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Cortical Language Mapping by Repetitive Transcranial Magnetic Stimulation – Localization of Language-Positive Cortical Regions by Different Task Types

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für

meine Eltern

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1. INTRODUCTION

1.1. Transcranial magnetic stimulation (TMS)

1.1.1. Development and principles of TMS

In 1980, Merton and Morton succeeded in non-invasively stimulating brain tissue and the spinal cord through the intact scalp by using external electrodes on the skin (Merton and Morton, 1980, Merton et al., 1982). They showed that transcranial electric stimulation (TES) over the motor cortex was able to produce motor-evoked potentials (MEPs) in the corresponding muscles. This finding was attributed great importance in medical research and therapeutic issues. Nevertheless, TES activates trigeminal pain fibers in the scalp and therefore is associated with discomfort. In 1985, Barker et al. (Barker et al., 1985) described for the first time external (non-invasive) brain stimulation by using a pulsed magnetic field and performed the first clinical examinations (Barker et al., 1986) with transcranial magnetic stimulation (TMS). Compared to TES, TMS is less painful. Additionally, the magnetic field is very effective, because it is able to pass through high resistant structures such as the scalp.

The basic principle of TMS is electromagnetic induction: a coil of wire, the magnetic coil, is placed tangentially on the subject's scalp and generates a current within the coil by a brief discharge of the capacitor. This primary current induces a time-varying magnetic field at right angles to the current, which passes through the scalp, the skull, and the cerebrovascular fluid. Perpendicular to itself, the magnetic field produces an electric field in the conductive brain tissue (Hallett, 2000, Krings et al., 2001, Cohen et al., 1990), which affects the transmembrane potential of the neurons. The changes at microscopic level lead to macroscopic responses, which can be detected with function imaging tools or behavioral observations (Ilmoniemi et al., 1999). The size of the electric field is proportional to the time-rate of change of the magnetic field (Cohen et al., 1990).

Electric field penetration and focality are important for obtaining spatially accurate information on cortical representations. Thereby, the shape, size, and orientation of the stimulating electric field depend on different variables such as the shape of the head, stimulation parameters, and on location, orientation, and geometry of the coil (Ruohonen and Ilmoniemi, 1999). Earlier studies investigated different coil types and concluded that a figure-eight shaped coil was the best suitable coil form (Cohen et al., 1990, Deng et al., 2013). In round coils, there is no current at the center itself, but in figure-eight shaped coils, which were also used in this study, the maximal current is in the middle at the intersection of the two round components (Figure 1).

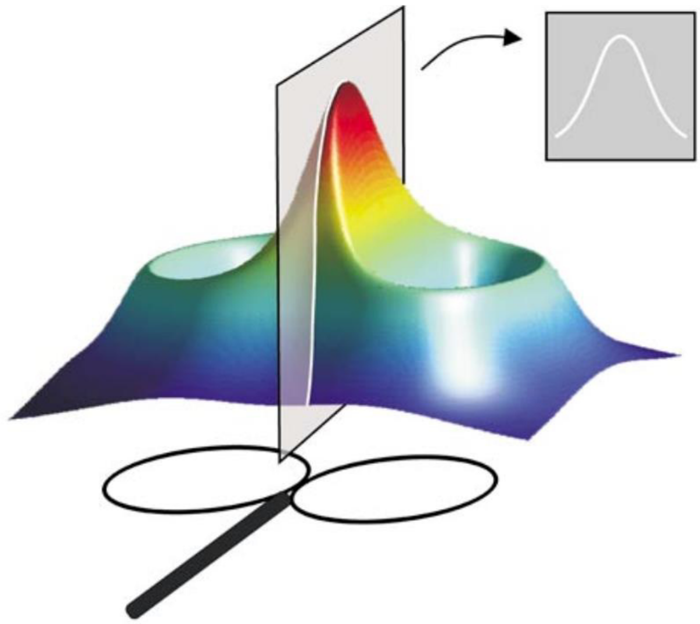

Figure 1: Electrical field induced by a figure-eight shaped coil. Maximal current is demonstrated in red. Reprinted from Thielscher & Kammer (Thielscher and Kammer, 2002), with permission from Elsevier.

Depending on stimulation parameters, TMS is capable of both facilitating and inhibiting cortical processes. Exciting effects of TMS are useful for mapping the motor cortex by stimulating motor eloquent regions and measuring the corresponding motoric answer in the contralateral hemibody by MEPs recorded with surface EMG electrodes. Inhibiting effects allow investigating causal relations between the brain and its function (i.e. functional mapping, by creating a temporary lesion in the stimulated neurons). This virtual lesion can be understood as TMS-induced disorder within the coordinated pattern of neural activity involved in a given task, which leads to interference of task performance (Pascual-Leone, 1999). Amassian et al. (Amassian et al., 1989) published the first results from TMS as a virtual-lesion technique in the visual cortex.

1.1.2. Repetitive TMS

Technical progresses led to the development of repetitive TMS, which enables the application of trains of magnetic stimuli at frequencies of up to 100 Hz. Depending on the utilized frequency, repetitive TMS allows improvement or inhibition of task performance. Generally, low stimulation frequencies (≤1 Hz) are assumed to rather decrease than to increase cortical excitability (Wassermann, 1998). However, parameters such as number of stimulation trains or stimulation duration also seem to influence the impact of stimulation on cortical excitability. Furthermore, a high inter-individual variability of these modulatory effects was observed (Maeda et al., 2000).

Altogether, the development of repetitive TMS opened up new fields of application, inter alia, the investigation of cortical language organization via induction of language interruption (Pascual-Leone et al., 1991), or the treatment of psychiatric diseases (Paus and Barrett, 2004).

1.1.3. Navigated TMS

For accurate interpretation of TMS results, knowledge of the exact location of the applied stimulus is evident. Wide inter-individual anatomical differences hamper the accuracy and reproducibility of TMS. For example, variations in the size and shape of the head and the thickness of the scalp and the skull, thus the distance between the coil and the tissue to be stimulated, should be taken into account. These variables affect the size and shape of the field before it reaches the neurons. The attempt to apply stimulation exactly over the desired location and the uncertainty over the actual precise point of stimulation led to the development of navigated TMS (nTMS). Therefore, an MRI of the subject’s brain was required. The coil location was determined with respect to the subject’s head, and landmarks of the head were tagged on the subject’s MRI. This allowed for calculation of the approximate position of the coil (Krings et al., 1997, Miranda et al., 1997, Rushworth et al., 2002, Neggers et al., 2004) and thus, of the stimulated region, when assuming that neurons in the region with the strongest induced current were activated preferentially (Thielscher and Kammer, 2002). Nevertheless, these methods did not include the location, orientation, and amplitude of the induced cortical electric field.

The shape, the strength, and the peak value of the strength of the induced electric field in turn highly depends on the shape of the brain. Therefore, the TMS technique was combined with a neuronavigation system, which takes into account the individual brain anatomy, coil parameters, and stimulation intensity and calculates the location, strength, and direction of the stimulating field. An optical tracking system realizes real-time navigation by recognizing the TMS tracking tools and visualizing the actual field overlaid directly in the 3D-reconstruction of the subject’s brain. Real-time monitoring of the coil and the head allowed the examiner to react to problematic head movements during the investigation by shifting the coil and thus, maintaining the maximum stimulation focused on the target (Hannula et al., 2005, Ruohonen and Karhu, 2010).

1.1.4. Applications of TMS

Within the recent decades, TMS has developed into a widely used diagnostic, therapeutic, and research tool. For example, TMS has been reported to show therapeutic effects on neurological and psychiatric disorders such as major depression (George et al., 1995, Berlim et al., 2013), schizophrenia (Hoffman et al., 2003, Franck et al., 2003, Dougall et al., 2015), anxiety disorders (Pallanti and Bernardi, 2009), movement disorders (Cunnington et al., 1996), epilepsy (Theodore, 2003, Kimiskidis, 2010), or tinnitus (Kim et al., 2014, Piccirillo et al., 2013, Meng et al., 2011), so that TMS is discussed as tool to be included into the toolbox of neurological and psychiatric treatment (Ridding and Rothwell, 2007, Lefaucheur et al., 2014, Slotema et al., 2010).

Moreover, TMS as primary brain-mapping tool has been utilized for investigating the human motor cortex. In the process of time, research applications have been extended and TMS was also applied over non-motor areas for investigating cognitive functions, for example, the cortical organization of language production (Pascual-Leone et al., 1991). The results are valuable for both neuropsychological research and clinical practice. Thereby, clinical applications are to be found mainly in the faculty of neurosurgery in preoperative detection of motor- and language-eloquent regions. Recent studies provided improvement of treatment outcomes in patients with rolandic lesions employing preoperative nTMS motor mapping (Krieg et al., 2014a, Frey et al., 2014). Furthermore, there exist data that also shows rTMS language mapping tends to ameliorate the clinical course of brain-tumor patients (Sollmann et al., 2015a). Nevertheless, although preoperative detection of motor-eloquent regions via nTMS is already well established in some departments, the presurgical investigation of language-eloquent areas is not yet used routinely thus far.

1.2. Cortical distribution of language

1.2.1. Reasons for language mapping

Besides the neuropsychological research aim of uncovering brain function in detail, knowledge about cortical organization is desirable in case of brain tumor surgery. Neurosurgeons on the one hand aim to maximize the resection of tumor-affected brain tissue; whereas on the other hand, they attempt to minimize the risk of permanent loss of neurological function by preserving particularly rolandic and language areas. Therefore, in case of lesions involving language areas, it is reasonable to detect tissue essential for language function as meticulously as possible. The safest method to spare those areas and to avoid postoperative decline in language processing is to intraoperatively map cortical function.

1.2.2. Classic language maps and current models of language mapping

Over a century ago, models on the cortical organization of language were based only on lesion studies of brain-damaged patients, mainly on patients with stroke. Thereby, the classic model of language developed, which included the posterior inferior frontal Broca area (Brodmann's area [BA] 44 and 45) for language planning and production (Broca, 1861), and the temporoparietal Wernicke area (BA 22) for identification and analysis of linguistic sensory stimuli and sound representation (Wernicke, 1874) (Figure 2).

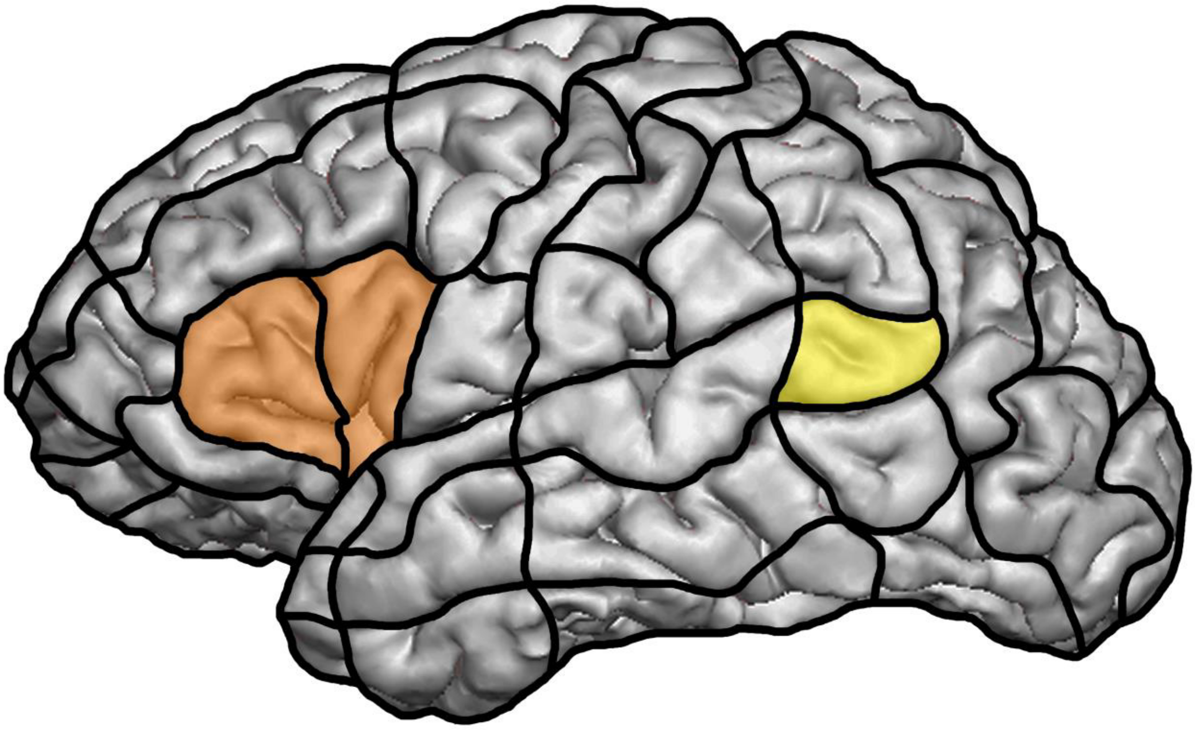

Figure 2: Broca's area (orange) and Wernicke's area (yellow) displayed in the cortical parcellation system (CPS) of the left hemisphere.

These findings were expanded by postulating the inferior parietal lobe and the arcuate fasciculus to connect the motor-related area with the comprehension-related area (Lichtheim, 1885, Geschwind, 1970) The so-called neurological model of language processing has represented the most popular and principal concept of cortical language organization for many years.

In the course of time, different brain mapping tools have gradually contributed to the present idea of cortical language organization; for example, Catani et al. (Catani et al., 2005) expanded Lichtheim's hypothesis of an additional pathway by investigating the connectivity of perisylvian language areas via fiber tracking: the study group found an additional, parallel, indirect pathway running laterally and connecting Geschwind's and Broca's territory (anterior segment), and Geschwind's and Wernicke's territory (posterior segment).

Additionally, the interindividual variability and the individual topographic extent of language-eloquent regions were found to be larger than actually proposed in the classic language model (Ojemann, 1979, Ojemann and Whitaker, 1978, Ojemann et al., 1989, Tzourio-Mazoyer et al., 2004). In recent investigations, we observed reorganization of the brain during physiological procedures, for example, learning mechanisms (Shtyrov et al., 2010). This reorganization was also observed during pathological events such as stroke or glioma, where distortion by the mass of the tumor and cortical plasticity mechanisms influence the organization of language (Seitz et al., 1995, Duffau, 2006, Duffau, 2005). Thus, the classic static view on functional organization of brain regions has been more and more replaced by the idea of a dynamic representation. This means, on the one hand, that many regions outside Broca's and Wernicke's territory could indeed be involved in language processing and might lead to functional consequences in case of damage. On the other hand, lesions located in critical brain regions can remain without cognitive disorders. Consequently, areas that have been considered as non-removable for a long time can instead be completely resected in some cases (Sarubbo et al., 2012, Southwell et al., 2016, Tate et al., 2014).

It is therefore not sufficient to anatomically determine essential brain areas (Pouratian and Bookheimer, 2010), but suggested to individually map the language cortex before and during brain surgery in order to minimize the postoperative aphasia risk.

1.2.3. Common language mapping modalities

Besides lesion-based patient studies, in which existing injuries were linked with clinical symptoms, the complexity of language processing has been investigated by several brain mapping modalities in the past decades.

Almost 70 years ago, Penfield et al.'s groundbreaking work in the development of direct cortical stimulation (DCS) revolutionized the language mapping field: they succeeded in producing speech arrest by applying electrical cortical stimulation to the precentral gyrus, the inferior frontal gyrus, and parietal areas (Penfield and Rasmussen, 1949, Penfield and Roberts, 1959). Thus, the idea arose to intraoperatively monitor the patients' brain function. In case of patients with tumors in or adjacent to language-eloquent regions, this meant having the awake craniotomied patient perform language tasks while the surgeon applies electrical stimulation and thus, detects areas essential for naming. During the following decades, neurosurgeons such as Ojemann and Berger extended the methods of awake surgery (Ojemann et al., 1989, Ojemann and Mateer, 1979). Today, DCS is considered as gold standard in language mapping (Corina et al., 2010, De Witt Hamer et al., 2013, Ojemann and Whitaker, 1978, Ojemann et al., 1989, Robles et al., 2008, Sacko et al., 2011, Sanai and Berger, 2008, Talacchi et al., 2013, Haglund et al., 1994). For a current protocol for awake craniotomy in language cortex tumor surgery, see for example Picht et al. (Picht et al., 2006). With regard to postoperative deficits, the outcome depends from the distance of the resection border to the closest language area (Haglund et al., 1994). This underlines the importance of an patient-by-patient language mapping. Nevertheless, the risk of perioperative adverse events is higher in awake craniotomies than under general anesthesia (Picht et al., 2006) and therefore it should be carefully assessed whether the patient is a suitable candidate to undergo awake surgery.

The most common non-invasive methods that are suitable for preoperative mapping or healthy volunteers are functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG), electroencephalography (EEG), and positron emission tomography (PET).

FMRI, a well-established technique of functional brain imaging (FitzGerald et al., 1997, Binder et al., 1997), relies on the measurement of cerebrovascular effects. Thereby, different magnetic characteristics of deoxygenated and oxygenated forms of hemoglobin were used to give information about activated brain areas and thus, regions involved in word processing (Ogawa et al., 1990). Over recent decades, it has been increasingly utilized for clinical and research applications. Nevertheless, especially in cases of tumor patients, fMRI shows a notable susceptibility to errors due to edema and oxygenation changes caused by the tumor. Hence, this technique failed to provide reliable preoperative language mapping by showing only minor correlation with intraoperative DCS (Giussani et al., 2010, Roux et al., 2003, Yetkin et al., 1997, Sollmann et al., 2013b, Picht et al., 2006).

MEG allows measuring the magnetic fields associated with electrical currents of activated neurons in the brain (Papanicolaou et al., 1999). In particular, its high temporal resolution is advantageous for studying the time course of language processing (Levelt et al., 1998, Pulvermuller et al., 2003). Additionally, it has been frequently used to investigate language lateralization (Breier et al., 2000, Kim and Chung, 2008).

Electroencephalography (EEG) records electrical activity within neurons of the brain with electrodes placed on the scalp. Its contribution to the research of language function is characterized by considerable temporal and spatial resolution (Weiss and Mueller, 2003, Michel et al., 2004, Ganushchak et al., 2011).

In PET, the scanner traces radiolabeled molecules that have diffused from blood vessels to activated brain tissue. Higher neural activity is correlated with higher metabolism and increased regional blood flow and thus can be visualized (Petersen et al., 1988, Liotti et al., 1994).

Contrary to the already named positive characteristics, the crucial disadvantage of the above named activation neuroimaging studies compared to (“virtual”) lesion-based studies is that they provide only information about the involvement of a specific area in language processing. Consequently, in contrast to lesion-based methods such as DCS, rTMS, and patient studies, fMRI, MEG, EEG, and PET cannot demonstrate regions that are essential for a particular function.

1.2.4. Previous TMS language mapping studies

In 1991, Pascual-Leone et al. for the first time evaluated repetitive TMS to examine human cortical language function. Thereby, the authors tested stimulation frequencies of 8 Hz, 16 Hz, and 24 Hz applied for 10 s (and stimulation intensities of 40%, 60%, and 80% of the total output), and epileptic patients had to perform a number-counting task. For each patient, repetitive TMS was able to induce speech arrest. Patients denied discomfort or facial muscle twitching being the reason for the inability to speak. However, the exact stimulated sites that caused the language disturbances could not be determined (Pascual-Leone et al., 1991). In the following years, a various number of studies were performed mainly in epileptic patients, but also in healthy volunteers, to investigate the reliability of those findings and the lateralization of language (Jennum et al., 1994, Wassermann et al., 1999, Michelucci et al., 1994), as well as to check safety of repetitive TMS (Michelucci et al., 1994, Pascual-Leone et al., 1993, Wassermann, 1998). Thereby, the research teams tested a variety of different language tasks, such as object naming, counting, and word reading, as well as stimulus parameters (Epstein et al., 1996, Wassermann et al., 1999). Epstein et al. (Epstein et al., 1996) published indicative results by showing that lower stimulation frequencies of 4 Hz to 8 Hz allow a clearer distinction between speech arrest and dysarthria from muscle twitching than higher frequencies of 16-32 Hz. Because previous studies have shown that different language regions were activated at different time points during the language production procedure (Salmelin et al., 1994, Wheat et al., 2012, Schuhmann et al., 2012), it is also important to choose the optimal timing of pulse train onset relative to picture presentation (Krieg et al., 2014b).

With the development of nTMS, cortical language mapping via repetitive navigated TMS (rTMS) gained more importance as useful preoperative investigation in neurosurgery (Sollmann et al., 2013b). Lioumis et al. (Lioumis et al., 2012) presented the first language mapping study that used rTMS combined with synchronous video and audio recording. A considerable number of rTMS language studies for general neuroscientific and neurosurgical purposes followed. E.g. Krieg et al (Krieg et al., 2016) applied rTMS combined with an object-naming task to 50 healthy subjects in order to design a “cortical language map.” Thereby, evoked language errors were divided into different sub-categories. The employed task succeeded in evoking a considerable number of language errors; nevertheless, neologisms, and phonological and semantic paraphasias (for definition of language errors see below) only appeared rarely. In recent investigations, rTMS combined with object naming was compared to DCS during awake craniotomy. Thereby, rTMS was demonstrated to identify language-positive regions in anterior brain areas quite reliably (Tarapore et al., 2013, Picht et al., 2013). Despite generally high sensitivity compared to DCS, sensitivity was higher in anterior regions than in posterior ones. Further, it was noted that altogether, rTMS tended to detect more areas as language positive than DCS did. Therefore, rTMS revealed a high number of false-positive responses and thus low specificity compared to the gold standard DCS. Hence, with the actual level of knowledge, rTMS positive points are not trustworthy enough for clinical utility. Moreover, clinical application of rTMS seems to be more valuable when preoperatively outlining language negative regions, which then can be safely resected during surgery. Regarding those false-negative responses, they were solely detected in posterior brain areas in a recent trial (Picht et al., 2013). We therefore aim to further improve rTMS language mapping of posterior regions and provide reliable negative-response maps to help the surgical team’s preoperative planning of the craniotomy location and size.

