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Non-invasive mapping of cortical neglect-like deficits via navigated repetitive transcranial magnetic stimulation

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Für meine Eltern

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1. INTRODUCTION

1.1. The importance of preoperative brain mapping

There are two main goals in oncological neurosurgery. On the one hand the resection of the largest amount of the brain tumor and on the other hand the facilitation of the best functional outcome for the patient. In this context, it is often a difficult approach to find the optimal way between these two highly important objectives. On the basis of preoperative diagnostic, like imaging, brain mapping or tumor grading and the current medical condition of the patient, the surgeon has to decide very precisely how aggressively he is willing to resect the tumor in possibly eloquent brain areas (Krieg et al., 2014a, Picht, 2015, Sollmann et al., 2015a, Krieg et al., 2013a). In this way, he would, at best, stop a further tumor progression or even prolong recurrence (Wang et al., 2017, Bond et al., 2017, Bette et al., 2017, Pessina et al., 2017, Stummer et al., 2008). Eloquent cortical areas are defined as the primary motor cortex/precentral gyrus (PrG), the primary somatosensory cortex/postcentral gyrus (PoG), Broca´s area/posterior inferior frontal gyrus (IFG) - pars opercularis (opIFG) and pars triangularis (trIFG), Wernicke´s area/superior temporal gyrus (STG), and the visual cortex/occipital lobe (Nightingale, 2003). The Abbreviations of the gyri and cortical areas refer to the publication of Corina et al. (Corina et al., 2005). Resection of these areas would expectedly lead to paralysis, impairment of sensory processing, and linguistic ability, or visual damage (Lin et al., 2015, Obermueller et al., 2015, Satoer et al., 2016). In order to avoid any kind of postoperative impairment, preoperative mapping is of prime importance in neurosurgery. In this context, the newly developed method of navigated transcranial magnetic stimulation is an additional and valuable tool for a neurosurgeon to prepare himself for the forthcoming operation. Intraoperatively, it provides a visual representation of several brain functions and their distributions individualized for each patient.

1.1.1 History of brain mapping

The aim of brain mapping is to create a differentiated and as much detailed as possible map of the neurological and neuropsychological functions of the brain in terms of their spatial representations. According to the definition by the Brain Mapping Foundation, brain mapping “is the study of the anatomy and function of the brain and spinal cord through the use of imaging (including intra-operative, microscopic, endoscopic and multimodality imaging), immunohistochemistry, molecular and optogenetics, stem cell and cellular biology, engineering (material, electrical and biomedical), neurophysiology and nanotechnology” (BrainMappingFoundation, 2013). In the early stages, brain mapping started with the observation and documentation of patients and experimental animals with brain lesions caused by disease, trauma or experimental setup.

Already in 1824 one of the first experimental neurophysiologists, Marie Jean Pierre Flourens, described his experimental investigations of removing different defined parts of the brain in pigeons and rabbits (Yildirim and Sarikcioglu, 2007, Flourens, 1824). By removing the cerebellum, the animal lost its balance. By taking out the cerebral hemispheres the ability of perception and judgment in general have dwindled away. By removing the brain stem the animal died.

Another important example was the case of the 25 year-old Phineas Gage. In 1848 a 1.1 m long and 3 cm thick iron rod was driven through the railroad construction foreman´s left side of the skull during an explosion and destroyed his left frontal lobe (Harlow, 1999, Barker, 1995, Thiebaut de Schotten et al., 2015). He survived this major accident and recovered very well apart from an irreversible damaged left eye and severe personality changes. He i.e. became impious, extremely capricious and impatient. At the time, the responsible doctor John Harlow explained the serious character changes because of the damage to the left frontal lobe (Thiebaut de Schotten et al., 2015, Harlow, 1999).

The probably most famous example for historical brain mapping is that of Paul Boca and his patient Monsieur Leporine, also known by the nickname “Monsieur Tan” (Domanski, 2013, Domanski, 2014, Thiebaut de Schotten et al., 2015). In 1839 the 30 year-old Mr Leporine was sent to a clinic in Paris after he experienced a sudden inability to speak a few months ago. The only word he could say, after the event, was “tan”. He used this syllable and accentuated it in different ways in combination with hand gestures to communicate with the outer world. Monsieur Leporine became an

inmate in this Parisian hospital for the remaining 21 years of his life and was paralyzed on his right side for the last 7 years. In 1861 he first met the anatomist, physician and anthropologist Paul Boca because Monsieur Leporine developed a gangrene in his right leg. This disease finally caused his death. Post-mortem Boca performed an autopsy of the patient and detected a lesion in the posterior third of the left inferior frontal gyrus (Thiebaut de Schotten et al., 2015). This way the anatomist could discover a cerebral localization related to speech production: Boca's area.

In 1870 Eduard Hitzig and Gustav Theodor Fritsch trepanised non-anesthetized dogs and applied electricity to their cerebral cortex (Fritsch and Hitzig, 2009, Hitzig, 1874). With this method, the researchers could induce muscular contractions in different contralateral parts of the dog´s body depending on the stimulated cortical area. This way, Hits and Fritsch mapped and identified localizations for motor-related cortical areas in the experimental animals.

Following the publications of Paul Boca another important physician, psychiatrist, anatomist and neuropathologist intensified his research in the field of speech and language impairment related to brain damage: Carl Wernicke (Wernicke, 1874, Koehler and Lanska, 2014). In 1874 Wernicke published the book: "Der aphasische Symptomenkomplex: eine psychologische Studie auf anatomischer Basis", in which he first described sensory aphasia related to temporal lobe damage in detail. Thus, he declared that aphasia was not only a result from lesions in Broca´s area and therefore reached another important milestone in the history of brain mapping.

At the same time, a british colleague of Hitzig and Fritsch, Sir David Ferrier, demonstrated his findings regarding the mapping of special function associated cortical areas (Ferrier, 1873). In his book "The functions of the brain" he described the results of experimental investigations in which the brains of many different animal species were electrically stimulated to create a map of cortical functions. He discussed the different movements, motor responses or pupil reactions in comparison to the stimulated cortical area and animal species. On this basis, he created a map defining 15 cortical areas of human brain functions.

In the early 20th century a famous pioneer in brain surgery used electrical stimulation for the examination of the human sensory cortex on anesthetized patients, Harvey Cushing (Uematsu et al., 1992). With his findings, he draw a map of the human brain published in 1908 in "Surgery of the Head" in Keen's volume *Surgery – Its Principles and Practice (Keen and Da Costa, 1909).* On top of it, he was the first brain surgeon

who performed a detailed sensory stimulation/examination of the human cortex during an awake surgery (Penfield and Boldrey, 1937, Cushing, 1909). As well at the beginning of the 20th century, the german neurologist Korbinian Brodmann divided the cerebral cortex into 52 regions based on their cellular and histological structure and therefore created a very detailed map of the human cortex (Brodmann, 1910, Brodmann, 1913). His goal was not only to divide the cortex into lobes or gyral complexes but on top of this to subdivide even the smallest parts of the gyri. In that way, he provided a topographical parcellation of the human cortical structures. In summary, all these scientists created the first maps of brain cortices.

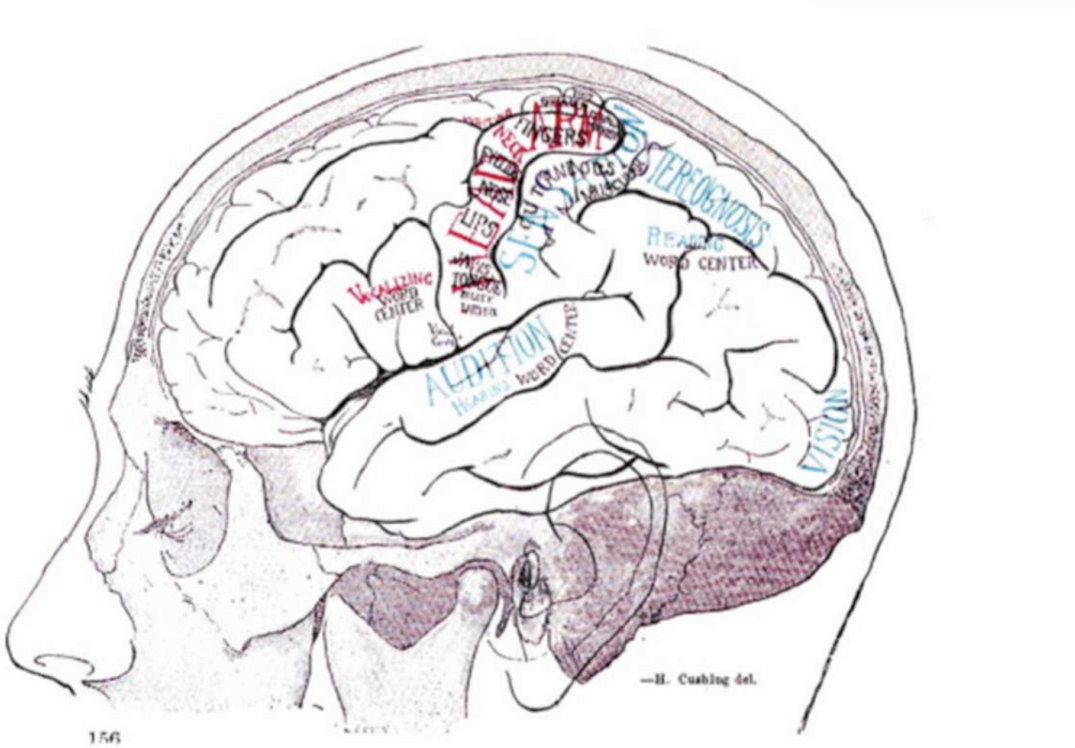

FIg 1: A brain map drawn by Harvey Cushing in 1906 and published in „Surgery of the Head" in Keen's volume *Surgery – Its Principles and Practice*

1.2. Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) is a non-invasive technique which induces an electric field within the cerebral cortex by using a stimulating coil, which generates

short magnetic pulses (Ilmoniemi et al., 1999, Epstein et al., 1996, Tarapore et al., 2013a, Krieg et al., 2017, Duffau, 2006). This magnetic field then passes through the skull and scalp of the examined subject and enables the induction of an intraparenchymal electric field. This focal electric field is able to change the transmembrane potential and thereby leads to a local membrane depolarization and an action potential (Griskova et al., 2006). The exact mechanism of TMS is not entirely clarified and understood until today (Ruohonen, 1998, Theodore, 2002). Because the pulses do not reach brain areas deeper than approximately 3 cm, this technique can be used to stimulate predefined cortical areas. During the single pulses, the magnetic coil is placed over the head of the examined person. This way TMS is able to neuromodulate and neurostimulate by causing a neuronal depolarization (Barker et al., 1985). Pascual-Leone called this process inducing a `virtual brain lesion` (Pascual-Leone et al., 2000, Pascual-Leone et al., 1999). In general, TMS can be used in two different ways, on the one hand to activate cortical neurons and therefore increase cortical excitability, and on the other hand, to inhibit or decrease their function (Horvath et al., 2011, Pascual-Leone et al., 2002, Pascual-Leone et al., 2000). The advanced method of repetitive transcranial magnetic stimulation (rTMS) gives the opportunity to distrubt neuronal activity for an individual amount of time during the stimulation. During a mapping of motorical functions the triggered action potential can then be measured as a motor-evoked potential (MEP). A further development was the generation of navigated transcranial stimulation (nTMS). This technique offers the opportunity to stimulate and map cortical areas very precisely in terms of their exact localization. In summary, the non-invasive technique of TMS provides a tool for the investigation of cortical functions in terms of their localization.

1.2.1. The history of TMS

The foundations for this technique have already been laid in 1881 with the work of an English physicist, Michael Faraday. This way, he discovered that an electric impulse, which is currently passing through a wire coil, is able to generate a magnetic field (Faraday, 1839, Horvath et al., 2011).
In 1985 Anthony Barker and his colleagues developed the first transcranial magnetic

stimulator while stimulating the human motor cortex (Barker et al., 1985). With this new method, it was possible to stimulate the cortex in a non-invasive and especially not painful way.

Just a few years later, the next major step forward was achieved by the already mentioned Dr. Alvaro Pascual-Leone. In 1991 he published an article in the journal Neurology, entitled `Induction of speech arrest and counting errors with rapid-rate transcranial magnetic stimulation`(Pascual-Leone et al., 1991). In this work, he described the use of rTMS in comparison to the previous utilized single-pulse TMS. Grimson et. al and Ruohoen and Ilmoniemi invented afterwards the new technique of nTMS (Grimson et al., 1996, Ruohonen and Ilmoniemi, 1999). Thereby they were able to offer a real-time-visualization and precise location of the stimulations.

1.2.2. The application of Transcranial Magnetic Stimulation today

Nowadays the advanced method of navigated repetitive transcranial magnetic stimulation (nrTMS) is used for many different approaches, most commonly for the preoperative mapping of motor and language function in brain tumor patients (Picht et al., 2013b, Krieg et al., 2014a, Tarapore et al., 2013b, Sollmann et al., 2015a). Beyond that, nTMS provides the examiner a wide range of diagnostic and therapeutic application possibilities. Over the last years, it became important in the treatment of several diseases, like major depression, tinnitus or chronical pain (Kleinjung et al., 2007, Ahdab et al., 2010, George et al., 2010). A study from 2004 could show that rTMS over Broca´s area was able to improve the naming of pictures in nonfluent aphasia-patients (Martin et al., 2004). In conjunction with patients who had suffered an acute ischemic stroke Eman et. al pointed out that rTMS applied over the contralateral motor cortex for ten days in total improved the outcome after the stroke (Khedr et al., 2005). It furthermore could be demonstrated that this technique seems feasible to detect distinctive neuropsychological cortical function, such as facial processing or calculation function (Renzi et al., 2013, Maurer et al., 2017, Ille et al., 2016, Maurer et al., 2016).

1.3. Neglect

The syndrome neglect is associated with a reduced awareness of several stimulations, e.g. acoustic signals, sensory perceptions or motoric expressions (Parton et al., 2004, Pedrazzini et al., 2017, Corbetta and Shulman, 2011). It is characterized by the inability to respond properly to a given stimulus on the opposite to the brain lesioned site of the body (Jehkonen et al., 2006). Patients suffering from this condition, for example, forget to shave one side of their face, eat only half of the food presented on the plate, collide with doorframes or do not respond to acoustic signals, e.g. questions coming from the affected site. In severe cases, the extremities on this site appear to be paralyzed and the patient does not even feel pain or discomfort concerning this part of his body. On the other hand, there exist mild forms of neglect, maybe not even noticed by the examiner. If the patient is, e.g. asked to fixate things or stimuli on the affected site, he is able to fulfill this task, but if the examiner gives stimuli on both sites, the patient will only react to the stimuli on the unaffected site (Farah, 2000). In general, the syndrome neglect occurs after a stroke, a unilateral brain injury, a trauma or in combination with another space-occupying process of the brain, like a brain tumor (Cocchini et al., 2001, Jehkonen et al., 2000, Kalra et al., 1997). Neglect symptoms are often described after stokes in the middle cerebral artery region, especially in the right cerebral hemisphere (Li and Malhotra, 2015). But it can also be caused by neurodegenerative diseases (Andrade et al., 2010). In the synopsis, the literature agrees, that the right hemisphere plays a dominant role in the emergence of neglect symptoms (Bartolomeo et al., 2012, Heilman and Van Den Abell, 1980, Corbetta and Shulman, 2011). Especially lesions in the right parietal cortex seem to cause neglect symptoms (Vallar, 1998, Sack, 2010, Driver and Mattingley, 1998). But researchers and clinicians pointed out, that it takes more than a small lesion in just one spot of the brain to create a neglect, it is more a loss of function network spread over several parts of the brain (Mesulam, 2000). Even the syndrome is not equally pronounced in all patients, it shows a lot of viarity within the patient collective. Thus, the literature divided this syndrome into several subtypes such as visual neglect, personal neglect, motor neglect or representational neglect (Robertson and Halligan, 1999). Furthermore, neglect can be divided into spatial and non-spatial deficits (Corbetta and Shulman, 2011). The term spatial deficit refers to spatial attention and short-term memory for example.

Non-spatial deficits, on the other hand, involve target detection, reorienting or vigilant. Understanding the cause of this syndrome means understanding the representation and perception of space and spatial attention in the brain (Churchland, 1986, Corbetta and Shulman, 2011, Driver and Mattingley, 1998).

