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DISSERTATION

Evaluierung der navigierten transkraniellen Magnetstimulation (nTMS) in der präoperativen Diagnostik neurochirurgischer Patienten – Fokus auf der Untersuchung des Einflusses biometrischer Faktoren auf das Ergebnis der nTMS Messung sprachrelevanter Areale neurochirurgischer Patienten

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1. Inhaltsverzeichnis

2.1 Abstract English

Objective: Navigated transcranial magnetic stimulation (nTMS) is a non-invasive mapping tool to locate functional areas of the brain, gaining importance as a preoperative diagnostic device. This is a summary of three studies, Schwarzer et al., Rosenstock et al. and Zdunczyk et al., whose aim it is to increase the accuracy and usability of nTMS in different neurosurgical patient groups. They intend to describe neurophysiological data gained through nTMS as a supportive measure for surgical planning to increase patient safety and improve outcome.

Methods: All patients and healthy subjects were examined via bihemispheric nTMS. Schwarzer et al. ascertained a baseline picture naming performance and used repetitive nTMS (rnTMS) to induce speech disruptions to identify individual language areas in patients with language eloquent lesions. Nine biometric factors were analyzed for correlation with elevated error occurrence. Rosenstock et al. concentrated on the primary motor cortex of patients with motor-eloquent glioma and performed correlation analyses to test the association of nTMS-related variables and postoperative motor outcome. Zdunczyk et al. examined patients with degenerative cervical myelopathy (DCM) and healthy volunteers to see differences in neurophysiological nTMS data due to disease severity.

Results: Schwarzer et al. showed a significant increase in error occurrence with increased severity of cognitive impairment ($p<0.05$) and aphasia ($p<0.005$). Rosenstock et al. found no new permanent deficits after surgery when the distance between tumor and motor tracts was >8mm ($p=0.014$). New postoperative deficits could be seen in patients with pathological excitability of the motor cortex (resting motor threshold ratio <90%/>110%, $p=0.031$). Patients with DCM had a reduced corticospinal excitability estimated by the recruitment curve ($p=0.022$), and patients with mild symptoms showed an increased activation on non-primary motor areas ($p<0.005$). Patients with severe symptoms showed a higher cortical inhibition ($p<0.05$) and a reduced motor area ($p<0.05$).

Conclusion: Most patients are eligible for rnTMS language mapping. A new protocol for language mapping is proposed for secure identification of patients eligible for reliable rnTMS in Schwarzer et al. Rosenstock et al. introduce a new risk stratification model, based on objective functional-anatomical and neurophysiological measures, which enables physicians to counsel patients about the risk of functional deterioration or the potential for recovery and supports surgical planning. Zdunczyk et al. propose a new concept for functional compensation for DCM on the cortical and spinal level: the corticospinal reserve capacity. nTMS is a viable diagnostic tool to characterize this and its parameters serve as valuable prognostic factors.

2.2 Abstract Deutsch

Fragestellung: Navigierte transkranielle Magnetstimulation (nTMS) ist eine nicht-invasive Untersuchungsmethode, um kortikale Funktionsareale zu identifizieren, welche zunehmend an Bedeutung als präoperatives diagnostisches Mittel gewinnt. Dies ist eine Zusammenfassung dreier Studien, Schwarzer et al., Rosenstock et al. und Zdunczyk et al. Die Studien haben als Ziel, die Benutzerfreundlichkeit und Genauigkeit von nTMS für unterschiedliche neurochirurgische Patientengruppen zu verbessern. Neurophysiologische Parameter wurden mittels nTMS erhoben, um die operative Planung zu unterstützen und das individuelle Patientenrisiko korrekt einzuschätzen und zu verbessern.

Methodik: Alle Patienten und Probanden wurden bihemisphärisch mittels nTMS untersucht. Schwarzer et al. erhoben vorher die individuelle Fähigkeit zur Objektbenennung (baseline) und nutzten repetitive nTMS (rnTMS), um Sprachunterbrechungen hervorzurufen und somit Kortexareale bei Patienten mit sprachrelevanten Hirnläsionen zu identifizieren. Neun biometrische Patienteneigenschaften wurden in ein Verhältnis mit der Fehleranfälligkeit gesetzt. Rosenstock et al. untersuchten den primär motorischen Kortex bei Gliompatienten und analysierten den Zusammenhang von nTMS-ermittelten Parametern mit dem postoperativen Patientenzustand. Zdunczyk et al. betrachteten Patienten mit degenerativer zervikaler Myelopathie (DCM), sowie gesunde Probanden und ermittelten die unterschiedlichen nTMS-Parameter in Abhängigkeit von der Symptomschwere.

Ergebnisse: Die meisten biometrischen Faktoren zeigten keinen statistischen Zusammenhang mit dem Stimulationsergebnis bei Schwarzer et al. Je schwerer der Aphasiegrad und die kognitiven Einschränkungen waren, desto mehr Sprachfehler wurden in der rnTMS Untersuchung gemacht (je $p<0.005$ und $p<0.05$). Rosenstock et al. konnten zeigen, dass bei einer Distanz von >8mm zwischen Tumor und kortikospinalem Trakt keine neuen permanenten postoperativen Defizite auftraten ($p=0.014$). Neue postoperative Defizite traten bei Patienten mit präoperativ pathologischer Kortexerregbarkeit (Ruhemotorschwellenverhältnis RMT <90%/>110%, $p=0.031$) auf. DCM Patienten wiesen eine reduzierte kortikospinale Erregbarkeit, gekennzeichnet durch ein Abflachen der recruitment curve, auf ($p=0.022$). Ein vergrößertes motorisch relevantes Kortexareal mit Aktivierung sekundärer Motorareale zeigte sich bei Patienten mit milder Symptomatik ($p<0.005$), während bei schwer betroffenen Patienten eine erhöhte kortikale Hemmung (CSP, $p<0.05$) und reduzierte motorische Kortexfläche auffiel ($p<0.05$).

Schlussfolgerung: Schwarzer et al. stellen ein neues Prüfungsprotokoll für die Eignung von Patienten für ein reliables rnTMS Ergebnis vor, wobei die statistische Analyse ergab, dass die meisten Patienten für eine reliable rnTMS Sprachuntersuchung geeignet sind. Rosenstock et al. präsentieren ein neues Risikostratifikationsmodell für Patienten mit

motorisch relevanten Gliomen, wodurch der Operateur anhand von funktionell-anatomischen und neurophysiologischen Parametern das individuelle Patientenrisiko für den postoperativen Verlauf einschätzen kann. Zdunczyk et al. beschreiben einen möglichen funktionellen Kompensationsmechanismus bei DCM Patienten auf kortikaler und spinaler Ebene: die kortikospinale Reservekapazität. Die durch nTMS ermittelten Parameter lassen damit objektivierbare prognostische Aussagen zu.

