reaction time analysis. A kappa of 1 was considered almost perfect (Landis & Koch, 1977). Bangdiwala's agreement chart for categorical data was used to additionally graphically compare inter-rater reliability (Bangdiwala, 1988; Bangdiwala & Shankar, 2013).

To ascertain the impact of noise caused by the nTMS application on participant's ability to hear the auditory stimulus presented simultaneously, a post-hoc comparison of the respective intensities in isolation was conducted. For this, audio recordings were taken of exemplary stimulation-noises of 20 pulses for different stimulation intensity settings as well as of 10 exemplary item presentations, with a distance of 3 cm between recording device and the stimulation coil/the PC-screen. Mean intensity values were extracted with Praat (Boersma & Weenink, 2023) and analyzed descriptively.

3. Results

3.1. Identifiable error categories

For all patients and controls, nTMS application led to recognizable comprehension-errors. Across patients and controls, the following comprehension error categories were identified and subsequently marked as comprehension-positive:

No response errors comprise stimulation-induced errors in which subjects did not select any item – similar to no response naming errors observed during naming-based language mapping (Corina et al., 2010).

Searching behavior were responses during which a subject did not select the target item promptly but was heading for different buttons with an obvious uncertainty while eventually pressing a correct target item.

Selection of wrong target item were errors in which a subject pressed a colored button corresponding to any of the other three visually presented items, e.g., “key” (red button) was pressed instead of the target “saw” (blue button). These errors correspond to the semantic error category, found in production-based language mapping, where an incorrect label is uttered during naming.

Hesitations/delayed responses were classified if subjects showed an obvious hesitant selection of the target item or chose the correct button with significant delay compared to baseline behavior.

All of these errors attributed to comprehension difficulties induced by stimulation were differentiated from hand-motor or coordinative difficulties. The latter was assigned on the basis of non-directed hand motor activation not clearly aimed at a specific button. Still, these error types appeared only very rarely since the left hand, ipsilateral to the stimulated hemisphere was used for button pressing.

3.2. Healthy subject characteristics and comprehension mapping results

Fifteen healthy subjects completed the comprehension language mapping. All subjects were able to perform the language comprehension task during baseline at ceiling levels, with 100.0% of items being identified correctly and promptly twice prior to nTMS application. Moreover, the language comprehension task was feasible during nTMS application in all subjects and nTMS-induced comprehension errors could be identified in all individuals. For a detailed overview of subject characteristics and individual error rates during nTMS see Table 2. The individual, illustrative error rates across CPS regions for the first six healthy controls (C1–C6) are additionally depicted in Fig. 3.

Table 2 – Overview of subject characteristics and error rate during nTMS application.

Subject	Age	Sex	Handedness	Error rate during nTMS
C1	31	Female	R	10.1%
C2	26	Male	R	3.0%
C3	25	Female	R	5.1%
C4	25	Female	R	8.0%
C5	24	Female	R	16.7%
C6	33	Male	R	12.3%
C7	26	Male	R	11.6%
C8	20	Female	R	9.4%
C9	24	Male	R	4.3%
C10	28	Female	R	7.2%
C11	24	Male	R	20.3%
C12	27	Male	R	7.2%
C13	23	Male	R	12.3%
C14	25	Female	R	12.3%
C15	22	Female	R	9.4%

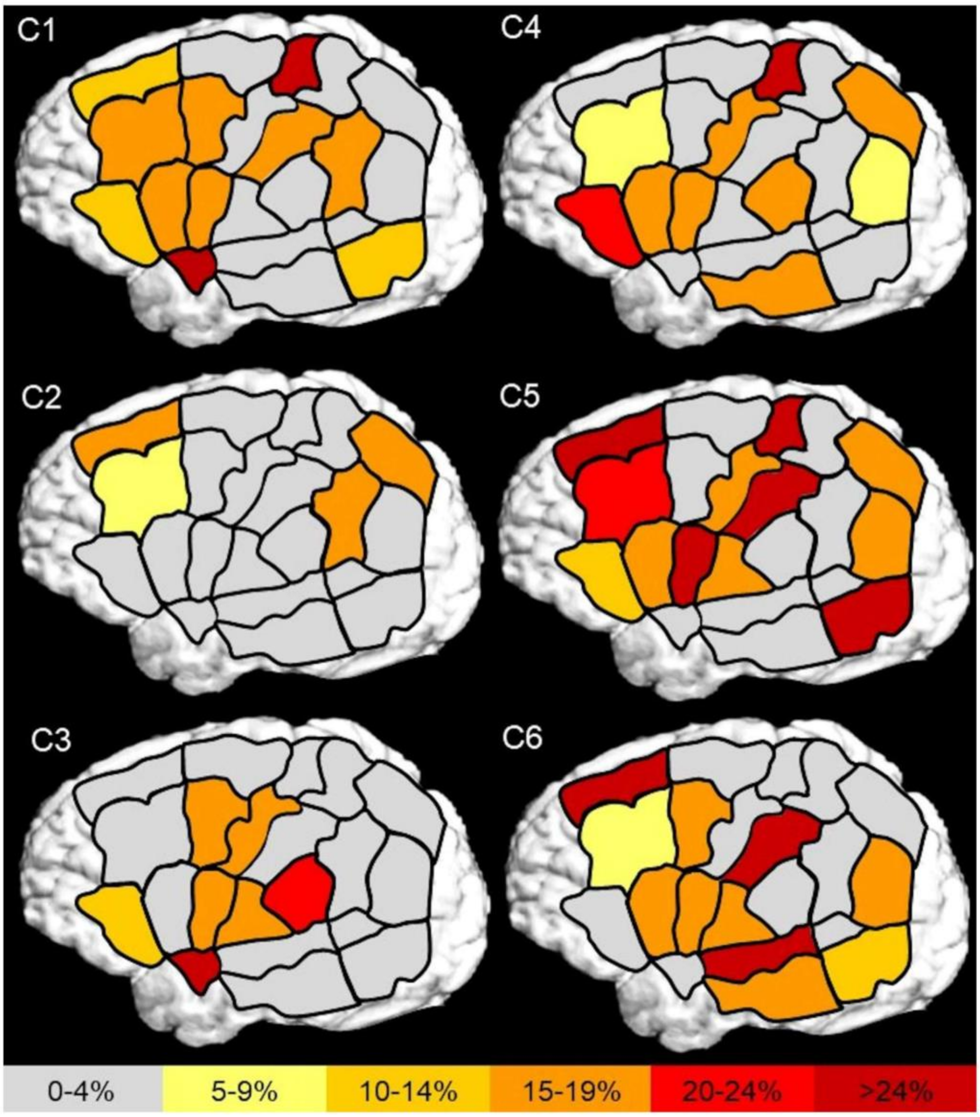

Fig. 3 – Error rate distribution in six illustrative healthy controls. Case-wise presentation of cortical error rate distribution in percent across predefined CPS regions for each healthy control (C1–C6).

3.3. Patient characteristics and comprehension mapping results

The new comprehension-based language mapping setup was piloted in six patients with language-eloquent intracranial lesions (overview of patient characteristics in Table 3). All patients presented with a severe expressive language deficit, i.e., classic object-naming-based language mapping was not feasible. Apart from case 2 who was still able to name numbers, none of the patient could perform any other expressive language task. Thus, for the latter five patients, the comprehension-positive nTMS results were used to prepare functionally relevant language tractography.

All patients were able to understand the instructions to the comprehension task and could reliably and reproducibly identify a sufficient number of items – on average 62.8% (±21.6%) – via button-press during the two baseline trials. The individual item set, which finally only comprised the items a patient identified correctly, was used during stimulation. A detailed overview of the patients' preexisting language deficit,

Table 3 – Overview of patient characteristics, tumor entity and location, as well as standardized language eloquence levels.

Patient	Age	Sex	Handedness	Tumor entity	Tumor location	Language eloquence
P1	63	Male	A	GBM Re	Parieto-occipital	7
P2	69	Male	R	GBM Re	Limbic	7
P3	71	Male	R	GBM	Temporo-occipital	8
P4	60	Female	R	GBM Re	Temporo-occipital	8
P5	43	Female	R	M	Frontal, temporal	5
P6	72	Female	R	GBM	Frontal	8

The table provides an overview of age, sex, handedness (R = right-handed, A = ambidextrous), tumor entity (GBM = glioblastoma, M = metastasis, Re = recurrence), tumor location and language eloquence level (0–9).

number of errors and error rate during the baseline prior to nTMS, number of stimulations applied in total and errors during nTMS, as well as the resulting error rate during nTMS are provided in Table 4. The individual error rates across CPS regions are additionally depicted in Fig. 4. In some of the cases, the placement of the individual targets was adjusted due to tumor location, edema or a previous resection. Moreover, as Appendix A shows, some patient cases did not tolerate the stimulation within some frontal or anterior temporal areas due to increased pain levels.

In the five cases, in which comprehension-based nTMS results and subsequent functionally-relevant tractographies were used to guide surgical planning and resection, four patients did not develop any new language deficits post-surgery. Case 6, however, showed a transient worsening of aphasic symptoms directly post-surgery which improved during the postsurgical one-week hospitalization.

In the following section, two illustrative cases will be described in detail. For these two patients, case 1 and case 6, the comprehension-based DTI-tractography results are illustrated in Fig. 5.

3.3.1. *Case 1*

This ambidextrous 63-year-old male patient was referred to our department after an external clinic suspected a left, parieto-occipital glioblastoma recurrence. The patient presented with a worsening of a pre-existing aphasia eight months after his first resection and subsequent radiochemotherapy. He had a high grade of language eloquence (grade: 7). The patient was unable to perform object or number naming preoperatively due to the highly severe expressive aphasia. However, he was able to understand the instructions to the comprehension task and could complete 47.6% of items correctly during the two baseline trials. Disruptions of nTMS predominantly elicited searching behavior or no responses, rarely selection of a wrong target item. The error rate under nTMS was 14.9%. Cortical areas with the highest error rates comprised parietal and temporal ones (Fig. 4, P1): anG, pSTG, pMTG and SPL. Since this was the only feasible task for case 1, the results of the nTMS language mapping were used to prepare functionally relevant language tractography and to guide intraoperative resection. Histopathology confirmed a WHO grade IV glioblastoma. Clinical assessment indicated no new language deficits post-surgery.

3.3.2. *Case 6*

Case 6, a 72-year-old right-handed, female patient, presented with increasing aphasic symptoms since 3–4 weeks. Preoperative imaging indicated a left glioblastoma within the opercular inferior frontal gyrus. Analysis indicated a high language eloquence (grade: 8). This diagnosis was supported by histopathological results post-surgery. Her language production abilities were severely impaired prior to craniotomy. The production of single-words alone was possible. However, rapid and prompt naming as needed for overt language mapping was not feasible. Additionally, the tumor also seemed to affect language comprehension skills, as she was only able to select 37.1% of comprehension items correctly. Since these, however, were possible reliably and repeatedly, the comprehension task was used for nTMS language mapping and its results for function-specific tractography and neurosurgical guidance. Under stimulation, case 6 made 25.4% comprehension errors, including no response errors and delayed responses, selection of wrong target item and searching behavior. P6 had overall high error rates particularly in parietal and temporal regions and in the opIFG (Fig. 4, P6). Directly post-surgery, her aphasic symptoms were transiently stronger pronounced, but improved substantially during clinical stay.

Table 4 – Overview of the individual language status and error rate during nTMS application.

