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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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A R T I C L E I N F O

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A B S T R A C T

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

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 pre-diagnosed 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

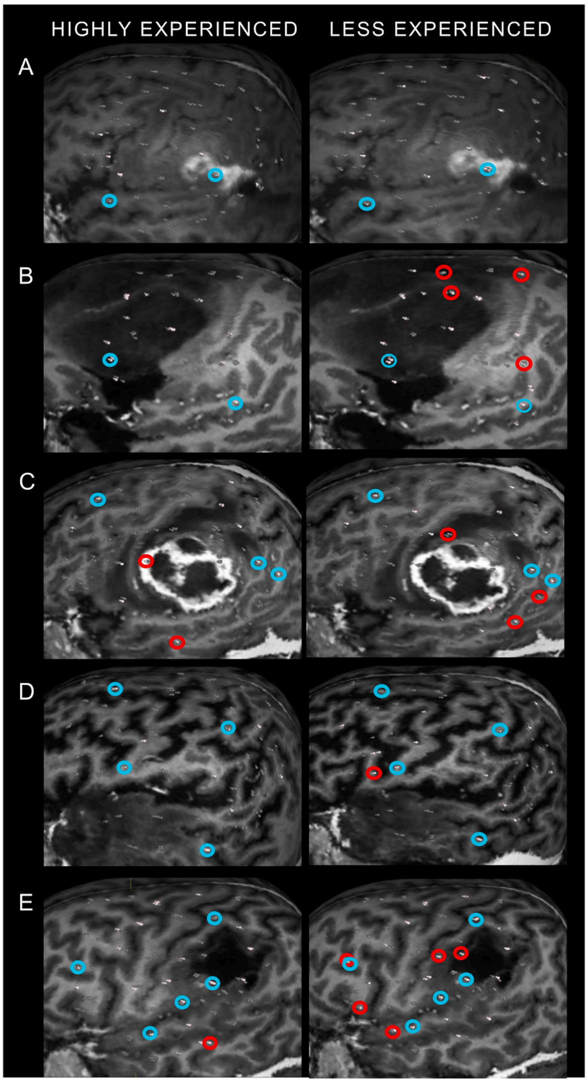

Fig. 1. Stuttering-caused misclassified language-positive stimuli. The figure shows the misclassified stuttering symptoms rated as stimulation-induced language errors by the highly experienced rater (left column) and by the less experienced rater (right column) for each patient individually (A: P1, B: 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

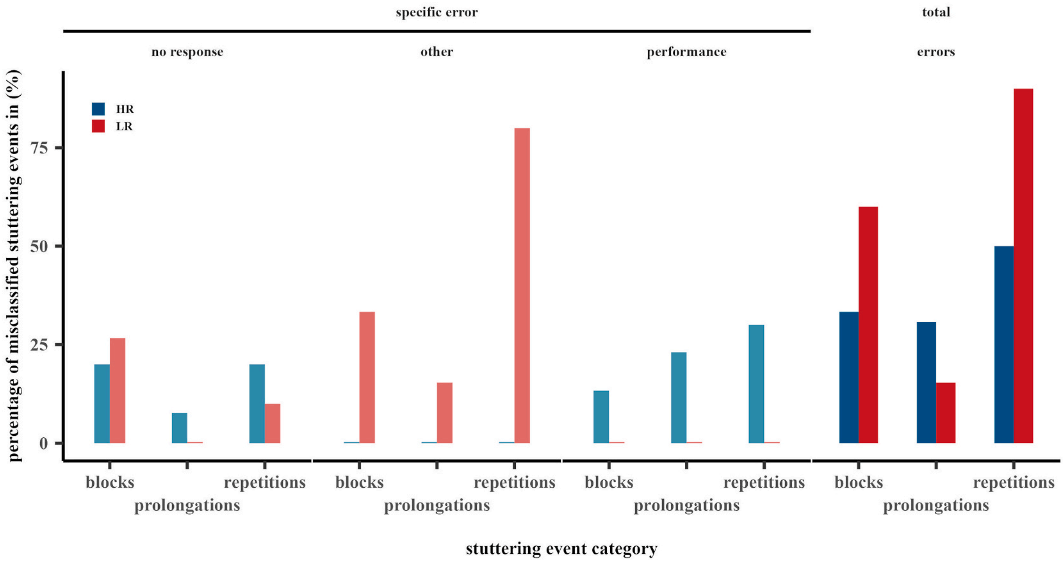

Fig. 2. Comparison of specific stuttering symptoms categories and classified language-error categories. The figure shows the percentage of misclassified stuttering symptoms across raters (red: less experienced rater LR, blue: highly experienced rater HR) across all (right column) and specific attributed 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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