2.3 List of Abbreviations

nTMS	navigated transcranial magnetic stimulation
rnTMS	repetitive navigated transcranial magnetic stimulation
DCM	degenerative cervical myelopathy
CNS	central nervous system
DCS	direct cortical stimulation
CST	corticospinal tract
BMRC	British Medical Research Council
BAS	Berlin Aphasia Score
KPS	Karnofsky Performance Scale
DOS	duration of symptoms
DTI	diffusion tensor imaging sequence
JOA	Japanese Orthopedic Association score
EMG	electromyography
FDI	first digital interosseus muscle
RMT	resting motor threshold
MEP	motor evoked potential
RC	recruitment curve
GTR	gross-total resection
STR	subtotal resection
PR	partial resection
M1	infiltration of the primary motor cortex and/or corticospinal tract
IntCaps	≤8mm distance from the corticospinal tract
M2	>8mm from the corticospinal tract and directly adjacent to primary motor cortex
M0	neither close to the corticospinal tract nor primary motor cortex

2.4 List of Tables

2.5 Introduction

Patients with lesions in their central nervous system (CNS) are often advised to undergo surgery, which promises an improvement of life quality but also bears the risk of further loss of function. Choosing against this measure though usually leads to a progression of the disease and consequently of the neurological impairment. A weighted assessment of risk and benefit preoperatively is therefore vital for an informed decision for both physician and patient.

Navigated transcranial magnetic stimulation (nTMS) has been recently introduced as an effective preoperative mapping tool[1,2]. It combines the integration of individual brain imaging data with the possibilities of non-invasively identifying spatial relations of lesion and functional cortex areas[3] and revealing changes in cortical activation and reorganization[4]. These factors contribute to an adequate risk assessment with more extensive resections possible while reducing postoperative functional deficits[5,6].

Examination of cortical areas related to language function is done by repetitive transcranial magnetic stimulation (rTMS), which is known to evoke language disruptions in patients and healthy volunteers[7]. In contrast to mapping of the primary motor cortex, which is well established[8], repetitive navigated transcranial magnetic stimulation (rnTMS) of language relevant areas lacks specificity and has only been suggested as a supporting tool for intraoperative direct cortical stimulation (DCS)[9].

This summary of three publications[10-12] addresses the further refinement of nTMS as a preoperative non-invasive mapping tool of cortical areas.

Patients with lesions in language-eloquent cortical regions have an elevated risk of aphasia after resection. The “gold standard” to reduce that risk, is direct cortical stimulation (DCS) during an awake surgery[13]. Not every patient is able to undergo this procedure and neither is every clinical center willing to take the increased risk and expenses that awake surgery imposes. A reliable non-invasive preoperative mapping tool is therefore needed. Since rnTMS language mapping still faces the challenge of increasing specificity and positive predictive value, the work “Aphasia and cognitive impairment decrease the reliability of rnTMS language mapping”[11], hereby referred to as Schwarzer et al., aims to identify factors influencing the rnTMS examination results independent of stimulation to improve the mapping protocol.

Motor area-related glioma surgery also faces difficulties with post-operative motor deficits, which, even when transient, affect the patient’s well-being as well as obstruct further treatment plans[14]. Improving surgical planning and individually preparing patients for the most-likely outcome is essential for an optimal treatment. The paper “Risk stratification in motor area-related glioma surgery based on navigated transcranial magnetic stimulation

data"[10], hereby referred to as Rosenstock et al., aims to add to known benefits by predicting the motor outcome after glioma surgery via preoperatively nTMS-acquired topographical and neurophysiological parameters.

Degenerative cervical myelopathy (DCM) is a progressive disease and the majority cause of disability in the elderly[15]. It is not yet possible to early discern which patients will benefit from surgery and which carry a high risk for developing further neurological impairment[16]. The work "The Corticospinal Reserve Capacity: Reorganization of Motor Area and Excitability As a Novel Pathophysiological Concept in Cervical Myelopathy" [12], hereby referred to Zdunczyk et al., aims to characterize the underlying pathophysiology of DCM through topographical and neurophysiological parameters to correctly identify vulnerable patient groups.

All three publications aim to improve the use of nTMS as a preoperative diagnostic tool for neurosurgical patients to minimize risk of surgery and identify the probable individual patient outcome.

2.6 Methods

All three studies are in accordance with the ethical standards of the Declaration of Helsinki and were approved by the Ethics Commission of the Charité University Hospital. All patients gave written informed consent for medical evaluation and treatments within the scope of the studies.

Patient samples

A preoperative nTMS was conducted on all included patients and healthy volunteers. The study of Schwarzer et al. included 101 patients with lesions in language-eloquent cortical regions or signs of aphasia with lesions in atypical locations. Rosenstock et al. included 113 patients with glioma that compressed or infiltrated the primary motor cortex as well as those that were in close relation to the corticospinal tract (CST). Patients with frequent generalized seizures or cranial implants were excluded in both studies. Zdunczyk et al. examined 18 patients suffering from symptomatic degenerative cervical myelopathy and 8 healthy volunteers. Patients, who had additional pathologies close to the CST above the lesion site, neuroinflammatory disease, high-grade paresis of the upper extremity (British Medical Research Council (BMRC)[17] stage ≤3), a cardiac pacemaker, deep brain stimulation electrodes or who were pregnant, were excluded.

Patient assessment before nTMS

Each study collected biometric and clinical data before applying nTMS. Each patient and healthy volunteer received a cerebral 1.5 or 3T MRI with a 3D gradient echo sequence

beforehand for assessment of location and histology of lesion and as a basis for the neuronavigational software.

Schwarzer et al. recorded the following biometric factors: age, gender, cognitive ability, aphasia status, histology of lesion and location of lesion. Cognitive ability was assessed by the DemTect test[18] and classified into three performance-dependent groups (1-3) with ascending severity of impairment. The aphasia status was assessed by the Berlin aphasia score (BAS)[9], a clinical test developed by Charité University physicians. Four groups with increasing signs of aphasia were identified (0-3). Histology of lesion was determined according to the World Health Organization and sorted into four categories: slow-growing intrinsic brain tumors, fast-growing brain tumors, meningioma and vascular malformation. The lesions were located temporal, parietal, frontal or insular. Before starting stimulation a baseline picture-naming performance was assessed. Patients had to name a set of pictures 2-3 times. All pictures not named properly and immediately or named with difficulty were excluded from the dataset used during stimulation to limit misnaming unrelated to nTMS. Over the patient acquisition time from 2010 to 2015 the baseline picture set was adjusted from 150 pictures gradually down to 80 pictures in two steps. This reduction is based on an in-house study, where 30 healthy volunteers, aged 18-72 and with diverse educational backgrounds, named all pictures. Only those objects, that were named consistently by at least 90% of the volunteers were retained for the final 80 picture dataset.

