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Cortical mapping of visuospatial attention function by repetitive navigated transcranial magnetic stimulation

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Für meine Eltern

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1. INTRODUCTION

1.1. Visuospatial attention function and visual neglect

The term “visuospatial attention” comprises a number of rather automatic, highly interconnected and quite elusive brain functions. Broadly speaking it makes us direct our attention to visual stimuli in space. However, a description that briefed cannot live up to the complexity of operations. Most of our basic activities are based on intact attentional processing. Only with the clinical observation of patients suffering from various disorders in visuospatial cognition physicians started to reflect about possibly coherent brain operations. They pooled and compared symptoms. They developed tasks to examine the diverse manifestations. And they formed models on the underlying brain networks. Today we call the corresponding neurological syndrome “visual neglect”. It is subject to a broad spectrum of scientific investigations.

1.1.1. First clinical descriptions

One of the earliest recorded descriptions of visual neglect-symptoms dates back to the second half of the 19th century. In 1876 Hughlings Jackson published the case of 59-year-old Eliza T. suffering from a glioma of the right posterior temporal lobe (Jackson, 1876). Although his writing came in an ophthalmological journal with focus on the emergence of optic neuritis in brain tumor patients, Jackson also detailed neurological symptoms. For example, he reported on Eliza losing her way even in acquainted places - she would not find the park, “although the park gates were just in front of her”. He also commented on problems in near visual space: “When told to read Snellen’s test types, she did not know how to set about it, began at the right lower corner and tried to read backwards” and “When set to read 12 Snellen … Having got to the end of the line, she did not know where to go”. Jackson called this phenomenon “Imperception”. He ascribed it to a defective process of “visual ideation” normally performed by the posterior lobes. Moreover, he assumed the right posterior lobe to be “the leading side” at it and the left “the more automatic”.

During the two world wars numerous reports followed on patients with cerebral gunshot wounds and visuospatial deficits (Holmes, 1918; Poppelreuter, 1917). In 1931, the German Hermann Pinéas described at length the case of a woman with severe loss of awareness of her left personal and external space and consistently used the term “neglect” (Pinéas, 1931). All of them detailed diverse features and symptoms of neglect, but it was not until W. Russell Brain that visual neglect became considered an isolated, specific syndrome. In 1941 Brain published collected observations of six patients with right-hemispheric damage (Brain, 1941a, b). Three patients showed visual disorientation in the opposite hemifield, three showed neglect of the external space and profound loss of route finding. Brain concluded among others that “the effect of a lesion of the posterior part of the right hemisphere is to cause the patient to neglect the left half of external space” (Brain, 1941b). With this he laid the foundation of visual neglect being treated as a distinct disorder that somehow restricts the awareness of perceptual space.

1.1.2. Neuropsychological testing

In the following decades researches started to consistently test patients for visual neglect. An impressive number of studies was published by the group round Oliver Zangwill in the forties and fifties (Humphrey and Zangwill, 1952; McFie et al., 1950; McFie and Zangwill, 1960; Paterson and Zangwill, 1944; Paterson and Zangwill, 1945). Examinations often were integrated in the clinical setting in terms of bedside paper-and-pencil tests. Common tasks were clock drawing, drawing from memory or copying as well as line bisection or star cancellation. Figure 1 and 2 show some typical examples.

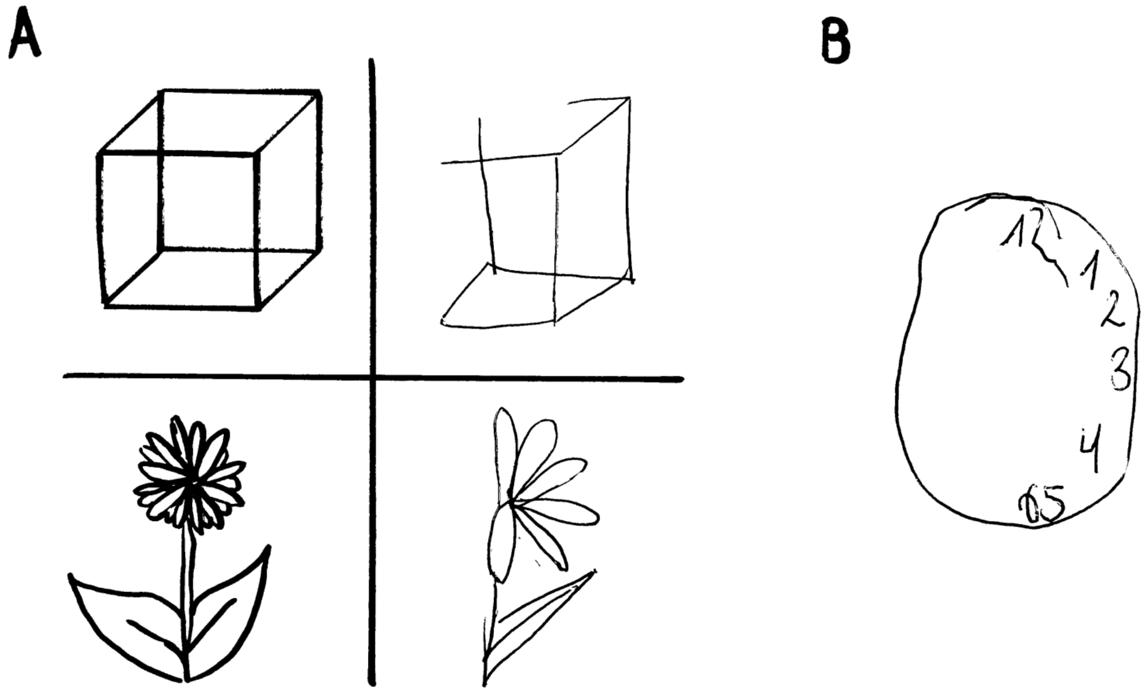

Fig. 1: *Typical results of a patient with left visual neglect. Task A was to copy the two objects on the left into the boxes on the right. In B the patient was asked to draw a clock from memory.*

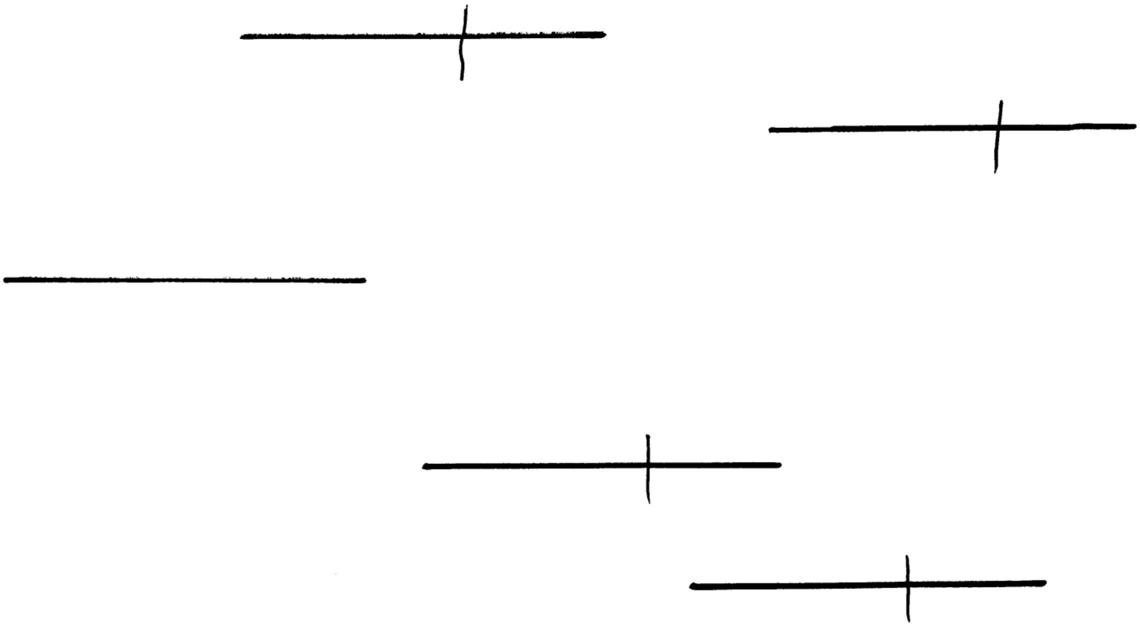

Fig. 2: Example of a bedside line bisection task. The patient was instructed to bisect all perceived horizontal lines. The result shows left visuospatial neglect of two forms: object-centered neglect (the bisection strokes slightly tend to the right) and subject-centered neglect (the most left-sided line got neglected).

Over the years testing became more specific. Increasing data was gathered, analyzed and compared. Researchers began to form theories on the underlying mechanisms of visuospatial attention (Bisiach et al., 1983; Bisiach and Luzzatti, 1978; Bisiach et al., 1986; Bowers and Heilman, 1980; De Renzi et al., 1970; De Renzi et al., 1989; Heilman, 1980; Kinsbourne, 1977; Mattingley et al., 1994). Around the turn of the century a discussion was launched about the diverse forms of neglect and their respectively diverse representations in clinical tasks. Terms tossed-in were object- vs. subject-centered neglect, ipsilesional vs. contralesional deficits, goal-directed vs. stimulus-driven, manual vs. oral testing or where- vs. what-tasks to name just a few. Researchers claimed a maximally differentiated examination to further understand nuances of the system (Bartolomeo et al., 2007; Bonato, 2012; Corbetta and Shulman, 2011; de Haan et al., 2012; Karnath and Rorden, 2012; Nicholls et al., 1999; Parton et al., 2004; Vallar, 1998). Furthermore, with increasing experience it was learned that neglect patients might develop sophisticated compensation mechanisms to mask deficits (Bonato, 2012; Learmonth et al., 2015). This initiated a - still ongoing - transition from classical paper-and-pencil tasks to computerized settings that facilitate highly specified and sensitive investigations.

1.1.3. The brain network

Already Hughlings Jackson admonished that the observation of a cerebral lesion that led to a functional deficit must not necessarily imply that the locus of function conformed to the locus of lesion (Jackson, 1884). Our brain commands an immense capacity to network. The higher the requested function, the more complex becomes the networking. The mechanisms of visuospatial attention function are nowhere near fully understood. However, researchers agree on some basic ideas and there exists a widely excepted network model by Corbetta and Shulmann (Corbetta and Shulman, 2002; Corbetta and Shulman, 2011).