1.2.5. Relevance of language tasks

In the past, the underlying anatomy of language has not only been investigated by different language mapping modalities, but also by different language tasks. Thereby, a variety of cortical regions were found to be involved in language production, which can be attributed to a certain degree to the diversity of applied language tasks (Binder et al., 1997). In particular, expressive rather than receptive language abilities were thereby supposed to be task dependent (Banerjee et al., 2015). Further, in the course of time, lesion studies demonstrated that different components of language could be affected separately (Daniele et al., 1994, Goodglass et al., 1966, Farah, 1996, Marshall and Newcombe, 1973). We therefore assume that task selection also influences effects in rTMS language mapping.

Different language tasks demand different language subfunctions and thus, reveal different types of language errors. Furthermore, this possibly leads to the detection of different localizations of language-positive regions, which can be important in casse of surgical resection of brain tumors. In other words, sub-optimal selection of language task due to disregard of the function of the area being tested can lead to false-negative results and thus, to severe postoperative defects. Previous studies reported postoperative language deficits despite intraoperative negative visual naming testing (Hermann et al., 1999, Hamberger et al., 2005). Hence, assuming that different tasks reveal different language-positive regions, choosing the “right” language tasks corresponding to the tumor-involved area might minimize the risk of determining false-negative language areas during awake craniotomy. In the present study, we therefore examined the effects of four different language tasks on language localization in cases of 20 healthy subjects. Principally, we selected tests that were commonly used in language production assessment and easy practicable, so that they were also suitable for application during awake surgery. The tasks should further be supposed to involve posterior language regions. Therefore, in addition to the standardly used object-naming task, we tested a pseudoword reading, verb generation, and action-naming task.

For most modalities, object naming represents the most frequently and standardly used language task in pre- and intraoperative mapping. Involving several cortical and subcortical sub-functions, its superiority to other tasks such as counting was previously demonstrated (Petrovich Brennan et al., 2007). As far as to our knowledge, until now, an object-naming task has been the only visual language task applied in rTMS investigations combined with a navigated system.

A pseudoword is a string of letters that has no semantic representations, but that can be spelled in predictable ways based on spelling to sound relationships. Pseudoword reading was shown to evoke a wide spreading of left-hemispheric activation clusters (Taylor et al., 2013). Disruption in posterior brain regions was related to difficulties in word and pseudoword reading (Shaywitz et al., 2002, Taylor et al., 2013). Because there exist frequent patient cases of noun- or verb-specific language deficits, both an action-naming and a verb-generation task was selected. The verb-generation task is thereby supposed to be more demanding in semantics than other tasks and thus, might reveal distinct positive language areas (Seger et al., 1999).

1.2.6. Research question and aim of the study

In synopsis with the above-described current state of knowledge, rTMS as a comparatively new mapping modality has already provided an important contribution to the study of cortical language organization. Nevertheless, its accuracy, especially in posterior brain regions, still has to be refined. To our knowledge, different language tasks have not yet been investigated with regard to their influence on language localization during rTMS combined with a navigation system. Therefore, in the current study, the research question was whether we can improve rTMS language mapping with other task types that are more specific to posterior language areas. It was hypothesized that 1) the localization of language-positive areas varies depending on to the applied language task and that 2) the distribution of error types varies among different tasks.

Altogether, this study aims to contribute improving the correlation of rTMS and DCS for more reliable preoperative planning via rTMS. Furthermore, we want to establish the use of different language tasks in rTMS language mapping. This would enable investigators to refer to a selection of tests corresponding to a patient’s cognitive deficit.

2. MATERIALS AND METHODS

2.1. Study subjects

We included 20 purely right-handed subjects (ten male, ten female) without any neurological disorders. Their right-handedness was verified and confirmed by the Edinburgh handedness test (Oldfield, 1971). The mean age of the volunteers was 24.6 ± 1.7 (range 22–29). German was the only mother tongue of all subjects. Further inclusion criteria were an age above 18 years and written informed consent. Exclusion criteria were implanted metallic hardware near the discharging coil (for example, pulse generators or cochlear implants) and other general TMS and MRI exclusion criteria such as pacemakers (Rossi et al., 2009). Additional exclusion criteria were previous seizures, aberrant medical history, and pathological findings on cranial MRI, bilateral handedness, second mother tongue, and developmental language deficits.

2.2. Ethics

The experimental procedures were approved by the local ethical committee of the Technische Universität München (registration number: 2793/10) in accordance with the Declaration of Helsinki. All subjects were educated in detail about the research protocol by the clinical investigator. Additionally, they were given an information sheet. All volunteers gave written informed consent to participate prior to MR imaging.

2.3. Study design

In this study, volunteers underwent language mapping of previously determined left-hemispheric cortical spots. During stimulation, they had to perform four different language tasks to examine the impact of language tasks on error rate and location of language-positive areas.

2.4. Navigational MRI scan

Prior to rTMS language mapping, all participants underwent a navigational MRI scan on the same three Tesla MR scanner (Achieva 3T, Philips Medical Systems, The Netherlands B.V.). Therefore, an eight-channel phased array head coil was used.

The scanning protocol consisted of a 3D fast field echo sequence (TR/TE 8.3/3.9 ms, 1 mm^3 isovoxel covering the whole head, 5 min and 56 s acquisition time) without intravenous contrast administration for anatomical co-registration. Subsequently, by using the DICOM standard, the 3D dataset was transferred to the rTMS system.

2.5. rTMS language mapping

2.5.1. Experimental setup

After uploading the each patient's MRI to the rTMS system, the actual language mapping procedure could start. Therefore, we used the Nexstim eXimia NBS system version 4.3 (Figure 3) and a NexSpeech module (Nexstim Oyi, Helsinki, Finland).

The volunteers were invited to sit down on a chair, a screen 60 cm in front of them. On top of the screen, a stereotactic camera was installed. All participants received a head strap containing an optical tracking system, the head tracker. Besides the head tracker, a registration pen and the stimulation coil served as further tracking tools. They could be located via the camera through infrared tracking using spheres coated with a retroreflective surface. For real time MRI-guided targeting of the induced electric fields, it is necessary to link the MRI's and a subject's head. Therefore, the investigator used the registration pen to assign 12 landmarks (right ear, left ear, nose, and 9 spots distributed over both hemispheres) on a subject's head. Now the nTMS-device is able to show the location of the potential E-field in the MRI data set. Furthermore, during the actual mapping procedure, it gives information about stimulation intensity, E-field orientation, and coil parameters. So this system enables the examiner to stimulate specific spots very exactly in a subject's brain. Each site to be stimulated during the mapping procedure is tagged on the 3D-reconstruction of a volunteer's brain and saved for later analysis.

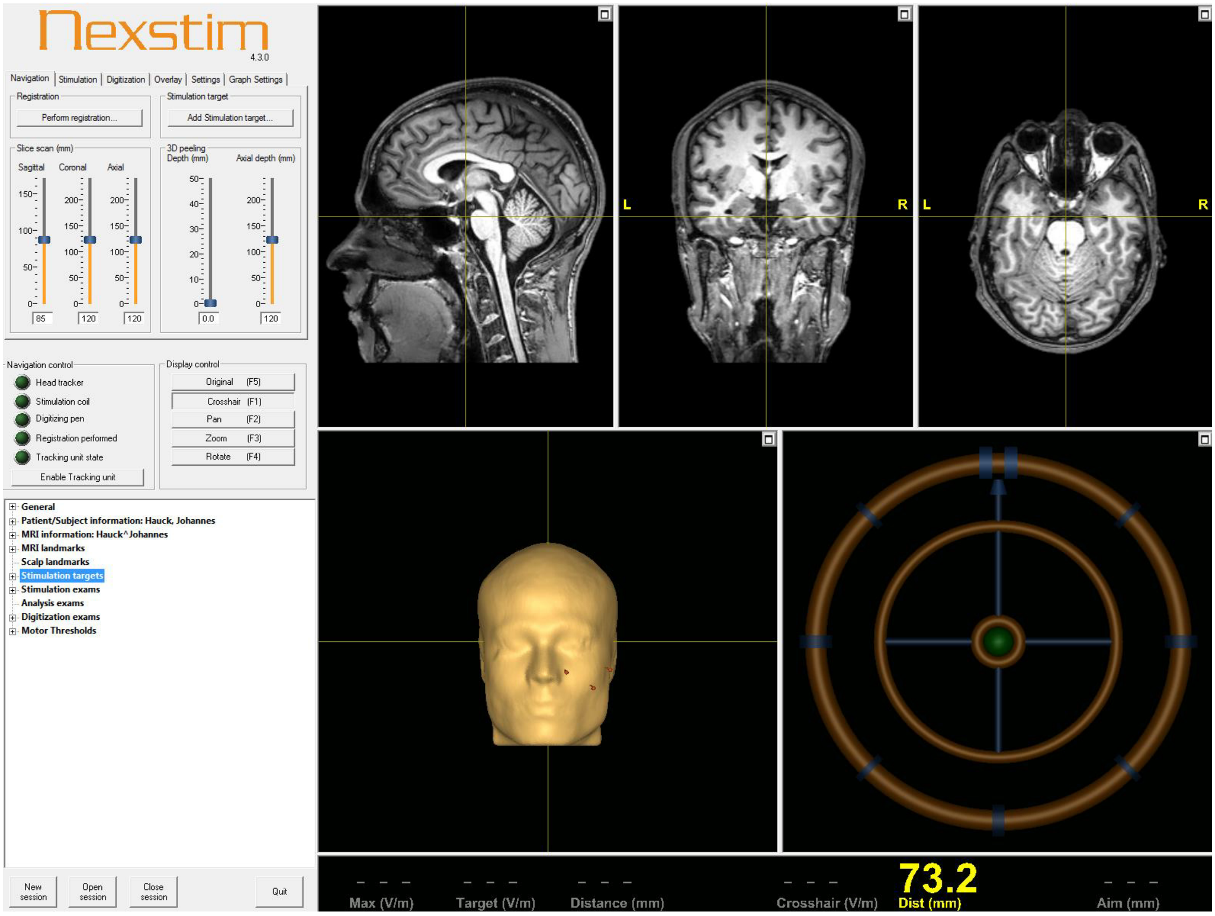

Figure 3: User interface of the Nexstim eXimia NBS system version 4.3 (Nexstim Oyi, Helsinki, Finland). The subject's MRI was uploaded and is demonstrated in a sagittal, coronal, and axial view. At the bottom left, the system shows the head shape reconstructed out of the MRI data. Coil angulation for "hotspot" determination can be verified by the image at the bottom right.

2.5.2. Motor threshold detection

Stimulus intensity had to be adjusted to each individual brain excitability by determining the resting motor threshold (RMT) of the abductor pollicis brevis (APB) muscle of the contralateral hand. The RMT is defined as the lowest stimulation intensity eliciting a motor response in the relaxed APB in five out of ten trials. For MT determination, we recorded EMG over the skin of right APB and the abductor digit minimi muscle (ADM) by pregelled Ag/AgCl electrodes (Neuroline 720, Ambu, Bad Nauheim, Germany). The reference electrode was located above the tendon of the biceps muscle of the ipsilateral elbow (Figure 4). Then, we detected the left-hemispheric "hotspot" (i.e., the spot showing the highest MEP amplitude for the right APB in the anatomically defined hand knob). Stimulation was applied repeatedly over this site. When five out of ten trials were positive, stimulation of this spot had to be continued, whereby the system aligned the stimulation intensity. Thus, the RMT could be determined. The individual amount of RMT was used as stimulation intensity during the following language mapping procedure.

Figure 4: Preparation of motor threshold determination. The subject is wearing a head strap with an optical tracking system for MRI-guided tracking of the stimulation. Pregelled Ag/AgCl electrodes were attached to the right abductor pollicis brevis (APB) muscle and the right abductor digiti minimi (ADM) muscle. The reference electrode was placed over the tendon of the biceps brachii muscle.

2.5.3. Language tasks

We tested four different visual language tasks, including naming, reading, and generation tasks: object naming, pseudoword reading, verb generation, and action naming. The tests had to be performed in German. Each task consisted of a set of 100 items that were randomly mixed within one task.

For the object-naming task, the colored items on the screen showed common objects, such as a ball, a ladder, or an apple (Figure 5). The demand was to name the displayed pictures as precisely and concisely as possible. Articles should be omitted. The pictures used in this task were similar to those in the Snodgrass and Vanderwart picture set.

Figure 5: Examples of items presented during the object-naming task.

The pseudoword task consisted of 50 real words, randomly mixed with 50 pseudowords (Figure 6). Hereby, the real words were used as a control. Both words and pseudowords should be read aloud clearly. The words were derived from a wordlist of Felty et al. (Felty, 2007), containing disyllabic nouns, verbs, and adjectives in a CVCCVC (C = Consonant, V = Vowel) pattern. Felty et al. created analog structured pseudowords out of those real words.

makpes

tichkik

löfnem

zungdim

schengschir

hikseß

gölgon

wekmek

Figure 6: Examples of items presented during the pseudoword-reading task.

For the verb-generation task, the volunteers were instructed to build verbs out of visually presented objects (Figure 7). We ensured that composed verbs including a substantive were avoided. The presented objects were those of the object-naming task.

Figure 7: Examples of items presented during the verb generation task.

In the fourth task, action naming, we demonstrated pictures showing daily activities (for example, dancing or playing; Figure 8). In this language test, we also made sure that subjects did not use word classes other than verbs.

Figure 8: Examples of the items presented during action naming.

2.5.4. Baseline performance

Before stimulating the brain, naming without stimulation (i.e., baseline performance) was recorded. Therefore, the subjects had to read or name the item on the screen quickly and fluently. In order to take into account individual differences in the volunteers' vocabulary, misread or misnamed items were discarded from the stimulus sequence. "Misread or misnamed" thereby meant that any error described under 2.6.1 occurred. Thus, only well-recognized items remained in the picture set for the following stimulation, and unfamiliar ones were excluded. Items were displayed for 700 ms for the object-naming, verb-generation, and action-naming tasks. Because some pseudowords were quite long, we therefore used a display time (DT) of 1.0 s. The inter-picture interval (IPI) for all tasks was 3.0 s. Directly after baseline performance of one task, language mapping followed for that task. Subsequently, the baseline and mapping procedure of the next task was performed. The number of correctly named baseline items was documented.

2.5.5. Language mapping procedure

For language mapping we used the same items as in the baseline session without the misnamed/misread ones. Exactly like in baseline performance, the subjects were asked to name or read, respectively, the randomly displayed items as quickly and precisely as possible. Magnetic pulses were applied simultaneously with picture presentation. The stimulation parameters for picture presentation were identical to those used in baseline performance: the DT was 700 ms for object naming, verb generation, and action naming; for pseudoword reading it was 1.0 s. We again used an IPI of 3.0 s. Stimulation intensity was 100% of RMT. Because this intensity succeeded in inducing language impairment in each case, it did not have to be augmented furthermore. The picture-to-trigger interval (PTI) was 0 ms (Indefrey, 2011, Krieg et al., 2014b). We applied ten bursts via each rTMS train with 5 Hz over 2 s. The coil was placed strictly tangential to the skull in anterior-posterior field orientation (Lioumis et al., 2012, Epstein et al., 1996, Wassermann et al., 1999). The software optimized the field strength by showing the optimal tilt of the coil. Accepted minimum electrical field strength at the region of interest was 55 V/m and ranged from 55-80 V/m across subjects.

2.5.6. Stimulated points

Altogether, rTMS was applied to 46 spots per subject, which were widely distributed over the left hemisphere (Figure 9) and easily reproducible in the healthy volunteers' cortical 3D reconstructions. We tagged those points prior to each language mapping session. Each of the 46 previously determined sites was stimulated three times per language task, which equals 138 stimulations per task and 552 stimulations for the entire language-mapping session. For superior description of positive points we used the terminology according to Corina et al. (Corina et al., 2005) (Table1).

Table 1: Anatomical names and abbreviations of the cortical parcellation system (CPS) according to Corina et al. (2005).

Abbreviation	Anatomy
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
orIFG	orbital part of the inferior frontal gyrus
pMFG	posterior middle frontal gyrus
pMTG	posterior middle temporal gyrus
polIFG	polar inferior frontal gyrus
polMFG	polar middle frontal gyrus
polMTG	polar middle temporal gyrus
polSFG	polar superior frontal gyrus
polSTG	polar superior 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

Due to extreme discomfort, the extent of stimulated areas had to be restricted. Thus, we did not map the anterior middle temporal gyrus (aMTG), the polar superior and polar middle temporal gyrus (polSTG, polMTG), the orbital part of the inferior frontal gyrus (orIFG), and the polar superior, polar middle, and polar inferior frontal gyrus (polSFG, polMFG, polIFG). Additionally, increasing distance between skin and brain in the inferior temporal gyrus (ITG) lead to decreasing stimulation intensity below 50 V/m, so that we also had to omit the ITG (Krieg et al., 2013, Krieg et al., 2016).

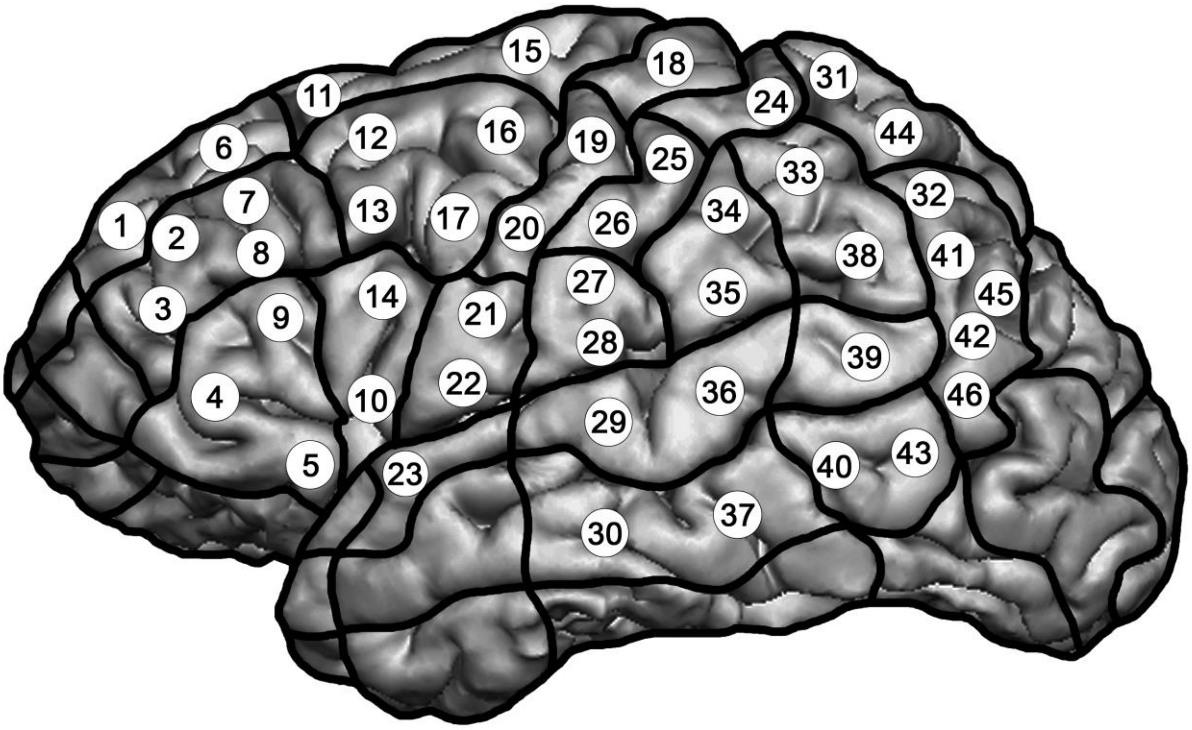

Figure 9: Outline of the 46 stimulated cortical sites.

2.5.7. Classification of stimulation related discomfort

Directly after the language mapping session, we asked the volunteers about discomfort during stimulation. To provide as much objectivity as possible, we used the visual analogue scale (VAS). The subjects were requested to classify their pain from 0 (“no pain”) to 10 (“maximum pain imaginable”) points for temporal and for nontemporal regions. Thus, we obtained two values for pain classification: “pain (VAS) temporal and pain (VAS) convexity”.

2.6. Data analysis

2.6.1. Video analysis and error categorization

Data analysis followed via video interpretation with the NexSpeech module (Nexstim Oyi, Helsinki, Finland). We evaluated performance during stimulation and directly compared it to the baseline. Thereby, we payed attention to language impairment and to differences in naming latencies. The analysis was blinded to the location of cortical spots and was conducted by one single investigator to avoid inter-individual differences in data analysis (Sollmann et al., 2013a). Because language impairment manifested itself in a various number of different kinds of errors, it was divided into the following error categories derived from Corina et al. (Corina et al., 2005): no-response errors, hesitations, performance errors, phonological and semantic paraphasias, and neologisms. Additionally, we introduced the category nominalization errors for the verb-generation and action-naming tasks. All error types were summarized in the category "all errors." In the following, the distinct error types are described in short:

No-response errors: Stimulation leads to lack of naming response; a subject is unable to give a verbal answer to a shown item.

Hesitations: A participant was able to name an item, but with a delayed onset compared to baseline. Sounds of hesitancy such as "hmm…" before pronouncing the correct word were also assigned to this error category.

Performance errors: This category included stuttered, imprecise, or slurred articulation, thus form-based distortions. Performance errors embraced disarthric and apractic errors.

Phonological paraphasias: A subject unintendedly changed a correct word by substitution, insertion, omission, or transposition of a letter or a segment of the word. Thereby, an already existing other word, or a completely new one could emerge. The pronounced word was phonologically different, but similar to the target word. If at least half of the phonemes of the produced form were identical to the target word, the error was classified as "phonological paraphasia"; sharing less than 50% of phonemes with the target word, it was categorized as "neologism."