Rosenstock et al. assessed age, gender, antiepileptic and antiedematous medication, the Karnofsky Performance Scale (KPS), motor status according to BMRC and duration of symptoms (DOS). In addition to the aforementioned MRI sequence, a FLAIR sequence and a diffusion tensor imaging sequence (DTI) for white matter fiber tracking were acquired.

Zdunczyk et al. recorded the motor status according to BMRC, tested the fine motor hand function by finger tapping test, and sorted patients into two groups according to the Japanese Orthopedic Association score (JOA)[19]. It defined patients with JOA ≤12 at a moderate stage of disease and JOA >12 as mild. Cervical myelopathy was radiologically confirmed by a structural T2 MRI.

Navigated transcranial magnetic stimulation

All patients and healthy subjects underwent bihemispherical nTMS brain mapping with nTMS (eXimia; Nexstim). The 3D MRI sequence described above was imported into the system and used as the basis for neuronavigation and the analytical software. A biphasic figure-of-eight coil generates a magnetic field with each stimulation, which penetrates the skull and creates an electric field in the underlying brain. The muscle output was recorded by an integrated electromyography unit (EMG) using surface electrodes (Neuroline 729; Ambu) over the first digital interosseus muscle (FDI) of both hands. Language performance was

recorded by an integrated video camera and microphone (NexSpeech Module), pictures remaining after the baseline performance test were shown on a monitor in front of the patient in random order.
The system locates the stimulation site via stereotactic reflectors, which were attached to the patient's head with an elastic band or specifically designed spectacle frame.

A mapping of the primary motor cortex and areas close to lesion was conducted in all patients and healthy volunteers. First the resting motor threshold (RMT), as a measure of cortical excitability, was determined over the "hotspot" of the FDI for each hemisphere. The hotspot was located by stimulation in a dense raster and different coil rotations along the primary motor cortex, identifying the spot with the highest EMG amplitude output of the FDI muscle. The RMT was then determined by the lowest output intensity producing at least 5 motor evoked potentials (MEP) ≥ 50 µV (peak to peak) out of 10 consecutive trials.

In Schwarzer et al., a language mapping was conducted afterwards. 1s-trains of rnTMS at 100% RMT were administered over 50-80 sites for each hemisphere, following the cortical parcellation system of Corina et al. [20]. Each site was stimulated at least 3 times – up to 5 times if a error was induced during examination. The stimulation frequency amounts to 5 Hz, and the stimulation intensity was at least 50 V/m at cortex level. In case of ineffective stimulation, frequency as well as inter-picture interval (2.5-4s) and picture presentation time (700-1000ms) were modified. All speech errors were assessed afterwards through evaluation of the video recordings by the examiner. In six cases the mapping of the hemisphere without a lesion was terminated before completion, due to patients' exhaustion. The level of pain due to stimulation was monitored and recorded for evaluation, sorting it into 3 groups measured by the Numeric Pain Rating Scale (NPRS) (no pain = NPRS 0, discomfort = NPRS 1-3, pain = NPRS 3-10).

Rosenstock et al. followed the determination of the RMT with a peritumoral mapping of the upper and lower extremity (at 110% and 130% RMT respectively). Then they outlined the primary motor cortex at high specificity (105% RMT) along the precentral gyrus. The MEP-positive points were used in the consecutive surgical planning.

Zdunczyk et al. continued after RMT determination with further evaluation of the corticospinal excitability through performing the recruitment curve (RC) protocol over the FDI hotspot. Single TMS pulses were delivered at varying stimulus intensities between 80%-140% RMT at random and each MEP amplitude was recorded. Following, the cortical silent period (CSP) was measured to detect cortical and corticospinal inhibition. The subject was instructed to clench both fists while 10 stimuli at 140% RMT were applied over the FDI hotspot. The latency (ms) from MEP offset to end of resumption of EMG activity marked the absolute CSP duration. Hereafter, a mapping of the motor area was conducted at 105% RMT and through

the convex hull method[21] the identified coordinates were used to calculate the cortical representation area via Matlab (Mathworks Inc).

Follow-up assessment

Rosenstock et al. used the located hotspots outlining the primary motor cortex to perform fiber tracking using the DTI sequence and DICOM format (iPlan 2.0, BrainLab). This tracks the patient-individual corticospinal tract in relation to the tumor for further surgical planning. The surgical team could then see a final map consisting of segmented tumor, TMS stimulation points outlining the primary motor cortex and TMS-based fiber tracts. After surgery the patients were sorted into groups according to extent of resection (measured by an MRI within 48 hours after surgery). The groups consisted of gross-total resection (GTR – no residual tissue), subtotal resection (STR, residue < $10cm^3$), partial resection (PR, residue > $10cm^3$) and biopsy. A neurological examination was performed 7 days and 3 months postoperatively.

Statistical Analysis

Schwarzer et al. and Rosenstock et al. used IBM SPSS Statistics 22 (IBM Corp.), with an additional use of Stata 13 (Stata IC) by Rosenstock et al. Zdunczyk et al. used SigmaPlot 11.0 (Systat Software Inc.) for statistical analysis.

In Schwarzer et al., all errors made were pooled together per hemisphere and given as the percentage per total stimulations made over that hemisphere, hereby called error rate. The hemispheres were classified as the hemisphere with a lesion (affected hemisphere) and the hemisphere without a lesion (unaffected hemisphere). Baseline errors were also given as the percentage of errors occurring in proportion to the total amount of objects shown, and are called the baseline rate. Multivariate analyses for non-parametric data were applied to test the significance of error rate distribution for each biometric variable (Mann-Whitney U test or Kruskal-Wallis test). In a post-hoc testing the Bonferroni correction was performed on the level of significance, then the Mann-Whitney U test was used. A regression analysis by Spearman was performed to analyze the relation of age to each error rate and the relation of the baseline rate to each error rate. A correlation was expected at $r_s > 0.6$ or $r_s < -0.6$.