1.1.3.1. Basic ideas

As aforementioned, from the beginning the right hemisphere and the parietal lobe turned out to be of special importance for an intact visuospatial attention processing. All primal descriptions included posterior right hemispheric damage and the occurrence of contralesional left neglect. In 1977 Kinsbourne proposed that there be crossed competences, namely of the right parietal region to shift attention to the left and of the left one to shift it to the right (Kinsbourne, 1977). Moreover he spoke about interhemispheric interactions and assumed the left hemisphere to hold the higher force. Three years later Heilman in contrast concluded from an electroencephalography (EEG) study that the right parietal region was able to shift attention to both the left and the right side, whereas the left parietal region solely shifts it to the right (Heilman, 1980). Universal network mechanisms got stated and then questioned, still, the idea of a right hemispheric lead or dominance and the subsequent interest in studies on the right hemisphere remained (Sack, 2010). Nevertheless, there seem to be highly individual differences. For example, researchers reported on left hemispheric lesions and contralesional right neglect; others observed lesions that resulted in ipsilesional deficits (Kim et al., 1999; Kwon and Heilman, 1991; Na et al., 2000; Robertson et al., 1994; Sacchetti et al., 2015; Suchan et al., 2012). A related point of interest forms the so-called “pseudoneglect”. Pseudoneglect terms the phenomenon that healthy people on average slightly tend to the left rather than the right. Bowers and Heilmann were the first to describe it in 1980 (Bowers and Heilman, 1980). Meanwhile a huge number of studies have focused on the issue (Brooks et al., 2014; Friedrich et al., 2016; Jewell and McCourt, 2000; Learmonth et al., 2017; Loftus and Nicholls, 2012; Petitet et al., 2015; Varnava et al., 2013). The examination of healthy beings gives most helpful insights into regular working processes of the brain. By the pooling of basic research and clinical data and by means of a broad spectrum of brain imaging techniques henceforth we can affirm the most prominent consideration. The right parietal lobe forms part of visuospatial attention processing and seems to be highly active in doing so. At the same time we found that also left hemispheric and frontal and temporal regions do belong to the - evidently complex - brain network.

1.1.3.2. Network model by Corbetta and Shulman

The basic modules of a brain network are cortical spots and connecting subcortical fiber tracts. The connections may be intra- and interhemispheric. As outlined before, eloquent cortical spots for visuospatial attention may be found in frontal areas, parietal areas and around the temporoparietal junction (TPJ). In 2011 Corbetta and Shulman reviewed the state of knowledge on attention networks (Corbetta and Shulman, 2011). In their understanding a universal model of processes required a sub-division in two networks as follows. Superior parietal and superior frontal areas form a dorsal network that is represented on both hemispheres roughly equally. This dorsal network maintains the basic competence of spatial attention processing. The TPJ and inferior frontal areas form a second, ventral network that is represented dominantly on the right hemisphere. The ventral network is responsible for one thing for non-spatial procedures and for another for supervision of the dorsal network. This model of two interconnected networks provides one of the best explanation foundations so far. It is seized on and further elaborated in many of the latest works (Bartolomeo and Seidel Malkinson, 2019; Duecker and Sack, 2014; Meehan et al., 2017; Ramsey et al., 2016).

1.2. Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) is a rather novel tool used therapeutically in a broad spectrum of diseases as well as diagnostically for cortical brain mapping (Hallett, 2007; Rossini et al., 2015). Within the field of brain mapping TMS represents a non-invasive, safe method to map both healthy subjects and patients (Rossi, 2009). For mapping of neuropsychological functions such as speech, calculation or visuospatial attention we use repetitive navigated TMS (rTMS), as will be explained further below. Similarly to Hughlings Jackson, however, referring to brain imaging studies Hugues Duffau stated that “it is not because an area has been activated on fMRI that its destruction will cause a deficit” (Duffau et al., 2014). Modalities like magnetoencephalography (MEG) or functional magnetic resonance imaging (fMRI) measure and depicture neuronal activity. By contrast, rTMS transiently creates a so-called “virtual lesion” (Pascual-Leone et al., 1999). That way it mimics what a loss of the respective stimulation site most probably would imply for the corresponding function, quite similarly to intrasurgical direct cortical stimulation (DCS), the uncontested gold standard of brain mapping (Krieg et al., 2012b).

1.2.1. Historical review

The first description of clinical TMS usage dates back to the eighties. It was in 1985 that Barker and his colleagues wrote a letter to the editor of Lancet reporting on a promising, new way of cortical stimulation by use of a pulsed magnetic field (Barker et al., 1985). They described the method to be "pain-free, without requirement of direct contact with the scalp, non-invasive, and easy-to-use". They also published the first record of a TMS-induced motor evoked potential (MEP) and concluded that „magnetic stimulation [was] a major advance" in the assessment and monitoring of functions. Another important publication followed some years later, in 1993, when Kujirai et al. surveyed the differences of TMS stimulation thresholds and frequencies and their corresponding activating or inhibiting effects (Kujirai et al., 1993). As TMS initially was checked out by stimulation of the motor cortex, other application fields followed soon. In 1991 Pascual-Leone performed the first language mapping by rapid-rate TMS (Pascual-Leone et al., 1991). Subsequently researchers started to systematically examine the significance of stimulation intensities and frequencies to trigger speech arrests (Epstein, 1996; Jennum et al., 1994; Pascual-Leone et al., 1999). In the further course the advanced form of "navigated" TMS was implemented by means of a navigation system originally designed for surgery (Grimson et al., 1996). From then on a three-dimensional reconstruction of the subject's magnetic resonance imaging (MRI) scan enabled the examiner to visualize the stimulation sites in real time. Additional improvements entailed detecting the induced electrical field over time including the measurement of its current strength and direction (Hannula et al., 2005; Ruohonen and Ilmoniemi, 1999). Evident advantages of these enhancements were that stimulation sites might be saved for later analysis or re-examination and that the individual mapping results might be displayed during surgery by data transfer via the navigation system (Lioumis et al., 2012).

1.2.2. Fields of application

The use of TMS today may be split into two branches, namely diagnostics and therapy. The latter one covers such a broad spectrum of diseases that a detailed description of all of them would take us too far afield. However, at least the most important domains ought to be named. TMS provides therapy options in the treatment of epilepsy, tinnitus and chronic pain and in psychiatric disorders such as major depression and schizophrenia (Ahdab et al., 2010; Brunoni et al., 2018; Chen et al., 2016; Fregni and Pascual-Leone, 2005; Janicak et al., 2013; Perera et al., 2016; Schneider et al., 2008; Theodoroff et al., 2017). Another big domain of application is the rehabilitation after stroke. Here, targeted TMS stimulation proved successful in the recovery of motor function, it reduced aphasia and improved symptoms of visual neglect (Brighina et al., 2003; Dionísio et al., 2018; Koch et al., 2012; Naeser et al., 2011). Back on diagnostics we already heard about the history of motor and language mapping. In clinical everyday life of today TMS already is well established for one thing for presurgical motor mapping. In tumor therapy neurosurgeons always have to balance the aim of resecting tumorous tissue to the best possible extent with the aim of saving necessary functions. In comparison to other non-invasive methods as fMRI or MEG, TMS showed preferably accurate results in localizing motor areas (Krieg et al., 2012b; Tarapore et al., 2012). Moreover, tumor patients with motor-eloquent lesions showed an improved outcome when they underwent TMS motor mapping prior to surgery (Frey et al., 2014; Krieg et al., 2014a). Apart from motor function the mapping of neuropsychological functions gains more and more interest. TMS language mapping already presents with a history of over 25 years of use in which both non-navigated repetitive TMS and later rTMS proved their applicability to localize human language function (Epstein, 1996; Epstein, 1998; Lioumis et al., 2012; Sparing et al., 2001). In comparison to the gold standard DCS, TMS showed excellent results, especially in mapping language-negative sites (Ille et al., 2015b; Picht et al., 2013; Tarapore et al., 2013). The clinical usefulness is widely appreciated. More recently ambitions in cortical brain mapping extend. Asked about important functions that should be involved in surgical decision-making there certainly comes more to our mind than motoric and speech. And so, studies increase that test rTMS for the mapping of further neuropsychological functions, as for instance calculation or face processing (Ille et al., 2018; Maurer et al., 2017; Maurer et al., 2015; Pitcher et al., 2007; Sliwinska and Pitcher, 2018; Solomon-Harris et al., 2013). One final application form - rather novel but promising - is the combination of TMS and diffusion tensor imaging fiber tracking (DTI-FT). It is used to visualize, additionally to the cortically mapped positive spots by TMS, their connected white matter pathways (Krieg et al., 2012a; Negwer et al., 2016; Sollmann et al., 2015a; Sollmann et al., 2016). This provides a further augmented knowledge of the individual's anatomic conditions. In a number of specialized centers the method is already incorporated in presurgical procedures by default.

1.3. Objective of the present studies

Visuospatial attention deficits, albeit subtle, are alarmingly frequent, not only after stroke, but also after oncological resections in neurosurgery. This substantially restricts the recovery of motor deficits and the total outcome of the patients (Jehkonen et al., 2000; Jehkonen et al., 2006; Katz et al., 1999). It naturally stands to reason to also map visuospatial attention function. There already are various intrasurgical approaches (Bartolomeo et al., 2007; Benwell et al., 2015; Roux et al., 2011). However, a non-invasive presurgical examination would entail clear advantages for planning the intervention. The underlying network is known to show highly individual differences and the potential of plastic reorganization especially in more slowly growing tumors is enormous. So, an accurate and preferably live method of visualization is to be sought. In many specialized neurooncological center rTMS, as pointed out above, is one of the standard tools for presurgical mapping and thus available. The objective of the presented two studies was to evaluate the applicability of rTMS for the mapping of visuospatial attention function. Thereto we decided to build on precursor studies of our group on calculation and face processing (Maurer et al., 2017; Maurer et al., 2015). As they also successfully did, we based our general mapping protocol on long-time approved language mapping procedures (Hauck et al., 2015; Krieg et al., 2017; Krieg et al., 2014b; Sollmann et al., 2015b; Tarapore et al., 2013). In our first study we embedded a classical landmark or bisection task in the rTMS mapping setup. This task could be both applied and analyzed the same way we were used to in testing language function by object naming. The second approach employed a more sensitive task with a quite sophisticated analysis. The main purpose of the present thesis was to evaluate a general feasibility. We did not compare mapping results of the two approaches because of their disparity of tasks and data analysis. We solely evaluated rTMS as a tool to create individual maps of visuospatial attention plus the back and forth of the two different tasks.

2. MATERIALS AND METHODS

2.1. Ethics approval

Both studies were conducted according to the Declaration of Helsinki, approved by the local ethics committee (Ethikkommission der Fakultät für Medizin der Technischen Universität München, Ismaninger Straße 22, 81675 Munich, Germany; registration number: 223/14). Prior to the procedures all subjects gave written informed consent to participate.

2.2. Study design

Both studies were designed to be prospective and non-randomized (Giglhuber et al., 2016; Giglhuber et al., 2018).

2.3. Subjects

Both studies were conducted on a collective of five men and five women, all of unimpaired mental and physical faculties. Their median age was 24 years.

