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Refining language mapping by repetitive navigated transcranial magnetic stimulation in patients with left-sided perisylvian brain lesions

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für Lena und Moritz

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1. INTRODUCTION

1.1. History of brain mapping

For many decades brain mapping—and the particular case of language mapping—was based on lesion studies that were conducted by relating observations of patients and the post-mortem dissection of their brains. In 1861, Paul Broca published the case of the 51-year-old patient Leborgne, who suffered from a non-fluent aphasia. The autopsy of Leborgne's brain revealed a lesion including the posterior part of the left inferior frontal gyrus (IFG), and Broca concluded the localization of speech respectively language production was within this area (Broca, 1861b; Broca, 1861c).

Broca's conclusion was strengthened a few months later, when the 84-year-old patient Lelong, who had suffered from a stroke one year before, was introduced to Broca. Lelong also appeared with reduced speech production, and the autopsy of his brain showed a lesion approximately within the same region as that found in Leborgne's brain (Broca, 1861a). Since that time, the terms *Broca's area* and *Broca's aphasia* have endured for more than a century. Similarly, Carl Wernicke proposed after observing patients with lesions within the middle and posterior parts of the left superior temporal gyrus (STG) that these regions were responsible for the comprehension of language (Wernicke, 1874).

Today, it is known that these kinds of lesion-based studies led to partially misleading conclusions regarding the localization of language, since they did not take subcortical structures into account (Duffau et al., 2013). At the time of his research, Broca decided against slicing the brains, hence he was not able to see what recent high resolution magnetic resonance imaging (MRI) studies of Leborgne's and Lelong's brain revealed: the lesions extended far deeper than initially assumed and, most importantly, even involved the insula and perisylvian white matter (Dronkers et al., 2007).

In 1870, Gustav Theodor Fritsch and Eduard Hitzig published their experiments on animals. They stimulated the brain of a living dog by electrical stimulation and were able to localize the precentral gyrus by measuring the resulting muscle contractions in the dog's body. Thus, they were the first to assign specific motor functions to cortical regions by direct electrical stimulation of the brain (Fritsch and Hitzig, 1870).

The progress in brain mapping and our knowledge of it today is not least due to neurosurgeons, thanks to their direct approach to the human brain. The work of David Ferrier (Fig. 1) on the electrical stimulation of the cortex and the localization of brain functions was continued and refined in the 1880s by a scientist who is now considered one of the pioneers of neurosurgery: Sir Victor Horsely (Macnalty, 1957). In 1887, his own maps of the human brain were published together with Ferrier's map—mainly based on experiments with monkeys, but partially influenced by observations in humans (Keen, 1887). The following year was crucial for the development of the electrical stimulation of human brains and the further refinement of brain maps. Within a few months of one another, W.W. Keen, J.H. Lloyd, and C.B. Nancrede read their findings of intraoperative electrical stimulation before different associations of physicians and surgeons (Keen, 1888; Lloyd and Deaver, 1888; Nancrede, 1888). Finally, C.K. Mills presented his results before the Congress of American Physicians and Surgeons in Washington, D.C., and later published his article in the journal *Brain* (Mills, 1890). Mills' brain map, as well as those of Nancrede and Lloyd, generally coincided with Horsley's work (Fig. 1) (Uematsu et al., 1992).

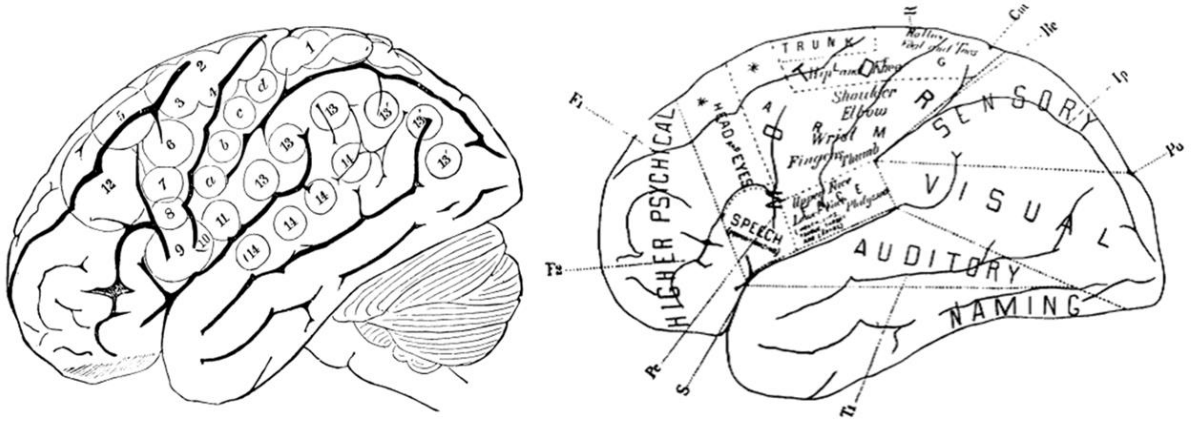

Fig. 1: Ferrier's (left) and Mills' (right) brain maps (Ferrier, 1876; Mills, 1890; Uematsu et al., 1992).

In the early years of the 20th century, another well-known brain surgeon, today known as a founder and first chairman of neurosurgery, started his own cortical stimulation studies: Harvey Cushing. Influenced by the work of the later Nobel laureate Charles Sherrington, Cushing initially performed cortical stimulation studies on anesthetized patients and drew a map of the human brain for the chapter "Surgery of the Head" in Keen's volume *Surgery – Its Principles and Practice* (Fig. 2) (Cushing, 1908; Fulton, 1946). Also in 1908, he conducted a sensory stimulation study on two conscious patients suffering from convulsive attacks; thereby, according to Wilder Penfield, he was the first to perform a detailed sensory stimulation study on the human brain during awake surgery (Cushing, 1909; Penfield and Boldrey, 1937). Cushing's patients underwent two-stage surgery: the first stage was an osteoplastic craniotomy under general anesthesia; in the second stage, general anesthesia was terminated after the original bone flap was removed, and the cortical stimulation mapping could be performed during the patient was awake.

In contrast, Penfield used direct cortical stimulation (DCS) and the procedure of awake surgery as we know it today (Uematsu et al., 1992). First, he published his own observations regarding motor and sensory representation within the human brain revealed by electrical stimulation studies. A revised version of his brain map, illustrated as *homunculus,* was published in 1950 (Penfield and Boldrey, 1937; Penfield and Rasmussen, 1950). In 1938, he started his collaboration with Herbert Jasper at the Montreal Neurological Institute and developed the clinical applicability of electroencephalography (EEG), even within the operating room (Feindel and Penfield, 1954; Jasper and Penfield, 1943; Penfield and Erickson, 1941; Penfield and Jasper, 1947; Penfield and Jasper, 1954). Moreover, he refined the surgical procedure of craniotomy under local anesthesia and thereby substantially influenced the possibilities for human brain mapping (Penfield and Rasmussen, 1950; Rasmussen and Penfield, 1947; Rasmussen, 1977). While his initial work focused on the human motor system, Penfield was later also concerned with language mapping (Penfield and Roberts, 1959).

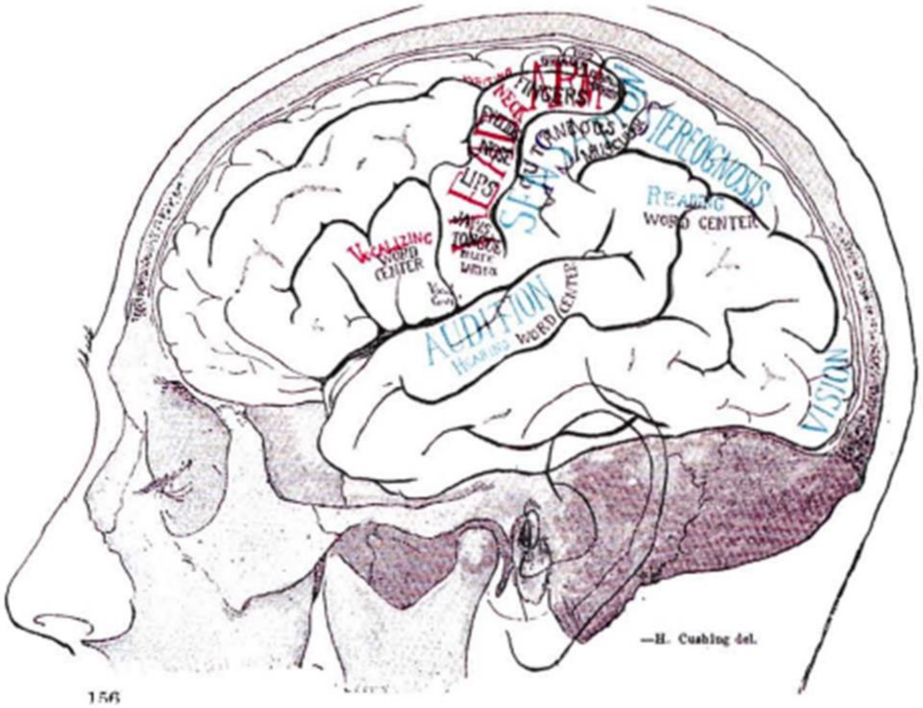

Fig. 2: One of Cushing's brain maps drawn in 1906, and published in Keen's "Surgery – Its Principles and Practice" in 1908 (Cushing, 1908; Uematsu et al., 1992).

1.2. Language mapping during awake surgery today

Brain mapping as it is performed today has impressively been influenced by George Ojemann. As he said himself, he directly extended the work of Penfield and Roberts, particularly in the field of human language mapping (Ojemann, 1999). While mapping of motor functions can be performed under general anesthesia, patients have to be awake during the intraoperative mapping of language functions. Further, the procedure of awake surgery also enables surgeons and neurophysiologists to map somatosensory functions, spatial cognition, calculation, judgment, executive functions, and emotional aspects (Duffau, 2013a; Talacchi et al., 2013a; Talacchi et al., 2013b). Today, DCS during awake surgery remains the gold standard for the mapping of human language functions, because of its reliability and the wealth of collective scientific experience with the technique (De Witt Hamer et al., 2012; Haglund et al., 1994; Ojemann et al., 1989; Ojemann and Whitaker, 1978; Sanai et al., 2008). In specialized centers, DCS is used for brain mapping when resecting tumors, vascular malformations, and epileptic foci within or adjacent to highly eloquent brain regions. Regarding the therapy of brain tumors—especially high- and low-grade gliomas—surgery, besides radiotherapy and chemotherapy, is the most important part of the multimodal approach (Capelle et al., 2013; De Witt Hamer et al., 2012; Jakola et al., 2012; Soffietti et al., 2010; Stummer et al., 2008). Furthermore, a maximum extent of resection is crucial for oncological considerations in terms of survival (Capelle et al., 2013; Sanai and Berger, 2008a; Smith et al., 2008; Stummer et al., 2008). With this in mind, achieving a sufficient extent of resection while preserving essential brain regions with respect to the patient's postoperative quality of life is one of the most pressing challenges in neurosurgery. With this background, the importance of using DCS during awake surgery in patients suffering from lesions within or adjacent to language-eloquent regions has recently been shown in a study that visualized resection probability maps. These maps, basing on intraoperative stimulation mapping, show regions that have to be spared during resection because they permanently retain their functions (Fig. 3) (De Witt Hamer et al., 2013). Meanwhile, it can be assumed that the human brain harbors a huge plastic potential, which enables a consecutive surgical approach to brain tumors within eloquent regions (Duffau, 2013c; Robles et al., 2008). Thus, reliable non-invasive mapping techniques are urgently required to analyze the plastic reshaping of brain functions and to perform longitudinal follow-up examinations to assess eligibility for further tumor resection in patients with remaining tumor mass (Duffau, 2005, 2012; Duffau et al., 2013; Martino et al., 2011). Moreover, since the anatomy of the human central nervous system still remains partially unclear, neurophysiologists above all basic researchers are in high demand for devising reliable, non-invasive methods (Duffau, 2013b; Krieg et al., 2013).

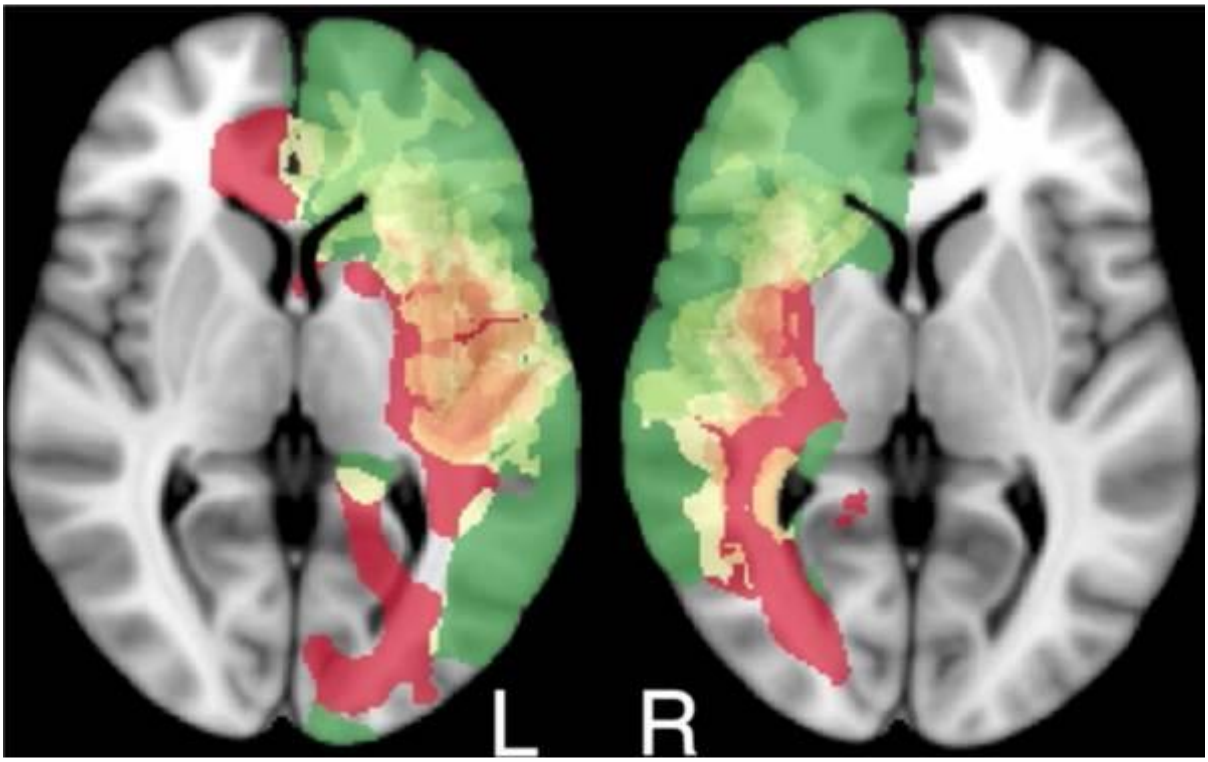

Fig. 3: Resection probability maps for left- and right-sided gliomas based on the results of direct cortical and subcortical stimulation. Tumors within red areas were never resected (probability of 0), tumors in green areas were resected in all patients (probability of 1) (De Witt Hamer et al., 2013).

1.3. Non-invasive language mapping

For non-invasive mapping of human language functions in pre- and post-operative assessments, multiple techniques are available, such as positron emission tomography (PET) (Sobottka et al., 2002), magnetoencephalography (MEG) (Tarapore et al., 2012a), diffusion tensor imaging fiber tracking (DTI-FT) (Leclercq et al., 2010), functional magnetic resonance imaging (fMRI), and repetitive navigated transcranial magnetic stimulation (rTMS).

1.3.1. Functional magnetic resonance imaging

Functional MRI was the standard for non-invasive language mapping for about two decades (FitzGerald et al., 1997). In 1890 the coupling of functional activity and changes in cerebral perfusion had already been noted by C.S. Roy and C.S. Sherrington (Roy and Sherrington, 1890). Over time this commonly accepted principle was refined and combined with the phenomena of different magnetic properties of deoxyhemoglobin and oxyhemoglobin (Ainslie and Tzeng, 2010; Ogawa et al., 1990a; Ogawa et al., 1990b). For the visualization of the latter by magnetic resonance imaging (MRI), Ogawa introduced the term *blood-oxygen level* *dependent* (BOLD) *contrast* in 1990 (Ogawa et al., 1990a). Two years later, he published his first fMR images obtained by visual stimulation of healthy subjects (Ogawa et al., 1992).

Since this time, different brain functions measured by fMRI have been compared to the gold standard. In terms of dependence on distinctly defined error margins, the results of fMRI motor mapping correlated partially with those revealed by intraoperative DCS (Bizzi et al., 2008; Lehericy et al., 2000; Roessler et al., 2005). Regarding the determination of language lateralization, large-scale studies with healthy subjects (Fig. 4) (Pujol et al., 1999; Springer et al., 1999) and several clinical studies with epilepsy patients have been conducted. The results of the latter were compared to highly controversial intracarotid amobarbital tests (IATs) and generally showed positive correlation (Gaillard et al., 2004; Rutten et al., 2002). In contrast, with respect to the detailed localization of language-eloquent brain regions in neurosurgical patients, Giussani et al. reviewed studies that compared fMRI with DCS language mapping during awake surgery, and found widely differing results (Giussani et al., 2010).

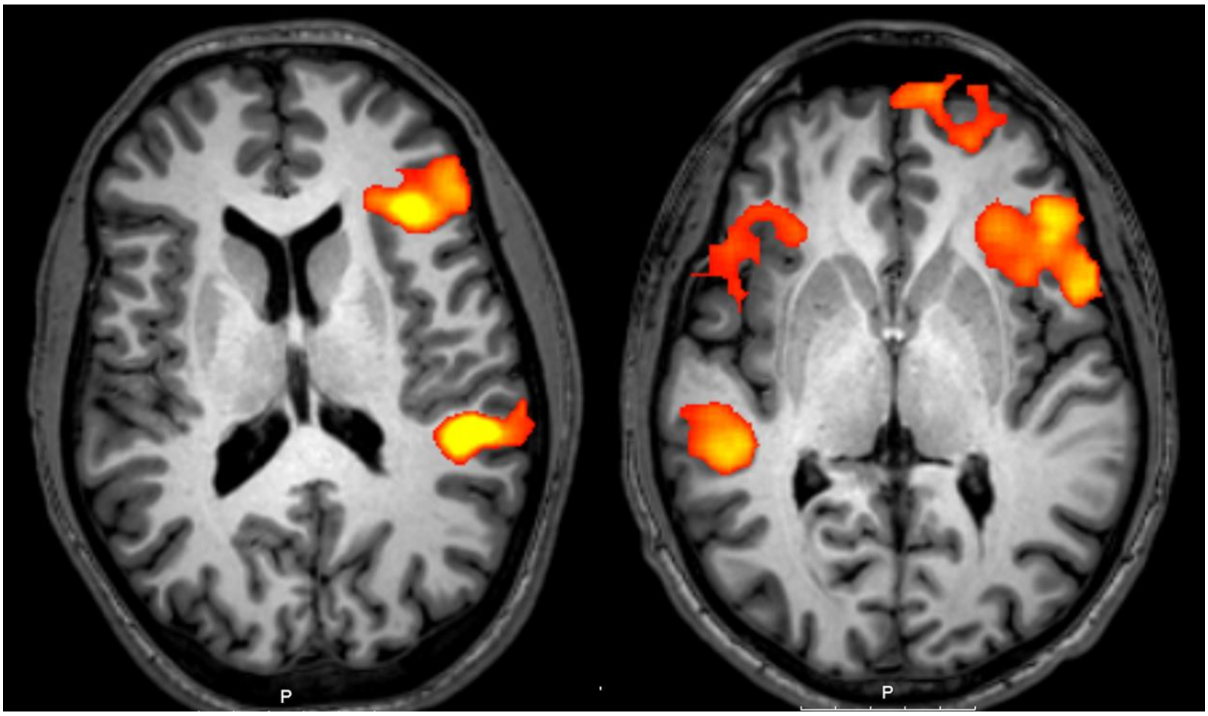

Fig. 4: Axial slices of fMRIs of two healthy subjects after performing an object naming task.

1.3.2. Transcranial magnetic stimulation

In comparison to the aforementioned methods, TMS is a relatively novel technique. The application of TMS can be divided into two overall branches: diagnostics and therapy. Since its implementation it has been used in the treatment of major depression, central pain after spinal injury, chronic pain, and tinnitus (Ahdab et al., 2010; Defrin et al., 2007; Janicak et al., 2013). Furthermore, TMS has shown positive effects on the motor function of patients with

Parkinson’s disease, improved reciprocal inhibition in patients suffering from dystonia, and could positively influence the rehabilitation of aphasia as well as motor learning in patients after stroke (Fregni et al., 2005; Huang et al., 2004; Kim et al., 2006; Naeser et al., 2011).

Initially, TMS was introduced by Barker in 1985 for the stimulation of the human motor cortex, according to the first utilizations of DCS (Barker et al., 1985). Probably one of the most crucial steps in the development of TMS was the implementation of navigated TMS (nTMS). Originally, the frameless stereotactic navigation system was invented for intraoperative applications during neurosurgical procedures (Grimson et al., 1996). Concurrently and by the same research group, it was applied on TMS and thereby enabled real-time-visualization of the stimulation sites over the three-dimensional (3D) reconstruction of the patient’s MRI data (Ettinger et al., 1998). This kind of neuronavigation has been advanced over time, resulting in real-time detection of the intracranially induced electric field and measurement of its strength by the system nTMS (Hannula et al., 2005; Ruohonen and Ilmoniemi, 1999). The system nTMS implies two important features: first, stimulation sites can be saved for later analysis (Fig. 5); and second, the revealed results—for example, language-positive sites—can be displayed in the operating room (Lioumis et al., 2012).

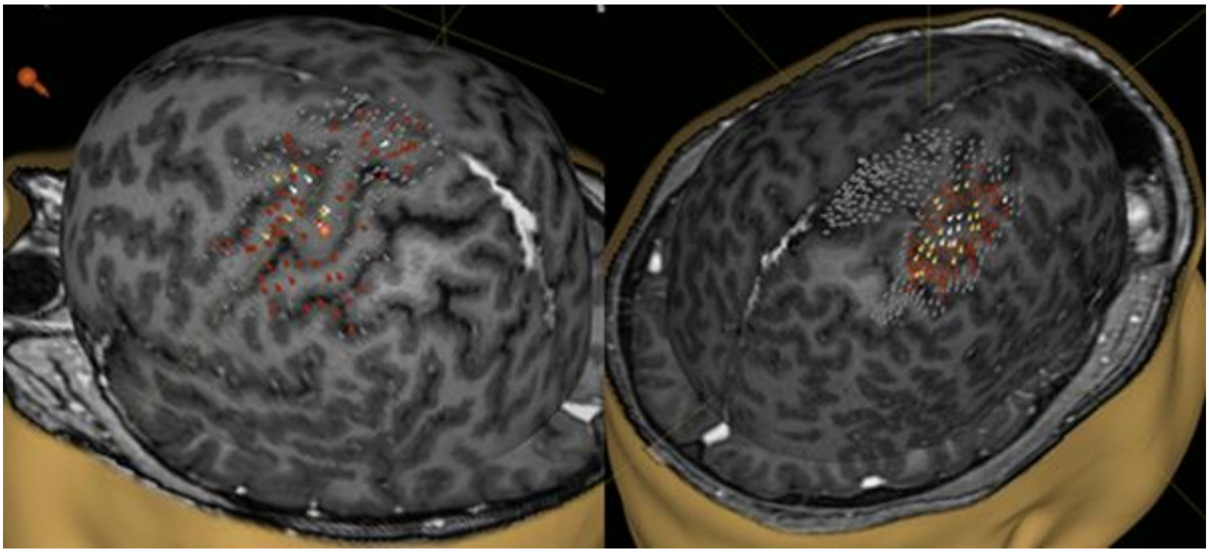

Fig. 5: Motor maps of the left and right hemisphere obtained by nTMS in two patients suffering from lesions adjacent to motor eloquent brain regions (white, yellow, and red sites describe positive electromyography [EMG] responses).

Today, motor mapping of patients suffering from lesions within or adjacent to the motor cortex by nTMS is a standard procedure in centers using this technique, since it has repeatedly shown its usefulness for clinical practice (Fig. 5). In comparison with the gold standard for motor mapping, intraoperative DCS, nTMS could show its advantages over other modalities, such as fMRI and MEG (Krieg et al., 2012b; Tarapore et al., 2012b). As specified in later paragraphs, the magnetic field generated by the TMS coil passes the skull and the induced electric field, which causes the effect of TMS, develops within the brain parenchyma—comparable to the functionality of DCS. Moreover, with level II evidence, it was recently demonstrated in two independent studies that nTMS motor mapping improves the outcome of patients with motor-eloquent lesions. In this respect, the positive effects of its application have been shown (Frey et al., 2014; Krieg et al., 2014a).

In contrast to motor functions, language-eloquent regions are more distributed and the variability between individuals is high; therefore, the mapping of language functions presents a major challenge (Ojemann and Whitaker, 1978; Sanai and Berger, 2009). The first language mapping study using rapid-rate TMS was performed by Pascual-Leone in 1991 (Pascual-Leone et al., 1991). Since that time, repetitive navigated TMS (rTMS) as well as non-navigated repetitive TMS have proven to be applicable in localizing human language functions (Epstein, 1998; Epstein et al., 1996; Lioumis et al., 2012; Sparing et al., 2001). According to the mapping of motor functions, rTMS language mapping has also shown its clinical usefulness within the preoperative assessment, not least due to its excellent correlation to the results of DCS during awake surgery regarding the mapping of language-negative sites (Picht et al., 2013; Tarapore et al., 2013). As already described, the plasticity of brain functions plays an important role in neurosurgery, particularly regarding oncological considerations (Duffau, 2013c; Robles et al., 2008). Even in this respect, rTMS language mapping has revealed good results regarding the possibility to re-examine a patient before his or her second surgery, and considering its ability to evaluate the shift of language function to the non-dominant hemisphere (Krieg et al., 2013). Likewise, rTMS language mapping has demonstrated its superiority over MEG, and, though only by the report of a single case, over fMRI language mapping as well (Sollmann et al., 2013b; Tarapore et al., 2013). While techniques like MEG or fMRI are used to measure neuronal activity indirectly, the principle function of rTMS is to create a *virtual lesion*, similar to DCS (Hallett, 2007). The term was introduced by Pascual-Leone and epitomizes the determining difference of rTMS from other non-invasive mapping-techniques (Pascual-Leone et al., 1999). As Duffau recently commented on fMRI language mapping, the fact that a brain region shows activation during a specific task does not automatically indicate a language deficit after its resection (Duffau et al., 2013). In contrast, rTMS tries to simulate what would most likely occur in case of the absence of a brain region. Although the term *virtual lesion* might sound frightening, TMS is a safe, non-invasive method for the mapping of both healthy subjects and patients (Rossi et al., 2009).

1.4. Objectives of the present studies

Despite the promising results of rTMS language mapping mentioned above, and particularly the high correlation to the results of DCS during awake surgery concerning language-negative sites, the technique is still not far from its infancy, at least in terms of the demanding challenge of mapping human language functions. This becomes apparent in the low specificity and positive predictive value (PPV) of rTMS language mapping compared to DCS in most of the previous studies (Krieg et al., 2014b; Picht et al., 2013). The objective of our first study, *Combined non-invasive language mapping by rTMS and fMRI and its comparison to direct cortical stimulation*, was to explore different thresholds for the analysis of the raw data revealed by rTMS language mapping. During the last two decades, primarily stimulation parameters (such as intensity or frequency) and protocols for the performance of language mappings have been determined (Epstein et al., 1996; Lioumis et al., 2012; Pascual-Leone et al., 1991). Although the publication of Lioumis et al. was very important concerning its documentation, little is known about the further analysis of rTMS-induced language errors (Lioumis et al., 2012). Therefore, we tried to find a protocol for the analysis of rTMS raw data to increase the correlation of language-positive sites in comparison with the results of DCS during awake surgery. Furthermore, we defined a protocol for a combined non-invasive language mapping, comprising the results of both rTMS and fMRI techniques. The underlying idea was to use the strengths of both methods, in order to find a higher correlation to the results of DCS language mapping than either method alone. As a sub-analysis within this study, we compared two different settings for the performance of rTMS language mappings, with the aim of reproducing the results of a recently published study (Krieg et al., 2014c).