1.3.1 Neglect tests

In order, to diagnose this syndrome researchers have developed several tests. The most common one is the line-bisection task (Fig. 2). In this bedside task, the patient is instructed to dissect a horizontal line on a paper at the midpoint (Farah, 2000). A patient with a rightward neglect will draw a leftward deviation from the real midpoint.

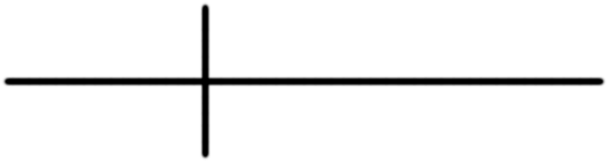

Fig. 2: Line bisection task in wich the patient is instructed to dissect the horizontal line at the midpoint. If he sufferes from a rightwarded neglect he will draw a leftward deviation from the real midpoint of the horizontal line

Another commonly used test is the line cancellation test. In this case, several short lines are widely spread over a piece of paper and the patient is asked to divide all the several lines with a pen. When he is suffering from a neglect, he will only divide the lines on the neglect-unaffected site and ignore the lines on the contralateral side of the paper as demonstrated in Fig. 3 (Farah, 2000).

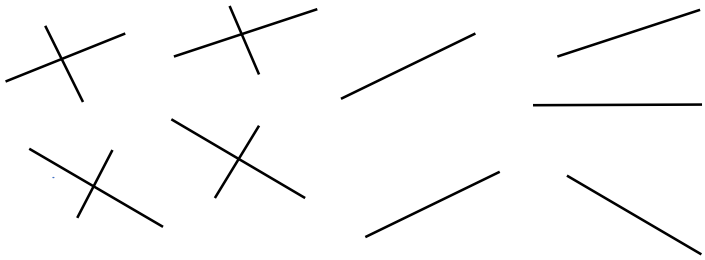

Fig.3: Line cancellation task in which the patient is asked to divide the lines on the paper unsing a pen. If he suffers from a neglect, he will only divide the lines on the neglect-unaffected side and spare the lines on the contralateral side of the paper

When patients are instructed to draw a clock or a house, they might draw just half of it, neglecting the opposite side (Fig. 4) (Mesulam, 2000).

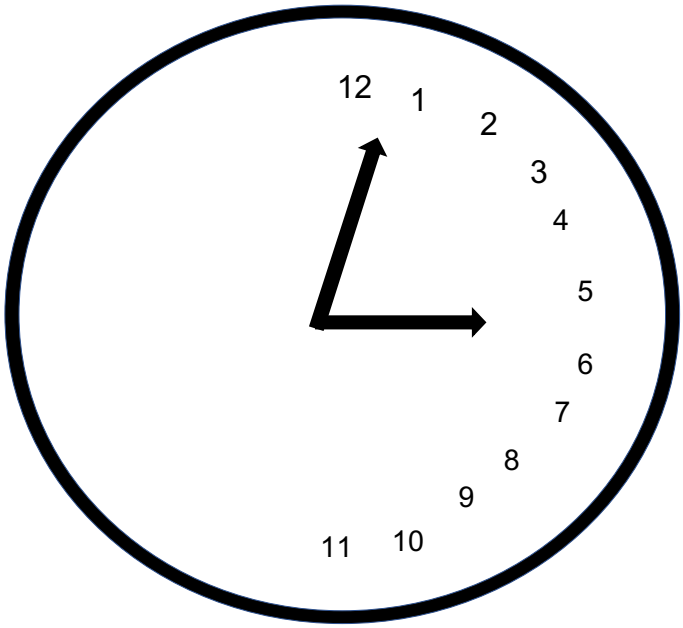

Fig 4: Drawing test for neglect patients. The patient ignores or neglects the opposite side of a clock and tries to insert all the numbers in just one side

There are two further tests for detecting neglect symptoms. The Behavioral Inattention Test-conventional (BIT) is a `6-paper-item-and-pencil-test` for subacute patients (2-18 months after brain injury) (Wilson et al., 1987, Goedert et al.). It validates the performances of the daily living. The Chatherine Bergego Scale (CBS) is a `10-item instrument` and validates daily activities like grooming and eating in subacute or chronic neglect-patients (Azouvi, 1996).

1.4 Objectives of the current study

The aim of the current study is to examine the feasibility of detecting cortical areas involved in the generation of neglect-symptoms via nrTMS and therefore creating a cortical map concerning this function. In neurosurgery, as well as in neuroscience, brain mapping is of broad interest (Krieg et al., 2012b, Picht et al., 2013b, Barker et al., 1985, Ilmoniemi et al., 1999). The outcome of a brain tumor patient after he underwent brain surgery depends not at least on the preoperative imaging and preparation for the surgery. One of the main goals in neurosurgery is to prevent postoperative impairment such as language or motor dysfunction (Krieg et al., 2012b, Kombos et al., 2001, Picht et al., 2006, Picht et al., 2011, Krieg et al., 2013b, Sanai and Berger, 2008). Sanai et al. furthermore presented a study in which 119 patients with gliomas in the left or right parietal lobe underwent an agressive operative resection (Sanai et al., 2011). Postoperatively, 8.4% of the patients developed a severe neuropsychological deficit like dysgraphia, dyscalculia, or neglect symptoms. Having these results in mind, not only the mapping and detection of motor and language function are of broad interest for the patient and his outcome, but also the prevention of neuropsychological impairment.

In this terms, the aim of this study is to examine the feasbility of locating cortical neglect-related areas via nrTMS and whether it is possible to create a map concerning this neuropsychological function in order to establish this non-invasive technique for future scientific applications.

2. MATERIALS AND METHODS

2.1 Ethics approval

The written informed consent for this study was provided prior to the first nrTMS mapping from all subjects. All aspects of the current trial were approved by the local ethics committee of the Technical University Munich (Ethics Committee Registration Number 5811/13) and in accordance with the Declaration of Helsinki.

2.2 Study design

This study was designed to be prospective. Every participant underwent two nrTMS mappings, one of each hemisphere, in a randomized way with 13-16 days delay between both mappings. Thereby, every mapping session was conducted by the author, who underwent manufacturer certification and nrTMS training prior to the study to preclude learning curve effects.

2.3 MRI acquisition

A 3 Tesla MR imaging combined with an 8-channel phased array head coil (Achieva 3 T, Philips Medical Systems, the Netherlands B.V.) was performed to every volunteer prior to the first nrTMS mapping. Therefore, the scanning protocol for anatomical co-registration comprised of a three-dimensional (3D) gradient echo sequence (TR/TE 9/4ms, 1 mm² isovoxel covering in each case the whole head, 6 min 58 s acquisition time) without any intravenous contrast administration. After this procedure, the generated 3D dataset was transferred to the nrTMS system using the DICOM standard.

2.4 Study subjects

For the current study, a total amount of twenty purely right-handed (according to the Edinburgh handedness test) and healthy subjects without suffering from any cerebral pathology were enrolled. The median age of the participants was 25.0 ± 1.7 years (range 22.0 – 29.5 years, Table 1). Nine volunteers were male, eleven were female. Inclusion criteria were right-handedness, age above 18 years, German as mother tongue and written informed consent. Exclusion criteria were according to Rossi et al. (Rossi et al., 2009), any kind of medication, cardiac pacemaker, second mother tongue, ambidexterity or left-handedness, aberrant medical history, deep brain stimulation treatment in the past, developmental language deficits, any pathological findings on the cranial MRI, cochlear implant, previous seizure or any further neurological impairment (Rossi et al., 2009).

2.5 Setup of the navigated nrTMS mapping

2.5.1 Neglect tasks

The neglect-mapping consisted of 80 line-bisection tasks, as demonstrated in Fig. 5 and Fig. 6. Each task was presented on a white background with black lines on a 15-inch screen. This screen was placed 20 inches in front of the participants. 40 of the tasks were usually used line bisection tasks where the subjects were instructed to determine whether a vertical line divided the horizontal line in the middle, the left or the right part of it. The other 40 line-bisection tasks were arranged as follows: The horizontal line was divided by seven vertical lines with numbers on it. In each case, the volunteers had to name the number displayed on the middle vertical line. During a baseline performance prior to each mapping without any nrTMS stimulation, the correct answers had to be given as fast as possible, accurately, correctly pronounced and without any filler words or stuttering. All falsely categorized, misnamed or wrongly pronounced tasks out of the randomly presented 80 line-bisection tasks were counted and afterwards excluded from the stimulus sequence.

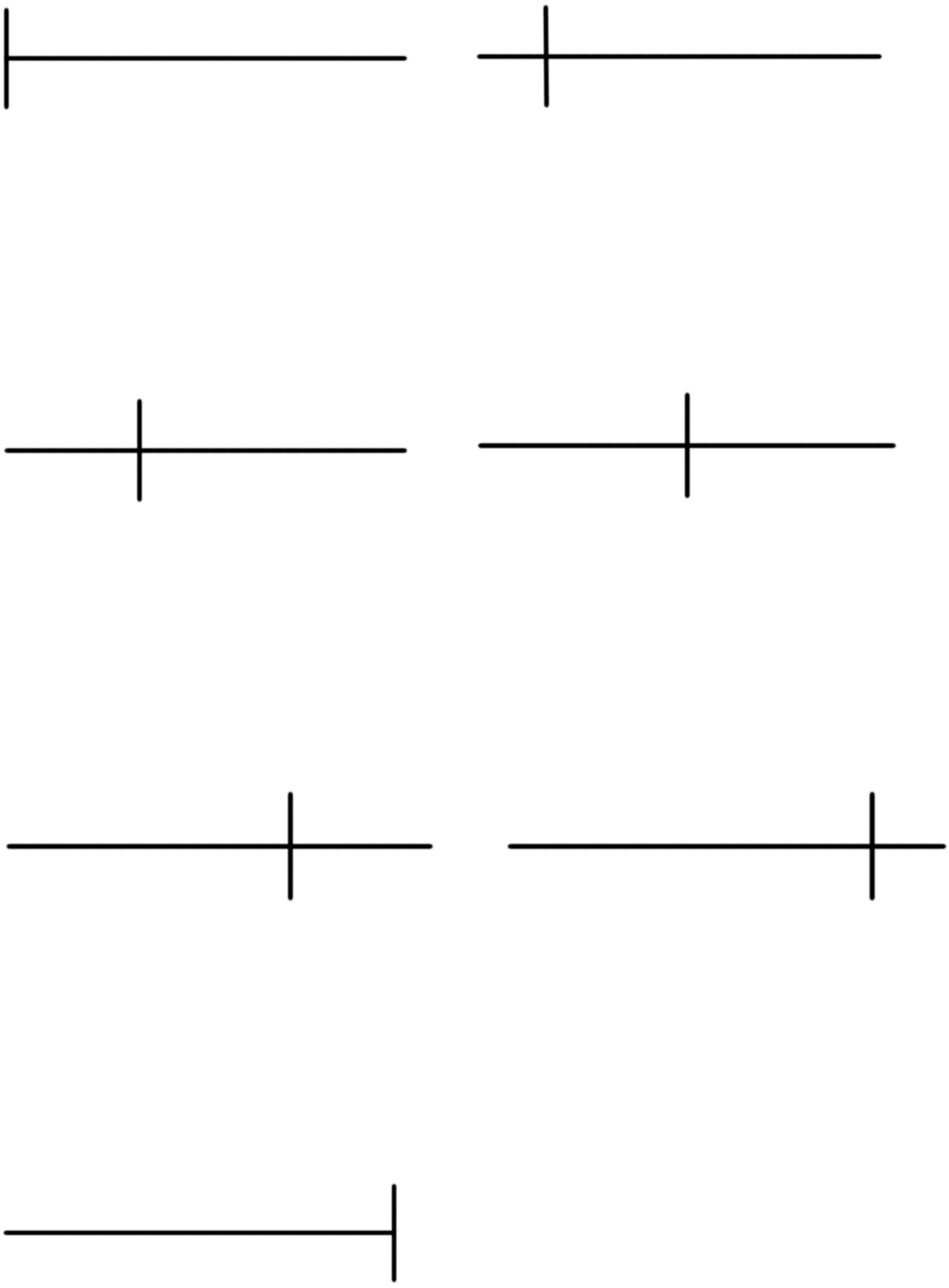

Fig. 5: The images show the 40 line-bisection tasks. The subjects were instructed to determine whether the vertical line divided the horizontal line in the left, the middle or the right part.

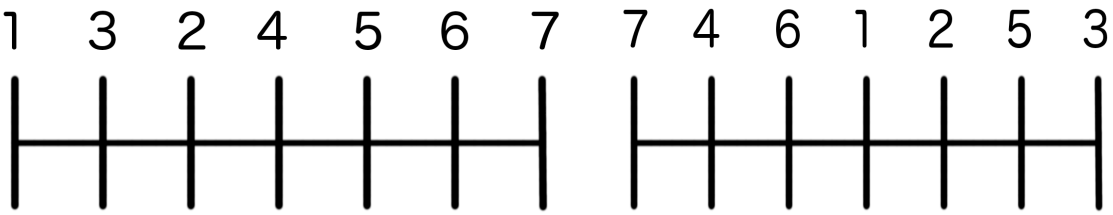

Fig. 6: Examples of the 40 nummbered line-bisection tasks. The volunteers had to name the number over the middle line of the task. For the left image the correct answer would have been “4”, and for the right image “1”.

2.5.2. Experimental setup

Each mapping was performed with the Nexstim eXima NBS system version 4.3 with a NexSpeech® module (Nexstim Plc, Helsinki, Finland) which included a biphasic figure-of-eight TMS coil in a magnetic stimulator with a radius of 50 mm as reported earlier (Krieg et al., 2013c, Picht et al., 2013a, Tarapore et al., 2013a, Picht et al., 2009, Ilmoniemi et al., 1999). An infrared tracking system (Polaris Spectra, Waterloo, Ontario, Canada) was connected to the magnetic stimulator (Ilmoniemi et al., 1999, Ruohonen and Karhu, 2010). Every participant underwent two nrTMS mapping sessions. At the beginning the rMT was determined during a motor mapping of the contralateral hemisphere, more precisely the cortical representation of the hand area (Musculus abductor pollicis brevis, Musculus abductor digiti minimi) as documented in previous studies (Krieg et al., 2012b, Sollmann et al., 2013a). To visually display the analog cortical area receiving rTMS pulses, a 3D T1-weighted MRI of each participant was used as an anatomically reference by a stereotactic infrared camera to track the coil position (Ilmoniemi et al., 1999, Ruohonen and Karhu, 2010, Ruohonen and Ilmoniemi, 1999). After this initial setup, the nrTMS neglect mapping

was performed using 100% rMT. The magnetic pulses had a frequency of 5 Hz and 10 pulses were applied.

2.5.3 Neglect mapping procedure

For an objective post-hoc analysis every baseline without stimulation, as well as the whole following mapping session, was video recorded (Lioumis et al., 2012, Picht et al., 2013a). Ahead of the nrTMS onset, the subjects were instructed to name and solve the 80 baseline pictures without any stimulation. Afterwards only the correctly solved line-bisection tasks were used for the nrTMS session. This way, the answers during the stimulation could be compared to the baseline performance subsequently. The line-bisection tasks were presented randomly during the baseline performance as well as during the mapping procedure. During the mapping session, the line-bisection tasks were presented with a fixed inter-picture interval (IPI) of 3 s, a display time of 700 ms and 0 ms picture-to-trigger interval (Baptiste and Fehlings, 2006). The time from showing the line-bisection task on the screen to the onset of the nrTMS pulse train is defined as the PTI.