Patient	Aphasia[a]	Number (percentage) of baseline errors	Number of repetitive stimulations applied	Number of errors during nTMS	Error rate during nTMS
P1	E5, R3	33 (52.4%)	121	18	14.9%
P2	E4, R0	3 (4.8%)	134	26	19.4%
P3	E5, R3	31 (50.0%)	137	24	17.5%
P4	E5, R1	6 (9.7%)	138	16	11.6%
P5	E5, R2	26 (41.9%)	125	26	20.8%
P6	E5, R3	39 (62.9%)	138	35	25.4%

[a] Severity 0–5, E = expressive, R = receptive.

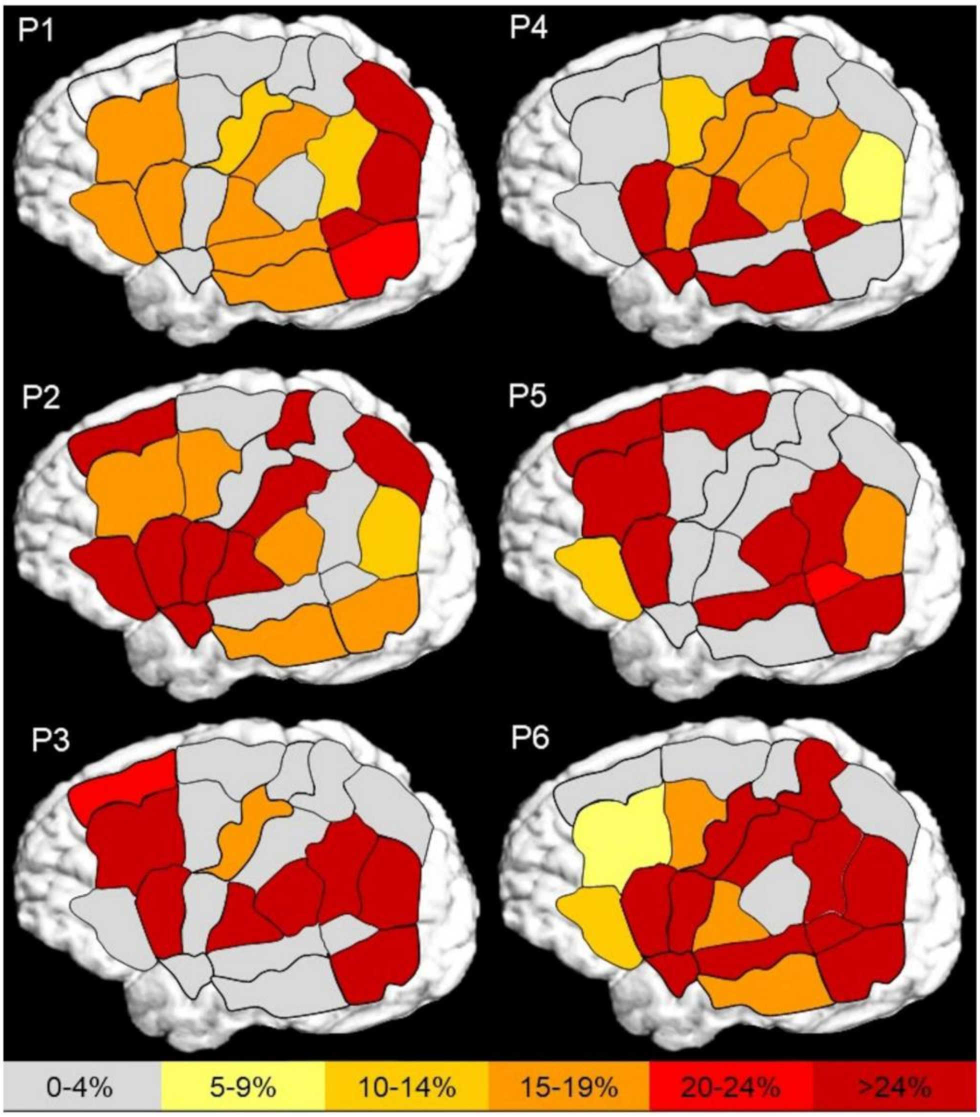

Fig. 4 – Error rate distribution in patient cohort. Case-wise presentation of cortical error rate distribution in percent across predefined CPS regions for each patient (P1–P6).

3.4. *Group-wise comparison of different comprehension error types*

While the sample sizes of patients included in this pilot study does not warrant any statistical group-wise comparisons, the preliminary mean cortical error rate for each cortically parcellated area was compared graphically between patients and controls (Fig. 6). As can already be seen in the group-wise comparison across comprehension errors (Fig. 6A), the distribution of comprehension errors elicited by nTMS were wide-spread across the entire left hemisphere. Overall, across categories, higher error rates were observed in patients. The error rate pattern for each error category (no response, searching behavior, selection of wrong target item and hesitant responses) specific to patients or controls is shown in Fig. 6(B–E). Of note, across controls no response errors as well as selection of wrong target items manifested only rarely and thus, did not allow a detailed error pattern analysis.

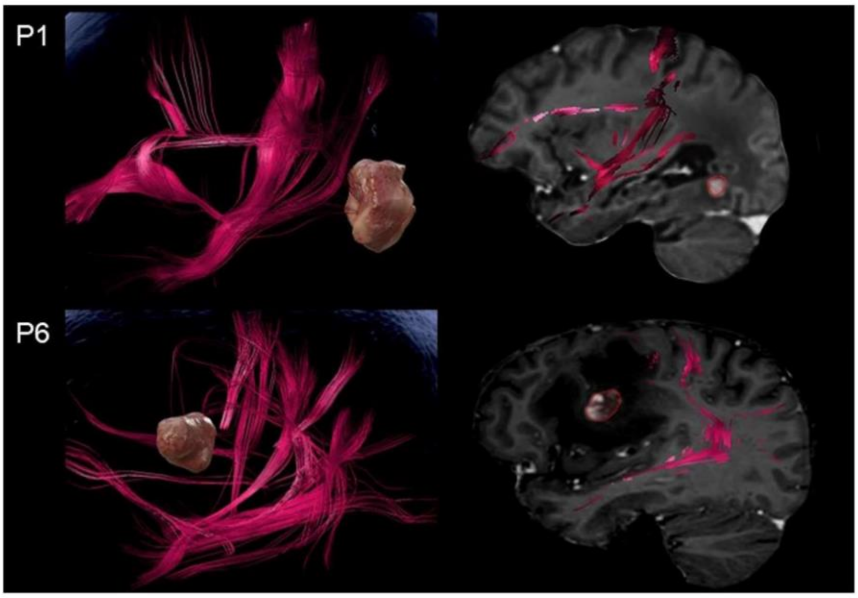

Fig. 5 – Exemplary function-based tractographies. Illustrations show the individual functional language network (pink) in relation to the respective glioblastoma (left column: brown, right column: red outline) of case 1 (P1) and case 6 (P6).

3.5. *Inter-rater reliability*

We compared the inter-rater agreement for stimuli identified as comprehension-positive or comprehension-negative between a neurolinguist and a SLT for patient and control data separately. Both groups showed a significant, substantial agreement strength (control group K = .65, *p* < .001; patient cohort K = .66, *p* < .001), across all comprehension-errors and comprehension-negative stimuli during the stimulation exam (Fig. 7). Additionally, we assessed the agreement between raters for each classified error category. Table 5 summarizes these results. For patients, both raters had a highly significant, substantial agreement for no response errors, searching behavior and selection of wrong target item (all *p* < .001), but not for hesitations. For controls, the inter-rater agreement was substantial for searching behavior, almost perfect for selection of wrong target item and fair for hesitations and no responses (all *p* < .001). Still, rater 2 classified a single and rater 1 five clear no responses across all healthy subjects. Three out of the latter five no responses attributed by rater 1 were classified as hesitations by rater 2.

3.6. *Reaction time-based analysis of delayed responses*

To establish whether the more subjective, video-based analysis is concordant with objective reaction time analyses, reaction times were measured for each item during the stimulation examination. Since no procedure to analyze reaction times systematically is readily available within the nTMS system in use, the manual extraction based on the respective audio track was performed within a third-party program. This additional analysis took on average 79.3 ± 8.9 min for patients and 53.3 ± 6.5 min for controls. Since inter-individual variability in naming latencies is well established (Jodzio et al., 2023), the mean and standard deviation of response times during the stimulation exam were determined for each individual. The descriptive results are summarized in Table 6. Durations exceeding two standard deviations of the individual mean response time were classified as delayed responses. The subsequent agreement analysis between this duration-based identification of hesitations and the analysis of rater 1 revealed a significant, yet slight agreement for patients (K = .132, *p* < .001) and for controls (K = .118, *p* < .001). Still, of 66 hesitations classified by rater 1 across patients and healthy subjects, only 22.7% were assigned on the basis of a response delay, whilst 71.2% were attributed based on hesitant hand motions such as halting or indecisive movements prior to a button press and 6.1% based on a combination of hesitant hand motions and delays. Out of all subjectively classified delayed responses by rater 1 (n = 15), 53.3% exceeded the mean individual reaction time by more than two standard deviations.

The additional analysis of the subset of items preceding each hesitation revealed that 60.0% of ten hesitations identified for patients and 33.9% of 56 hesitations identified for controls had a delay of more than two standard deviations from the mean of the five error-less items preceding each identified hesitation by rater 1. Moreover, if only the fifteen hesitations identified by rater 1 on the basis of seemingly delayed response behavior were considered, 66.7% of 12 delayed responses for controls and 100.0% of 3 delayed responses for patients were concordant with the objective reaction time cut-off criteria.

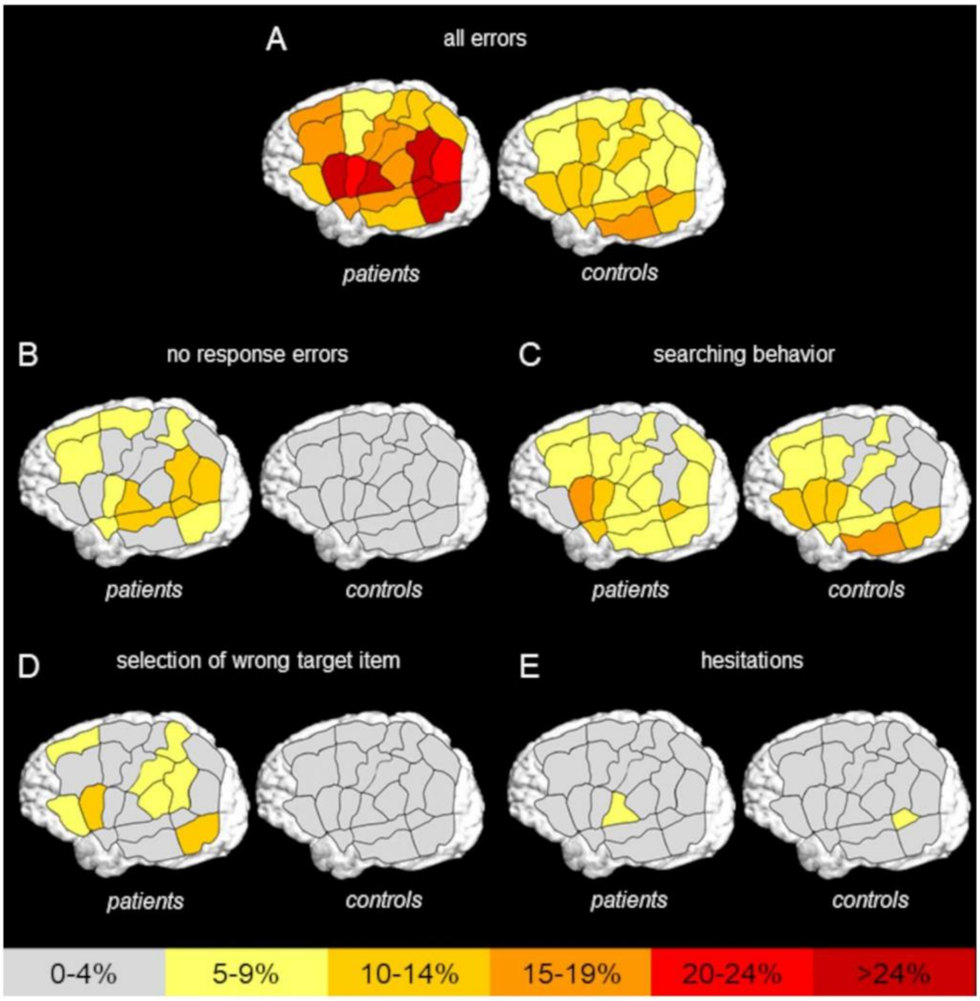

Fig. 6 – Group-wise presentation of cortical error rate distribution in percent across predefined CPS regions for all stimulation-induced errors (A) and specific error types: no response errors (B), searching behavior (C), selection of wrong target item (D) and hesitations (E).