Also in the second study, *Impairment of non-invasive language mapping by lesion location - a fMRI, nTMS, and DCS study*, we compared the results of the two non-invasive techniques to those obtained by intraoperative mapping. The objective of this study was to evaluate the influence of brain lesions on the accuracy of rTMS and fMRI language mapping. It is of substantial importance that both non-invasive and intraoperative mapping techniques work reliably, especially in the proximity of brain lesions, since false findings could result in wide-ranging negative consequences for the patient (Duffau, 2013b). A recently published meta-analysis by De Witt Hamer et al. has once more proven the reliability of DCS language mapping as well as its high clinical impact (De Witt Hamer et al., 2012). In contrast, the accuracy of fMRI language mappings in the preoperative assessment of patients and its comparisons to DCS are controversial (Giussani et al., 2010). The underlying reasons of these results might be based on the functionality of fMRI. Malignant processes alter the tissue's vascularization and obviously affect parenchymal oxygenation levels—and therefore the BOLD contrast—negatively (Holodny et al., 2000). Hence, we evaluated the dependency of fMRI and rTMS language mapping on the location of lesions by comparing them to DCS.

The main purpose of this thesis was to investigate and improve the reliability of rTMS and fMRI language mapping as supportive, non-invasive techniques in comparison to the gold standard. This was done for each technique alone as well as for their combined application. In particular, we intended to refine the promising technique of rTMS for language mapping by improving the analysis of its results and by investigating its clinical applicability on patients with left-sided perisylvian brain lesions.

2. MATERIALS AND METHODS

2.1. Ethics approval

Both studies were approved by the local ethical committee of the Technische Universität München in accordance to the Declaration of Helsinki (Ethics committee registration number 2793/10). All patients provided written informed consent before the rTMS language mapping procedures (Ille et al., 2015a; Ille et al., 2015b).

2.2. Study design

The studies were designed to be prospective and non-randomized (Ille et al., 2015a; Ille et al., 2015b).

2.3. Patients

The studies were performed on consecutive patients who were scheduled for awake craniotomy in the neurosurgical department of the Technische Universität München.
All patients met the following inclusion criteria:

- presence of a left-sided perisylvian brain lesion
- planned awake craniotomy
- signed informed consent

We did not include patients who met at least one of the following exclusion criteria:

- age below 18 years
- too-severe aphasia
- general TMS exclusion criteria (e.g. cochlear implant or pacemaker)

2.4. Direct cortical stimulation during awake surgery

2.4.1. Preparation of the patient

For awake surgery it is of paramount importance that the patient is thoroughly informed about the procedures within the operating room, so it is only conducted by experienced and skilled surgeons in our department. Although awake craniotomies show fewer postoperative complications, result in less procedure-related morbidity, and lead to better neurological outcome and quality of resection, patients have to be prepared for the condition—in simplified terms—of an open skull in full consciousness (Fig. 6) (Sacko et al., 2011; Taylor and Bernstein, 1999). On the one hand, the patient's capability to cooperate and his or her motivation is mandatory and should be tested—e.g. by the mini-mental state examination within the preoperative assessment (Folstein et al., 1975; Picht et al., 2006). On the other hand, the patient's language function has to be sufficient enough for intraoperative mapping. Hence, we performed a preoperative aphasia grading adapted from the *Aachener Aphasia Test*, and excluded patients who were not able to undergo language mapping from our studies (Huber W, 1980; Ille et al., 2015a; Ille et al., 2015b).

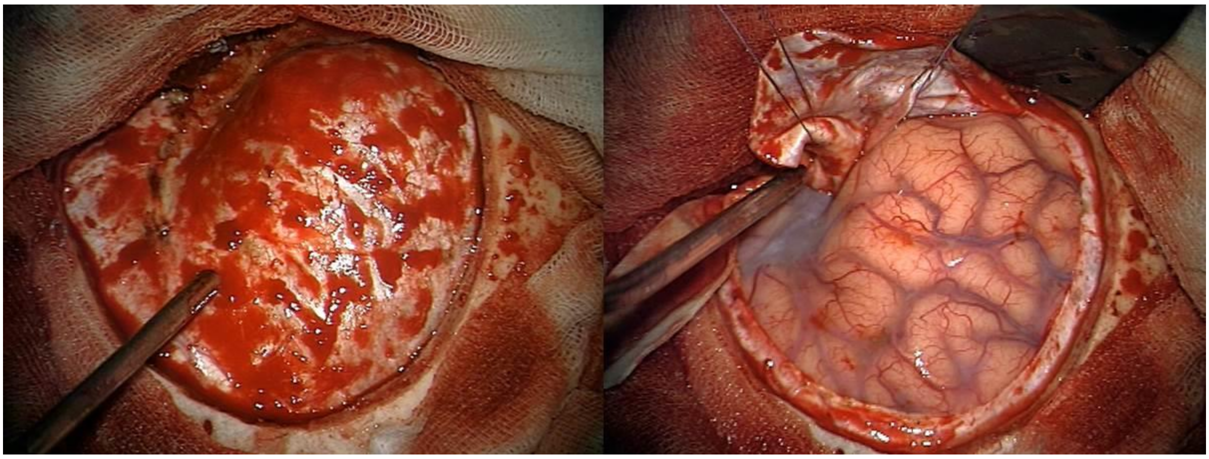

Fig. 6: Patient suffering from a lesion within the left hemisphere before language mapping began. The figures show the situation before (left) and after (right) the opening of the dura.

In the operating room, each patient was positioned semi-lateral on the right side and the head was fastened with a Mayfield clamp. The galea and dura were infiltrated with a mixture of bupivacaine and epinephrine, and the patient received a continuous remifentanil and propofol infusion; the parameters of respiratory rate, expiratory CO_2, O_2 saturation, electrocardiography, blood pressure, and temperature were controlled throughout the duration of the surgery. About ten minutes before the language mapping procedure began, sedation was adapted to a Ramsay sedation score of 2, equivalent to an awake, calm, and cooperative patient (Picht et al., 2006).

2.4.2. Intraoperative language mapping procedure

The surgeons performed cortical stimulation mapping according to a protocol for intraoperative language mappings published in 2006 (Picht et al., 2006). All mappings were conducted with a bipolar stimulation electrode (Inomed Medizintechnik GmbH, Emmendingen, Germany) and the following parameters: 5 mm distance between electrodes, stimulation intensity of 0–20 mA, frequency of 50 Hz, and a duration of 4 s. The usage of monopolar vs. bipolar electrodes is controversially discussed in the literature, but currently the bipolar stimulation electrode is most frequently used and seems to be most effective and sensitive (Fig. 7) (Kombos et al., 1999; Picht et al., 2006; Szelenyi et al., 2010). Moreover, a surface EEG monitored local brain activity for the early detection of epileptic seizures. In contrast to rTMS language mapping, the intraoperative naming was introduced with the matrix sentence “Das ist ein …”.

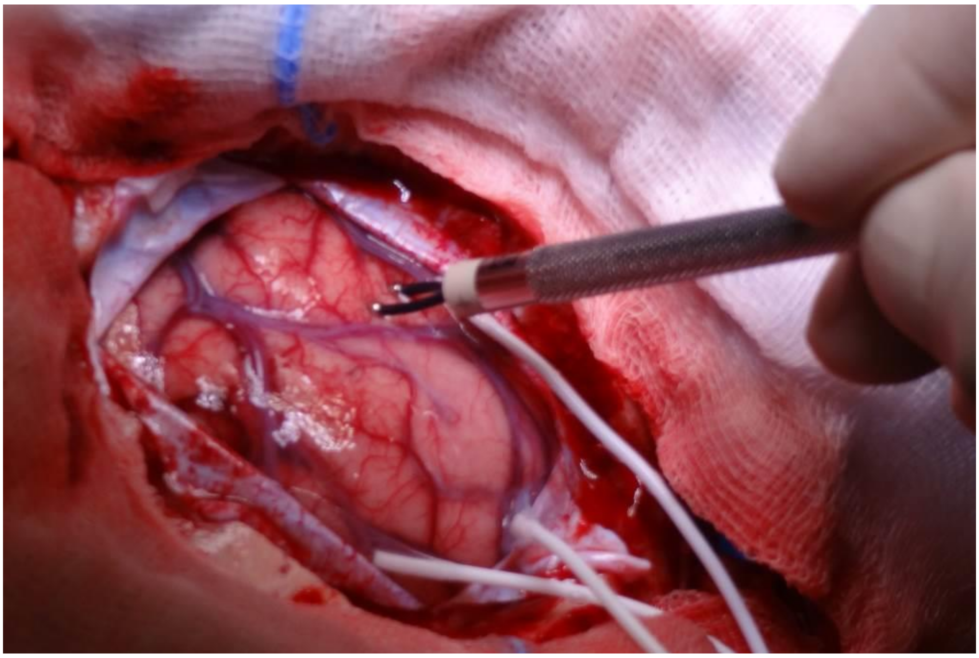

Fig. 7: Procedure of DCS using a bipolar stimulation electrode.

A stimulation site was defined as language-positive in terms of DCS if at least two out of three stimulations led to a language error (2-out-of-3 rule) (Haglund et al., 1994; Sanai and Berger, 2008b). Since the Mayfield clamp and the navigation pointer were equipped with reflectors, the stimulation sites could be accurately located within the patient’s navigational MRI scan, which was the same as used for rTMS language mapping (Fig. 8). In the same way, the stimulation sites could be transferred to the neuronavigation system (BrainLAB Vectorvision Sky® or BrainLAB Curve®, BrainLAB AG, Feldkirchen, Germany) and were thereby saved for later analysis (Krieg et al., 2014b; Picht et al., 2006; Picht et al., 2013).

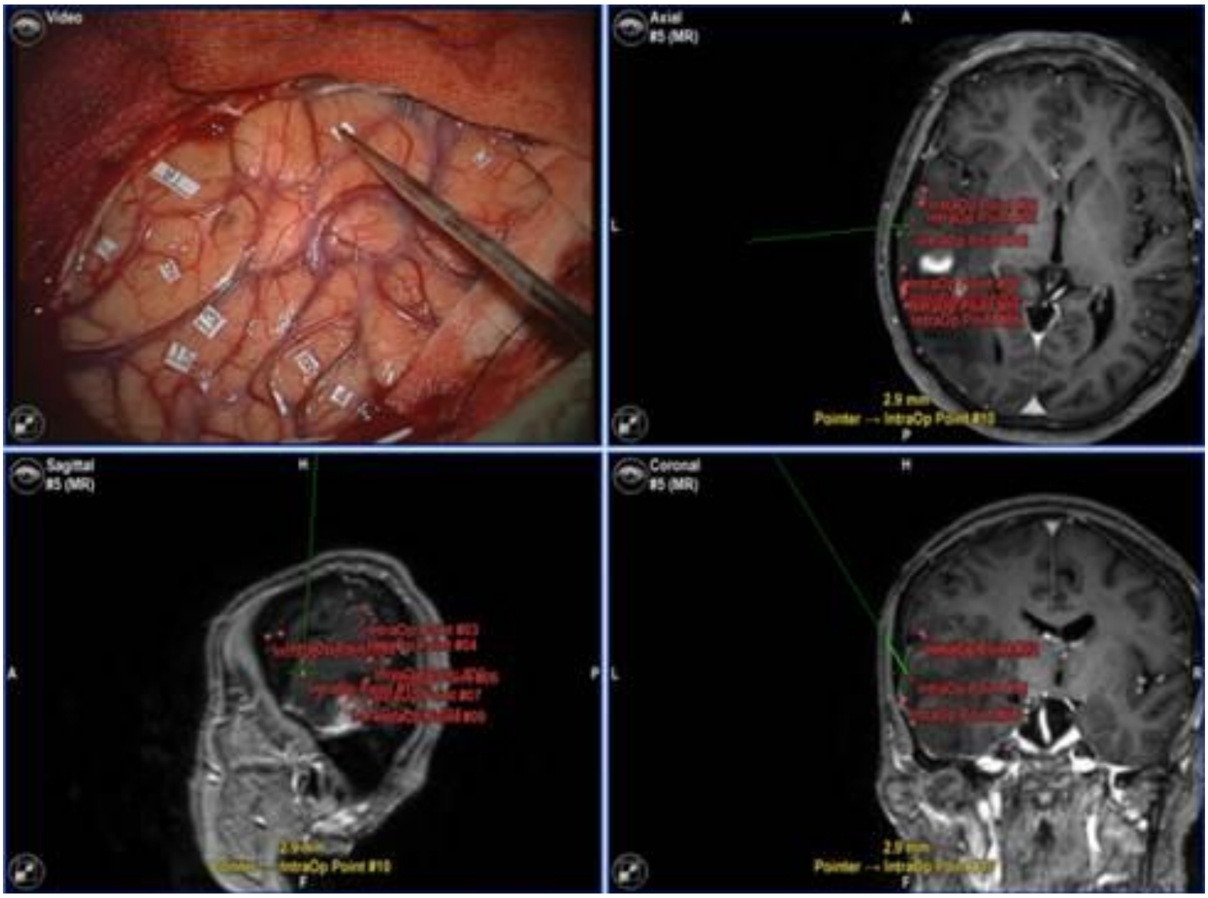

Fig. 8: Data transfer of intraoperatively observed language-positive sites (white and red tags) via neuronavigation system (BrainLAB Curve®, BrainLAB AG, Feldkirchen, Germany) for statistical analysis.

2.5. Functional magnetic resonance imaging

2.5.1. Basic principles of MRI

For the comprehension of fMRI, MRI's functions should be understood. When the patient or subject is lying inside the MR scanner, each point of his or her body defines a single unit, called a voxel, in the final image. Within the MRI system's magnetic field, which is generated by a superconductive magnet, the magnetic moment of a certain part of the tissue's protons becomes aligned with the main magnetic-field vector (Lange, 1996). These magnetic moments, caused by the spin of the protons, can be aligned perpendicular to the main magnetic field when a radiofrequency pulse is applied by the MRI system. This orientation of magnetic fields induces a voltage, comparable to the induction of the magnetic field and the resulting electrical field generated by TMS coils, as described in section 2.6.1. The MRI system is able to measure this radiofrequency voltage and match it with its respective source position in the body. These radiofrequency signals rely on numerous factors, such as their origin (e.g. fatty tissue or other tissue components) or their mode of formation (e.g. relaxation times). Meanwhile, various pulse sequences have been developed in order to optimize the MR signal according to distinct interrogations (Amaro and Barker, 2006).

2.5.2. Blood oxygen-level dependent contrast

The distinct magnetic characteristics of the molecule hemoglobin are the underlying reason of fMRI’s manner of functioning: with a full saturation of oxygen (oxyhemoglobin) blood is diamagnetic; contrarily, in case of fewer oxygen molecules (deoxyhemoglobin) it is paramagnetic. Broadly speaking, the distinction between these two conditions can be perceived by MR scanners and is called *BOLD contrast* (Ogawa et al., 1990a). For the most part, each brain function stimulated by the associated task is able to induce this BOLD contrast (Fig. 9). Indeed, the detailed mechanisms regarding the combination of neural activity and the resulting increase of cerebral blood flow, called neurovascular coupling, are not yet fully explored and still highly controversial. However, it has been confirmed by several studies that the BOLD contrast can reflect neural activity, and the underlying reasons have been investigated (Logothetis et al., 2001; Logothetis and Pfeuffer, 2004; Mathiesen et al., 1998).

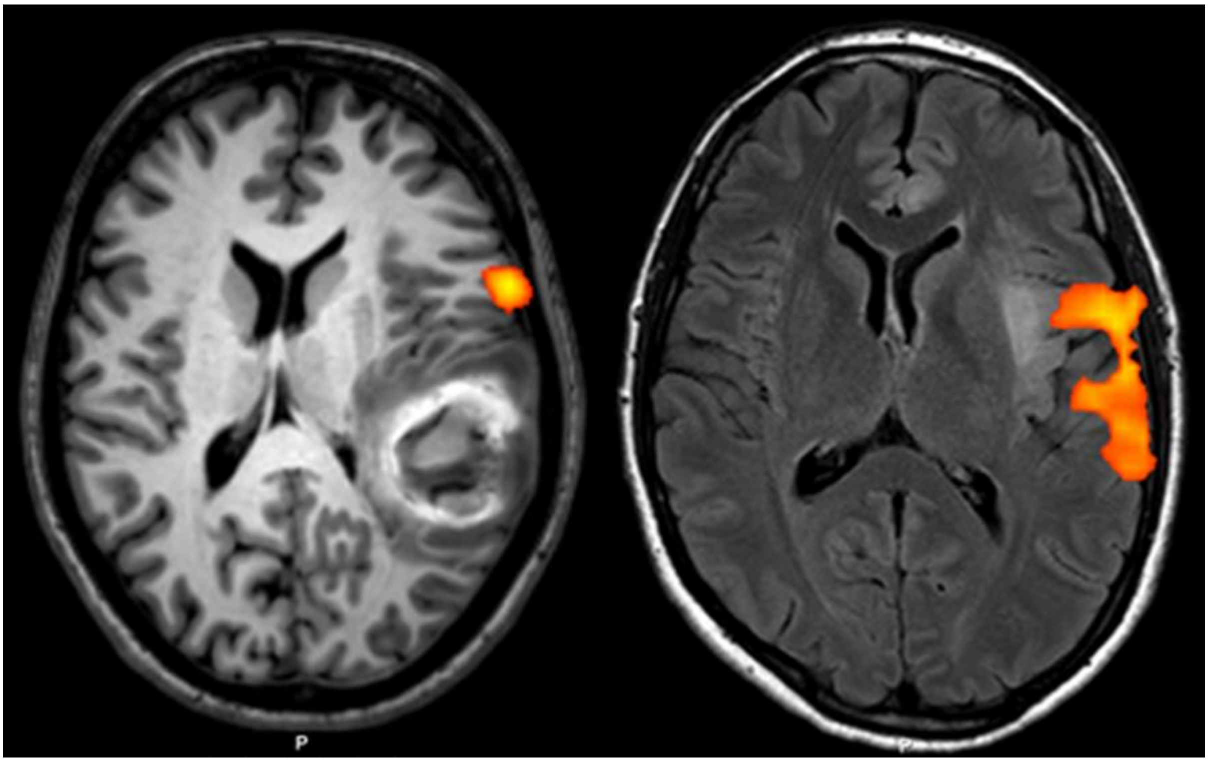

Fig. 9: Slices of fMRI language activity of two patients suffering from language eloquent lesions within the left hemisphere.

2.6. Repetitive navigated transcranial magnetic stimulation

According to the nomenclature of currently valid safety guidelines, we use *fast* or *high-frequency* rTMS, which has replaced the previously used terms *rapid* or *rapid-rate* TMS (Rossi et al., 2009). For language mappings in the present studies, we used the nTMS system eXimia 3.2.2 and its successor version eXimia 4.3 with a NexSpeech® module (Fig. 10). Additionally, we used the related NexSpeech® Analyzer software for later analysis of induced language errors (Nexstim Oy, Helsinki, Finland).

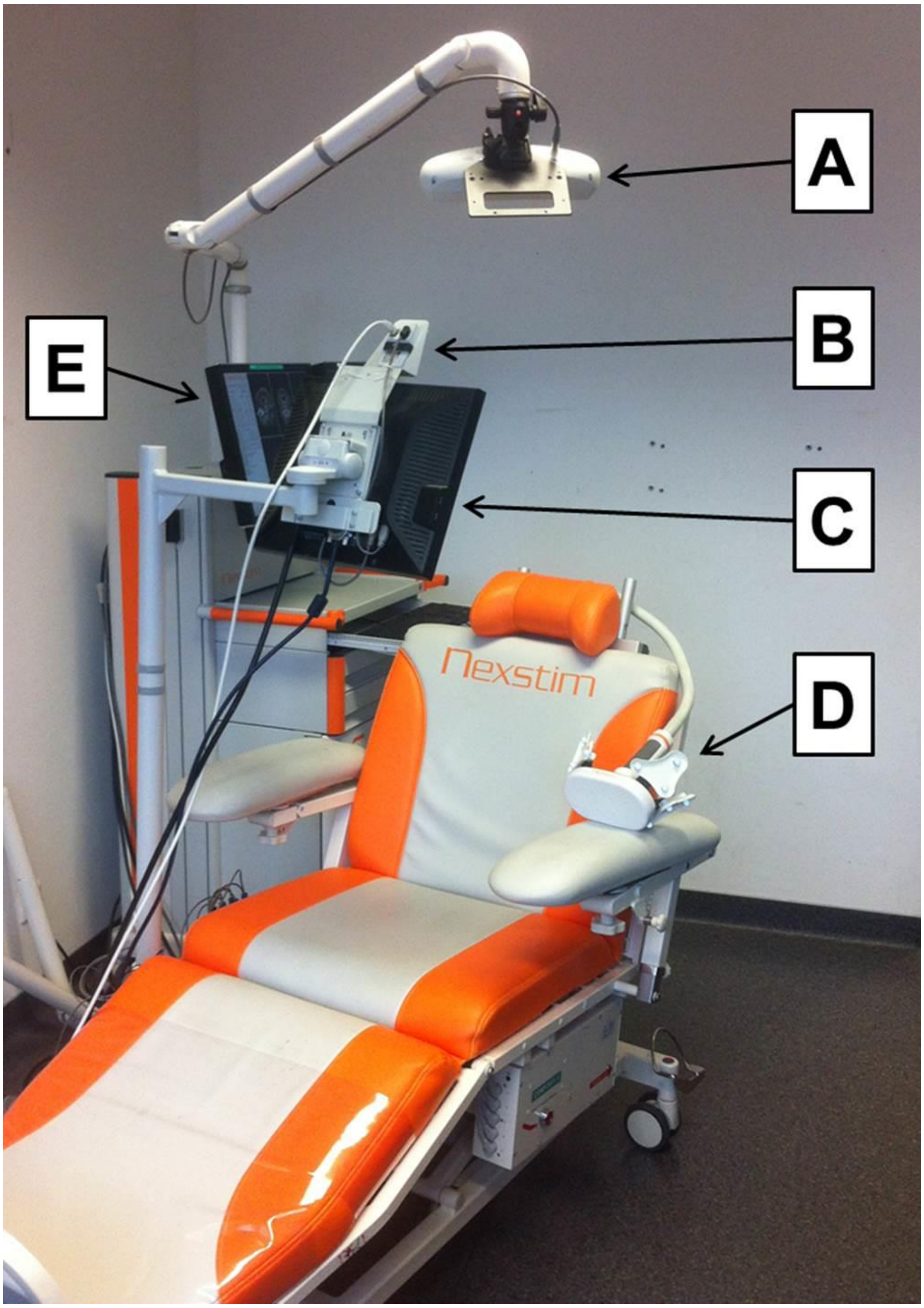

Fig. 10: The experimental setup of the Nexstim eXimia system (Nexstim Oy, Helsinki, Finland) consists of the stereotactic camera (A) for the neuronavigation, the video camera (B) for the recording of language mapping procedures, the screen (C) where the pictures of the object naming test are displayed, the stimulation coil (D), and two further screens (E) for the navigation and the settings of the language mapping procedure.

2.6.1. Basic principles of TMS

TMS works based on the principles of Faraday's law of electromagnetic induction, published in 1831 (Faraday, 1965). The magnetic coil is available in different shapes. We performed the language mappings of the present studies with a biphasic figure-of-eight coil with a 50 mm radius, as most commonly used. This kind of coil produces maximal current at the intersection of its two round components and thus enables the induction of a more focal electric field (Fig. 11) (Hallett, 2000). As opposed to the figure-of-eight coil, circular or double-cone coils are able to induce stronger but less focal electric fields. These coil shapes are used for the stimulation of deeper parts of the brain and the cerebellum (Rossi et al., 2009).

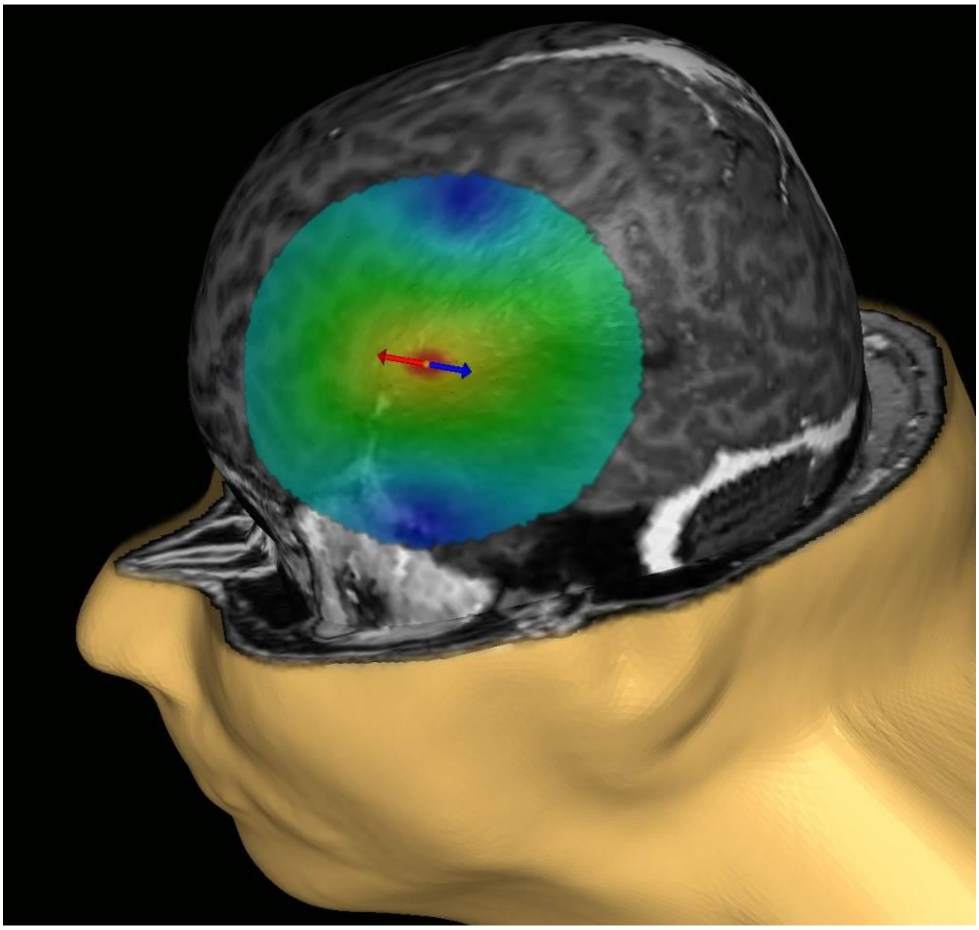

Fig. 11: Visualized electric field of the figure-of-eight coil. The electric field strength is the highest within the red colored area. The red and blue colored arrows show the orientation of the coil.

The coil develops a magnetic field strength of 2.2 Tesla, which induces an intraparenchymal electric field. This electric field changes the transmembrane potential and causes a local membrane depolarization. The macroscopic responses—like evoked neuronal activity, changes in blood flow and metabolism, muscle twitches, and changes in behavior—can be measured by other functional imaging tools such as EEG, PET, fMRI, and EMG (Fig. 12) (Ruohonen, 1998). Thus, TMS enables the stimulation of cortical neurons without pain (Rossi et al., 2009). The full microscopic mechanisms of TMS's functionality on the neuronal level are not yet completely understood and are controversially discussed (Ruohonen, 1998; Theodore, 2002). However, it is assumed that TMS indirectly activates corticospinal neurons through synaptic inputs (Di Lazzaro et al., 1998). Thereby, TMS is able to excite or inhibit brain functions and creates transient functional lesions (Hallett, 2000).