Neologisms: A volunteer created a completely new, non-existent word.

Semantic paraphasias: Hereby, the target word was replaced by a semantically associated or related word. This category included more specific (subordinate), more general (superordinate), and same-leveled terms when compared to the word originally used in the baseline.

Nominalization errors: In the verb generation and action-naming task, it occurred that some volunteers were unable to pronounce the correct verb, but the correspondent noun. For those cases we introduced the error category “nominalization.”

Especially in temporal areas, there appeared errors attributed to discomfort or muscle stimulations, which were discarded from further analysis.

The NexSpeech Analyzer Software (Nexstim Oyi, Helsinki, Finland) allowed us to tag any kind of error directly in the recorded video (Figure 10), and to use this data to generate a summary report containing all marked errors and the corresponding numbers of stimulation trains. During this analysis, the examiner was blinded to the location of cortical stimulation spots. Subsequently, the error-evoking stimulation train was matched to the previously determined cortical stimulation spots. Therefore, we selected the corresponding number in the list of all stimulation points in the nTMS system, which automatically displayed the respective location of the coil in the 3D-reconstruction of a subject’s head.

As mentioned above, each spot was stimulated three times. If at least one out of three stimulations caused any error, we considered that site as language positive.

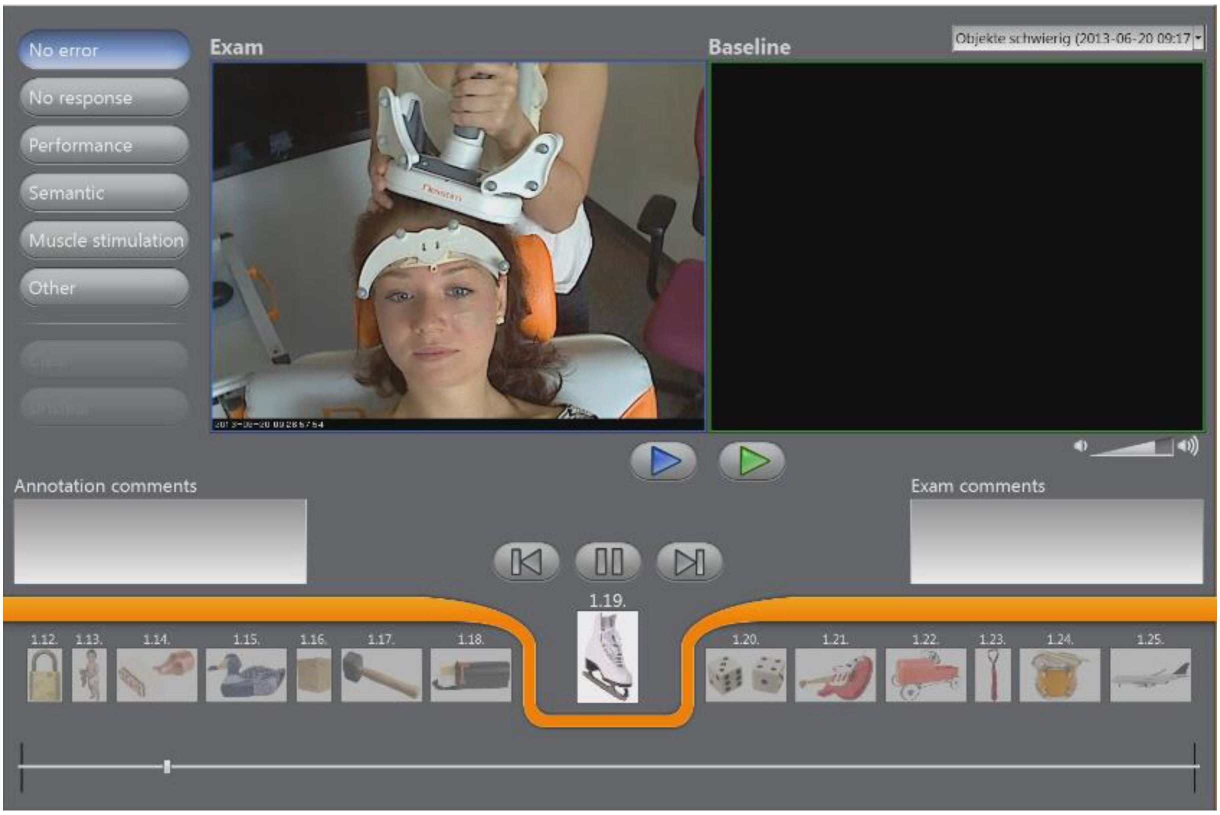

Figure 10: Language mapping analysis via NexSpeech Analzyer Software (Nexstim Oyi, Helsinki, Finland). Performance during mapping session ("Exam") can directly be compared to the recorded baseline ("Baseline"). Language impairment was annotated and classified into different error types.

2.6.2. Discription of language error localization

In order to facilitate comparison of our data with previous DCS/rTMS studies, we divided the stimulated spots into two groups: the anterior group comprised stimulation points 1 to 22; the posterior one included points 23 to 46. Furthermore, besides presenting the absolute number of language errors, we additionally calculated the error rates per stimulation point, per anterior region, per posterior region, and overall separately for each language task and each error category within the tasks. The error rate resulted from the number of evoked errors divided by the number of stimulations and is expressed as a percentage. We visualized our data by employing templates that show the 46 stimulation points and the corresponding error rates, whereby the points were colored according to the level of error rate. For results and discussion we also used the CPS (Table 1) presented by Corina et al. (Corina et al., 2005) to describe the localization of language-positive points in an appropriate way.

2.6.3. Statistics

RMT, number of correctly named baseline pictures, and pain (VAS) were presented as mean ± standard deviation (SD). Differences between pain in temporal and nontemporal areas were compared via Wilcoxon-signed rank test for matched groups. Friedman's test for nonparametric matched groups was performed to test differences between baseline performances within each language task. For testing correlation between the baseline error rate of each task and the error rate during stimulation of that task, we performed nonparametric Spearman correlation with a two-tailed p value and 95% confidence interval. Furthermore, we tested differences among distribution of error rates per stimulation point in different tasks using Friedman's test followed by Dunn's post hoc test. A value of $p < 0.05$ was considered significant (Graph Pad Prism 6.0, La Jolla, CA, USA).

3. RESULTS

3.1. Study subjects

None of the 20 enrolled subjects had pathological findings in the navigational MRI, so that we have excluded no one from the study so far.

3.2. Stimulation-related discomfort and incidents

One male subject out of the 20 included participants developed vegetative symptoms including nausea and perspiration while applying single pulses during RMT determination prior to rTMS. Additionally, he complained about intensive pain. Thus, we canceled his investigation immediately and excluded him from further analysis. Stimulation was well tolerated without any further incidents by the remaining 19 subjects.

The mean VAS score for maximum painful stimuli was significantly higher in temporal than in non-temporal areas ($p < 0.0001$) and varied enormously among subjects (Table 2).

Table 2: Pain during stimulation according to the visual analogue scale (VAS). Pain in temporal and non-temporal (convexity) areas are presented as mean ± SD and range.

	mean ± SD	range
pain (VAS) convexity	1.7 ± 1.6	0-5
pain (VAS) temporal	5.4 ± 2.2	2-10

3.3. rTMS mapping parameters

Motor threshold intensity was 33.1 ± 4.8 % (range 24–44%) of maximum stimulator output. Because stimulation intensity of 100% of RMT was sufficient to elicit language errors in each participant, we did not augment the intensity for language mapping as we had done in several cases in previous studies (Krieg et al., 2016, Sollmann et al., 2013a). The chosen repetition rate of 5 Hz over a time span of 2.0 s (10 pulses) was also well-tolerated by the subjects and thus was constantly applied in each session.

3.4. Errors in different language tasks

3.4.1. Overview of overall error rates

Generally, comparing the overall error rates, the highest number of errors was observed during the object-naming task (13.7%), followed by the verb-generation (13.5%) and action-naming tasks (11.1%). The lowest error rate appeared during the pseudoword-reading task (4.0%; Table 3). Object naming, pseudoword reading, and verb generation revealed higher error rates in anterior regions; action naming showed a higher error rate in posterior regions than in anterior regions (Table 3, Figure 11, Figure 12, Figure 13).

Table 3: Summary of naming errors. Summary of naming errors in percentage induced by rTMS: error rates of each error type in the tested language tasks. Friedman's test shows significant differences among distribution of error rates per stimulation point in different tasks. EC=Error Category, NR=No response, H=Hesitation, P=Performance, Ph=Phonological paraphasia, S=Semantic paraphasia, Neo=Neologism, No=Nominalization, AE=All errors.

EC	**Object naming**			**Pseudoword reading**			**Verb generation**			**Action naming**			**Friedman's test**		
	all	ant.	post.	all	ant.	post.	all	ant.	post.	all	ant.	post.	all	ant.	post.
NR	0.02	1.90	1.40	0.00	0.10	0.00	1.60	1.40	1.80	1.80	1.10	2.40	p<0.0001	p=0.0020	p<0.0001
H	9.90	10.80	9.10	1.50	1.80	1.20	9.50	10.30	8.70	7.80	8.00	7.60	p<0.0001	p<0.0001	p<0.0001
P	1.30	1.40	1.20	0.80	1.00	0.70	1.00	1.10	0.80	0.60	0.60	0.70	p=0.1084	p=0.2309	p=0.3384
Ph	0.20	0.20	0.30	1.60	1.80	1.50	0.40	0.70	0.10	0.40	0.70	0.10	p<0.0001	p=0.0011	p=0.0004
S	0.60	1.00	0.20	0.00	0.00	0.0	0.30	0.40	0.30	0.30	0.30	0.20	p=0.0041	p=0.0066	p=0.3916
Neo	0.00	0.10	0.00	0.00	0.00	0.10	0.10	0.10	0.10	0.00	0.10	0.00			
No	0.00	0.00	0.00	0.00	0.00	0.00	0.60	0.60	0.60	0.20	0.10	0.20			
AE	13.70	15.30	12.10	4.00	4.60	3.40	13.50	14.50	12.50	11.10	10.80	11.30	p<0.0001	p<0.0001	p<0.0001

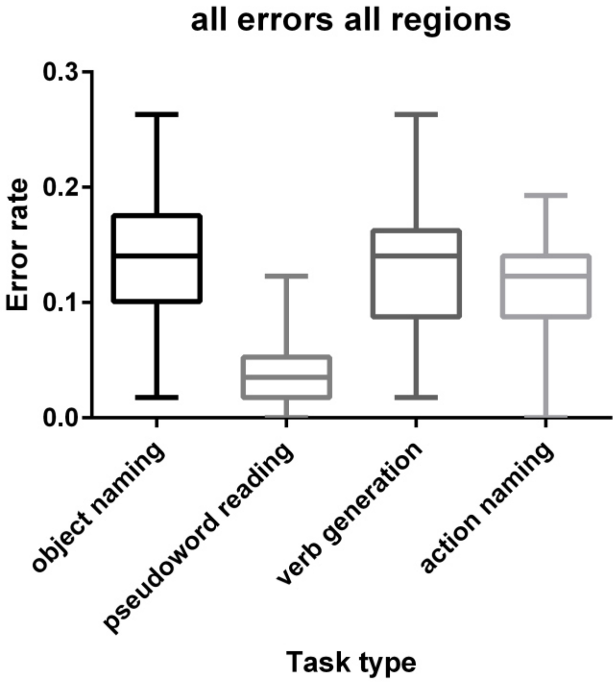

Figure 11: Overall error rates per stimulation site in all regions. Results are demonstrated for object naming, pseudoword reading, verb generation and action naming.

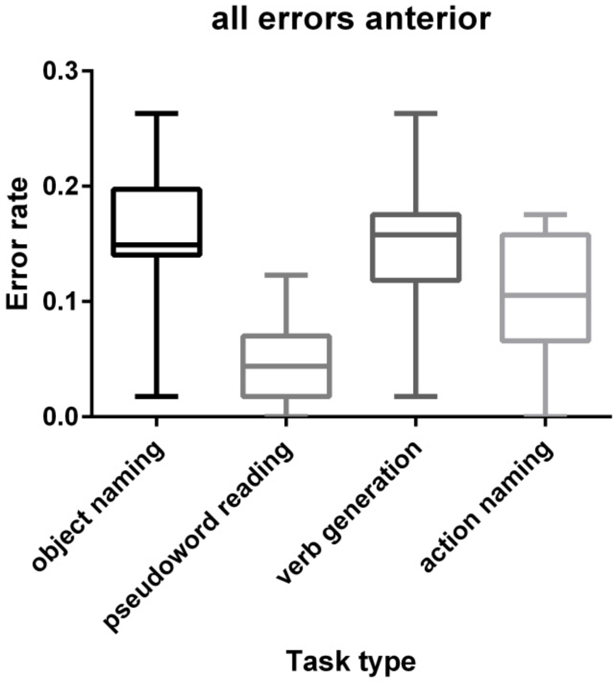

Figure 12: Overall error rates per stimulation site in anterior regions. Results are demonstrated for object naming, pseudoword reading, verb generation and action naming.

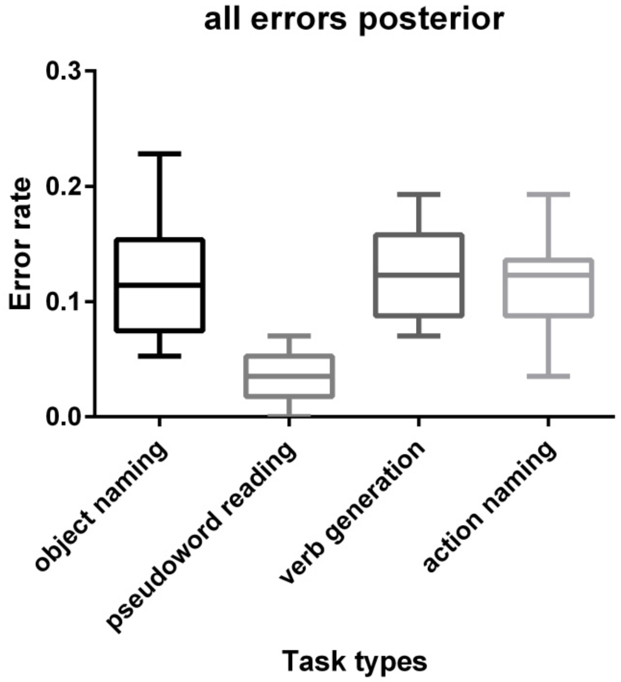

Figure 13: Overall error rates per stimulation site in posterior regions. Results are demonstrated for object naming, pseudoword reading, verb generation and action naming.

3.4.2. Object naming

First, when regarding the overall error rates, we observed a considerably high number of errors and language impairment at each stimulation point. Sites with highest overall error rates were found in the triangular inferior frontal gyrus (trIFG), ventral pre-central gyrus (vPrG), ventral post-central gyrus (vPoG), and middle middle temporal gyrus (mMTG), followed by the middle superior frontal gyrus (mSFG), posterior middle frontal gyrus (pMFG), and opercular inferior frontal gyrus (opIFG) (Figure 14).

Within the four tasks, object naming showed language impairment the most frequently. Specifically, during this task performance, we found the highest number of all errors, hesitations, performance errors, and semantic paraphasias (Table 3).

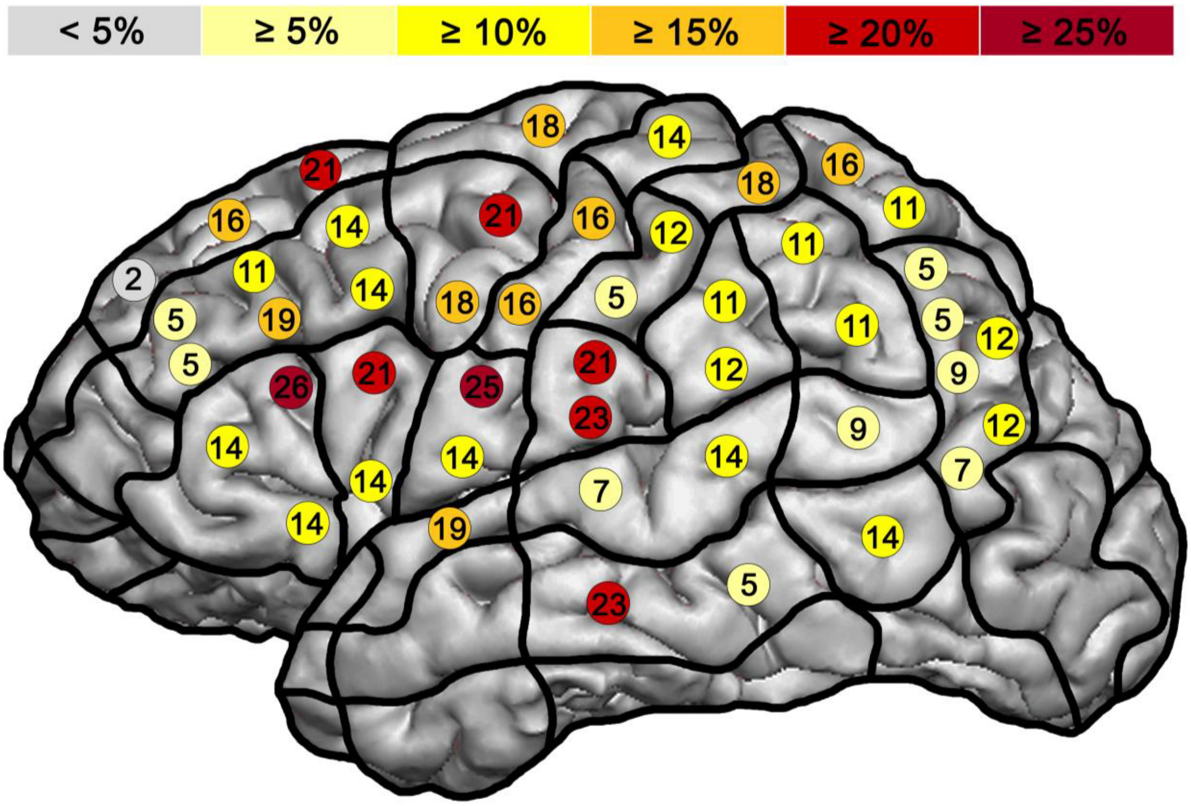

Figure 14: Overall error rates per stimulation site revealed by language mapping via rTMS. Distribution of elicited naming errors while performing object naming.

rTMS evoked the highest rate of no-response errors in trIFG, vPrG, and mMTG (Figure 15, Table 4). In total, we observed more errors in anterior than in posterior regions (Table 3).

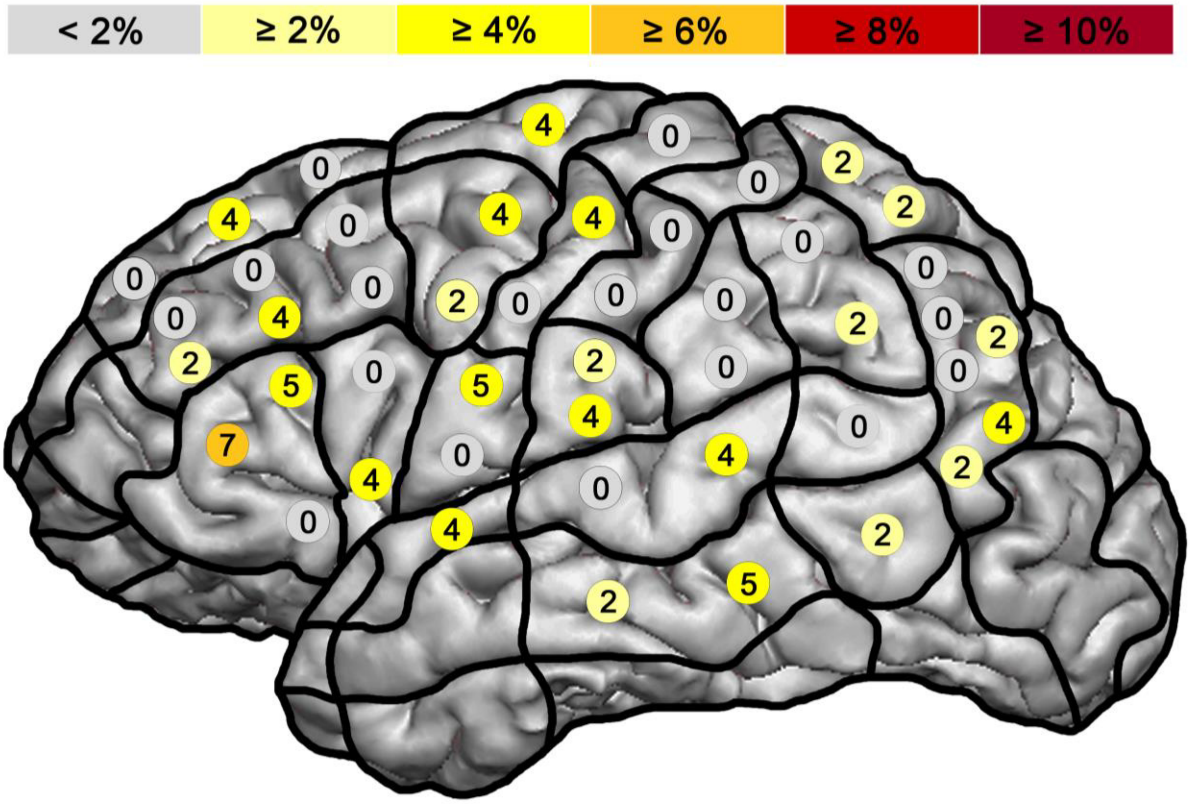

Figure 15: No response error rates per stimulation site revealed by language mapping via rTMS. Distribution of elicited no response errors while performing object naming.

Hesitations represented the category with the highest number of errors (error rate of 9.9%, Table3) and appeared mainly in mSFG, mMTG, vPoG, opIF, vPrG, and dorsal post-central gyrus (dPoG) (Figure 16, Table 4).