Subjects had to meet the following inclusion criteria:

- Pure right-handedness with an Edinburgh inventory score >40
- German as a first language

Subjects who met at least one of the following exclusion criteria were not included:

- General MRI exclusion criteria (pacemaker, cochlea implant, deep brain stimulation)
- Seizures in medical history
- Other neurological or neuropsychological deficits in medical history

2.4. Magnetic resonance imaging

Prior to the examinations all subjects underwent MR imaging by a 3 Tesla MRI scanner with eight-channel phased-array head coil (Achieva 3 T, Philips Medical Systems, Amsterdam, The Netherlands B.V.). We scanned two sequences: a T2- weighted FLAIR sequence (TR: 12,000 ms, TE: 140 ms, voxel size: $0.9 \times 0.9 \times 4$ mm^3, acquisition time: 3 min) and a T1- weighted 3-D gradient echo sequence without intravenous contrast administration (TR: 9 ms, TE: 4 ms, 1 mm^3 isovoxel covering the whole head, acquisition time: 6 min 58 s). For the rTMS mapping we transferred the three-dimensional dataset by DICOM standard.

2.5. Repetitive navigated transcranial magnetic stimulation

rTMS mapping was conducted using a Nexstim eXimia system version 4.3 with NexSpeech® module. For later analysis we operated with the appropriate NexSpeech® Analyzer software (Nexstim Oy, Helsinki, Finland). All mapping procedures were in accordance to current safety guidelines (Rossi, 2009).

2.5.1. Basic principles of TMS

Properly speaking the term “transcranial magnetic stimulation” is lacking some conclusiveness because a magnetic field per se does not stimulate. It would rather be accurate and complete to speak of a transcranial magnetically induced electric stimulation as that actually outlines the underlying principle (Fig. 3).

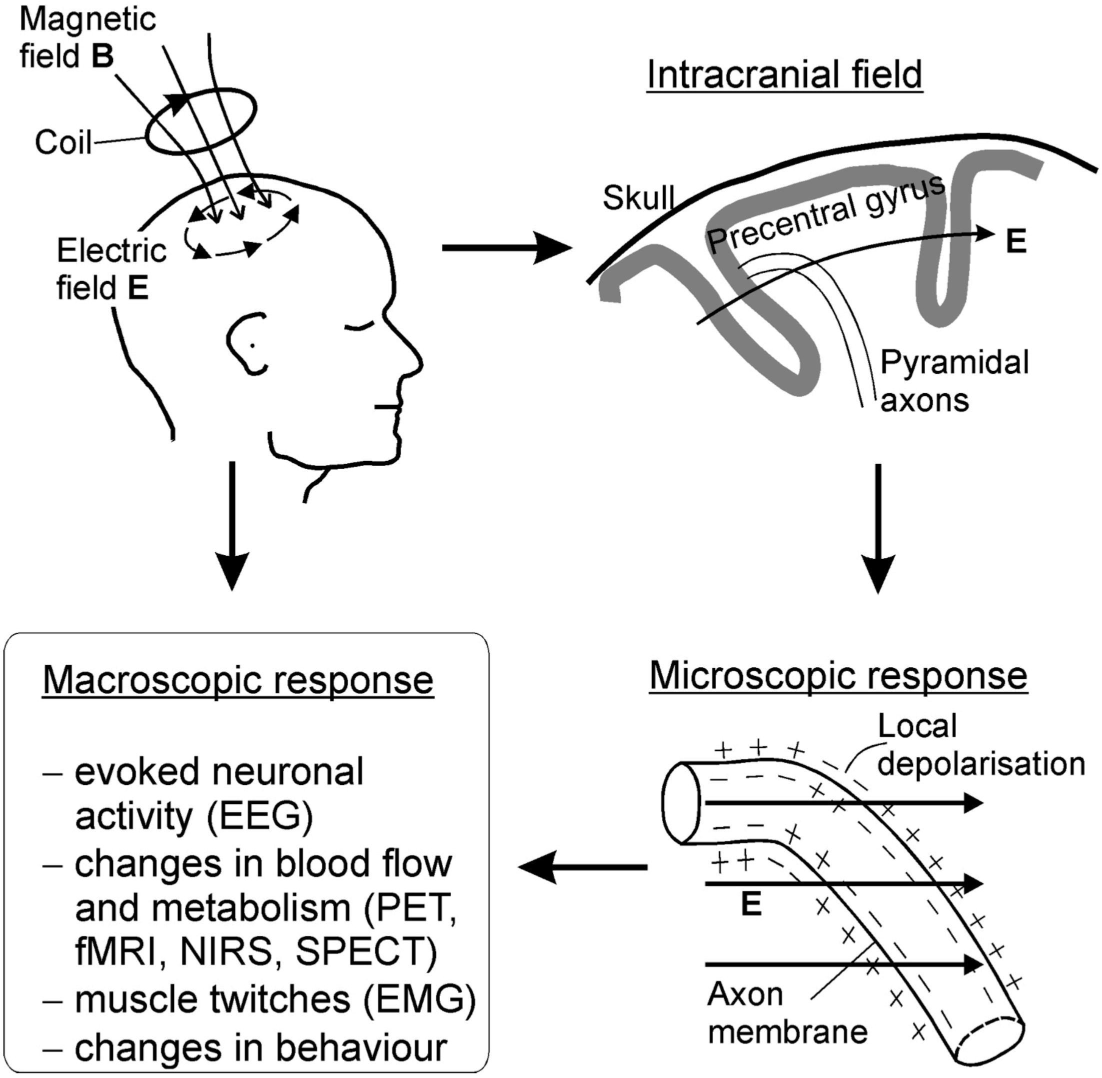

Fig. 3: Principles of TMS (Ruohonen, 1998)

Current flow inside of the stimulation coil induces a magnetic field, which in turn induces an intracranial electric field. The electric field leads to local changes in the neurons' transmembrane potential and as the case may be to a membrane depolarization. That way TMS is able to electrically stimulate cortical neurons non-invasively and without pain (Rossi, 2009). Macroscopic effects may be neuronal activity in EEG, changes in various imaging techniques for cerebral blood flow and -metabolism, peripheral muscle responses or altered behavior or task performance in neuropsychological tasks (Ruohonen, 1998). The latter one is particularly associated with the application of so-called repetitive or rapid rate stimulation. In this context we may revisit the term "virtual lesion" (Hallett, 2000; Pascual-Leone, 2002; Pascual-Leone et al., 1999). Though the microscopic mechanisms are not fully understood, for the time span of application the electric field induced by rTMS changes the transmembrane potential of affected neurons in a somehow inhibitory way. To adhere to the example of language function rTMS over language eloquent cortical areas can alter the performance of a simultaneously conducted object-naming test. Conversely, altered performances may point to a functional involvement of the particular stimulation sites. According to this principle rTMS is used for the cortical mapping of various neuropsychological functions.

There are different forms of stimulation coils with different effects and applications (Fig. 5). In our studies for cortical mapping we used a figure-of-eight coil. By the particular shape two electric fields get bundled at the center of the eight. This results in a greatly focal electric field at quite superficial cortical regions (Hallett, 2000; Ilmoniemi et al., 1999; Ruohonen and Ilmoniemi, 1998). By way of comparison in circular or double-cone coils focality and thus superficial spatial resolution are crucially smaller. Instead these shapes may cover wider areas with an effective field strength or provide great penetration depth (Rossi, 2009).

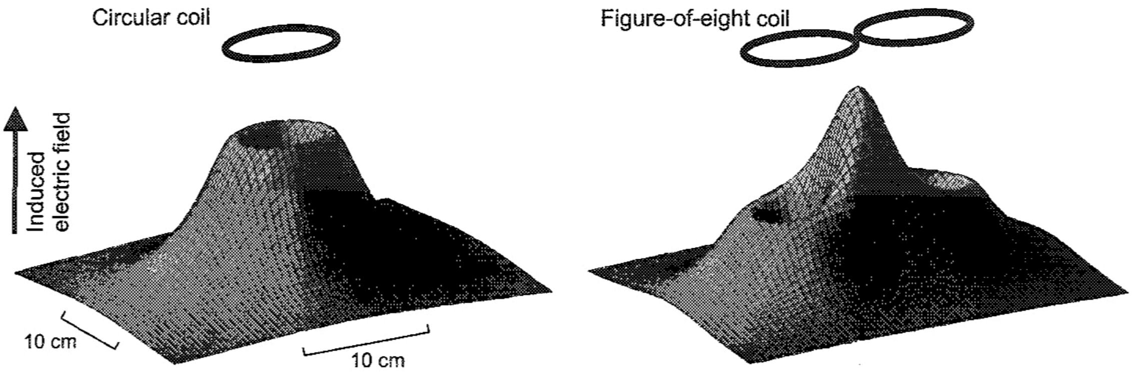

Fig. 4: Induced electric fields dependent on coil shapes. Circular coils provide deeper stimulation, the figure-of-eight coil scores with great focality.

To briefly address one additional issue the electric field diffusion also is affected by the coil's diameter. In fact the smaller the coil is, the higher is the focality, though the smaller the tissue penetration (Pascual-Leone, 2002; Rossi, 2009). The radius of our deployed figure-of-eight coil came to 50 mm and was thus rather small.

2.5.2. Navigational setup

As already introduced, the great advancement of rTMS is its embedded neuronavigation system. For an illustration of our setup see Figure 3.

Fig. 5: Setup of the Nexstim eXimia system with stereotactic camera, stimulation coil, video screen for task pictures, video camera, and two further screens for navigation control and task adjustments.

Procedures for neuronavigation were identical for both studies. By use of a stereotactic camera we marked the subject`s head with a tracker headband and linked some easily accessible bone landmarks with anatomical landmarks of the subject’s MRI reconstruction. By further registration of the stimulation coil its position could be visualized as corresponding electric field within the 3-D image. Moving the coil the induced electric field co-moved in real time. Brain regions could be accurately selected and stimulated (Krieg et al., 2013; Picht et al., 2013; Sollmann et al., 2014; Tarapore et al., 2013). The additional language mapping software implied a video screen and a video camera. It synchronized the presentation of task pictures and the application of rTMS pulses. Moreover, the integrated camera recorded mapping and task performance and enabled a subsequently detailed analysis (Lioumis et al., 2012).

2.5.3. rTMS visuospatial attention mapping

Both studies underlay a mapping protocol based on our group's standard rTMS language mapping procedure that is also similar to those of other centers (Hauck et al., 2015; Ille et al., 2015b; Maurer et al., 2015; Picht et al., 2013; Sollmann et al., 2015b; Tarapore et al., 2013).