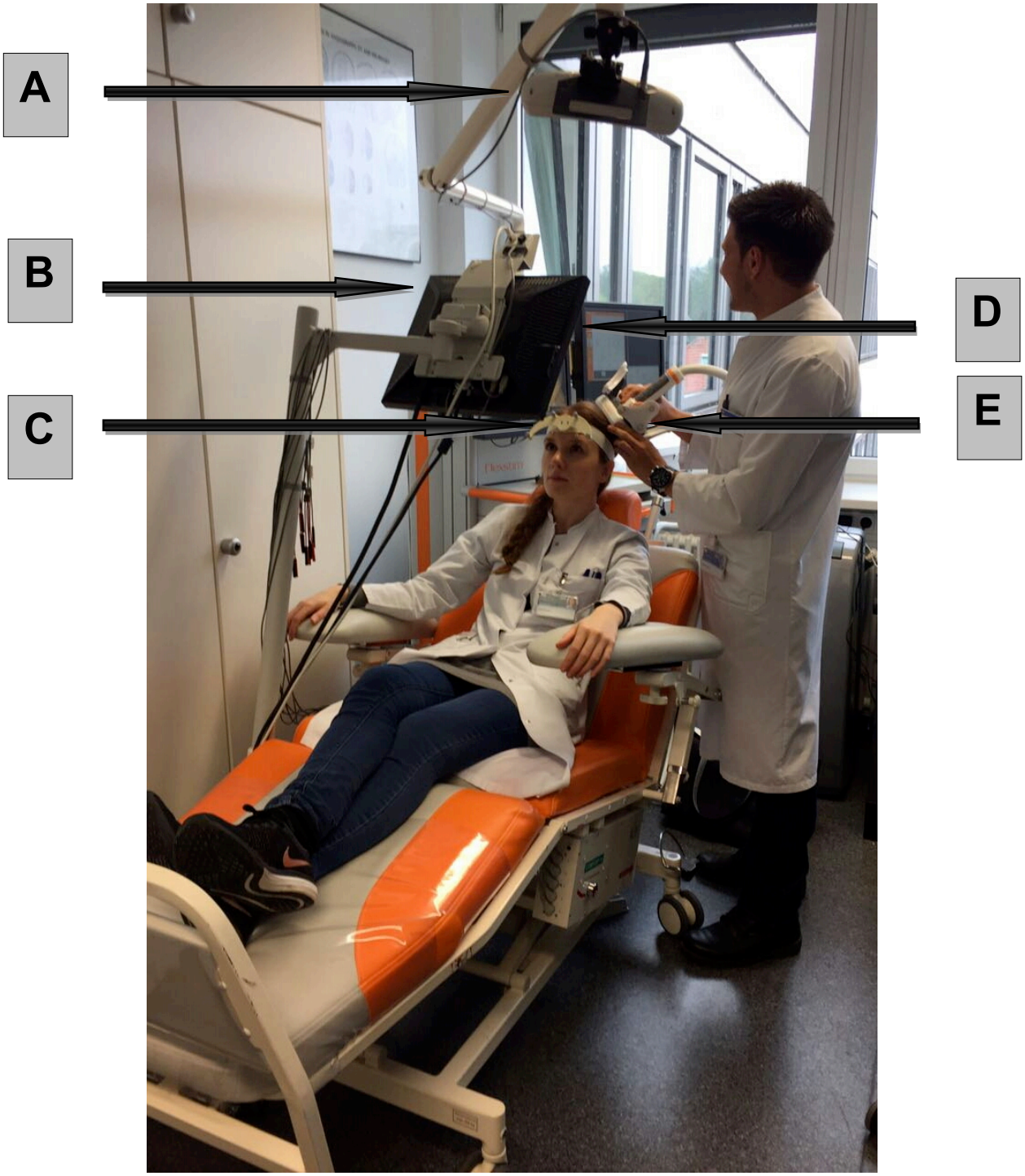

Fig. 7: The experimental setup of the Nexstim eXimia system (Nexstim Plc, Helsinki, Finland). A: Stereotactic camera for neuronavigation; B: 15-inch screen 40 inches in front of the subject for the neglect-mapping task; C: Headband with tracking system for the neuronavigation; D: 2 screens for the navigation; E: Stimulation coil;

2.5.4. Stimulated cortical spots

During the nrTMS mapping 52 anatomically identified and determined cortical spots, spread over the whole hemispheres, were stimulated (Fig. 8). Prior to the mappings these cortical spots were marked and highlighted on the 3D MRI of every participant. The names and localizations of the cortical spots are leaned on the publication of Corina et. al (2005) who published a cortical parcellation system (CPS) (Table 1) (Corina et al., 2005). Each spot was stimulated for three times during the mapping procedure. For all the participants, the electric field strength at cortical level ranged between 55-80 V/m within the cortical region of interest. Not every cortical location could be reached via nrTMS pulses due to the maximum pain their stimulation could cause and their accessibility for the stimulation coil (Krieg et al., 2013c, Picht et al., 2013a). Because of the increasing distance between the brain and the skin the stimulation intensity decreases below 50 V/m. Consequently, there were absences of stimulation spots in the inferior temporal gyrus (ITG), polar superior (polSTG) and middle temporal gyrus (MTG), anterior middle temporal gyrus (aMTG), orbital part of the inferior frontal gyrus (orIFG) and the middle (MFG), and inferior frontal gyrus (IFG). After the visual display of one image and ahead of the visual display of the following image the coil was relocated to the next cortical spot numerically. In order to reach maximum field induction, the stimulation coil was positioned tangentially to the participants´ skull in strict anterior-posterior field orientation (Epstein et al., 1996, Wassermann et al., 1999).

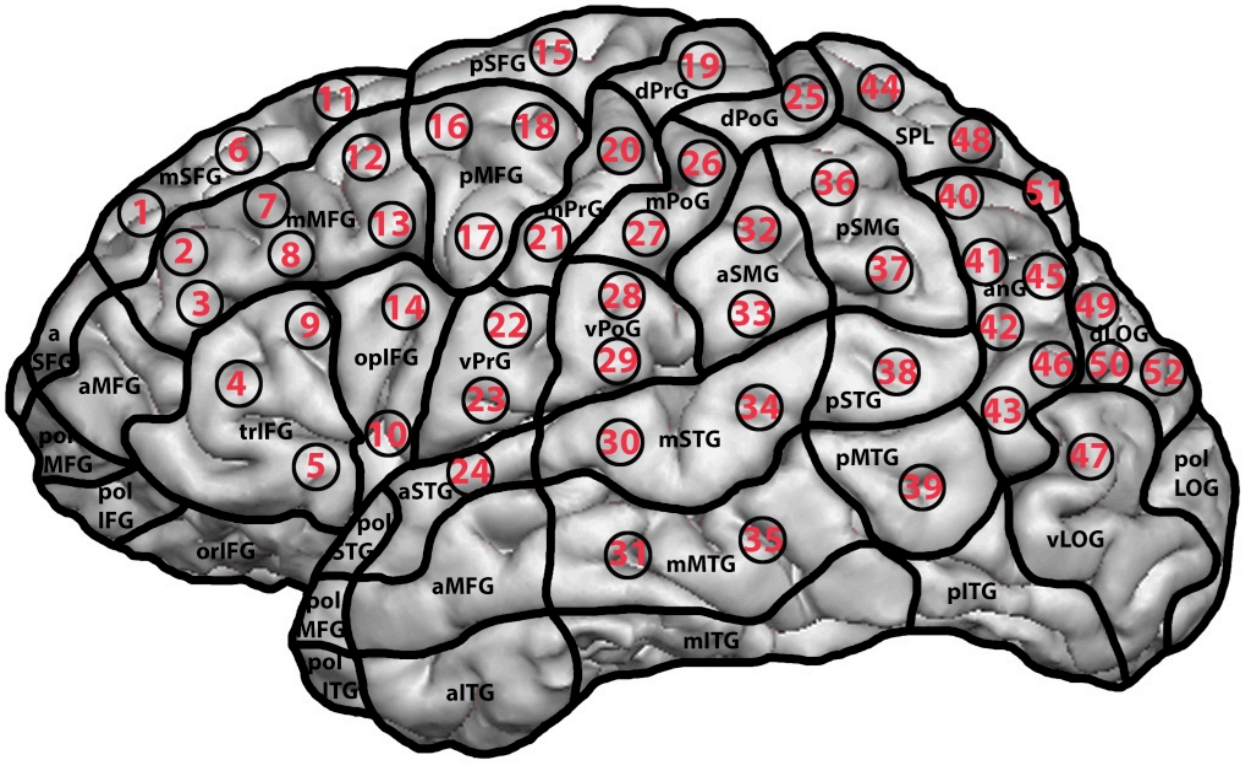

Fig. 8: nrTMS mapping template with 52 cortical spots. Every spot was stimulated for three times using 5 Hz and 10 pulses. The abbreviations are referring to the cortical parcellation system from Corina et. al (2005) (Table 1).

Abbreviation	Anatomy
aITG	anterior inferior temporal gyrus
aMFG	anterior middle frontal gyrus
aMTG	anterior middle temporal gyrus
anG	angular gyrus
aSFG	anterior superior frontal gyrus
aSMG	anterior supramarginal gyrus
aSTG	anterior superior temporal gyrus
dLOG	dorsal lateral occipital gyrus

dPoG	dorsal post-central gyrus
dPrG	dorsal pre-central gyrus
mITG	middle inferior temporal 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
pITG	posterior inferior temporal gyrus
pMFG	posterior middle frontal gyrus
pMTG	posterior middle temporal gyrus
polFG	polar frontal gyri
polTG	polar temporal gyri
polLOG	polar lateral occipital gyrus
pSFG	posterior superior frontal gyrus
pSMG	posterior supramarginal gyrus
pSTG	posterior superior temporal gyrus
SPL	superior parietal lobe
trIFG	triangular inferior frontal gyrus
vLOG	ventral lateral occipital gyrus
vPoG	ventral post-central gyrus
vPrG	ventral pre-central gyrus

Table 1: This table demonstrates the anatomical names and abbreviations according to Corina et al. (2005)

2.6 Video data analysis

The examiner was blinded to the stimulated cortical spots and previous results in every video data based analysis. Every analysis was performed as published in earlier studies (Lioumis et al., 2012, Sollmann et al., 2013b, Tarapore et al., 2013a, Krieg et al., 2014b). The baseline, as well as the following neglect-mapping procedure were analyzed. Therefore, every falsely solved line-bisection task, as well as language deficits or hesitations under stimulation were compared to the baseline performance. If at least one out of the 3 cortical stimulated spots evoked an error rate (ER), this spot was defined as error positive. The ER is defined as the number of errors per number of stimulations per each predefined stimulated spot or CPS region. The generated ER were analyzed in two different ways:

- ER for all evoked errors per total number of stimulations. This ER pictures the generated errors per category in percentage.

- ER generated for all volunteers who evoked errors per all stimulated volunteers.

On the other hand, we analyzed the error ratio. The error ratio is defined as the distribution on a percentage basis of the observed errors in a specific error category compared to all stimulations or all examined participants. The errors induced by nrTMS were categorized into the six following error types:

- All generated errors

- No response errors (no answer during nrTMS at all)

- Hesitation errors (delayed answer during nrTMS)

- Divergated line-bisection task to the left (the participant, for example, misnames a line-bisection task “left” although the vertical line divided the horizontal line in the middle of the screen)

- Divergated line-bisection task to the right (the participant, for example, misnames a line-bisection task “right” although the vertical line divided the horizontal line in the left of the screen)

- Wrong number over the middle line (the participant names a wrong number over the middle of the horizontal line)

2.6 Statistical analysis

Differences between the two hemispheres concerning the generated ER were tested using the Mann-Whitney-Wilcoxon test for multiple comparisons on ranks for independent samples for nonparametric distributions. Therefore, the ER for each task in the right versus the left hemisphere were compared. Furthermore, for distribution testing of various attributes, a Chi-square test was performed. The ER were defined as the quotient of the number of the stimulation-induced errors divided by the number of line-bisection tasks. The level of significance was determined as 0.05 (two-sided) for every statistical test. The results are demonstrated as odds ratios (OR) with a 95% confidence interval (CI) (GraphPad Prism 6.04, La Jolla, CA, USA).

3. RESULTS

3.1 Subject characteristics

The errors during the line-bisection baseline performance ranged from 0-3 out of 80 presented tasks. The median for correctly solved line-bisection tasks was 80 for both hemispheres (CI range 0.95 to 1.0). In summary, the following mapping procedure was well tolerated and performed by all 20 subjects. The pain or discomfort was measured with the VAS and ranged from 1-8, with median levels of 4.9 ± 1.7 for temporal regions, and 2.5 ± 1.7 with a range of 0-7 for the whole convexity. The stimulation of temporal regions is more painful due to temporal muscle activation. The rMT of the maximum stimulator output ranged between 25-42% with a mean of 33.2 ± 4.9%. The age of the volunteers ranged between 21-29, with a median of 25. In total, 11 female and 9 male were stimulated. Table 2 provides an overwiew of further mapping procedure and subject characteristic.

Subject No.	Age years	Gender	rMT (% output)		Correct baseline pictures		Pain convexity		Pain temporal	
			Left	Right	Left	Right	Left	Right	Left	Right
1	23	F	28	25	80	80	2	2	5	6
2	25	M	32	39	80	80	2	3	6	6
3	29	M	37	29	80	80	2	1	6	5
4	25	M	29	25	80	79	1	1	4	7
5	23	F	27	32	80	80	0	2	4	5
6	25	M	29	28	80	80	1	1	2	2
7	24	F	35	40	79	80	2	2	4	4
8	21	M	35	31	80	80	0	1	5	3
9	26	M	37	39	80	80	5	7	6	8
10	23	F	42	33	80	80	4	1	7	5
11	24	F	38	41	80	79	4	5	7	6
12	23	F	27	27	80	78	0	2	1	6
13	23	F	40	33	78	79	2	2	3	3
14	26	M	40	33	80	79	5	4	6	7
15	26	F	39	35	80	80	1	1	3	3
16	24	F	30	29	80	80	5	5	5	7
17	24	M	30	29	78	77	4	4	7	6
18	23	F	37	32	80	80	1	2	4	3
19	27	M	35	29	80	77	2	1	3	2
20	27	F	41	32	80	80	6	4	8	5
Median	25	-	35	32	80	80	2	2	4.5	5
P value	-	-	0.997	-	-	-	0.975	-	0.992	-

Table 2: Shows the subject characteristics, including age, sex, gender and pain during the nrTMS procedure

3.2 ER relative to all stimulations during the line-bisection tasks

3.2.1 Error distribution for all error types

In total, the line bisection tasks generated the highest ER for all errors of all stimulations of 15% in the right ventral lateral occipital gyrus (vLOG) as demonstrated in Figure 9. These ER include speech related no response and

hesitation errors, neglected line-bisection tasks to the left/right and incorrectly numbered tasks (Table 3). Concerning the left hemisphere, we observed the highest ER of 22% in the middle post-central gyrus (mPoG) (Fig. 10). In total the right hemisphere generated an ER of 6% with the highest ER of 8% in the occipital lobe (Table 4). The entire left hemisphere generated an ER of 7% in total, with the highest ER of 8% in the frontal lobe. Comparing both hemispheres using a chi-square test we did not reach statistical significance (p-value 0.118).