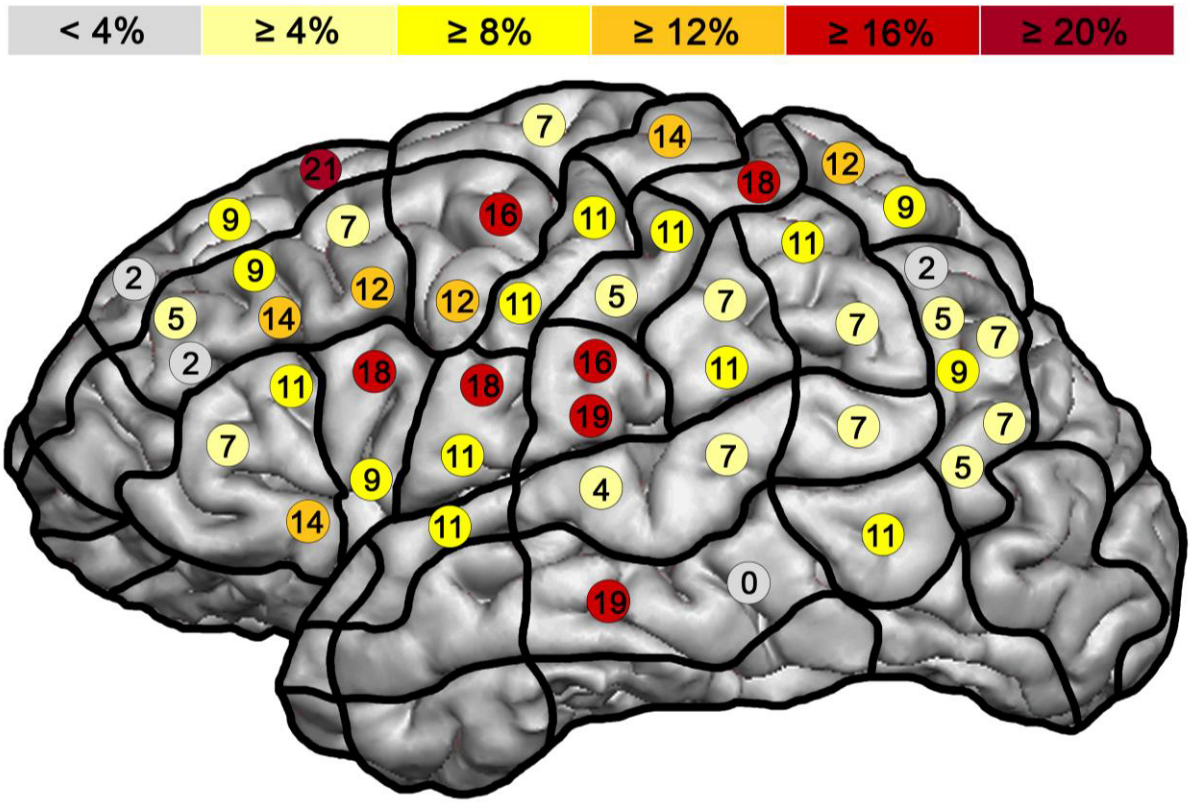

Figure 16: Hesitation error rates per stimulation site revealed by language mapping via rTMS. Distribution of elicited hesitations while performing object naming.

Performance errors built the second most frequent group of naming errors during object naming (error rate of 1.3%, Table 3). RTMS elicited errors of this type predominantly in trIFG and middle pre-central gyrus (mPrG) (Figure 17, Table 4).

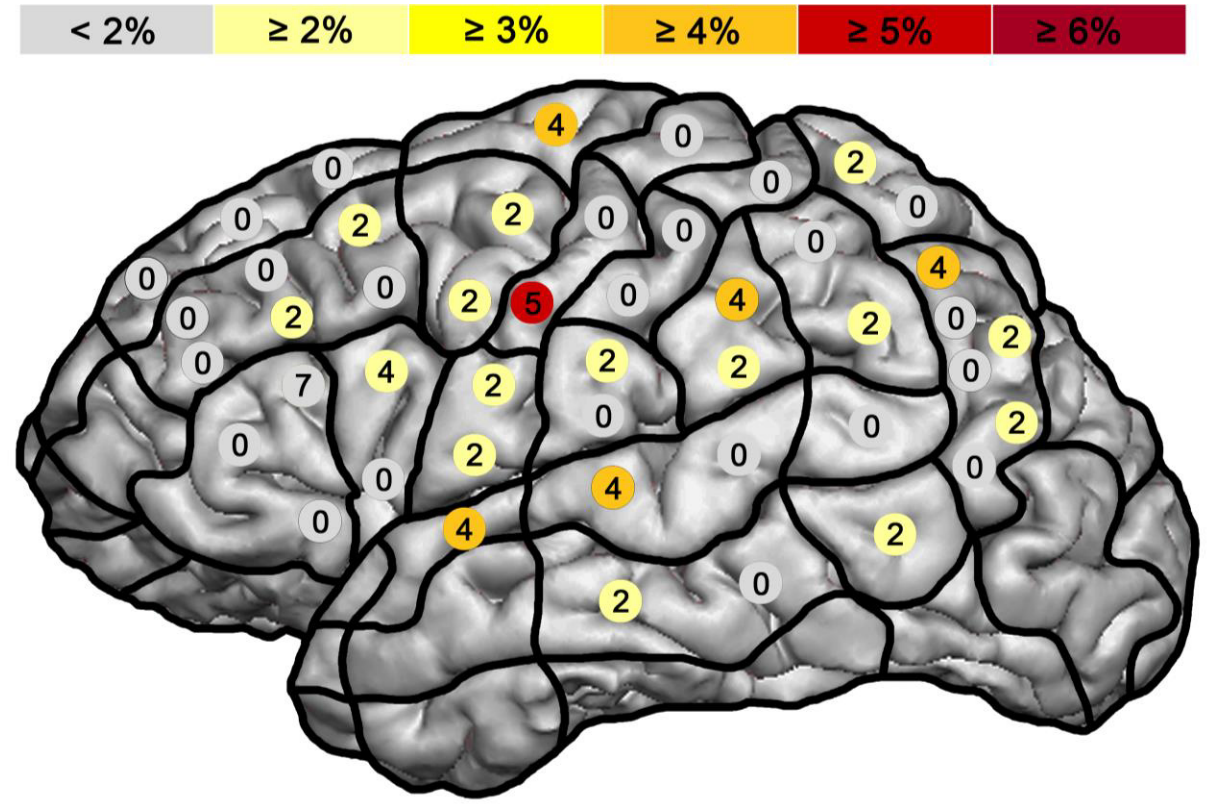

Figure 17: Performance error rates per stimulation site revealed by language mapping via rTMS. Distribution of elicited performance errors while performing object naming.

Semantic and phonological paraphasias, as well as nominalization errors, comprised only a very small number of errors (Table 3, Table 4).

Altogether, except for phonological paraphasias, there appeared more errors in anterior regions than in posterior regions (Table 3, Table 4).

Table 4: Language errors during object naming. Summary of all naming errors induced by rTMS trains during object naming. Results are demonstrated as absolute values and error rates per stimulation point, as sum of errors of all stimulation points, and separately for anterior (ANT.) and posterior (POST.) regions.

	No response		**Performance**		**Hesitation**		**Neologism**		**Phonological**		**Semantic**		Totals	
Stim. point	Errors	Rate	Errors	Rate	Errors	Rate	Errors	Rate	Errors	Rate	Errors	Rate	Errors	Rate
1	0	0.00	0	0.00	1	0.02	0	0.00	0	0.00	0	0.00	1	0.02
2	0	0.00	0	0.00	3	0.05	0	0.00	0	0.00	0	0.00	3	0.05
3	1	0.02	0	0.00	1	0.02	0	0.00	0	0.00	1	0.02	3	0.05
4	4	0.07	0	0.00	4	0.07	0	0.00	0	0.00	0	0.00	8	0.14
5	0	0.00	0	0.00	8	0.14	0	0.00	0	0.00	0	0.00	8	0.14
6	2	0.04	0	0.00	5	0.09	0	0.00	0	0.00	2	0.04	9	0.16
7	0	0.00	0	0.00	5	0.09	0	0.00	0	0.00	1	0.02	6	0.11
8	2	0.04	1	0.02	8	0.14	0	0.00	0	0.00	0	0.00	11	0.19
9	3	0.05	4	0.07	6	0.11	0	0.00	0	0.00	2	0.04	15	0.26
10	2	0.04	0	0.00	5	0.09	0	0.00	0	0.00	1	0.02	8	0.14
11	0	0.00	0	0.00	12	0.21	0	0.00	0	0.00	0	0.00	12	0.21
12	0	0.00	1	0.02	4	0.07	0	0.00	0	0.00	3	0.05	8	0.14
13	0	0.00	0	0.00	7	0.12	0	0.00	0	0.00	1	0.02	8	0.14
14	0	0.00	2	0.04	10	0.18	0	0.00	0	0.00	0	0.00	12	0.21
15	2	0.04	2	0.04	4	0.07	1	0.02	0	0.00	1	0.02	10	0.18
16	2	0.04	1	0.02	9	0.16	0	0.00	0	0.00	0	0.00	12	0.21
17	1	0.02	1	0.02	7	0.12	0	0.00	1	0.02	0	0.00	10	0.18
18	0	0.00	0	0.00	8	0.14	0	0.00	0	0.00	0	0.00	8	0.14

19	2	0.04	0	0.00	6	0.11	0	0.00	1	0.02	0	0.00	9	0.16
20	0	0.00	3	0.05	6	0.11	0	0.00	0	0.00	0	0.00	9	0.16
21	3	0.05	1	0.02	10	0.18	0	0.00	0	0.00	0	0.00	14	0.25
22	0	0.00	1	0.02	6	0.11	0	0.00	0	0.00	1	0.02	8	0.14
23	2	0.04	2	0.04	6	0.11	0	0.00	0	0.00	1	0.02	11	0.19
24	0	0.00	0	0.00	10	0.18	0	0.00	0	0.00	0	0.00	10	0.18
25	0	0.00	0	0.00	6	0.11	0	0.00	1	0.02	0	0.00	7	0.12
26	0	0.00	0	0.00	3	0.05	0	0.00	0	0.00	0	0.00	3	0.05
27	1	0.02	1	0.02	9	0.16	0	0.00	0	0.00	1	0.02	12	0.21
28	2	0.04	0	0.00	11	0.19	0	0.00	0	0.00	0	0.00	13	0.23
29	0	0.00	2	0.04	2	0.04	0	0.00	0	0.00	0	0.00	4	0.07
30	1	0.02	1	0.02	11	0.19	0	0.00	0	0.00	0	0.00	13	0.23
31	1	0.02	1	0.02	7	0.12	0	0.00	0	0.00	0	0.00	9	0.16
32	0	0.00	2	0.04	1	0.02	0	0.00	0	0.00	0	0.00	3	0.05
33	0	0.00	0	0.00	6	0.11	0	0.00	0	0.00	0	0.00	6	0.11
34	0	0.00	2	0.04	4	0.07	0	0.00	0	0.00	0	0.00	6	0.11
35	0	0.00	1	0.02	6	0.11	0	0.00	0	0.00	0	0.00	7	0.12
36	2	0.04	0	0.00	4	0.07	0	0.00	1	0.02	1	0.02	8	0.14
37	3	0.05	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	3	0.05
38	1	0.02	1	0.02	4	0.07	0	0.00	0	0.00	0	0.00	6	0.11
39	0	0.00	0	0.00	4	0.07	0	0.00	1	0.02	0	0.00	5	0.09
40	1	0.02	1	0.02	6	0.11	0	0.00	0	0.00	0	0.00	8	0.14
41	0	0.00	0	0.00	3	0.05	0	0.00	0	0.00	0	0.00	3	0.05

42	0	0.00	0	0.00	5	0.09	0	0.00	0	0.00	0	0.00	5	0.09
43	1	0.02	0	0.00	3	0.05	0	0.00	0	0.00	0	0.00	4	0.07
44	1	0.02	0	0.00	5	0.09	0	0.00	0	0.00	0	0.00	6	0.11
45	1	0.02	1	0.02	4	0.07	0	0.00	1	0.02	0	0.00	7	0.12
46	2	0.04	1	0.02	4	0.07	0	0.00	0	0.00	0	0.00	7	0.12
SUM	43	0.02	33	0.01	259	0.10	1	0.00	6	0.00	16	0.01	358	0.14
ANT.	24	0.02	17	0.01	135	0.11	1	0.00	2	0.00	13	0.01	192	0.15
POST.	19	0.01	16	0.01	124	0.09	0	0.00	4	0.00	3	0.00	166	0.12

3.4.3. Pseudoword reading

In total, pseudoword reading barely generated errors (4.0%; Table 3). Regarding the sum of all errors, spots including the highest error rates were found in opIFG, followed by trIFG, mPrG, and middle middle frontal gyrus (mMFG; Figure 18).

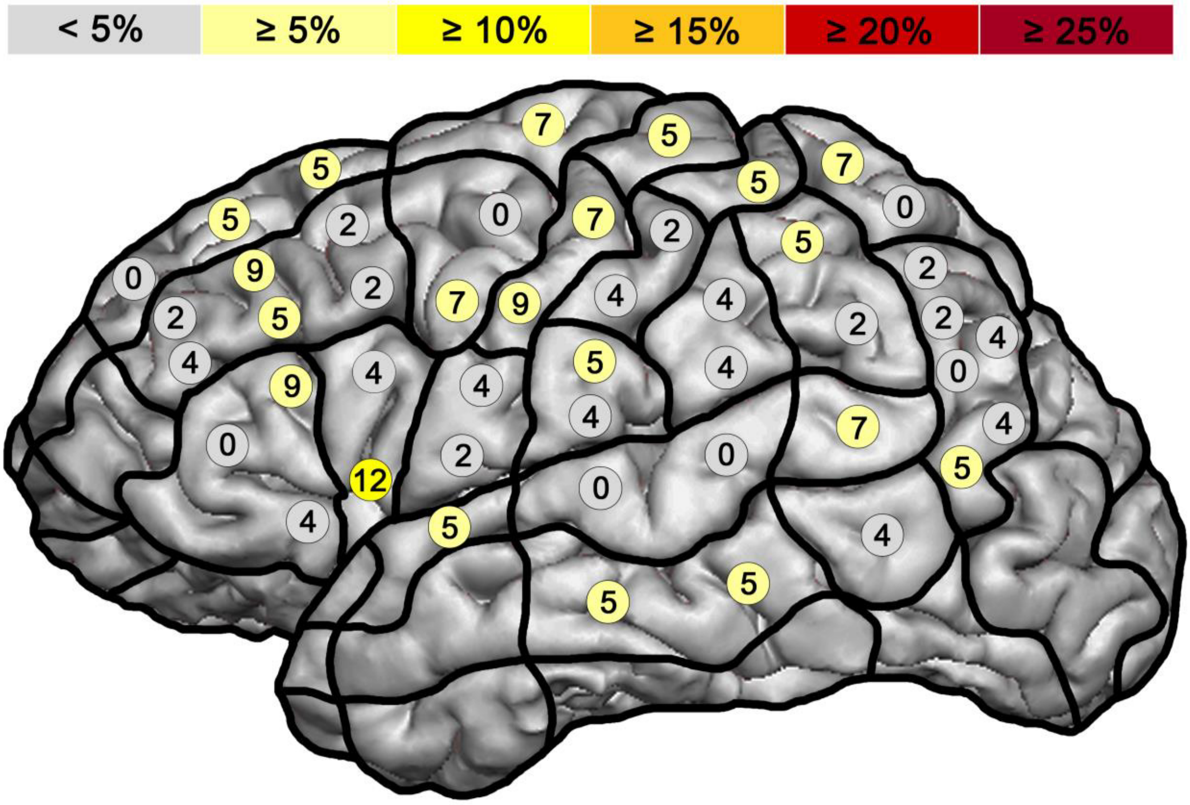

Figure 18: Overall error rates per stimulation site revealed by language mapping via rTMS. Distribution of elicited naming errors while performing pseudoword reading.

Concerning no-response errors, performance errors, neologisms, and semantic paraphasias, this task type failed to evoke a considerable number of positive sites (error rates regarding all areas ≤ 0.8%). Hesitations also appeared comparatively rarely (Table 3).

Nevertheless, within our four tasks, this task was able to evoke the largest amount of phonological paraphasias, which showed a widely distributed pattern all over the hemisphere (Figure 19, Table 3, Table 5).

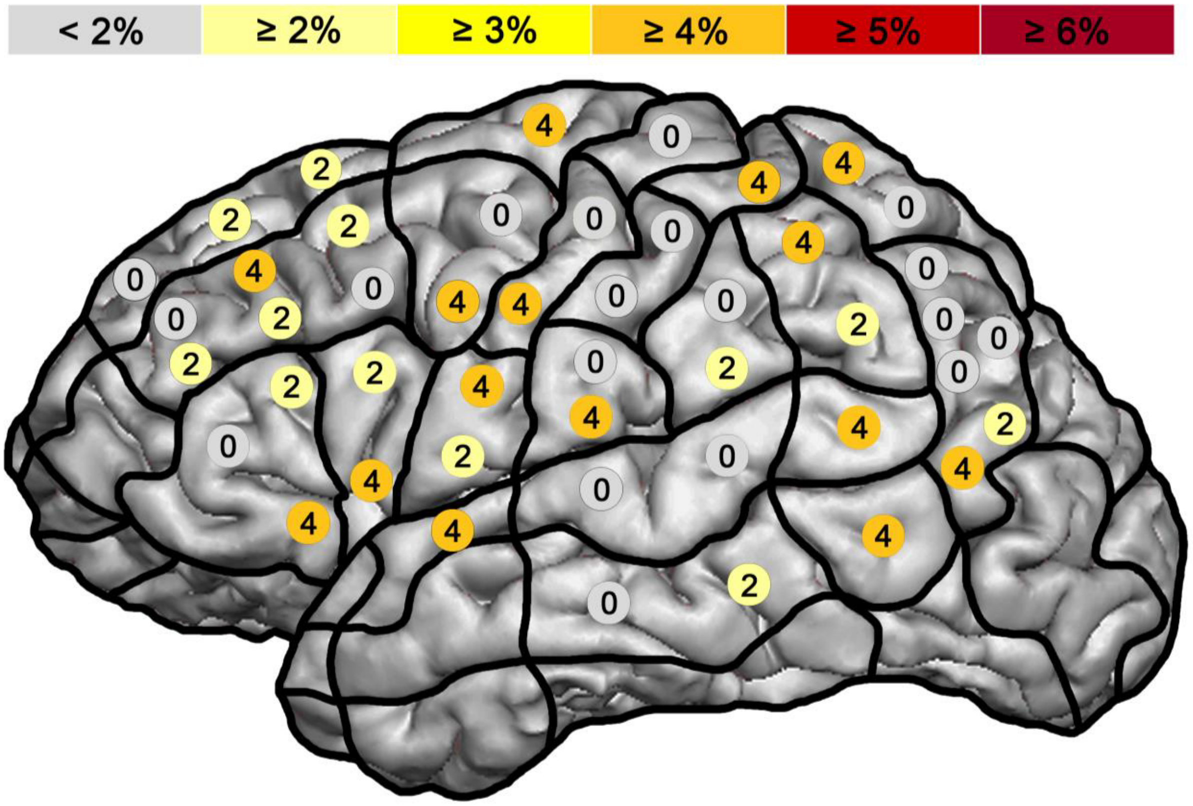

Figure 19: Phonological error rates per stimulation site revealed by language mapping via rTMS. Distribution of elicited naming errors while performing pseudoword reading.

Apart from neologisms, pseudoword reading constantly showed a lower rate of induced language impairment in posterior regions compared to anterior regions (Table 3).

Table 5: Language errors during pseudoword reading. Summary of all naming errors induced by rTMS trains during pseudoword reading. Results are demonstrated as absolute values and error rates per stimulation point, as sum of errors of all stimulation points, and separately for anterior (ANT.) and posterior (POST.) regions.