2.5.3.1. Mapping parameter

To measure the individual motor cortex excitability we determined resting motor thresholds (RMT) of the respectively contralateral abductor pollicis brevis muscles, as reported earlier (Krieg et al., 2012b). The stimulation intensity for the mapping of each hemisphere was set to 100% RMT. In case of significant pain, to leave the subject's task performance unaffected, the intensity was reduced to 80% RMT (Lioumis et al., 2012). We reported two such cases (Giglhuber et al., 2016). Each rTMS stimulation train comprised 10 pulses that were delivered at a repetition frequency of 5 Hz. Each train took 1800 ms. We triggered the onset of the first train pulse with the appearance of the task picture on the video screen to be simultaneous. This picture-to-trigger intervall of 0 ms was in accordance with recent studies on rTMS language mapping (Krieg et al., 2014b; Sollmann et al., 2015b; Tarapore et al., 2013). For tachistoscopic testing the picture presentation time was set to 50 ms. This proved to be useful in earlier neglect studies (Fierro, 2000; Jewell and McCourt, 2000; Salatino et al., 2014). The inter-picture interval was set to 3000 ms. A black screen separated two consecutive pictures.

2.5.3.2. Mapping procedure

Each rTMS mapping was performed following the same procedure. We tested 52 cortical sites on both hemispheres (Fig. 6). They were allocated to 24 brain areas of Corina's cortical parcellation system as listed in Table 1 (Corina et al., 2005). We omitted some areas that are known to yield unusable results. Due to muscle stimulation and pain we could not test the orbital part of the inferior frontal gyrus (orIFG), the polar frontal gyrus (polFG), the anterior superior and middle frontal gyri (aSFG, aMFG), the polar temporal gyri (polTG) and the anterior middle temporal gyrus (aMTG). Also the inferior temporal gyrus (ITG) was left out. Here the oversized gap between skull and cerebrum would have delivered incomparable effects (Hauck et al., 2015; Krieg et al., 2013). The selected 52 sites were individually identified in the subject's MRI reconstruction and tagged as stimulation targets. These were identical for both studies. One by one, in random order, we mapped all targets of the left hemisphere, then all targets of the right hemisphere, and then repeated this sequence once. A target always was tested five subsequent times, thus ten times in total. Yet, because of difficulties with the navigation setting during the procedure this number varied a little. During the mapping we placed the stimulation coil strictly tangentially to the skull and in anterior-posterior field orientation as this practice has been reported to provide maximal field induction (Epstein, 1996; Lioumis et al., 2012; Miranda, 2013).

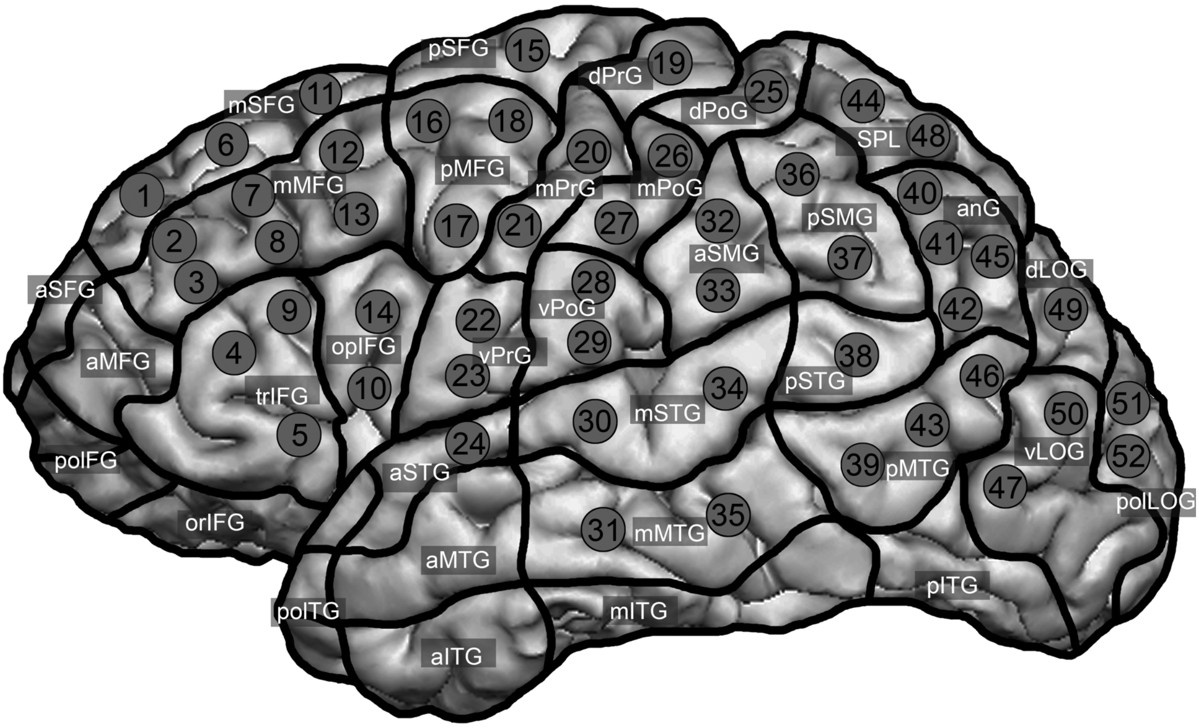

Fig. 6: *Mapping template with 52 stimulation targets. For abbreviations of the cortical parcellation system see Table 1* (Giglhuber et al., 2016).

Tab. 1: Designations of the cortical parcellation system

Abbreviated	Written-out
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
poIFG	polar frontal gyri
poITG	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

2.5.3.3. Evaluation of discomfort

After each mapping we evaluated discomfort and pain. Subjects were asked to differentiate between the two hemispheres and always between the temporal muscle area and all other parts of the head surface. As index we made use of the visual analogue scale with a range from zero to ten. Zero represented no pain, ten represented maximal pain.

2.5.4. Data analysis

The analysis of the rTMS mapping data comprised two separated steps (Ille et al., 2015a; Lioumis et al., 2012). First we had a look at the video recording. We evaluated the subject's task performance independently to stimulation sites. The specific analyses of both tasks will be explained in the next section. Moreover and that counts for both studies we checked the recording for unwanted side effects of the stimulation that influenced the subject's performance. Among such disturbances numbered eye blinking, pain and muscle stimulation. Respective responses were discarded. After this we proceeded with the second step and related the video results with the corresponding stimulation sites. Additionally, we had a look at the effectiveness of the single rTMS pulse trains. To deem the simulation effective the train of 10 rTMS pulses had to have been applied completely and with the continuous effect of an induced electric field at cortical level of above 55 V/m (Picht et al., 2013). Finally, in each study on its way, we pooled the results of all subjects per stimulation sites. Thus, later discussion always addressed the differences between the 104 examination targets.

2.6. Visuospatial attention tasks

While the procedure of rTMS mapping was identical for both studies, they differed from each other in the respectively set visuospatial attention task. Both tasks were composed of a batch of slides whereby each slide conformed to one quest and required an answer. The slides were presented on the video screen in random order. In the following we will outline the different characteristics of design and analysis of both tests.

2.6.1. Landmark task

Our first study made use of a classical line bisection judgment task, the landmark task (Giglhuber et al., 2016).

2.6.1.1. Task design

Task pictures showed black horizontal lines with a black vertical bisection line on a white background (Fig. 7). The vertical bar was 29 mm tall and 1 mm wide. It was adjusted to the middle of the screen in all pictures and thus lay in the subject's body midline. The horizontal lines differed in the length of their left and right segments. This ranged from 31 mm to 150 mm. The width of the horizontal line was 1 mm again. In total the task set contained 72 pictures, all distinct. 24 pictures showed a symmetrically bisected line, meaning that the two horizontal line segments were equal in length. 48 pictures showed asymmetries, which means that either the right or the left segment was longer than its counterpart. Performance requirements were to rate each line in respect of the two segments' length. Subjects had to tell which one appeared to be longer or whether they were identical. The selection was communicated by oral response (Fierro, 2000). Before the actual rTMS mapping we conducted one round of picture presentation without stimulation, the so-called baseline session (Lioumis et al., 2012; Sollmann et al., 2015c). Baseline conditions paralleled the earlier listed mapping conditions. On the one hand the baseline performance was recorded as a point of comparison for later analysis of the mapping performance. On the other hand by discarding all baseline slides with hesitant or wrong responses we created an individual set of those lines that had been answered positively correctly. That way an altered performance during the rTMS mapping was most probably linked to the mapping itself.

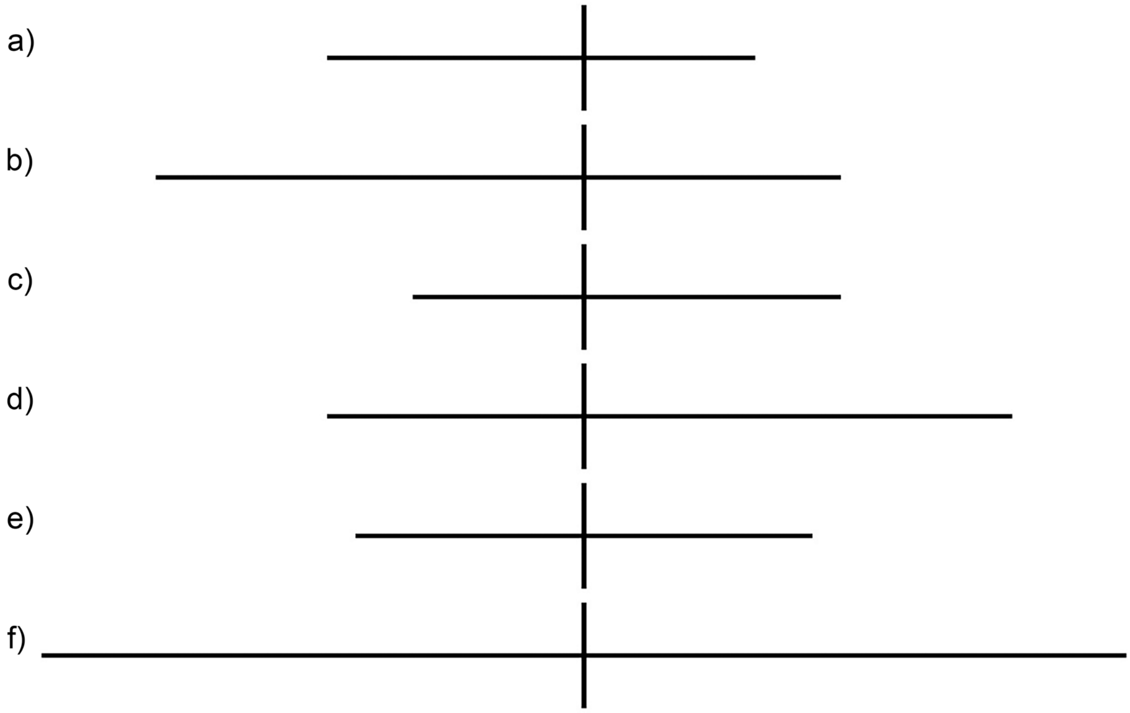

Fig. 7: Six exemplary slides of the landmark task. The set consisted of lines with longer left segments (a, b), lines with longer right segments (c, d) and lines with identical segments (Giglhuber et al., 2016).