3.7. *Analysis of noise impact on capability of hearing auditory stimuli*

Finally, the impact of the noise arising from the nTMS system and the applied pulses on the capability to hear the auditory stimuli presented was analyzed. This post-hoc analysis considered recordings of stimulations applied with a non-cooled stimulation coil at a stimulation intensity of 20–50% (in steps of 10%) based on a mean motor threshold of 31.7% (range: 25–39%) across patients and controls. The mean intensity in dB for the exemplary 20 pulse recordings was 57.3 dB while the one for the exemplary 10 items was higher with a mean of 73.4 dB. Moreover, the mean number of correctly identified target items out of 138 stimulations applied per participant were 119.5 across patients and controls, demonstrating that target items could be heard while stimulation was applied simultaneously.

4. Discussion

Preoperative nTMS-based language mapping is constantly gaining importance in neurosurgical context due to its ability

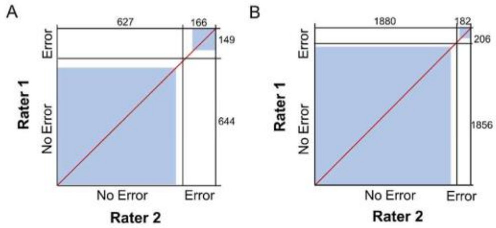

Fig. 7 – Bangdiwala's agreement charts. Charts compare the analysis agreement of stimuli identified as comprehension-positive (error) or comprehension-negative (no error) by rater 1 (SLT) and rater 2 (neurolinguist) for patients (A) and controls (B).

to identify areas necessary for language function, to inform surgical planning and to guide resections of language-eloquent brain tumors (Haddad et al., 2021; Ille, Sollmann, et al., 2016; Sollmann, Zhang, Fratini, et al., 2020). However, thus far the pre- and intraoperative language tasks for stimulation-based language mapping are mainly limited to overt production or complex comprehension paradigms. This, however, precludes brain tumor patients with severe expressive language impairments from stimulation-based language mapping. To account for this, we developed a novel comprehension-based language mapping task suitable for patients with severe expressive aphasia to be used for pre- as well as intraoperative mapping of the remaining language function.

4.1. *Feasibility and utility of the single-word auditory nTMS comprehension task*

The auditory single-word comprehension test, CompreTAP, was feasible in all patients and healthy controls. All healthy controls performed this task without difficulty and within the time limits, hence no item needed to be excluded retrospectively. This highlights the simplicity of the task which was necessary to allow language comprehension mapping under the time-restricted conditions in our severely aphasic patient cohort. Whereas language production was severely impaired in all patients, the receptive language comprehension skills of our aphasic patient cohort were preserved to varying extends prior to surgery. Especially case 1 and 6 presented with pre-existing moderate language comprehension deficits. Yet, they were able to identify sufficient items correctly and reproducibly during the two baseline trials to be used during mapping. In contrast, none of the patients could produce sufficient object naming items for classic naming-based approaches. This underlines the usefulness of this novel short single-word task as this comprehension

Table 5 – Overview of classified errors by each rater and Inter-rater agreement coefficient.

Comprehension error category	Patients Number of errors		Cohen's Kappa Patients (K)	Controls Number of errors		Cohen's Kappa Controls (K)
	Rater 1	Rater 2		Rater 1	Rater 2	
No response	47	32	.6***	5	1	.3***
Searching behavior	54	62	.6***	145	121	.6***
Selection of wrong target item	39	40	.7***	2	2	1.00***
Hesitation/delayed response	6	35	<.1	54	58	.3***

p-value: *<.05, **<.01, ***<.001.

Table 6 – Descriptives of individual response times across patients and healthy subjects.

ID	Patients		ID	Controls	
	RT in sec Mean ± SD (range)	n hesitations		RT in sec Mean ± SD (range)	n hesitations
P1	2.0 ± .4 (1.1–3.5)	4	C1	1.2 ± .2 (.1–1.8)	3
P2	1.7 ± .3 (1.0–3.0)	4	C2	1.3 ± .3 (.7–2.4)	5
P3	2.4 ± .4 (1.5–3.5)	2	C3	1.5 ± .3 (1.1–3.4)	3
P4	2.0 ± .3 (1.4–3.2)	5	C4	1.2 ± .3 (.7–3.2)	6
P5	2.4 ± .5 (1.3–4.1)	5	C5	1.0 ± .2 (.6–2.4)	4
P6	2.1 ± .6 (1.2–3.9)	5	C6	1.2 ± .2 (.9–2.0)	5
			C7	1.4 ± .3 (.8–2.2)	5
			C8	1.3 ± .3 (.8–2.1)	4
			C9	1.5 ± .3 (1.0–2.7)	7
			C10	1.2 ± .2 (.9–2.1)	6
			C11	1.4 ± .3 (.8–2.6)	5
			C12	1.3 ± .2 (.9–2.3)	3
			C13	1.4 ± .3 (.8–2.4)	8
			C14	1.2 ± .2 (.8–2.3)	2
			C15	1.7 ± .3 (1.0–3.4)	3

The table provides an overview of the mean, standard deviation (SD) and range of individual reaction times (RT) in seconds (sec) and the number (n) of hesitations identified as delayed response times exceeding the individual mean of a subject by more than two standard deviations.

setup was suitable even for patients with severe expressive aphasia.

Moreover, our results provide first support for the utility of this task for the preservation of residual language function if the results are used in combination with function-based tractography to guide tumor removal. Only in case 6, a transient worsening of aphasia symptoms was reported following comprehension-based nTMS guided surgery, which is often described following overt production tasks as well. This patient presented with the most severe comprehension deficit of the investigated cohort even prior to surgery. Only 23 out of the 62 target items presented could be used during stimulation which may limit the validity of mapping results as this reduced number of items may not be an adequate representation of the residual language comprehension abilities. Still, even this limited representation provided valuable insights into the patient's functional language comprehension network and may have supported the preservation of residual comprehension skills as no permanent worsening of symptoms arose. Moreover, since the task in use has not been evaluated prior to this study, adequate cut-off criteria need yet to be established. For case 1, 3, 4, and 5, however, for whom comprehension-based mapping results were used intraoperatively, no worsening of language deficits was identified even if the resected tumors were moderately (case 5) to highly language-eloquent (case 1, 3 and 4). Still, further studies assessing the benefit of this task for postoperative outcome in a larger cohort are needed.

4.2. *Test construction and theoretical considerations*

In this auditory single-word comprehension task, subjects are asked to choose the auditorily presented target item out of a set of four picture stimuli by button press. Due to methodological differences this setup is not directly comparable to other comprehension mapping paradigms. Few studies so far have tested specific intraoperative comprehension setups requiring only a pointing-based response from the patient and in line with our task no overt responses (Roux et al., 2015). Still, most intraoperative comprehension setups are based on tasks in which a patient must produce an overt response (De Witte et al., 2015; Martin-Monzon et al., 2022). A single study piloted a preoperative mapping based on sentence comprehension and picture matching in children with nTMS without overt responses (Rejno-Habte Selassie et al., 2020). In these non-overt comprehension stimulation-based approaches, visually presented association tests or complex auditory comprehension tasks were implemented, such as adaptions of classic "Token Test" (De Renzi & Vignolo, 1962) or sentence comprehension tests. The former association test based on visually presented images of objects fails to examine additional auditory comprehension levels such as acoustic-phonological categorization and lexical access processes (DeWitt & Rauschecker, 2012; Friederici, 2012; Okada et al., 2010). At the same time, tasks utilizing comprehension of sentences or connected speech involve additional syntactic, semantic and prosodic processing steps next to the aforementioned acoustic-phonological and lexical ones (Friederici, 2002) which in turn increase the difficulty of the task. Whilst sentence comprehension seems to recruit widespread frontal and temporal language areas, neuroimaging, stimulation and lesion studies indicate the involvement of partly similar areas in single-word comprehension (Bornkessel et al., 2005; DeWitt & Rauschecker, 2016; Herrmann et al., 2009; Mesulam et al., 2019; Roux et al., 2015; Zaccarella & Friederici, 2017). Our results show that this single-word-based comprehension mapping allowed to identify extensive cortical comprehension sites. Consequently, more complex auditory setups on sentence level might not necessarily be beneficial for identifying wide-spread comprehension-relevant sites across the entire left hemisphere. What is even more, the time-restricted presentation mode during stimulation-based language mappings limits the possibilities of introducing more complex and consequently more lengthy comprehension paradigms. Still, direct comparisons between sentence-based and single-word nTMS tasks would be needed to answer this question.

More and more comprehensive language testing batteries tailored to patients needs and individual lesion characteristics as well as locations are employed during awake stimulation-based language mapping (De Witte et al., 2015; Fernandez Coello et al., 2013; Martin-Monzon et al., 2022; Rofes et al., 2015). For the same reason, new tasks for preoperative stimulation-based language mapping are developed (Hauck et al., 2015; Ohlerth et al., 2020). Whilst object naming remains the method of choice and is one of the most frequently utilized tools pre- and intraoperatively, benefits of multiple-task approaches were verified (Ohlerth, Bastiaanse, Nickels, et al., 2021). Up to date, however, especially these preoperative tasks are based on assessing the language production network. Thus, CompreTAP might not only be suitable for patients with severe expressive aphasia but may also add valuable insights into the localization of language functions in context of multi-task approaches irrespective of aphasia severity.

4.3. *Comprehension errors and reliability of this comprehension task*

As opposed to classic nTMS language protocols, this new comprehension-based setup is based on button press. This, however, alters the process of error evaluation drastically and, therefore, deserves further validation: By comparing the analysis agreement of two highly experienced specialists, we showed that this new task has a substantial inter-rater reliability for patient and control data.

Both raters classified the error pattern across healthy subjects and patients into four error categories: no responses, selection of a wrong target item, searching behavior, and hesitant or delayed responses. All of these errors can potentially be caused by stimulation-induced interference on the ability to visually identify figures and to select the target item via a button press based on adequately matched colors. Still, whilst in classic naming-based approaches the same potential of disrupting the ability to identify figures adequately exists, ample research has shown that the results of these mappings can be used for preserving language function (Hendrix et al., 2017; Ille et al., 2021; Ille, Sollmann, et al., 2016; Natalizi et al., 2022; Raffa et al., 2019). The preliminary results of the present study additionally provide first indications that the comprehension-based setup may support the preservation of residual language function as no new or only a single transient worsening of aphasic symptoms manifested post-surgery. Thus, the majority of results generated seem to reflect disrupted higher-order language processes. Whilst no responses are one of the most frequent errors during naming-based stimulation approaches, underlying mechanisms causing this error type are not well understood (Corina et al., 2010). In production-based approaches, the origin of no response errors is difficult to disentangle since they may result from blocked speech motor planning as well as word finding difficulties. Our comprehension-based approach can circumvent this issue by using the ipsilateral hand to press the corresponding button to minimize stimulation-effects on the hand-motor response. Thus, this setup may allow an even clearer interpretation of disrupted language processing manifesting in no response errors compared to overt naming tasks. At the same time, like production-based nTMS, hesitations elicited by comprehension-based nTMS may reflect acoustic-phonetic, conceptual or lexico-semantic retrieval difficulties. Since the time-restricted presentation mode of nTMS did not allow to include any semantically or phonologically related distractor items, these processes cannot be clearly disambiguated. Similarly, the selection of a wrong item and searching behavior may indicate either conceptual or lexico-semantic word finding difficulties or a breakdown of the acoustic-phonetic comprehension stage, and can, therefore not be clearly attributed to just one of these comprehension processes.