	No response		**Performance**		**Hesitation**		**Neologism**		**Phonological**		Totals	
Stim. point	Errors	Rate	Errors	Rate	Errors	Rate	Errors	Rate	Errors	Rate	Errors	Rate
1	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
2	0	0.00	0	0.00	1	0.02	0	0.00	0	0.00	1	0.02
3	0	0.00	0	0.00	1	0.02	0	0.00	1	0.02	2	0.04
4	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
5	0	0.00	0	0.00	0	0.00	0	0.00	2	0.04	2	0.04
6	0	0.00	0	0.00	2	0.04	0	0.00	1	0.02	3	0.05
7	0	0.00	0	0.00	3	0.05	0	0.00	2	0.04	5	0.09
8	0	0.00	0	0.00	2	0.04	0	0.00	1	0.02	3	0.05
9	0	0.00	1	0.02	3	0.05	0	0.00	1	0.02	5	0.09
10	0	0.00	4	0.07	1	0.02	0	0.00	2	0.04	7	0.12
11	0	0.00	0	0.00	2	0.04	0	0.00	1	0.02	3	0.05
12	0	0.00	0	0.00	0	0.00	0	0.00	1	0.02	1	0.02
13	0	0.00	1	0.02	0	0.00	0	0.00	0	0.00	1	0.02
14	0	0.00	2	0.04	1	0.02	0	0.00	1	0.02	4	0.07
15	0	0.00	0	0.00	0	0.00	0	0.00	2	0.04	2	0.04
16	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
17	0	0.00	2	0.04	0	0.00	0	0.00	2	0.04	4	0.07

18	0	0.00	0	0.00	3	0.05	0	0.00	0	0.00	3	0.05
19	1	0.02	0	0.00	3	0.05	0	0.00	0	0.00	4	0.07
20	0	0.00	3	0.05	0	0.00	0	0.00	2	0.04	5	0.09
21	0	0.00	0	0.00	0	0.00	0	0.00	2	0.04	2	0.04
22	0	0.00	0	0.00	0	0.00	0	0.00	1	0.02	1	0.02
23	0	0.00	0	0.00	1	0.02	0	0.00	2	0.04	3	0.05
24	0	0.00	1	0.02	0	0.00	0	0.00	2	0.04	3	0.05
25	0	0.00	0	0.00	1	0.02	0	0.00	0	0.00	1	0.02
26	0	0.00	2	0.04	0	0.00	0	0.00	0	0.00	2	0.04
27	0	0.00	1	0.02	1	0.02	1	0.02	0	0.00	3	0.05
28	0	0.00	0	0.00	0	0.00	0	0.00	2	0.04	2	0.04
29	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
30	0	0.00	1	0.02	2	0.04	0	0.00	0	0.00	3	0.05
31	0	0.00	0	0.00	2	0.04	0	0.00	2	0.04	4	0.07
32	0	0.00	0	0.00	1	0.02	0	0.00	0	0.00	1	0.02
33	0	0.00	0	0.00	1	0.02	0	0.00	2	0.04	3	0.05
34	0	0.00	0	0.00	2	0.04	0	0.00	0	0.00	2	0.04
35	0	0.00	0	0.00	1	0.02	0	0.00	1	0.02	2	0.04
36	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
37	0	0.00	2	0.04	0	0.00	0	0.00	1	0.02	3	0.05
38	0	0.00	0	0.00	0	0.00	0	0.00	1	0.02	1	0.02
39	0	0.00	2	0.04	0	0.00	0	0.00	2	0.04	4	0.07
40	0	0.00	0	0.00	0	0.00	0	0.00	2	0.04	2	0.04

41	0	0.00	0	0.00	1	0.02	0	0.00	0	0.00	1	0.02
42	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
43	0	0.00	0	0.00	1	0.02	0	0.00	2	0.04	3	0.05
44	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
45	0	0.00	0	0.00	2	0.04	0	0.00	0	0.00	2	0.04
46	0	0.00	0	0.00	1	0.02	0	0.00	1	0.02	2	0.04
SUM	1	0.00	22	0.01	39	0.01	1	0.00	42	0.02	105	0.04
ANT.	1	0.00	13	0.01	22	0.02	0	0.00	22	0.02	58	0.05
POST.	0	0.00	9	0.01	17	0.01	1	0.00	20	0.01	47	0.03

3.4.4. Verb generation

Taking into account all error categories, verb generation elicited language errors in each stimulated site (Figure 20). CPS regions containing spots with highest error rates were pMFG and mMFG (Figure 20).

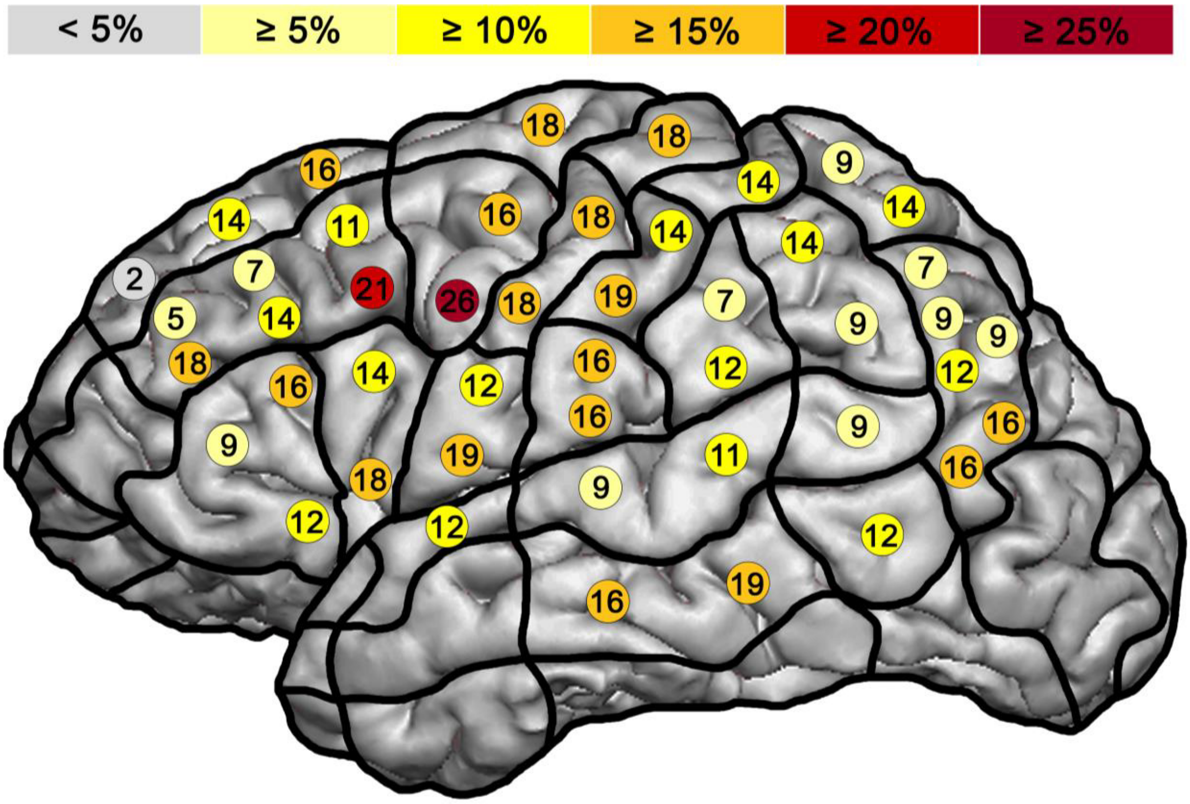

Figure 20:Overall error rates per stimulation site revealed by language mapping via rTMS. Distribution of elicited naming errors while performing verb generation.

Sites with no-response errors occurred most frequently in mMTG and mSFG, and the cortical regions high in hesitation errors were located in mMFG and mPoG (Figure 21, Figure 22). Hesitations clearly represented the category comprising the highest error rate (Table 3, Table 6).

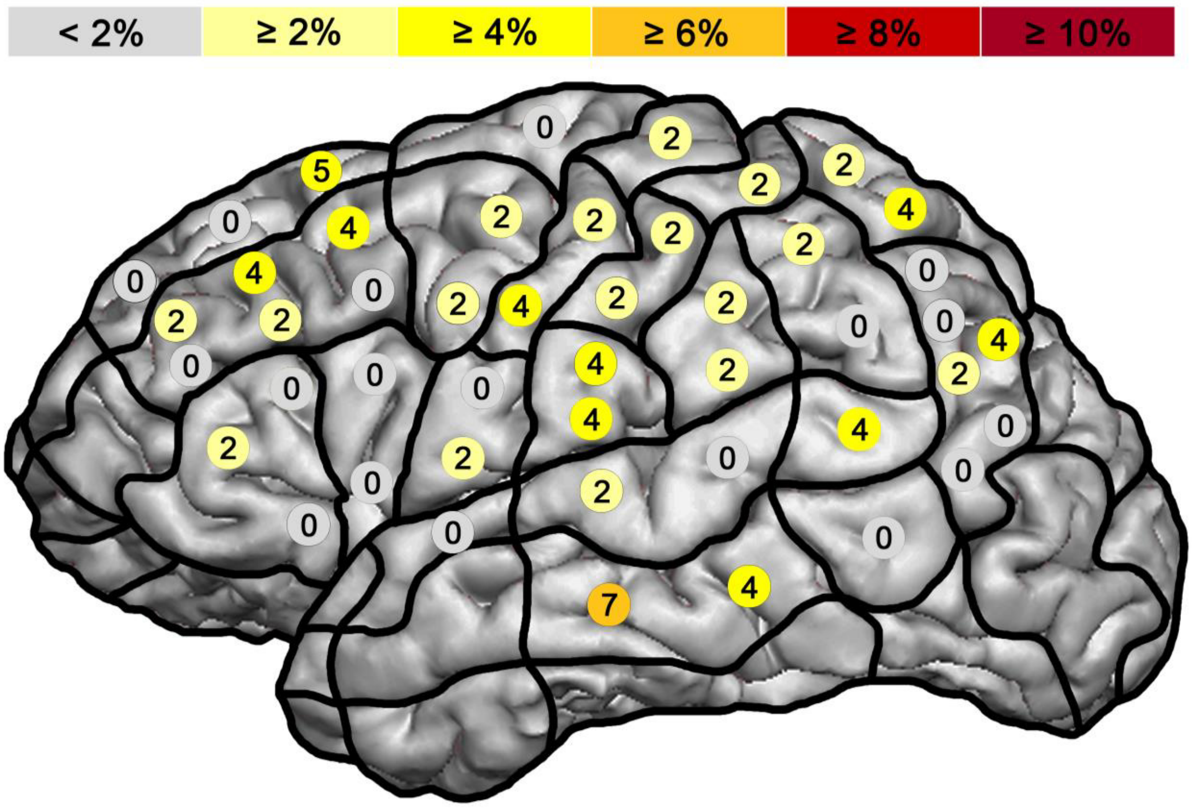

Figure 21: No response error rates per stimulation site revealed by language mapping via rTMS. Distribution of elicited naming errors while performing verb generation.

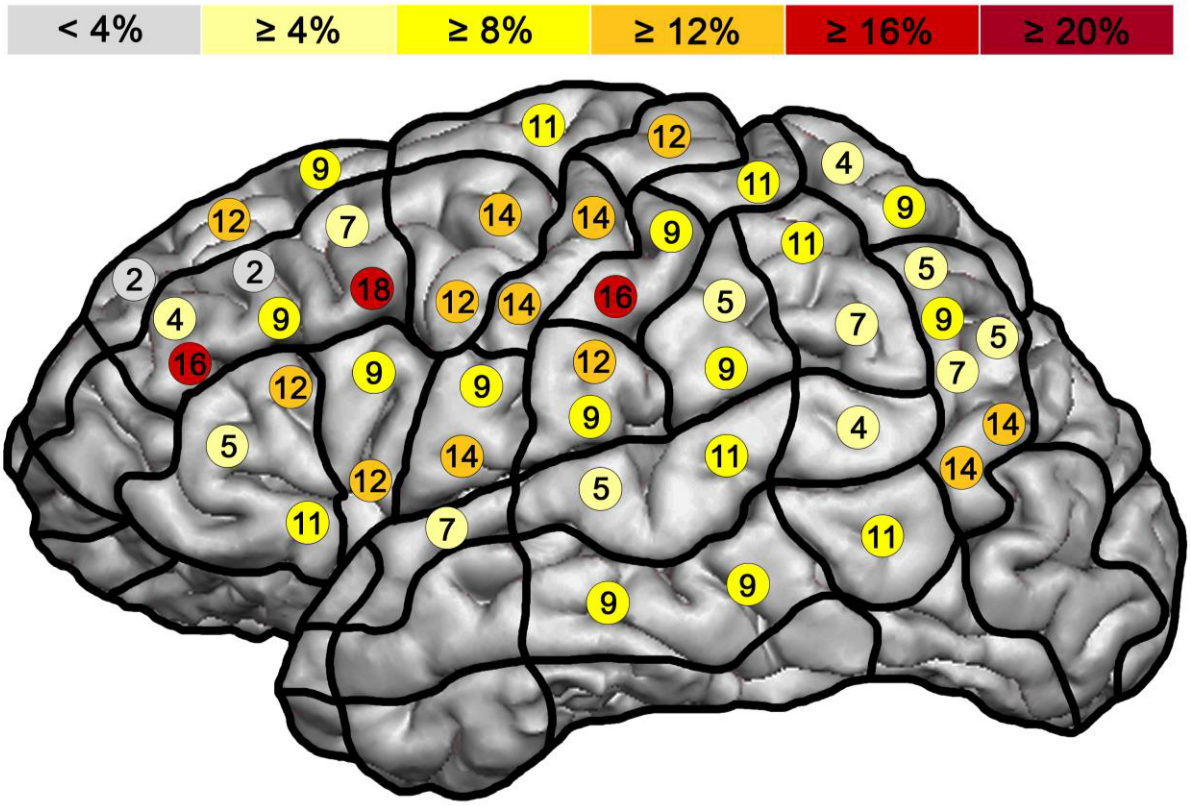

Figure 22: No response error rates per stimulation site revealed by language mapping via rTMS. Distribution of elicited naming errors while performing verb generation.

Verb generation showed performance errors upon stimulation, especially in pSFG, pMFG, vPrG, and anterior superior temporal gyrus (aSTG; Table 6).

Neologisms and both phonological and semantic paraphasias rarely occurred during verb generation (error rates regarding all regions ≤ 0.4%; Table 3, Table 6).

In total, 15 nominalization errors could be observed, which also equals a low error rate of 0.6%. This kind of error was found most frequently in pMFG and mPoG (Table 3, Table 6).

Altogether, the rate for occurrence of any error is higher in anterior than in posterior regions, except for the category “no response,” which appeared more often in posterior areas (Table 3).

Table 6: Language errors during verb generation. Summary of all naming errors induced by rTMS trains during verb generation. Results are demonstrated as absolute values and error rates per stimulation point, as sum of errors of all stimulation points, and separately for anterior (ANT.) and posterior (POST.) regions.

	No response		**Performance**		**Hesitation**		**Neologism**		**Phonological**		**Semantic**		**Nominalization**		Totals	
Stim. point	Errors	Rate	Errors	Rate	Errors	Rate	Errors	Rate	Errors	Rate	Errors	Rate	Errors	Rate	Errors	Rate
1	0	0.00	0	0.00	1	0.02	0	0.00	0	0.00	0	0.00	0	0.00	1	0.02
2	1	0.02	0	0.00	2	0.04	0	0.00	0	0.00	0	0.00	0	0.00	3	0.05
3	0	0.00	1	0.02	9	0.16	0	0.00	0	0.00	0	0.00	0	0.00	10	0.18
4	1	0.02	0	0.00	3	0.05	0	0.00	1	0.02	0	0.00	0	0.00	5	0.09
5	0	0.00	1	0.02	6	0.11	0	0.00	0	0.00	0	0.00	0	0.00	7	0.12
6	0	0.00	1	0.02	7	0.12	0	0.00	0	0.00	0	0.00	0	0.00	8	0.14
7	2	0.04	0	0.00	1	0.02	0	0.00	0	0.00	0	0.00	1	0.02	4	0.07
8	1	0.02	0	0.00	5	0.09	0	0.00	2	0.04	0	0.00	0	0.00	8	0.14
9	0	0.00	1	0.02	7	0.12	0	0.00	0	0.00	1	0.02	0	0.00	9	0.16
10	0	0.00	1	0.02	7	0.12	0	0.00	2	0.04	0	0.00	0	0.00	10	0.18
11	3	0.05	0	0.00	5	0.09	0	0.00	0	0.00	0	0.00	1	0.02	9	0.16
12	2	0.04	0	0.00	4	0.07	0	0.00	0	0.00	0	0.00	0	0.00	6	0.11
13	0	0.00	0	0.00	10	0.18	0	0.00	1	0.02	1	0.02	0	0.00	12	0.21
14	0	0.00	0	0.00	5	0.09	0	0.00	2	0.04	0	0.00	1	0.02	8	0.14
15	0	0.00	3	0.05	6	0.11	0	0.00	0	0.00	1	0.02	0	0.00	10	0.18
16	1	0.02	0	0.00	8	0.14	0	0.00	0	0.00	0	0.00	0	0.00	9	0.16
17	1	0.02	2	0.04	7	0.12	1	0.02	0	0.00	1	0.02	3	0.05	15	0.26

18	1	0.02	0	0.00	7	0.12	0	0.00	0	0.00	1	0.02	1	0.02	10	0.18
19	1	0.02	1	0.02	8	0.14	0	0.00	0	0.00	0	0.00	0	0.00	10	0.18
20	2	0.04	0	0.00	8	0.14	0	0.00	0	0.00	0	0.00	0	0.00	10	0.18
21	0	0.00	1	0.02	5	0.09	0	0.00	1	0.02	0	0.00	0	0.00	7	0.12
22	1	0.02	2	0.04	8	0.14	0	0.00	0	0.00	0	0.00	0	0.00	11	0.19
23	0	0.00	2	0.04	4	0.07	0	0.00	0	0.00	0	0.00	1	0.02	7	0.12
24	1	0.02	1	0.02	6	0.11	0	0.00	0	0.00	0	0.00	0	0.00	8	0.14
25	1	0.02	0	0.00	5	0.09	0	0.00	0	0.00	0	0.00	2	0.04	8	0.14
26	1	0.02	1	0.02	9	0.16	0	0.00	0	0.00	0	0.00	0	0.00	11	0.19
27	2	0.04	0	0.00	7	0.12	0	0.00	0	0.00	0	0.00	0	0.00	9	0.16
28	2	0.04	0	0.00	5	0.09	0	0.00	0	0.00	1	0.02	1	0.02	9	0.16
29	1	0.02	1	0.02	3	0.05	0	0.00	0	0.00	0	0.00	0	0.00	5	0.09
30	4	0.07	0	0.00	5	0.09	0	0.00	0	0.00	0	0.00	0	0.00	9	0.16
31	1	0.02	1	0.02	2	0.04	0	0.00	1	0.02	0	0.00	0	0.00	5	0.09
32	0	0.00	1	0.02	3	0.05	0	0.00	0	0.00	0	0.00	0	0.00	4	0.07
33	1	0.02	0	0.00	6	0.11	1	0.02	0	0.00	0	0.00	0	0.00	8	0.14
34	1	0.02	0	0.00	3	0.05	0	0.00	0	0.00	0	0.00	0	0.00	4	0.07
35	1	0.02	1	0.02	5	0.09	0	0.00	0	0.00	0	0.00	0	0.00	7	0.12
36	0	0.00	0	0.00	6	0.11	0	0.00	0	0.00	0	0.00	0	0.00	6	0.11
37	2	0.04	0	0.00	5	0.09	0	0.00	1	0.02	2	0.04	1	0.02	11	0.19
38	0	0.00	1	0.02	4	0.07	0	0.00	0	0.00	0	0.00	0	0.00	5	0.09
39	2	0.04	0	0.00	2	0.04	1	0.02	0	0.00	0	0.00	0	0.00	5	0.09
40	0	0.00	0	0.00	6	0.11	0	0.00	0	0.00	0	0.00	1	0.02	7	0.12

41	0	0.00	0	0.00	5	0.09	0	0.00	0	0.00	0	0.00	0	0.00	5	0.09
42	1	0.02	1	0.02	4	0.07	0	0.00	0	0.00	0	0.00	1	0.02	7	0.12
43	0	0.00	0	0.00	8	0.14	0	0.00	0	0.00	0	0.00	1	0.02	9	0.16
44	2	0.04	0	0.00	5	0.09	0	0.00	0	0.00	1	0.02	0	0.00	8	0.14
45	2	0.04	0	0.00	3	0.05	0	0.00	0	0.00	0	0.00	0	0.00	5	0.09
46	0	0.00	1	0.02	8	0.14	0	0.00	0	0.00	0	0.00	0	0.00	9	0.16
SUM	42	0.02	25	0.01	248	0.09	3	0.00	11	0.00	9	0.00	15	0.01	353	0.13
ANT.	17	0.01	14	0.01	129	0.10	1	0.00	9	0.01	5	0.00	7	0.01	182	0.15
POST.	25	0.02	11	0.01	119	0.09	2	0.00	2	0.00	4	0.00	8	0.01	171	0.13

3.4.5. Action naming

Concerning the sum of all errors, rTMS induced language disruption less frequently during action naming than during object naming and verb generation (Table 3). Nevertheless, language-positive sites were widely spread and excepting stimulation point number 1, we observed naming errors in all stimulated spots during that task (Figure 23). CPS regions including highest number of errors were mSTG, opIFG, and pMFG.

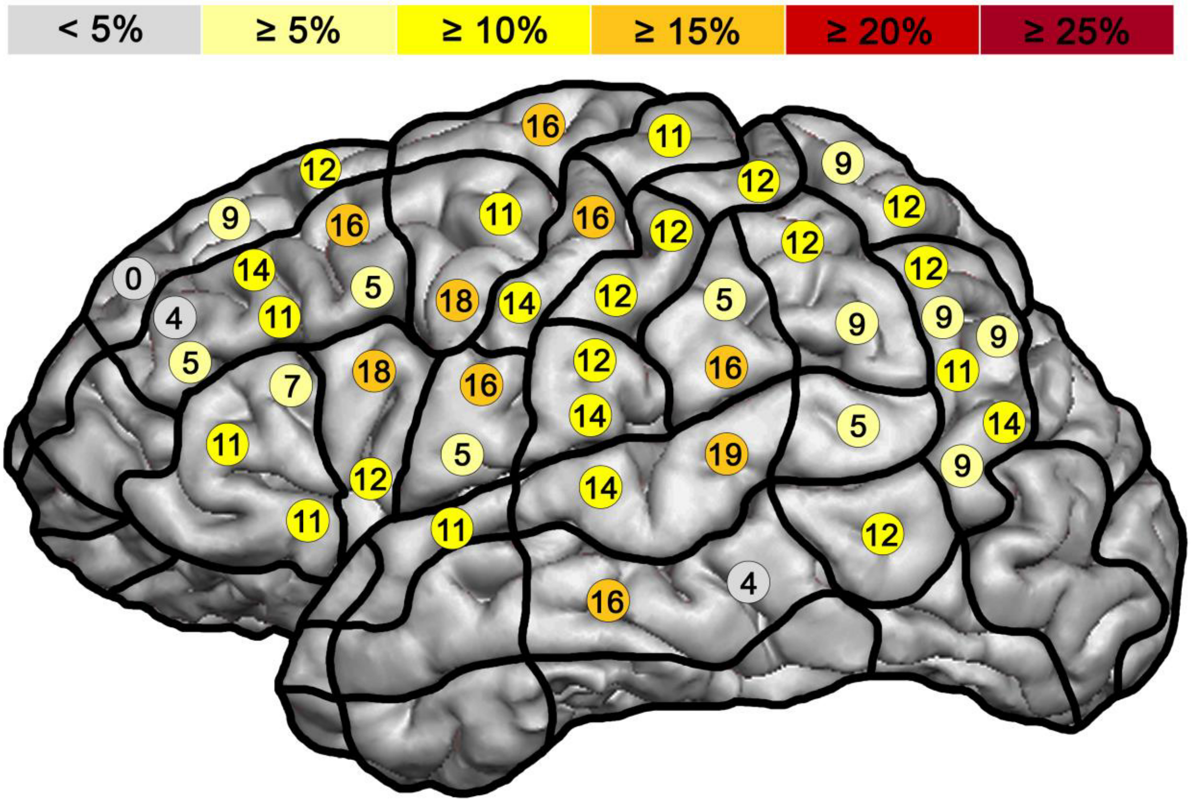

Figure 23: Overall error rates per stimulation site revealed by language mapping via rTMS. Distribution of elicited naming errors while performing action naming.