2.6.1.2. Data analysis

As outlined before, the first part of analysis was pure evaluation of the task performance. We compared each response to the subject's baseline response on the respective slide. Errors were categorized into no-response, leftward and rightward errors. No-response was defined as silentness all but due to speech arrest or any kind of expression of disorientation and uncertainty. Unclear cases were discarded. Leftward errors occurred when the subject either underestimated the right or overestimated the left line segment. Respectively, rightward errors equaled an underestimation of the left line segment or an overestimation of the right one. In our second step of analysis we linked the errors with the stimulation sites. A cortical spot was labeled "positive" if at least one error of any kind occurred during rTMS over its position. Additionally we counted the number of effective rTMS stimulations on every site. Finally we pooled this information from all subjects. For all 104 stimulation sites we calculated the following two ratios:

- The error rate (ER) represents the number of errors per number of stimulations.
- The subject rate stands for the number of subjects in which the stimulation site was labeled "positive" out of 10 stimulated subjects.

2.6.1.3. Statistics

We presented all results as mean ± standard deviation. To compare ratios of the two hemispheres among one another we used the Mann Whitney U test, for intrahemispheric comparison the Wilcoxon matched-pairs signed rank test. By means of a Chi-square test we analyzed the category "positive" vs. "negative". A p-value <0.05 was regarded significant (GraphPad Prism 6.0, La Jolla, CA, USA).

2.6.2. Greyscales task

In our second study we applied a brightness judgment task based on the greyscales task by Mattingley et al. (Giglhuber et al., 2018; Mattingley et al., 1994).

2.6.2.1. Task design

The picture slides of this task presented pairs of horizontal rectangles. Figure 8 depicts an exemplary slide. The rectangles were placed one above another and shown on grey background. Their height came uniformly to 30 mm. The length varied in 30 mm steps from 180 to 330 mm, whereby two rectangles of a pair always equaled one another in length. Each rectangle had a black frame of 0.7 mm. The fillings depicted greyscales gradients from black to grey. The shading of two paired rectangles was mirror-reversed but identical. Our task set consisted of 12 different slides, namely six rectangle lengths per always two shading orientations. The task required on each picture a judgment on which of the two greyscales appeared darker overall. Subjects were asked to answer orally with “top” or “bottom.” As described, the two rectangles were identical, thus there was no correct answer to be made. Prior to the rTMS mapping session we performed a baseline session of 72 pictures without stimulation.

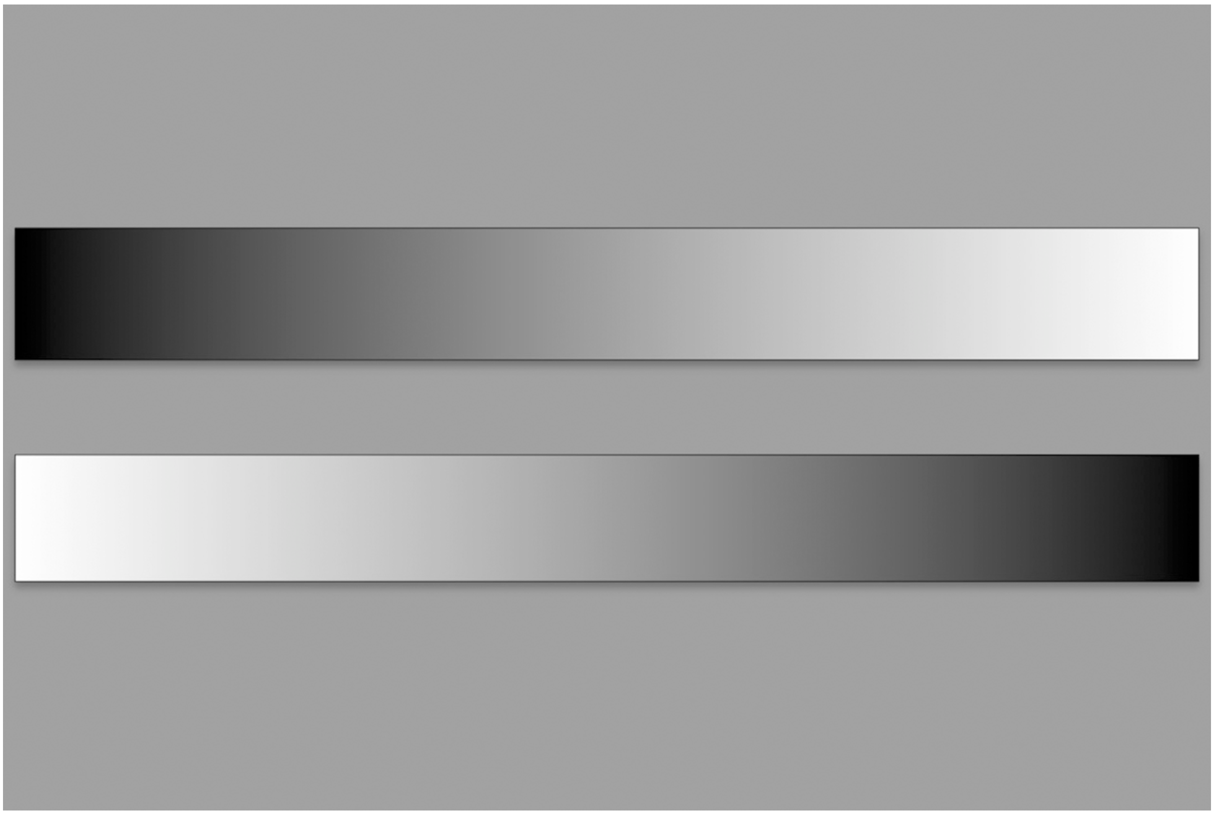

Fig. 8: Example slide of the greyscales task (Giglhuber et al., 2018).

2.6.2.2. Data analysis

The first step of analysis again concerned the subject’s task performance. We went through the video records and labeled each single response. According to which rectangle was chosen, the response was categorized as “leftward” for a chosen rectangle with darker left end or “rightward” for the rectangle with the darker end on the right. The second step meant relating the responses to the respective stimulation sites. Per spot we counted the number of leftward and rightward responses. From this we computed a score. We calculated the difference of rightward minus leftward responses and divided this by their total number. The score ranged from - 1.00 to 1.00. Moreover, on the same principle, we computed a score of the baseline performance without stimulation, the baseline score. To consider actual mapping effects, we calculated the difference of the two scores, i.e. the firstly computed minus the baseline score. This final score was documented as so-called deviation score for each stimulation site.

Additionally, we documented the particular categorical outcome, again as leftward or rightward, depending on whether the deviation score was negative or positive.

The information of all the subjects was pooled as follows:

- Per spot we calculated the number of subjects with leftward deviation scores and the mean of their scores, i.e. the mean of all leftward deviation scores.
- Per spot we calculated the number of subjects with rightward deviation scores and the mean of their scores, i.e. the mean of all rightward deviation scores.

All mean deviation scores were handled in terms of their magnitude.

2.6.2.3. Statistics

We provided all results as mean ± standard deviation and when applicable added median and range. To compare stimulations sites among themselves we made use of the Mann–Whitney U test for independent samples. For single-spot analysis, to look at the categorical outcome “leftward” vs. “rightward”, we applied the Wilcoxon matched-pairs signed rank test. Tests were regarded significant at a *p*-value <0.05 (GraphPad Prism 6.0, La Jolla, CA, USA).

3. RESULTS

3.1. Evoking visual neglect-like deficits in healthy volunteers – an investigation by repetitive navigated transcranial magnetic stimulation

In our first study we proved it feasible to elicit visual neglect by rTMS. We observed visuospatial deficits during the stimulation of the left and the right hemisphere. They corresponded to both ipsilesional and contralesional deficits. Pooled ERs were considerably small. However, we found decisive differences. We observed rightward errors significantly more often during stimulation of the right rather than the left hemisphere. The mean rightward ER for the right hemisphere was 1.6 ± 1.3 % whilst the mean rightward error rate for the left hemisphere came to 1.0 ± 1.0 % (p=0.0141). Moreover, within the left hemisphere leftward errors prevailed in comparison to rightward errors. We found a mean leftward ER of 2.0 ± 1.3 % and a mean rightward ER of 1.0 ± 1.0 % (p=0.0005).

3.2. Mapping visuospatial attention – the greyscales task in combination with repetitive navigated transcranial magnetic stimulation

Our second study approved that rTMS combined with the greyscales task and its specific characteristics and analysis is greatly useful to create cortical maps of visuospatial attention. By means of the task we found classic pseudoneglect in baseline conditions in 9 of our 10 subjects. Leftward effects also prevailed during mapping conditions. However, rightward deviations were strikingly greater in magnitude than leftward deviations (p<0.0001). Moreover the right hemisphere was far more suggestible by rTMS than the left hemisphere. Both rightward and leftward deviation scores were higher for rTMS of this brain side (p<0.0001). Referring to cortical maps, especially the found right hemispheric distributions accorded well with the already introduced model of Corbetta and Shulman (Corbetta and Shulman, 2011). Within their proclaimed dorsal network, namely at stimulation sites of superior frontal and posterior parietal areas, rTMS elicited considerable leftward deviations. rTMS within inferior frontal areas and the TPJ, according to Corbetta's ventral network, lead to significant rightward deviations.

4. DISCUSSION

4.1. rTMS-based mapping of visuospatial attention function

The aim of our two investigations was to prove the feasibility of visuospatial attention mapping by rTMS. By means of both the landmark task as well as the greyscales task we were able to elicit visual neglect-like deficits in all our subjects. More specifically we elicited contralesional and ipsilesional deficits. The kind of neglect at it depended on the combination of stimulated hemisphere and caused type of error (referring to the landmark task) or deviation score (referring to the greyscales task). Stimulation caused a virtual lesion. Classic contralesional left neglect by rTMS of the right hemisphere thus equaled either rightward errors or rightward deviation scores. Contralesional right neglect by rTMS of the left hemisphere equaled either leftward errors or leftward deviation scores. With ipsilesional neglect the situation was quite the reverse. Ipsilesional rTMS effects for the right hemisphere paralleled either leftward errors or leftward deviation scores. Ipsilesional rTMS effects for the left hemisphere paralleled either rightward errors or rightward deviation scores. By means of the neuronavigation system all these effects were related accurately to cortical stimulation sites. At least so as we know no such approach was reported before. Its usefulness for neglect research may thus be regarded as proven.

4.2. Task design and tachistoscopic testing

Both studies were conducted under equal task conditions. Both represented pilot studies. As outlined before, the landmark task was our first approach, the greyscales task a more specific follow-up.