For specific error categories, searching behavior and selection of wrong target item could be assigned with a high inter-rater-reliability. Whilst additionally no responses were assigned with high concordance across the two raters for patients, the agreement was only fair for controls. This may be attributable to the low overall occurrence of clear no response errors within the present healthy cohort. Moreover, during no responses, hesitant response behavior may simultaneously be observable. This may explain the attribution of errors to different categories across the raters since rater 2 classified 60.0% of no response errors assigned by rater 1 as hesitations. At the same time, the overall agreement for differentiating stimulation-induced disruptions from no errors irrespective of the type of error category assigned was substantial. Thus, whilst error types may not be attributable to just a single category, classifying deviations in response behavior induced by nTMS was shown to be highly reliable. Still, hesitations seem to be the most uncertain error category as the agreement was limited for controls and non-significant for patients. This is in line with naming-based approaches, in which hesitations errors remain the most subjective error category. Up to date, no programs for objective individual response time analysis are readily available for the present setup without employing third-party programs (Schramm et al., 2020). However, these are due to their high time-extensiveness not feasible for clinical applications. As this study shows, a manual analysis within a third-party program takes on average nearly an hour in healthy subjects and even longer in the patient cohort (mean = 79.3 min). While the decision whether a response was delayed or hesitant is a highly subjective and less accurate one, these errors can still result from stimulation-induced disruptions of the language network. Therefore, they are frequently considered for analysis (Krieg et al., 2016; Ohlerth, Bastiaanse, Negwer, et al., 2021).

For this reason, reaction time analyses, which are standard procedures in psycholinguistic experiments, were performed, since they offer a more objective identification of delays in response time induced by nTMS. Whilst this analysis showed only a slight, yet significant agreement with the analysis of rater 1 for patients and controls, just over a fifth of hesitations identified by the rater were attributed on the basis of a seemingly delayed button press. The largest proportion of hesitations were identified based on halting or indecisive hand movements showing a clear hesitant, yet not necessarily substantially delayed response behavior. Thus, by reducing the dimension of the analysis format to audio tracks more objective measurements of reactions times became possible whilst reluctant hand motions as identifiable within the video recordings could not support the identification of nTMS-induced hesitant errors anymore. Still, approximately half of the seemingly delayed reaction times assigned by rater 1 were concordant with the objective reaction time analysis. Hence, the latter analysis may substantially increase reliability for differentiating delayed responses. However, no rule of thumb or definite cut-off criteria for which delays constitute a clear hesitant response induced by nTMS are consistently described across studies. It is well established that response times not only vary considerably between subjects (Jodzio et al., 2023), but may also change significantly throughout the stimulation exam of a single subject. Based on this, Sollmann et al. (2017) suggested to identify hesitations during nTMS-based naming tasks as delays of at least 200 msec compared to preceding or subsequent items named. Thus, a separate analysis of all hesitations identified by rater 1 and the respectively preceding items was performed. Here, a high concordance across patients and controls was verified for the 15 items identified solely on the basis of delayed button press behavior by rater 1 and the item-subset specific reaction time analysis. Hence, to account for intra-subject variations throughout the stimulation examination, subset-specific cut-off criteria would be required. Consequently, by employing the objective, intra-subject specific identification of delayed responses next to the video-based identification of hesitant hand motions, searching behavior, no responses and selection of a wrong target item, reliability and reproducibility of mapping results may be substantially supported. Still, to make this clinically applicable, a system-integrated approach is necessary as this additional analysis within a third-party program considerably increases analysis duration.

4.4. *Cortical language comprehension relevant sites*

Whilst intraoperative mapping is determined by the cortex area exposed during a craniotomy, the non-invasive nature of nTMS allows to create individual, large-scale maps of language-relevant cortical areas and to examine functional reorganization (Ille et al., 2019; Krieg et al., 2013). Our results highlight the heterogeneity of cortical language areas seemingly involved in comprehension. The areas with the highest error rates were widely distributed across patients and controls. This, furthermore, emphasizes the necessity of individual localization of language function prior to surgery to allow individually guided surgical planning and resection of tumors located in language areas. Still, some common patterns across patients and particularly the larger control group were identifiable: All patients had high error rates and the group of 15 healthy controls had moderate to high error rates within temporal regions. Separate analyses of different error types showed that this pattern occurred particularly for searching behavior. In patient case 1, 4, 5 and 6 as well as across the 15 controls, high error rates were found for areas that are typically described as the classic "Wernicke's" area that is the middle and posterior superior temporal gyrus (Binder, 2017). Across the whole patient group stimulation over these cortical sites elicited no responses and searching behavior, whilst only very few no response errors were found within the controls.

Moreover, five of the patient cases (P1, P2, P3, P5 and P6) and nearly half of the control cases (see Appendix Table B) had additionally moderate to high error rates in the posterior MTG. This cortical region was shown to be a critical language comprehension hub since its connectivity profile of the comprehension network was considerably high especially in comparison to other cortical comprehension areas (Turken & Dronkers, 2011). As stimulation of this area resulted in low to moderate error rates for no response, searching behavior and selection of wrong target item across patients and for searching behavior across healthy participants – all comprehension error types which were identifiable with high reliability – the present results underline the important role of posterior MTG in auditory single-word comprehension. Half of the patients (P2, P4, P6) and one third of the healthy subjects (see Appendix Table B) had additional high error rates in anterior STG. As error type analyses revealed this was mainly driven by moderate error rates for searching behavior in patients and controls. Although this area is frequently associated with word comprehension, partial removal of this section during surgery does not typically cause persistent language impairments (DeWitt & Rauschecker, 2013). However, our findings do not only indicate involvement of these rather classic temporal comprehension regions but also point towards an extensive involvement of frontal and parietal ones across patients and controls, in line with naming-based nTMS language mapping results (Krieg et al., 2016). For instance, 83.3% of the patient cases presented with high error rates within the opercular IFG, and 66.7% of patients had at least a moderate error rate in the triangular IFG. Moreover, apart from three cases, all healthy subjects showed moderate to high error rates within trIFG or opIFG. Whereas the IFG was originally attributed with language production, more recent findings increasingly corroborate its involvement in language production and comprehension, particularly a dissociation of phonological processing in the opercular and semantic processing in the anterior IFG (Gough et al., 2005; Klaus & Hartwigsen, 2019).

4.5. *Surgical perspective*

There is a considerable number of glioma patients with severe impairment of language capabilities but who are still able to communicate and have an independent life. Thus, we need to treat these patients – and surgery is still the most powerful therapeutic option today – but we also need to preserve their limited but useful language capabilities. Hence, the presented mapping workflow and setup helps us to identify the underlying network to preserve this residual function. Some years ago, we still operated those patients awake but realized that their language abilities are worse after craniotomy then the days before and mapping was almost impossible. Having a methodology at hand which allows patients being mapped in a calm, relaxing atmosphere with video-recorded evaluation and a lot of time to tailor tests and setup, helps us to produce a much better visualization of the underlying language network.

4.6. *Limitations and perspectives*

This study is the first to present a comprehension-based nTMS language mapping paradigm for brain tumor patients with severe expressive aphasia. While the results of this case series are promising, all implications are based on a relatively small patient sample size. Inclusion of larger cohort sizes may allow for a more differential error pattern analysis in patients and in-depth group-wise comparisons of cortical error pattern distribution as well as of the subcortical language comprehension network. To identify strong and generalizable differences between patients and controls, a larger sample size needs to be recruited and both groups, moreover, need to be matched in age. In addition, while all six patients included in the present study presented with severe expressive deficits, their language comprehension was additionally impaired to varying extends. Even if the number of items included varied across patients, all patients were able to select the correct target item reliably and reproducibly prior to stimulation. Still, since the presence of severe aphasia may limit the reliability of stimulation-based mappings (Schwarzer et al., 2018), this may have impacted the present mapping results in case 1, 3 and 6. Hence, subsequent studies with a large sample size of patients without or light receptive deficits are warranted. This may substantially advance the understanding of single-word comprehension and functional reorganization in brain tumor patients with severe aphasia. Moreover, conducting thorough qualitative and quantitative analyses of the cortical and subcortical components involved in the four identified different error categories may support the delineation of different comprehension processes in lesioned patient populations.

Furthermore, subsequent studies may compare the functional cortical and subcortical language comprehension network between patients with semantic and phonologic comprehension deficits. A wealth of imaging, stimulation, neurologic and neurodegenerative lesion studies indicate a relevance of anterior for phonological and posterior language network components for semantic processes during comprehension and production as opposed to the classic language models building on Broca's and Wernicke's original work (Butler et al., 2014; Ingram et al., 2020; Klaus & Hartwigsen, 2019; Mesulam et al., 2015; Mirman et al., 2015; Tremblay & Dick, 2016). The present task required patients to select an auditorily presented target item out of a set of four picture stimuli via the push of a button matched in color to the background of the correct target item while stimulation is applied. Since task demands can impact the expression of semantic deficits (Jefferies & Lambon Ralph, 2006), this task may potentially impact the mapping reliability in semantically impaired patients. Moreover, this task demand may explain some of the cortical sites identified as comprehension relevant. For instance, Lambon Ralph et al. (2017) linked inferior frontal and posterior middle temporal activation to executively demanding semantic processes.

In addition, since patient 1 is ambidextrous, his mapping results may not necessarily be directly comparable to right-handed patients and subjects. While a left-hemispheric dominance for language in right-handed people is widely established, in left-handers and to a lesser extent in ambidextrous people, a higher possibility of right-hemispheric language dominance has been reported (Isaacs et al., 2006; Knecht et al., 2000). Performing a bihemipsheric comprehension mapping may additionally provide a more comprehensive picture of the healthy and the impaired comprehension processes across subjects as even in right-handed subjects a right-hemispheric involvement during comprehension has been corroborated (Gajardo-Vidal et al., 2018).

Furthermore, whereas we did not observe any impact of the noise of the stimulation application on the ability of controls and patients to hear the auditory target item, the present setup does not allow to delineate whether next to complex language comprehension processes additional lower-order hearing processes are disrupted by stimulation. However, across all healthy participants and patients heterogeneous left-hemispheric areas were linked to language comprehension many of which are thought to comprise cortical language-relevant ones. Still, a control task testing non-verbal auditory comprehension may allow to delineate these lower-order hearing and complex language comprehension processes.

Moreover, this study did not evaluate the feasibility and utility of this new comprehension-based stimulation language mapping in context of intraoperative awake language monitoring, the gold standard for preservation of language function in language-eloquent brain tumors. Whilst the timing of the task may already fit the time-restricted intraoperative conditions, slight adaptions of screen and button setup might be needed. As the results of the present study already demonstrated, language comprehension disruptions through stimulation are identifiable with a high inter-rater reliability. Since naming-based approaches elicit similar error patterns with nTMS as with DES (Corina et al., 2010; Lioumis et al., 2012; Talacchi et al., 2013), it is expected that comprehension errors under DES resemble the error pattern under nTMS. Consequently, the task itself may easily be transferable into the operating room and may allow for an instant identification of cortical language comprehension sites. This may enable awake surgeries in patients with severe expressive aphasia whose language impairment thus far precluded them from pre- and intraoperative naming-based language mappings, respectively, and may substantially support the preservation of residual language function.