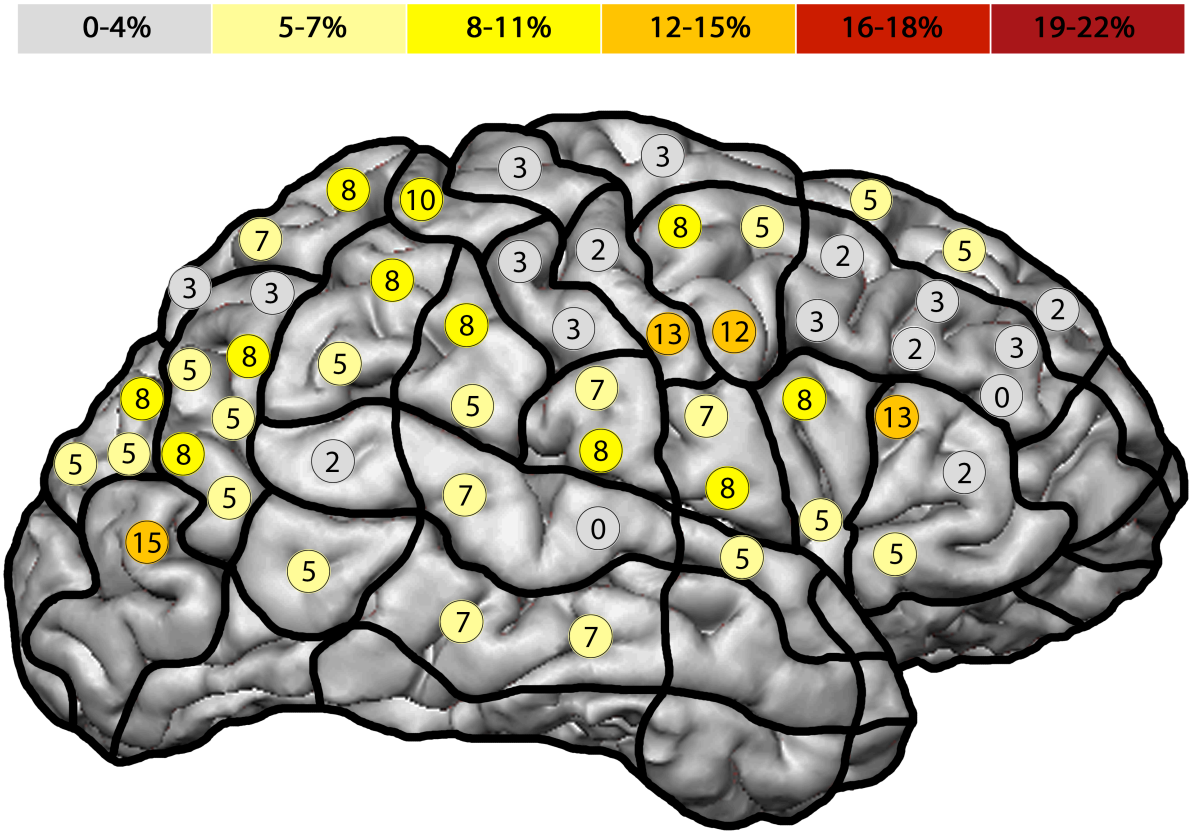

Fig. 9: This template shows the highest ER for all errors of all stimulations concerning the right hemisphere

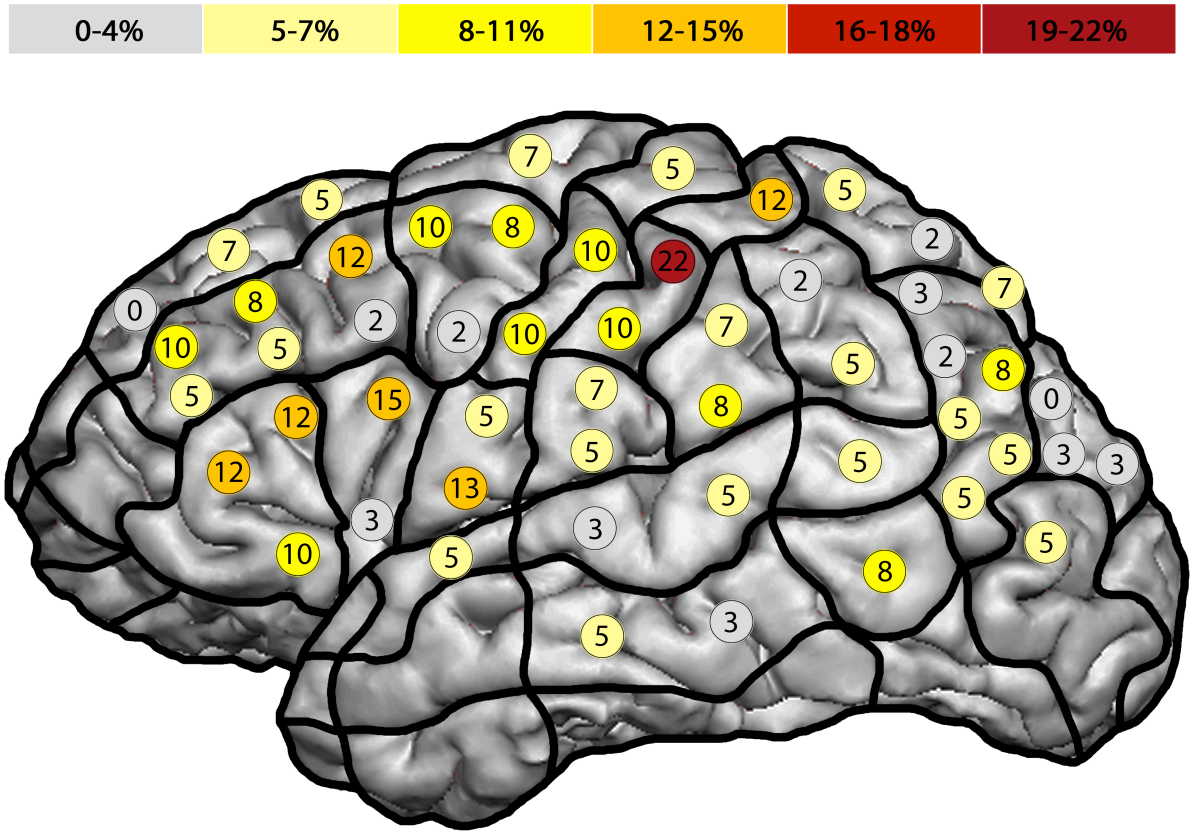

Fig. 10: This figure illustrates the highest ER for all errors of all stimulations in the left hemisphere

3.2.2 No response and hesitation errors

In terms of all errors of all stimulations, the highest ER for no response errors of 2% was found in the right hemisphere´s anterior supramarginal gyrus (aSMG), the angular gyrus (anG), the vLOG and the dorsal lateral occipital gyrus (dLOG). The left hemisphere generated highest ER of 2% in the posterior superior frontal gyrus (pSFG), and the mPoG. In total, both hemisphere´s achieved an ER of 0% as demonstrated in Table 3. In terms of speech related hesitation errors, the right hemisphere generated highest ER of 13% in the middle pre-central gyrus (mPrG) as shown in Figure 11. In comparison, we found ER of 18% in the left mPoG (Fig. 12). In a synopsis, the right hemisphere generated ER of 5% in total, with highest ER of 7% in the occipital lobe (Table 4). We found ER of 6% in the whole left hemisphere, and 7% highest ER of all lobes in the frontal lobe.

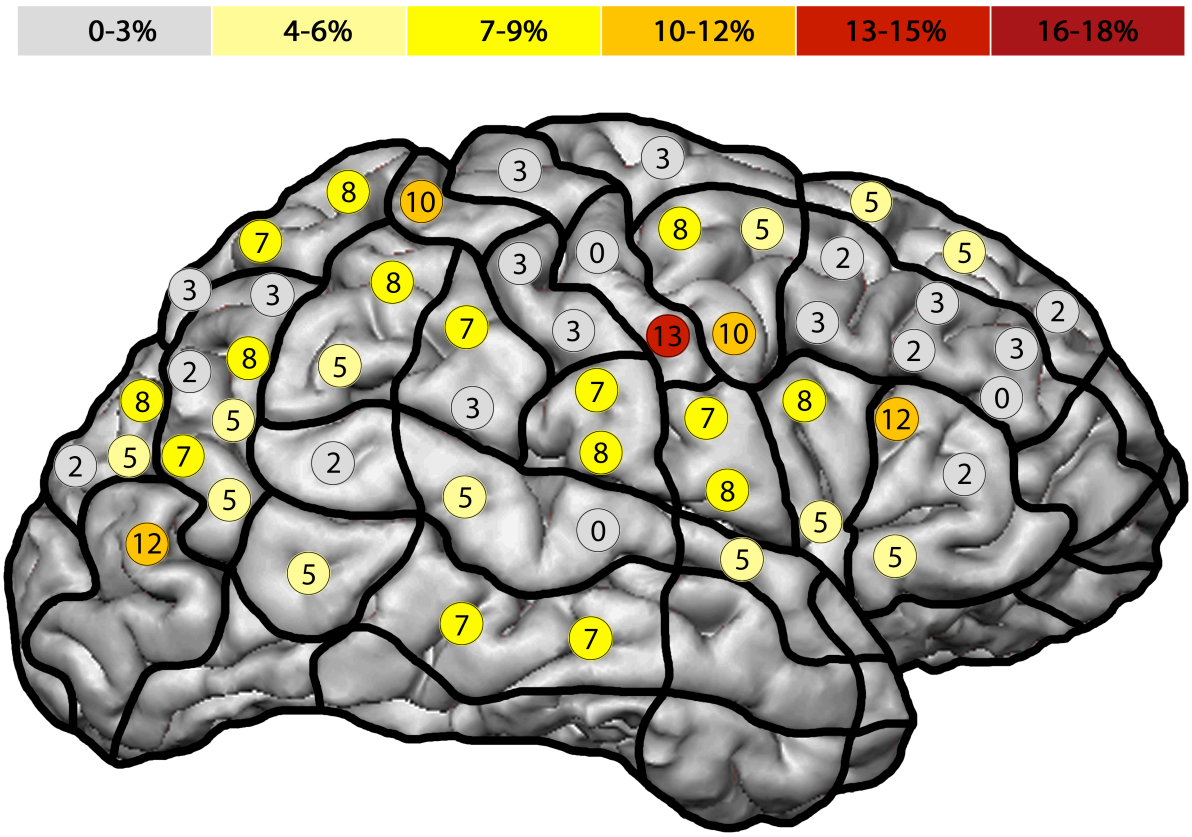

Fig. 11: This picture demonstrates the highest ER of all speech related hesitation errors of all stimulations in the right hemisphere

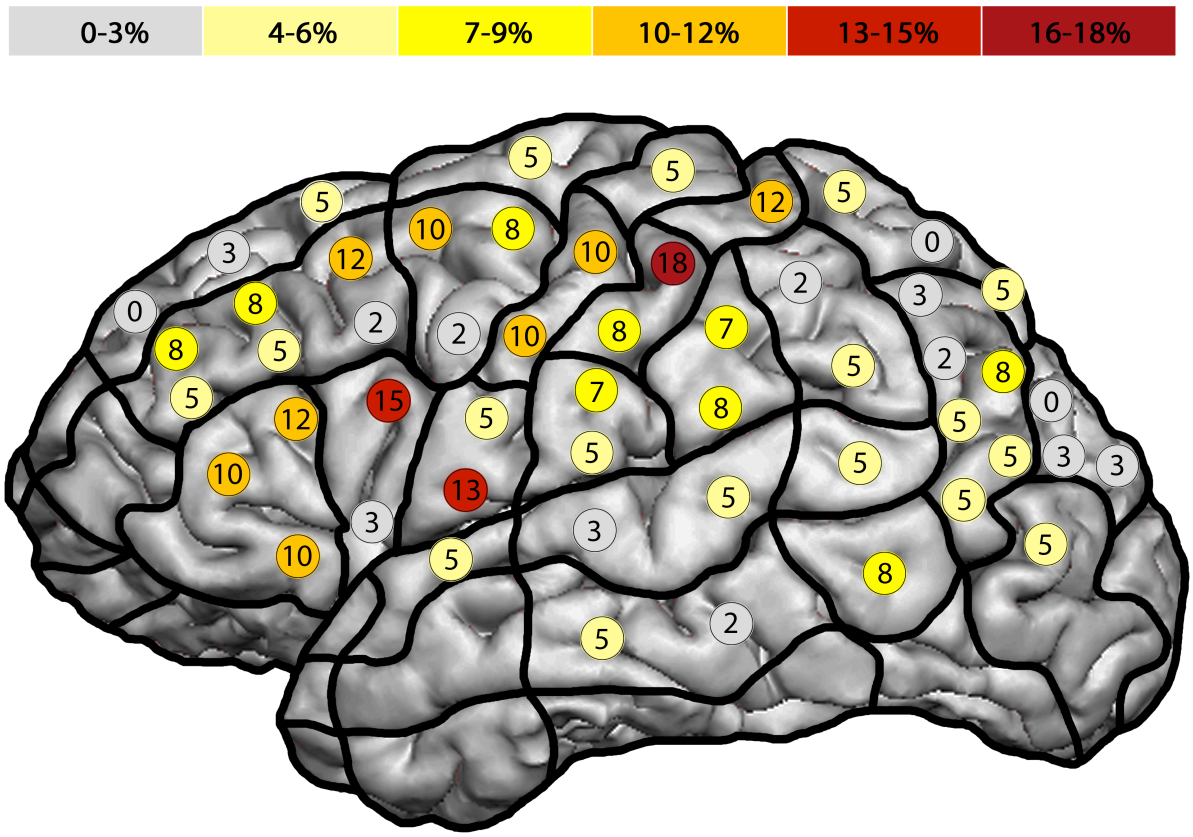

Fig. 12: This template shows the highest ER concerning the speech related hesitation errors of all stimulations in the left hemisphere

3.2.3 Divergent line-bisection tasks to the right

The highest ER of 2% were located in the right triangular inferior frontal gyrus (trIFG), the mPrG, the aSMG, the middle superior temporal gyrus (mSTG) and the dLOG (Table 3). Concerning the left hemisphere, the highest ER were observed in the middle middle frontal gyrus (mMFG) and the trIFG with 2% each. Both hemispheres generated no errors in the divergent line-bisection tasks to the right (Table 4).

3.2.4 Divergent line-bisection tasks to the left

The right posterior middle frontal gyrus (pMFG) and vLOG generated the highest ER of 2%, as well as the left hemisphere´s mPoG and superior parietal lobe (SPL) as

shown in Table 3. In terms of the ER, both hemispheres generated no errors concerning the divergent line-bisection task to the left (Table 4).

3.2.5 Wrong number over the middle line

We observed the highest ER of 2% in the right anG. The left middle superior frontal gyrus (mSFG) on the other hand, achieved an 3% ER (Table 3). Both whole hemispheres generated error rates close to 0% in total as demonstrated in Table 4.

Different errors and error ratio per stimulation spot

a) Right hemisphere

Spot	No response		Hesitation		Deviation to the right		Deviation to the left		Wrong number		All errors	
	E	R	E	R	E	R	E	R	E	R	E	R
1	0	0.00	1	0.02	0	0.00	0	0.00	0	0.00	1	0.02
2	0	0.00	2	0.03	0	0.00	0	0.00	0	0.00	2	0.03
3	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
4	0	0.00	1	0.02	0	0.00	0	0.00	0	0.00	1	0.02
5	0	0.00	3	0.05	0	0.00	0	0.00	0	0.00	3	0.05
6	0	0.00	3	0.05	0	0.00	0	0.00	0	0.00	3	0.05
7	0	0.00	2	0.03	0	0.00	0	0.00	0	0.00	2	0.03
8	0	0.00	1	0.02	0	0.00	0	0.00	0	0.00	1	0.02
9	0	0.00	7	0.12	1	0.02	0	0.00	0	0.00	8	0.13
10	0	0.00	3	0.05	0	0.00	0	0.00	0	0.00	3	0.05
11	0	0.00	3	0.05	0	0.00	0	0.00	0	0.00	3	0.05
12	0	0.00	1	0.02	0	0.00	0	0.00	0	0.00	1	0.02
13	0	0.00	2	0.03	0	0.00	0	0.00	0	0.00	2	0.03
14	0	0.00	5	0.08	0	0.00	0	0.00	0	0.00	5	0.08
15	0	0.00	2	0.03	0	0.00	0	0.00	0	0.00	2	0.03
16	0	0.00	3	0.05	0	0.00	0	0.00	0	0.00	3	0.05
17	0	0.00	6	0.10	0	0.00	1	0.02	0	0.00	7	0.12
18	0	0.00	5	0.08	0	0.00	0	0.00	0	0.00	5	0.08
19	0	0.00	2	0.03	0	0.00	0	0.00	0	0.00	2	0.03
20	0	0.00	0	0.00	1	0.02	0	0.00	0	0.00	1	0.02
21	0	0.00	8	0.13	0	0.00	0	0.00	0	0.00	8	0.13
22	0	0.00	4	0.07	0	0.00	0	0.00	0	0.00	4	0.07
23	0	0.00	5	0.08	0	0.00	0	0.00	0	0.00	5	0.08
24	0	0.00	3	0.05	0	0.00	0	0.00	0	0.00	3	0.05
25	0	0.00	6	0.10	0	0.00	0	0.00	0	0.00	6	0.10
26	0	0.00	2	0.03	0	0.00	0	0.00	0	0.00	2	0.03
27	0	0.00	2	0.03	0	0.00	0	0.00	0	0.00	2	0.03
28	0	0.00	4	0.07	0	0.00	0	0.00	0	0.00	4	0.07
29	0	0.00	5	0.08	0	0.00	0	0.00	0	0.00	5	0.08
30	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
31	0	0.00	4	0.07	0	0.00	0	0.00	0	0.00	4	0.07
32	0	0.00	4	0.07	1	0.02	0	0.00	0	0.00	5	0.08
33	1	0.02	2	0.03	0	0.00	0	0.00	0	0.00	3	0.05
34	0	0.00	3	0.05	1	0.02	0	0.00	0	0.00	4	0.07
35	0	0.00	4	0.07	0	0.00	0	0.00	0	0.00	4	0.07
36	0	0.00	5	0.08	0	0.00	0	0.00	0	0.00	5	0.08
37	0	0.00	3	0.05	0	0.00	0	0.00	0	0.00	3	0.05
38	0	0.00	1	0.02	0	0.00	0	0.00	0	0.00	1	0.02
39	0	0.00	3	0.05	0	0.00	0	0.00	0	0.00	3	0.05
40	0	0.00	2	0.03	0	0.00	0	0.00	0	0.00	2	0.03
41	0	0.00	5	0.08	0	0.00	0	0.00	0	0.00	5	0.08
42	0	0.00	3	0.05	0	0.00	0	0.00	0	0.00	3	0.05
43	0	0.00	3	0.05	0	0.00	0	0.00	0	0.00	3	0.05
44	0	0.00	5	0.08	0	0.00	0	0.00	0	0.00	5	0.08
45	1	0.02	1	0.02	0	0.00	0	0.00	1	0.02	3	0.05
46	1	0.02	4	0.07	0	0.00	0	0.00	0	0.00	5	0.08
47	1	0.02	7	0.12	0	0.00	1	0.02	0	0.00	9	0.15
48	0	0.00	4	0.07	0	0.00	0	0.00	0	0.00	4	0.07
49	0	0.00	5	0.08	0	0.00	0	0.00	0	0.00	5	0.08
50	0	0.00	3	0.05	0	0.00	0	0.00	0	0.00	3	0.05
51	0	0.00	2	0.03	0	0.00	0	0.00	0	0.00	2	0.03
52	1	0.02	1	0.02	1	0.02	0	0.00	0	0.00	3	0.05
MIN	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
MAX	1	0.02	8	0.13	1	0.02	1	0.02	1	0.02	9	0.15
MED	0	0.00	3	0.05	0	0.00	0	0.00	0	0.00	3	0.05