4.2.1. Landmark task

We already commented on the ongoing discussion about task differences and neglect subforms. By means of the landmark task we decided to test visuospatial, object-centered attention in a computerized format under tachistoscopic test conditions. A similar approach was reported earlier (Fierro, 2000). By the short duration of task picture presentation we were able to prevent any eye reorienting or midpoint fixation. This increased the task sensitivity. The setup proved applicable and effective albeit the pooled error rates tended to be rather small upon both baseline and mapping terms. To further impede the conditions one could consider presenting lines with even smaller segment differences. However, we have to be conscious of our kind of cohort. All subjects were young and healthy. In such a cohort aggravated task demands may be conceivable. For clinical settings and the testing of tumor patients we would rather cast doubt on it. Concluding, the setting provided suitable results for this pilot study. Further judgments require follow studies on a greater number of test persons and also on patients.

4.2.2. Greyscales task

Our second task was equally embedded in a computerized, tachistoscopic setting. It brought along some special characteristics, though. The greyscales task is known to measure perceptual biases sensitively. It can be applied in healthy subjects and in patients. Moreover, it has been reported to unmask deficits in patients that performed perfectly well in basic clinical testing (Mattingley et al., 2004; Mattingley et al., 1994). The main advantage of the greyscales task is that it works without a right-or-wrong system. Subjects are urged to select, the selection expresses a tendency and a number of tendencies can be documented as score. This way a huge amount of data can be exploited at the final analysis. Moreover, the usability of the greyscales task is not in any way restricted by already existing deficits. As detailed above the resulting score of a stimulation site is always considered in relation to the individual baseline score. Taking that into account it becomes clear that patients with a preexisting bias may be tested with our study's setup just the same. Also the existence of pseudoneglect does not pose a problem. There are studies reporting on a decrease of pseudoneglect in old age (Benwell et al., 2014; Learmonth et al., 2017). Friedrich in contrast found pseudoneglect to be even more prominent in elderly people compared to the young (Friedrich et al., 2016). For one our study was conducted on a homogenously young cohort. But also for future approaches one has the same principle: However strong or faint, a basic bias would be represented in and minded by the baseline score. This main advantage was the foundation of our decision for the greyscales task. We fully approve our choice as well as the total construction. The combination scored with a great applicability and a high sensitivity.

4.3. Results in comparison to the current literature

We already outlined in our objectives that a comparison of the two studies' particular results was neither scheduled nor meaningful. In the following two paragraphs we will comment on our findings one by one. At large, the literature on visuospatial attention still provides a quite uneven quantity of information on the right compared to the left hemisphere. Visual neglect may be observed more frequently after damage to the right hemisphere and this may be the reason why a great many investigations rather cover this brain side (Sack, 2010). At the same time we know that severity and outcome of visual neglect after left hemispheric damage act closely identically (Suchan et al., 2012). Especially as we assume there to be a complex network including interhemispheric white matter connections, an entire examination should be regarded essential, if procurable. Bearing this in mind and as our studies' design rendered this possible, we decided to equally investigate both brain sides in large part. We did so by means of a small cohort of young and healthy volunteers. This implicated a favorable homogeneity. Especially on patient studies the observance of highly individual differences often complicated the survey of generalizable statements (Kwon et al., 2011; Pierce and Saj, 2018; Roux et al., 2011; Sacchetti et al., 2015; Shinoura et al., 2009).

4.3.1. Evoking visual neglect-like deficits in healthy volunteers – an investigation by repetitive navigated transcranial magnetic stimulation

The cohort homogeneity of our first study was ascertained by joint assessment of error and subject rates. At no stimulation site we found one single subject driving the results. Overall we observed effects during stimulation of all lobes of both hemispheres. Such general suggestibility by rTMS has been reported before (Brighina et al., 2002; Fierro, 2000). The effects corresponded either contralesional or ipsilesional neglect whereas rightward errors occurred significantly more often during stimulation of the right rather than the left hemisphere. This combination of right hemispheric stimulation or “lesioning” and rightward errors paralleled classic contralesional left neglect, as commonly known its most prevalent form of appearance (Bartolomeo et al., 2012; Bartolomeo and Seidel Malkinson, 2019; Meehan et al., 2017; Sack, 2010; Thiebaut de Schotten et al., 2011). However, we looked at both brain sides firstly with regard to the general cortical distributions and secondly to the spread of particular error types. It figures they presented with lucid regional differences. To keep on the right hemisphere best results were found in the areas of the TPJ and the middle and inferior frontal gyri. Both locations matched the idea of a ventral network as proposed by Corbetta and already detailed in the introduction section (Bartolomeo and Seidel Malkinson, 2019; Corbetta and Shulman, 2002; Corbetta and Shulman, 2011; Meehan et al., 2017). The distribution of error types within the right hemisphere was less decisive. Leftward errors rather showed a wide spread over all lobes whilst conspicuous rightward results boldly belonged to frontal areas. In 2011 Roux et al. found similar results in a patient study on DCS of the right hemisphere (Roux et al., 2011). Regarding the left hemisphere there were striking results in anterior and superior parietal areas and within inferior and superior frontal gyri. The superior (or dorsal) locations again may concord with Corbetta's dorsal circuits (Corbetta and Shulman, 2011; Meehan et al., 2017). Besides, clear similarities about the parietal locations could be found in former TMS studies (Duecker and Sack, 2014; Fierro, 2000; Salatino et al., 2014). The distribution of rightward and leftward errors turned out to be rather less striking in reference to the current literature insights. To sum up, we found some lucid characteristics of both brain sides that corresponded well with our referenced network model by Corbetta and Shulman.

4.3.2. Mapping visuospatial attention: the greyscales task in combination with repetitive navigated magnetic stimulation

Our second study dealt with data that reflected individual peculiarities quite sensitively. We observed leftward tendencies on baseline conditions in all our subjects but one. This went well in line with all recent literature on pseudoneglect (Benwell et al., 2015; Brooks et al., 2014; Cicek et al., 2009; Goedert et al., 2010; Jewell and McCourt, 2000; Loftus and Nicholls, 2012; Petitet et al., 2015; Thiebaut de Schotten et al., 2011; Varnava et al., 2013). We observed contra- and ipsilesional effects during stimulation of both hemispheres. Our findings for the right hemisphere proved especially promising as classed with the recognized network models. In greater detail, we observed striking rightward deviations around the TPJ and within the inferior frontal gyrus. They equaled contralateral left neglect and corresponded very well with a ventral network. Interestingly, within the location of a possible dorsal network, namely in superior frontal and parietal regions, we predominantly found leftward deviations that thus equaled ipsilesional deficits. Although this might not perfectly match the responsibilities Corbetta and Shulman suggested for their networks, there are numerous publications on ipsilesional neglect after damage to right hemisphere (Kwon et al., 2011; Na et al., 2000; Robertson et al., 1994; Roux et al., 2011). We even came across a study on ipsilesional right neglect in patients with left hemianopia (Chokron et al., 2018). The underlying mechanisms are far from being fully understood, yet, the roles of frontal areas as well as subcortical fiber tracts seem preferentially discussed (Bartolomeo and Seidel Malkinson, 2019; Kim et al., 1999; Sacchetti et al., 2015). To now we just may state that with these findings, we contributed to some obviously unresolved mechanisms within the otherwise highly conclusive networks. Turning to the left hemisphere, we found outstanding stimulation points at frontal and parietal regions that unfortunately could not be specifically distributed to a dorsal or ventral network. Finally, although we will not compare single results of this study to the fore one, we may say that the cortical distributions of both went well together. Particularly outlined should be the results for the right hemisphere, its TPJ and the middle frontal gyrus. Regarding clinical purposes we may conclude that the greyscales task advantageously combined easy applicability and bearable task demands. At the same time it delivered preferably sensitive results.

4.4. Limitations

Notwithstanding, we have to address a number of limitations. Both our studies were designed to be pilot approaches to generally evaluate feasibilities. We set our priority on the broad examination of the entire left and right hemisphere. Therefore we had to build on a simply actable stimulation protocol. We used a fixed mapping template. The stimulation frequency was uniformly determined to 5 Hz. The coil orientation was strictly anterior-posterior with angulation perpendicular to the scull. At all this we confirmed to the current standards of rTMS mapping. Yet, several variations of the protocol could have influenced the results (Sollmann et al., 2015b). A second important constraint of pilot studies is the usually small examination collective. Our subjects presented a very small and throughout young cohort. This afforded homogeneity. At the same time it naturally gives rise to question the generalizability of our findings. We certainly have to be aware of this limitation and consider the results proportionately. Hence we can plan and design following investigations. To agitate two more subjects, our studies did not include test-retest evaluations of positive or striking stimulation sites. Also they lacked a control group with sham stimulation to filter potential effects on the subjects' performances that were not rTMS-induced.

4.5. Future prospects

Neuroscientific investigations increasingly focus on the subcortical level. We already introduced DTI-FT as a promising method to visualize white matter pathways. DTI already has been used in basic neglect research on healthy subjects (Suchan et al., 2014). In other studies it gave information about recovery mechanisms when applied in stroke patients at intervals after the incident (Lunven et al., 2015; Umarova et al., 2017; Umarova et al., 2014). The combination of cortical mapping by rTMS and subcortical fiber tracking by DTI definitely presents a conceivable diagnostic tool for the imaging of visuospatial attention networks. For instance it may present a useful addition to standard presurgical imaging procedures. Also concerning the second big application field of TMS, therapeutics, our setup and especially the greyscales results give another point to be integrated. There are approaches to reduce visual neglect after stroke by several brain stimulation techniques (Brighina et al., 2003; Dionisio et al., 2018; Fierro et al., 2006; Jacquin-Courtois, 2015; Kashiwagi et al., 2018; Koch et al., 2012). Our protocol provides accurate and individual cortical maps that would allow targeting essential cortical sites specifically. As one last point we want to refer to the frequent discussion that rTMS may have remote effects over subcortical fiber tract connections that also may be influencing study results. To render such effects visible, mixed studies of brain stimulation plus fMRI were conducted, yet (Blankenburg et al., 2010; Leitão et al., 2015; Petitet et al., 2015; Ruff et al., 2008). Combining our rTMS protocol with fMRI would certainly be a likewise interesting approach. For one thing actual effects at the stimulation site could be visualized and confirmed. For another thing potentially remote effects could be detected and the underlying white matter connections further investigated.

5. SUMMARY

5.1. English

Visuospatial attention function and its corresponding deficits at loss issue a challenge for both researchers and clinicians. This thesis is based on two publications that investigated the cortical mapping of visuospatial attention networks in ten healthy volunteers by means of repetitive navigated transcranial magnetic stimulation (rTMS).