Rosenstock et al. calculated an RMT ratio for each patient by dividing the RMT value of the affected hemisphere by the RMT value of the healthy hemisphere. For analyzing the association between the different variables and the postoperative motor status the Mann-Whitney U test and Fisher's exact test were applied, as well as Monte Carlo simulations for greater precision. To identify the association of different characteristics with a change in motor status, a general ordinal regression model was used (Stata gologit2). Those variables that showed a significant association in the aforementioned analyses were subsequently

tested in a multiple general ordinal regression model for their relation to the change in motor status at both 7 days and 3 months postoperatively.

The comparison of groups by Zdunczyk et al. was done with t-testing und univariate analysis of variance, with dependent variables as paired design and non-parametric data through the Wilcoxon signed-rank test. A regression analysis by Pearson was used to test the relationship of RC and finger tapping, as well as RC and CSP.

The level of significance was at $p < 0.05$ in all studies (excluding the post-hoc analysis with Bonferroni correction by Schwarzer et al.).

2.7 Results

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101 patients were examined. All patients completed the baseline performance test and rnTMS of the affected hemisphere. 95 patients completed rnTMS of the unaffected hemisphere as well, terminating the examination mainly due to exhaustion. The distribution of subgroups is displayed in **Table 1**.

Table 1. Patients' characteristics

Gender		**Age**		**Affected Hemisphere**		**DemTect Score**	
male	56 (55%)	median	49	left	89 (88%)	1	40 (51%)
female	45 (45%)	range	21-81	right	12 (12%)	2	22 (28%)
						3	17 (21%)
Histology		**Location of Lesion**		**Baseline Dataset**		**Berlin Aphasia Score**	
SGT	11 (11%)	temporal	44 (44%)	150	62 (61%)	0	68 (68%)
FGT	73 (72%)	parietal	11 (11%)	118	17 (17%)	1	17 (17%)
meningeoma	4 (4%)	frontal	39 (39%)	80	21 (21%)	2	13 (13%)
vascular malformations	12 (12%)	insular	7 (7%)	96	1 (1%)	3	2 (2%)
no biopsy	1 (1%)						
NPRS							
	rnTMS affected hemisphere		rnTMS unaffected hemisphere				
no pain (0)	23 (27%)		19 (24%)				
discomfort (1-3)	11 (13%)		10 (12%)				
pain (3-10)	51 (60%)		51 (64%)				

SGT = Slow Growing Intrinsic Brain Tumor. FGT = Fast Growing Brain Tumor. NPRS = Numeric Pain Rating Scale; rnTMS = repetitive navigated transcranial magnetic stimulation

Most factors did not influence the error rates during the baseline performance test or rnTMS mapping significantly.

During the baseline performance test, the following biometric factors significantly contributed to an elevated baseline rate: histology of lesion, the used baseline dataset, increased cognitive impairment and increased severity of aphasia. The results are shown in **Table 2.**

The error rate depended significantly on the location of lesion only during stimulation of the affected hemisphere (data not shown). The baseline dataset and histology statistically

influenced the error rate only during stimulation of the unaffected hemisphere (data not shown). A significant increase in error rate during stimulation of both hemispheres was found with decreasing cognitive ability and progressing degree of aphasia (see **Table 3**). The post-hoc analysis confirmed this finding. Looking at cognitive impairment the baseline rate significantly rose from DemTect grade 2 on. This finding continued comparing grade 1 with grade 3 for the error rates during stimulation, so a cut-off point for inclusion in the future language mapping protocol was made at DemTect grade 3.

Table 2. Significant elevation in baseline rate

Histology	median (%)	25. percentile (%)	75. percentile (%)	p value
SGT	23.33	6.67	35.33	
FGT	25.33	13	44.37	
meningeoma	22.96	19.31	48.17	0.037[a]
VM	12.29	4.08	16.83	
Baseline dataset				
150	27	15.17	44.17	
118	9.32	6.78	36.05	< 0.001[a]
80	10	5.63	16.88	
DemTect score				
1	13.54	7.53	24.5	
2	24	13.65	44.33	< 0.001[a]
3	44.67	23	61	
Berlin aphasia score				
0	14.54	7.63	26.33	
1	44.67	18.67	59.67	< 0.001[a]
2	46.67	38.9	56.67	
3	47.66	44.07	51.25	

Statistical test:a - Kruskal-Wallis-Test.
SGT = slow growing intrinsic brain tumor. FGT = fast growing intrinsic brain tumor. VM = vascular malformations

The BAS post-hoc analysis revealed a continued significant rise in error incidence during baseline performance testing and rnTMS stimulation over both hemispheres when comparing no aphasia with moderate signs (grade 2). A cut-off point at grade 2 aphasia is therefore proposed (data not shown).

To conclude this paper's findings, the results were summarized in a final calculation. Patients with DemTect grade 3 (signs of dementia) and moderate signs of aphasia (BAS grade 2) presented with a conspicuous tendency for more errors during all examinations. In a final analysis all patients potentially eligible for rnTMS language mapping (DemTect grade 2 or lower, BAS grade 1 or lower) were pooled and their baseline rate examined compared to those potentially not eligible (DemTect grade 3, BAS grade 2-3)

Table 3. Significant elevation of error rate during rnTMS

	Affected hemisphere				Unaffected hemisphere			
DemTect score	median (%)	25. percentile (%)	75. percentile (%)	p value	median (%)	25. percentile (%)	75. percentile (%)	p value
1	4.20	2.61	7.91		3.13	1.79	6.27	
2	4.59	3.62	8.90	0.022[a]	5.21	2.61	9.97	0.007[a]
3	8.45	5.7	12.05		7.05	3.61	13.05	
Berlin aphasia score								
0	4.27	2.69	7.8		3.48	2.08	6.03	
1	8.06	4.53	9.28	0.001[a]	5.18	2.72	11.47	0.001[a]
2	8.97	6.95	15.35		11.26	6.12	16.18	
3	9.34	1.6	17.09		9.73	4.38	15.08	

Statistical test: a - Kruskal-Wallis-Test.

Patients eligible presented with a median baseline rate of 14.67% (25th percentile 8.05%, 75th percentile 27.67%), while patients not eligible presented with a median baseline rate of 45% (25th percentile 28.33%, 75th percentile 54.83%). Comparing those groups lead to a highly significant difference (p<0.0001).

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113 patients with a median age of 51 years (range 20-82) were included. 60 patients were preoperatively treated with antiepileptic drugs and 18 with steroids.