b) Left hemisphere

Spot	No response		Hesitation		Deviation to the right		Deviation to the left		Wrong number		All errors	
	E	R	E	R	E	R	E	R	E	R	E	R
1	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
2	0	0.00	5	0.08	1	0.02	0	0.00	0	0.00	5	0.08
3	0	0.00	3	0.05	0	0.00	0	0.00	0	0.00	3	0.05
4	0	0.00	6	0.10	1	0.02	0	0.00	0	0.00	7	0.12
5	0	0.00	6	0.10	0	0.00	0	0.00	0	0.00	6	0.10
6	0	0.00	2	0.03	0	0.00	0	0.00	2	0.03	4	0.07
7	0	0.00	5	0.08	0	0.00	0	0.00	0	0.00	5	0.08
8	0	0.00	3	0.05	0	0.00	0	0.00	0	0.00	3	0.05
9	0	0.00	7	0.12	0	0.00	0	0.00	0	0.00	7	0.12
10	0	0.00	2	0.03	0	0.00	0	0.00	0	0.00	2	0.03
11	0	0.00	3	0.05	0	0.00	0	0.00	0	0.00	3	0.05
12	0	0.00	7	0.12	0	0.00	0	0.00	0	0.00	7	0.12
13	0	0.00	1	0.02	0	0.00	0	0.00	0	0.00	1	0.02
14	0	0.00	9	0.15	0	0.00	0	0.00	0	0.00	9	0.15
15	1	0.02	3	0.05	0	0.00	0	0.00	0	0.00	4	0.07
16	0	0.00	6	0.10	0	0.00	0	0.00	0	0.00	6	0.10
17	0	0.00	1	0.02	0	0.00	0	0.00	0	0.00	1	0.02
18	0	0.00	5	0.08	0	0.00	0	0.00	0	0.00	5	0.08
19	0	0.00	3	0.05	0	0.00	0	0.00	0	0.00	3	0.05
20	0	0.00	6	0.10	0	0.00	0	0.00	0	0.00	6	0.10
21	0	0.00	6	0.10	0	0.00	0	0.00	0	0.00	6	0.10
22	0	0.00	3	0.05	0	0.00	0	0.00	0	0.00	3	0.05
23	0	0.00	8	0.13	0	0.00	0	0.00	0	0.00	8	0.13
24	0	0.00	3	0.05	0	0.00	0	0.00	0	0.00	3	0.05
25	0	0.00	7	0.12	0	0.00	0	0.00	0	0.00	7	0.12
26	1	0.02	11	0.18	0	0.00	1	0.02	0	0.00	13	0.22
27	1	0.02	5	0.08	0	0.00	0	0.00	0	0.00	6	0.10
28	0	0.00	4	0.07	0	0.00	0	0.00	0	0.00	4	0.07
29	0	0.00	3	0.05	0	0.00	0	0.00	0	0.00	3	0.05
30	0	0.00	2	0.03	0	0.00	0	0.00	0	0.00	2	0.03
31	0	0.00	3	0.05	0	0.00	0	0.00	0	0.00	3	0.05
32	0	0.00	4	0.07	0	0.00	0	0.00	0	0.00	4	0.07
33	0	0.00	5	0.08	0	0.00	0	0.00	0	0.00	5	0.08
34	0	0.00	3	0.05	0	0.00	0	0.00	0	0.00	3	0.05
35	1	0.02	1	0.02	0	0.00	0	0.00	0	0.00	2	0.03
36	0	0.00	1	0.02	0	0.00	0	0.00	0	0.00	1	0.02
37	0	0.00	3	0.05	0	0.00	0	0.00	0	0.00	3	0.05
38	0	0.00	3	0.08	0	0.00	0	0.00	0	0.00	3	0.05
39	0	0.00	5	0.08	0	0.00	0	0.00	0	0.00	5	0.08
40	0	0.00	2	0.03	0	0.00	0	0.00	0	0.00	2	0.03
41	0	0.00	1	0.02	0	0.00	0	0.00	0	0.00	1	0.02
42	0	0.00	3	0.05	0	0.00	0	0.00	0	0.00	3	0.05
43	0	0.00	3	0.05	0	0.00	0	0.00	0	0.00	3	0.05
44	0	0.00	3	0.05	0	0.00	0	0.00	0	0.00	3	0.05
45	0	0.00	5	0.08	0	0.00	0	0.00	0	0.00	5	0.08
46	0	0.00	3	0.05	0	0.00	0	0.00	0	0.00	3	0.05
47	0	0.00	3	0.05	0	0.00	0	0.00	0	0.00	3	0.05
48	0	0.00	0	0.00	0	0.00	1	0.02	0	0.00	1	0.02
49	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.03
50	0	0.00	2	0.03	0	0.00	0	0.00	0	0.00	2	0.03
51	0	0.00	3	0.05	0	0.00	1	0.02	0	0.00	4	0.07
52	0	0.00	2	0.03	0	0.00	0	0.00	0	0.00	2	0.03
MIN	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
MAX	1	0.02	11	0.18	1	0.02	1	0.02	0	0.03	13	0.22
MED	0	0.00	3	0.05	0	0.00	0	0.00	0	0.00	3	0.05

Table 3: Different errors types during the line-bisection tasks induced by nrTMS stimulation trains per stimulation spot.

a) Errors and error ratio found in the whole right hemisphere.

b) Errors and error ratio observed in the whole left hemisphere.

E: Errors; R: Ratio: MED: Median

Different ER for all stimulations per CPS regions and lobes

a) Right hemisphere

CPS region	No response		Hesitation		Deviation to the left		Deviation to the right		Wrong number		All errors	
	E	R	E	R	E	R	E	R	E	R	E	R
AnG	0	0.00	2.5	0.04	0	0.00	0	0.00	0	0.00	3	0.05
aSMG	0.5	0.01	3	0.05	0	0.00	0.5	0.01	0	0.00	4	0.07
aSTG	0	0.00	3	0.05	0	0.00	0	0.00	0	0.00	3	0.05
dPOG	0	0.00	6	0.10	0	0.00	0	0.00	0	0.00	6	0.10
dPrG	0	0.00	2	0.03	0	0.00	0	0.00	0	0.00	2	0.03
vLOG	0	0.00	4	0.07	0	0.00	0	0.00	0	0.00	4	0.07
mMFG	0	0.00	1.5	0.03	0	0.00	0	0.00	0	0.00	1.5	0.03
mMTG	0	0.00	4	0.07	0	0.00	0	0.00	0	0.00	4	0.07
mPoG	0	0.00	2	0.03	0	0.02	0	0.00	0	0.00	2	0.03
mPrG	0	0.00	4	0.07	0	0.00	0.5	0.01	0	0.00	4.5	0.08
mSFG	0	0.00	3	0.05	0	0.00	0	0.00	0	0.00	3	0.05
mSTG	0	0.00	1.5	0.03	0	0.00	0.5	0.01	0	0.00	2	0.03
opIFG	0	0.00	5	0.08	0	0.00	0	0.00	0	0.00	5	0.08
pITG	1	0.02	7	0.12	1	0.02	0	0.00	0	0.00	9	0.15
pMFG	0	0.00	5	0.08	0	0.00	0	0.00	0	0.00	5	0.08
pMTG	0	0.00	3	0.05	0	0.00	0	0.00	0	0.00	3	0.05
polLOG	0	0.00	1.5	0.03	0	0.00	0.5	0.01	0	0.00	2	0.03
pSFG	0	0.00	2	0.03	0	0.00	0	0.00	0	0.00	2	0.03
pSMG	0	0.00	4	0.07	0	0.00	0	0.00	0	0.00	4	0.07
pSTG	0	0.00	1	0.02	0	0.02	0	0.00	0	0.00	1	0.02
SPL	0	0.00	4.5	0.08	0	0.00	0	0.00	0	0.00	4.5	0.08
trIFG	0	0.00	2	0.03	0	0.00	0	0.00	0	0.00	2	0.03
vPoG	0	0.00	4.5	0.08	0	0.00	0	0.00	0	0.00	4.5	0.08
vPrG	0	0.00	4.5	0.08	0	0.00	0	0.00	0	0.00	4.5	0.08
Frontal	0	0.00	69	0.05	1	0.00	2	0.00	0	0.00	72	0.05
Parietal	2	0.00	53	0.06	0	0.00	1	0.00	1	0.00	57	0.06
Occipital	0	0.00	11	0.05	0	0.00	1	0.00	0	0.00	12	0.05
Temporal	2	0.00	32	0.05	1	0.00	1	0.00	0	0.00	36	0.06
MEDIAN	0	0.00	3	0.05	0	0.00	0	0.00	0	0.00	3	0.05
SD	0.21	0.00	1.80	0.03	0.19	0.00	0.18	0.00	0.00	0.00	1.97	0.03
MIN	0	0.01	4	0.02	0	0.00	0	0.00	0	0.00	1	0.02
MAX	1	0.02	7	0.12	1	0.02	0.5	0.01	0	0.00	9	0.15

b) Left hemisphere

CPS region	No response		Hesitation		Deviation to the left		Deviation to the right		Wrong number		All errors	
	E	R	E	R	E	R	E	R	E	R	E	R
AnG	0	0.00	2.5	0.04	0	0.00	0	0.00	0	0.00	2.5	0.04
aSMG	0	0.00	4.5	0.08	0	0.00	0	0.00	0	0.00	4.5	0.08
aSTG	0	0.00	3	0.05	0	0.00	0	0.00	0	0.00	3	0.05
dPOG	0	0.00	7	0.12	0	0.00	0	0.00	0	0.00	7	0.12
dPrG	0	0.00	3	0.05	0	0.00	0	0.00	0	0.00	3	0.05
vLOG	0	0.00	1	0.02	0	0.00	0	0.00	0	0.00	1	0.02
mMFG	0	0.00	4	0.07	0	0.00	0	0.00	0	0.00	4	0.07
mMTG	0.5	0.01	2	0.03	0	0.00	0	0.00	0	0.00	2.5	0.04
mPoG	1	0.02	8	0.13	0.5	0.01	0	0.00	0	0.00	9.5	0.16
mPrG	0	0.00	6	0.10	0	0.00	0	0.00	0	0.00	6	0.10
mSFG	0	0.00	2	0.03	0	0.00	0	0.00	0	0.00	3	0.05
mSTG	0	0.00	2.5	0.04	0	0.00	0	0.00	0	0.00	2.5	0.04
opIFG	0	0.00	7	0.12	0	0.00	0	0.00	0	0.00	7	0.12
pITG	0	0.00	3	0.05	0	0.00	0	0.00	0	0.00	3	0.05
pMFG	0	0.00	5	0.08	0	0.00	0	0.00	0	0.00	5	0.08
pMTG	0	0.00	3	0.05	0	0.00	0	0.00	0	0.00	3	0.05
polLOG	0	0.00	2.5	0.04	0.5	0.01	0	0.00	0	0.00	3	0.05
pSFG	1	0.02	3	0.05	0	0.00	0	0.00	0	0.00	4	0.07
pSMG	0	0.00	2	0.03	0	0.00	0	0.00	0	0.00	2	0.03
pSTG	0	0.00	3	0.05	0	0.00	0	0.00	0	0.00	3	0.05
SPL	0	0.00	1.5	0.03	0.5	0.01	0	0.00	0	0.00	2	0.03
trIFG	0	0.00	6	0.10	0	0.00	0.5	0.01	0	0.00	6.5	0.11
vPoG	0	0.00	3.5	0.06	0	0.00	0	0.00	0	0.00	3.5	0.06
vPrG	0	0.00	5.5	0.09	0	0.00	0	0.00	0	0.00	5.5	0.09
Frontal	1	0.00	100	0.07	0	0.00	2	0.00	0	0.00	105	0.08
Parietal	2	0.00	57	0.06	2	0.00	0	0.00	0	0.00	61	0.07
Occipital	0	0.00	7	0.03	1	0.00	0	0.00	0	0.00	8	0.03
Temporal	1	0.00	29	0.05	0	0.00	0	0.00	0	0.00	30	0.05
MEDIAN	0	0.00	3	0.05	0	0.00	0	0.00	0	0.00	3	0.05
SD	0.28	0.00	2.13	0.04	0.16	0.00	0.10	0.00	0.00	0.00	2.24	0.04
MIN	0	0.00	1	0.02	0	0.00	0	0.00	0	0.00	1	0.02
MAX	1	0.02	8	0.13	0.5	0.01	0.5	0.01	0	0.00	9.5	0.16

Table 4: Summary of different error types regarding the ER for all errors of all stimulations induced by nrTMS stimulations per CPS region and lobe. E: Errors; R: Ratio

a) Errors and error ratio found in the right hemisphere.

b) Errors and error ratio generated in the left hemisphere.

3.3 ER relative to all subjects during the line-bisection tasks

3.3.1 Error distribution for all error types

The right hemisphere observed the highest error rates of 35% in the trIFG, the pMFG and the mPrG. Concerning the left hemisphere, we found 40% error rates in the opercular inferior frontal gyrus (opIFG) and the mPoG. Regarding the entire hemispheres, a total error rate of 15% was achieved in the right hemisphere, with a maximum of 20% in the occipital lobe, as well as an 18% error rate in the entire left hemisphere (maximum 20% in the frontal lobe). Comparing both hemispheres with a chi-square test we nearly reached statistical significance with a p.value of 0.06.