The first study, *Evoking visual neglect-like deficits in healthy volunteers – an investigation by repetitive navigated transcranial magnetic stimulation*, examined the combination of rTMS with a classic landmark task. Subjects were supposed to proportionally judge the two partial lengths of a bisected line. Task pictures were presented tachistoscopically. Simultaneously we conducted a cortical mapping of 52 spots within both hemispheres. Analysis picked out judgment errors, categorized them by kind of error and connected them to the corresponding stimulation site. The results of all subjects were pooled in the form of error rates. First of all, we did observe errors and thus proved it feasible to mimic visual neglect by rTMS, namely in both directions. Moreover, we learned that rightward errors, which equaled to left neglect, were more frequent for stimulation of the right rather than the left hemisphere. Within the left hemisphere the occurrence of leftward errors prevailed – again corresponding to contralateral albeit in this case right neglect. Summarizing, we could successfully present a non-invasive approach to perform an accurate cortical mapping of visuospatial attention function.

The second study, *Mapping visuospatial attention: the greyscales task in combination with repetitive navigated transcranial magnetic stimulation*, was conducted to further evaluate the usability and possible advantages of a more sophisticated task demand. Mapping was performed the same way, again under tachistoscopic conditions, only this time subjects had to perform a greyscales task. Task pictures showed vertically arranged pairs of rectangles with identical but mirror-inversed greyscales grading. Performance requirement was to report which of the two rectangles appeared darker overall. There were no right or wrong answers to be made. Depending on the side of the darker end of the chosen rectangle the response was categorized into “leftward” or “rightward”. The analysis was made of calculated scores on these two orientation tendencies. The baseline tendency showed classic pseudoneglect to the left in nine out of our ten subjects. Again, the results of all subjects during stimulation were pooled. Central findings of this study indicated that rTMS influenced the right hemisphere much more effectively than the left hemisphere. Furthermore, rightward deviation scores were strikingly greater in magnitude than it was the case for leftward deviation scores. The cortical distributions of our findings corresponded well with the current literature, especially the findings within the right brain hemisphere. In conclusion, our second approach yielded further encouraging results by means of a task that due to its way of analysis proved to be preferably sensitive for the detection of stimulation effects.

By these two studies we were able to show the feasibility and usability of rTMS for the cortical mapping of visuospatial attention. We could further broaden the applicability of this future-oriented technique and contribute to the constantly ongoing research on the mechanisms of visuospatial attention function. This holds some promising future prospects.

Applying to both studies, I participated in the decision-making on concept and design, recruited the participants, handled data acquisition and analysis, performed literature research and drafted the manuscripts.

5.2. Deutsch

Visuell-räumliche Aufmerksamkeit und die entsprechenden Defizite bei Schädigung stellen sowohl für Forscher, als auch für Kliniker eine Herausforderung dar. Die vorliegende Doktorarbeit basiert auf zwei Publikationen. Diese untersuchten an zehn gesunden Probanden die kortikale Kartierung von Netzwerken für visuell-räumliche Aufmerksamkeit mit Hilfe von repetitiver navigierter transkranieller Magnetstimulation (rTMS).

Die erste Studie, *Evoking visual neglect-like deficits in healthy volunteers – an investigation by repetitive navigated transcranial magnetic stimulation*, testete die Kombination von rTMS mit einem klassischen Landmark-Test. Die Probanden waren dazu aufgefordert, die zwei Teil-Längen einer zweigeteilten Linie im Verhältnis zu bewerten. Die Aufgaben-Bilder wurden tachistoskopisch dargestellt. Währenddessen kartierten wir 52 kortikale Stimulationspunkte auf beiden Hemisphären. Die Auswertung eruierte falsche Wertungen, kategorisierte sie nach Art des Fehlers und verknüpfte sie mit dem entsprechenden Stimulationspunkt. Die Ergebnisse aller Probanden wurden in Form von Fehlerraten zusammengefasst. Allem voran konnten wir Fehler beobachten und folglich zeigen, dass rTMS visuellen Neglect imitieren kann, und zwar in beide Richtungen. Weiterhin zeigten sich Fehler nach rechts, entsprechend einem linken Neglect, häufiger bei Stimulation der rechten Hemisphäre im Vergleich zu der linken. Innerhalb der linken Hemisphäre überwogen die Fehler nach links, wiederum entsprechend einem kontralateralen, aber in diesem Fall rechten Neglect. Zusammenfassend konnten wir erfolgreich eine nicht-invasive Methode präsentieren, um visuell-räumliche Aufmerksamkeit kortikal akkurat zu kartieren.

Die zweite Studie, *Mapping visuospatial attention: the greyscales task in combination with repetitive navigated transcranial magnetic stimulation*, diente dazu, die Anwendbarkeit und mögliche Vorteile einer anspruchsvolleren Aufgabenstellung zu testen. Während die Kartierung in identischem Ablauf und wieder unter tachistoskopischen Bedingungen erfolgte, mussten die Probanden in dieser Studie einen Greyscales-Test durchführen. Dargestellt wurden Bilder mit zwei vertikal angeordneten Rechtecken mit identischem, aber spiegelbildlichem Graustufen-Farbverlauf. Aufgabe war es, anzugeben, welches der Rechtecke insgesamt dunkler erschien. Es gab keine richtigen oder falschen Antworten. Je nachdem, welches Rechteck gewählt wurde und welches das dunkle Ende dieses Rechtecks war, wurde die Antwort als “rechtsgerichtet” oder “linksgerichtet” klassifiziert. Die Analyse erfolgte an Hand von berechneten Werten zu dieser Orientierungs-Tendenz. Die Grund-Tendenz ohne Stimulation entsprach bei neun unserer zehn Probanden einem klassischen Pseudoneglect nach links. Die Ergebnisse aller Probanden während Stimulation wurden wieder zusammengefasst. Zentrale Erkenntnis war es, dass die rechte Hemisphäre durch rTMS eindeutig effektiver beeinflusst werden konnte, als die linke Hemisphäre. Darüber hinaus fanden wir deutlich größere Tendenz-Abweichungen nach rechts, als dies für Abweichungen nach links der Fall war. Die kortikalen Zuordnungen stimmten mit Daten der aktuellen Literatur gut überein, insbesondere für die rechte Hirnhälfte. Zusammenfassend brachte unser zweiter Ansatz weitere erfreuliche Ergebnisse mit Hilfe eines Tests, der bedingt durch seine Auswertung eine besonders sensitive Fehler-Detektion bewies.

Anhand unserer Studien konnten wir zeigen, dass die kortikale Kartierung von visuell-räumlicher Aufmerksamkeit mit rTMS realisier- und nutzbar ist. Wir konnten das Anwendungsspektrum dieser vielverheißenden Methode erweitern und durften unseren Teil zu der ständig im Wandel begriffenen Forschung über die Mechanismen von visuell-räumlicher Aufmerksamkeit beitragen. Dies birgt einige vielversprechender Zukunfts-Aussichten.

Für beide Studien war ich am Entscheidungsprozess zu Konzept und Design beteiligt, rekrutierte die Probanden, erhob und analysierte die Daten, führte Literaturrecherchen durch und entwarf die Manuskripte.

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7. ABBREVIATIONS

3D	three dimensional
DCS	direct cortical stimulation
DTI	diffusion tensor imaging
DTI-FT	diffusion tensor imaging fiber tracking
EEG	electroencephalography
ER	error rate
fMRI	functional magnetic resonance imaging
MEG	magnetoencephalography
MEP	motor evoked potential
MRI	magnetic resonance imaging
RMT	resting motor threshold
rTMS	repetitive navigated transcranial magnetic stimulation
TMS	transcranial magnetic stimulation
TPJ	temporoparietal junction

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Evoking visual neglect-like deficits in healthy volunteers – an investigation by navigated repetitive transcranial magnetic stimulation
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10. APPENDIX: ORIGINAL ARTICLES AND PERMITS

10.1. Evoking visual neglect-like deficits in healthy volunteers – an investigation by repetitive navigated transcranial magnetic stimulation

Evoking visual neglect-like deficits in healthy volunteers – an investigation by repetitive navigated transcranial magnetic stimulation

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ABSTRACT

Background: In clinical practice, repetitive navigated transcranial magnetic stimulation (rTMS) is of particular interest for non-invasive mapping of cortical language areas. Yet, rTMS studies try to detect further cortical functions. Damage to the underlying network of visuospatial attention function can result in visual neglect—a severe neurological deficit and influencing factor for a significantly reduced functional outcome. This investigation aims to evaluate the use of rTMS for evoking visual neglect in healthy volunteers and the potential of specifically locating cortical areas that can be assigned for the function of visuospatial attention.

Methods: Ten healthy, right-handed subjects underwent rTMS visual neglect mapping. Repetitive trains of 5 Hz and 10 pulses were applied to 52 pre-defined cortical spots on each hemisphere; each cortical spot was stimulated 10 times. Visuospatial attention was tested time-locked to rTMS pulses by a landmark task. Task pictures were displayed tachistoscopically for 50 ms. The subjects' performance was analyzed by video, and errors were referenced to cortical spots.

Results: We observed visual neglect-like deficits during the stimulation of both hemispheres. Errors were categorized into leftward, rightward, and no response errors. Rightward errors occurred significantly more often during stimulation of the right hemisphere than during stimulation of the left hemisphere (mean rightward error rate (ER) 1.6 ± 1.3% vs. 1.0 ± 1.0%, $p=0.0141$). Within the left hemisphere, we observed predominantly leftward errors rather than rightward errors (mean leftward ER 2.0 ± 1.3% vs. rightward ER 1.0 ± 1.0%; $p=0.0005$).

Conclusion: Visual neglect can be elicited non-invasively by rTMS, and cortical areas eloquent for visuospatial attention can be detected. Yet, the correlation of this approach with clinical findings has to be shown in upcoming steps.

ABBREVIATIONS

DTI	diffusion tensor imaging
ER	error rate
FEF	frontal eye field
fMRI	functional magnetic resonance imaging
FT	fiber tracking
IPI	inter-picture-interval
MRI	magnetic resonance imaging
RMT	resting motor threshold
nTMS	navigated transcranial magnetic stimulation
rTMS	repetitive navigated transcranial magnetic stimulation
TMS	transcranial magnetic stimulation
TPJ	temporoparietal junction
SD	standard deviation
VAS	visual analogue scale
3-D	three-dimensional

Keywords: cortical mapping; landmark task; neuropsychology; tachistoscopic testing; transcranial magnetic stimulation; visual neglect

1 INTRODUCTION

Repetitive navigated transcranial magnetic stimulation (rTMS) is increasingly used for mapping of cortical functions (Hauck et al., 2015a; Krieg et al., 2015; Pascual-Leone et al., 1991; Picht et al., 2013). Researchers appreciate the combination of non-invasiveness and high spatial accuracy (Ille et al., 2015; Kim et al., 2014). As a “virtual lesion” technique, rTMS can mimic functional deficits transiently by impairing the performance during a certain task, thus detecting cortical areas that can be assigned for the certain function, e.g., language (Pascual-Leone et al., 1991). In clinical practice, it already serves as a tool for pre-surgical language mapping for neurosurgeons, and preclinical studies also investigate its use for mapping of further neuropsychological functions.