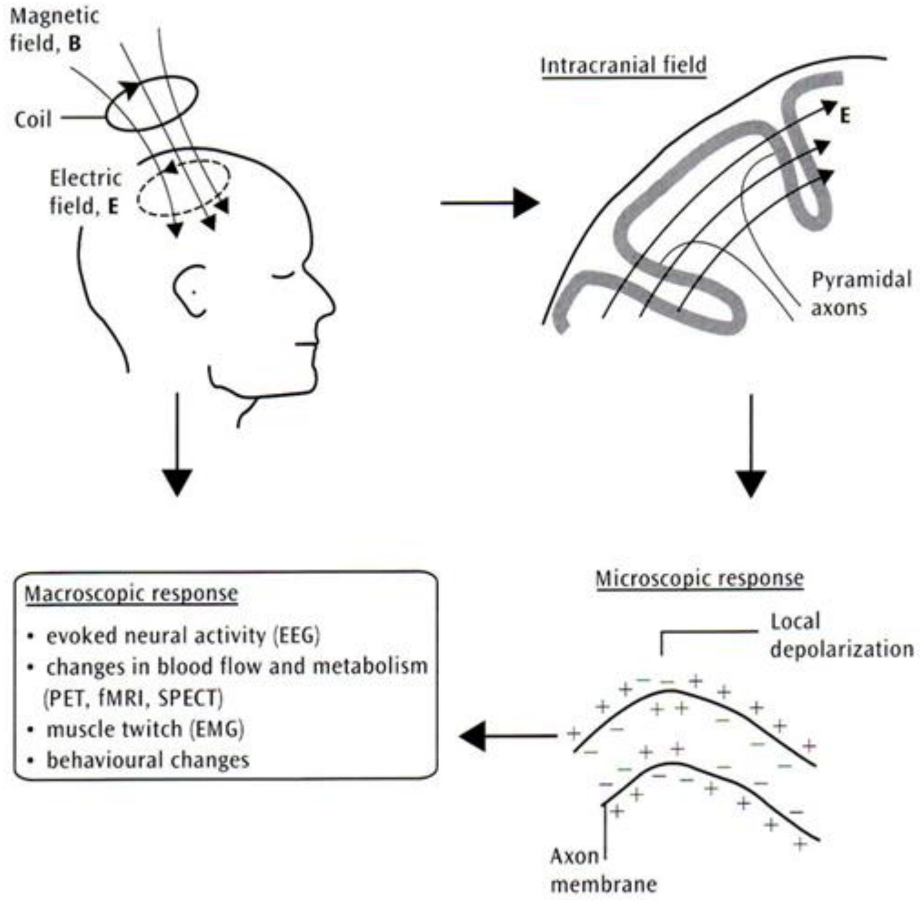

Fig. 12: The processes and effects of the functionality of TMS (Ruohonen, 1998).

2.6.2. Procedure of a language mapping sequence

As already mentioned, one of the most crucial advantages of TMS against other non-invasive mapping techniques is its combination with neuronavigation, called nTMS. We therefore used the nTMS system of Nexstim (Nexstim Oy, Helsinki, Finland), which considers the shape of the copper wiring of the coil, its 3D position and orientation, and the overall shape of the patient’s head and brain. By taking these parameters into account, nTMS is able to calculate the distribution and strength of the intracranial electric field; in application-oriented terms, it enables the examiner to exactly locate the stimulation sites (Fig. 11) (Hannula et al., 2005; Ruohonen and Ilmoniemi, 1999). Hence, the first step before each mapping was a T1-weighted MRI scan of the patient’s head, combined with an intravenous contrast administration of gadopentetate dimeglumine (Magnograf, Marotrast GmbH, Jena, Germany)

(Picht et al., 2013). Based on the MRI scan the nTMS system reconstructs a 3D model of the patient's head and brain, which is displayed on the screen during the whole mapping sequence (Fig. 13). By the use of a linked stereotactic camera and reflectors fastened to the patient's head and the navigation pointer, we performed the co-registration of the patient's head and its 3D reconstruction (Picht et al., 2013).

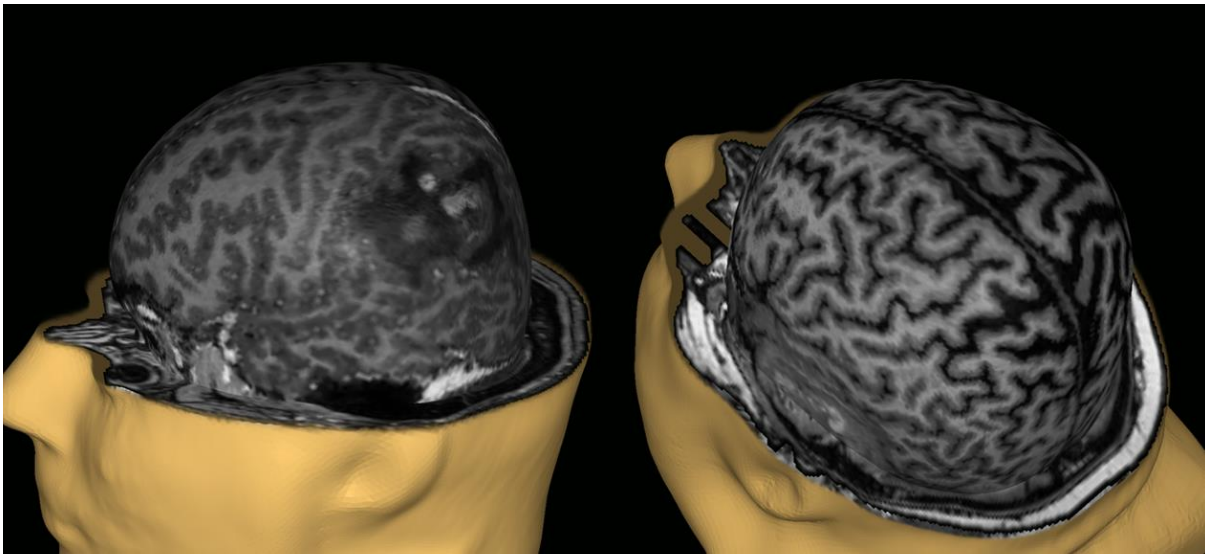

Fig. 13: 3-D-reconstructions of two patients prior to rTMS language mapping.

On the one hand, the co-registration combined with the visualization of the calculated electric field enables the examiner to target specific sites and to control the stimulation strength in real-time; on the other hand, it allows the analysis of the stimulation sites after the mapping (Fig. 14 C & 16) (Ilmoniemi et al., 1999; Lioumis et al., 2012; Ruohonen and Ilmoniemi, 1999; Ruohonen and Karhu, 2010). As a next step, we identified the patient's resting motor threshold (RMT) of the left hemisphere (Fig. 14 A). The RMT is defined by the lowest stimulation intensity that evokes a positive muscle response. This was done by a motor mapping of the cortical representation of the patient's right abductor pollicis brevis (APB) muscle after our standard protocol (Krieg et al., 2012b). With a basic intensity of 100% RMT we then determined the mapping frequency and intensity (Pascual-Leone et al., 1991; Sollmann et al., 2013a; Sollmann et al., 2013b). While the following protocol was modified and adapted over time, it is largely based on the recommended procedure for rTMS language mappings published by Lioumis and colleagues (Lioumis et al., 2012): As a first step, the patient performed the baseline recording of the picture data set (the patient was shown a series of 131 colored pictures without stimulation, and asked to name each object; Fig. 15). This was done twice in order to discard objects that the patient could not clearly name even without the effects of rTMS. This baseline recording would be used for comparison with rTMS-induced language errors during later analysis. Hence, after the baseline recording we removed the misnamed pictures from the picture data set. Next, the remaining pictures were presented time-locked to rTMS pulses, while the examiner moved the stimulation coil over the patient's head. In this way, we stimulated 80–120 cortical sites (Fig. 14 C). Each of these sites was stimulated thrice, with the following parameters:

- display time (DT = time of picture presentation on screen) of 700 ms
- inter-picture interval (IPI = time between two pictures) of 2500 ms
- picture-to-trigger interval (PTI = time between presentation of the picture and onset of the rTMS burst) of 0 ms or 300 ms (Ille et al., 2015b; Krieg et al., 2014c)

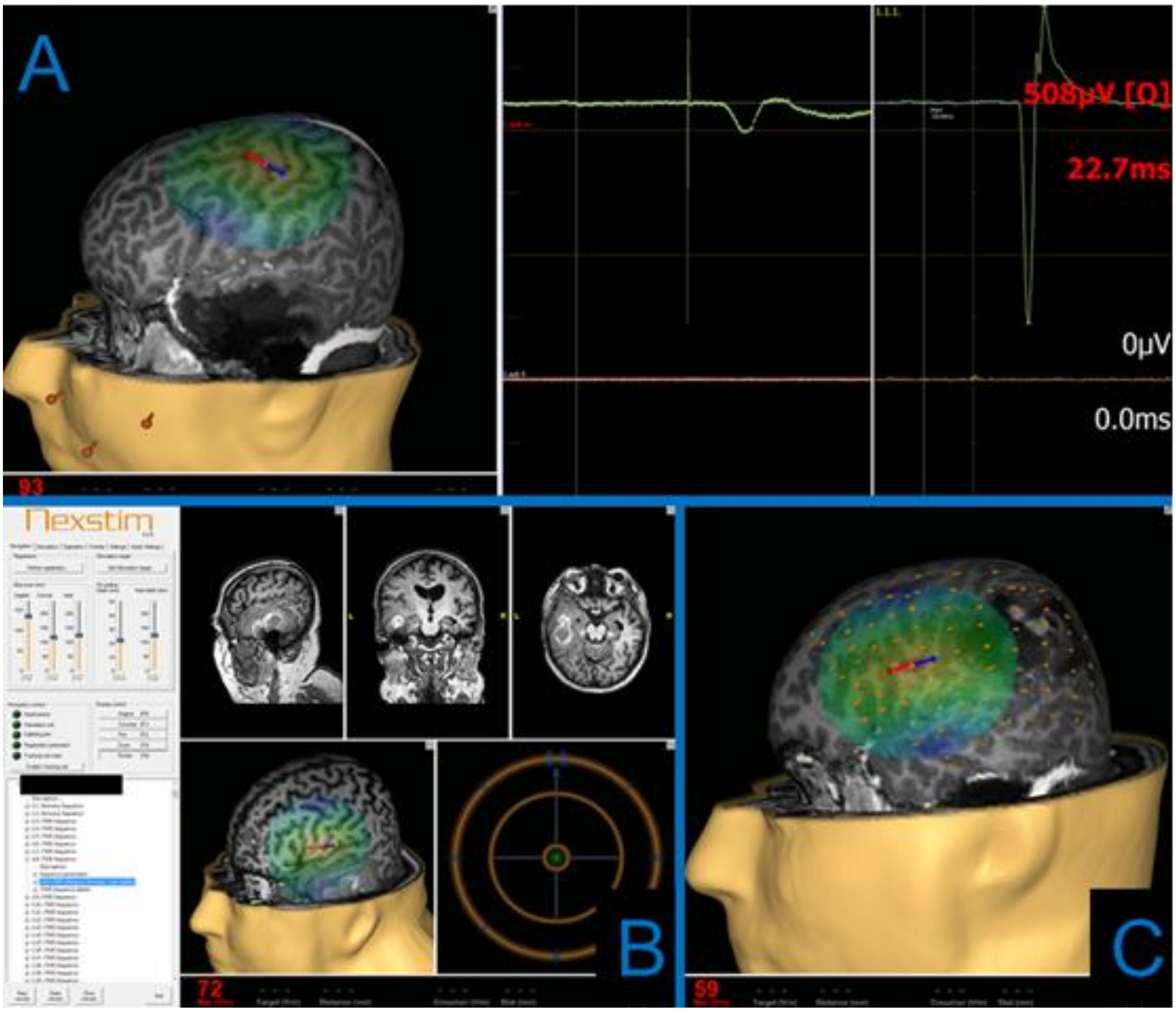

Fig. 14: The three screenshots of illustrative cases show the determination of the patient's RMT (A; stimulation site within the precentral gyrus on the left screen, EMG response is displayed on the right screen), the navigation screen (B) of Nexstim's nTMS system eXimia 4.3 (Nexstim Oy, Helsinki, Finland), and a completed rTMS language mapping sequence (C). The stimulated sites are indicated with orange pins.

Fig. 15: Examples for pictures of the object naming task.

2.6.3. TMS data analysis

The video-recording of both the baseline performance and the stimulation sequence enabled a differentiated analysis and ensured an objective examination of the stimulation sites without knowledge of their location (Lioumis et al., 2012).

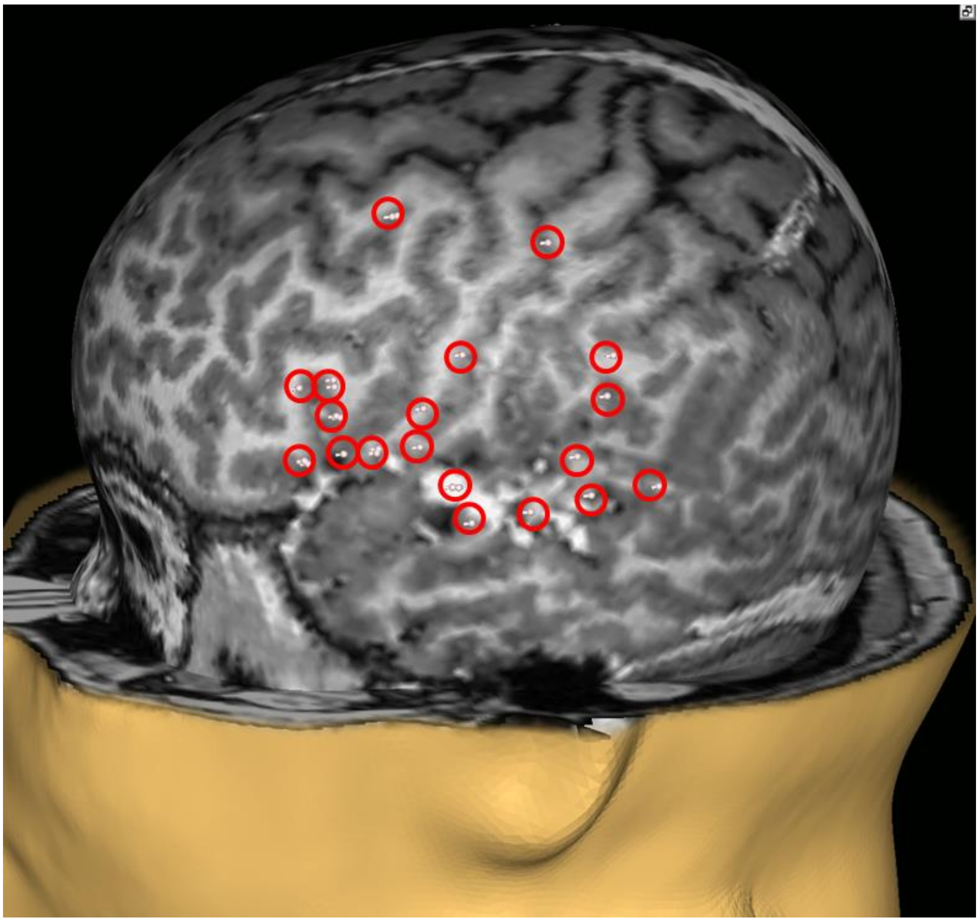

Fig. 16: Illustrative case of a patient suffering from an arteriovenous malformation within the left temporal lobe. After language mapping by rTMS was completed, we compared each stimulation site with the baseline recording. The tagged white pins within the red circles describe language errors induced by rTMS.

We matched the observed language errors to six error classes defined by Corina et al. in 2010, which were extended by a further one by Sollmann et al. in 2013 (Corina et al., 2010; Sollmann et al., 2013a):

- No-response errors: stimulation results in a lack of naming response
- Performance errors: object is imprecisely articulated, stuttered, or slurred (form-based dysarthric and apraxic errors)
- Phonological errors: phonetic modification of the object
- Semantic errors: semantically associated word instead of the target word
- Neologism: possible but non-existent words (Blumstein, 2001)
- Circumlocutions: talking around the target word rather than naming it
- Hesitations: delayed naming in comparison with the baseline recording (Sollmann et al., 2013a)

We also discarded language errors that were caused by muscle stimulation or pain (Picht et al., 2013). According to the standard of our department we used Corina's cortical parcellation system (CPS) for the assignment of the induced language errors, which is adapted for the Foundational Model of Anatomy *NeuroNames* terminology (Bowden and Martin, 1995; Corina et al., 2005). For the second publication (*Impairment of non-invasive language mapping by lesion location – a fMRI, rTMS, and DCS study*) we additionally grouped the CPS into anterior and posterior language-related regions (Ille et al., 2015a).

2.7. Statistical analysis

2.7.1. Error rates and error rate thresholds

One of the main objectives of the first publication was to define different error rate thresholds (ERTs) for the optimization of the analysis of rTMS language mappings (Ille et al., 2015b). Initially, we calculated the error rates (ER), defined as the number of errors per number of stimulations for each CPS region (Krieg et al., 2013; Picht et al., 2013). As a next step, we analyzed the rTMS raw data by twelve ERTs (Ille et al., 2015b). For the second publication, we also calculated the ERs of rTMS language mapping and subsequently compared them to the according results of the intraoperative mappings (Ille et al., 2015a).

2.7.2. Receiver operating characteristics

The core findings of both studies are expressed by receiver operating characteristics (ROC). In order to find distinctions and correspondences of the non-invasive mapping techniques in comparison with DCS as the gold standard for language mapping, the intraoperative results by DCS were defined as ground truth for each calculation. According to this key rule, we compared the pre- and intraoperative results of each patient (Ille et al., 2015a; Ille et al., 2015b). We summed up the true and false positives (TP, FP) as well as the true and false negatives (TN, FN) of all patients and specifically to each CPS region. Eventually, we calculated the ROCs as follows:

- Sensitivity = TP / (TP + FN)
- Specificity = TN / (TN + FP)
- Positive predictive value (PPV) = TP / (TP + FP)
- Negative predictive value (NPV) = TN / (TN + FN)

In order to visualize the analysis of different ERTs as well as the results of the mapping of language-negative sites, we used ROC curves in both publications. We therefore plotted the *true positive fraction* (sensitivity) against the *false positive fraction*, calculated by the term *1 – specificity,* in both studies (Ille et al., 2015a; Ille et al., 2015b; Lalkhen and McCluskey, 2008). In the second publication, we additionally plotted the sensitivity of the two non-invasive methods against the term *1 – NPV* (Ille et al., 2015a).

For the calculation of the ROCs, including the 95% confidence intervals, we used the GraphPad Prism® version 6.04 (La Jolla, CA, USA).

3. RESULTS

3.1. Combined non-invasive language mapping by nTMS and fMRI and its comparison with direct cortical stimulation

In order to refine the analysis of rTMS raw data and with the aim of increasing the specificity and PPV of rTMS language mappings as compared to DCS during awake surgery, we investigated language mapping data of 35 patients with left-sided perisylvian brain lesions obtained by rTMS, fMRI, and DCS. For this study, I performed the rTMS language mappings, the analysis of the raw data, and the statistical analysis for the comparisons of rTMS language mapping results to the results of fMRI and DCS language mapping. From the number of errors per number of stimulations of each region of the CPS I calculated the ERs, and subsequently we determined different ERTs (ER at which a CPS region is defined as language-positive in terms of rTMS) (Corina et al., 2005; Krieg et al., 2013; Picht et al., 2013). As a sub-analysis, I compared rTMS language mappings performed with a PTI (time between stimulus presentation and stimulation onset) of 0 ms and 300 ms (Krieg et al., 2014c). Moreover, we suggested and evaluated a protocol for a combined non-invasive language mapping by rTMS and fMRI.

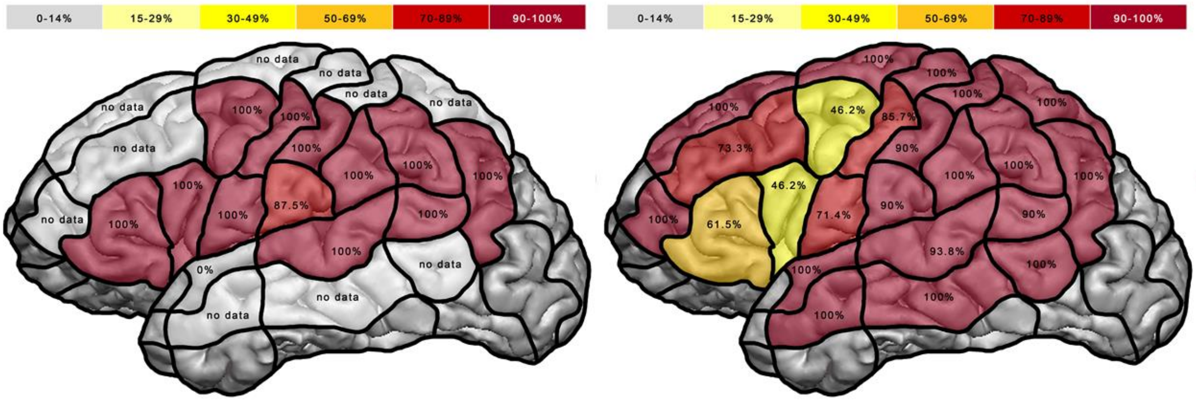

Fig. 17: The schemes visualize the strengths and advantages of the two non-invasive techniques, rTMS and fMRI. The brain template on the left shows the sensitivity of rTMS language mapping as compared to DCS; the brain template on the right illustrates fMRI's specificity in comparison with the intraoperative language mapping results.

By the present results, we showed that rTMS language mapping should be performed with a PTI of 0 ms, and that its raw data should be analyzed with an ERT of 15%, 20%, 25%, or the 2-out-of-3 rule (stimulation site was defined as language-positive in terms of rTMS, if at least two out of three stimulations led to a language error). Additionally, we proved the feasibility of combined non-invasive language mappings, and revealed a higher correlation to DCS for our proposed protocol than with either technique alone (Fig. 17).

3.2. Impairment of non-invasive language mapping by lesion location – a fMRI, nTMS, and DCS study

Language mapping by rTMS has been demonstrated accurate as compared to DCS during awake surgery in several studies (Krieg et al., 2013; Krieg et al., 2014b; Picht et al., 2013; Sollmann et al., 2013b; Tarapore et al., 2013). In contrast, Giussani and colleagues re-evaluated former studies on the comparison of language mapping by fMRI and DCS. They reported a lack of correlation and concluded that fMRI is currently not precise enough for preoperative language mapping (Giussani et al., 2010).

We also observed this shortcoming in our department (Sollmann et al., 2013b); thus, we compared the results of rTMS and fMRI language mapping with the corresponding data of DCS during awake surgery within one patient cohort. The objective of this study was to investigate the impairment of non-invasive language mapping by left-sided perisylvian brain lesions.

We therefore conducted language mapping in 27 patients by the three mapping techniques, and registered the language-positive sites of each method to the CPS (Corina et al., 2005). After subdividing the CPS into anterior and posterior language-related regions, we analyzed the ROCs for the comparisons rTMS vs. DCS and fMRI vs. DCS, with respect to the situations *with* (W) and *without* (WO) lesion in the mapped region. Also for this study, I performed the rTMS language mappings, the analysis of the rTMS raw data, and the statistical analysis for the comparisons of the different language mapping techniques.

For the comparison of rTMS vs. DCS language mapping, we obtained a sensitivity and NPV of 100% each for both the W and the WO subgroups. Moreover, within the W subgroup we revealed a specificity of 8% (WO: 5%) and a PPV of 34% (WO: 53%). The comparison of fMRI vs. DCS within the W subgroup revealed a sensitivity of 32% (WO: 62%), a specificity of 88% (WO: 60%), a PPV of 56% (WO: 62%), and a NPV of 73% (WO: 60%). The results show that—particularly for the mapping of language-negative cortical regions—rTMS is a reliable language mapping tool both with and without lesion in the mapped region. With this in mind we were able to prove that rTMS language mapping is less impaired by brain lesions than fMRI (Fig. 18).

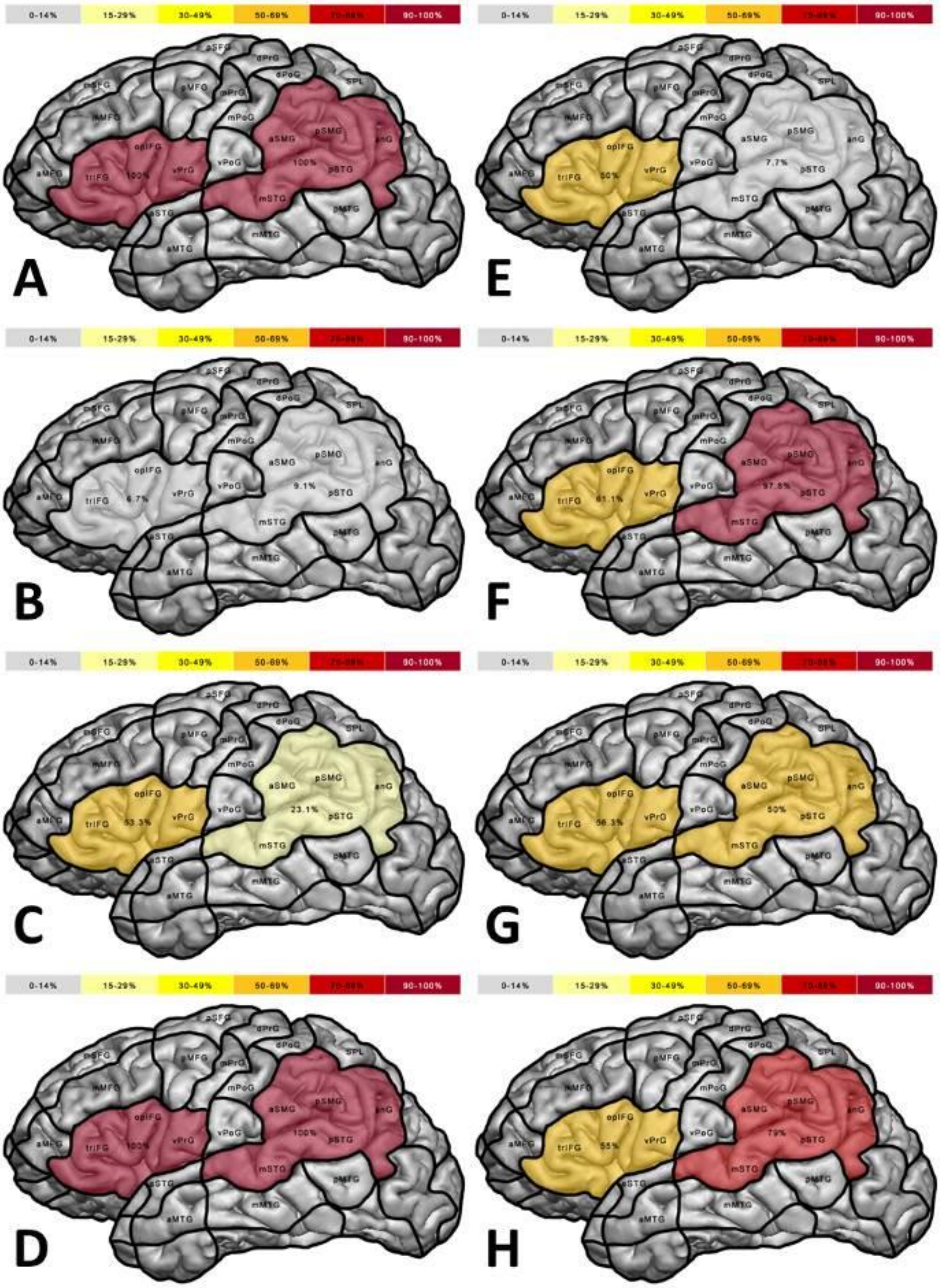

Fig. 18: The left column (A–D) demonstrates the ROCs for the comparison of rTMS and DCS language mapping, the right column (E–F) illustrates the comparison of fMRI and DCS language mapping. The schemes A & E show sensitivities, B & F specificities, C & G PPVs, and D & H NPVs for non-invasive language mapping with lesion in the mapped regions.