Table 4. Patients' characteristics at baseline, according to postoperative motor status

	no. of	MRC grade at 7 days postop			no. of	MRC grade at 3 months postop		
variable	patients	median	IQR	p Value	patients	median	IQR	p Value
Sex				0.735*				0.566*
male	58 (51%)	4.0	4.0-5.0		44 (51%)	4.0	3.25-5.0	
female	55 (49%)	4.0	4.0-5.0		43 (49%)	4.0	4.0-5.0	
Preop motor status				<0.001°				0.001°
MRC grade ≤ 3	12 (11%)	3.0	2.25-3.0		9 (10%)	3.0	2.5-4.0	
MRC grade 4	41 (36%)	4.0	4.0-4.5		32 (37%)	4.0	3.0-4.0	
MRC grade 5	60 (53%)	5.0	4.0-5.0		46 (53%	5.0	4.0-5.0	
KPS Score				0.007°				0.045°
≤70%	17 (15%)	4.0	3.0-4.0		10 (11%)	4.0	3.0-4.0	
80%	24 (21%)	4.0	3.0-5.0		20 (23%)	4.0	3.0-5.0	
90%	44 (39%)	5.0	4.0-5.0		34 (39%)	4.5	4.0-5.0	
100%	28 (25%)	5.0	4.0-5.0		23 (26%)	5.0	4.0-5.0	
DOS§				0.017°				0.003°
no deficit	58 (53%)	5.0	4.0-5.0		45 (53%)	5.0	4.0-5.0	
< 4 weeks	34 (31%)	4.0	3.0-4.0		27 (32%)	4.0	3.0-4.0	
4-12 weeks	8 (7%)	4.0	3.25-4.75		6 (7%)	4.0	2.75-4.25	
> 12 weeks	9 (8%)	4.0	3.0-4.0		7 (8%)	3.0	3.0-3.0	
Affected hemisphere				0.963*				0.071*
right	57 (50%)	4.0	4.0-5.0		40 (46%)	4.0	3.0-5.0	
left	56 (50%)	4.0	4.0-5.0		47 (54%)	5.0	4.0-5.0	
nTMS based tumor localization^				0.010°				0.139°
M1	21 (39%)	4.0	2.5-5.0		16 (38%)	4.0	3.0-5.0	
IntCaps	17 (31%)	4.0	3.0-5.0		14 (33%)	4.0	2.75-5.0	
M2	6 (11%)	4.5	4.0-5.0		5 (12%)	5.0	4.0-5.0	
M0	10 (18%)	5.0	4.0-5.0		7 (17%)	4.0	4.0-5.0	
Tumor histology				0.672¶				0.825¶
LGG	17 (15%)	4.0	4.0-5.0		14 (16%)	4.0	3.0-5.0	
HGG	96 (85%)	4.0	4.0-5.0		73 (84%)	4.0	4.0-5.0	
RMT ratio				0.792°				0.968°
<90%	36 (32%)	4.0	4.0-5.0		26 (30%)	4.5	4.0-5.0	
90%-110%	38 (34%)	4.0	4.0-5.0		31 (36%)	4.0	3.0-5.0	
>110%	39 (34%)	4.0	3.0-5.0		30 (34%)	4.0	3.0-5.0	

IQR=interquartile range; DOS= duration of motor symptoms; M1=primary motor cortex and/or CST infiltrated;

IntCaps=tumor ≤8mm from CST; M2= >8mm from CST and directly adjacent to M1; M0=>8mm from CST and not directly adjacent to M1;

LGG=low grade glioma; HGG=high grade glioma; * Mann-Whitney U test; ° Linear trend test (using Monte Carlo simulations for precision);

§ 4 patients at 7 days and 2 patients at 3 months were unable to explain their medical histories and excluded;

^ based on no. of patients with DTI: 54 patients at 7 days after surgery and 42 patients at 3 months after surgery;

¶ Fisher`s exact test (using Monte Carlo simulations for precision)

The patients' clinical characteristics and their association with postoperative motor status are shown in **Table 4**. Motor function deteriorated in 20%, and improved in 8% and 11% (respectively severe and mild paresis preoperatively). Patients with a shorter case history (DOS < 4 weeks) had better chances of recovery and a lower risk of increased motor function impairment after 3 months.

A higher KPS score preoperatively was associated with a better motor function postoperatively. Histology did not lead to a significant difference in postoperative change of motor status or extent of resection (STR vs GTR, p= 0.190).

No significant interhemispheric differences regarding RMT could be found. The RMT of the tumorous hemisphere showed no significant correlation with the preoperative motor status. MEP latency and amplitude values were not significantly associated with the postoperative motor status or outcome. At a RMT ration of > 110% patients showed no functional improvement after 3 months and even showed an increased chance of developing a new deficit or experiencing deterioration of an existing motor deficit compared to patients with a RMT ratio of ≤ 110% (data not shown).

Navigated TMS-based fiber tracking was conducted in all 54 cases, in which DTI-capable MRI sequences were acquired. According to this data the tumor localization was determined: infiltration of the primary motor cortex and/or CST (M1), ≤ 8mm distance from CST (IntCaps), tumor > 8mm from CST and directly adjacent to the primary motor cortex (M2) and neither close to CST nor primary motor cortex (M0) (see data **Table 4**).

Table 5. Multiple ordinal logistic regression analysis of factors significantly associated with postoperative motor change

	model for motor change at 7 days postop*			model for motor change at 3 mos postop°		
variable	OR§	95% CI	p Value	OR§	95% CI	p Value
Preoperative motor status						
MRC grade ≤ 3	0.35	0.05-2.72	0.318	0.03	0.00-0.38	0.007
MRC grade 4	0.22	0.04-1.15	0.073	0.72	0.17-3.00	0.653
MRC grade 5	1			1		
RMT ratio						
<90%	1			–	–	–
90%-110%	13.11	2.05-83.71	0.007	–	–	–
>110%	2.71	0.51-14.32	0.240	–	–	–
nTMS based tumor localization						
M1	18.81	2.32-152.76	0.006	9.05	1.05-78.27	0.045
IntCaps	22.54	2.59-196.42	0.005	7.62	0.86-67.72	0.068
M2	4.73	0.32-70.39	0.259	1.14	0.08-15.80	0.920
M0	1			1		
Model fit						
R2 (pseudo)	0.30			0.19		
no. correctly classified	43 (79.6%)			26 (61.9%)		

–=variable excluded because it lacked significance in further steps of analysis; * 54 patients; ° 42 patients

§ an OR higher than 1 stands for a higher probability of deterioration in the preoperative motor status

Critical tumor location (M1 and IntCaps) was responsible for all postoperative motor deteriorations. A distance of ≤ 8mm was therefore used as a limiting value for further statistical regression analysis. A greater distance was associated with a better postoperative BMRC grade (data not shown). The tumor location also influenced the extent of resection. Critical locations were associated with a higher rate of STR and a lower rate of GTR (data not shown).