If, furthermore, both stimulation-based language mapping methods were employed, the concordance of identifying relevant and non-relevant cortical language comprehension sites can be evaluated. Thus far, nTMS-based language mappings are known for their high sensitivity and negative predictive values compared to the gold standard, particularly in comparison to other preoperative functional neuroimaging methods (Ille et al., 2015; Picht et al., 2013; Tarapore et al., 2013). Hence, the largest limitation of nTMS-based language mappings remains the poor specificity which results in a high reliance on negative mapping results. Still, the present study did not only show a high inter-rater reliability for the differentiation of comprehension positive and negative sites but also the induction of multiple errors for the stimulation of the same cortical sites. This in combination with preserved residual abilities supports the reliability of the current mapping approach. However, to confirm that these sites are indeed functionally relevant, direct comparisons with intraoperative stimulation mapping, the gold standard for the preservation of functionality (Duffau, 2015), would be required. While it is not yet the standard of care, nTMS is increasingly integrated into the preoperative workflow across many centers especially in cases for whom DES-based mappings are not an option (Ille, Sollmann, et al., 2016; Raffa et al., 2022).

At the same time, due to methodological and technical limitations, contemporary white matter imaging techniques thus far inaccurately represent the anatomical network (Catani et al., 2013). The results of Maier-Hein et al. (2017) show that DTI-based tractographies are limited by reconstructing a large proportion of non-existing, anatomically non-valid tracts while the reconstruction contained approximately 90% of anatomical valid connections. Conversely, preclinical imaging studies show a high rate of anatomically valid tracts missed by DTI tractography (Aydogan et al., 2018; Grisot et al., 2021). Hence, the potential of false positive or negative subcortical reconstructions may result in the preservation functionally non-relevant or the resection of relevant subcortical tracts impacting life expectancy or a patient's quality of life (Brown et al., 2016; Hervey-Jumper & Berger, 2016). The most direct way to investigate the functional role of the subcortical language network in neurosurgical patients remains subcortical stimulation during awake surgeries (Duffau, 2015) which is not impacted by the methodological and technical limitations of the preoperative techniques presented within the current study. Nevertheless, DTI offers a unique, in-vivo and non-invasive way to investigate subcortical connections. Multiple studies show that by using nTMS-based cortical sites to derive DTI-based tractographies of the functional language network, the preservation of functionality and preoperative risk stratification can be supported already non-invasively prior to a resection (Giampiccolo et al., 2020; Ille et al., 2018; Raffa et al., 2019; Sollmann, Zhang, Fratini, et al., 2020).

5. Conclusion

This study tested the feasibility and reliability of a new non-overt language-comprehension task for pre- as well as intraoperative language mapping. The task was feasible and its analysis highly reliable for patient and control data. The present setup not only allowed a language mapping in patients with severe expressive aphasia thus far precluded from classic overt language-production based mapping, but also enabled to preserve residual language function if the results were employed in combination with function-based tractography for surgical planning and resection.

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CRediT author statement

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Data availability statement

All data required to reproduce the reported analyses appear in the figures of this article, the error rates for individual subjects and per group are provided within the Appendix. The data is stored in an institutional repository and not publicly available due to hospital legislation and medical ethical objections. All data presented in this study are available upon reasonable request, access will be granted to named individuals in accordance with ethical procedures governing the reuse of sensitive data, i.e., if the ethical committee approves and if the data sharing agreement is signed by both a demanding and providing party. Readers seeking access to the data are advised to contact the corresponding author, Prof. Dr. med. S.M. Krieg.

Legal copyright restrictions do not permit us to publicly archive or share the full set of stimuli used in this experiment in a trusted digital repository. All items used stem from the "verb and noun test for peri-operative testing (Van-POP)", the copyright of the pictures belongs to the Rijksuniversiteit Groningen, the Netherlands. Readers seeking access to the stimuli are advised to contact the author, Dr. A.-K. Ohlerth [Ann-Katrin.Ohlerth@mpi.nl; ann.katrin.ohlerth@gmail.com]. Stimuli will be released if the declaration of usage agreement is signed, and all points of the agreement are followed closely. This agreement can be received upon request.

Code availability

The data set for reproducing the inter-rater analysis together with the respective R analysis code is available within the supplementary data.

Declaration of competing interest

B.M. received honoraria, consulting fees, and research grants from Medtronic (Meerbusch, Germany), Icotec ag (Altstätten, Switzerland), and Relievant Medsystemy Inc. (Sunnyvale, CA, USA), honoraria and research grants from Ulrich Medical (Ulm, Germany), honoraria and consulting fees from Spineart Deutschland GmbH (Frankfurt, Germany) and DePuy Synthes (West Chester, PA, USA), royalties from Spineart Deutschland GmbH (Frankfurt, Germany). S.M.K. is consultant for Ulrich medical (Ulm, Germany) and Brainlab AG (Munich, Germany) and received honoraria from Nexstim Plc (Helsinki, Finland), Spineart Deutschland GmbH (Frankfurt, Germany), Medtronic (Meerbusch, Germany) and Carl Zeiss Meditec (Oberkochen, Germany). BM received research grants and is consultant for Brainlab AG (Munich, Germany). SI is consultant for Brainlab AG (Munich, Germany). None of the authors state any conflict of interest.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cortex.2023.09.023.

Appendix A. Stimulation-induced error rates (number or errors/number of stimulations applied) across all error types of patients and controls for each parcellated cortical region.

CPS region specific stimulation-induced error rates across all error types for patients.

Cortical area	Patient						Total[a]
	P1	P2	P3	P4	P5	P6	
anG	.25 (3/12)	.14 (2/14)	.25 (3/12)	.07 (1/14)	.17 (2/12)	.42 (5/12)	.22 (16/76)
aSMG	.00 (0/6)	.17 (1/6)	.33 (2/6)	.17 (1/6)	.25 (2/8)	.00 (0/6)	.15 (6/38)
aSTG	.00 (0/3)	.33 (1/3)	.00 (0/2)	.33 (1/3)	.00 (0/1)	.33 (1/3)	.17 (3/15)
dPoG	.00 (0/3)	.00 (0/3)	.00 (0/3)	.00 (0/3)	.00 (0/3)	.67 (2/3)	.11 (2/18)
dPrG	.00 (0/3)	.33 (1/3)	.00 (0/3)	.25 (1/4)	.00 (0/3)	.00 (0/3)	.10 (2/19)
mMFG	.15 (2/13)	.15 (3/20)	.35 (6/17)	.00 (0/18)	.25 (5/20)	.06 (1/18)	.16 (17/106)
mMTG	.17 (1/6)	.17 (1/6)	.00 (0/6)	.25 (2/8)	.00 (0/6)	.17 (1/6)	.13 (5/38)
mPoG	.17 (1/6)	.33 (2/6)	.00 (0/6)	.17 (1/6)	.00 (0/6)	.33 (2/6)	.17 (6/36)
mPrG	.13 (1/6)	.00 (0/4)	.17 (1/6)	.17 (1/6)	.00 (0/3)	.50 (3/6)	.16 (6/31)
mSFG	/ (0/0)	.29 (2/7)	.20 (2/10)	.00 (0/9)	.25 (1/4)	.00 (0/9)	.15 (5/39)
mSTG	.17 (1/6)	.00 (0/3)	.00 (0/6)	.00 (0/6)	.25 (2/8)	.67 (4/6)	.18 (7/35)
opIFG	.17 (1/6)	.33 (2/6)	.33 (2/6)	.33 (2/6)	.43 (3/7)	.33 (2/6)	.32 (12/37)
pMFG	.00 (0/6)	.20 (1/5)	.00 (0/6)	.14 (1/7)	.00 (0/1)	.17 (1/6)	.08 (3/31)
pMTG	.22 (2/9)	.17 (2/12)	.30 (3/10)	.00 (0/6)	.50 (5/10)	.33 (3/9)	.25 (15/56)
pSFG	.00 (0/3)	.00 (0/2)	.00 (0/3)	.00 (0/3)	.50 (1/2)	.00 (0/3)	.08 (1/16)
pSMG	.17 (1/6)	.00 (0/6)	.33 (2/6)	.17 (1/6)	.50 (3/6)	.33 (2/6)	.25 (9/36)
pSTG	.33 (1/3)	.00 (0/3)	.00 (0/3)	.33 (1/3)	.20 (1/5)	.67 (2/3)	.26 (5/20)
SPL	.33 (2/6)	.33 (2/6)	.00 (0/6)	.00 (0/6)	.00 (0/6)	.00 (0/6)	.11 (4/36)
trIFG	.17 (1/6)	.29 (2/7)	.00 (0/8)	.00 (0/6)	.13 (1/8)	.11 (1/9)	.11 (5/44)
vPoG	.17 (1/6)	.33 (2/6)	.50 (3/6)	.33 (2/6)	.00 (0/3)	.17 (1/6)	.25 (9/33)
vPrG	.00 (0/6)	.33 (2/6)	.00 (0/6)	.17 (1/6)	.00 (0/3)	.67 (4/6)	.20 (7/33)

[a] The total error rate for each cortically parcellated area was calculated as the mean of error rates for each cortical area across patients, thus, slight deviations from calculations on the basis of the absolute numbers may be present.

CPS region specific stimulation-induced error rates across all error types for controls (C1 - C9).

Cortical area	Controls								
	C1	C2	C3	C4	C5	C6	C7	C8	C9
anG	.00	.00	.00	.08	.17	.17	.08	.00	.00
aSMG	.00	.00	.20	.17	.00	.00	.00	.17	.00
aSTG	.67	.00	.33	.00	.00	.00	.00	.00	.33
dPoG	.00	.00	.00	.00	.00	.00	.00	.33	.33
dPrG	.33	.00	.00	.33	.33	.00	.00	.00	.00
mMFG	.17	.07	.00	.06	.22	.06	.17	.11	.00
mMTG	.00	.00	.00	.17	.00	.17	.33	.17	.00
mPoG	.17	.00	.00	.00	.33	.33	.00	.00	.00
mPrG	.00	.00	.17	.17	.17	.00	.17	.17	.00
mSFG	.11	.17	.00	.00	.33	.33	.00	.00	.00
mSTG	.00	.00	.00	.00	.00	.50	.17	.00	.17
opIFG	.17	.00	.00	.17	.17	.17	.11	.33	.00
pMFG	.17	.00	.17	.00	.00	.17	.17	.17	.17
pMTG	.11	.00	.00	.00	.44	.11	.00	.17	.00
pSFG	.00	.00	.00	.00	.00	.00	.67	.33	.00
pSMG	.17	.17	.00	.00	.00	.00	.17	.00	.17
pSTG	.00	.00	.00	.00	.00	.00	.67	.00	.33
SPL	.00	.17	.00	.17	.17	.00	.00	.00	.00
trIFG	.11	.00	.11	.22	.11	.00	.17	.11	.00
vPoG	.00	.00	.17	.00	.17	.17	.00	.11	.00
vPrG	.17	.00	.17	.17	.33	.17	.00	.00	.00

CPS region specific stimulation-induced error rates across all error types for controls (C10 - C15).