4. DISCUSSION

4.1. Mapping of human language function

4.1.1. Challenges of language mapping

When discussing the mapping of human brain functions, the kind of function subject to the mapping has to be distinguished. Since the definition of quality of life is highly individual, it is difficult to categorize the different human brain functions according to their importance. Yet, regarding the historic development of human brain mapping and its current implementation within the operating room, language and motor functions have priority. Even these two functions differ in terms of the complexity of mapping them.

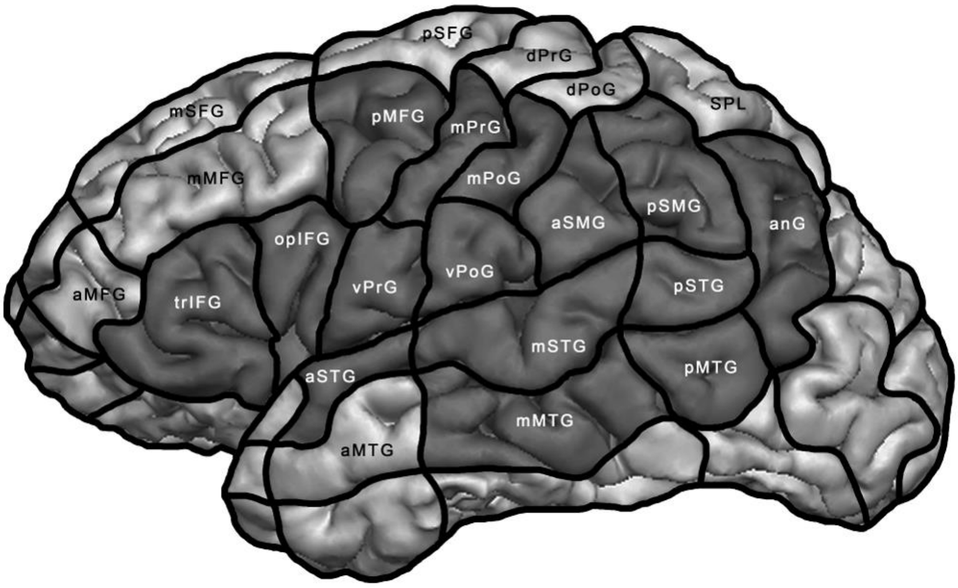

Fig. 19: Summation of language-positive cortical regions examined by DCS during awake surgery in the present studies' patient cohort showing the complexity and individuality of human language function (Ille et al., 2015a; Ille et al., 2015b).

It would be overconfident to assume that the mapping of human motor function is straightforward; yet, motor function is restricted to relatively well-known cortical regions. Moreover, reactions to the stimulation of the motor cortex can be recorded by clearly defined motor-evoked potentials (MEPs) (Saisanen et al., 2008). In contrast, language function is a distributed network with a higher variability of eloquent parts and has an enormous level of individuality (Fig. 19). These features show the difficulty of language mapping and the high demands on mapping techniques. The classic language models referring to the work of

Broca and Wernicke, as indicated above, are no longer up to date, and even the contribution of these important regions towards current language models has to be reassessed (Baum et al., 2012; Briganti et al., 2012; Dronkers et al., 2007; Duffau et al., 2013). It is proven that both the classical Broca's area (Duffau et al., 2005; Vigneau et al., 2006) and the classical Wernicke's area (Boatman et al., 2000; Gatignol et al., 2004) contribute to the production and comprehension of language. Mainly due to this fact, we chose these areas—in addition to a further one—for the cortical subdivision in the second study (Fig. 18) (Ille et al., 2015a). Coincidentally, the assignment of classical language areas to current language models such as Levelt's LRM (Levelt-Roelofs-Meyer) model or Duffau's hodotopical model of language show the complexity of human language functions (Duffau et al., 2013; Indefrey, 2011; Levelt et al., 1999). If one additionally considers the brain's capabilities for plasticity after structural damage or tumor infiltration (Duffau, 2013c; Duffau et al., 2003; Robles et al., 2008; Thiel et al., 2001), and from a more surgical point of view the publications of probability maps for tumor resection (Fig. 1) (De Witt Hamer et al., 2013; Ius et al., 2011), the necessity of reliable methods for the preoperative mapping of human language functions is obvious.

4.1.2. Mapping of language-positive cortical regions

Our current knowledge about the distribution of human language functions is based in large part on the results of DCS during awake surgery. Justified by its direct access to the human brain and the long time it has been applied, DCS is considered to be the gold standard for language mapping (De Witt Hamer et al., 2012; Haglund et al., 1994; Ojemann et al., 1989; Ojemann and Whitaker, 1978; Sanai et al., 2008). In any field of research, new techniques should preferably match the gold standard (Ille et al., 2015b). Through the present studies, we have twice conducted such matching, in different ways. In both studies we observed a lack of correlation regarding language-positive sites, represented by low PPVs (Ille et al., 2015a; Ille et al., 2015b). As detailed in the first publication, the high sensitivity of rTMS leads to false positive results compared to DCS language mapping because rTMS is yet not able to differentiate between language-involved and language-eloquent cortical areas. We tried to solve this issue and were able to reduce the false positive results by proposing a new kind of analysis. However, even gold standard methods have to be brought into question, as we have discussed the distinctions regarding language analysis pre- and intraoperatively (Ille et al., 2015b). Among other factors, the low PPV of language-positive sites in rTMS is the greatest inhibitor of its ability to differentiate between language-involved and language-eloquent cortical regions (Ille et al., 2015a; Ille et al., 2015b; Picht et al., 2013). Nevertheless, the most important fact regarding language-positive sites is that rTMS is able to locate all of the intraoperatively defined language-positive sites.

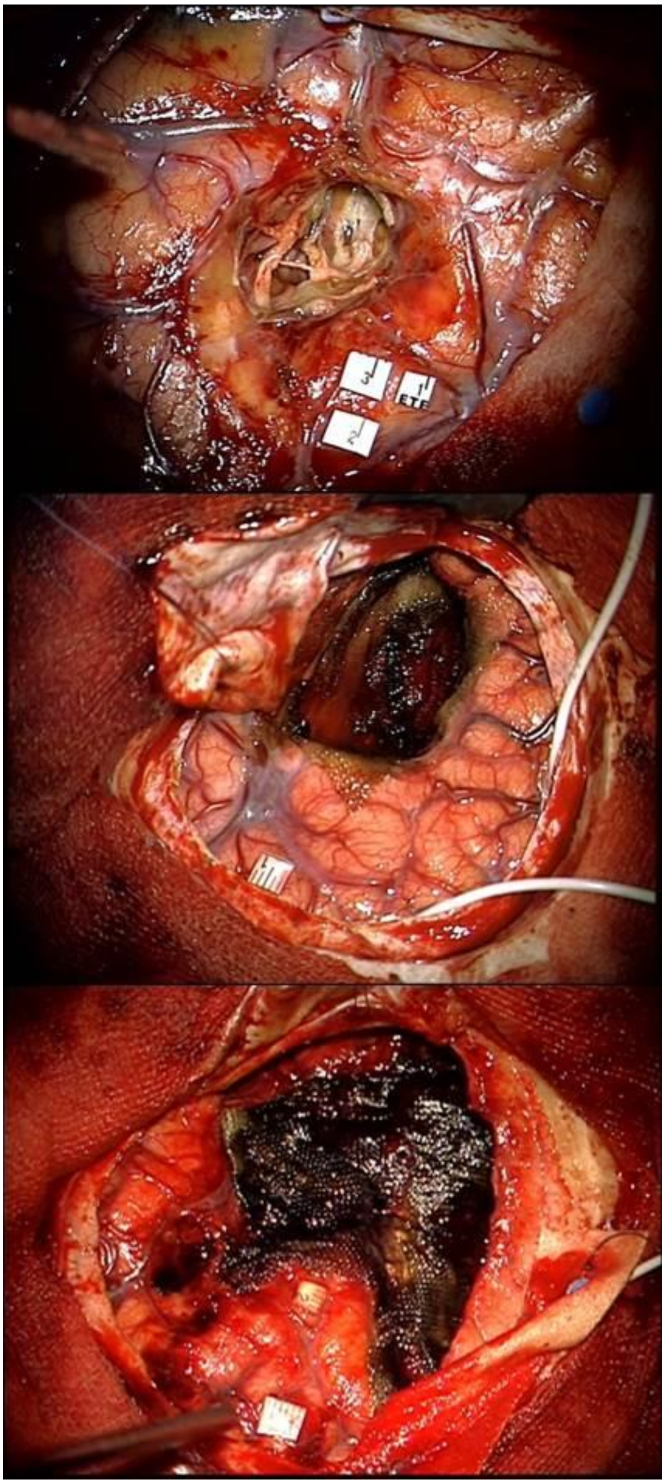

Fig. 20: Three illustrative cases with status post tumor resection. Language-positive sites in terms of DCS are tagged with numbers.

4.1.3. Mapping of language-negative cortical regions

The aforementioned high sensitivity of rTMS language mapping is coincidentally associated with the absence of false negative results. These results suggest the use of rTMS for negative language mapping (Ille et al., 2015a; Ille et al., 2015b). The approach of negative mapping has not been born out of necessity, but describes a paradigm shift of language mapping techniques, already stated earlier by highly experienced neurosurgeons such as Sanai and Berger (Sanai et al., 2008). Negative mapping might also enable more tailored and thereby smaller craniotomies and faster intraoperative mapping and tumor resection *per se*. With the approach of intraoperative negative mapping, data based on 250 cases show a new or increased postoperative language deficit in 1.6% of cases 6 months after surgery (Sanai et al., 2008). Yet, when discussing brain mapping, particularly language mapping, no technique will be a hundred percent secure. Both single-case reports of deficits after negative mapping (Taylor and Bernstein, 1999) and resections of positive sites without postoperative deficit (Duffau, 2006; Robles et al., 2008) have already been published. However, by the results of our studies, we were able to show that rTMS is a reliable tool for the mapping of language-negative cortical regions. Moreover, we were able to demonstrate that rTMS language mapping is less affected by brain lesions than the previous standard for non-invasive language mapping, fMRI (Ille et al., 2015a; Ille et al., 2015b).

4.2. Applicability of TMS

4.2.1. Patients

Language mapping by rTMS is feasible. The basis of this statement was established during the last decades and has been consistently confirmed by several groups of researchers (Epstein, 1998; Epstein et al., 1996; Lioumis et al., 2012; Pascual-Leone et al., 1991; Sparing et al., 2001). The objectives of the present studies were influenced in part by a single case in our department, which has been published by our group. Sollmann and colleagues reported this case of a 43-year-old man suffering from a glioblastoma within the opercular part of the left inferior frontal gyrus. Preoperative fMRI detected language-eloquent regions only within the right hemisphere, whereas preoperative rTMS identified the left hemisphere as language-dominant. The patient then underwent awake surgery; the intraoperative language map created by DCS examination correlated well with the preoperative results of rTMS language mapping (Sollmann et al., 2013b). At that time, fMRI was considered to be the standard for preoperative language mapping (FitzGerald et al., 1997). Since the results obtained by intraoperative mapping always count in the final analysis, the language map revealed by fMRI in this single case could not implicate extensive surgical decisions.

However, the clinical applicability of mapping techniques is not least defined by its usefulness for clinical procedures and gains in diagnostic information. The present studies are not the first to prove this for rTMS language mapping; however, we also showed the applicability of a combined preoperative language assessment and the advantages of rTMS versus fMRI language mapping (Ille et al., 2015a; Ille et al., 2015b). Moreover, we support the following proposal for clinical procedures: indeed, due to its high sensitivity, rTMS over-identifies language-positive sites—at least in comparison with language-positive sites obtained by DCS. However, these sites can be transferred to the operating room by neuronavigation systems and later verified by intraoperative DCS language mapping (Fig. 21). This application might shorten the intraoperative mapping procedure and the overall operation time as well (Ille et al., 2015a; Tarapore et al., 2013).

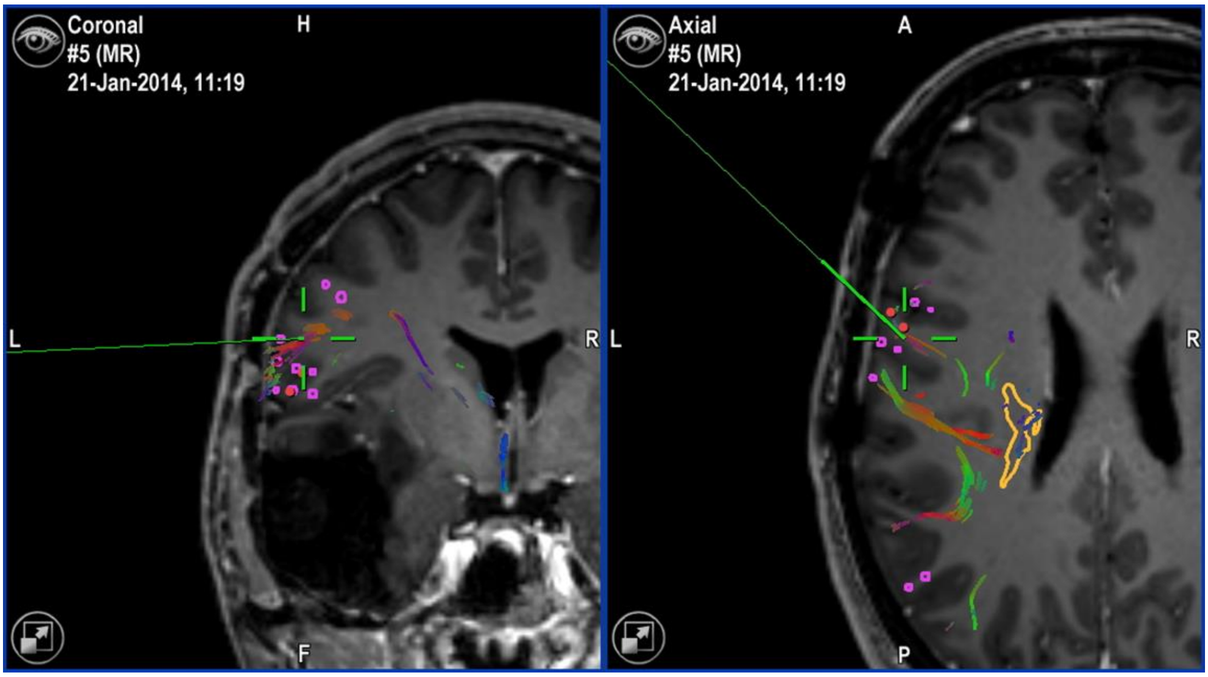

Fig. 21: Data transfer of language-positive sites in terms of rTMS (pink spots) via neuronavigation system (BrainLAB Curve®, BrainLAB AG, Feldkirchen, Germany) into the operating room. These sites can be targeted with the navigation pointer (tip is displayed with the green cross) and verified by DCS. The screenshots also illustrate the visualization of the corticospinal tract by nTMS-based DTI-FT (outlined in yellow) and rTMS-based DTI-FT of language pathways (subcortical red and green fibers) as explained in section 4.3.

4.2.2. Healthy subjects

TMS is a safe technique (Rossi et al., 2009). Naturally, this property is highly significant for its clinical applicability, but it also provides the opportunity of examining healthy subjects (Ille et al., 2015a; Krieg et al., 2013). This is advantageous in several aspects. On the one hand, rTMS can be further refined with respect to mapping protocols, error analysis, and different kinds of language or behavioral tasks. On the other hand, rTMS and DCS operate on the same neurophysiological principle: the virtual lesion. The results derived by this model are indispensable for human brain mapping, but DCS is obviously not applicable to healthy subjects. Hence, the gain in knowledge originates from patients, whose brains are influenced by malignant processes or other kinds of disorders. Thus, there is a need for non-invasive methods that enable the examination of healthy brains. As described in the second publication, fMRI plays a highly significant role in the examination of healthy subjects; despite our results showing that rTMS is more accurate in patients, they do not support a similar conclusion for language mapping in healthy subjects (Ille et al., 2015a).

4.3. Future aspects

4.3.1. rTMS-based DTI-FT

As previously discussed, the human brain harbors a tremendous plastic potential, but this potential is largely limited to the cortex. In contrast to cortical lesions, damage of white matter pathways mostly leads to severe neurological disorders (De Benedictis and Duffau, 2011; Duffau, 2013c). Thus, it is of paramount importance to safeguard these subcortical fibers during neurosurgical interventions. This becomes obvious on viewing two resection probability maps based on resection margins of several hundred cases (Fig. 1). These maps show, when functionality should be preserved, subcortical structures are in large parts non-resectable (De Witt Hamer et al., 2013; Mandonnet et al., 2007). Consequently, the localization of these pathways is of high interest, particularly for neurosurgeons. On the one hand, they can be tracked intraoperatively by direct cortical and subcortical stimulation (Freyschlag and Duffau, 2014; Jimenez de la Pena et al., 2013; Taniguchi et al., 1993), but ideally, they are visualized preoperatively and then included in surgical planning. The latter can be done by DTI-FT (Clark et al., 2003; Coenen et al., 2001; Nimsky et al., 2007).

DTI-FT illustrates the subcortical white matter tracts based on different regions of interest (ROI). It has already been shown that ROIs within the precentral gyrus defined by nTMS motor mapping are suitable for the tracking of the corticospinal tract (CST) (Frey et al., 2012; Krieg et al., 2012a). As Fig. 22 shows, even language-eloquent cortical regions examined by rTMS language mapping are available as ROIs for DTI-FT.

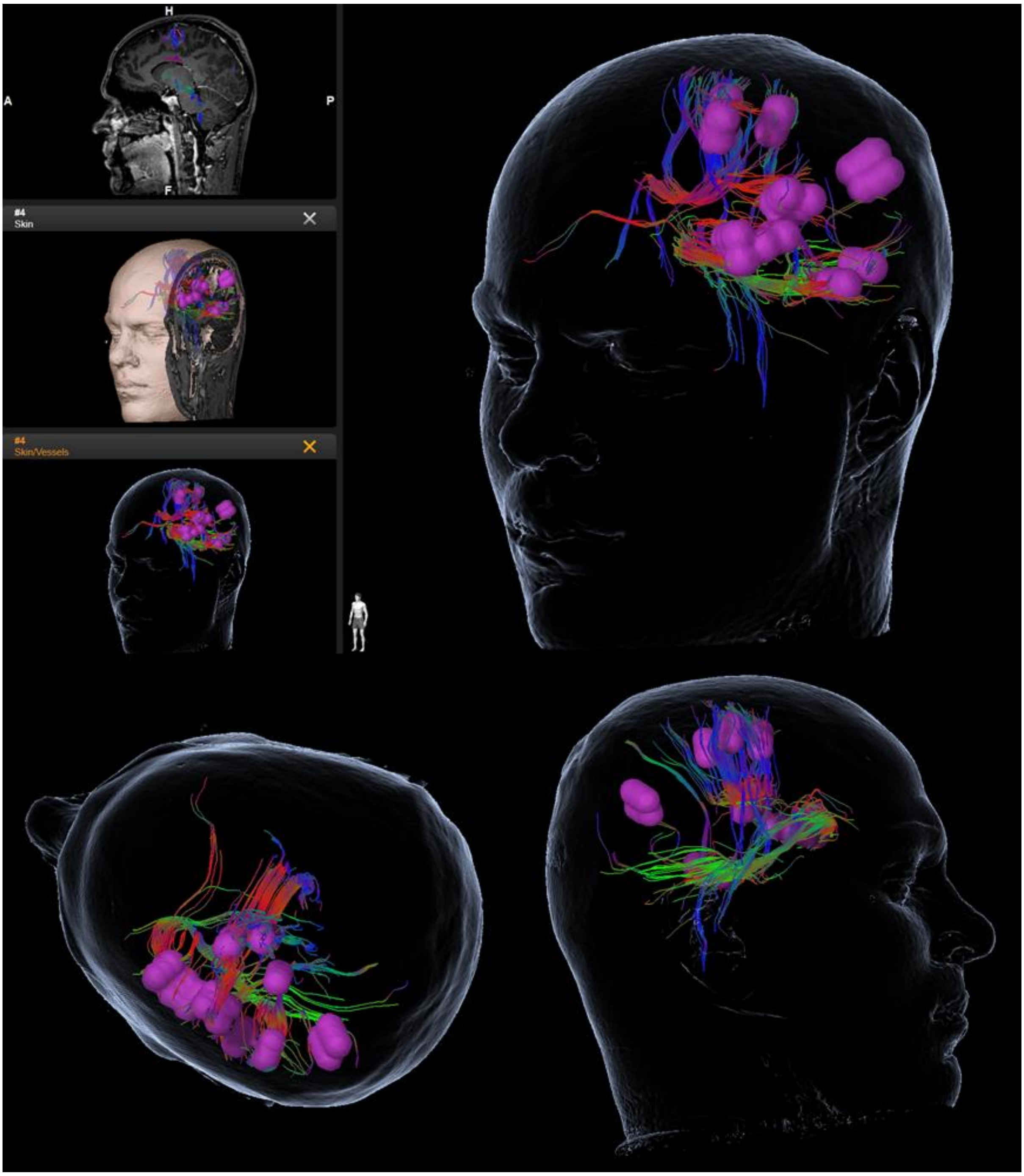

Fig. 22: Illustration of rTMS-based DTI-FT. Starting from the pink spots, which were determined by rTMS language mapping, the red, green, and blue fibers visualize language pathways as calculated by the planning software (BrainLAB BUZZ® & Brain LAB iPlanNet® Cranial, BrainLAB AG, Feldkirchen, Germany).

4.3.2. Incorporation of rTMS language data into current language models

The further refinement of rTMS-based DTI-FT might reveal even more detailed insights into human language functions. Current models of language processing and comprehension, such as Duffau's hodotopical model of language, show the importance of functional connectivity (Duffau et al., 2013). This connectivity is embodied by the subcortical language pathways. Neither rTMS language mapping nor DTI-FT affects the subject's health; therefore, the combined application of the two methods could be used to review these models and the underlying functional connectivity in healthy brains. Most of our knowledge of human language function is based on patient DCS data, which have been collected over several years. Indeed, these results are indispensable, but regarding quantity, the same amount of data could be collected in shorter periods by rTMS studies with healthy subjects. Moreover, by initializing large-scale multicenter studies, a vast amount of data examined by a reliable and standardized mapping technique could be pooled. The results could be used to create rTMS-based models of language function, which could in turn be compared to existing models.

4.4. Limitations

Indeed, rTMS is a promising and aspiring technique, but it is also a relatively novel technique, particularly for language mapping. New techniques always have to cope with some difficulties, especially when they are proposed for use in complex fields like brain mapping. At the same time, even the most experienced technique should never be considered completely matured, since specific advancements are always possible. Within the two publications, we referred to several limitations of rTMS such as the analysis of specific language error categories, the application of the object naming task, and the categorization of induced language errors to the CPS (Krieg et al., 2013; Sollmann et al., 2013a; Tarapore et al., 2013). Consequently, we tried to provide approaches to resolve these shortcomings (Ille et al., 2015a; Ille et al., 2015b); most of these limitations are the subjects of current research. For example, a recently published study could prove the advantages of an immediate pulse train onset coincidentally with picture presentation (PTI 0 ms) (Krieg et al., 2014c).

With this in mind, rTMS is a reliable technique for the mapping of human language functions that has to undergo consistent further development. However, by the present studies we have been able to contribute to this refinement and show accordance and advantages in comparison with other mapping techniques (Ille et al., 2015a; Ille et al., 2015b).

5. SUMMARY

5.1. English

Both the mapping of human language functions and the treatment of patients with brain lesions are serious challenges. The present thesis is based on two publications for which we performed language mapping in patients suffering from left-sided perisylvian brain lesions by repetitive navigated transcranial magnetic stimulation (rTMS), functional magnetic resonance imaging (fMRI), and direct cortical stimulation (DCS) during awake surgery.

In the first study, *Combined non-invasive language mapping by nTMS and fMRI and its comparison with direct cortical stimulation*, we determined and evaluated distinct error rate thresholds (ERTs) for the analysis of rTMS raw data. Moreover, we designed a protocol for the combination of the two non-invasive mapping techniques, rTMS and fMRI, and compared both the ERTs and the protocol to the according results of DCS language mapping. In summary, we ascertained that rTMS language mappings should be analyzed with an ERT of 15%, 20%, 25%, or the 2-out-of-3 rule (stimulation site was defined as language-positive in terms of rTMS if at least two out three stimulations led to a language error) in order to avoid false-positive results. Furthermore, we showed that by the combination of language mapping results obtained by rTMS and fMRI, the strengths of both techniques are available for preoperative language mapping assessment.

In the second study, *Impairment of non-invasive language mapping by lesion location – a fMRI, nTMS, and DCS study*, we compared the results of rTMS and fMRI language mappings with the gold standard technique, DCS during awake surgery, but with respect to the impairment of the non-invasive methods by perisylvian brain lesions. We therefore subdivided the cortex into anterior and posterior language-related regions, and evaluated the results with and without lesion in the mapped regions. The core findings of this study indicated that, in case of negative language mapping, rTMS is less affected by a brain lesion than fMRI.

Indeed, by our studies we were able to contribute to the further development of the promising technique of rTMS for language mapping, and we were able to show its reliability and clinical applicability. However, the treatment of patients suffering from brain lesions and the research of human brain functions are in constant progress.

5.2. Deutsch

Sowohl die Kartierung der menschlichen Sprachfunktion als auch die Behandlung von Patienten mit Hirnläsionen stellen große Herausforderungen dar. Die vorliegende Doktorarbeit basiert auf zwei Publikationen für welche wir Patienten mit linksseitigen perisylvischen Hirnläsionen mittels repetitiver navigierter transkranieller Magnetstimulation (rTMS), funktioneller Magnetresonanztomographie (fMRT) und direkter kortikaler Stimulation (DCS) während Wachkraniotomie, sprachkartiert haben.

In der ersten Studie, *Combined non-invasive language mapping by nTMS and fMRI and its comparison with direct cortical stimulation*, bestimmten und evaluierten wir verschiedene Fehlerraten-Schwellenwerte (ERT) für die Analyse von rTMS-Rohdaten. Des Weiteren entwarfen wir ein Protokoll für die Kombination der beiden nicht-invasiven Techniken rTMS und fMRT und verglichen die ERTs sowie das Protokoll mit den zugehörigen Ergebnissen der DCS Sprach-Kartierung. Zusammenfassend konnten wir feststellen, dass rTMS Sprach-Kartierungen mit einem ERT von 15%, 20%, 25% oder nach der 2-aus-3 Regel (Stimulations-Punkt wurde als sprach-positiv im Sinne von rTMS gewertet, wenn mindestens zwei von drei Stimulationen zu einem Sprach-Fehler führten) ausgewertet werden sollten um falsch-positive Ergebnisse zu vermeiden. Zudem konnten wir zeigen, dass durch die Kombination der Ergebnisse von rTMS und fMRT Sprach-Kartierungen die Stärken beider Techniken für die präoperative Sprachkartierung nutzbar sind.

Auch für die zweite Studie, *Impairment of non-invasive language mapping by lesion location – a fMRI, nTMS, and DCS study,* verglichen wir die Ergebnisse von rTMS und fMRT Sprach-Kartierungen mit dem Goldstandard DCS während Wachkraniotomie, allerdings in Bezug auf die Beeinträchtigung der nicht-invasiven Methoden durch perisylvische Hirnläsionen. Dafür unterteilten wir den Kortex in anteriore und posteriore sprach-zugehörige Regionen und werteten die Ergebnisse mit und ohne Läsion in der kartierten Region aus. Das zentrale Ergebnis dieser Studie ist, dass im Falle von negativer Sprach-Kartierung rTMS weniger durch Hirnläsionen beeinträchtigt wird als fMRT.