GTR was achieved in 54 patients, SRT in 36 patients, PR in 13 and a biopsy was performed in 5 cases. There was no significant association of extent of resection and postoperative motor status (data not shown).

The multiple ordinal logistic regression analysis revealed that preoperative motor status, RMT ratio and tumor localization were significantly associated with the postoperative motor change at 7 days after surgery. 3 months after surgery the RMT ratio did not correlate significantly anymore, the preoperative motor status and tumor localization remained as significant correlates for motor performance change (see **Table 5**).

Table 6.Equations for the individual probability for postoperative motor outcome

utcome	Equation
After 7 days	Probability p = 1/(1+exp[L]) for improvement:
	L=1.07 - 1.50*(MRC grade4) - 1.04 *(MRC grade ≤3) + 1.00 *(RMT ratio <90%) + 2.57 *(RMT ratio >110%) + 2.93 *M1 + 3.12 *IntCaps + 1.55 *M2
	Probability p = 1/(1+exp[L]) for worsening:
	L= 4.33 + 1.50 *(MRC grade 4) + 1.04 *(MRC grade ≤3) - 1.00 *(RMT ratio <90%) - 2.57 *(RMT ratio > 110%) - 2.93 *M1 - 3.12 *IntCaps - 1.55 *M2
	Probability for no change is p=1- p (improvement) - p(worsening)
After 3 months	Probability p = 1/(1+exp[L]) for improvement:
	L= 2.10 - 0.33 *(MRC grade 4) - 3.51 *(MRC grade ≤3) + 2.20 *M1 + 2.03 *IntCaps + 0.13 *M2
	Probability p = 1/(1+exp[L]) for worsening:
	L= 2.11 + 0.33 *(MRC grade 4) + 3.51 *(MRC grade ≤3) - 2.20 *M1 - 2.03 *IntCaps - 0.13 *M2
	Probability for no change is p=1- p (improvement) - p(worsening)
Example	Here, we calculate the risk for motor deterioration in a patient without preop deficit (MRC grade 5) whose tumor infiltrates the motor cortex (M1) and whose interhemispheric RMT ratio is >110%.
	L7days= 4.33 + ~~1.50 *(MRC grade 4) + 1.04 *(MRC grade ≤3) - 1.00 *(RMT ratio <90%)~~ - 2.57 *(RMT ratio >110%) - 2.93 *M1 ~~- 3.12 *IntCaps - 1.55 *M2~~ =-1.17
	p(worsening $_{7days}$)= 1/(1+exp[-1.17])=76%
	L3mos= 2.11 ~~+ 0.33 *(MRC grade 4) + 3.51 *(MRC grade ≤3)~~ - 2.20*M1 ~~- 2.03 *IntCaps - 0.13 *M2~~= -0.09
	p(worsening$_{3mos}$)=1/(1 + exp[-0.09]) =52%

exp(L) =e^{L}, where e is Euler`s number.

* the value in front of the sterisk should be applied when the condition behind the sterisk is fulfilled.

Using those results, patients were classified into a high- and low-risk group for postoperative deterioration of motor function. Critical tumor location (M1, IntCaps) and a pathological excitability of the motor cortex (RMT ratio <90% or >110%) are high-risk criteria. Regarding this, there were 46 high-risk cases among patients, and 8 low-risk cases. It was more likely for the low-risk group to show an improvement in motor function and not develop any new

permanent deficits after surgery. The individual probability for the postoperative motor outcome after 7 days and 3 months can be calculated using the equation shown in **Table 6**.

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18 patients, predominantly with single-level cervical stenosis, participated in this study. All patients had neurological symptoms with 61% reaching a JOA score > 12 and 39% a JOA score ≤12. nTMS was performed for each hemisphere on all patients and all 8 healthy volunteers.

The RMT was comparable between all 3 groups. Patients with severe symptoms showed a tendency for prolonged MEP latency. Compared to the healthy volunteers, patients in general had significantly longer MEP latencies. Overall the RC slope steepness was not significantly different. Compared to the control group, severely impaired patients with JOA ≤12 had a significantly less steep RC. In addition, a positive correlation between a less steep RC and a lower finger tapping test score (fine motor hand function) could be seen in both patient groups (r^2=0.446, p=0.037). Analyzing the cortical inhibition, a significant increase could be shown in the severely symptomatic patient group. Data is shown in **Table 7**.

Table 7. nTMS results for the 3 examination groups

nTMS	healthy	JOA > 12	JOA ≤ 12
MEP latency (ms)	23.8 ± 1.7**	26.7 ± 4.3*	28.6 ± 3.7**
RMT (%)	24.9 ±2.9	39.5 ± 12.0	38.6 ± 15.8
RC (slope)	94.6 ± 67.1*	73.5 ± 82.9	38.0 ± 35.3*
CSP (ms)	143.6 ± 42.4*	147.5 ± 37.8	181.1 ± 73.2*
area (mm^2)	390.3 ± 183.8*	406.4 ± 286.9	191.4 ± 121.3*

Data left/right hemisphere displayed as mean ± standard deviation.
Student's t test/Wilcoxon signed rank test; * significant at p < 0.05
** significant at p < 0.005

The motor area size analysis unveils an association between area size and neurological status. In comparison with healthy volunteers, patients with mild symptoms (JOA > 12) had an enlarged motor area, with a significant activation of non-primary motor areas (p=0.001, data not shown). The size decreased significantly in patients with severe symptoms, getting even smaller than the area of the control group (p=0.012, data not shown). A smaller motor area was also associated with an increased cortical inhibition represented by a prolonged CSP (r^2=-0.451, p=0.016).

2.8 Discussion

The results presented above emphasize the progress nTMS has made as a diagnostic method in the neurosurgical context and underline its importance for clinical use.

For quite some time, neurobiological research has disputed the classic language localization model[22], offering alternative models for language organization in the brain[23] and acknowledging the individuality of cortical organization[24]. Schwarzer et al.'s findings add to the latter argument, with their statistical analysis not confirming a sole increased error

occurrence in patients with lesions in “classic” language areas. This provides reason to investigate patients with lesions in non-”classic” language areas of the cortex via preoperative non-invasive language mapping. Since DCS is too invasive to be applied over broad cortical areas intraoperatively, a non-invasive mapping tool like rnTMS can contribute to a proper risk assessment for all patients individually.