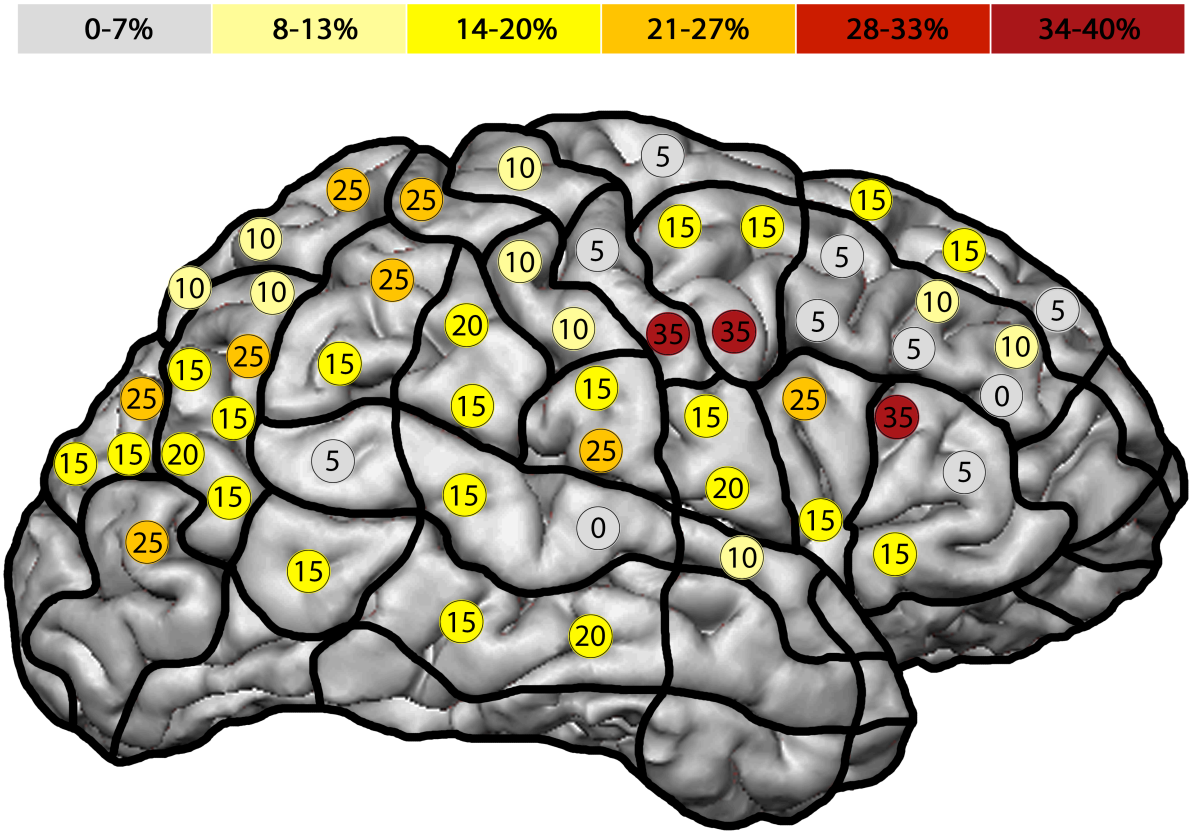

Fig. 13: Illustration of the entire errors of all error types relative to all subjects concerning the right hemisphere

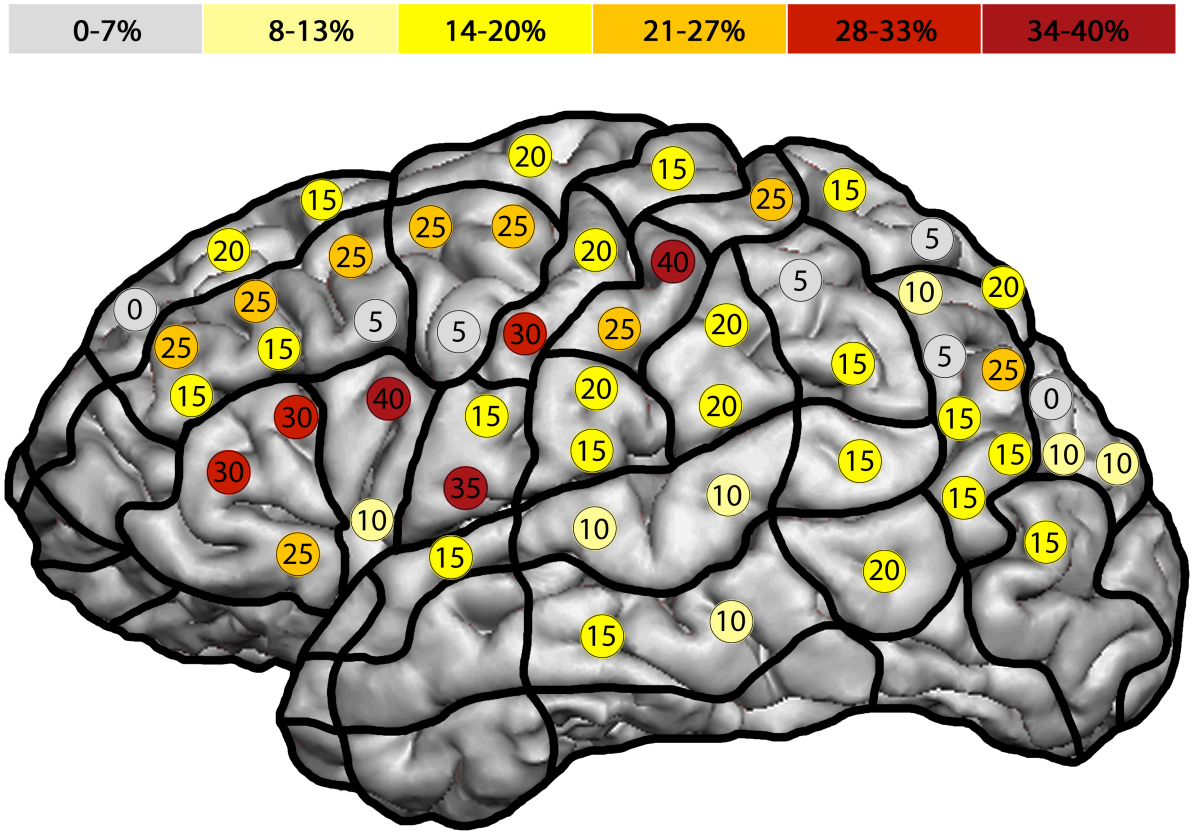

Fig. 14: This template shows the entire errors of all error types relative to all subjects in the left hemisphere

3.3.2 No response errors

The highest error rates of 5% were observed in the right aSMG, the anG, the vLOG and the dLOG. In terms of the left hemisphere, 5% error rates could be observed in the posterior frontal gyrus (pSFG), the mPoG and the middle middle temporal gyrus (mMTG). The entire right hemisphere generated a total error rate of 0%, with a maximum of 3% in the occipital lobe. In the left hemisphere, we found a total error rate of 0% as well, with a maximum of 1% in the parietal and temporal lobe. Comparing the two hemispheres using a Mann-Whitney test we could not reach statistical significance (p.value 0.934).

3.3.3 Hesitation errors

A highest error rate of 35% was generated in the right mPrG. We could furthermore observe an error rate of 40% in the left opIFG. Concerning the right hemisphere, a total rate of 14% was achieved (maximum of 18% in the occipital lobe). On the other hand, an 17% error rate was found in the left hemisphere with a maximum rate of 20% in the left frontal lobe. Using a Mann-Whitney test, we were not able to show statistical significance (p-value 0.364).

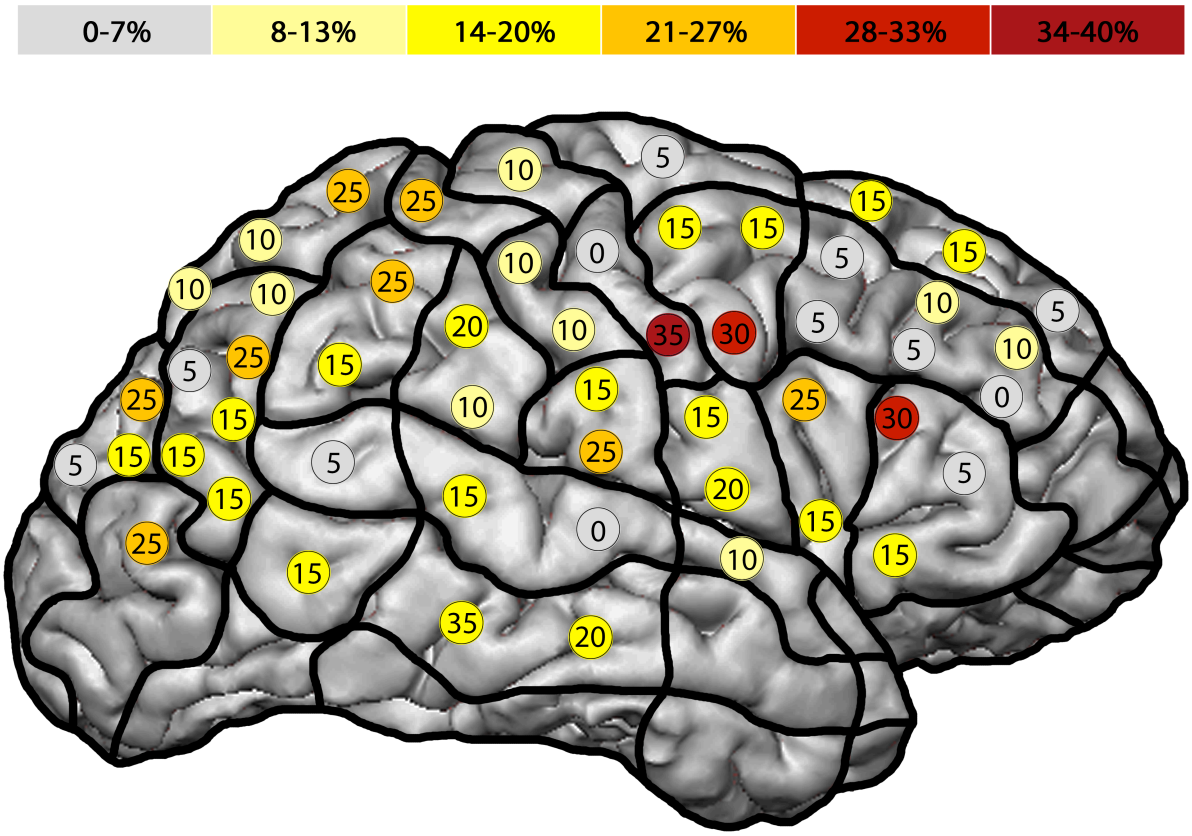

Fig. 15: Template of all hesitation errors relative to all subjects in the right hemisphere

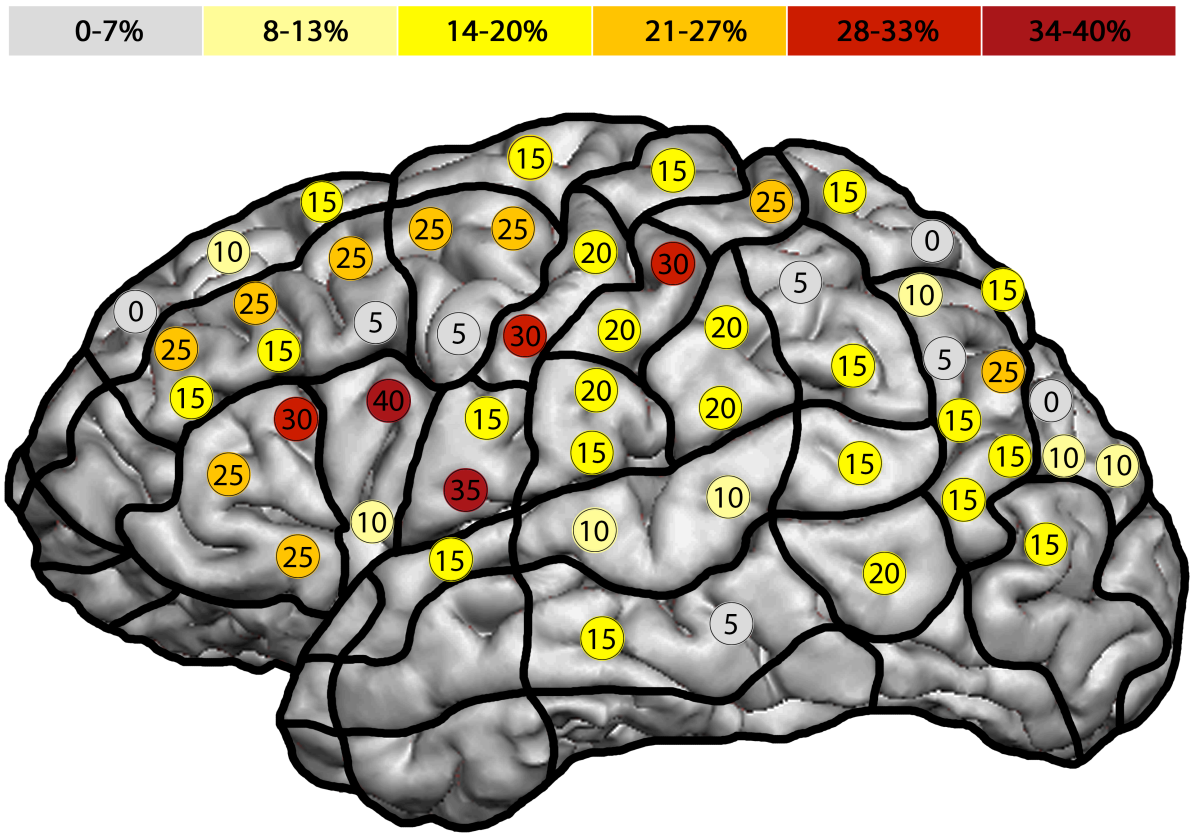

Fig. 16: Illustration of all hesitation errors relative to all subjects regarding the left hemisphere

3.3.4 Divergent line-bisection tasks to the right

We were able to achieve the highest error rates of 5% in the right trIFG, the mPrG, the aSMG, the mSTG and the dLOG. The left hemisphere showed the highest error rates of 5% in the mMFG and the trIFG as well. In total, the right hemisphere generated a 0% error rate (maximum 1% in the temporal and occipital lobe). A 0% error rate was found in the left hemisphere and the four different lobes. Comparing the hemispheres with a Mann-Whitney test for unpaired data we observed no statistical significance (p-value 0.501).

3.3.5 Divergent line-bisection tasks to the left

The highest error rate of 5% was observed in the right pMFG and the vLOG. The left mPoG and SPL achieved the highest error rate of 5% as well. The right hemisphere

generated a total error rate of 0% with a maximum of 1% in the occipital lobe. In terms of the left hemisphere, we found a total error rate of 0% with a maximum of 1% in the parietal lobe. When again using the Mann-Whitney test comparing the two hemispheres, we can not present statistical significance (p-value 0.661).

Different error rates for all subjects per CPS regions and lobes

a) Right hemisphere

CPS region	No response		Hesitation		Deviation to the left		Deviation to the right		Wrong number		All errors	
	Errors	Ratio	Errors	Ratio	Errors	Ratio	Errors	Ratio	Errors	Ratio	Errors	Ratio
AnG	0	0.00	2.5	0.12	0	0.00	0	0.00	0	0.00	3	0.15
aSMG	0.5	0.03	3	0.15	0	0.00	0.5	0.03	0	0.00	3.5	0.18
aSTG	0	0.00	2	0.10	0	0.00	0	0.00	0	0.00	2	0.10
dPOG	0	0.00	5	0.25	0	0.00	0	0.00	0	0.00	5	0.25
dPrG	0	0.00	2	0.10	0	0.00	0	0.00	0	0.00	2	0.10
vLOG	0	0.00	4	0.20	0	0.00	0	0.00	0	0.00	4	0.20
mMFG	0	0.00	1	0.05	0	0.00	0	0.00	0	0.00	1	0.05
mMTG	0	0.00	3.5	0.18	0	0.00	0	0.00	0	0.00	3.5	0.18
mPoG	0	0.00	2	0.10	0	0.00	0	0.00	0	0.00	2	0.10
mPrG	0	0.00	3.5	0.18	0	0.00	0.5	0.03	0	0.00	4	0.20
mSFG	0	0.00	3	0.15	0	0.00	0	0.00	0	0.00	3	0.15
mSTG	0	0.00	1.5	0.08	0	0.00	0.5	0.03	0	0.00	1.5	0.08
opIFG	0	0.00	5	0.25	0	0.00	0	0.00	0	0.00	5	0.25
pITG	1	0.05	5	0.25	1	0.05	0	0.00	0	0.00	5	0.25
pMFG	0	0.00	3	0.15	0	0.00	0	0.00	0	0.00	3	0.15
pMTG	0	0.00	3	0.15	0	0.00	0	0.00	0	0.00	3	0.15
polLOG	0.5	0.03	1.5	0.08	0	0.00	0.5	0.03	0	0.00	2.5	0.13
pSFG	0	0.00	1	0.05	0	0.00	0	0.00	0	0.00	1	0.05
pSMG	0	0.00	4	0.20	0	0.00	0	0.00	0	0.00	4	0.20
pSTG	0	0.00	1	0.05	0	0.00	0	0.00	0	0.00	1	0.05
SPL	0	0.00	3.5	0.18	0	0.00	0	0.00	0	0.00	3.5	0.18
trIFG	0	0.00	2	0.10	0	0.00	0	0.00	0	0.00	2	0.10
vPoG	0	0.00	4	0.20	0	0.00	0	0.00	0	0.00	4	0.20
vPrG	0	0.00	3.5	0.18	0	0.00	0	0.00	0	0.00	3.5	0.18
Frontal	0	0.00	61	0.13	1	0.00	2	0.00	0	0.00	64	0.14
Parietal	2	0.01	49	0.16	0	0.00	1	0.00	1	0.00	52	0.17
Occipital	1	0.01	11	0.14	0	0.00	1	0.01	0	0.00	13	0.16
Temporal	2	0.01	27	0.14	1	0.01	1	0.01	0	0.00	28	0.14
MEDIAN	0	0.00	3	0.15	0.00	0.00	0.00	0.00	0.00	0.00	3	0.15
SD	0.22	0.01	1.48	0.07	0.19	0.01	0.18	0.01	0.00	0.00	1.48	0.07
MIN	0	0.00	1	0.05	0	0.00	0	0.00	0	0.00	1	0.05
MAX	1	0.05	5	0.25	1	0.05	0.5	0.03	0	0.00	5	0.25