Zwar konnten wir durch unsere Studien einen Teil zur Weiterentwicklung der vielversprechenden Sprach-Kartierungs-Technik rTMS beitragen und ihre Zuverlässigkeit sowie klinische Anwendbarkeit zeigen. Dennoch befindet sich sowohl die Behandlung von Patienten welche an Läsionen des Gehirns erkrankt sind als auch die Erforschung der Hirnfunktionen des Menschen in einem steten Prozess.

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7. ABBREVIATIONS

3D	three dimensional
APB	abductor pollicis brevis muscle
BOLD	blood oxygen-level dependent
CPS	cortical parcellation system
CST	corticospinal tract
DCS	direct cortical stimulation
DT	display time
DTI-FT	diffusion tensor imaging fiber tracking
EEG	electroencephalography
EMG	electromyography
ER	error rate
ERT	error rate threshold
fMRI	functional magnetic resonance imaging
FN	false negative
FP	false positive
IAT	intracarotid amobarbital test
IPI	inter picture interval
MEG	magnetoencephalography
MEP	motor evoked potential
nTMS	navigated transcranial magnetic stimulation
NPV	negative predictive value
PET	positron emission tomography
PPV	positive predictive value
PTI	picture-to-trigger interval
ROC	receiver operating characteristics
ROI	region of interest
rTMS	repetitive navigated transcranial magnetic stimulation
RMT	resting motor threshold
TN	true negative
TP	true positive
W	with lesion in the mapped region
WO	without lesion in the mapped region

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10. PUBLICATIONS

Original papers

Krieg SM, Sollmann N, Hauck T, Ille S, Foerschler A, Meyer B, Ringel F
Functional language shift to the right hemisphere in patients with language-eloquent brain tumors.
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Ille S, Sollmann N, Hauck T, Maurer S, Tanigawa N, Obermueller T, Negwer C, Droese D, Zimmer C, Meyer B, Ringel F, Krieg SM
Combined non-invasive language mapping by nTMS and fMRI and its comparison with direct cortical stimulation
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Sektionstagung Neurophysiologie der DGNC, Würzburg, 17.1.2014

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Multimodale Sprachkartierung in Patienten mit perisylvischen Hirntumoren: ein Vergleich von DCS, rTMS und fMRT
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Preoperative language mapping and its impairment by lesion location: A comparison of DCS, rTMS, and fMRI
15th European Congress of Neurosurgery, Prag, 12.-17.10.2014

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Preoperative language mapping and its impairment by lesion location: A comparison of DCS, rTMS, and fMRI
6th International Symposium on NBS in Neurosurgery, Berlin, 10.-11.10.2014

11. APPENDIX: ORIGINAL ARTICLES

11.1. Combined non-invasive language mapping by nTMS and fMRI and its comparison with direct cortical stimulation

Combined Non-invasive Language Mapping by nTMS and fMRI and Its Comparison with Direct Cortical Stimulation

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ABSTRACT

Object: Repetitive navigated transcranial magnetic stimulation (rTMS) is now increasingly used for preoperative language mapping in patients with lesions in language-related areas of the brain. Yet, its correlation with intraoperative direct cortical stimulation (DCS) has to be improved. To increase rTMS’s specificity and positive predictive value, we aim to provide thresholds for rTMS's positive language areas. Moreover, we propose a protocol for combining rTMS with functional magnetic resonance imaging (fMRI) to combine the strength of both methods.

Methods: We performed multimodal language mapping in 35 patients with left-sided perisylvian lesions by rTMS, fMRI, and DCS. The rTMS mappings were conducted with a picture to trigger interval (PTI, time between stimulus presentation and stimulation onset) of either 0 or 300 ms. The error rates (ER = number of errors per number of stimulations) were calculated for each region of the cortical parcellation system (CPS). Subsequently the rTMS mappings were analyzed through different error rate thresholds (ERT = ER, at which a CPS region was defined as language-positive in terms of rTMS), and the 2-out-of-3 rule (2/3 rule, a stimulation site was defined as language-positive in terms of rTMS, if at least 2 out of 3 stimulations caused an error).

As a second step, we combined the results of fMRI and rTMS in a predefined protocol of combined non-invasive mapping. In order to validate this non-invasive protocol, we correlated its results to DCS during awake surgery.

Results: The analysis by different rTMS ERTs obtained the highest correlation regarding sensitivity and a low rate of false positives for the ERTs 15%, 20%, 25%, and the 2/3 rule.

However, when comparing the combined fMRI and rTMS results with DCS, we observed an overall specificity of 83%, a PPV of 51%, a sensitivity of 98%, and a NPV of 95%.

Conclusions: In comparison to fMRI, rTMS is a more sensitive but less specific tool for preoperative language mapping compared to DCS. Moreover, rTMS is most reliable when using ERTs of 15%, 20%, 25%, or the 2 out of 3 rule and a PTI of 0 ms. Furthermore, the combination of fMRI and rTMS leads to a higher correlation to DCS than both techniques alone, and the presented protocols for combined non-invasive language mapping might play a supportive and preliminary role in the language mapping assessment prior to the gold standard DCS.

Ethics Committee Registration Number: 2793/10

1 INTRODUCTION

The resection of tumors within or adjacent to language-eloquent brain regions is still a neurosurgical quest, and a profound presurgical workup is crucial to achieving the best functional and oncological result [6,68]. Today, the most precise way to localize individual language-eloquent regions is direct cortical stimulation (DCS) during awake craniotomy [9,12,26,43,44,52,59,62,71]. Using only DCS, however, we cannot provide the longitudinal non-invasive follow-up examinations that might enable us to include plastic reshaping of cortical language function in our oncological considerations [11,16,17,20,41,52,73].

Although we are gaining more and more information about the distribution of human language function and the associated networks, its mapping is still very complex and has to be further refined [10,16,30,45,52,62].

Thus, there is a need to assess functional cortical organization of language function by non-invasive methods. Navigated transcranial magnetic stimulation (nTMS) is one of these non-invasive techniques. Regarding the mapping of motor function, nTMS has already demonstrated its usefulness for clinical practice [22,32,34,50,51,74]. Furthermore, repetitive navigated TMS (rTMS) and non-navigated TMS are able to localize cortical language function [18,19,39,47,66,77]. Its clinical applicability and correlation to DCS during awake surgery have repeatedly been shown as well [35,36,65,72]. Although rTMS language mapping has already experienced some improvement [39], the standard for preoperative, non-invasive language mapping remains functional magnetic resonance imaging (fMRI) [21]. Yet this technique, though well-established, has failed to provide reliable preoperative language mapping, showing only minor correlation with intraoperative DCS [24,55,79]. Another study regarding the localization of language and motor areas by fMRI has confirmed the selection of a more aggressive therapeutic approach for the use of preoperative fMRI [48]. On the other hand, a review of studies for the preoperative mapping of language function by fMRI has concluded that the effect on surgical planning is to be the only approved clinical use and that even this technique has to be further investigated [4].

Thus, this study has been designed to investigate how the results of rTMS language mapping have to be analyzed to find the highest correlation with DCS, and to refine this promising and in this field aspiring technique to play a supportive role towards a multimodal approach in the future. Moreover, and with the same purpose, we have evaluated the data to create a protocol for non-invasive language mapping by the combination of rTMS and fMRI and correlated its results to intraoperative DCS as well.

2 MATERIAL AND METHODS

2.1 Ethics approval

The experimental setup was approved by the local ethical committee of our university in accordance to the Declaration of Helsinki (Ethics committee registration number: 2793/10). All patients provided written informed consent to this study before rTMS.

2.2 Study design

The study was designed to be prospective and non-randomized.

2.3 Patients

The study was conducted on 35 consecutive patients (22 male, 13 female) with left-sided perisylvian brain lesions. Inclusion criteria were the presence of a left-sided perisylvian brain lesion, planned awake craniotomy, an age of at least 18 years, and signed informed consent.

Exclusion criteria were general TMS exclusion criteria, such as pacemaker or cochlear implant [54], as well as severe aphasia and an age below 18 years.

All patients were scheduled for awake craniotomy in our neurosurgical department between April 2011 and January 2014, and all of them underwent preoperative language mapping by rTMS. Additionally, 27 patients (17 male, 10 female) were preoperatively examined by fMRI using an object naming paradigm (Table 1). Moreover an aphasia grading adapted from the Aachener Aphasia Test was done 3 times: before operation, the 5th day after surgery, and 3 months after surgery [28]. All lesions were located in the left-hemispheric perisylvian brain regions, and 32 patients were right-handed. Table 1 gives an overview on the patient cohort including age, aphasia, and tumor location. To some extent, the data of some of these patients have already been part of former studies [35,36,65].

Patient No.	Age (years)	Tumor type	Lesion location	Mapping techniques			Aphasia grading		
				DCS	fMRI	rTMS	Pre-OP	5th POD	3rd POM
1	25	C	trIFG	yes	yes	yes	0	0	0
2	28	AA	anG	yes	yes	yes	0	1A	0
3	62	GBM	opIFG	yes	yes	yes	0	0	0
4	56	AA	mMTG	yes	yes	yes	0	3B	2A
5	53	AA	pMTG	yes	yes	yes	0	0	0
6	43	GBM	opIFG	yes	yes	yes	1A	1A	1A
7	51	GBM	anG	yes	yes	yes	2B	2B	2B
8	50	GBM	anG	yes	yes	yes	2A	3A	1A
9	51	GBM	vPrG	yes	yes	yes	1A	2A	0
10	40	GBM	pSTG	yes	yes	yes	2B	0	0
11	34	C	mMFG	yes	yes	yes	0	0	0
12	63	DA	pSTG	yes	yes	yes	1B	2B	1B
13	47	GBM	pMTG	yes	yes	yes	2B	2B	2B
14	56	GBM	pMTG	yes	yes	yes	0	2A	0
15	47	AA	aSMG	yes	yes	yes	1B	2B	0
16	33	GBM	mSTG	yes	no	yes	0	3A	0
17	53	GBM	opIFG	yes	yes	yes	1A	2A	1A
18	32	C	anG	yes	no	yes	3A	0	0
19	47	GBM	opIFG	yes	yes	yes	0	0	0
20	52	GBM	opIFG	yes	no	yes	2A	2A	2A
21	43	DA	opIFG	yes	yes	yes	0	2A	0
22	30	AA	anG	yes	yes	yes	1A	1A	0
23	48	GBM	opIFG	yes	yes	yes	0	2A	1A
24	74	GBM	aSTG	yes	yes	yes	2A	2A	--
25	41	AA	pSTG	yes	yes	yes	2B	1B	1B
26	47	GBM	anG	yes	yes	yes	1A	0	0
27	49	DA	opIFG	yes	yes	yes	0	1B	0
28	27	AVM	mSTG	yes	yes	yes	0	1A	0
29	66	DA	opIFG	yes	no	yes	0	1A	0
30	38	AA	opIFG	yes	no	yes	0	1A	0
31	33	OA	trIFG	yes	no	yes	0	0	0
32	31	GNT	vPrG	yes	no	yes	0	0	0
33	51	GBM	vPrG	yes	yes	yes	2A	1A	1A
34	24	DA	mPrG	yes	yes	yes	0	0	--
35	27	GBM	anG	yes	no	yes	0	1B	--

Table 1: Patient characteristics: *Patient characteristics include each patient's aphasia grading, tumor type, and mapping techniques. Abbreviations: AA = anaplastic astrocytoma WHO grade III; AVM = arteriovenous malformation; C = cavernoma; DA = diffuse astrocytoma WHO grade II; GBM =*

glioblastoma WHO grade IV; GNT = glioneural tumor WHO grade I; OA = oligoastrocytoma WHO grade III;

Aphasia grading: 0 = no aphasia, 1 = mild aphasia, 2 = moderate aphasia, 3 = severe aphasia, A = predominantly motor impairment, B = predominantly sensory impairment.

2.4 Navigational MRI scan

All patients received a navigational MRI scan on a 3 Tesla MR scanner (Achieva 3T, Philips Medical System, The Netherlands B.V.) using an 8-channel phased array head coil. The protocol contained a three-dimensional (3D) gradient echo sequence (TR/TE 9/4 ms, 1 mm^3 isovoxel covering the whole head, 6-minute 58-second acquisition time) and an intravenous contrast administration of 0.1 mmol/kg body weight gadopentetate dimeglumine (Magnograf, Marotrast GmbH, Jena, Germany) for anatomical co-registration. This 3D dataset was then used for the preoperative rTMS language mapping and for the intraoperative neuronavigation [64,65].

Besides these sequences, the scanning protocol contained a T2 FLAIR (TR/TE 12,000/140, inversion time of 2,500 ms, 30 slices with 1 mm gap, voxel size 0.9 × 0.9 × 4 mm, 3 min acquisition time).

2.5 Preoperative fMRI language mapping

For blood-oxygen-level-dependent (BOLD) functional imaging (fMRI), each subject underwent an fMRI object naming task. The sequence parameters were as follows. For fMRI, the echo planar imaging was performed with the following parameters: the train length was 43 ms, with a TR of 2500 ms and a TE of 35 ms. Within 2 minutes and 53 seconds, 64 dynamic sets were acquired, each consisting of 32 contiguous axial 4 mm slices with an in-plane resolution of 2.75 mm × 2.75 mm. Parallel imaging (SENSE) was used to diminish susceptibility-related artifacts (SENSE factor 2).

After the examination, the fMRI data were transferred to an external workstation (Extended MR Workspace, Philips Medical Systems, The Netherlands B.V.) and were post-processed by the IViewBOLD package blinded to the rTMS results. After motion correction and spatial smoothing (2D Gaussian filter with 4 mm FWHM, kernel 2×2 pixel) statistical parametric maps were generated by use of the general linear model. We chose a hemodynamic delay of 2 × TR, a single predictor, and a t-value threshold of 2.5. Only clusters with positive correlation, bigger than 40 voxels in size, were considered to be activated areas. The validity of the results was checked by review of the time-intensity diagrams of the activated voxels, as also described before [33,65].

2.6 Preoperative rTMS language mapping

2.6.1 Experimental setup

The rTMS language mapping was conducted with nTMS eXimia NBS version 3.2.2 and Nexstim NBS 4.3 with a NEXSPEECH® module (Nexstim Oy, Helsinki, Finland), as described earlier [65,72]. First, the 3D T1-weighted MRI scan of each patient and the patient's head were coregistered. The stimulated brain area during the examination was visualized by a stereotactic camera and reflectors fastened to the patient's head with an elastic strap to track the coil position [65]. The induced electric field in the brain was visualized over the 3D reconstruction, and the intracranial stimulation points were saved for later examination [29,56]. After the coregistration, the individual patient's resting motor threshold (RMT) was defined by motor mapping of the cortical representation of the contralateral abductor pollicis brevis muscle, as also published before [33]. This RMT was then used as a basic value for the rTMS mapping procedure, using an object naming task, consisting of 131 colored pictures of common objects [39,65]. The pictures were displayed with an interpicture interval (IPI) of 2.5 s. As already described before, the individual mapping frequency and intensity was defined by using our standard protocol [47,64,65]:

1. RMT in the left hemisphere was determined thoroughly;
2. A train of 5 to 7 rTMS bursts was administered to vPrG and opIFG:

a) 5 Hz, 5 pulses, 100% RMT,

b) 7 Hz, 5 pulses, 100% RMT,

c) 7 Hz, 7 pulses, 100% RMT;

3. The setup (a–c) that caused the most language errors was identified by the patient's and examiner's impressions and in unclear cases supported by video analysis;
4. If there was no clear difference in the effect on language, the most comfortable frequency was chosen;
5. If naming was not interrupted clearly by rTMS, the intensity was increased to 110–120% RMT, and step 1 was repeated; and
6. If significant pain was reported, the stimulation intensity was lowered to 80–90% RMT to avoid any discomfort that might interfere with the consecutive-response evaluation [19]. This was also done if 100% RMT was painful.

The display time (DT), the time the pictures were presented on the screen, was 700 ms. Another parameter for the variation of rTMS language mapping is the picture-to-trigger interval (PTI). The PTI describes the time between the presentation of the stimulus on the screen and the onset of the rTMS burst. Twenty-five patients were examined with a

PTI of 300 ms, and 10 patients were examined with a PTI of 0 ms. There is evidence in former studies for the justification of both PTIs [30,53,60,78]. Thus, our protocol was modified after 25 patients.

2.6.2 TMS language mapping procedure

Before rTMS language mapping, the baseline recording was performed twice without stimulation to adapt the picture data set to the individual vocabulary. The patients had to name the presented pictures in their mother tongue as quickly and precisely as possible, and the number of baseline errors was documented for each patient. Misnamed pictures were discarded. The remaining pictures were presented time locked to a train of rTMS pulses, and the stimulation coil was randomly moved in between the visual display of two images. To achieve maximum field induction, the coil was placed perpendicular to the skull [39] and 80 to 120 sites were stimulated thrice each with a distance of approximately 10 mm. Minimum cortical field strength of the induced electric field was 55 V/m.

For later detailed and objective analysis, the baseline performance and the stimulation trials were video recorded [39].

2.6.3 TMS data analysis

First, the videorecorded rTMS language mappings were analyzed in comparison with the baseline performance. The detected language errors were documented and categorized into seven groups: no responses, performance errors, hesitations, neologisms, semantic paraphasias, phonologic paraphasias, and circumlocutions [9,64]. Language errors related to muscle stimulations or pain were discarded.

To ensure that the evaluation was performed objectively, we analyzed the mappings blinded to the stimulation sites or the tumor location [36,39,65]. After the video analysis, the detected language errors sorted by error type were assigned to the cortical parcellation system (CPS) as published by Corina et al. [8]. Figure 1A shows the CPS, including the abbreviations of the mapped cortical regions. The abbreviations are further explained in Table 2. The next step was to calculate the error rates (ERs). The ERs were calculated for each area of the CPS, defined by the number of errors per number of stimulations [35,65]. Moreover, each area of the CPS was analyzed regarding the 2-out-of-3 rule (2/3 rule). As already mentioned, each stimulation site was stimulated thrice. A CPS region was defined as language-positive in terms of the 2/3 rule if at least 2 out of 3 stimulations caused a predefined language error [26,62].

Subsequently, the rTMS raw data were analyzed with 12 error rate thresholds (ERTs). The ERT is defined as the ER at which a CPS region has been defined as language-positive in terms of TMS. The 12 ERTs were determined ongoing from 0%, in 5% steps, to 50% of stimulations (ERTs >0%, ≥5%, ≥10%, ≥15%, ≥20%, ≥25%, ≥30%, ≥35%, ≥40%, ≥45%, ≥50%) and the 2/3 rule.

2.7 Language mapping during awake craniotomy

2.7.1 Setup

A mixture of bupivacaine and epinephrine was used for local anesthesia of galea and dura. By continuous infusion of remifentanil and propofol, an adequate level of anesthesia and sedation was maintained. The patient’s head was fixed in a Mayfield clamp, the reflector for navigation was attached to it, and a neuronavigation system

(BrainLAB Vectorvision Sky® or BrainLAB Curve®, BrainLAB AG, Feldkirchen, Germany) was used to locate the surgical tools and the cortical stimulation electrode based on the same 3D MRI used during the rTMS session.

Ten minutes before language mapping, analgesia and sedation were discontinued. Regarding the wakefulness, a Ramsay sedation score of 2 (patient awake, calm, cooperative) was targeted for the language mapping procedure. After completion of cortical mapping, the operation was continued under conscious sedation [49].

2.7.2 Language mapping procedure

The cortical stimulation was performed with a bipolar-stimulation electrode (distance of 5 mm, Inomed Medizintechnik GmbH, Emmendingen, Germany). The stimulation intensity was between 0 and 20 mA, with a frequency of 50 Hz and duration of 4 seconds. The stimulation sites were placed 5 to 10 mm apart, and a surface electroencephalogram with a bandpass filter of 10 Hz to 1.5 kHz was recorded in order to detect epileptic seizures. For the intraoperative mapping by DCS and the preoperative mapping by rTMS the same pictures were used, with the difference of starting the object naming during operation with the matrix sentence “This is a …” [31]. The cortical sites were stimulated thrice, and a site was considered language-positive if at least 2 out of 3 stimulations led to a language error. Thus the 2/3 rule was used. The positive sites were marked with letters and were transferred to the navigation system using the navigation pointer [43,49,65].

2.8 Data analysis

2.8.1 Anatomical localization

The 37 regions of the CPS as defined by Corina et al. were used to compare the results of the different techniques of language mapping and to provide sufficient statistical data to compare the methods (Fig. 1A)[8]. First, the positive and negative language sites of the intraoperative mapping by DCS were assigned to the CPS. The stimulated sites, then transferred to the neuronavigation system by the navigation pointer, could be located exactly in a 3D environment for further analysis.

After the video analysis, the rTMS-induced language errors were matched with the associated stimulation sites on the 3D MRI. This was separately done for the 12 ERT groups (0% ERT to 50% ERT in 5% steps and by the 2/3 rule).

The positive language sites examined by fMRI with an object-naming task were anatomically located through the coronal, sagittal, and axial slices, which were fused with the BOLD signal. They were assigned to the CPS as well. In order to compare the overall results of rTMS and DCS with fMRI language mapping, we calculated an activation rate (AR) by the total number of positive BOLD signals per number of patients who performed fMRI language mapping (27).

2.8.2 Stimulation assessment for the comparison of rTMS and DCS

Representing the gold standard, the results of DCS's intraoperative language mappings provided the *ground truth* for every comparison. For the comparison of rTMS and DCS language mapping, the results of both methods were assigned to the CPS separately for each patient. Then the raw data for calculating the receiver operating characteristics (ROC) were created as follows: if a CPS region gave rise to language positivity during

DCS and rTMS mapping (according to the chosen ERT), the region was documented as a true positive for this patient. If both mappings indicated this region to be language-negative, it was documented as a true negative. When rTMS mapping led to an ER above the respective ERT in the corresponding CPS region but the DCS mapping did not, the CPS region was defined as a false positive for this patient. Moreover, a CPS region was documented as a false negative when the region's DCS mapping led to language errors but the ER was below the ERT during rTMS mapping.

For the definition of language positivity and negativity in terms of rTMS, we used the different ERTs. For a better understanding, we provide some examples: For the analysis with an ERT of 0%, a CPS region was counted as language-positive in terms of rTMS if any stimulation of this region elicited a language error. For the comparison of DCS to rTMS with an ERT of 5%, the CPS regions were taken as language-positive only if the ER was at least equal to 5% percent. In the same way, the ROCs were also calculated up to an ERT of 50%. Moreover, we used the 2/3 rule as an ERT.

Ten rTMS language mappings were performed with a PTI of 0 ms, and 25 patients were mapped with a PTI of 300 ms. Therefore, we additionally compared these two groups to each other with the objective of detecting the optimal PTI in combination with different ERTs.

2.8.3 Comparison of fMRI and DCS

After assigning the results of fMRI language mapping to the CPS, we compared them with the language sites defined by DCS as well, in the same manner in which we had compared the results of rTMS and DCS. Once more, we took the DCS data as gold standard and compared the corresponding results of each patient and each region of the CPS. According to the comparison of rTMS and DCS, we documented the true positives and negatives, but without using an ERT. For example, if a CPS region was language-positive during DCS mapping without a positive BOLD signal, we defined the region as a false negative in terms of fMRI for this patient; conversely, if a CPS region was language-negative by DCS and language-positive by fMRI, we counted this region as a false positive in terms of fMRI.

2.8.4 Statistical analysis

For statistical analysis of the various comparisons, we summed up the obtained results of each patient, viz. the true and false positives and the true and false negatives and calculated the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). This we did separately for each region of the CPS [65].

To visualize and interpret the preserved data with the aim of figuring out an optimal protocol for the analysis of rTMS and for combined non-invasive language data, we issued ROC curves for all distinct kinds of analysis. In these ROC curves the sensitivity (y axis) is graphed against the formula *1 – specificity* (x axis) [37].

3 RESULTS

3.1 Single results of DCS, rTMS, and fMRI language mapping

Figure 1 outlines the total number of language-positive sites obtained by DCS (B) and rTMS (C), as well as the total number of stimulations implemented by the respective mapping technique in all patients. Accordingly, Figure 1D shows the total number of positive BOLD signals per CPS region in all patients.

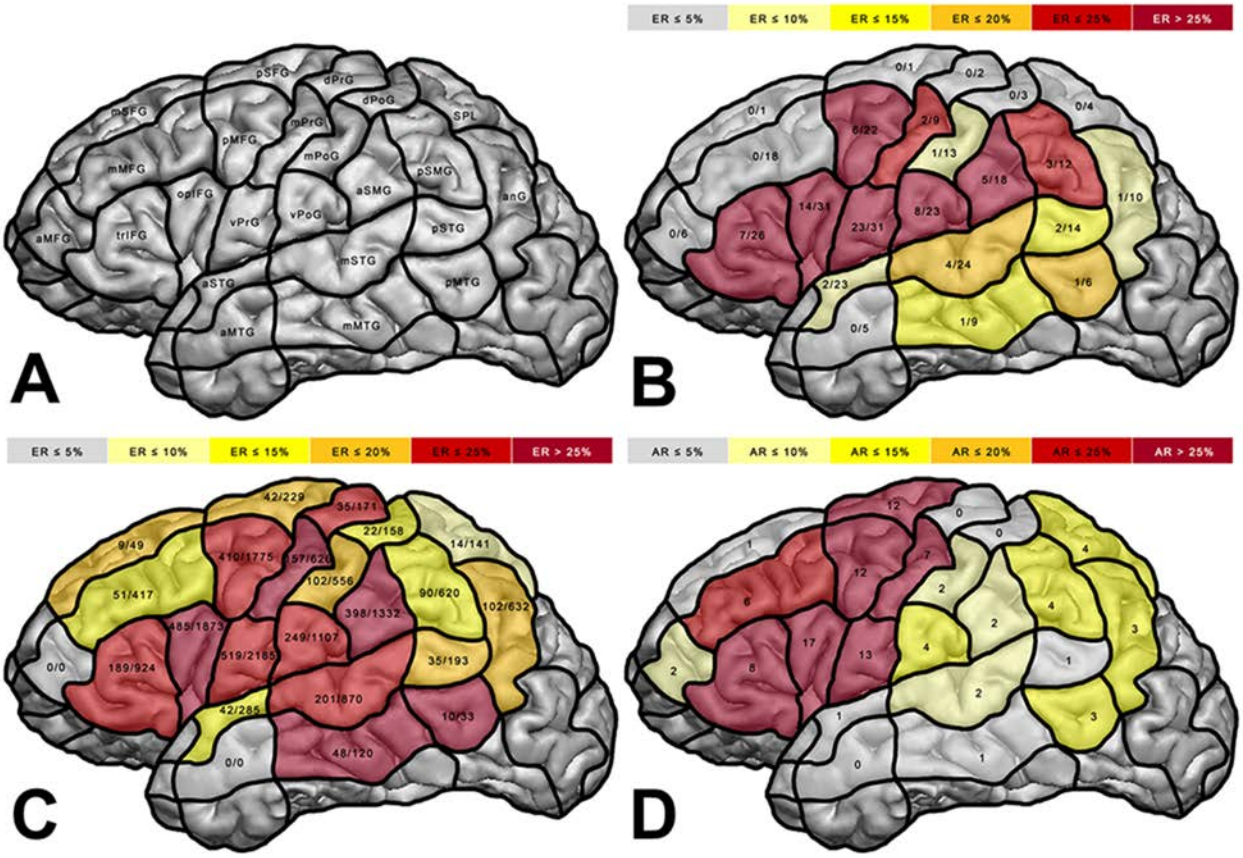

Fig. 1: CPS and total number of errors per stimulations and activations of each method: *Figure 1 (A) shows the CPS known from Corina [8], including the abbreviations of the mapped regions. The abbreviations are explained in Table 2. For DCS (B) and rTMS (C) language mapping we illustrate the total number of errors per stimulations for each CPS region, highlighted by the respective color of the associated ER. For fMRI (D) language mapping we demonstrate the total number of positive BOLD*

signals. The related AR is calculated by the total number of positive BOLD signals per number of patients who performed fMRI language mapping.