The main finding of Schwarzer et al. though is the establishment of a new protocol for identifying patients eligible for rnTMS speech mapping. This is vital for conducting future comparison studies with DCS to improve specificity and positive predictive value and to introduce a reliable non-invasive mapping tool to increase patient safety and better outcome[9,25]. It is well known that cognitive impairment as well as all kinds of aphasia lead to speech disruptions[26,27]. The final analysis confirmed that patients with suspected dementia (DemTect grade 3) and patients with distinct signs of aphasia (BAS grade 2) have a statistically significant stimulation independent error occurrence and should therefore not be examined by standard protocol. The paper suggests a three-step system to easily identify eligible patients in a clinical setting. First, all patients undergo the essential baseline test. All patients with an error rate lower than 28% can be examined via rnTMS. 28% was the threshold of error occurrence between patients without significant influencing factors (75th percentile) and patients with suspected dementia and distinct aphasia (25th percentile) in the analysis. Patients with a baseline rate of 28% or higher should undergo a clinical examination for cognitive impairment and aphasia. Schwarzer et al. strongly recommend standardized tests like the DemTect for quick objective examinations. All patients with no or mild cognitive impairment or only slight forms of aphasia can also be confidently mapped. It was noticed that most patients in general were eligible for rnTMS language mapping.

The risk-benefit assessment is especially relevant in glioma surgery. Better long-term survival of greater extent of resection stands in contrast to loss of function through more resection and its correlation with low life quality and shorter survival[14]. Other studies could already show that nTMS benefits patients through a higher rate of GTR while reducing the rate of permanent deficits[5,8]. In addition, using nTMS data for CST fiber tracking increases the accuracy and specificity of this method in a user-independent way[28]. Rosenstock et al. propose an added model of nTMS-based risk stratification to identify high risk cases for new postoperative motor deficits and to predict potential recovery with preexisting deficits based on objective measures. This provides a preoperative risk-benefit balancing which enables better patient counseling and consequent decision making. Rosenstock et al. sort patients into a low-risk group, where GTR is the surgical goal, and a high-risk group, where a weighing of surgical options with mandatory intraoperative monitoring and adapted treatment plans should ensue. Low-risk cases are defined by a minimum distance of tumor and CST or motor area of > 8mm and a RMT ratio between 90%-110%. High-risk cases are defined by a

tumor distance of ≤ 8mm to the primary motor cortex or CST and a pathological RMT ratio (<90%, >110%).

Research has revealed that acute spinal cord injury can cause an immediate change of cortical networks[29]. If an increased activation of supplementary motor areas and an expansion of the primary motor area could be seen after a spinal cord injury, patients recovered better from neurological deficits[30]. The study by Zdunczyk et al. provides a deeper understanding to the mechanisms of functional reorganization in DCM and identifies patient groups and their expected potential for recovery through nTMS. As shown in other studies, the finding that patients with DCM present with a prolonged MEP latency could be reproduced[31]. While the recruitment curve describes the excitability of the corticospinal system it also serves as an indirect measure of axonal integrity[32]. The severely symptomatic patient group (JOA≤12) displayed a significantly reduced RC and showed a positive correlation with reduced fine motor function. This patient group presented a prolonged CSP. The CSP, as a measure of intracortical and corticospinal inhibition, is presumably caused by spinal inhibition in its first phase (50-75ms), whereas the long-lasting inhibition is mediated by gamma aminobutyric acid ($GABA_B$)[33,34]. Recent studies on stroke and multiple sclerosis associated a high cortical inhibition with poor recovery[35,36]. Another contributor to recovery is cortical reorganization by unmasking pre-existing latent lateral connection, facilitation of ineffective synapses and formation of new synaptic connection within the precentral gyrus[37,38]. Studies analyzing traumatic spinal cord injury found an increased volume of M1 activation and activation of non-primary motor areas, which was associated with favorable motor recovery[39,40]. The study by Zdunczyk et al. revealed that a smaller motor area was associated with higher impairment. Patients with mild symptoms (JOA>12) showed a decreased M1 activation while recruiting non-primary motor areas, which indicated adaptive mechanisms. This study's findings support the theory of a functional corticospinal reserve capacity in DCM: patients with DCM and mild symptoms can retain motor function through recruitment of secondary motor areas and disinhibition. This state of "compensation" is marked by a preserved motor area, a beginning decrease of RC and a preserved CSP. This group might benefit from surgery. This stage is followed by "exhaustion", which displays with a highly increased motor area, decreased cortical inhibition and further reduced RC. This group should undergo short-term surgery to prevent a progression of impairment. With a worsening of symptoms the "deterioration" stage is reached, which is characterized by a reduced motor area, prolonged CSP and a low RC. For those patients, surgery might only preserve the existing state of symptoms or have no benefit at all.

2.9 Conclusion

In this sample of studies, nTMS was able to contribute to a highly specified categorization of patients and their individual risk factors, providing necessary additional information for surgery planning. Schwarzer et al. were able to improve the examination protocol and lay an important stepping-stone for increasing rnTMS reliability for language mapping. Both Rosenstock et al. and Zdunczyk et al. introduced data found by nTMS, which adds to surgical planning and predictive accuracy for patient outcome. nTMS is a viable non-invasive preoperative diagnostic tool for a variety of neurosurgical patients.

2.10 References

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3. Eidesstattliche Versicherung

„Ich, Vera Schwarzer, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: „Evaluierung der navigierten transkraniellen Magnetstimulation (nTMS) in der präoperativen Diagnostik neurochirurgischer Patienten - Fokus auf der Untersuchung des Einflusses biometrischer Faktoren auf das Ergebnis der nTMS Messung sprachrelevanter Areale neurochirurgischer Patienten" selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.
Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren beruhen, sind als solche in korrekter Zitierung gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) entsprechen den URM und werden von mir verantwortet.
Mein Anteil an der ausgewählten Publikation entspricht dem, der in der untenstehenden gemeinsamen Erklärung mit dem Betreuer, angegeben ist. Sämtliche Publikationen, die aus dieser Dissertation hervorgegangen sind und bei denen ich Autor bin, entsprechen den URM und werden von mir verantwortet.
Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§156,161 des Strafgesetzbuches) sind mir bekannt und bewusst."

Datum: Mainz, 06.09.2018

_____
Unterschrift

4. Ausführliche Anteilserklärung an der erfolgten Publikation

Publikation 1:
Vera Schwarzer, Ina Bährend, Tizian Rosenstock, Felix R. Dreyer, Peter Vajkoczy, Thomas Picht. Aphasia and cognitive impairment decrease the reliability of rnTMS language mapping. Acta Neurochir (Wien). 2018 Feb.