Within the four tasks, action naming evoked the highest rate of no-response errors (Table 3). Thereby, stimulated spots located in posterior regions such as the angular gyrus (anG), dPoG, vPoG, anterior supramarginal gyrus (aSMG), middle superior temporal gyrus (mSTG), and mMTG showed the highest rates of no-response errors (Figure 24, Table 7).

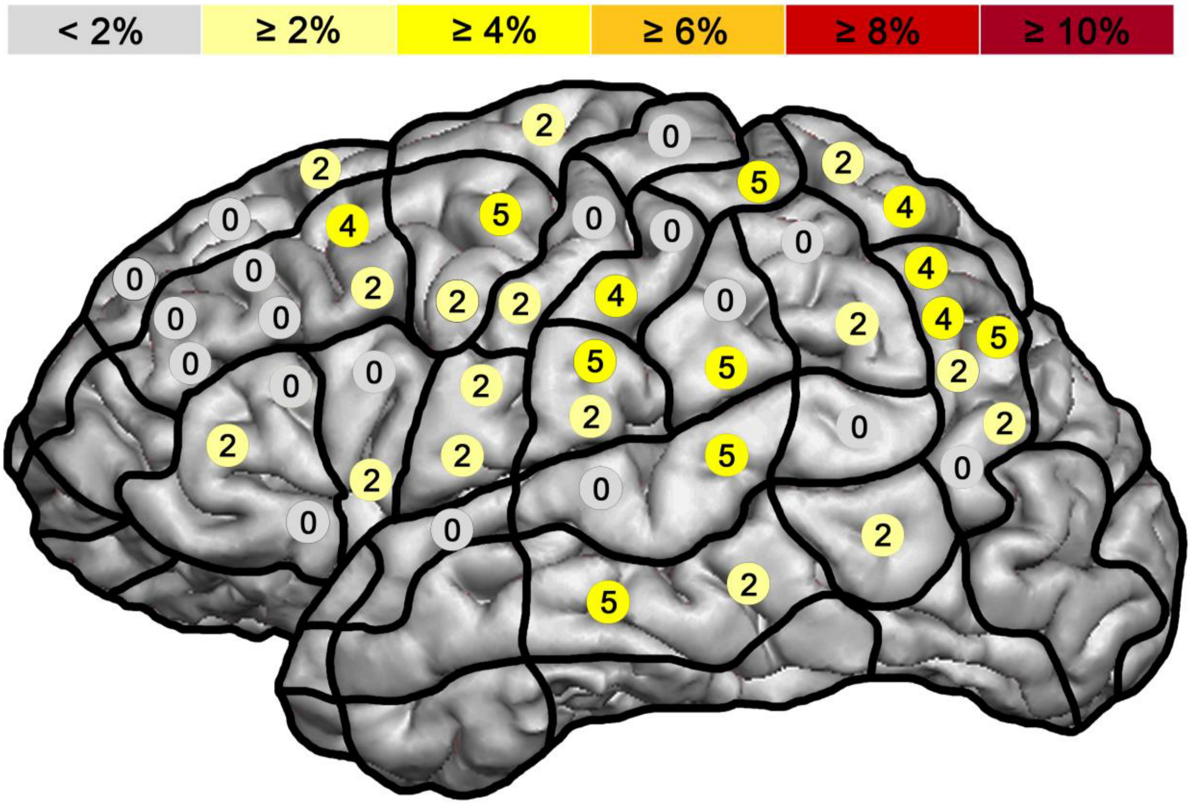

Figure 24: No response error rates per stimulation site revealed by language mapping via rTMS. Distribution of elicited naming errors while performing action naming.

Also during action naming, hesitations represented the category containing most of the errors (Table 3, Table 7). Hesitations did not seem to accumulate in any CPS region, but rather were widely spread over the entire hemisphere (Figure 25, Table 7).

Again, the occurrence of phonological paraphasias, semantic paraphasias, and neologisms was very rare (error rates considering all areas ≤ 0.4%; Table 3, Table 7).

Regarding nominalization errors, we found a very small number of four total errors, which equals an error rate of 0.2% (Table 7).

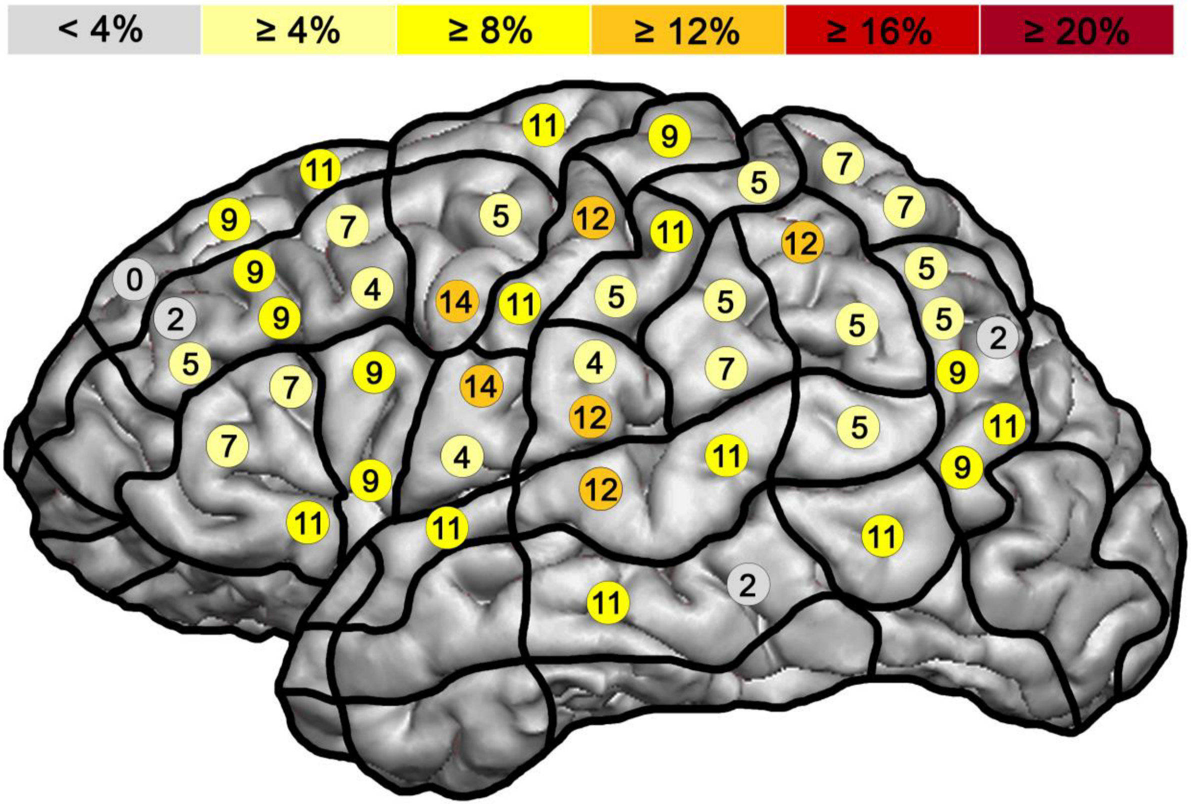

Figure 25: Hesitation error rates per stimulation site revealed by language mapping via rTMS. Distribution of elicited naming errors while performing action naming.

Table 7: Language errors induced by action naming. Summary of all naming errors induced by rTMS trains during action naming. Results are demonstrated as absolute values and error rates per stimulation point, as sum of errors of all stimulation points, and separately for anterior (ANT.) and posterior (POST.) regions.

	No response		**Performance**		**Hesitation**		**Neologism**		**Phonological**		**Semantic**		**Nominalization**		Totals	
Stim. point	Errors	Rate	Errors	Rate	Errors	Rate	Errors	Rate	Errors	Rate	Errors	Rate	Errors	Rate	Errors	Rate
1	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
2	0	0.00	0	0.00	1	0.02	0	0.00	0	0.00	1	0.02	0	0.00	2	0.04
3	0	0.00	0	0.00	3	0.05	0	0.00	0	0.00	0	0.00	0	0.00	3	0.05
4	1	0.02	1	0.02	4	0.07	0	0.00	1	0.02	0	0.00	0	0.00	6	0.11
5	0	0.00	0	0.00	6	0.11	0	0.00	0	0.00	0	0.00	0	0.00	6	0.11
6	0	0.00	0	0.00	5	0.09	0	0.00	0	0.00	0	0.00	0	0.00	5	0.09
7	0	0.00	1	0.02	5	0.09	0	0.00	0	0.00	0	0.00	0	0.00	8	0.14
8	0	0.00	0	0.00	5	0.09	0	0.00	2	0.04	0	0.00	0	0.00	6	0.11
9	0	0.00	0	0.00	4	0.07	0	0.00	0	0.00	0	0.00	0	0.00	4	0.07
10	1	0.02	1	0.02	5	0.09	0	0.00	2	0.04	0	0.00	0	0.00	7	0.12
11	1	0.02	0	0.00	6	0.11	0	0.00	0	0.00	0	0.00	0	0.00	7	0.12
12	2	0.04	0	0.00	4	0.07	0	0.00	0	0.00	1	0.02	0	0.00	9	0.16
13	1	0.02	0	0.00	2	0.04	0	0.00	1	0.02	0	0.00	0	0.00	3	0.05
14	0	0.00	2	0.04	5	0.09	0	0.00	2	0.04	0	0.00	0	0.00	10	0.18
15	1	0.02	2	0.04	6	0.11	0	0.00	0	0.00	0	0.00	0	0.00	9	0.16
16	3	0.05	0	0.00	3	0.05	0	0.00	0	0.00	0	0.00	0	0.00	6	0.11

17	1	0.02	0	0.00	8	0.14	0	0.00	0	0.00	0	0.00	1	0.02	10	0.18
18	0	0.00	0	0.00	5	0.09	0	0.00	0	0.00	1	0.02	0	0.00	6	0.11
19	0	0.00	0	0.00	7	0.12	0	0.00	0	0.00	1	0.02	0	0.00	9	0.16
20	1	0.02	0	0.00	6	0.11	1	0.02	0	0.00	0	0.00	0	0.00	8	0.14
21	1	0.02	0	0.00	8	0.14	0	0.00	1	0.02	0	0.00	0	0.00	9	0.16
22	1	0.02	0	0.00	2	0.04	0	0.00	0	0.00	0	0.00	0	0.00	3	0.05
23	0	0.00	0	0.00	6	0.11	0	0.00	0	0.00	0	0.00	0	0.00	6	0.11
24	3	0.05	0	0.00	3	0.05	0	0.00	0	0.00	1	0.02	0	0.00	7	0.12
25	0	0.00	1	0.02	6	0.11	0	0.00	0	0.00	0	0.00	0	0.00	7	0.12
26	2	0.04	1	0.02	3	0.05	0	0.00	0	0.00	0	0.00	1	0.02	7	0.12
27	3	0.05	1	0.02	2	0.04	0	0.00	0	0.00	0	0.00	1	0.02	7	0.12
28	1	0.02	0	0.00	7	0.12	0	0.00	0	0.00	0	0.00	0	0.00	8	0.14
29	0	0.00	0	0.00	7	0.12	0	0.00	0	0.00	1	0.02	0	0.00	8	0.14
30	3	0.05	0	0.00	6	0.11	0	0.00	0	0.00	0	0.00	0	0.00	9	0.16
31	1	0.02	0	0.00	4	0.07	0	0.00	1	0.02	0	0.00	0	0.00	5	0.09
32	2	0.04	2	0.04	3	0.05	0	0.00	0	0.00	0	0.00	0	0.00	7	0.12
33	0	0.00	0	0.00	7	0.12	0	0.00	0	0.00	0	0.00	0	0.00	7	0.12
34	0	0.00	0	0.00	3	0.05	0	0.00	0	0.00	0	0.00	0	0.00	3	0.05
35	3	0.05	1	0.02	4	0.07	0	0.00	0	0.00	1	0.02	0	0.00	9	0.16
36	3	0.05	1	0.02	6	0.11	0	0.00	0	0.00	0	0.00	1	0.02	11	0.19
37	1	0.02	0	0.00	1	0.02	0	0.00	1	0.02	0	0.00	0	0.00	2	0.04
38	1	0.02	1	0.02	3	0.05	0	0.00	0	0.00	0	0.00	0	0.00	5	0.09
39	0	0.00	0	0.00	3	0.05	0	0.00	0	0.00	0	0.00	0	0.00	3	0.05

40	1	0.02	0	0.00	6	0.11	0	0.00	0	0.00	0	0.00	0	0.00	7	0.12
41	2	0.04	0	0.00	3	0.05	0	0.00	0	0.00	0	0.00	0	0.00	5	0.09
42	1	0.02	0	0.00	5	0.09	0	0.00	0	0.00	0	0.00	0	0.00	6	0.11
43	0	0.00	0	0.00	5	0.09	0	0.00	0	0.00	0	0.00	0	0.00	5	0.09
44	2	0.04	1	0.02	4	0.07	0	0.00	0	0.00	0	0.00	0	0.00	7	0.12
45	3	0.05	0	0.00	1	0.02	0	0.00	0	0.00	0	0.00	0	0.00	5	0.09
46	1	0.02	0	0.00	6	0.11	0	0.00	0	0.00	0	0.00	0	0.00	8	0.14
SUM	47	0.02	16	0.01	204	0.08	1	0.00	11	0.00	7	0.00	4	0.00	290	0.11
ANT.	14	0.01	7	0.01	100	0.08	1	0.00	9	0.01	4	0.00	1	0.00	136	0.11
POST.	33	0.02	9	0.01	104	0.08	0	0.00	2	0.00	3	0.00	3	0.00	154	0.11

3.5. Task comparison

Considering the total number of correctly named baseline items, our data provided statistically significant differences among the four language tasks (*p* < 0.0001, Table 8). Baseline performance was most successful in pseudoword reading, and the fewest baseline items were recognized during action naming.

The low Spearman's rank correlation coefficient suggests that there is no correlation between the error rates during baseline performance and the error rates induced by rTMS (Table 8).

Table 8: Baseline performance and correlation between error rates in baseline testing and error rates induced by rTMS. Representative correct baseline pictures and statistical dependence between error rate during baseline performance and error rate induced by stimulation via Spearman's rank correlation coefficient.

	Number of correctly identified baseline items (mean ± SD)	Spearman's rank correlation coefficient (rs)	p-value
Object naming	90.9 ± 4.5	0.0253	p=0.9182
Pseudoword reading	95.6 ± 2.4	0.4733	p=0.0407
Verb generation	88.2 ± 4.9	-0.1169	p=0.6337
Action naming	87.4 ± 5.1	0.1140	p=0.6423

Comparing the error rates of the four tasks, we found different clusters of cortical regions representative of language functions.

With regard to all errors in all regions, our data showed a statistically significant difference among the distribution of language-positive regions in pseudoword reading and the remaining tasks (*p* < 0.0001, Table 3). Concerning all errors in anterior regions, object naming differed significantly from action naming (Table 3). Furthermore, our data revealed significant differences between pseudoword reading and the other tasks in terms of no-response errors, hesitations, and phonological paraphasias in all regions ($p < 0.0001$), and in both anterior (no response: $p = 0.002$; hesitations: $p < 0.0001$; phonological paraphasias: $p = 0.001$) and posterior regions ($p < 0.0001$, Table 3). Regarding semantic errors, we found differences between tasks in all regions ($p = 0.004$) and in anterior regions ($p = 0.007$) but not in posterior regions ($p = 0.392$; Table 3). However, there was no significant difference in the cluster of cortical regions representative for performance errors between the language tasks (all regions: $p = 0.1084$, anterior regions: $p = 0.2309$, posterior regions: $p = 0.3384$; Table 3).

Regarding the distribution of different error categories within the language tasks, most no-response errors were observed during action naming, whereas the highest numbers of semantic paraphasias and performance errors were revealed during object naming (Figure 26). Concerning anterior regions, object naming showed the highest no-response, semantic, and performance error rates (Figure 27). In contrast, action naming revealed the highest number of no-response errors in posterior regions. Furthermore, verb generation revealed a slightly higher error rate in semantic paraphasias than the other tasks did (Figure 28).

Pseudoword reading elicited the highest number of phonological paraphasias in both the anterior and posterior regions (Figure 26, Figure 27, Figure 28).

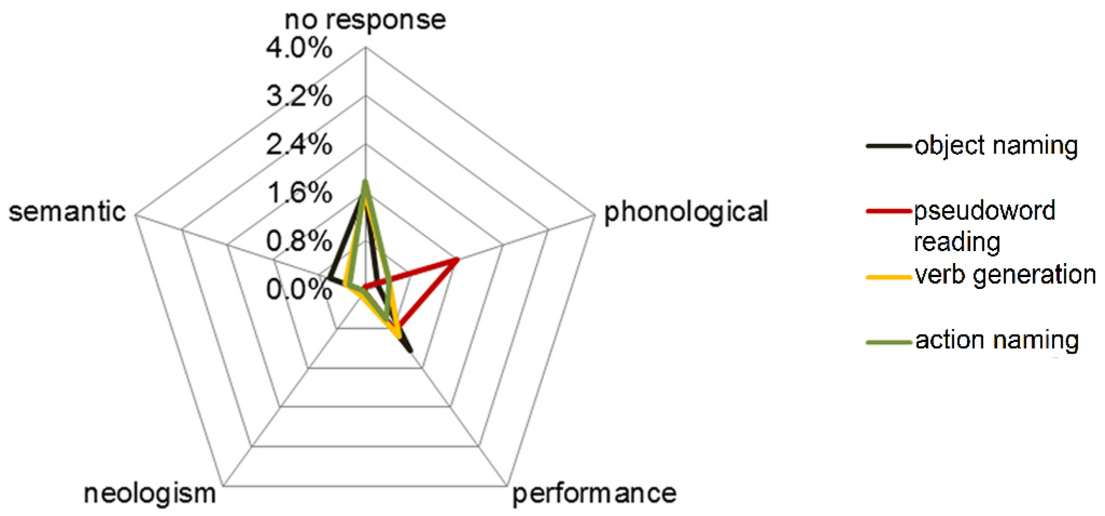

Figure 26: Error type differences across task types. Error rates [percentage] per error category are presented for object naming, pseudoword reading, verb generation, and action naming for all regions.

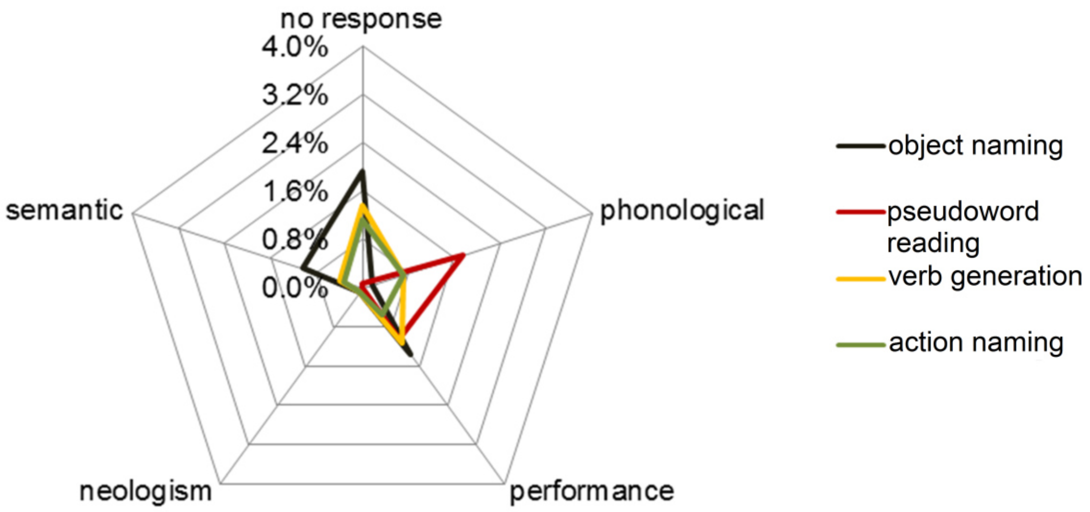

Figure 27: Error type differences across task types. Error rates [percentage] per error category are presented for object naming, pseudoword reading, verb generation, and action naming for anterior regions.