Abbreviation	Anatomy
aMFG	Anterior middle frontal gyrus
aMTG	Anterior middle temporal gyrus
anG	Angular gyrus
aSMG	Anterior supramarginal gyrus
aSTG	Anterior superior temporal gyrus
dPoG	Dorsal post-central gyrus
dPrG	Dorsal pre-central gyrus
mMFG	Middle middle frontal gyrus
mMTG	Middle middle temporal gyrus
mPoG	Middle post-central gyrus
mPrG	Middle pre-central gyrus
mSFG	Middle superior frontal gyrus
mSTG	Middle superior temporal gyrus
opIFG	Opercular inferior frontal gyrus
pMFG	Posterior middle frontal gyrus
pMTG	Posterior middle temporal gyrus
pSFG	Posterior superior frontal gyrus
pSMG	Posterior supramarginal gyrus
pSTG	Posterior superior temporal gyrus
SPL	Superior parietal lobe
trIFG	Triangular inferior frontal gyrus
vPoG	Ventral post-central gyrus
vPrG	Ventral pre-central gyrus

***Table 2: Abbreviations of the cortical parcellation system:** Abbreviations of the anatomical cortical areas according to the cortical parcellation system (CPS) [8].*

3.2 Comparison of rTMS and DCS language mapping

The mapping data of the two methods overlapped in 19 regions of the CPS. In total, we compared rTMS and DCS language mapping in 252 regions. Depending on the rTMS ERT, the true-positive results ranged from 28% (ERT 0%) to 3% (ERT 50%). As expected, the true-negative results increased from 10% (ERT 0%) to 68% (ERT 50%). Thus, the false-positive results decreased from 62% (ERT 0%) to 3% (ERT 50%).

According to the decrease of true-positive results due to an enhanced ERT, the false-negative results increased from less than 1% (ERT 0%) to 26% (ERT 50%). The overall ROC values for this comparison are illustrated in Table 3.

rTMS ERT	2/3 rule	≥0%	≥5%	≥10%	≥15%	≥20%	≥25%	≥30%	≥35%	≥40%	≥45%	≥50%
PPV	34%	31%	31%	32%	30%	31%	33%	31%	35%	39%	45%	47%
NPV	79%	92%	84%	81%	74%	73%	74%	72%	73%	73%	73%	73%
Sensitivity	67%	97%	92%	83%	63%	47%	40%	25%	18%	17%	13%	10%
Specificity	49%	13%	18%	28%	43%	58%	67%	78%	87%	89%	94%	96%

Table 3: ROC for the comparison of rTMS (0 & 300 ms PTI) and DCS language mapping: *This table shows the sums of all mapped CPS regions for positive predictive value (PPV), negative predictive value (NPV), sensitivity, and specificity for the comparison of rTMS and DCS language mapping as functions of the rTMS error rate threshold (ERT). The rTMS data for these calculations include both the 0 ms and the 300 ms picture-to-trigger interval (PTI) groups.*

In addition, we compared the results of rTMS language mapping performed with a PTI of 0 ms or 300 ms. In comparison with DCS, we achieved the highest sensitivity and the lowest rate of false positives by using an ERT of 15%, 20%, 25%, and the 2/3 rule in combination with a PTI of 0 ms (Fig. 2, Table 4).

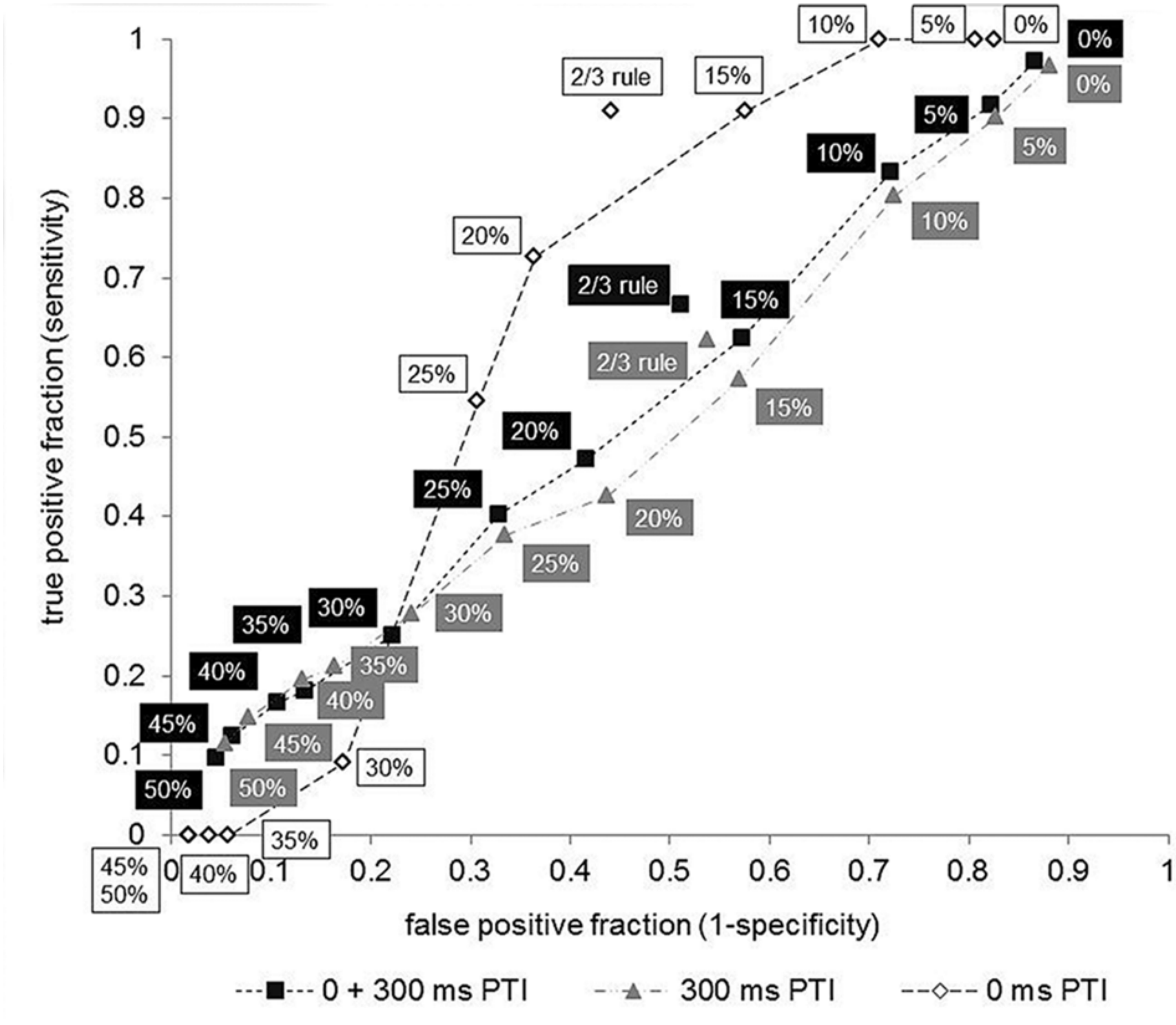

Fig. 2: ROC curves for the comparison of PTI: *The Figure illustrates the results for the comparisons of rTMS language mapping performed with a PTI of 0 ms and/or 300 ms with DCS language mapping. The associated boxes describe the respective rTMS ERTs.*

rTMS ERT	**2/3 rule**	**≥0%**	**≥15%**	**≥20%**	**≥25%**	**≥50%**
PPV	30%	20%	25%	30%	27%	0%
NPV	97%	100%	96%	92%	88%	82%
Sensitivity	91%	100%	91%	73%	55%	0%
Specificity	56%	17%	42%	63%	69%	98%

Table 4: ROC for the comparison of rTMS (0 ms PTI) and DCS: *This table highlights the results regarding the correlation of a high sensitivity and a low rate of false positives for the comparison between rTMS language mapping performed with a PTI of 0 ms and DCS language mapping.*

3.3 Comparison of fMRI and DCS language mapping

Across the 27 patients who were additionally examined by fMRI using an object naming paradigm, the data overlapped with the intraoperative results in 22 regions of the CPS and we compared these two methods in 258 regions altogether. In 11% of these comparisons we yielded a true-positive result and in 61% a true-negative result. Furthermore, we obtained false-positive results for 12% and false-negative results for 16% of the comparisons. Subsequently, we calculated the ROCs for this comparison (Table 5). In comparison with rTMS language mapping with an ERT of 0% (Table 3), Table 5 shows the key advantages of fMRI language mapping reflected in its specificity.

PPV	48%
NPV	79%
Sensitivity	40%
Specificity	84%

Table 5: ROC for the comparison of fMRI and DCS: *This table outlines the comparison of fMRI and DCS language mapping.*

3.4 Additional analysis protocols for combined non-invasive language mapping

3.4.1 Protocol

In order to combine the strengths of rTMS (high sensitivity and NPV) and fMRI language mapping (high specificity), we combined the results of both methods, using two distinct protocols for a combined non-invasive language mapping. The objective of the additional analysis protocol 1 (A1) was to decrease the false-positive results of rTMS language mapping by qualifying them with fMRI negative results. In contrast, the objective of the additional analysis protocol 2 (A2) was to decrease fMRI's false-negative results by qualifying them with rTMS positive results. Table 6 gives a detailed overview of the adapted rules for both protocols. To evaluate the effect of the protocols, we compared the created assertions about language positivity and negativity A1 and A2 with the results of DCS language mapping.

	result of rTMS	**result of fMRI**	**definition in additional analysis protocol**
protocol A 1	+	+	A1-positive
	-	-	A1-negative
	+	-	A1-negative
	-	+	A1-negative
protocol A 2	+	+	A2-positive
	-	-	A2-negative
	+	-	A2-positive
	-	+	A2-positive

Table 6: Definitions of the protocols for additional analysis: *This table gives an overview of the rules for the two protocols with the intent of a combined non-invasive language mapping protocol. The objective of protocol 1 was to decrease rTMS false-positive results by qualifying them with fMRI negative results. The objective of protocol 2 was to decrease fMRI false-negative results by qualifying them with rTMS positive results.*

3.4.2 Results

Equally to the comparison of rTMS and DCS language mapping and the comparison of fMRI and DCS language mapping, in this comparison, too, the DCS results were taken as gold standard for the calculation of the ROCs (Table 7). Moreover, we demonstrate the single results of each mapped CPS region regarding specificity and NPV for protocol 1 (Fig. 3B & D) and sensitivity and PPV for protocol 2 (Fig. 3A & C). According to the comparison of rTMS with DCS (Table 3), and in order to be more comparable with the comparison of fMRI with DCS (Table 5), the single results of Figure 3 are analyzed with an ERT of 0%.

Again, we observed the highest correlation to the results of DCS language mapping, regarding a high sensitivity and a low rate of false positives, for the combination of fMRI data and the results of rTMS language mappings performed with a PTI of 0 ms and an ERT of 20% (Fig. 4).

A)

rTMS ERT	2/3 rule	≥0%	≥5%	≥10%	≥15%	≥20%	≥25%	≥30%	≥35%	≥40%	≥45%	≥50%
PPV	55%	51%	50%	52%	54%	52%	63%	70%	75%	71%	67%	67%
NPV	75%	76%	75%	75%	74%	72%	72%	71%	71%	71%	70%	70%
Sensitivity	33%	41%	38%	36%	30%	20%	19%	11%	9%	8%	6%	3%
Specificity	88%	83%	83%	85%	89%	92%	95%	98%	99%	99%	99%	99%

B)

rTMS ERT	2/3 rule	≥0%	≥5%	≥10%	≥15%	≥20%	≥25%	≥30%	≥35%	≥40%	≥45%	≥50%
PPV	35%	34%	34%	34%	34%	36%	38%	40%	43%	44%	48%	48%
NPV	77%	95%	89%	82%	75%	76%	76%	76%	76%	76%	77%	77%
Sensitivity	73%	98%	95%	88%	72%	66%	61%	55%	50%	50%	48%	48%
Specificity	40%	13%	17%	25%	37%	48%	55%	63%	70%	72%	76%	77%

Table 7: ROC for protocol 1 and 2: *The tables show the results for the combined fMRI/rTMS language mapping according to protocol 1 (A) and protocol 2 (B) compared with DCS language mapping. The data include the results of all mapped CPS regions and both PTI groups.*

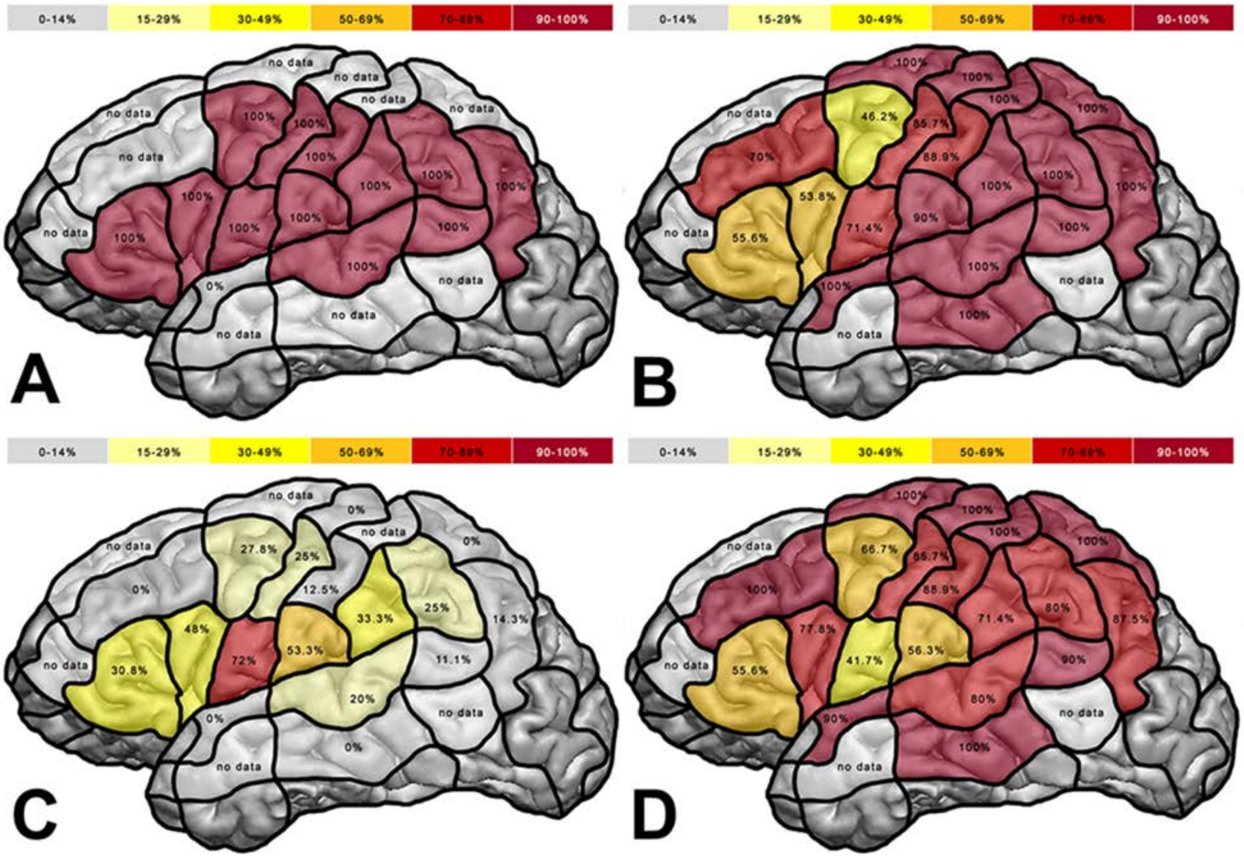

Fig. 3: Combined fMRI/rTMS (ERT 0%, 0 ms & 300 ms PTI) language mapping compared with DCS: *The schemes show the results for each mapped CPS regions for the comparison of combined fMRI/rTMS language mapping against DCS language mapping. For protocol 1 we demonstrate specificity (B) and NPV (D). The schemes for protocol 2 show sensitivity (A) and PPV (C). The TMS part of both protocols has been analyzed with an ERT of 0%, and the results include both PTI groups (0 ms & 300 ms PTI).*

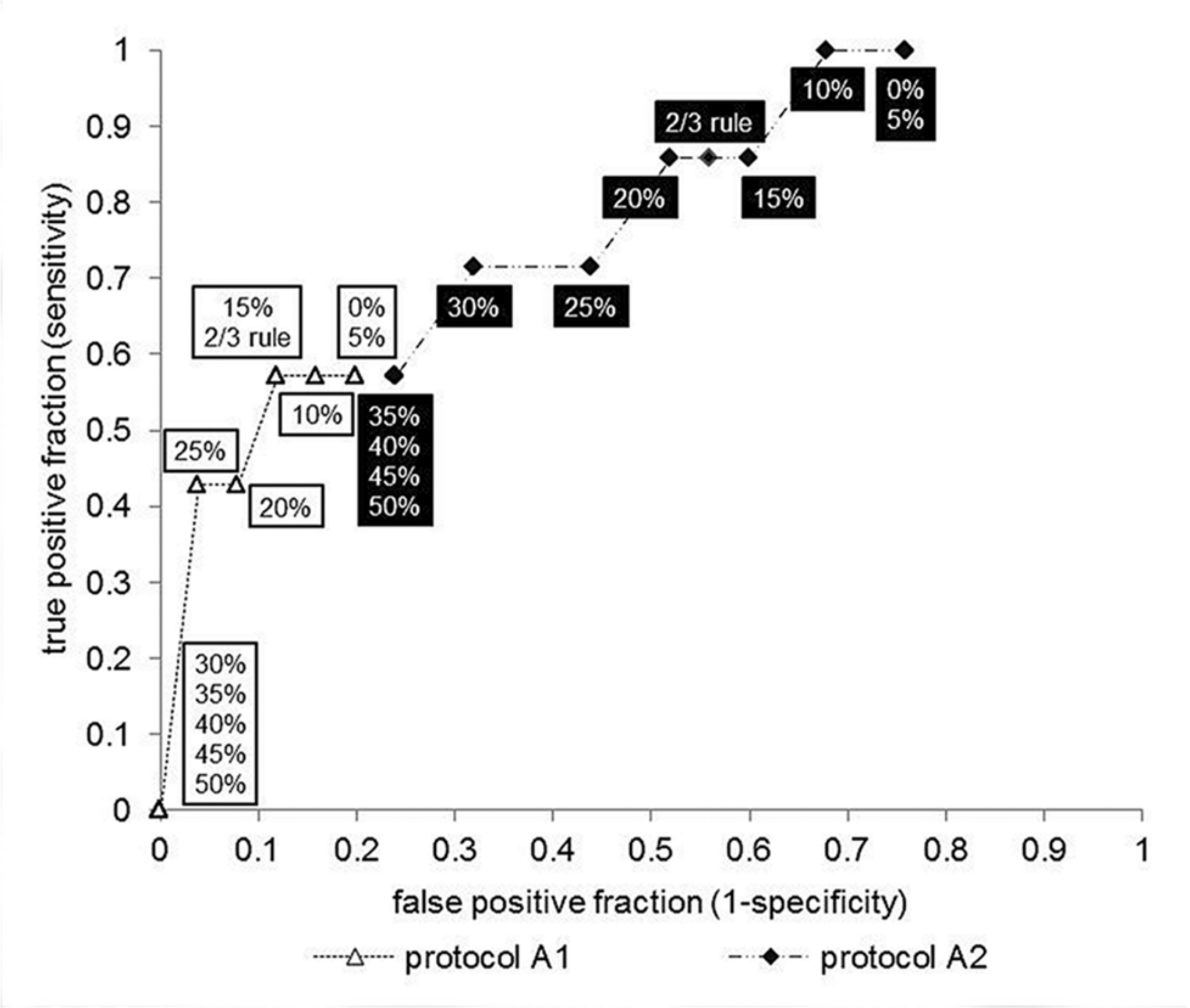

Fig. 4: ROC curves for combined non-invasive language mapping: *The figure shows the ROC curves for the comparison of protocol 1 and 2 with DCS language mapping. The rTMS language mappings leading to these results were performed with a PTI of 0 ms. The associated boxes describe the rTMS ERTs.*

4 DISCUSSION

4.1 rTMS vs. DCS language mapping

Most importantly, it has to be stressed that the results of DCS are absolutely essential for language mapping in patients with left-sided perisylvian brain lesions and for brain mapping in its entirety. It should not be the aim to replace this gold standard, but to improve and advance the encouraging non-invasive technique rTMS in respect of playing a supportive role within the preoperative assessment. For clinical usefulness, either the combination of a high specificity and NPV for the mapping of language-negative sites or the combination of a high sensitivity and PPV for the mapping of language-positive sites seems applicable. While negative mapping is sufficient for neurosurgical applications, positive mapping has to be aimed at for a general use in neuroscience [30,65]. The most basic difficulty of rTMS language mapping is determining language-positive sites accurately, at least in comparison with DCS. The constellation of a high sensitivity (overall (PTI 0 & 300 ms) 97%, PTI 0 ms 100%) but a low PPV (overall (PTI 0 & 300 ms) 31%, PTI 0 ms 20%) using an ERT of 0% does not give sustainable information for neurosurgeons in the operating room and for basic researchers, respectively (Table 3 & 4). In other words, rTMS language mapping is currently too sensitive for the mapping of language-positive sites. Most likely this is because it identifies not only language-eloquent but also language-involved cortical areas in general.

Like former studies, however, which compared the results of preoperative rTMS language mapping with DCS during awake surgery, we revealed high sensitivity and NPV with an ERT of 0% (Table 3) [36,65,72]. Most importantly, when regarding current protocols for DCS language mapping during awake surgery, some authors also rely only on negative language mapping intraoperatively [61,72]. In this respect, the absence of false negative results, as revealed for rTMS language mapping performed with a PTI of 0 ms and analyzed with an ERT of 0%, is of paramount importance (Table 4)[15]. Thus, the high sensitivity and NPV of our presented protocol seem already applicable in the daily clinical routine [36]. These values promise very reliable negative results and accordingly enable a more extensive resection, which has proved crucial in neurooncology [6,68]. In addition, our analysis of different ERTs shows that rTMS provides sufficient negative language maps (specificity: overall (PTI 0 & 300 ms) 96%; PTI 0 ms 98% and NPV overall (PTI 0 & 300 ms) 73%; PTI 0 ms 82%) compared with DCS language mapping, by analyzing the results with a high ERT (≥50%) (Fig. 2, Table 3 & 4).

Even particularly with regard to negative language mapping, because of the increase of true-negative results, we could show a reduction of false-positive results by performing rTMS language mapping with a PTI of 0 ms according to a recent report [30]. We therefore compared rTMS language mapping with PTIs of 0 ms and 300 ms. The obviously higher correlation of the immediate rTMS stimulation beginning at the same time as the picture presentation could confirm other non-invasive data (Fig. 2, Table 3 & 4) [30]. This analysis showed the highest correlations for sensitivity, combined with a low rate of false-positive results and a high NPV, using ERTs of 15% (sensitivity 91%, NPV 96%), 20% (sensitivity 73%, NPV 92%), 25% (sensitivity 55%, NPV 88%), and the 2/3 rule (sensitivity 91%, NPV 97%) (Fig. 2, Table 4). These ERTs should be the basis for further research to refine the promising method of rTMS in language mapping.

Nevertheless, for the comparison of rTMS and DCS language mapping, the occurrence of false-positive results has to be discussed. But are these false positives truly false positives? Yes, they are, regarding the wealth of experience of DCS and its status as the gold standard for the detection of language-eloquent brain regions [7,9,26,43,44,59,62]. Non-invasive mapping techniques for identifying human language function have to compete with results mapped during awake surgery. Having no other modalities, however, we still do not know exactly the role played by these DCS-identified language-positive points. Since resection of these areas is associated mostly with a consecutive and at least transient language deficit, we have to name them language-eloquent [16,23,40,52]. Since rTMS is very sensitive, language-positive cortical areas as identified by rTMS are most likely not only language-eloquent but also involved in language function in general. This can also be taken into account regarding the false-positive results of rTMS language mapping. The high sensitivity concerning language-involved regions might also be reflected in the evocation of language errors in CPS regions defined as language-negative by DCS. The rTMS ERs of these regions are largely on an intermediate level, while relatively few stimulations were delivered to them by DCS. Additionally, the distribution of CPS regions with a high ER is similar in both the rTMS and DCS language map (Fig. 1B & C). Yet, this explanation of false-positive results and high ERs can only be contemplated for the total language maps, since the overall rate of false-positives is calculated by the sums of results of all patients. Nevertheless, both techniques operate on the same theory - the “virtual lesion” - and rTMS has already proved effective concerning language tasks [14,19,75,78]. In other words, rTMS language mapping is already feasible, but there are some differences regarding the comparison with DCS language mapping.

Furthermore, the classical distribution of human language function to Broca’s and Wernicke’s areas is no longer current, and it is even not definitely resolved how essential these two regions are [2,5,43]. Several studies assume and partially prove that human language function is organized in a complex network with the possibility of reorganization [10,16,30,45,52]. In this context it may be appropriate to ask whether rTMS maps language function more precisely than DCS. It is definitely easier to analyze language errors using the video data recorded during rTMS language mapping than to detect language errors in the operating room, although the neuropsychologist can concentrate exclusively on evaluating language performance during awake surgery. For the analysis of rTMS language mapping, unclear sequences can be reviewed several times; in comparison with baseline, moreover, the pronunciation is more distinct, and the setting is less stressful for the patient. This may be a reason for the occurrence of errors in rTMS language maps, which perhaps do not define essential language sites, but rather define regions participating in language-related networks which are involved in language production but may not be essential. Thus, applying rTMS to these stimulations may cause only minor but detectable language impairment. That the resection of some of these sites does not lead inevitably to a permanent postoperative deficit is comparable to the results of former studies concerning the resection of positive language sites defined by DCS [16,23,40,52,65].

Another difference may be the impact of rTMS on functional connectivity, since rTMS may affect subcortical pathways more significantly than bipolar DCS [17,25,40,61,70]. This may be a reason for rTMS's producing more false-positive results than DCS. On the other hand, the subcortical affection by rTMS may be an approach toward the mapping of language-positive sites in the future. To enable a safer resection by preoperative mapping even of deeper-located parts, the subcortical affection should be verified by the results of diffusion tensor imaging fiber tracking (DTI-FT), even if this technique has to be further investigated, too [15,38].

4.2 Combined fMRI and rTMS language mapping

Despite rTMS language mapping's already encouraging results in comparison with DCS, especially with a PTI of 0 ms, we combined the results of rTMS and fMRI language mapping. This combination was to combine the advantages of each method based on the two methods' respective comparisons with DCS language mapping. In addition to the already mentioned results of rTMS, we revealed a high specificity (84%) for the comparison of fMRI and DCS, as other studies had done before [55] (Table 3 & 5).

The objective of protocol 1 was to decrease rTMS's false-positive results (Table 6). On the one hand, specificity and PPV greatly increased, since many of the initially false-positive results could be unmasked as true negatives (Fig. 3B, Table 7A). But there was also a huge decrease in sensitivity and NPV in comparison with the sole use of rTMS (Table 3 vs. 7A, Fig. 3D). This result suggests that fMRI's negative spots additionally masked some of the rTMS's true-positive results. Nevertheless, as Figure 3B shows, protocol 1 provides sufficient negative language maps in comparison with DCS.

Accordingly, the effect of decreasing fMRI false-negative results by the use of protocol 2 is impressive regarding sensitivity and NPV compared with the sole use of fMRI language mapping (Fig. 3A, Table 5 vs. 7B). But as protocol 1 transferred some of the initially true-positive rTMS results into false negatives (Fig. 3D, Table 3 vs. 7A), protocol 2 transferred some of the fMRI's true-negative results into false positives (Fig. 3C, Table

5 vs. 7B). Even protocol 2, however, yields sufficient language maps to map negative sites (Table 7B).