Cortical area	Controls						Total
	C10	C11	C12	C13	C14	C15	
anG	.08	.08	.00	.17	.00	.08	.06
aSMG	.00	.17	.00	.17	.00	.33	.08
aSTG	.00	.33	.00	.00	.33	.00	.13
dPoG	.33	.00	.00	.00	.00	.00	.07
dPrG	.33	.33	.00	.00	.00	.00	.11
mMFG	.06	.17	.11	.06	.11	.00	.09
mMTG	.00	.50	.17	.67	.50	.17	.19
mPoG	.00	.17	.17	.00	.33	.00	.10
mPrG	.00	.17	.00	.00	.17	.00	.08
mSFG	.00	.00	.00	.00	.11	.00	.07

(continued)

Cortical area	Controls						Total
	C10	C11	C12	C13	C14	C15	
mSTG	.17	.17	.00	.17	.00	.17	.10
opIFG	.17	.33	.17	.33	.00	.00	.14
pMFG	.33	.17	.33	.00	.00	.17	.13
pMTG	.00	.17	.00	.00	.67	.17	.12
pSFG	.00	.00	.00	.00	.00	.00	.07
pSMG	.00	.17	.00	.17	.17	.00	.08
pSTG	.00	.67	.33	.00	.33	.33	.18
SPL	.00	.17	.00	.00	.00	.17	.06
trIFG	.00	.44	.11	.33	.11	.00	.12
vPoG	.11	.22	.11	.11	.00	.22	.09
vPrG	.17	.17	.00	.17	.00	.33	.12

Appendix B. Error type specific error rates across patient- and control-group

Cortical area	Group	Error type[a]			
		NR	SB	SW	H
anG	Patient	.10	.08	.04	.00
	Control	.00	.04	.00	.02
aSMG	Patient	.03	.05	.05	.03
	Control	.01	.03	.00	.04
aSTG	Patient	.06	.11	.00	.00
	Control	.00	.09	.00	.04
dPoG	Patient	.06	.00	.06	.00
	Control	.00	.04	.00	.02
dPrG	Patient	.00	.06	.04	.00
	Control	.02	.07	.02	.00
mMFG	Patient	.06	.05	.04	.01
	Control	.00	.06	.00	.03
mMTG	Patient	.03	.08	.02	.00
	Control	.01	.16	.00	.02
mPoG	Patient	.03	.08	.06	.00
	Control	.00	.07	.00	.03
mPrG	Patient	.00	.08	.03	.03
	Control	.01	.03	.00	.03
mSFG	Patient	.05	.06	.06	.00
	Control	.00	.05	.00	.03
mSTG	Patient	.10	.06	.02	.00
	Control	.00	.09	.00	.01
opIFG	Patient	.03	.19	.10	.00
	Control	.00	.10	.00	.04
pMFG	Patient	.00	.08	.00	.00
	Control	.00	.08	.01	.04
pMTG	Patient	.05	.08	.10	.02
	Control	.00	.10	.00	.02
pSFG	Patient	.08	.00	.00	.00
	Control	.00	.04	.00	.02
pSMG	Patient	.14	.00	.08	.03
	Control	.00	.04	.00	.03
pSTG	Patient	.11	.11	.03	.00
	Control	.00	.11	.00	.07
SPL	Patient	.03	.06	.03	.00
	Control	.00	.03	.00	.02
trIFG	Patient	.02	.03	.05	.03
	Control	.00	.10	.00	.02
vPoG	Patient	.11	.08	.00	.06
	Control	.00	.08	.00	.02
vPrG	Patient	.05	.11	.03	.00
	Control	.00	.10	.00	.02

[a] NR = no response, SB = searching behavior, SW = selection of wrong target, H = hesitant responses.

REFERENCES

Alarcon, G., Bird Pedersen, M., Juarez-Torrejon, N., Martin-Lopez, D., Ughratdar, I., Selway, R. P., & Valentin, A. (2019). The single word auditory comprehension (SWAC) test: A simple method to identify receptive language areas with electrical stimulation. *Epilepsy & Behavior, 90*, 266–272. https://doi.org/10.1016/j.yebeh.2018.10.022

Aydogan, D. B., Jacobs, R., Dulawa, S., Thompson, S. L., Francois, M. C., Toga, A. W., Dong, H., Knowles, J. A., & Shi, Y. (2018). When tractography meets tracer injections: A systematic study of trends and variation sources of diffusion-based connectivity. *Brain Structure & Function, 223*(6), 2841–2858. https://doi.org/10.1007/s00429-018-1663-8

Bährend, I., Muench, M. R., Schneider, H., Moshourab, R., Dreyer, F. R., Vajkoczy, P., Picht, T., & Faust, K. (2020). Incidence and linguistic quality of speech errors: A comparison of preoperative transcranial magnetic stimulation and intraoperative direct cortex stimulation. *Journal of Neurosurgery, 134*(5), 1409–1418. https://doi.org/10.3171/2020.3.JNS193085

Bangdiwala, S. I. (1988). *The agreement chart*. The University of North Carolina.

Bangdiwala, S. I., & Shankar, V. (2013). The agreement chart. *BMC Medical Research Methodology, 13*, 97. https://doi.org/10.1186/1471-2288-13-97

Bello, L., Gallucci, M., Fava, M., Carrabba, G., Giussani, C., Acerbi, F., … Gaini, S. M. (2007). Intraoperative subcortical language tract mapping guides surgical removal of gliomas involving speech areas. *Neurosurgery, 60*(1), 67–82. https://doi.org/10.1227/01.NEU.0000249206.58601.DE

Binder, J. R. (2017). Current controversies on Wernicke's area and its role in language. *Current Neurology and Neuroscience Reports, 17*(8), 58. https://doi.org/10.1007/s11910-017-0764-8

Boersma, P., & Weenink, D. (2023). *Praat: Doing phonetics by computer [computer program]*. version 6.3.04. Retrieved 24 January 2023 from http://www.praat.org/.

Bornkessel-Schlesewsky, I., Staub, A., & Schlesewsky, M. (2016). The timecourse of sentence processing in the brain. In G. Hickok, & S. L. Small (Eds.), *Neurobiology of language* (pp. 607–620). https://doi.org/10.1016/b978-0-12-407794-2.00049-3

Bornkessel, I., Zysset, S., Friederici, A. D., von Cramon, D. Y., & Schlesewsky, M. (2005). Who did what to whom? The neural basis of argument hierarchies during language comprehension. *NeuroImage, 26*(1), 221–233. https://doi.org/10.1016/j.neuroimage.2005.01.032

Brown, T. J., Brennan, M. C., Li, M., Church, E. W., Brandmeir, N. J., Rakszawski, K. L., Patel, A. S., Rizk, E. B., Suki, D., Sawaya, R., & Glantz, M. (2016). Association of the extent of resection with survival in glioblastoma: A systematic review and meta-analysis. *JAMA Oncology, 2*(11), 1460–1469. https://doi.org/10.1001/jamaoncol.2016.1373

Butler, R. A., Lambon Ralph, M. A., & Woollams, A. M. (2014). Capturing multidimensionality in stroke aphasia: Mapping principal behavioural components to neural structures. *Brain, 137*(12), 3248–3266. https://doi.org/10.1093/brain/awu286

Catani, M., Thiebaut de Schotten, M., Slater, D., & Dell'Acqua, F. (2013). Connectomic approaches before the connectome. *NeuroImage, 80*, 2–13. https://doi.org/10.1016/j.neuroimage.2013.05.109

Chang, E. F., Raygor, K. P., & Berger, M. S. (2015). Contemporary model of language organization: An overview for neurosurgeons. *Journal of Neurosurgery, 122*(2), 250–261. https://doi.org/10.3171/2014.10.JNS132647

Corina, D. P., Gibson, E. K., Martin, R., Poliakov, A., Brinkley, J., & Ojemann, G. A. (2005). Dissociation of action and object naming: Evidence from cortical stimulation mapping. *Human Brain Mapping, 24*(1), 1–10. https://doi.org/10.1002/hbm.20063

Corina, D. P., Loudermilk, B. C., Detwiler, L., Martin, R. F., Brinkley, J. F., & Ojemann, G. (2010). Analysis of naming errors during cortical stimulation mapping: Implications for models of language representation. *Brain and Language, 115*(2), 101–112. https://doi.org/10.1016/j.bandl.2010.04.001

De Renzi, E., & Vignolo, L. A. (1962). The token test: A sensitive test to detect receptive disturbances in aphasics. *Brain, 85*, 665–678. https://doi.org/10.1093/brain/85.4.665

De Witt Hamer, P. C., Robles, S. G., Zwinderman, A. H., Duffau, H., & Berger, M. S. (2012). Impact of intraoperative stimulation brain mapping on glioma surgery outcome: A meta-analysis. *Journal of Clinical Oncology, 30*(20), 2559–2565. https://doi.org/10.1200/JCO.2011.38.4818

De Witte, E., Satoer, D., Robert, E., Colle, H., Verheyen, S., Visch-Brink, E., & Marien, P. (2015). The Dutch linguistic intraoperative protocol: A valid linguistic approach to awake brain surgery. *Brain and Language, 140*, 35–48. https://doi.org/10.1016/j.bandl.2014.10.011

DeWitt, I., & Rauschecker, J. P. (2012). Phoneme and word recognition in the auditory ventral stream. *Proceedings of the National Academy of Sciences of the United States of America, 109*(8), E505–E514. https://doi.org/10.1073/pnas.1113427109

DeWitt, I., & Rauschecker, J. P. (2013). Wernicke's area revisited: Parallel streams and word processing. *Brain and Language, 127*(2), 181–191. https://doi.org/10.1016/j.bandl.2013.09.014

DeWitt, I., & Rauschecker, J. P. (2016). Convergent evidence for the causal involvement of anterior superior temporal gyrus in auditory single-word comprehension. *Cortex, 77*, 164–166. https://doi.org/10.1016/j.cortex.2015.08.016

Duffau, H. (2015). Stimulation mapping of white matter tracts to study brain functional connectivity. *Nature Reviews Neurology, 11*(5), 255–265. https://doi.org/10.1038/nrneurol.2015.51

Duffau, H., & Mandonnet, E. (2013). The "onco-functional balance" in surgery for diffuse low-grade glioma: Integrating the extent of resection with quality of life. *Acta Neurochirurgica, 155*(6), 951–957. https://doi.org/10.1007/s00701-013-1653-9

Eckstein, K., & Friederici, A. D. (2006). It's early: Event-related potential evidence for initial interaction of syntax and prosody in speech comprehension. *Journal of Cognitive Neuroscience, 18*(10), 1696–1711. https://doi.org/10.1162/jocn.2006.18.10.1696

Faulkner, J. W., Wilshire, C. E., Parker, A. J., & Cunningham, K. (2017). An evaluation of language in brain tumor patients using a new cognitively motivated testing protocol. *Neuropsychology, 31*(6), 648–665. https://doi.org/10.1037/neu0000374

Fernandez Coello, A., Moritz-Gasser, S., Martino, J., Martinoni, M., Matsuda, R., & Duffau, H. (2013). Selection of intraoperative tasks for awake mapping based on relationships between tumor location and functional networks. *Journal of Neurosurgery, 119*(6), 1380–1394. https://doi.org/10.3171/2013.6.JNS122470

Fridriksson, J., Fillmore, P., Guo, D., & Rorden, C. (2015). Chronic Broca's aphasia is caused by damage to Broca's and Wernicke's areas. *Cerebral Cortex, 25*(12), 4689–4696. https://doi.org/10.1093/cercor/bhu152

Friederici, A. D. (2002). Towards a neural basis of auditory sentence processing. *Trends in Cognitive Sciences, 6*(2), 78–84.

Friederici, A. D. (2011). The brain basis of language processing: From structure to function. *Physiological Reviews, 91*(4), 1357–1392. https://doi.org/10.1152/physrev.00006.2011

Friederici, A. D. (2012). The cortical language circuit: From auditory perception to sentence comprehension. *Trends in Cognitive Sciences, 16*(5), 262–268. https://doi.org/10.1016/j.tics.2012.04.001

Friederici, A. D. (2017). *Language in our brain: The origins of a uniquely human capacity*. MIT Press.