Der Beitrag der Promovendin, Vera Schwarzer, an dieser Promotion umfasste im Einzelnen das Erlernen und die Durchführung der nTMS Messungen, die vorausgehende Erfassung der biometrischen Faktoren und die Durchführung der Aphasie und Demenz- Screening Scores (DemTect, Berliner Aphasie Score). Diese Aufgaben wurden durch die Co-Autoren an zweiter und dritter Stelle anteilmäßig mit übernommen.

Desweiteren umfasste der Beitrag der Promovendin die Erstellung der SPSS Datenbank, die statistische Analyse mittels SPSS und die Auswertung der Daten (s. Tabellen 1 bis 5, Darstellung 1 bis 4). An der Auswertung der ermittelten Primärdaten hatten die Co-Autoren keinen Anteil. Eine zweimalige statistische Beratung erfolgte durch das Institut für Biometrie der Charié Universitätsmedizin Berlin.

Die Skizzierung des Projektes und Stellung des Ethikantrages oblag den Letztautoren PD Dr. med. Thomas Picht und Prof. Dr. med. Peter Vajkoczy und hinsichtlich des linguistischen Anteils auch Felix. R. Dreyer. Die Konzeptionalisierung des Projektes erstellte die Promovendin mit Unterstützung des Letztautors.

Das Manuskript für die Publikation erstellte die Promovendin selbstständig. Eine Kontrolle vor Veröffentlichung in der Acta Neurochirurgica erfolgte durch die Co-Autoren. Die umfangreiche Literaturrecherche führte die Promovendin ebenfalls eigenständig durch.

Publikation 2:
Tizian Rosenstock, Ulrike Grittner, Güliz Acker, Vera Schwarzer, Nataliia Kulchytska, Peter Vajkoczy, Thomas Picht. Risk stratification in motor area-related glioma surgery based on navigated transcranial magnetic stimulation data. J Neurosurg. 2017 Apr.

Der Beitrag der Promovendin, Vera Schwarzer, umfasste das Erlernen und die Durchführung der hierfür notwendigen nTMS Messungen, die vorausgehende Erfassung der klinischen Verfassung des Patienten (Motor Status, Karnofsky Index, Dauer der Symptome), die Nachuntersuchung der Patienten (7 Tage und 3 Monate post-operativ), sowie das Erlernen der DTI tracking Technologie. Die Konzeptionalisierung des Projektes, die Miterfassung und Auswertung der Daten und das Schreiben des Manuskripts erfolgte durch den Erstautor Dr. med. Tizian Rosenstock und unter Mithilfe der weiteren Co-Autoren.

Publikation 3:
Anna Zdunczyk, Vera Schwarzer, Michael Mikhailov, Brendon Bagley, Tizian Rosenstock, Thomas Picht, Peter Vajkoczy. The Corticospinal Reserve Capacity: Reorganization of Motor Area and Excitability As a Novel Pathophysiological Concept in Cervical Myelopathy. Neurosurgery. 2017 Nov 18. [Epub ahead of print]

Der Beitrag der Promovendin, Vera Schwarzer, an oben genannter Publikation umfasste das Erlernen und die Durchführung der hier notwendigen nTMS Messungen, der vorausgehenden Erfassung des JOA Scores, sowie Finger tapping Tests und Erstellung und Übertragung der Daten in die Datenbank. Die Konzeptionalisierung des Projektes, sowie die Auswertung der Daten und das Schreiben des Manuskripts erfolgte durch Anna Zdunczyk und unter Mithilfe der weiteren Co-Autoren.

Unterschrift des Doktoranden/der Doktorandin

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5. Druckexemplar „Aphasia and cognitive impairment decrease the reliability of rnTMS language mapping“

Vera Schwarzer, Ina Bährend, Tizian Rosenstock, Felix R. Dreyer, Peter Vajkoczy, Thomas Picht. Aphasia and cognitive impairment decrease the reliability of rnTMS language mapping. Acta Neurochir (Wien). 2018 Feb.

URL: https://doi.org/10.1007/s00701-017-3397-4

6. Druckexemplar „Risk stratification in motor area-related glioma surgery based on navigated transcranial magnetic stimulation data“

Tizian Rosenstock, Ulrike Grittner, Güliz Acker, Vera Schwarzer, Nataliia Kulchytska, Peter Vajkoczy, Thomas Picht. Risk stratification in motor area-related glioma surgery based on navigated transcranial magnetic stimulation data. J Neurosurg. 2017 Apr.

URL: https://doi.org/10.3171/2016.4.JNS152896

7. Druckexemplar „The Corticospinal Reserve Capacity: Reorganization of Motor Area and Excitability As a Novel Pathophysiological Concept in Cervical Myelopathy“

Anna Zdunczyk, Vera Schwarzer, Michael Mikhailov, Brendon Bagley, Tizian Rosenstock, Thomas Picht, Peter Vajkoczy. The Corticospinal Reserve Capacity: Reorganization of Motor Area and Excitability As a Novel Pathophysiological Concept in Cervical Myelopathy. Neurosurgery. 2017 Nov 18.

URL: https://doi.org/10.1093/neuros/nyx437

8. Lebenslauf

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version nicht veröffentlicht.

9. Publikationsliste mit Impact Faktor

Vera Schwarzer, Ina Bährend, Tizian Rosenstock, Felix R. Dreyer, Peter Vajkoczy, Thomas Picht.

Aphasia and cognitive impairment decrease the reliability of rnTMS language mapping.

Acta neurochirurgica. 2018;160(2):343-356.

Impact Faktor: 1.881

Tizian Rosenstock, Ulrike Grittner, Güliz Acker, Vera Schwarzer, Nataliia Kulchytska, Peter Vajkoczy, Thomas Picht.

Risk stratification in motor area-related glioma surgery based on navigated transcranial magnetic stimulation data.

J Neurosurg. 2017;126(4):1227-1237.

Impact Faktor: 4.059

Anna Zdunczyk, Vera Schwarzer, Michael Mikhailov, Brendon Bagley, Tizian Rosenstock, Thomas Picht, Peter Vajkoczy.

The Corticospinal Reserve Capacity: Reorganization of Motor Area and Excitability As a Novel Pathophysiological Concept in Cervical Myelopathy.

Neurosurgery. 2017 [Epub ahead of print]

Impact Faktor: 4.889

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