At first view, the application of protocol 1 or 2 does not bring advantages in comparison with language mapping using rTMS alone. The mapping of language-negative sites renders comparable results for specificity and NPV for protocol 1 (Fig. 3B & D, Table 7A) and the sole use of rTMS language mapping with an ERT of 50% (Table 3). Yet the PPVs of protocol 1 are constantly equal to or higher than 50%, and even up to 75% (Table 7A). More importantly, the specificities of protocol 1 are higher than 80% across all ERTs. Thus, protocol 2 shows comparable results for sensitivity and NPV as well as rTMS language mapping alone (Table 3 vs. 7B, Fig. 3A). But the sensitivities do not decrease similarly, especially for higher ERTs.

Although several studies have found an incomplete match between fMRI and DCS language mapping, fMRI is still the most distributed modality for non-invasive language mapping [21,24,55,65,79]. This status similarly testifies an extensive experience, not least in the field of language mapping. Yet a review of studies about the mapping of language function by fMRI has concluded that even this well-established technique has to be further refined; another study has confirmed the selection of a more aggressive therapeutic approach [4,48]. Still, as other studies conclude, the results of fMRI and DCS will never completely agree, because the two methods have fundamental differences [57,65].

As already mentioned, the quest of mapping human language function lies in its complexity and associated networks. With our protocols for a combined non-invasive language mapping, we pay attention to this issue. The strength of fMRI is the visualization of cortical networks, whereas the mapping of language function by rTMS seems to be more targeted at a higher spatial resolution, as has been shown for cortical motor function [22,33]. The basic principle of fMRI is the assumption that task-related brain function and its related neural activity can be measured by the effect of increases in deoxyhemoglobin from activated neurons' consuming more oxygen. These BOLD signals therefore visualize activated cortical regions [42]. It has to be mentioned, however, that the destruction of a formerly activated region does not automatically cause a deficit in language function [17,24]. In contrast, rTMS mapping shows the effect of a temporary functional lesion in the depolarization and therefore inactivation of a designated brain region and the whole connected functional network [14,19,46,76,78]. A recently reported case shows fMRI and rTMS yielding contrary results, but the use of our protocols would make it possible to combine lesion-based and blood-flow-based techniques even in this case [65]. That these two principles can complement each other has already been shown in former studies [58,78]. Moreover, as other authors, in particular surgeons, suggest and already perform consecutive awake surgery on oncological patients, combined language mapping by fMRI and rTMS makes it possible to back this approach up and to support the oncological considerations by longitudinal non-invasive follow-up examinations for the inclusion of plastic reshaping of cortical language function [11,16,17,20,41,52,73]. Of course, the two protocols, being mutually exclusive, cannot be applied at the same time. Nevertheless, the results show that the combination of the results of fMRI and rTMS language mapping is able to achieve a high sensitivity and a high specificity.

In summary, with our present data we contribute to the development of more standardized protocols for both the performance and the analysis of rTMS language mapping. In addition, we have evaluated two new protocols for the combined application of rTMS and fMRI, to ensure a safer and more reliable preoperative language mapping.

4.3 Limitations

One of the general limitations of preoperative mapping is the effect of brain shift after the durotomy [27,69]. This may be a reason for slightly differing results from mapping that was done before operation and during operation. Yet the intraoperative location of DCS positive points has also been detected by pial venous structures allowing the identification of the correct CPS region after durotomy [34]. The CPS per se might be a further limitation of our study, since the error margins are larger than 10 mm, while it can be assumed that the spatial resolution of DCS is even smaller than 10 mm [23]. In this study we used the CPS for statistical analysis in order to combine the two non-invasive techniques with the gold standard. Still, our present results should be reproduced in any case, and it should be considered to use optimized systems for the comparisons in the future. Another limitation of our study is the sole use of an object-naming task for both preoperative mapping techniques. This limitation should not affect the comparisons with DCS language mapping, since we have also used an object naming task for the intraoperative language mapping. Yet, in the basic research of language function and the further refining of our protocols, it is especially tasks for the comprehension of language that should be applied. The object-naming task, however, is able to reproduce the whole process of word production and incorporates all presumably language-eloquent brain regions [13,17,30,63]. This has been shown in several studies and for each of the three modalities [9,30,39].

However, it has also been shown that fMRI language mapping is more sensitive to anterior than to posterior language-related cortical regions [3]. The more frequently detected occurrence of positive BOLD signals within the anterior language-related regions could be approved by our study and these circumstances have to be considered in case of assessing the accuracy of fMRI language mapping (Fig. 1D).

What is more, examination by fMRI depends heavily on the patient's compliance [1,40,46,55,67]. Of course, compliance always plays an important role in the analysis of human brain function, especially regarding the detection of language-eloquent regions by DCS [70]. But the examiners cannot control compliance during the object-naming task in the MR scanner. In contrast, a lack of cooperation is immediately noticeable during the rTMS language mapping. This has to be considered when combining the results of rTMS and fMRI language mapping.

On the other hand and in the respect of the two non-invasive methods, it has to be mentioned that rTMS language mapping is currently still more time-consuming, costlier, and less standardized than fMRI. However, especially by means of the present study, we refine this promising and aspiring technique, among others, and to provide data towards a higher grade of standardization in order to face these shortcomings.

In addition, the two PTI groups (0 ms & 300 ms PTI) have not been randomized. Even though a recently published study has proved the advantages of rTMS language mapping performed with a PTI of 0 ms, and our results regarding this analysis are like theirs, yet this fact has to be noted as a limitation of our study [30].

5 CONCLUSIONS

The results of our study show that the raw data of rTMS language mapping should be analyzed with an ERT of 15%, 20%, 25%, or the 2/3 rule to obtain a high prediction of DCS language mapping. Moreover, we can support previous data suggesting that rTMS language mapping should be performed with a PTI of 0 ms. We can also conclude that combining the more sensitive technique rTMS and the more specific technique fMRI leads to a higher correlation to DCS language mapping than either technique alone. With this in mind, our presented protocols 1 and 2 provide a promising non-invasive approach which could be helpful for language mapping assessment prior to the gold standard of intraoperative DCS.

6 DISCLOSURE

The other authors declare that they have no conflict of interest affecting this study. The study was completely financed by institutional grants of the Department of Neurosurgery and the Section of Neuroradiology, TU Munich. SK is consultant for BrainLAB AG (Feldkirchen, Germany). The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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11.2. Impairment of non-invasive language mapping by lesion location – a fMRI, nTMS, and DCS study

Impairment of preoperative language mapping by lesion location – a fMRI, nTMS, and DCS study

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ABSTRACT

Object: Language mapping by repetitive navigated transcranial magnetic stimulation (rTMS) is increasingly used and already replaces functional magnetic resonance imaging (fMRI) in some institutions for preoperative mapping of neurosurgical patients. Yet, some factors affect the concordance of both methods with direct cortical stimulation (DCS); most likely by lesions affecting cortical oxygenation levels. We therefore analyze the impairment of the accuracy of rTMS and fMRI compared to DCS during awake surgery by intraparenchymal lesions.

Methods: We performed language mapping in 27 patients with left-sided perisylvian lesions by DCS, rTMS, and fMRI using an object-naming task, and assigned the induced language errors of each method to the cortical parcellation system (CPS). Subsequently we calculated the receiver operating characteristics for rTMS and fMRI compared to DCS as ground truth for regions with (W) and without (WO) the lesion in the mapped regions.

Results: Within the W subgroup we revealed a sensitivity of 100% (WO: 100%), a specificity of 8% (WO: 5%), a PPV of 34% (WO: 53%), and a NPV of 100% (WO: 100%) for the comparison of rTMS vs. DCS. For the comparison of fMRI vs. DCS within the W subgroup, we obtained a sensitivity of 32% (WO: 62%), a specificity of 88% (WO: 60%), a PPV of 56% (WO: 62%), and a NPV of 73% (WO: 60%).

Conclusion: Although both methods have their strengths and weaknesses, we were able to show that rTMS is less affected by a brain lesion than fMRI, especially when performing mapping of language-negative cortical regions based on sensitivity and NPV.

1 INTRODUCTION

Since transcranial magnetic stimulation (TMS) was introduced for stimulating the human motor cortex by Barker et al. in 1985, it has become more sophisticated and was extensively refined [1]. Pascual-Leone introduced the term “virtual lesion” and was already in 1991 able to induce speech arrests and counting errors by the use of rapid-rate TMS [35,36]. In the late 1990s and early 2000s, the combination of TMS with optically tracked stereotactic navigation systems was established, whereby it was possible to visualize the stimulation sites via the 3D reconstructed magnetic resonance imaging (MRI) data of the patient’s brain [31,37]. Thus, the door to the operating theater was opened, since the recorded and analyzed stimulation sites could be used for presurgical planning and could be transferred via neuronavigation [22,30,43,44]. Meanwhile, repetitive navigated TMS (rTMS) is increasingly used for preoperative language mapping of patients with left-sided perisylvian brain lesions [39]. The results of rTMS language mapping of this study were correlated to direct cortical stimulation (DCS) during awake surgery, which is currently the most precise way for the localization of individual language-eloquent brain regions [8,19,33,34,48]. Especially regarding the mapping of language-negative cortical regions, rTMS obtained promising results in comparison with DCS in further studies, reflected in an excellent sensitivity and negative predictive value (NPV) [39,52]. These results are very reliable, particularly with regard to current protocols for DCS language mapping, since some authors also rely on negative language mapping by DCS during awake surgery [46,52]. Considering these results, rTMS already replaces functional magnetic resonance imaging (fMRI) for preoperative language mapping in some institutions. Moreover, in 2010 Giussani et al. reviewed comparisons of fMRI and DCS during awake surgery with the conclusion that fMRI appears to not be appropriate for preoperative mapping of cortical language function [18].

However, fMRI was considered to be the standard for non-invasive language mapping for a long time [16]. But since fMRI is supposed to be mainly affected by impaired oxygenation levels in the proximity of intracerebral lesions, this study was designed to investigate the impact of adjacent brain lesions on the correlation of rTMS and fMRI language mapping with intraoperative DCS during awake surgery. Against this backdrop, the present study is the first to examine the results obtained by rTMS and fMRI language mapping within one cohort of patients.

2 METHODS

2.1 Ethics approval

The experimental setup of this study was permitted by the local ethical committee of our university in accordance with the Declaration of Helsinki (Ethics committee registration number: 2793/10). Before the examination by rTMS, all patients provided written informed consent to this study.

2.2 Study design

The study was designed to be prospective and non-randomized.

2.3 Patients

Twenty-seven consecutive patients (18 male, 9 female) with left-sided perisylvian brain lesions met the following inclusion criteria: presence of a left-sided perisylvian brain lesion, planned awake craniotomy, and an age of at least 18 years. All of the patients signed written informed consent. We did not include patients below the age of 18 years, or those with severe aphasia. The latter criterion was controlled by an aphasia grading adapted from the Aachener Aphasia Test [21]. Further exclusion criteria were general TMS exclusion criteria, such as pacemaker or cochlear implant [41].

All patients were scheduled for awake craniotomy in our neurosurgical department, and all of them underwent preoperative language mapping by rTMS and fMRI using an object-naming task the day before surgery. All lesions were located in the left-hemispheric perisylvian brain regions, and 25 patients (93%) were right-handed (Table 1).

Patient No.	**Age** (years)	**Gender**	**Lesion type**	**Main lesion location**	**Infiltrated CPS regions**	**Preoperative aphasia grading**
A1	25	M	C	trIFG	-	0
A2	62	M	GBM	opIFG	trIFG, aSTG, pMFG	0
A3	43	M	GBM	opIFG	vPrG, pMFG	1A
A4	51	F	GBM	vPrG	opIFG, pMFG, aSTG, vPoG,	1A
A5	34	M	C	mMFG	-	0
A6	53	M	GBM	opIFG	vPrG, pMFG	1A
A7	47	M	GBM	opIFG	trIFG, vPrG, pMFG	0
A8	43	M	DA	opIFG	vPrG, mPrG, pMFG	0
A9	48	M	GBM	opIFG	trIFG, vPrG, pMFG	0
A10	49	M	DA	opIFG	vPrG, aSTG, trIFG	0
A11	51	F	GBM	vPrG	vPoG, opIFG	2A
A12	24	M	DA	mPrG	pMFG, vPrG, mMFG	0
P1	28	F	AA	anG	pSMG, pSTG, pMTG	0
P2	56	F	AA	mMTG	mSTG, aSTG	0
P3	53	M	AA	pMTG	pSTG, anG	0
P4	51	M	GBM	anG	pSMG, pSTG	2B
P5	50	M	GBM	anG	aSMG, pSMG	2A
P6	40	M	GBM	pSTG	mSTG, pMTG	2B
P7	63	F	DA	pSTG	mSTG, pMTG	1B
P8	47	F	GBM	pMTG	pSTG, anG	2B
P9	56	F	GBM	pMTG	pSTG, anG	0
P10	47	M	AA	aSMG	pSMG, SPL, mPrG, mPoG	1B
P11	30	F	AA	anG	pSMG, pSTG, pMTG	1A
P12	74	M	GBM	aSTG	mSTG, mMTG	2A
P13	41	M	AA	pSTG	mSTG, mMTG, pMTG, anG	2B
P14	47	M	GBM	anG	SPL, pSMG	1A
P15	27	F	AVM	mSTG	-	0

Table 1. Lesion location: *Patient characteristics include each patient's preoperative aphasia grading, lesion type, and lesion location. The patients are grouped according to the location of their lesions, whether they are located within the anterior language-related CPS regions (= A1-12), or within the posterior language-related CPS regions (= P1-15). Further abbreviations: AA = anaplastic astrocytoma WHO grade III; AVM = arteriovenous malformation; C = cavernoma; DA = diffuse astrocytoma WHO grade II; GBM = glioblastoma WHO grade IV; Aphasia grading: 0 = no aphasia, 1 = mild aphasia, 2 = moderate aphasia, 3 = severe aphasia, A = predominantly non-fluent aphasia, B = predominantly fluent aphasia. CPS regions are defined in Table 2.*

Abbreviation	Anatomy
aMFG	Anterior middle frontal gyrus
aMTG	Anterior middle temporal gyrus
anG	Angular gyrus
aSMG	Anterior supramarginal gyrus
aSTG	Anterior superior temporal gyrus
dPoG	Dorsal post-central gyrus
dPrG	Dorsal pre-central gyrus
mMFG	Middle middle frontal gyrus
mMTG	Middle middle temporal gyrus
mPoG	Middle post-central gyrus
mPrG	Middle pre-central gyrus
mSFG	Middle superior frontal gyrus
mSTG	Middle superior temporal gyrus
opIFG	Opercular inferior frontal gyrus
pMFG	Posterior middle frontal gyrus
pMTG	Posterior middle temporal gyrus
pSFG	Posterior superior frontal gyrus
pSMG	Posterior supramarginal gyrus
pSTG	Posterior superior temporal gyrus
SPL	Superior parietal lobe
trIFG	Triangular inferior frontal gyrus
vPoG	Ventral post-central gyrus
vPrG	Ventral pre-central gyrus

Table 2. Abbreviations of the cortical parcellation system: *Abbreviations of the anatomical cortical areas according to the cortical parcellation system (CPS).*

2.4 Navigational MRI scan

As described earlier, the same three-dimensional (3D) dataset was used for preoperative rTMS language mapping and intraoperative neuronavigation as well [39,50]. The navigational MRI scans of all patients were performed on a 3 Tesla MR scanner (Achieva 3T, Philips Medical System, The Netherlands B.V.) combined with an 8-channel phased array head coil. Our standard protocol consisted of a T2 FLAIR (TR/TE 12,000/140, inversion time of 2,500 ms, 30 slices with 1 mm gap, voxel size 0.9 × 0.9 × 4 mm, 3 min acquisition time), a 3D gradient echo sequence (TR/TE 9/4 ms, 1 mm^3

isovoxel covering the whole head, 6 minute 58 second acquisition time), and an intravenous contrast administration of 0.1 mmol/kg body weight gadopentetate dimeglumine (Magnograf, Marotrast GmbH, Jena, Germany) for anatomical co-registration.

2.5 Preoperative fMRI language mapping

Each of the included patients received a blood-oxygen-level dependent (BOLD) functional imaging (fMRI) using an object-naming task. The echo planar sequence was performed with a train length of 43 ms (TR/TE 2,500/35 ms). Each of the acquired 64 dynamic sets (2 minutes 53 seconds) consisted of 32 contiguous axial 4 mm slices (in-plane resolution of 2.75 mm × 2.75 mm). We used parallel imaging (SENSE) to decrease susceptibility-related artifacts (SENSE factor 2).

As also described before, we transferred the fMRI data to an external workstation (Extended MR Workspace, Philips Medical Systems, The Netherlands B.V.) and post-processed them, using the IViewBOLD package [25,50]. This was done by an independent investigator blinded to the rTMS results. By use of the general linear model we generated statistical parametric maps after motion correction and spatial smoothing (2D Gaussian filter with 4 mm full width at half maximum, kernel 2 × 2 pixel). The hemodynamic delay was 2 × TR, and we used a single predictor and a t-value threshold of 2.5. Furthermore, we only accepted clusters with positive correlation, bigger than 40 voxels in size to be activated areas. Finally, the time-intensity diagrams of the activated voxels were reviewed. Thus, we checked the validity of the results.

2.6 Preoperative rTMS language mapping

2.6.1 Experimental setup

We performed rTMS language mapping using the eXimia NBS system version 3.2.2 and Nexstim NBS 4.3 with a NEXSPEECH® module (Nexstim Oy, Helsinki, Finland) according to the repetitively published standard protocol for rTMS language mapping [30,39,50]. In short, after coregistration of the 3D T1-weighted MRI scan and the patient's head, we conducted a motor mapping of the cortical representation of the contralateral abductor pollicis brevis muscle [25]. The thereby determined individual patient's resting motor threshold (RMT) was afterwards used as a basic value for the rTMS language mapping procedure [26,30,39,50]. As a next step, the patients performed the baseline object-naming task (131 colored pictures of common objects) twice without stimulation to adapt the picture data set to the patient's individual vocabulary. The misnamed pictures were discarded [30]. For defining the individual patient's mapping frequency and intensity, 3 different setups of rTMS bursts (5 Hz, 5 pulses; 7 Hz, 5 pulses; 7 Hz, 7 pulses) were applied to vPrG and opIFG, each with an intensity of 100 % RMT [36,49,50]. The most effective setup regarding the evocation of language errors was then used for the language mapping of the whole hemisphere. If there was no distinct effect on naming, the intensity was increased to 110 – 120% RMT, while it was decreased to 80 – 90% RMT if significant pain was reported. By the latter, we could avoid the interference of pain or discomfort with the consecutive-response evaluation, hence, we even lowered the stimulation intensity if 100% RMT was painful [15]. This was necessary in 2 patients (7%).

2.6.2 TMS language mapping procedure

According to the setup of the baseline recording and the determination of the individual mapping frequency, the rTMS language mapping procedure was performed with the following parameters. The picture-to-trigger interval (PTI; time between presentation of stimulus and onset of rTMS burst) was 300 ms for 22 patients (81%), and 0 ms for 5 patients (19%). Both PTIs proved to be effective in former studies [39,52]. The display time (DT; time of picture presentation on screen) was 700 ms, and the interpicture interval (IPI; time between two pictures) was 2,500 ms. During the IPI the stimulation coil was moved to the next stimulation site. The remaining pictures of the baseline recording were presented time locked to the rTMS pulses, while the stimulation coil was moved over the whole hemisphere. This was done randomly, and each site was stimulated three nonconsecutive times. The distance between two sites was approximately 10 mm. The coil position was tracked by the use of a stereotactic camera and reflectors fastened to the patient's head with an elastic strap. Thus, the intracranial stimulation sites were visualized over the 3D reconstruction of the patient's brain, and were saved for later examination [22,43,44]. By placing the coil perpendicular to the skull we obtained maximum field induction, and the induced electric field had a minimum cortical field strength of 55 V/m [30].

2.6.3 TMS data analysis

Since the baseline performance and the stimulation trials were video-recorded, rTMS language mappings were analyzed objectively, and blinded to the stimulation sites and lesion location [26,30,39,50]. In comparison with the baseline performance, we categorized the rTMS-induced language errors into seven subgroups (no responses, performance errors, hesitations, neologisms, semantic paraphasias, phonologic paraphasias, and circumlocutions [7,49]), rejected errors related to muscle stimulations or pain, and assigned the language errors to Corina's cortical parcellation system (CPS) (Fig. 1, Table 2) [6]. Moreover, the definition of anterior (= A) and posterior (= P) language-related CPS regions is provided in Fig. 1. Subsequently, the error rate (ER; number of errors per number of stimulations) was calculated for each region of the CPS [26,39]. A CPS region was defined as language-positive in terms of rTMS, if any of the trains applied to this region led to any language error. Accordingly, a CPS region was defined to be language-negative in terms of rTMS, if the region was stimulated, but no language errors were generated [26,49]. This was done purposing a better comparability to the results of fMRI language mapping, which were also analyzed without threshold.

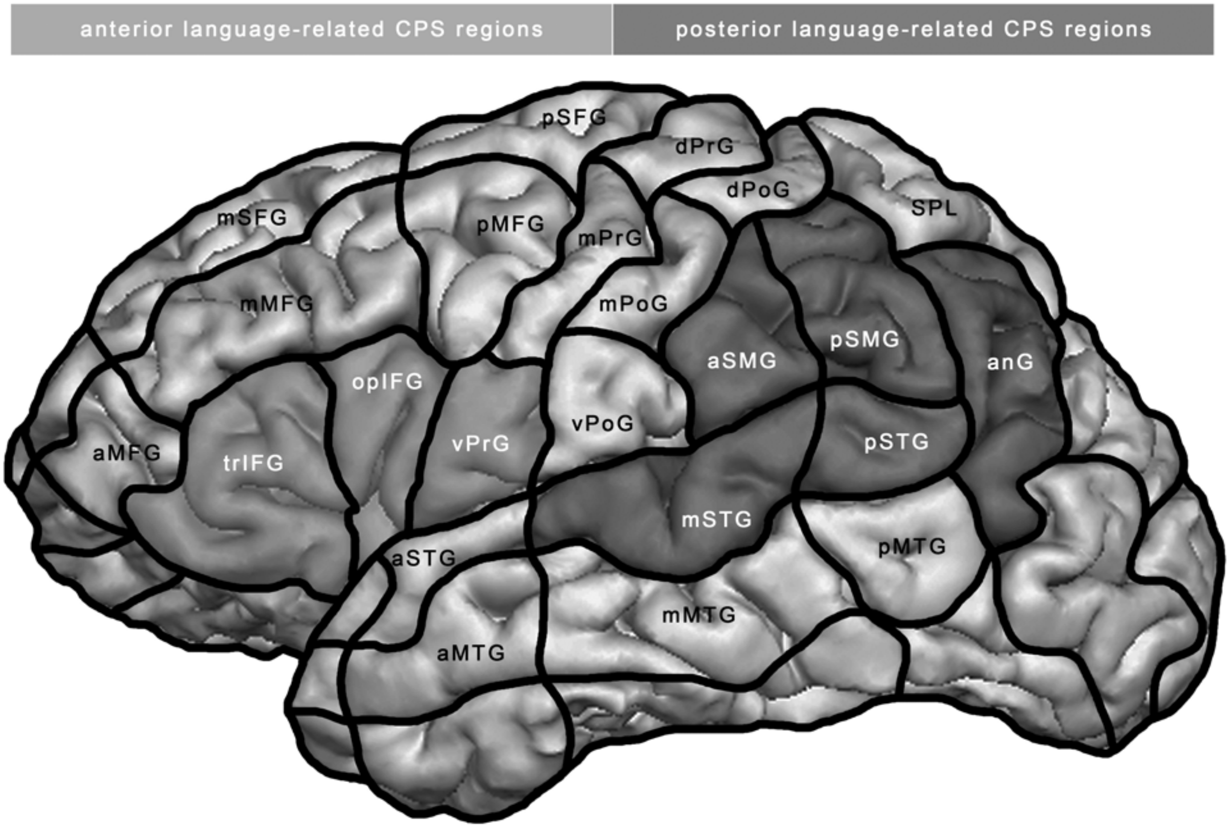

Fig. 1. Cortical parcellation system: *This scheme shows the CPS including the abbreviations of all mapped regions. The abbreviations are explained in Table 2. The scheme also contains the definition of the anterior (trIFG, opIFG, vPrG; shaded with lighter grey), and posterior language-related CPS regions (aSMG, pSMG, anG, pSTG, mSTG; shaded with darker grey).*

2.7 Language mapping during awake craniotomy

The setup and procedure of language mapping during awake craniotomy were performed as also published by others [38]. A bipolar-stimulation electrode with a distance of 5 mm (Inomed Medizintechnik GmbH, Emmendingen, Germany) was used for cortical stimulation (intensity of 0 – 20 mA, frequency of 50 Hz, duration of 4 seconds). The distance between the stimulation sites was 5 to 10 mm, and we recorded a surface electroencephalogram (bandpass filter of 10 Hz – 1.5 kHz) to detect epileptic seizures.

We used the same 3D MRI for the intraoperative mapping by DCS and for the preoperative mapping by rTMS, and we also used the same pictures for the object naming of both methods. The intraoperative naming task started with the matrix sentence, “This is a …”, and each cortical site was stimulated three times as well. The stimulated sites were considered to be language-positive in terms of DCS if at least 2 out of 3 stimulations led to a language error (2/3 rule). These positive sites were marked and transferred to the neuronavigation system (BrainLAB Vectorvision Sky® or BrainLAB Curve®, BrainLAB AG, Feldkirchen, Germany) [33,38,39].

2.8 Data analysis

2.8.1 Anatomical localization and stimulation assessment

The induced language errors by DCS and rTMS as well as the regions with a positive BOLD signal detected by fMRI were assigned to the CPS [6]. Since representing the gold standard for language mapping, the intraoperative results determined by DCS provided the ground truth for every comparison. The assertion regarding language positivity or negativity of a CPS region defined by the non-invasive techniques rTMS and fMRI was compared to the results of DCS language mapping as follows: if a CPS region was defined as language-positive by DCS and the non-invasive method, the region was documented as a true positive for rTMS or fMRI. Accordingly, if DCS and the non-invasive method indicated a CPS region to be language-negative, the region was documented as a true negative for the non-invasive method. When rTMS or fMRI defined a CPS region as language-positive, but DCS did not, the region was documented as a false positive for this method. Eventually, a CPS region was documented as a false negative for the non-invasive method, when there was no positive BOLD signal on the fMRI map for this region or rTMS did not induce a language error in this region, but DCS indicated the region to be language-positive. This was done separately for each method and for each patient [27,39,50,52].

2.8.2 *Statistical analysis*

We calculated the receiver operating characteristics (ROC) sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for each region of the CPS. In the context of our study, the sensitivity of the non-invasive mapping technique refers to the ability of rTMS or fMRI to correctly identify language-positive cortical regions as determined by the ground truth DCS. In contrast, the specificity of rTMS or fMRI refers to the ability to correctly identify language-negative cortical regions. The PPV of rTMS or fMRI indicates the probability that a language-positive cortical region in terms of rTMS or fMRI is afterwards defined as language-positive by DCS as well, while the NPV is the probability that a language-negative cortical region in terms of rTMS or fMRI will even be defined as language-negative by DCS [28]. As a first step, we summed up the results of all patients, i.e., we analyzed the non-invasive methods vs. DCS without dependency on lesion location. We separated the obtained ROCs into three subgroups: all mapped CPS regions, only the anterior language-related CPS regions (= A), and only the posterior language-related CPS regions (= P) [49]. The subgroups included the following CPS regions (Fig. 1, Table 2):

(1) A: trIFG, opIFG, and vPrG

(2) P: aSMG, pSMG, anG, mSTG, and pSTG

The selected CPS regions of subgroup A were based on predominantly motor-related language regions including the classic Broca's area [5], whereas the regions of subgroup

P were based on predominantly sensory-related language regions including the classic Wernicke's area [55], and the classic Geschwind's area [54].