Gajardo-Vidal, A., Lorca-Puls, D. L., Hope, T. M. H., Parker Jones, O., Seghier, M. L., Prejawa, S., Crinion, J. T., Leff, A. P., Green, D. W., & Price, C. J. (2018). How right hemisphere damage after stroke can impair speech comprehension. *Brain, 141*(12), 3389–3404. https://doi.org/10.1093/brain/awy270

Gamer, M., Lemon, J., & Singh, I. F. P. (2019). *irr: Various coefficients of interrater reliability and agreement*. R package version 0.84.1 https://CRAN.R-project.org/package=irr.

Gatignol, P., Capelle, L., Le Bihan, R., & Duffau, H. (2004). Double dissociation between picture naming and comprehension: An electrostimulation study. *NeuroReport, 15*(1), 191–195. https://doi.org/10.1097/01.wnr.0000099474.09597.6a

Getz, L. M., & Toscano, J. C. (2021). The time-course of speech perception revealed by temporally-sensitive neural measures. *Wiley Interdisciplinary Reviews: Cognitive Science, 12*(2), e1541. https://doi.org/10.1002/wcs.1541

Giampiccolo, D., Howells, H., Bährend, I., Schneider, H., Raffa, G., Rosenstock, T., Vergani, F., Vajkoczy, P., & Picht, T. (2020). Preoperative transcranial magnetic stimulation for picture naming is reliable in mapping segments of the arcuate fasciculus. *Brain Communications, 2*(2), 1–15. https://doi.org/10.1093/braincomms/fcaa158

Gogos, A. J., Young, J. S., Morshed, R. A., Hervey-Jumper, S. L., & Berger, M. S. (2020). Awake glioma surgery: Technical evolution and nuances. *Journal of Neuro-oncology, 147*(3), 515–524. https://doi.org/10.1007/s11060-020-03482-z

Gough, P. M., Nobre, A. C., & Devlin, J. T. (2005). Dissociating linguistic processes in the left inferior frontal cortex with transcranial magnetic stimulation. *The Journal of Neuroscience: the Official Journal of the Society for Neuroscience, 25*(35), 8010–8016. https://doi.org/10.1523/JNEUROSCI.2307-05.2005

Grisot, G., Haber, S. N., & Yendiki, A. (2021). Diffusion MRI and anatomic tracing in the same brain reveal common failure modes of tractography. *NeuroImage, 239*, 118300. https://doi.org/10.1016/j.neuroimage.2021.118300

Haddad, A. F., Young, J. S., Berger, M. S., & Tarapore, P. E. (2021). Preoperative applications of navigated transcranial magnetic stimulation. *Frontiers in Neurology, 11*, 628903. https://doi.org/10.3389/fneur.2020.628903

Hagoort, P., Hald, L., Bastiaansen, M., & Petersson, K. M. (2004). Integration of word meaning and world knowledge in language comprehension. *Science, 304*(5669), 438–441. https://doi.org/10.1126/science.1095455

Hauck, T., Tanigawa, N., Probst, M., Wohlschlaeger, A., Ille, S., Sollmann, N., Maurer, S., Zimmer, C., Ringel, F., Meyer, B., & Krieg, S. M. (2015). Task type affects location of language-positive cortical regions by repetitive navigated transcranial magnetic stimulation mapping. *PLoS One, 10*(4), Article e0125298. https://doi.org/10.1371/journal.pone.0125298

Hendrix, P., Senger, S., Simgen, A., Griessenauer, C. J., & Oertel, J. (2017). Preoperative rTMS language mapping in speech-eloquent brain lesions resected under general anesthesia: A pair-matched cohort study. *World Neurosurgery, 100*, 425–433. https://doi.org/10.1016/j.wneu.2017.01.041

Herrmann, B., Maess, B., Hasting, A. S., & Friederici, A. D. (2009). Localization of the syntactic mismatch negativity in the temporal cortex: An MEG study. *NeuroImage, 48*(3), 590–600. https://doi.org/10.1016/j.neuroimage.2009.06.082

Hervey-Jumper, S. L., & Berger, M. S. (2016). Maximizing safe resection of low- and high-grade glioma. *Journal of Neuro-oncology, 130*(2), 269–282. https://doi.org/10.1007/s11060-016-2110-4

Huber, W., Poeck, K., & Springer, L. (1983). *Aachener Aphasietest (AAT)*. Hogrefe.

IJzerman-Korevaar, M., Snijders, T. J., de Graeff, A., Teunissen, S., & de Vos, F. Y. F. (2018). Prevalence of symptoms in glioma patients throughout the disease trajectory: A systematic review. *Journal of Neuro-oncology, 140*(3), 485–496. https://doi.org/10.1007/s11060-018-03015-9

Ille, S., Engel, L., Albers, L., Schroeder, A., Kelm, A., Meyer, B., & Krieg, S. M. (2019). Functional reorganization of cortical language function in glioma patients – A preliminary study. *Frontiers in Oncology, 9*, 446. https://doi.org/10.3389/fonc.2019.00446

Ille, S., Engel, L., Kelm, A., Meyer, B., & Krieg, S. M. (2018). Language-eloquent white matter pathway tractography and the course of language function in glioma patients. *Frontiers in Oncology, 8*, 572. https://doi.org/10.3389/fonc.2018.00572

Ille, S., Kulchytska, N., Sollmann, N., Wittig, R., Beurskens, E., Butenschoen, V. M., Ringel, F., Vajkoczy, P., Meyer, B., Picht, T., & Krieg, S. M. (2016a). Hemispheric language dominance measured by repetitive navigated transcranial magnetic stimulation and postoperative course of language function in brain tumor patients. *Neuropsychologia, 91*, 50–60. https://doi.org/10.1016/j.neuropsychologia.2016.07.025

Ille, S., Schroeder, A., Albers, L., Kelm, A., Droese, D., Meyer, B., & Krieg, S. M. (2021). Non-invasive mapping for effective preoperative guidance to approach highly language-eloquent gliomas—A large scale comparative cohort study using a new classification for language eloquence. *Cancers, 13*(2), 207. https://doi.org/10.3390/cancers13020207

Ille, S., Sollmann, N., Butenschoen, V. M., Meyer, B., Ringel, F., & Krieg, S. M. (2016b). Resection of highly language-eloquent brain lesions based purely on rTMS language mapping without awake surgery. *Acta Neurochirurgica, 158*(12), 2265–2275. https://doi.org/10.1007/s00701-016-2968-0

Ille, S., Sollmann, N., Hauck, T., Maurer, S., Tanigawa, N., Obermueller, T., Negwer, C., Droese, D., Zimmer, C., Meyer, B., Ringel, F., & Krieg, S. M. (2015). Combined noninvasive language mapping by navigated transcranial magnetic stimulation and functional MRI and its comparison with direct cortical stimulation. *Journal of Neurosurgery, 123*(1), 212–225. https://doi.org/10.3171/2014.9.JNS14929

Ingram, R. U., Halai, A. D., Pobric, G., Sajjadi, S., Patterson, K., & Lambon Ralph, M. A. (2020). Graded, multidimensional intra- and intergroup variations in primary progressive aphasia and post-stroke aphasia. *Brain, 143*(10), 3121–3135. https://doi.org/10.1093/brain/awaa245

Isaacs, K. L., Barr, W. B., Nelson, P. K., & Devinsky, O. (2006). Degree of handedness and cerebral dominance. *Neurology, 66*(12), 1855–1858. https://doi.org/10.1212/01.wnl.0000219623.28769.74

Jefferies, E., & Lambon Ralph, M. A. (2006). Semantic impairment in stroke aphasia versus semantic dementia: A case-series comparison. *Brain, 129*(8), 2132–2147. https://doi.org/10.1093/brain/awl153

Jodzio, A., Piai, V., Verhagen, L., Cameron, I., & Indefrey, P. (2023). Validity of chronometric TMS for probing the time-course of word production: A modified replication. *Cerebral Cortex*. https://doi.org/10.1093/cercor/bhad081

Kertesz, A. (2007). *WAB-R: Western aphasia battery-revised*. The Psychological Corporation.

Klaus, J., & Hartwigsen, G. (2019). Dissociating semantic and phonological contributions of the left inferior frontal gyrus to language production. *Human Brain Mapping, 40*(11), 3279–3287. https://doi.org/10.1002/hbm.24597

Knecht, S., Dräger, B., Deppe, M., Bobe, L., Lohmann, H., Flöel, A., Ringelstein, E.-B., & Henningsen, H. (2000). Handedness and hemispheric language dominance in healthy humans. *Brain, 123*, 2512–2518. https://doi.org/10.1093/brain/123.12.2512

Krieg, S. M., Lioumis, P., Mäkelä, J. P., Wilenius, J., Karhu, J., Hannula, H., Savolainen, P., Lucas, C. W., Seidel, K., Laakso, A., Islam, M., Vaalto, S., Lehtinen, H., Vitikainen, A. M., Tarapore, P. E., & Picht, T. (2017). Protocol for motor and language mapping by navigated TMS in patients and healthy volunteers; workshop report. *Acta Neurochirurgica, 159*(7), 1187–1195. https://doi.org/10.1007/s00701-017-3187-z

Krieg, S. M., Sollmann, N., Hauck, T., Ille, S., Foerschler, A., Meyer, B., & Ringel, F. (2013). Functional language shift to the right hemisphere in patients with languagelanguage-eloquent brain tumors. *PLoS One, 8*(9), Article e75403. https://doi.org/10.1371/journal.pone.0075403

Krieg, S. M., Sollmann, N., Tanigawa, N., Foerschler, A., Meyer, B., & Ringel, F. (2016). Cortical distribution of speech and language errors investigated by visual object naming and navigated transcranial magnetic stimulation. *Brain Structure & Function, 221*(4), 2259–2286. https://doi.org/10.1007/s00429-015-1042-7

Lambon Ralph, M. A., Jefferies, E., Patterson, K., & Rogers, T. T. (2017). The neural and computational bases of semantic cognition. *Nature Reviews. Neuroscience, 18*(1), 42–55. https://doi.org/10.1038/nrn.2016.150

Landis, J. R., & Koch, G. G. (1977). The measurement of observer agreement for categorical data. *Biometrics, 33*(1), 159–174. https://doi.org/10.2307/2529310

Lioumis, P., Zhdanov, A., Mäkelä, N., Lehtinen, H., Wilenius, J., Neuvonen, T., Hannula, H., Deletis, V., Picht, T., & Mäkelä, J. P. (2012). A novel approach for documenting naming errors induced by navigated transcranial magnetic stimulation. *Journal of Neuroscience Methods, 204*(2), 349–354. https://doi.org/10.1016/j.jneumeth.2011.11.003

Maier-Hein, K. H., Neher, P. F., Houde, J. C., Cote, M. A., Garyfallidis, E., Zhong, J., Chamberland, M., Yeh, F. C., Lin, Y. C., Ji, Q., Reddick, W. E., Glass, J. O., Chen, D. Q., Feng, Y., Gao, C., Wu, Y., Ma, J., He, R., Li, Q., … Descoteaux, M. (2017). The challenge of mapping the human connectome based on diffusion tractography. *Nature Communications, 8*(1), 1349. https://doi.org/10.1038/s41467-017-01285-x

Mandonnet, E., Winkler, P. A., & Duffau, H. (2010). Direct electrical stimulation as an input gate into brain functional networks: Principles, advantages and limitations. *Acta Neurochirurgica, 152*(2), 185–193. https://doi.org/10.1007/s00701-009-0469-0