b) Left hemisphere

CPS region	No response		Hesitation		Deviation to the left		Deviation to the right		Wrong number		All errors	
	Errors	Ratio	Errors	Ratio	Errors	Ratio	Errors	Ratio	Errors	Ratio	Errors	Ratio
AnG	0	0.00	2.5	0.12	0	0.00	0	0.00	0	0.00	2.5	0.13
aSMG	0	0.00	4	0.20	0	0.00	0	0.00	0	0.00	4	0.20
aSTG	0	0.00	3	0.15	0	0.00	0	0.00	0	0.00	3	0.15
dPOG	0	0.00	5	0.25	0	0.00	0	0.00	0	0.00	5	0.25
dPrG	0	0.00	3	0.15	0	0.00	0	0.00	0	0.00	3	0.15
vLOG	0	0.00	1	0.05	0	0.00	0	0.00	0	0.00	1	0.05
mMFG	0	0.00	4	0.20	0	0.00	0	0.00	0	0.00	4	0.20
mMTG	0.5	0.03	2	0.10	0	0.00	0	0.00	0	0.00	2.5	0.13
mPoG	1	0.05	5	0.25	0.5	0.03	0	0.00	0	0.00	6.5	0.33
mPrG	0	0.00	5	0.25	0	0.00	0	0.00	0	0.00	5	0.25
mSFG	0	0.00	2	0.10	0	0.00	0	0.00	0	0.00	3	0.15
mSTG	0	0.00	2	0.10	0	0.00	0	0.00	0	0.00	2	0.10
opIFG	0	0.00	6	0.30	0	0.00	0	0.00	0	0.00	6	0.30
pITG	0	0.00	3	0.15	0	0.00	0	0.00	0	0.00	3	0.15
pMFG	0	0.00	5	0.25	0	0.00	0	0.00	0	0.00	5	0.25
pMTG	0	0.00	3	0.15	0	0.00	0	0.00	0	0.00	3	0.15
polLOG	0	0.00	2.5	0.13	0.5	0.03	0	0.00	0	0.00	3	0.15
pSFG	1	0.05	3	0.15	0	0.00	0	0.00	0	0.00	4	0.20
pSMG	0	0.00	2	0.10	0	0.00	0	0.00	0	0.00	2	0.10
pSTG	0	0.00	3	0.15	0	0.00	0	0.00	0	0.00	3	0.15
SPL	0	0.00	1.5	0.10	0.5	0.03	0	0.00	0	0.00	2	0.10
trIFG	0	0.00	5	0.25	0	0.00	0.5	0.03	0	0.00	5.5	0.27
vPoG	0	0.00	3.5	0.18	0	0.00	0	0.00	0	0.00	3.5	0.18
vPrG	0	0.00	5	0.25	0	0.00	0	0.00	0	0.00	5	0.25
Frontal	1	0.00	90	0.20	0	0.00	2	0.00	0	0.00	94	0.20
Parietal	2	0.01	48	0.16	2	0.01	0	0.00	0	0.00	52	0.21
Occipital	0	0.00	7	0.09	1	0.01	0	0.00	0	0.00	8	0.21
Temporal	1	0.01	27	0.14	0	0.00	0	0.00	0	0.00	28	0.14
MEDIAN	0	0.00	3	0.15	0	0.00	0	0.00	0	0.00	3	0.15
SD	0.27	0.01	1.64	0.10	0.16	0.01	0.10	0.00	0.00	0.00	1.72	0.10
MIN	0	0.00	1	0.02	0.05	0.00	0	0.00	0.00	0.00	1	0.05
MAX	1	0.05	6	0.13	0.30	0.03	0.5	0.03	0.00	0.00	6.5	0.33

Table 5: Summary of different errors types regarding the error rates for all errors of all stimulations induced by nrTMS stimulation trains per CPS region and lobe.

a) Errors and error ratio found in the whole right hemisphere

b) Errors and error ratio generated in the whole left hemisphere

3.3.6 Wrong number over the middle line

Regarding wrongly named numbers the right anG showed the highest error rate of 5%. Concerning the left hemisphere, we were able to observe the highest error rate of 10% in the mSFG. Again, the total error rate for both hemispheres, as well as for all the lobes, in this case, was 0% (p-value >0.999).

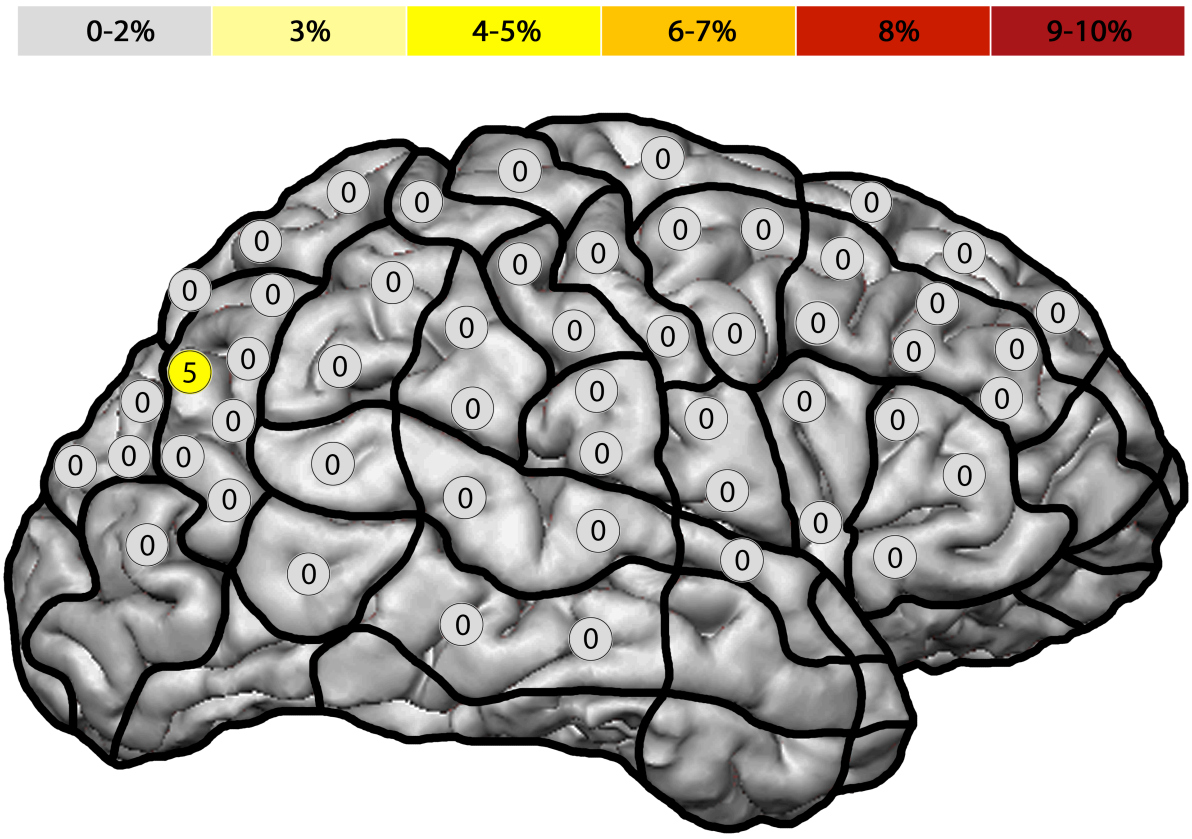

Fig. 17: This right hemisphere demonstrates the error rate for wrong numbers over the middle line relative to all subjects

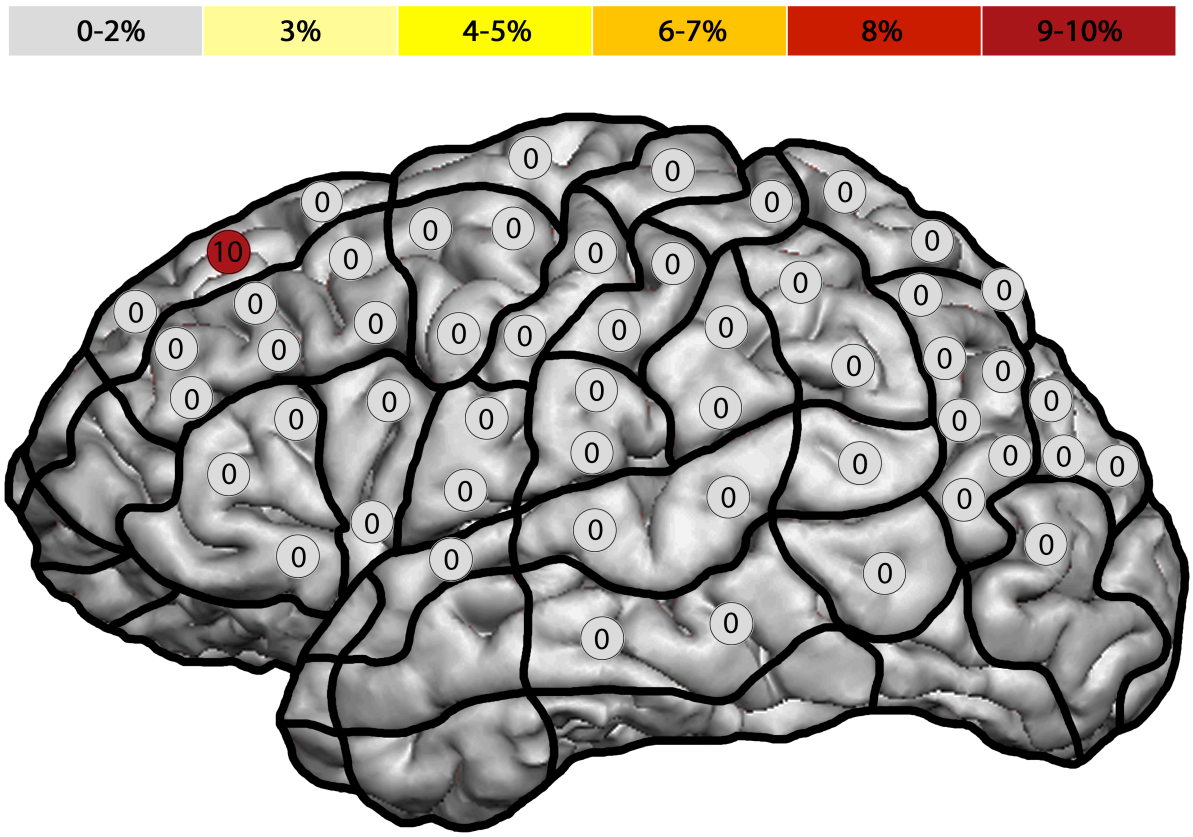

Fig. 18: This template shows the error rate for wrong numbers over the middle line concerning the left hemisphere relative to all subjects

Summary of different error types induced by nrTMS stimulation trains per subject

a) Right hemisphere

Subject	No response		Hesitation		Deviation to the right		Deviation to the left		Wrong number		All errors	
	Errors	Rate	Errors	Rate	Errors	Rate	Errors	Rate	Errors	Rate	Errors	Rate
1	0	0.00	5	0.13	1	0.03	0	0.00	0	0.00	6	0.15
2	0	0.00	18	0.46	0	0.00	0	0.00	0	0.00	18	0.46
3	5	0.13	7	0.18	0	0.00	0	0.00	0	0.00	12	0.31
4	0	0.00	18	0.46	0	0.00	1	0.03	0	0.00	19	0.49
5	0	0.00	8	0.21	0	0.00	0	0.00	0	0.00	8	0.21
6	0	0.00	11	0.28	0	0.00	0	0.00	0	0.00	11	0.28
7	0	0.00	9	0.23	0	0.00	0	0.00	0	0.00	9	0.23
8	0	0.00	3	0.08	0	0.00	1	0.03	1	0.03	5	0.13
9	0	0.00	10	0.26	0	0.00	0	0.00	0	0.00	10	0.26
10	0	0.00	7	0.18	0	0.00	0	0.00	0	0.00	7	0.18
11	0	0.00	2	0.05	0	0.00	0	0.00	0	0.00	2	0.05
12	1	0.03	18	0.46	1	0.03	0	0.00	0	0.00	20	0.51
13	0	0.00	10	0.26	1	0.03	0	0.00	0	0.00	11	0.28
14	0	0.00	3	0.08	0	0.00	0	0.00	0	0.00	3	0.08
15	0	0.00	2	0.05	0	0.00	0	0.00	0	0.00	2	0.05
16	0	0.00	8	0.20	0	0.00	0	0.00	0	0.00	8	0.21
17	0	0.00	3	0.08	0	0.00	0	0.00	0	0.00	3	0.08
18	0	0.00	16	0.41	2	0.05	0	0.00	0	0.00	18	0.46
19	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
20	0	0.00	6	0.15	0	0.00	0	0.00	0	0.00	6	0.15
MEDIAN	0	0.00	7.5	0.19	0	0.00	0	0.00	0	0.00	8	0.21
MIN	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
MAX	5	0.13	18	0.46	2	0.05	1	0.03	1	0.03	20	0.51
SD	1.10	0.03	5.51	0.14	0.54	0.01	0.30	0.01	0.22	0.01	5.88	0.15

b) Left hemisphere

Subject	No response		Hesitation		Deviation to the right		Deviation to the left		Wrong number		All errors	
	Errors	Rate	Errors	Rate	Errors	Rate	Errors	Rate	Errors	Rate	Errors	Rate
1	0	0.00	3	0.08	0	0.00	1	0.03	1	0.00	4	0.10
2	0	0.00	2	0.05	0	0.00	0	0.00	0	0.00	2	0.05
3	0	0.00	11	0.28	0	0.00	0	0.00	0	0.00	11	0.28
4	1	0.03	8	0.21	0	0.00	0	0.00	0	0.00	9	0.23
5	0	0.00	2	0.05	0	0.00	0	0.00	0	0.00	2	0.05
6	0	0.00	12	0.31	0	0.00	0	0.00	0	0.00	12	0.31
7	0	0.00	9	0.23	0	0.00	0	0.00	0	0.00	9	0.23
8	0	0.00	7	0.18	0	0.00	0	0.00	0	0.00	7	0.18
9	0	0.00	12	0.31	0	0.00	0	0.00	0	0.00	12	0.31
10	0	0.00	7	0.18	0	0.00	0	0.00	0	0.00	7	0.18
11	1	0.03	16	0.41	0	0.00	0	0.00	0	0.00	17	0.44
12	2	0.05	11	0.28	1	0.03	1	0.03	0	0.00	15	0.39
13	0	0.00	15	0.39	0	0.00	0	0.00	0	0.00	15	0.39
14	0	0.00	14	0.36	0	0.00	0	0.00	0	0.00	14	0.36
15	0	0.00	13	0.33	0	0.00	0	0.00	0	0.00	13	0.33
16	0	0.00	18	0.46	0	0.00	0	0.00	0	0.00	18	0.46
17	0	0.00	5	0.13	0	0.00	0	0.00	0	0.00	5	0.13
18	0	0.00	11	0.26	1	0.03	1	0.03	1	0.03	14	0.36
19	0	0.00	1	0.03	0	0.00	0	0.00	0	0.00	1	0.03
20	0	0.00	14	0.36	0	0.00	1	0.03	0	0.00	15	0.39
MEDIAN	0	0.00	11	0.28	0	0.00	0	0.00	0	0.00	11.5	0.29
MIN	0	0.00	1	0.03	0	0.00	0	0.00	0	0.00	1	0.26
MAX	2	0.05	18	0.46	1	0.03	1	0.03	1	0.03	18	0.46
SD	0.51	0.01	4.90	0.13	0.30	0.01	0.40	0.01	0.13	0.30	5.14	0.13

Table 6: Summary of different error types induced by nrTMS stimulation trains per subject. a) Errors and error rate observed in the whole right hemisphere. b) Errors and error rate generated in the whole left hemisphere

4. DISCUSSION

The topic of neglect-like symptoms and the syndrome of neglect was investigated from many researchers by different disciplines (Azouvi, 1996, Bartolomeo et al., 2012, Corbetta and Shulman, 2011, Li and Malhotra, 2015, Parton et al., 2004, Pedrazzini et al., 2017). Nonetheless, the aim of this study was to verify, whether it is feasible to detect the cortical locations involved in the neuropsychological function/syndrome of neglect via nrTMS in healthy subjects and thereby to create a cortical map of this function. It could have been shown that neuropsychological cortical function, like calculation or face recognition-function was successfully examined and mapped in healthy volunteers and patients with nrTMS before (Maurer et al., 2017, Maurer et al., 2016, Ille et al., 2016, Renzi et al., 2013). The mentioned studies were able to detect these functions precisely and thereby provided cortical maps of neuropsychological functions for the neuroscientists and clinicians.