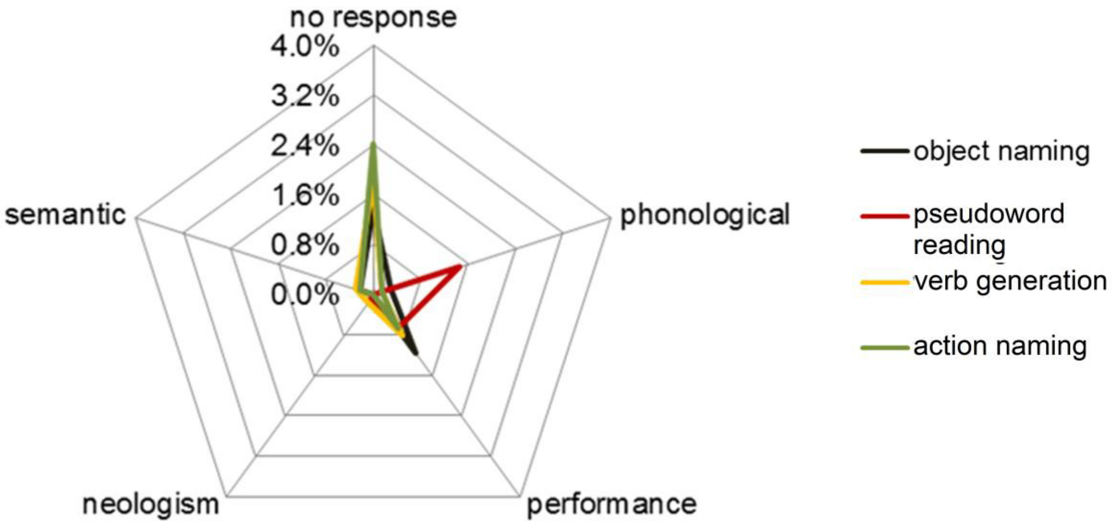

Figure 28: Error type differences across task types. Error rates [percentage] per error category are presented for object naming, pseudoword reading, verb generation, and action naming for posterior regions.

4. DISCUSSION

Among patients suffering from brain tumors in or adjacent to language areas, language disorders are very common. Language is one of our most important communication tools, and problems with language usage affect, inter alia, an individual's activities of daily living, relationships, and self-confidence (Dalemans et al., 2008, Darrigrand et al., 2011). To spare language-positive areas in these patients, today's resections of brain tumors demand preoperative planning (Chang et al., 2015). Therefore, a selection of sound techniques for noninvasive language localization is indispensable. Object naming thereby serves as the most widespread task and involves presumed cortical and subcortical language regions to a large extent (DeLeon et al., 2007). Object naming is also commonly used intraoperatively in the course of DCS of language-sensitive areas (Ojemann, 1983, Ojemann et al., 1989, Ruge et al., 1999, Walker et al., 2004, Picht et al., 2006, Sanai et al., 2008). Unlike to automatic speech tasks such as number counting, the superiority of object naming concerning the detection of classical language regions has already been demonstrated (Petrovich Brennan et al., 2007, Vanlancker-Sidtis et al., 2003). Although other tests such as word or pseudoword reading, word generation, or visual naming of non-objects are well-established in the study of language localization, up to now, the object-naming task has nearly been the only visual task to be combined with a navigated system. Nevertheless, because the accuracy of rTMS combined with an object-naming task leaves room for improvement (Picht et al., 2013), in the current study, we perform other language tests to examine diverse aspects of language and to improve language mapping via rTMS. The broad distribution of regions contributing to semantic processing, in particular, might be captured via diverse tasks.

In the following, the results are discussed with particular focus on congruencies of and differences between existing models of language processing. They furthermore are compared in view of their suitability to preoperative language mapping. When we do not mention the hemisphere of the considered area explicitly, we are looking at regions in the left hemisphere.

4.1. Error categories

Because of occurrence of different error types during stimulation, we divided language disturbance into several categories. Thereby, the no-response category can be regarded as one of the most impressive error types. Areas in which stimulation caused a high number of this kind of error very likely play an essential role in language processing for the respective task. Hesitations constituted the most frequent error types. Because we excluded all items that were named delayed during baseline testing, we attached value to each hesitation during stimulation and regarded hesitations as interference with a structure involved in (but probably not essential to) language processing for this task. Neither no-response errors nor hesitations give any information about underlying mechanisms that lead to the language disruption. In contrast, error types such as semantic and phonological paraphasias and neologisms, provide more detailed information about the function of the stimulated area. Performance errors appear mainly when stimulating sites that participate in articulation. During verb generation and action naming, we observed a further sort of language disruption during stimulation: Amidst a set of correctly built verbs out of the according images, the subject abruptly just named the (correct) object and thus was unable to think of a verb. This was a very small fraction of errors, but it occurred in eight out of nineteen subjects during verb generation. Because of this impressive selective impairment of language, we noted this occurrence by introducing the “nominalization” error category. The occurrence of nominalization errors might be indicative for verb-specific areas.

4.2. Distribution of language sites

4.2.1. Object naming

A variety of studies in recent decades has investigated the involvement of brain regions in visual object naming. Despite many inconsistencies concerning exact contribution of single brain regions, there appears to exist broad consensus on the general word-production process, especially for Levelt’s model of word production and enhanced models including the time course of word production (Levelt et al., 1999, Levelt, 2001, Indefrey and Levelt, 2004, Indefrey, 2011). The processing of word production is thereby described as follows: First, object naming starts with visual object recognition; this is followed by selection of the fitting item in the mental lexicon (lexical memory). Once the speaker has decided on the target item, the conforming phonological codes are activated and phonological encoding (syllabification) proceeds. The syllables are composed of a phonological word, which in turn passes phonetic encoding. Subsequently, articulatory scores enable the preparation of appropriate articulatory gestures, and, in a final step, articulation (via laryngeal and supralaryngeal muscles) creates overt speech.

Within this progress, several specific brain areas are involved. Very roughly outlined (and described more in detail below), the middle temporal gyrus (MTG) represents semantic and phonological functions. The inferior frontal gyrus (IFG) receives phonological information and processes syllabification. Motor command for articulation is initiated in vPrG (Indefrey, 2011).

In the current study, we found higher error rates in the anterior than in the posterior regions, which agrees with earlier findings of false-negative points during object naming when comparing rTMS to DCS. We observed highest error rates in the inferior frontal gyrus (IFG; trIFG and opIFG), pMFG, mSFG, vPrG, vPoG, and the MTG (mMTG; Figure 14).

Regarding anterior regions, the role of the left IFG in language processing has been widely discussed in previous studies. This region has repeatedly been shown to be involved in semantic and phonological decisions for the production processes of single words (Gold and Buckner, 2002). Thereby, it has been suggested that, within this region, there are several areas responsible for different functions and that these regions highly interact with one another. Despite findings that disagree with the theory of the strong spatial division of function within the inferior frontal lobe, the results of other studies indicate that the anterior part (pars orbitalis and trIFG) is relatively more involved in semantic decisions and that the posterior part (opIFG) is more activated in phonological decisions (Devlin et al., 2003, Binder and Desai, 2011, Bookheimer, 2002). Regarding our results, trIFG and opIFG were among the areas with the highest error rates (Figure 14, Table 4). Although the object-naming task generated the highest number of semantic errors, this error category appeared to be generally rare. Nonetheless, trIFG is one of the three regions in which stimulation evoked a higher percentage of semantic errors (Table 4). This indicates, in accordance with previous findings, that the anterior part is more likely than the adjacent posterior part to be part of the semantic system. However, we could not elicit phonological errors, which barely exist during object naming, within the inferior frontal gyrus, so we could not make a reliable statement on the distinction between semantics and phonological processing in this region. Moreover, we obtained a high percentage of no-response and hesitation errors within the mapped areas of the IFG. The underlying mechanism of no-response errors and hesitations, however, is unclear within the limits of the current mapping protocol. Hence, under the given circumstances, we can only hypothesize that interference of phonological and semantic processing during application of stimulation contributed to no-response and hesitation errors in these areas.

In addition, the MFG, particularly pMFG, showed a high error rate during object naming (Figure 14, Table 4). Representing a part of the supplementary motor area, the MFG is regarded as a key structure for the planning and execution of speech motor commands (Alario et al., 2006). Its role in terms of word retrieval from semantics in the course of language processing is relatively consistent in the literature, and several authors have described semantic impairment in correlation with damage to the pMFG (Binder and Desai, 2011, Price, 2012). This is in accordance with our current findings of a comparably high rate of semantic errors within pMFG.

Errors in the pre- and postcentral gyrus reflect disruption of speech-motor command. Motor representation of the orofacial and laryngeal musculature is represented in the ventral part of the precentral gyrus (Penfield and Boldrey, 1937, Bouchard et al., 2013, Simonyan and Horwitz, 2011, Conant et al., 2014, Penfield and Rasmussen, 1950), so the lesions in this area interfere with articulation, which manifests mainly in dysarthria. We expected to obtain a particularly high amount of performance errors in this area. However, the high error rate in vPrG mainly consists of hesitations and no-response errors, which nevertheless can also appear due to a lack of speech-motor command. The disruption of language in the form of "speech arrests" (no-response errors) can occur because of both contraction of the orbicularis oris muscle and interference with language processing, per se (Stewart et al., 2001).

Rather surprisingly, our findings revealed a remarkable number of errors in the middle part of the SFG and a non-negligible amount in the posterior part of the SFG (Figure 14, Table 4). SFG is not standard in the well-established models of word production. In general, the function of the SFG has been less well investigated than have other parts of the brain. Focal lesions in the left SFG were described as causing dynamic aphasia (Luria and Tsvetkova, 1968). In this special form of language disorder, the patient's active speech (i.e., his or her ability to build even simple sentences) is disturbed. However, the patient still performs quite normally in naming objects. However, why then did stimulation of this area result in a decline in object naming in the current study? MSFG was attributed a role in facilitating semantic comprehension (Scott et al., 2003), and pSFG is considered a key component in working memory (du Boisgueheneuc et al., 2006). A meta-analysis of 120 functional neuroimaging studies revealed the participation of SFG in semantic processing across trials (Binder et al., 2009). Binder et al. (Binder and Desai, 2011) presumed that the mSFG activated and selected the information stored in the parietal and temporal lobes so that the lesions within this region would impair access to stored information, but it did not cause a loss of this knowledge. Regarding our error distribution in SFG, hesitation errors constitute a large fraction of errors; this can be explained with Binder's theory of impaired (and thus delayed) access to information. Furthermore, in the current study, stimulation in mSFG caused a high rate of semantic impairment (Table 4). Altogether, SFG might rather play a supportive role and contribute to the robustness of language processing.

Regarding the posterior regions, within the temporal lobe, lesion studies have found significant declines in naming to be associated with resections in the midtemporal and posterior temporal areas (Wilson et al., 2015, Haglund et al., 1994). Our data revealed an extraordinarily high error rate in the anterior part of the mMTG (Figure 14, Table 4). This area is activated in picture naming; both lemma retrieval and selection are assumed to be located there (Indefrey, 2011). In the current study, we found no single semantic error in mMTG among the 19 subjects, and stimulation revealed primary hesitations and no-response errors (Table 4). In principal, each error type, if particularly pronounced, can be imagined to cause hesitations or no-response errors. It is quite conceivable that interference of lemma retrieval and selection could lead to naming latency and thus cause these types of errors.

The superior temporal gyrus is suggested as an important site for phonological processing by lesion and imaging investigations. PSTG was demonstrated to specifically contribute in phonological code retrieval (Graves et al., 2008), but mSTG was proposed to be involved in phonological code storage (Wilson et al., 2009). With our current protocol, only six sites showed phonological errors, of which two were in the posterior mSTG and pSTG (Table 4).

Altogether, our findings showed sparse language disruption for object naming in the temporal lobe (aside from in the mMTG). Sanai et al. also observed comparably small participation of the temporal lobe during the naming of line drawings (Sanai et al., 2008). This differs from classical language studies, which attributed an outstanding role to the temporal lobe in object naming.

Other posterior regions that have been reported to be involved in the semantic network of word-processing—predominantly SMG and anG (Gow, 2012, Henseler et al., 2014, Seghier, 2013)—were rare. SMG has emerged as important site for semantic processing, particularly when word retrieval is more semantically challenging (Wise et al., 2001). Against expectations, our stimulation protocol did not have an extraordinarily increased error rate in these areas during the object-naming task. No semantic errors were revealed. Again, mainly hesitations (and a few no-response errors) appeared (Table 4). Nevertheless, resection of tumors in the parietal lobe was demonstrated to cause dysphasia, which was the most common postoperative neurological deficit (Sanai et al., 2012). The authors emphasized the value of the superior longitudinal fasciculus (SLF), which runs through the inferior parietal gyrus and connects the posterior temporal cortex with the inferior frontal gyrus and the vPrG. They suggested preserving the SLF to reduce postoperative language decline. Taking into account that rTMS can reach structures within approximately 45 mm of the coil surface, stimulation likely does not reach the SLF and therefore does not evoke many errors in this area.

4.2.2. Pseudoword reading

Altogether, pseudoword reading emerged as the task evoking the fewest overall errors; a no-response error could only be evoked in one subject (Table 5). We attribute this effect to different causes. First, in visual naming or generating tasks, the pictures have to be linked with their semantic labels. The subject has to make a semantic decision and then detect one of several expressions. Thus, naming tasks involve the selection of semantic information. In contrast, reading is supposed to constitute a more automatic mechanism (Binder et al., 1999), which seems to be less vulnerable to disruption with rTMS. This was also found in previous studies. For instance, Wassermann et al. could not evoke a significant effect in word reading with rTMS but could do so in picture naming (Wassermann et al., 1999). Also Sanai et al. (Sanai et al., 2008) also found many more DCS-induced language disturbances during a naming task than during a reading task. Second, the utilized error categories were primarily tailored for a naming task, so they might not be ideal for reading, which might contribute to the low error rate. Third, other recent studies demonstrated improvement in reading when applying stimulation over left-hemispheric sites (Costanzo et al., 2012). However, enhancement of language performance was also observed in rTMS combined with other language tasks such as picture naming (Sparing et al., 2008, Topper et al., 1998). Hence, cortical excitability is assumed to be dependent on several further factors, such as stimulation parameters (frequency) or stimulation location (Sparing et al., 2008, Holland et al., 2011, Guse et al., 2010, Andoh et al., 2006).

Another observation regarding pseudoword reading is that this task evoked the highest number of phonological errors (Table 3). In the past, pseudoword-reading tasks have been utilized frequently in conjunction with brain-damaged patients who suffer from phonological dyslexia (Riley and Thompson, 2015, Brunswick et al., 1999). Considering that phonological information is supposed to be evident for reading ability (Dérouesné and Beauvois, 1979, Sartori et al., 1984), it is not surprising that stimulation during pseudoword reading reveals mainly phonological errors.

However, the exact underlying mechanism of functional impairment in poor pseudoword reading remains unclear to a certain degree. As one of several cognitive models of reading, Coltheart et al.'s dual-route cascaded (DRC) model describes both non-lexical and lexical routes for decoding orthography into phonology. The lexical route involves phonological and orthographic lexica and the semantic system. The non-lexical route enters the course of word production after the lexical stage and is especially important for reading pseudowords, as it translates graphemes into phonemes (Coltheart et al., 2001).

Previous meta-analysis findings revealed, largely in correspondence with reading model components, that the following regions are involved in reading words and pseudowords: the posterior and anterior fusiform cortex (for non-lexical orthographic processing and as an orthographic lexicon); the angular gyrus (AnG; as a phonological lexicon and for semantic processing), the MTG (for semantic processing), and the inferior parietal gyrus (for spelling-sound conversion). The IFG is assumed to implement phonological output (Taylor et al., 2013).

Further neuroimaging studies on phonological dyslexia found that impaired pseudoword reading also correlated with deficits in the pSTG (Brambati et al., 2009). Activation in the pSTG during reading was also shown in healthy participants, which is in accordance with the high error rate in pSTG in our current study (Price et al., 2006). This area has been demonstrated to include phonological storage (Simos et al., 2002, Graves et al., 2008).

Comparing our data with other previously detected brain regions, we also observe reading interference within the AnG (Roux et al., 2004, Graves et al., 2010) (Figure 18), to which lexical analysis was attributed (Rumsey et al., 1999). In the current study, however, we only found reading errors in the ventrolateral part of the AnG.

Regarding the MTG, as expected, we could also evoke a higher error rate in this area; the remarkable disruption of language seen in the inferior parietal gyrus was missing (Figure 18). This differs from previous lesion study findings (Sanai et al., 2008).

Articulatory interferences were described in pre-and postcentral gyri (Roux et al., 2004), which correlates with the higher performance error rate in the mPrG in the current study. The highest error rates (with a large number of performance and phonological errors) were detected in the opIFG. A potential cause for this could be the reversion of both the lexical and non-lexical routes (word and pseudoword reading) to the inferior frontal gyrus when converting the information into articulatory codes.

For completeness when talking about reading mechanisms, a further involved area should be briefly mentioned: the so-called visual word form area, a functional region in the left occipitotemporal sulcus. This was first documented in the 19th century (Dejerine, 1891), and it has been demonstrated to play a causal role in reading and to represent a site of visual orthographic lexical knowledge (Dehaene and Cohen, 2011, Nobre et al., 1994, Cohen and Dehaene, 2004). As we already mentioned above, stimulation intensity in rTMS is lacking in this area, so we did not map the inferior temporal lobe (including the fusiform gyrus). Thus, unfortunately, we cannot make any statement about this brain region. The same applies for the cerebellum, which was also shown to be activated when reading pseudowords (Mechelli et al., 2003).

4.2.3. Verb generation

Verb generation has been used more frequently in brain imaging studies than in brain stimulation studies. It has been suggested to be the most successful task for testing language in adult MEG studies (Pirmoradi et al., 2010). Like object naming, verb generation is ranked among the semantic association tasks, for which the participant has to select one of many associations of the presented item. A previous trial demonstrated the validity of verb generation based on pictures and showed its superiority compared to verb generation based on words (Pang et al., 2011). Therefore, in the current study, we used colored images and had each subject rapidly speak a single action word related to each picture.

In general, regions participating in verb generation overlap widely with the above-described areas involved in object naming (Ojemann et al., 2002) (Figure 20), which can be attributed to the instruction of building verbs out of visually presented objects. Broaching the issue of the cortical areas that contribute to the production of verbs, non-mapped areas also have to be mentioned. Recent studies showed activation of the cerebellum, primarily the dentate nucleus, during verb generation (Thurling et al., 2011, Frings et al., 2006). Additionally, the anterior cingulate cortex was suggested to be activated for competing alternative responses (Kircher et al., 2001).

With regard to our results, verb generation revealed a higher overall error rate in the anterior regions than in the posterior regions. However, when taking into account the essential no-response errors, more errors were evoked in the posterior sites (Table 3).

Regarding anterior regions, in the current study, rTMS elicited no notable number of language errors within the IFG, and the language disturbance in IFG was more infrequent than it was during object naming (Figure 15, Figure 21). Previous studies repeatedly emphasized activation in IFG during verb generation (Wang et al., 2012, Bak et al., 2001), so that we actually expected more errors in IFG. The authors attributed the construction of verbs (and the selection of an associated verb among several alternatives) mainly to areas in IFG (Thompson-Schill et al., 1997). However, reconsidered findings from Thompson-Schill and coworkers suggested that the IFG is rather relevant for association strength between the presented noun and the most frequently produced verb (Martin and Cheng, 2006). In turn, a recent study presented data showing that both factors (association strength and selection of alternatives) are related to the IFG (Crescentini et al., 2010).

Instead, we detected the highest overall error rate in pMFG, followed by the posterior part of mMFG (with a large number of hesitations in this area; Figure 20). MFG has been ascribed a role in semantically driven word retrieval (Buckner et al., 1995), though our data revealed no notable number of semantic errors in this region. However, errors in the category nominalization were observed mainly in pMFG. This indicates that pMFG might play an essential role in verb processing. Furthermore, previous trials ascribed activation in MFG to its function as a (pre-) supplementary motor area in the initiation of language (Wise et al., 1991, Crosson et al., 2001), which might be expressed in the hesitation errors in our study.

In posterior regions, errors were mainly evoked in mMTG (Figure 20). In this area, we primarily found the profound no-response (Figure 21) and semantic errors (Table 6). A cortical-stimulation mapping study also found disruption of verb generation in temporoparietal areas (Ojemann et al., 2002). Furthermore, some previous non-lesion based PET studies demonstrated the involvement of the MTG in both verb-generation and naming tools (Martin et al., 1996, Martin et al., 1995, Herholz et al., 1996, Damasio et al., 1996). MTG is thereby suggested to play a role in semantic associations (Allendorfer et al., 2012). In general, non-lesion-based imaging studies revealed lower activation in the temporal lobe and higher activation in frontal areas during verb generation. However, the current study supports the previous lesion-based findings (Ojemann et al., 2002), showing that posterior areas are also essential in this language task.

4.2.4. Action naming

Studies of brain-damaged patients revealed selective, or relatively selective, impairment in the production of nouns and verbs. Thereby, cases were reported in which disorders of noun processing were attributed to damage in posterior regions (mainly within the temporal lobe); declines in verb processing, on the other hand, were related to frontal lesions (Daniele et al., 1994, Damasio and Tranel, 1993). On the other hand, dissociations in verb and noun processing were suggested to be present in anomic patients but not in healthy volunteers. Thus, a common neural system for noun and verb processing was also proposed (Soros et al., 2003), and different findings for noun and verb localization were attributed to different linguistic and general processing demands (Siri et al., 2008). A frequently discussed aspect in the literature on the performance of nouns and verbs is the principle reason for different neural substrata of verbs and nouns within their respective task designs. Thereby, the underlying semantic differences between the items of the noun and the verb task (rather than grammatical class effects) were what led to different associations within the brain (Moseley and Pulvermuller, 2014).

Because selective impairment in both object and action naming has been confirmed in awake surgery (Corina et al., 2005), we considered that distinction was clinically relevant and decided to conduct an action-naming task in addition to the object-naming task.

With the action-naming task, we thereby selected a further task based on the construction of verbs. In contrast to the verb-generation task, we used pictures not of objects but of people doing something. Thus, the correct answer was more predetermined; the subject had fewer alternatives of fitting verbs, so the action-naming task might have been less semantic challenging than the verb-generation task. Over all, in the current study, we indeed observed a smaller error rate in action naming than in verb generation (Table 3). Comparing action naming with object naming, an earlier study concluded that the former was more demanding than the latter (Matzig et al., 2009). Other previous findings from a cortical stimulation study demonstrated less interference during action naming than during object naming (Lubrano et al., 2014). On the other hand, a recent study observed that electric stimulation during brain surgery had a higher correlation with action naming than with object naming; the authors concluded that action naming might be superior in avoiding post-operative language decline (Havas et al., 2015). It is conceivable that these distinct effects rely on the difficulty of the respective task per se. With regard to our results, action naming led to fewer errors than object naming did (Table 3).