Furthermore, we analyzed the non-invasive methods in comparison to DCS with dependency on lesion location.

Considering that, we divided the patient cohort into two subgroups (Table 1):

(1) A1-12: patients with lesions within the anterior language-related CPS regions

(2) P1-15: patients with lesions within the posterior language-related CPS regions

We then summed up the ROCs of the abovementioned eight CPS regions (A and P) for six different subgroups and for each of the two comparisons:

(1) anterior language-related CPS regions of patient P1-15 (WO-a)

(2) posterior language-related CPS regions of patient A1-12 (WO-p)

(3) without lesion in mapped CPS regions = (1) + (2) (WO)

(4) anterior language-related CPS regions of patient A1-12 (W-a)

(5) posterior language-related CPS regions of patient P1-15 (W-p)

(6) with lesion in mapped CPS regions = (4) + (5) (W)

For interpretation of the obtained data and for the comparison of the two non-invasive methods in relation to the intraoperative results, we issued ROC curves for all subgroups. In Fig. 2 we plotted the results for sensitivity (y axis) against *1 – specificity* (x axis). Moreover, with the aim of outlining the results for the mapping of language-negative regions, we plotted the results for sensitivity (y axis) against the term *1 – NPV* (x axis) in Fig. 3.

3 RESULTS

3.1 Patients

The 27 patients (18 male, 9 female) who met our inclusion criteria had a mean age of 46 ± 12 years. The mean age of the 12 patients (10 male, 2 female) of subgroup A was 44 ± 11 years, and the mean age of the 15 patients (8 male, 7 female) of subgroup P was 47 ± 12 years (Table 1). Regarding age, there was no significant difference between the two subgroups ($p = 0.511$).

3.2 Comparison of rTMS and fMRI with DCS language mapping

Across the 27 patients we compared the results of rTMS and DCS language mapping in 207 CPS regions in total. The results of fMRI language mapping using an object-naming paradigm and DCS overlapped in 258 CPS regions in total. The overall ROCs of all mapped CPS regions without dependency on lesion location are demonstrated for both comparisons in Fig. 2 and Table 3. Table 3 also shows the overall results for the anterior as well as for the posterior language-related CPS regions.

Moreover, we additionally calculated the ROC for the dependency on lesion location. Table 4 outlines the results for the comparisons *with* and *without lesion in mapped regions* (W and WO) (Fig. 3). For a more detailed analysis we additionally show the results only for the anterior (W-a and WO-a) and for the posterior (W-p and WO-p) language-related regions, which met these requirements (Fig. 3, Table 4).

The NPV within the subgroup WO-a could not be calculated for the comparison rTMS vs. DCS, because we did not obtain either true negative or false negative results for this analysis. This was also due to obviously less intraoperative results of regions without lesion (Fig. 3, Table 4).

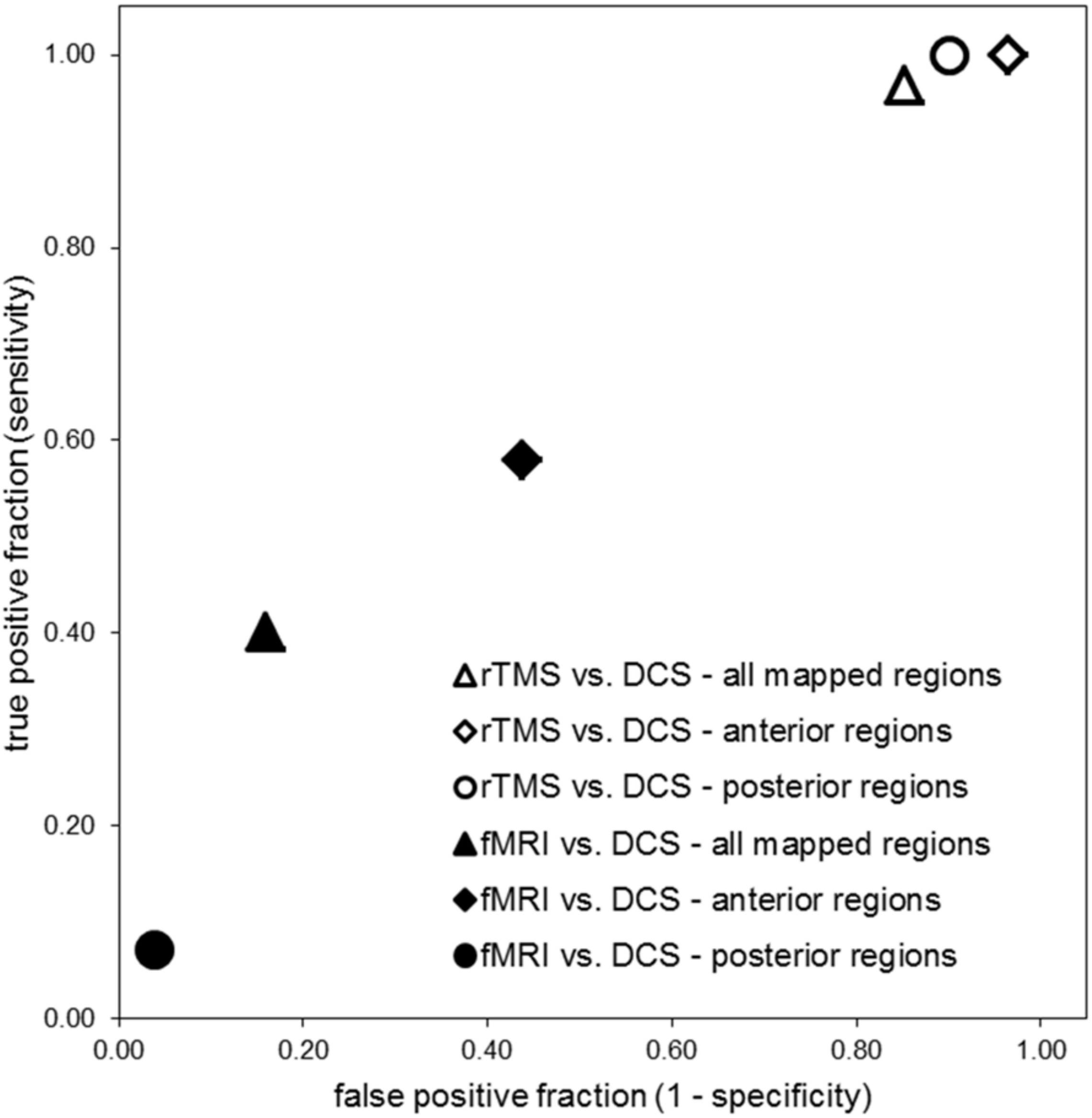

Fig. 2. ROC curve without dependency on lesion location: *The results for sensitivity are plotted against 1 – specificity for the comparisons of rTMS vs. DCS, and fMRI vs. DCS. The graph includes the results of anterior, posterior, and all mapped CPS regions, each without dependency on lesion location.*

	rTMS vs. DCS			**fMRI vs. DCS**		
	all mapped regions	anterior regions	posterior regions	all mapped regions	anterior regions	posterior regions
PPV	34% (27-41)	56% (43-69)	22% (13-35)	48% (35-62)	61% (43-77)	33% (0-91)
NPV	91% (72-99)	100% (2-100)	100% (48-100)	79% (73-84)	53% (35-70)	79% (67-89)
Sensitivity	97% (89-100)	100% (90-100)	100% (75-100)	40% (28-52)	58% (41-74)	7% (0-34)
Specificity	15% (9-22)	4% (0-18)	10% (3-22)	84% (78-89)	56% (38-74)	96% (87-100)

Table 3. Overall results without dependency on lesion location: *This table shows the overall results including all mapped CPS regions for the comparisons of rTMS vs. DCS and fMRI vs. DCS. We additionally demonstrate the results for anterior (trIFG, opIFG, and vPrG) and posterior (aSMG, pSMG, anG, pSTG, and mSTG) language-related CPS regions (Fig. 1, Table 2). The receiver operating characteristics (ROC) of these results were calculated without dependency on lesion location. The 95% confidence interval (95% CI) is indicated in parenthesis.*

	rTMS vs. DCS					
	anterior regions **with lesion** anterior	posterior regions **with lesion** posterior	**with lesion** in mapped regions	anterior regions **without lesion** anterior	posterior regions **without lesion** posterior	**without lesion** in mapped regions
PPV	53% (34-72)	23% (13-37)	34% (24-45)	59% (41-76)	17% (0-64)	53% (36-69)
NPV	100% (2-100)	100% (40-100)	100% (48-100)	no data	100% (3-100)	100% (3-100)
Sensitivity	100% (79-100)	100% (74-100)	100% (88-100)	100% (82-100)	100% (3-100)	100% (83-100)
Specificity	7% (0-32)	9% (3-22)	8% (3-19)	0% (0-25)	17% (0-64)	5% (0-26)
	fMRI vs. DCS					
	anterior regions **with lesion** anterior	posterior regions **with lesion** posterior	**with lesion** in mapped regions	anterior regions **without lesion** anterior	posterior regions **without lesion** posterior	**without lesion** in mapped regions
PPV	56% (30-80)	50% (1-99)	56% (31-78)	65% (41-85)	0% (0-98)	62% (38-82)
NPV	55% (32-77)	79% (66-89)	73% (61-82)	50% (23-77)	83% (36-100)	60% (36-81)
Sensitivity	50% (26-74)	8% (0-36)	32% (17-51)	65% (41-85)	0% (0-98)	62% (38-82)
Specificity	61% (36-83)	98% (88-100)	88% (77-94)	50% (23-77)	83% (36-100)	60% (36-81)

Table 4. Results with dependency on lesion location: *This table shows the results of rTMS and fMRI language mapping in comparison with DCS language mapping. The ROCs in column 3 (with lesion in mapped regions) respectively include the results of column 1 (anterior regions with lesion anterior) and column 2 (posterior regions with lesion posterior). Accordingly, the ROCs in column 6 (without lesion in mapped regions) were calculated by the summed results of column 4 (anterior regions without lesion anterior) and column 5 (posterior regions without lesion posterior). The NPV within the subgroup WO-a could not be calculated for the comparison rTMS vs. DCS, because we did not obtain either true negative or false negative results for this analysis. The anterior regions comprise the CPS regions trIFG, opIFG,*

and vPrG, whereas the posterior regions comprise the CPS regions aSMG, pSMG, anG, pSTG, and mSTG (Fig. 1, Table 2). The 95% CI is indicated in parenthesis.

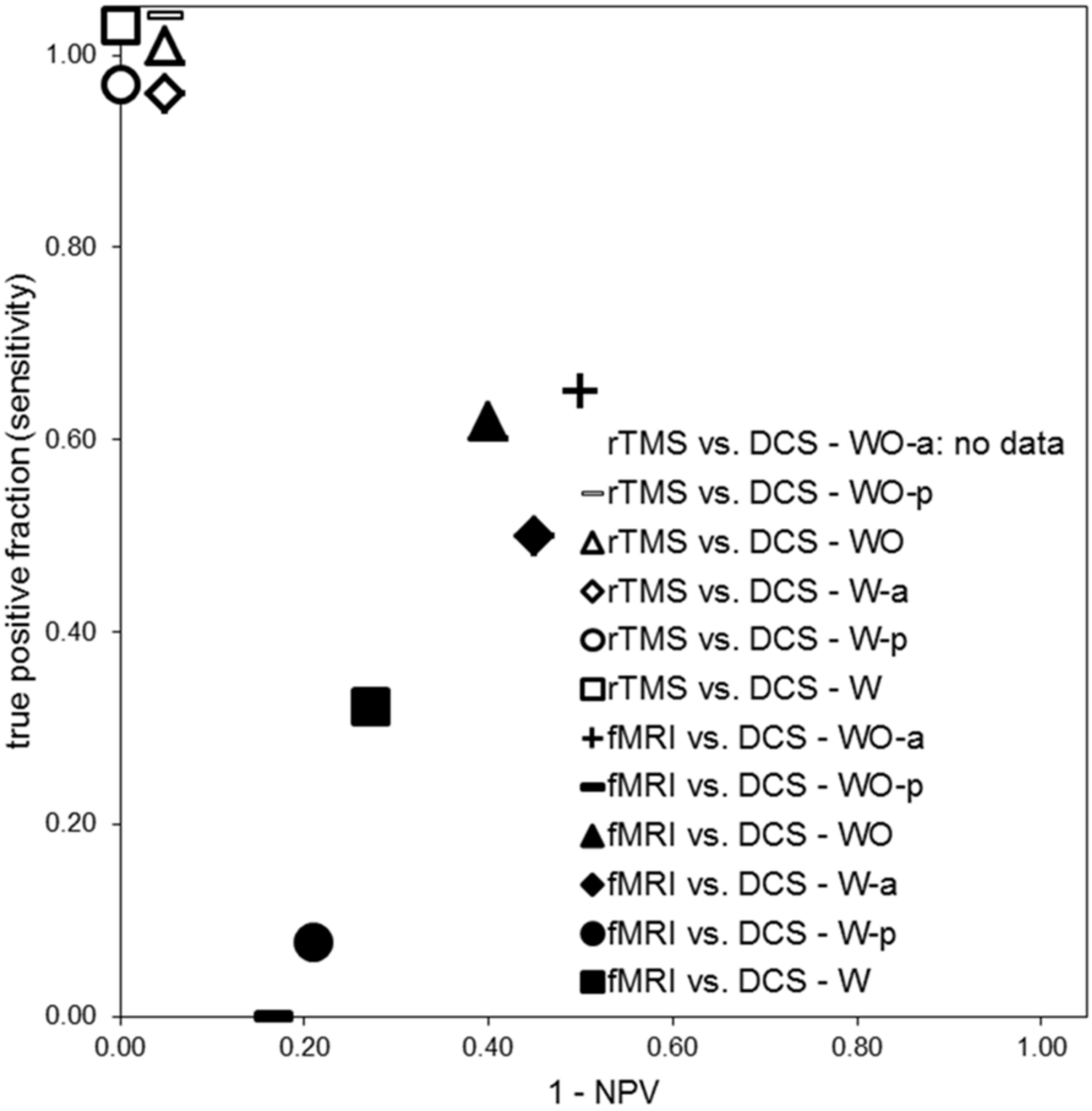

Fig. 3. Mapping of language-negative regions with dependency on lesion location: *In Figure 3 we demonstrate the results for the comparisons of rTMS vs. DCS and fMRI vs. DCS, each related to the mapping of language-negative regions. Considering that, we plotted sensitivity against the term 1 - NPV. The illustrated ROC were calculated with dependency on lesion location, and include the summed results of the anterior and posterior language-related CPS regions with lesion in the mapped regions (= W), and without lesion in the mapped regions (= WO). Additionally, we provide data for anterior language-related regions with lesion anterior (= W-a), and lesion posterior (= WO-a), as well as for posterior language-*

related regions with lesion posterior (= W-p), and lesion anterior (WO-p). We arranged the symbols for the results of rTMS vs. DCS around their proper coordinate, because we obtained a sensitivity and NPV of 100% each for the subgroups WO-p, WO, W-a, W-p, and W, respectively. The NPV within the subgroup WO-a could not be calculated for the comparison rTMS vs. DCS, because we did not obtain either true negative or false negative results for this analysis. The sensitivity for this comparison was 100%.

4 DISCUSSION

4.1 Non-invasive mapping of language-negative cortical regions

In previous studies, rTMS yielded high overall sensitivity (90% and 90.2%) and NPV (99% and 83.9%) in comparison with DCS language mapping [39,52]. In our study, we also revealed high overall sensitivity (97%) and NPV (91%) (Fig. 2, Table 3). Most importantly, we obtained a sensitivity and NPV of 100%, respectively, for both the anterior and posterior language-related CPS regions (Fig. 2 & 3, Table 3 & 4). That these CPS regions are at least crucial cortical entry sites to the highly individualized language networks has already been proven in former studies [5,54,55]. By using negative mapping due to the perfect sensitivity and NPV, rTMS could once more prove an excellent correlation to DCS, especially within critical cortical regions [39,52]. Since sensitivity and NPV predict reliable negative results, high values for these two ROCs are of particular importance for the mapping of language-negative brain regions. This in turn is relevant since some authors and surgeons also trust the mapping of language-negative sites when performing DCS during awake surgery [46,52]. Moreover, the reliability of negative results allows a more extensive resection, which is essential regarding oncological considerations [4,51]. In contrast, fMRI language mapping using an object-naming task could not reach the results of rTMS concerning the mapping of language-negative sites (Fig. 2 & 3, Table 3 & 4). Like other previous studies, we obtained comparable overall specificity for the comparison of fMRI vs. DCS, when analyzing them without dependency on lesion location (Fig. 2, Table 3) [3,42]. However, we detected many false negative results for the comparison fMRI vs. DCS (fMRI vs. DCS: 42 within all mapped regions, 29 within the anterior and posterior language-related regions; rTMS vs. DCS: 2 within all mapped regions, 0 within the anterior and posterior language-related regions) (Fig. 2, Table 3). This determining factor seems to be dangerous regarding the abovementioned approach of mapping language-negative sites. Results of non-invasive techniques, incorrectly identified as language-negative, could lead to harmful surgical decisions, as it has recently been described for diffusion tensor imaging fiber tracking (DTI-FT) [10]. Alternatively, fMRI — just like rTMS — cannot be consulted for the mapping of language-positive sites due to its limited PPV, which varies around chance level (Table 3) [45]. Giussani and colleagues reviewed nine language mapping studies, which compared the results of fMRI and DCS in 2010. Despite the fact that these studies were not homogenous concerning several criteria, they have found an incomplete match between fMRI and DCS: sensitivity ranged from 59 – 100% and specificity from 0 – 97% [18]. In contrast, previous studies on rTMS language mapping, including the present, could show robust results for the mapping of language-negative regions regarding the comparison with intraoperative results independently from the performing institution [27,39,50,52]. With these previous findings in mind, the present study is the first to show the advantages of rTMS language mapping as compared to fMRI within one patient cohort.

4.2 Comparison with dependency on lesion location

The core of our study was to analyze the impact of left-sided perisylvian brain lesions on the results of rTMS and fMRI language mapping and their reliability when relating to DCS. As Fig. 3 and Table 4 show, we could not detect any impairment by lesions for rTMS mapping of language-negative cortical regions, either for subgroup W-a or for subgroup W-p. This is important since non-invasive methods, as part of the preoperative management of patients with brain lesions, should work with maximum accuracy particularly in the vicinity of lesions [10]. The stimulation by rTMS induces a transient virtual lesion [35]. Accordingly, DCS, defining the gold standard for language mapping, also maps the cortex by creating a virtual lesion [8,19,33,34]. Obviously, this electrophysiological approach seems to not be affected by the presence of a brain lesion [50]. This is reflected by a robust correlation between rTMS and DCS, whether analyzed for regions with or without lesion, even when specificity and PPV are around chance level or far below (Fig. 3, Table 4). Especially the plotting of sensitivity against *1 – NPV* in Fig. 3 shows that rTMS was able to detect all language-positive sites as determined by DCS, equivalent to the fact that the comparison of these two methods revealed not a single false negative result within language-related cortical regions. In contrast, the blood flow dependent approach of fMRI seems to be more affected by the presence of cerebral pathologies, as shown in many previous trials [18]. This is probably based on methodological differences [45]. The task-related increase of deoxyhemoglobin from activated neurons is supposed to be the basic principle of fMRI. The measured BOLD signals should then show activated cortical regions, because of their increased consumption of oxygen [32]. But particularly the dependency on oxygen extraction seems to be the crucial point of disappointing results for fMRI in patients with brain lesions. On the one hand, tumors induce the proliferation of vessels. Hence, the blood volume of the affected region is increased, which is associated with an additional extraction of oxygen, and a higher baseline blood flow resulting in smaller changes in the concentration of deoxyhemoglobin [20]. On the other hand, when healthy parenchyma is infiltrated by gliomas, the contact between capillary cells and astrocytes is decreased, and neurotransmitters cannot be released as they should. This in turn even changes the relations of blood flow and the extraction of oxygen [53]. Furthermore, it is known that tumor vasculature in malignant gliomas is unable to auto-regulate and the existing neural activity cannot be measured by the change of regional blood flow and BOLD signals [20]. All of these mechanisms result in decreased or unavailable BOLD signals, which is potentially dangerous regarding the use for any preoperative assessment in brain tumor patients [53]. Even though the following is speculative, the listed essentials of decreased BOLD signals in patients also explain our results. We obtained higher specificity and NPV in subgroup W than in subgroup WO (Fig. 3, Table 4). This makes a good impression on the first view regarding the clinical applicability, despite the fact that even these results do not provide a safe and precise mapping of language-negative sites. The detection of language-negative sites by fMRI may be due to the lack of BOLD signals based on the affection by lesions. Thus we suspect that fMRI revealed a high rate of true negative results in comparison with DCS, but also a crucial high rate of false negative results. In contrast, there were no false negative results within language eloquent brain regions for rTMS language mapping.

4.3 Clinical implications and future aspects of rTMS

First of all, it must be highlighted that the results of DCS during awake surgery are indispensable in patients suffering from lesions within or adjacent to language-eloquent brain regions. With our current knowledge, it should not be the aim to replace DCS by rTMS [39,52]. DCS is and will remain the gold standard for language mapping justified by the comprehensive experience of this technique [8,19,33,34,47,48]. Particularly for the mapping of cortical language function, non-invasive methods should be more sophisticated toward a multimodal approach including intraoperative mapping as the last step. The preference for multimodality bases on the principle to combine the advantages of each method to finally gain the best possible understanding of each patient's individual functional anatomy [25,39,47,52]. Nowadays, rTMS language mapping is able to play a supportive role in this and there are two main advantages regarding clinical procedures, not least proven by the present study: Firstly, based on its high sensitivity, language-positive sites near critical regions identified by rTMS can be transferred to intraoperative neuronavigation for the verification by DCS. This might accelerate the intraoperative procedure. Secondly, because of the excellent NPV in the vicinity of lesions, surgeons can be more confident of language-negative sites in cases of pre- and intraoperative identification and are maybe able to plan a more extensive resection beforehand [39,52].

Moreover, rTMS represents a non-invasive method, which could be consulted for the preoperative management of patients unwilling or unable to undergo the physically and sometimes psychologically demanding procedure of awake surgery [39]. Currently, this should only be done in combination with other non-invasive mapping techniques like positron emission tomography, fMRI, or DTI-FT and even then harbors the risk of surgery-related deficit or limited extent of resection.

Even if the latter technique has also not yet matured enough and has to be validated before it can be included in decision making, the combination of rTMS and DTI-FT could yield useful and supportive information toward the hodotopical model of human language function, and for the resection of brain lesions in the future [10,13,29]. The feasibility of this combination has already been shown for the motor system [24].

Moreover, by performing non-invasive language mapping, we are able to provide longitudinal follow-up examinations. Thus, it might be possible to incorporate information about plastic reshaping of language function received by rTMS into oncological considerations when reoperation of recurrent tumor has to be considered. This additional information could even be supportive and useful regarding the approach of consecutive awake surgery of brain tumor patients [12,13,40].

4.4 Limitations

One of the limitations of our study is the analysis of hesitation errors. To date, we are not able to categorize these errors objectively, but only in comparison with baseline performance. Despite this having been done by experienced examiners blinded to the results of intraoperative language mapping, a certain kind of subjectivity cannot be ruled out. This kind of error type is contrarily discussed anyway, while some authors do not even include them in their analysis [30]. With this in mind, the interpretation of hesitation errors might be a reason for the high rate of false positive results as compared to DCS. Apart from that, particularly with regard to current models of language processing, hesitation errors should be deemed to be a correlate of disrupted language processing [23,49]. Most certainly, the analysis of raw data obtained by mapping methods and its reliability are crucial. Based on the functional imaging analysis contest in 2005, Bennett and colleagues described that the same fMRI raw dataset leads to different results when analyzed by different examiners [2]. However, certain discrepancies have also been reported for rTMS language mapping, even though variability was relatively low regarding the most important *no response* errors [49]. Another determining factor and simultaneously a potential limitation lies in the CPS map to which the results are assigned. Despite Corina's CPS being well established and the subregions especially reflecting critical cortical areas for the mapping of language, the error margins exceed the size of 10 mm. Moreover, by combining DCS with direct subcortical stimulation, the spatial resolution is even smaller than 10 mm [14,17]. Hence, optimized systems and methods for the comparison of rTMS and DCS should be taken into account in future studies. It might be that this aspect could decrease the occurrence of false positive results of rTMS language mapping in comparison with DCS, too [27,39,52]. Yet, the CPS is used since the different regions allow us statistical comparisons of different approaches to further improve our rTMS setup.

Moreover, the three mapping modalities were performed by the sole use of an object-naming task. As Rutten and Ramsay concluded in their review, the combination of multiple fMRI language tasks is the best strategy for reproducible and reliable results [45]. This might be true, but this would protract the mapping procedures at the same time. The difficulty of checking the patient's compliance regarding the performance of tasks within the MR scanner has to be considered anyway [35,42]. By the use of more than one task, especially for the mapping of patients, it must be assumed that the patient's concentration and the effect on the results will be impaired. Of course, this pertains to all mapping techniques. Anyway, we used only one task for all modalities, providing that the present results are comparable. Most importantly, the object-naming task has shown to mirror the entire word production process and includes all language-eloquent brain regions [9,13,23]. Furthermore, as recently described, object naming has to be considered a cornerstone for intraoperative language mapping [11,33]. The reproducibility and reliability regarding this task have been shown for both fMRI and rTMS language mapping as well [23,30]. However, the usage of more than one task for studying further stages of language is recommendable, in particular for examinations with healthy subjects and concerning the basic research of human language function per se [26].

Despite the encouraging results of rTMS language mapping, further and in particular randomized studies are required to check the reproducibility of our results. This is necessary not least due to the fact that our patient cohort is not homogenous regarding the distribution of lesion types to the two subgroups (Table 1). Yet, it has not been described that different types of lesions lead to different results of rTMS language mapping, but this interrogation has to be evaluated in future studies. The present study has not been the first to compare rTMS and DCS; however, in relation to others, rTMS is still a novel technique, especially in the field of language mapping. On the one hand, as with each other method, it has to be further refined, for example regarding its specificity and PPV. On the other hand, since rTMS is non-invasive and lesion-based, it may contribute substantially to the basic research of human language function.

Nonetheless, we also have to point out that several brain areas cannot be mapped with a high reliability, e.g. the temporo-basal regions, because rTMS may induce pain. This is a serious limit for many lesions located in these areas. In addition, the specificity of rTMS is only around 8%, with a PPV of 34%. This means that rTMS is currently too sensitive for the mapping of language-positive cortical regions and that the wrong interpretation of rTMS can be very dangerous in clinical practice, because it could lead surgeons not to select patients for surgery due to a false positive result during rTMS, while the lesion was in fact resectable. This is another crucial issue. These false-positive regions in terms of DCS might only be language-involved. However, our suggested clinical procedure permits the intraoperative verification of language-positive cortical regions in terms of rTMS.

5 CONCLUSION

The present study is the first to investigate distinct results of language mapping by rTMS and fMRI within one patient cohort. With certainty, fMRI for language mapping is an enormously important mapping tool for studying human language function in healthy subjects. However, its results regarding the comparison with intraoperative language mapping during awake surgery are considerably affected by the presence of a brain lesion. In contrast, we could show that rTMS language mapping in patients suffering from brain lesions is less affected by these circumstances, especially when performing mapping of language-negative cortical regions based on sensitivity and NPV.

6 DISCLOSURE

SK and FR are consultants for BrainLAB AG (Feldkirchen, Germany). All other authors declare that they have no conflict of interest. The study was completely financed by institutional grants of the Department of Neurosurgery and the Section of Neuroradiology. The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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