Martin-Monzon, I., Rivero Ballagas, Y., & Arias-Sanchez, S. (2022). Language mapping: A systematic review of protocols that evaluate linguistic functions in awake surgery. *Applied Neuropsychology Adult, 29*(4), 845–854. https://doi.org/10.1080/23279095.2020.1776287

Mesulam, M. M., Rader, B. M., Sridhar, J., Nelson, M. J., Hyun, J., Rademaker, A., Geula, C., Bigio, E. H., Thompson, C. K., Gefen, T. D., Weintraub, S., & Rogalski, E. J. (2019). Word comprehension in temporal cortex and Wernicke area: A PPA perspective. *Neurology, 92*(3), e224–e233. https://doi.org/10.1212/WNL.0000000000006788

Mesulam, M. M., Thompson, C. K., Weintraub, S., & Rogalski, E. J. (2015). The Wernicke conundrum and the anatomy of language comprehension in primary progressive aphasia. *Brain, 138*(8), 2423–2437. https://doi.org/10.1093/brain/awv154

Mirman, D., Chen, Q., Zhang, Y., Wang, Z., Faseyitan, O. K., Coslett, H. B., & Schwartz, M. F. (2015). Neural organization of spoken language revealed by lesion-symptom mapping. *Nature Communications, 6*, 6762. https://doi.org/10.1038/ncomms7762

Natalizi, F., Piras, F., Vecchio, D., Spalletta, G., & Piras, F. (2022). Preoperative navigated transcranial magnetic stimulation: New insight for brain tumor-related language mapping. *Journal of Personalized Medicine, 12*(10), 1589. https://doi.org/10.3390/jpm12101589

Negwer, C., Ille, S., Hauck, T., Sollmann, N., Maurer, S., Kirschke, J. S., Ringel, F., Meyer, B., & Krieg, S. M. (2017). Visualization of subcortical language pathways by diffusion tensor imaging fiber tracking based on rTMS language mapping. *Brain Imaging and Behavior, 11*(3), 899–914. https://doi.org/10.1007/s11682-016-9563-0

Ohlerth, A.-K., Bastiaanse, R., Negwer, C., Sollmann, N., Schramm, S., Schröder, A., & Krieg, S. M. (2021a). Bihemispheric navigated transcranial magnetic stimulation mapping for action naming compared to object naming in sentence context. *Brain Sciences, 11*(9), 1190. https://doi.org/10.3390/brainsci11091190

Ohlerth, A.-K., Bastiaanse, R., Nickels, L., Neu, B., Zhang, W., Ille, S., Sollmann, N., & Krieg, S. M. (2021b). Dual-task nTMS mapping to visualize the cortico-subcortical language network and capture postoperative outcome – A patient series in Neurosurgery. *Frontiers in Oncology, 11*, Article 788122. https://doi.org/10.3389/fonc.2021.788122

Ohlerth, A. K., Valentin, A., Vergani, F., Ashkan, K., & Bastiaanse, R. (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 Neurochirurgica, 162*(2), 397–406. https://doi.org/10.1007/s00701-019-04159-x

Okada, K., Rong, F., Venezia, J., Matchin, W., Hsieh, I. H., Saberi, K., Serences, J. T., & Hickok, G. (2010). Hierarchical organization of human auditory cortex: Evidence from acoustic invariance in the response to intelligible speech. *Cerebral Cortex, 20*(10), 2486–2495. https://doi.org/10.1093/cercor/bhp318

Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychology, 9*(1), 97–113. https://doi.org/10.1016/0028-3932(71)90067-4

Ottenhausen, M., Krieg, S. M., Meyer, B., & Ringel, F. (2015). Functional preoperative and intraoperative mapping and monitoring: Increasing safety and efficacy in glioma surgery. *Neurosurgical Focus, 38*(1), E3. https://doi.org/10.3171/2014.10.FOCUS14611

Picht, T., Krieg, S. M., Sollmann, N., Rösler, J., Niraula, B., Neuvonen, T., Savolainen, P., Lioumis, P., Mäkelä, J. P., Deletis, V., Meyer, B., Vajkoczy, P., & Ringel, F. (2013). A comparison of language mapping by preoperative navigated transcranial magnetic stimulation and direct cortical stimulation during awake surgery. *Neurosurgery, 72*(5), 808–819. https://doi.org/10.1227/NEU.0b013e3182889e01

R Core Team. (2020). *R: A language and environment for statistical computing*. R Foundation for Statistical Computing https://www.R-project.org/.

Raffa, G., Marzano, G., Curcio, A., Espahbodinea, S., Germanò, A., & Angileri, F. F. (2022). Personalized surgery of brain tumors in language areas: The role of preoperative brain mapping in patients not eligible for awake surgery. *Neurosurgical Focus, 53*(6). https://doi.org/10.3171/2022.9.Focus22415

Raffa, G., Quattropani, M. C., & Germanò, A. (2019). When imaging meets neurophysiology: The value of navigated transcranial magnetic stimulation for preoperative neurophysiological mapping prior to brain tumor surgery. *Neurosurgical Focus, 47*(6), E10. https://doi.org/10.3171/2019.9.FOCUS19640

Rejno-Habte Selassie, G., Pegenius, G., Karlsson, T., Viggedal, G., Hallbook, T., & Elam, M. (2020). Cortical mapping of receptive language processing in children using navigated transcranial magnetic stimulation. *Epilepsy & Behavior, 103*(Pt A), Article 106836. https://doi.org/10.1016/j.yebeh.2019.106836

Rofes, A., & Miceli, G. (2014). Language mapping with verbs and sentences in awake surgery: A review. *Neuropsychology Review, 24*(2), 185–199. https://doi.org/10.1007/s11065-014-9258-5

Rofes, A., Spena, G., Miozzo, A., Fontanella, M. M., & Miceli, G. (2015). Advantages and disadvantages of intraoperative language tasks in awake surgery: a three-task approach for prefrontal tumors. *Journal of Neurosurgical Sciences, 59*, 337–349.

Roux, F. E., Miskin, K., Durand, J. B., Sacko, O., Rehault, E., Tanova, R., & Demonet, J. F. (2015). Electrostimulation mapping of comprehension of auditory and visual words. *Cortex, 71*, 398–408. https://doi.org/10.1016/j.cortex.2015.07.001

Schramm, S., Tanigawa, N., Tussis, L., Meyer, B., Sollmann, N., & Krieg, S. M. (2020). Capturing multiple interaction effects in L1 and L2 object-naming reaction times in healthy bilinguals: A mixed-effects multiple regression analysis. *BMC Neuroscience, 21*(1), 3. https://doi.org/10.1186/s12868-020-0549-x

Schwarzer, V., Bährend, I., Rosenstock, T., Dreyer, F. R., Vajkoczy, P., & Picht, T. (2018). Aphasia and cognitive impairment decrease the reliability of rnTMS language mapping. *Acta Neurochirurgica, 160*(2), 343–356. https://doi.org/10.1007/s00701-017-3397-4

Sollmann, N., Hauck, T., Hapfelmeier, A., Meyer, B., Ringel, F., & Krieg, S. M. (2013). Intra- and interobserver variability of language mapping by navigated transcranial magnetic brain stimulation. *BMC Neuroscience, 14*, 150. https://doi.org/10.1186/1471-2202-14-150

Sollmann, N., Ille, S., Boeckh-Behrens, T., Ringel, F., Meyer, B., & Krieg, S. M. (2016). Mapping of cortical language function by functional magnetic resonance imaging and repetitive navigated transcranial magnetic stimulation in 40 healthy subjects. *Acta Neurochirurgica, 158*(7), 1303–1316. https://doi.org/10.1007/s00701-016-2819-z

Sollmann, N., Ille, S., Negwer, C., Boeckh-Behrens, T., Ringel, F., Meyer, B., & Krieg, S. M. (2017). Cortical time course of object naming investigated by repetitive navigated transcranial magnetic stimulation. *Brain Imaging and Behavior, 11*(4), 1192–1206. https://doi.org/10.1007/s11682-016-9574-x

Sollmann, N., Kelm, A., Ille, S., Schroder, A., Zimmer, C., Ringel, F., Meyer, B., & Krieg, S. M. (2018). Setup presentation and clinical outcome analysis of treating highly language-eloquent gliomas via preoperative navigated transcranial magnetic stimulation and tractography. *Neurosurgical Focus, 44*(6), E2. https://doi.org/10.3171/2018.3.FOCUS1838

Sollmann, N., Zhang, H., Fratini, A., Wildschuetz, N., Ille, S., Schroder, A., Zimmer, C., Meyer, B., & Krieg, S. M. (2020a). Risk assessment by presurgical tractography using navigated TMS maps in patients with highly motor- or language-eloquent brain tumors. *Cancers, 12*(5), 1264. https://doi.org/10.3390/cancers12051264

Sollmann, N., Zhang, H., Schramm, S., Ille, S., Negwer, C., Kreiser, K., Meyer, B., & Krieg, S. M. (2020b). Function-specific tractography of language pathways based on nTMS mapping in patients with supratentorial lesions. *Clinical Neuroradiology, 30*(1), 123–135. https://doi.org/10.1007/s00062-018-0749-2

Szelényi, A., Bello, L., Duffau, H., Fava, E., Feigl, G. C., Galanda, M., Neuloh, G., Signorelli, F., Sala, F., & Workgroup for

Intraoperative Management in Low-Grade Glioma Surgery within the European Low-Grade Glioma Network. (2010). Intraoperative electrical stimulation in awake craniotomy: Methodological aspects of current practice. *Neurosurgical Focus, 28*, E7. https://doi.org/10.3171/2009.12.FOCUS09237

Talacchi, A., Santini, B., Casartelli, M., Monti, A., Capasso, R., & Miceli, G. (2013). Awake surgery between art and science. Part II: Language and cognitive mapping. *Functional Neurology, 28*(3), 223–239. https://doi.org/10.11138/FNeur/2013.28.3.223

Tarapore, P. E., Findlay, A. M., Honma, S. M., Mizuiri, D., Houde, J. F., Berger, M. S., & Nagarajan, S. S. (2013). Language mapping with navigated repetitive TMS: Proof of technique and validation. *NeuroImage, 82*, 260–272. https://doi.org/10.1016/j.neuroimage.2013.05.018

Tarapore, P. E., Picht, T., Bulubas, L., Shin, Y., Kulchytska, N., Meyer, B., Berger, M. S., Nagarajan, S. S., & Krieg, S. M. (2016). Safety and tolerability of navigated TMS for preoperative mapping in neurosurgical patients. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology, 127*(3), 1895–1900. https://doi.org/10.1016/j.clinph.2015.11.042

Tremblay, P., & Dick, A. S. (2016). Broca and Wernicke are dead, or moving past the classic model of language neurobiology. *Brain and Language, 162*, 60–71. https://doi.org/10.1016/j.bandl.2016.08.004

Tremblay, P., Dick, A. S., & Small, S. L. (2011). New insights into the neurobiology of language from functional brain imaging. In H. Duffau (Ed.), *Brain mapping: From neural basis of cognition to surgical applications* (pp. 131–143). Vienna, Austria: SpringerWienNewYork.

Turken, A. U., & Dronkers, N. F. (2011). The neural architecture of the language comprehension network: Converging evidence from lesion and connectivity analyses. *Frontiers in Systems Neuroscience, 5*, 1. https://doi.org/10.3389/fnsys.2011.00001

Zaccarella, E., & Friederici, A. D. (2017). The neurobiological nature of syntactic hierarchies. *Neuroscience and Biobehavioral Reviews, 81*(Pt B), 205–212. https://doi.org/10.1016/j.neubiorev.2016.07.038

Zulko. (2020). *MoviePy (python module for video editing)* (vol. accessed on 19.05.23) https://github.com/Zulko/moviepy.