4.1 Feasibility of locating cortical areas involved in generating neglect symptoms via nrTMS

Regarding another kind of neuropsychological functions, like calculation function, several studies were able to detect the cortical localizations precisely with the non-invasive technique of nrTMS in healthy subjects as well as in patients (Ille et al., 2016, Maurer et al., 2016). They showed and confirmed that the bilateral angular gyrus and adjacent frontal areas play an important role in processing and solving simple arithmetic problems. Furthermore, it could have been demonstrated that it seems feasible to detect and locate cortical areas involved in facial procession and face recognition via nrTMS (Maurer et al., 2017, Renzi et al., 2013). The identified regions, especially in the right frontal lobe are well in accordance with other literature using different modalities/lesion studies (Haxby et al., 1994, Rapcsak et al., 2001). The results of the current study though, are presenting different conclusions in terms of mapping cortical regions involved in generating neglect-like symptoms. The studies mentioned above examining neuropsychological functions via nrTMS, observed a total amount of 80% error rates for all errors of all subjects concerning facial processing in the right mMFG, or 80% error rates for all errors of all subjects in

terms of calculation function in the right vPrG. The current study only presents highest error rates of 40% for all errors of all subjects in the left hemisphere´s opIFG and mPoG. Concerning the right hemisphere, we observed the highest error rates for all subjects of only 35% in the trIFG, the pMFG and the mPrG. In this context, it appears that the mapping of neglect-related impairment is more complex or difficult than the mapping of other neuropsychological functions. Furthermore, the setup of the current study including the two different types of line-bisection tasks might be not appropriate for this kind of investigation and needs to be reviewed.

On the whole, current literature agrees that the right hemisphere plays a dominant role in the emergence of neglect symptoms (Heilman and Van Den Abell, 1980, Corbetta and Shulman, 2011, Bartolomeo et al., 2012). Especially the right parietal cortex is pointed out for the development of neglect symptoms (Driver and Mattingley, 1998, Sack, 2010, Vallar, 1998). In the current observation, we detected higher error rates for all errors of all subjects in the left hemisphere than in the right hemisphere. A possible explanation might be the generation of language-related errors and their development in the left frontal lobe. We observed the highest error rates in the left trIFG and adjacent frontal areas. In this context, we tried to differ presicely during the analysis of the mapping-session, whether the generated mistakes during the neglect-mapping were made because of language impairment or due to the inability to fulfill the line-bisection tasks. Every volunteer was asked following the stimulation, whether he felt unable to speak or articulate at some point or whether he felt unable to solve the line-bisection task on the other hand. Summarising, none of the subjects indicated, that he felt unable to speak or recognized difficulties concerning the language production during the nrTMS sessions. In comparison, regarding the calculation- and facial processing mappings, we generated higher error rates in non-language dominant parts of the cortex than in language associated cortical areas.

4.2 Differences between the cortical regions and hemispheres

Researchers and clinicians agree that the syndrome of neglect can occur after many different lesions or diseases in the brain, like a trauma with following brain injuries, a brain tumor, a stroke, neurovascular diseases or in combination with another space-

occupying process of the brain (Kalra et al., 1997, Jehkonen et al., 2000, Cocchini et al., 2001). In general, the exact localization or the emergence of neglect-symptoms still remains debatable. As mentioned above the right hemisphere seems to play a more important role in generating the syndrome of neglect. Patients with damage to their right hemisphere more often develop a neglect than patients with injuries in the left hemisphere. Neglect symptoms often follow massive strokes in the right middle cerebral artery region or right hemisphere´s brain unilateral injury (Li and Malhotra, 2015). More precisely, Neglect development seems to correlate with brain damage or injury to the right temporoparietal junction or posterior parietal cortex (Vallar, 1998). Moreover, the right hemisphere appears to be specialized for spatial perception, attention and processing, and furthermore, able to compensate the loss of these functions of the left hemisphere, but not the other way around (Farah, 2000). It seems even possible to expand this subject into the appearance of spatial neglect symptoms in dreams (Figliozzi 2007 doricchi the ways we look at dreams). In this case, the eye movement of a sleeping neglect patient was tracked during his REM cycle. The researchers observed that most of the eye movements were directed to the right side of the patient as if the pictures in his dreams were also influenced by his neglect symptoms.

4.3 Preoperative mapping of brain tumor patients in terms of neglect-related areas

In order to examine and understand anatomical correlates of neuropsychological functions, it is necessary to create studies including the examination of healthy volunteers without brain lesions. In this case, the homogenous cohort of 20 healthy subjects might be seen as a benefit for the current study. The next step might be the observation of patients with the same study set-up. Some studies even mention the possibility of treating a spatial neglect with TMS (Luaute et al., 2006).

4.4 Limitations

To start with, this study was designed as a pilot study including a homogeneous cohort of healthy subjects. It is the first step in the examination of the neglect syndrome via nrTMS. So far, there exists no gold standard technique in examining and mapping these neuropsychological functions in contrast to the examination of motor and language function. In general, nrTMS is not able to examine or map deeper areas of the brain, like the amygdala or the hippocampus. This non-invasive technique is limited to investigate cortical areas of both hemispheres in terms of different interesting research items. A possible approach in this context might be the combination of nrTMS and diffusion tensor imaging fiber tracking as published before regarding motor function (Krieg et al., 2012a, Frey et al., 2014) and language function (Ille et al., 2015). Additionally, nrTMS cannot be applied over every cortical area of the human cortex due to the pain the stimulation can cause. Furthermore, it is possible that adjacend cortical regions are activated or inhibited as well during the stimulation of a neighboring area because of their functional connectivity. In general, during the nrTMS mapping procedure we stimulated with a strict anterior-posterior field orientation. Using another mapping setup, for instance, another field orientation or other protocol changes, it is possible that the tasks might have generated different or modified results (Sollmann et al., 2015b). This study does not include a second or controlling examination of the subjects, like a test-retest examination. Neither it can offer a sham-stimulation control-group or intraoperative validation of our results, for instance with direct cortical stimulation. This lack of information must be seen as a possible next step concerning the examination of neglect-like symptoms in healthy subjects or brain tumor patients. Furthermore, the observed hesitation errors were only compared to the previously performed baseline testing, without an exact reaction time measurement. As already mentioned, it moreover can be a difficulty to distinguish between mistakes made because of language impairment, for instance in the vPrG, due to impairment of visual function or due to the wanted generation of neglect-like symptoms. In order to gain a deeper insight, visual function and processing begin after about 120ms. The pathway of solving the line-bisection tasks then ends with language/speech production starting after approximately 400-600ms. In the meantime, the brain/cortex, along with other functions, solves the line bisection-task. In summary, so far it does not seem possible to categorize the emergence of the mistakes precisely. A potential solution would be the invention of a

language control task for the participants. This way, the tasks would be evaluated not only in terms of the generated neglect related mistakes but also with regard to the language correllated mistakes.

5. SUMMARY

English

Oncological neurosurgery defines two main goals, first the resection of the largest possible amount of the brain tumor and second the facilitation of the best functional outcome for the patient. The resection of eloquent brain areas would expectedly lead to paralysis, impairment of sensory processing, linguistic ability, or visual damage. In order to avoid any kind of postoperative impairment, preoperative mapping is of prime importance. Today, the advanced method of navigated repetitive transcranial magnetic stimulation (nrTMS) is used for many different approaches, most commonly for the preoperative mapping of motor and language function in brain tumor patients. It furthermore could be demonstrated that this technique seems feasible to detect distinctive neuropsychological cortical functions, such as facial processing or calculation function. The aim of the current study was to examine the feasibility of detecting cortical areas involved in the generation of neglect-symptoms via nrTMS and therefore creating a cortical map concerning this function.
20 healthy and purely right-handed volunteers (11 female, 9 male) underwent nrTMS mapping for the detection of cortical neglect-related areas using 5 Hz/ 10 pulses. During the sessions, 52 cortical spots spread over the hemispheres were stimulated. Both hemispheres were investigated randomly and with 2 weeks delay between both mappings. The task consisted of 80 line-bisection tasks, which the volunteers were instructed to solve while nrTMS pulses were applied.
In total, the right hemisphere observed the highest error rates of 35% in the trIFG, the pMFG and the mPrG for all errors of all subjects. Concerning the error rate for all errors of all stimulations, the highest error rate of 15% was observed in the right vLOG. Regarding the left hemisphere, we found 40% error rates for all errors of all subjects in the opIFG and the mPoG, as well as a 22% error rate for all errors of all stimulations in the mPoG.
In conclusion, although we already were able to generate error rates of 40% in this pilot study, the line-bisection tasks in order to evoke neglect-like symptoms need to be improved. Furthermore, clinical applicability for preoperative mapping in brain tumor patients has to be evaluated as the upcoming step.

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Deutsch

Die wichtigsten Zielsetzungen in der onkologischen Neurochirurgie beziehen sich auf die operative Resektion der größtmöglichen Tumormasse, sowie die Erzielung des längstmöglichen progressionsfreien Überlebens inklusive eines komplikationslosen postoperativen Verlaufs mit wenig funktionellen Einschränkungen. Die Resektion von sogenannten eloquenten Hirnarealen kann z.B. zu permanenten oder residuellen Einschränkungen der Motorik, des sensorischen Empfindens, der visuellen Wahrnehmung oder zu Sprachdefiziten führen. Um diese postoperativen Funktionseinschränkungen zu minimieren, ist die präoperative Kartierung der eloquenten Hirnareale von großer Bedeutung. Die weiterentwickelte Methode der navigierten transkraniellen Magnetstimulation (nTMS) wird dieser Tage für verschiedene therapeutische, wie auch diagnostische Interventionen genutzt. Zumeist findet es Anwendung in der Katierung von motorischen und sprachassoziierten Kortexarealen in Hirntumorpatienten. Darüber hinaus konnte gezeigt werden, dass diese Untersuchungsmethode für die Detektierung von kortikalen neuropsychologischen Funktionen, wie Rechnen oder Gesichtserkennung, anwendbar ist. Das Ziel dieser Studie war die Detektierung Neglekt assoziierter kortikaler Areal mittels nrTMS in einer Kohorte von gesunden Probanden.

11 Frauen und 9 Männer unterzogen sich jeweils einer Hirnkartierung von jeder Hemisphäre. Dabei wurde mit 5 Hertz stimmultiuert a 10 Impulsen pro Stimulus. Nach der Durchführung einer Testbenennung/Baseline wurden die Probanden aufgefordert 80 verschiedene Linienhalbierungstest zu lösen, während sie magnetstimuliert wurden.

Die höchsten Fehlerraten in Bezug auf alle Probanden fanden sich in dem rechten trIFG, pMFG und mPrG mit 35%, sowie eine 15% Fehlerrate für alle Stimulationen in dem rechten vLOG. In Bezug auf die linke Hemisphäre detektierten wir die höchsten Fehlerraten von 40% für alle Probanden in dem opIFG und mPoG, und eine 22% Fehlerrate in Hinsicht auf alle Stimulationen im linken mPoG.

Nachdem bei dieser Pilotstudie nur maximale Fehlerraten von 40% generiert werden konnten, erscheint eine Nachfolgestudie zur Optimierung der Ergebnisse an gesunden Probanden sinnvoll. Darüber hinaus kann die präoperative Kartierung von Patienten in Hinblick auf neglektassoziierte Areale eine Zielsetzung für kommende Studien darstellen.

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7. ABBREVIATIONS

3D	three-dimensional
aMTG	anterior middle temporal gyrus
anG	angular gyrus
aSMG	anterior supramarginal gyrus
BIT	Behavioral Inattention Test-conventional
CBS	Chatherine Bergego Scale
CPS	cortical percellation system
dLOG	dorsal lateral occipital gyrus
ER	Error rate
IFG	inferior frontal gyrus
IPI	inter-picture interval
ITG	inferior temporal gyrus
MEP	motor evoked potential
mMFG	middle middle frontal gyrus
mMTG	middle middle temporal gyrus
mPoG	middle postcentral gyrus
mPrG	middle precentral gyrus
mSFG	middle superior frontal gyrus
mSTG	middle superior temporal gyrus
MTG	middle temporal gyrus
nTMS	navigated transcranial magnetic stimulation
opIFG	opercular inferior frontal gyrus
orIFG	orbital part of the inferior frontal gyrus
pMFG	posterior middle frontal gyrus

PoG	postcentral gyrus
polIFG	polar inferior frontal gyrus
polMFG	polar middle frontal gyrus
polSFG	polar superior frontal gyrus
polSTG	polar superior temporal gyrus
PrG	precentral gyrus
pSFG	posterior superior frontal gyrus
PTI	Picture-to trigger interval
rMT	resting motor threshold
rTMS	repetitive transcranial magnetic stimulation
SBMT	Society for Brain Mapping and Therapeutics
SPL	superior parietal lobe
STG	Superior temporal gyrus
trIFG	Triangular inferior frontal gyrus
VAS	visual analogue scale
vLOG	ventral lateral occipital gyrus

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9. CURRICULUM VITAE

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2009-2012	Ludwig-Maximilians-Universität and Technische Universität München,
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Further professional activities

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Further skills

2005-2007	Traditional Chinese Medicine/Acupuncture, Paracelsus Schule Bielefeld

10. PUBLICATIONS

Original papers

Ille S, Drummer K, Giglhuber K, Conway N, Maurer S, Meyer B, Krieg SM
Mapping of arithmetic processing by nrTMS in patients with parietal brain tumors and correlation with postoperative outcome
Submitted

Giglhuber K, Maurer S, Zimmer C, Meyer B, Krieg SM
Mapping visuospatial attention – the greyscales task in combination with repetitive navigated transcranial magnetic stimulation
Submitted

Negwer C, Beurskens E, Sollmann N, Maurer S, Ille S, Giglhuber K, Kirschke JS, Ringel F, Meyer B, Krieg SM,
Loss of subcortical language pathways correlates with surgery-related aphasia in brain tumor patients: an investigation via rTMS-based DTI fiber tracking
Submitted

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Oral presentations

Non-invasive mapping of categorization function by navigated transcranial magnetic stimulation
European Association of Neurosurgical Societies (EANS), 2017, Venice

Non-invasive mapping of categorization function by navigated transcranial magnetic stimulation
Deutsche Gesellschaft für Neurochirurgie (DGNC), 2017, Magdeburg

Non-invasive mapping of categorization function by navigated transcranial magnetic stimulation
Symposium on Navigated Brain Stimulation (NBS), 2016, Berlin

Non-invasive mapping of face recognition function by navigated transcranial magnetic stimulation
Neuroonkologische Sektionstagung, 2016, Düsseldorf

Non invavive mapping of prosopagnosia by navigated transcranial magnetic stimulation
Neurophysiologische Sektionstagung der DGNC, 2015, München

Non-invasive mapping of neuropsychological cortical function by navigated rTMS
Deutsche Gesellschaft für Neurochirurgie (DGNC), 2014, Dresden

Neuropsychologische Kartierung des Kortex mittels repetitiver navigierter transkranieller Magnetstimulation
Neurophysiologische Sektionstagung der DGNC, 2014, Würzburg

Non-invasive mapping of neuropsychological cortical function by rTMS
Symposium on Navigated Brain Stimulation (NBS), 2013, Berlin

Posters

Non invasive mapping of face recognition function by navigated transcranial magnetic stimulation
European Association of Neurosurgical Societies (EANS), 2016, Athen

Non-invasive mapping of prosopagnosia by navigated transcranial magnetic stimulation
Deutsche Gesellschaft für Neurochirurgie (DGNC), 2016, Frankfurt

Non-invasive mapping of categorization function by navigated transcranial magnetic stimulation
Symposium on Navigated Brain Stimulation (NBS), 2016, Berlin

Non-invasive mapping of higher cortical function by navigated rTMS: Calculation
European Association of Neurosurgical Societies (EANS), 2015, Madrid

Non-invasive mapping of higher cortical function by navigated rTMS: Calculation
Deutsche Gesellschaft für Neurochirurgie (DGNC), 2015, Karlsruhe

Non-invasive mapping of prosopagnosia by navigated transcranial magnetic stimulation
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Non-invasive mapping of higher cortical function by navigated rTMS: Calculation
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