In addition to the previous findings, which revealed the involvement of frontal cortical regions in action naming (Cappa et al., 2002), the current study also demonstrated the important role of posterior regions. We even observed a slightly higher overall error rate in the posterior regions than in the anterior regions, and the highest no-response error rate appeared in the posterior regions (Table 3).

In the anterior regions, language disturbance in action naming was mainly observed in opIFG and in the posterior part of MFG (Figure 23). Stimulation in the latter revealed a remarkable no-response error rate (Figure 24). These areas were also identified by Lubrano et al. (Lubrano et al., 2014). Thereby, the prefrontal (premotor) gyrus is supposed to be associated with actions; it showed greater involvement in verb production than in noun production in the past (Cappelletti et al., 2008). According to this, semantic errors (which were very rare during this task) and nominalization errors were observed in midfrontal regions in the current study.

Concerning posterior regions, stimulation induced disruptions of action naming, mainly in mSTG (Figure 23). STG was found to be more activated in the production of verbs than in the production of nouns, and it was supposed to be associated with lexical item retrieval (Shapiro et al., 2006). Martin et al. (Martin et al., 1995) found activation in MTG during action naming, whose involvement is supported by the high error rate in mMTG in the current study. Moreover, those temporal regions showed a high rate of no-response errors (Figure 24).

Another region in which we found a noteworthy amount of errors is the SPL. No-response errors thereby occupied a relevant amount (Figure 25). SPL was also frequently disrupted during object naming, as was already described in previous findings (Krieg et al., 2016). However, the percentage of no-response errors was higher in verb generation than in object naming. SPL has been described as a region for lexical decisions for nouns and verbs. Thereby, activation in SPL was significantly higher when processing verbs compared to nouns (Shapiro et al., 2006, Perani et al., 1999).

Though stimulation in the angular gyrus only showed average overall error rates, it produced one of the highest numbers of no-response errors (Figure 24). Regarding the other applied tasks, fewer no-response errors could be observed within the AnG. Recently, the angular gyrus was attributed an important role within the semantic system (Binder et al., 2009, Seghier, 2013). Sörös et al. (Soros et al., 2003) observed a stronger response in the angular gyrus during action naming than during object naming, which is in accordance with our results regarding the relevance of the AnG in action naming.

4.3. Task comparison

RTMS induced errors during the performance of all applied language tasks, but the number and distribution of errors varied significantly among tasks (Table 3). Regarding the number of correctly named baseline pictures, we observed considerable differences between naming and reading tasks: Subjects performed significantly better in reading than in naming or generation tasks during baseline testing (Table 8). This indicates that reading, which represents a rather automatized mechanism, is the least challenging task. Nevertheless, we observed no correlation between the error rate during baseline analysis and the error rate induced by rTMS. Thus, a participant with a low number of accurately identified baseline items would not necessarily have a high error rate during stimulation.

Object naming has been repeatedly tested in the past, showing a large-scale distribution of language errors (DeLeon et al., 2007, Price et al., 2005). In the current study, rTMS combined with object naming evoked errors over all stimulated sites and induced the highest overall, performance, and semantic error rates (Figure 26, Table 3). No-response errors and neologisms occurred at a similar percentage during object naming, verb generation, and action naming (Table 3). Therefore, among the four tested language tasks, object naming seems to be the most discriminative. However, we have to consider that the utilized error categories have been customized for an object-naming task and that they thus should include all errors that could potentially appear during object naming but not necessarily during the other tasks. This might have the largest effect on pseudoword reading, resulting in lower error rates. Pseudoword reading barely generated errors in the current study and varied significantly from the other applied tasks, which might be attributed to different underlying cortical mechanisms of reading and naming or generation. Previous findings described earlier, longer, and higher activation in the generic language production processes for reading than for object naming (Price et al., 2006), which apparently is associated with low vulnerability to rTMS. Altogether, this task generally cannot be recommended as the sole preoperative language-mapping task in cases with non-language-impaired patients. Nevertheless, rTMS combined with a reading task does provide information about the phonological system; therefore, it can serve as a useful tool in neuropsychological research.

Concerning the verb-generation task, authors have suggested involving semantic analysis other than the object-naming task (Seger et al., 1999, Herholz et al., 1997). This seems plausible when regarding the large set of different response options for a related verb. For example, the responses of our participants to the noun “Wecker” (English: “alarm clock”) varied, inter alia, including obvious characteristics (what the object does, for example “klingeln”/”wecken”; English: “to ring”/”to waken”), a related activity (“ausschalten”; English: “to turn off”), or personal experience (“nerven”; English: “to annoy”). Nevertheless, contrary to expectations that verb generation involves a significantly larger number of errors, it elicited slightly fewer errors, both overall and semantic, than object naming did (Table 3). In posterior regions, it revealed a slightly higher no-response error rate. Altogether, the verb-generation task did not show convincing benefits compared to object or action naming. In contrast, action naming revealed a higher error rate in posterior regions than in anterior regions (Table 3). Action naming significantly differed from object naming, which is indicative that distinct cortical areas are involved in the processing of nouns and verbs.

4.4. Limitations

The general limitations of rTMS are important contributing factors to the limitations of the study. One of those general limiting factors is that the extension of stimulation is limited to areas near the cortical surface, because the effect of stimulation decreases with the distance of the coil. Hence, areas such as the fusiform gyrus have to be restricted due to insufficient stimulation intensity. Furthermore, discomfort during stimulation when affecting peripheral muscles or nerves does not allow for mapping of the entire hemisphere. As we noticed in the current study, not all subjects tolerate rTMS well; in the case of one volunteer, we had to stop the investigation due to unacceptable pain.

To minimize discomfort, stimulation trains should be as short as possible. However, for investigating grammatical class and for distinguishing between speech and language impairment in the case of no-response errors, hesitations, or performance errors, the presentation of sentences instead of single words would be most appropriate. On the other hand, the exact timed correlation of stimulation and stimulus presentation is evident. With our current rTMS protocol, the presentation of sentences would therefore not be suitable. Another limitation of our protocol is that it does not measure naming, generation, or reading latencies. The resulting consequences were as follows: First, it was impossible to access the time course of word production in different language tasks. Second, we compared hesitations only to baseline test results, so we could not exclude a certain degree of subjectivity concerning the detection of this error type.

As another limitation of this study, we did not investigate white fiber tracks. The reconsidered model of language processing supports the essential function of large-scale subcortical connectivity in language (Catani and ffytche, 2005, Almairac et al., 2014). Thus, the idea of a delocalized, hodotopical model with distributed clusters of connected neurons replaced the static view of single language centers (Papagno et al., 2011, Bonner et al., 2013, Duffau, 2008). Damage in subcortical regions has repeatedly been shown to be associated with language deficits (Banerjee et al., 2015), and intraoperative advantages of preoperative diffusion tensor imaging (DTI) have been demonstrated (Bello et al., 2008). Considering this revisited model, the current trend is toward virtual lesion studies at the cortical and subcortical levels. Therefore, the recent development of DTI, which allows noninvasive mapping of white fiber tracks, combined with rTMS seems to be a promising technique for language analysis.

4.5. Clinical implications

First, rTMS will not serve as replacement for awake DCS now or in the near future. However, it allows superior preoperative planning and management by creating a precise language map. Intraoperatively, the surgeon has a better concept of the location of potential positive language sites, which might contribute to shorter operation times. The patients might also be better prepared with regard to their postoperative outcomes. For example, when language-eloquent sites are detected within the tumor, patients can be educated about potential residual tumor tissues and postoperative declines in language processing. Furthermore, the patients can imagine the procedure in theatre so that their performance during rTMS also allows for preoperative practice in naming. This a) leads to less excitement before and during surgery and b) intraoperatively prevents the necessary detailed explanations.

Language-positive areas detected via object naming are regarded as essential to language, and their resection should be avoided to preserve postoperative language impairment. However, despite intraoperatively preserving those areas, some patients present deficits in language processing or alexia after surgery (Petrovich Brennan et al., 2007, Hermann et al., 1999), so the implementation of only one task is insufficient.

Applying several tasks during preoperative rTMS investigations might therefore optimize language mapping. By investigating numerous language sub-functions, the examiner can obtain a more detailed map of the individual cortical neuronal networks and thus might manage to reduce postoperative language decline. Furthermore, in some cases, it is useful to offer an alternative to the classical object-naming task to thus better correspond to the patient's cognitive deficits. Patients with limited abilities (e.g., those who suffer from word finding disorders) might be able to perform an easy task such as reading but not a harder task such as object naming. On the other hand, patients might be selectively impaired in producing nouns but still succeed in performing a verb-generation task. Hence, having the possibility to select a task that best fits the patient's abilities would constitute a great benefit for the clinical ability of rTMS. It was also already suggested, intraoperatively during DCS, to select a task tailored to the underlying functional networks close to the lesion (Fernandez Coello et al., 2013). Thus, aside from its role in preoperative language localization, rTMS individually provides a reasonable method to detect the most appropriate task(s) prior to awake surgery.

Despite all these advantages and the importance of testing different neuronal functions, we have to be aware that language mapping investigations are time-consuming and that longer pre- or intraoperative examination times cause reduced patient concentration and compliance. Consequently, it is important to achieve a compromise between detailed detection of language localization and the patient's reliable attention so as to maximize the effectiveness of the mapping.

4.6. Further considerations

In the past, clinical studies demonstrated postoperative aphasia despite intraoperative protection of areas that were positively tested in visual naming tasks (Hamberger et al., 2005). These findings indicated that naming sites were identified not only visually but also from auditory cues that might be relevant for normal naming function, especially in the anterior temporal lobe (Hamberger et al., 2001, Hamberger et al., 2005, Serafini et al., 2013).

Therefore, it is suggested to use of a combination of different task modalities to obtain a more comprehensive language map and minimize postoperative word-finding difficulties.

In this study, we concentrated on language localization in the left hemisphere. Nevertheless, the relevance of the nondominant hemisphere in single-word production has been shown for patients both with and without left-hemispheric damage (Thiel et al., 2005, Thiel et al., 2006, Duffau et al., 2008); this conclusion has recently been supported for healthy subjects as well (Sollmann et al., 2014). Reading, in particular, is supposed to involve the nondominant hemisphere (Coslett and Monsul, 1994). Therefore, investigation of the dependence of right-hemispheric language distribution on different word-production tests would be beneficial (Sollmann et al., 2014).

Apart from expanding the language task's variability, it is also important to refine the parameters of the rTMS language-mapping protocol. As recent studies have outlined, parameters such as stimulation intensity, frequency, and coil angulation are responsible for different results in terms of the number and location of language-positive sites (Sollmann et al., 2015b, Hauck et al., 2015). Higher stimulation intensities are thereby correlated with a longer influence on language function and, thus, with greater language impairment (Sparing et al., 2001). Concerning the applied frequency, the location of the stimulation, rather than the frequency, has been suggested to determine whether stimulation has facilitating or suppressing effects (Andoh et al., 2006). Thus, more systematic data about stimulation parameters is needed for a precise examination; even small adjustments might decisively improve mapping results with regard to the accuracy and reproducibility of rTMS. Thereby, a concept for individually targeting and dosing rTMS would be desirable.

Concerning brain-tumor patients, optimizing the selection of an appropriate task is necessary to ensure the most precise individual detection of neuronal network localization in preoperative mapping (Fernandez Coello et al., 2013). Therefore, the application of no primarily language-based tasks should also be considered. Other neuropsychological tasks such as calculating or neglect tasks might be useful, depending on the patient's profession. Furthermore, the combination of several preoperative imaging techniques provides more safety in the detection of the relevant cortical regions (Grummich et al., 2006).

Additionally, for better comprehension of rTMS effects, further investigations into the spatial resolution of rTMS is evident. This would provide more detailed information on functionally relevant and irrelevant cortical areas.

Finally, as mentioned above, the important role of language pathways, as described in recent studies, should be considered in future research. Therefore, the combined application of rTMS and DTI constitutes a promising technique for future language analysis.

5. SUMMARY

5.1. English

Navigated repetitive transcranial magnetic stimulation (rTMS) has developed into a technique that is widely used in clinical utility and in neuropsychological research. For most beneficial clinical application of rTMS in preoperative language mapping, it was suggested to outline language-negative regions, which can be carefully excised intraoperatively (Picht et al., 2013). Compared to the current gold standard of intraoperative DCS, rTMS combined with object naming already shows high sensitivity in anterior regions, but in posterior regions, sensitivity has to be improved. Hence, in the current study, the research question was if rTMS combined with other language tasks would affect the localization of language-positive areas.

19 healthy, right-handed subjects were enrolled. In addition to object naming, the participants were asked to perform pseudoword-reading, verb-generation, and action-naming tasks. Synchronically, rTMS language mapping of the left hemisphere was performed with 5 Hz/10 pulses and a picture to trigger interval of 0 ms. Induced errors were evaluated via video analysis and divided into eight error categories (overall errors, no-response errors, hesitations, performance errors, semantic paraphasias, phonological paraphasias, neologisms, and nominalization errors).

The object-naming task induced the highest overall error rate (14%), followed by verb generation (13%), and action naming (11%). Pseudoword reading only evoked an error rate of 4%. The localization of language-positive regions significantly differed among language tasks ($p < 0.0001$). Object naming, pseudoword reading, and verb generation revealed higher error rates in anterior regions, whereas action naming showed more errors in posterior regions. Concerning different error types, object naming induced the highest no-response (1.6%), semantic (0.6%), and performance (1.3%) error rates. The highest rate of phonological paraphasias (1.6%) was observed during pseudoword reading.

In conclusion, this study is one of the first to focus on the influence that utilized language tasks have on the localization of language-positive areas and on error rates during rTMS. The localization of language-positive areas varies depending on to the applied language task, and the distribution of error types varies among different tasks. In general, all four language tasks appeared to be easily feasible when combined with rTMS, whereby areas detected as language positive are mostly consistent with common language models. Within the applied tasks, the object-naming task appeared to be the most discriminative one to reveal language-positive areas. rTMS combined with action naming can reasonably be used when aiming to map the posterior half of the hemisphere. Selecting a language task according to the location of the lesion or the patient's deficit might improve preoperative language mapping via rTMS. Additionally, the combination of several tasks allows for more detailed information about individual language organization.

5.2. Deutsch

Repetitive navigierte transkranielle Magnetstimulation (rTMS) hat sich zu einer weit verbreiteten Methode entwickelt, die sowohl im klinischen Bereich als auch im Rahmen neuropsychologischer Forschung Verwendung findet. Um rTMS im Rahmen der präoperativen Sprachkartierung möglichst sinnvoll klinisch einsetzen zu können schlugen die Autoren einer vorausgehenden Studie vor, sich auf die präoperative Darstellung negativer Sprachareale zu konzentrieren, welche im Anschluss intraoperativ reseziert werden können. Im Vergleich zum aktuellen Goldstandard, der direkten kortikalen Stimulation (DCS), zeigte die rTMS in Kombination mit einem Objektbennungstest bereits eine hohe Sensitivität in anterioren Arealen. In posterioren Gebieten hingegen ist die Sensitivität der rTMS gegenüber der DCS noch verbesserungsfähig. Deshalb gilt es herauszufinden, ob durch die Kombination aus rTMS mit anderen Sprachtests die Lokalisation der detektierten Sprachareale beeinflussbar ist.

In die Studie wurden neunzehn gesunde, rechtshändige Probanden eingeschlossen. Neben dem Objektbenennungstest wurden Pseudowörter Lesen, Verbgenerierung und Aktionsbenennung durchgeführt. Synchron mit der Bildpräsentation wurde die rTMS mit 5 Hz/10 Pulsen und einem Intervall von 0 ms zwischen Aufzeigen des Bildes und dem Stimulationsbeginn appliziert. Die provozierten Sprachfehler wurden via Videoanalyse identifiziert und in 8 Fehlerkategorien eingeteilt (alle Fehlertypen, Sprachausfall, Verzögerungen, Sprachleistungsfehler, semantische und phonologische Fehler, Neologismen und Nominalisierung).

Der Objektbenennungstest induzierte die höchste Fehlerrate von 14%, darauf folgend der Verbgenerierungstest mit einer Fehlerrate von 13% und der Aktionsbenennungstest mit einer Fehlerrate von 11%. Der Pseudowörter-Lesen-Test rief nur eine geringe Fehlerrate von 4% hervor. Zwischen den Sprachtests variierte die Lokalisation der positiven Sprachareale signifikant ($p<0.0001$). Während Objektbenennung, Pseudowörter-Lesen und Verbgenerierung wurde eine höhere Fehlerrate in anterioren Regionen beobachtet, wohingegen der Aktionsbenennungstest mehr Fehler in posterioren Regionen zeigte. Bei Betrachten der unterschiedlichen Fehlerkategorien fällt auf, dass der Objektbenennungstest die meisten keine Antwort Fehler (1.6%), semantischen Fehler (0.6%) und Sprachleistungs-Fehler (1.3%) aufweist. Die höchste Anzahl an phonologischen Fehlern wurde während des Pseudowörter Lesens identifiziert.

Zusammenfassend ist diese Studie eine der ersten, die den Einfluss des verwendeten Sprachtests auf die Lokalisation der sprachpositiven Areale und auf die Fehlerraten im Rahmen der rTMS untersucht. Es konnte gezeigt werden, dass die Lokalisation sprachpositiver Areale und die Verteilung der verschiedenen Fehlerkategorien je nach

Sprachtest variieren. Generell zeigten sich alle vier verwendeten Tests als gut geeignet in Kombination mit rTMS und die als sprachpositiv detektierten Regionen waren größtenteils identisch mit denen geläufiger Sprachmodelle. Der Objektbenennungstest scheint dabei der am stärksten differenzierende Test zu sein. Außerdem zeigte rTMS in Kombination mit einem Aktionsbenennungstest eine gute Eignung für die Kartierung der posterioren Gehirnhälfte. In Zukunft sollte eine Verbesserung der präoperativen Sprachkartierung in Betracht gezogen werden, indem ein Sprachtest passend zur Lokalisation der bestehenden Läsion bzw. zum bestehenden Sprachdefizit des Patienten gewählt wird. Außerdem erlaubt eine Kombination aus rTMS mit mehreren unterschiedlichen Sprachtests eine detailliertere Aussage über die individuelle Verteilung der Sprachareale.

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7. ABBREVIATIONS

AE	all errors
APB	abductor pollicis brevis muscle
ANT	anterior regions
BA	Brodmann's area
CPS	cortical parcellation system
DCS	direct cortical stimulation
DT	display time
DTI	diffusion tensor imaging
EEG	electroencephalography
EC	error category
EMG	electromyography
fMRI	functional magnetic resonance imaging
H	hesitation
IPI	inter-picture interval
MEG	magnetoencephalography
MEP	motor evoked potential
MRI	magnetic resonance imaging
Neo	neologism
No	nominalization
NR	no response
nTMS	navigated transcranial magnetic stimulation
P	performance
PET	positron emission tomography
Ph	phonological paraphasia
POST	posterior regions
PTI	picture-to-trigger interval

RMT	resting motor threshold
rTMS	navigated repetitive transcranial magnetic stimulation
S	semantic paraphasia
TES	transcranial electric stimulation
TMS	transcranial magnetic stimulation
VAS	visual analogue scale

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9. PUBLICATIONS

Original papers

Sollmann N, **Hauck T**, Tussis L, Ille S, Maurer S, Boeckh-Behrens T, Ringel F, Meyer B, Krieg SM.

Results on the spatial resolution of repetitive transcranial magnetic stimulation for cortical language mapping during object naming in healthy subjects.

BMC Neurosci. 2016 Oct 24;17(1):67

Negwer C, Ille S, **Hauck T**, Sollmann N, Maurer S, Kirschke JS, Ringel F, Meyer B, Krieg SM.

Visualization of subcortical language pathways by diffusion tensor imaging fiber tracking based on rTMS language mapping.

Brain Imaging Behav. 2016 Jun 20. [Epub ahead of print]

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J Neurosurg. 2016 Apr 1:1-12. [Epub ahead of print]

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Task type affects location of language-positive cortical regions by repetitive navigated transcranial magnetic stimulation mapping.

PLoS One. 2015 Apr 30;10(4):e0125298. doi: 10.1371/journal.pone.0125298. eCollection 2015.

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Ille S, Sollmann N, **Hauck T**, Maurer S, Tanigawa N, Obermueller T, Negwer C, Droese D, Boeckh-Behrens T, Meyer B, Ringel F, Krieg SM.

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Inter- and intraobserver variability in motor mapping of the hotspot for the abductor policis brevis muscle.

BMC Neurosci. 2013 Sep 5;14:94. doi: 10.1186/1471-2202-14-94.

Oral presentations

Hauck T, Tanigawa N, Ringel F, Meyer B, Krieg SM

Task type and frequency determine the distribution of language positive cortical regions during rTMS

65. Jahrestagung der Deutschen Gesellschaft für Neurochirurgie (DGNC), Dresden, 13.5.2014

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Sprachtest und Frequenz bestimmen die Lokalisation Sprachpositiver Areale mittels rTMS

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Task type and frequency determine the distribution of language positive cortical regions during rTMS

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Hauck T*, Sollmann N*, Meyer B, Ringel F, Krieg SM

Inter- & intraobserver variability of language mapping by rTMS

4th International Symposium on NBS in Neurosurgery, Berlin, 16.11.2012

Posters

Hauck T, Wohlschlaeger A, Probst M, Tanigawa N, Zimmer C, Ringel F, Meyer B, Krieg SM

Concordance of rTMS and fMRI using different tasks for language mapping in healthy subjects

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Task type and frequency determine the distribution of language positive cortical regions during rTMS

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4th International Symposium on NBS in Neurosurgery, Berlin, 16.11.2012