Visual neglect is a severe neurological deficit that is often observed after right-hemispheric stroke, but also described as a consequence of various other left- and right-hemispheric brain injuries, including glioma resection (Bonato, 2012; Sanai et al., 2012). There are several theories about the neuronal structures involved in visuospatial attention processing (Corbetta et al., 2005; Heilman, 1980; Kinsbourne, 1977); the latest studies give promising insights in white matter pathways (Lunven et al., 2015; Suchan et al., 2014; Umarova et al., 2014); all agree on one thing, that we are dealing with a complex network of cortical spots interacting via both intra- and inter-hemispheric subcortical structures (Bartolomeo et al., 2012; Duecker et al., 2014).

The clinical importance of this network becomes apparent from the fact that, especially in patients with chronic rather than early-recovered neglect, functional outcome and quality of life are significantly reduced (Jehkonen et al., 2000; Jehkonen et al., 2006; Katz et al., 1999). Thus, we require reliable mapping tools to understand better the anatomical correlates of visuospatial attention, potentially to find new treatment options on the one hand and to create accurate cortical maps of visual neglect-eloquent areas for resection planning prior to glioma surgery on the other hand (Corbetta et al., 2005; Fierro et al., 2006; Sack, 2010).

This study was designed to detect cortical areas in healthy volunteers that can be assigned for the function of visuospatial attention by mimicking its corresponding functional deficit: visual neglect.

Hence, this study aims to answer the following hypotheses:

1) rTMS is able to evoke visual neglect-like deficits in healthy volunteers by an adapted version of the landmark task during tachistoscopic test conditions
2) rTMS can specifically locate cortical areas enrolled in visuospatial attention processing
3) our results correspond to the current literature.

2 MATERIAL AND METHODS

2.1 Structure and definitions

In the following paragraphs we will outline study design and data collection step by step. In advance we want to define one term used to describe error occurrences: Throughout the text, “error rate” (ER) will describe the number of induced errors per number of applied rTMS pulse trains, pooled across all stimulated subjects. Further explanations are provided below.

2.2 Subjects

The study was conducted on 10 healthy subjects, 5 women and 5 men, with a median age of 24 years (range 21 to 31 years). Inclusion criteria were pure right-handedness (Edinburgh handedness inventory score >40) and age >18 years. Exclusion criteria were general MRI or TMS exclusion criteria (pacemaker, cochlear implant, deep brain stimulation) as well as previous seizures or any other neurological or neuropsychological deficits (Rossi et al., 2009).

2.3 Ethics

The local ethics committee approved our experimental protocol in accordance with the Declaration of Helsinki (registration number: 223/14). All subjects gave their written informed consent prior to the MRI examination.

2.4 MR imaging

Before rTMS mapping, the subjects underwent MR imaging by use of a 3 Tesla MRI scanner with eight-channel phased-array head coil (Achieva 3T, Philips Medical Systems, Amsterdam, The Netherlands B.V.). The scanning protocol contained a T2-weighted FLAIR sequence (TR: 12,000 ms, TE: 140 ms, voxel size: $0.9 \times 0.9 \times 4$ mm^3, acquisition time: 3 min) and a T1-weighted 3-D gradient echo sequence without intravenous contrast administration (TR: 9 ms, TE: 4 ms, 1 mm^3 isovoxel covering the whole head, acquisition time: 6 min 58 s). We then transferred the three-dimensional dataset to our rTMS system using the DICOM standard.

2.5 Navigated rTMS mapping

2.5.1 Experimental setup

The rTMS mapping was performed with a Nexstim eXimia System Version 4.3. with the NEXSPEECH® module (Nexstim Oy, Helsinki, Finland). The system operates with a stereotactic camera to link the subject's head (registered via anatomical landmarks and marked by a "tracker" headband) with the 3-D MRI dataset as an anatomical reference. Thus, while moving the stimulation coil across the head, the induced electric field inside the brain is visualized in real-time in the 3-D MRI reconstruction and we can stimulate selected brain regions accurately (Krieg et al., 2013; Picht et al., 2013; Ruohonen et al., 2010; Sollmann et al., 2014). The visuospatial task was set by use of NEXSPEECH software, providing a time-locked delivery of visual stimuli and applied rTMS pulses. Visual stimuli were presented on a 15-inch video screen; the screen was installed centrally to the subject's body midline at a viewing distance of approximately 24 inches (nose to screen). For later analysis, the subject's performance was recorded on video (Lioumis et al., 2012).

2.5.2 Mapping parameter

This approach being a pilot study to evaluate general feasibility and gain experience we required a stimulation protocol easy to handle and preferably familiar to the examiners. Thus, we adapted our protocol from reports on rTMS language mapping (Picht et al., 2013; Sollmann et al., 2015c; Tarapore et al., 2013), similar to another pilot study on calculation function by our group that has been published recently (Maurer et al., 2015). Stimulation intensity was adjusted in each subject to its individual resting motor threshold (RMT), which was determined as described earlier by various groups (Krieg et al., 2012). We determined the RMT for the right and left abductor pollicis brevis muscles reflecting the motor cortex excitability for the left and right hemisphere, respectively. According to our protocol, rTMS mapping was performed at 100% RMT. Two subjects reported significant pain, and we decreased the intensity to 80%

RMT, not to confound the subjects' task performance with discomfort (Epstein, 1996; Lioumis et al., 2012). Each rTMS stimulation train consisted of 10 pulses delivered at a repetition frequency of 5 Hz; each train thereby lasted 1800 ms. Pulse onset and appearance of the visual stimulus were triggered synchronously according to recent data on rTMS language mapping (Krieg et al., 2014; Sollmann et al., 2015b; Tarapore et al., 2013).

2.5.3 Visual stimuli

To test the subject's function of visuospatial attention, we chose a line bisection judgment task. We adapted the "landmark task" originally used in patients to measure the perceptual component of neglect (Harvey et al., 1995). Visual stimuli were designed as white background-pictures with black horizontal lines bisected by a black vertical landmark (Fig. 2). The vertical transection bar (height 29 mm, width 1 mm) was positioned middle-centered on the screen and to the subject's midline. The horizontal - left and right - line segments (width 1 mm) varied in length from 31 mm to 150 mm. Our task set consisted of 72 different pictures. In 24 pictures the line was bisected symmetrically with an equal length of the left and right segment, and in 48 pictures the line was bisected asymmetrically, to the right (with a longer left segment) or rather left (with a longer right segment). As described in previous studies, we decided to present the task pictures tachistoscopically with a display time of 50 ms (Fierro, 2000; Salatino et al., 2014). The inter-picture-interval (IPI) was set to 3000 ms; two consecutive pictures were therefore separated by a black screen for 2950 ms. The order of pictures was randomized. On each picture the subject was asked to report whether the presented line appeared to be longer left, longer right, or equal in length by naming the appropriate selection orally (Fierro, 2000). To familiarize subject and task setting, we conducted a baseline session before rTMS stimulation (Lioumis et al., 2012; Sollmann et al., 2015c). Baseline conditions equaled the outlined mapping conditions; baseline performance was recorded on video. We discarded all wrongly or hesitantly named pictures. In all cases, these were the first pictures presented; due to the short display time of 50 ms subjects needed to accommodate to situation and task set-up. We then made up a personalized task set for each volunteer for the following mapping.

2.5.4 Stimulation points and mapping procedure

Our mapping template contained 52 cortical spots per hemisphere, distributed to brain areas by use of the cortical parcellation system (CPS; Fig. 1, Table 1) (Corina et al., 2005). As reported recently, some brain regions could not be stimulated because stimulation is known to trigger unacceptable pain, i.e., the orbital part of the inferior frontal gyrus (orIFG), polar and anterior frontal regions (polFG, aSFG, aMFG), the polar temporal gyri (polTG) and the anterior middle temporal gyrus (aMTG). The inferior temporal gyrus (ITG) was not stimulated because stimulation is known not to trigger comparable effects due to increased distance to the skull and decreased stimulation intensity in the brain (Hauck et al., 2015a; Krieg et al., 2013). We anatomically identified the spots within both hemispheres in each subject's 3-D MRI reconstruction and tagged them as stimulation points prior to each volunteer's mapping. First, the baseline session was performed as mentioned above, then the mapping session was conducted as follows: Each hemisphere was stimulated twice, taking it in turns and starting with the left hemisphere; each stimulation point was stimulated 5 times, thus 10 times in total. For a maximal field induction the stimulation coil was placed tangentially to the skull in anterior-posterior field orientation (Epstein, 1996; Lioumis et al., 2012; Miranda, 2013).

2.5.5 Evaluation of discomfort

Eventually, the subject was asked to quantify discomfort and pain during rTMS stimulation. We differentiated between the temporal muscle area and all other parts of the head surface (convexity); rating was made by a visual analogue scale (VAS) from 0 to 10, with 0 representing no pain, and 10 representing maximal pain.

2.6 rTMS data analysis

rTMS data were analyzed in a two-step process (Ille et al., 2015; Lioumis et al., 2012). At first, we evaluated the video-recorded task performance blinded to stimulation sites. Each response was linked with the subject's baseline response to the respective picture. Errors were categorized as follows:

1) No-response errors: The subject did not answer at all or stated in any other way not to feel certain. No-response errors in terms of a noticeable speech arrest were discarded; vague cases were talked over with the subject and if remaining unclear discarded as well.
2) Leftward errors: The subject overestimated the left line segment or rather underestimated the right line segment.
3) Rightward errors: the subject overestimated the right line segment or rather underestimated the left line segment.

Additionally, the volunteer's face was analyzed on video to check if eye blinks, pain, or muscle stimulation impaired the result. All such errors were systematically discarded, also if co-occurring with an induced visuospatial deficit. In a second step, we related errors with stimulated cortical spots. For every spot we gathered information about the number of effective stimulations and the number of particular error types during stimulation; we computed the total number of errors (as the sum of all types of errors), and labeled the spot "positive" if at least 1 out of 10 stimulations elicited any error. We then looked at each spot from two different perspectives:

1) Number of errors per stimulation at this spot, pooled across all subjects (error rate (ER) = number of errors per number of stimulations)
2) Number of subjects, for which this spot is labeled "positive" (subject rate = number of positive subjects out of 10 stimulated subjects).

2.7 Statistics

Results are presented as mean ± standard deviation (SD). We compared the ER of both hemispheres by use of the Mann-Whitney U test and ER within one hemisphere by use of the Wilcoxon matched-pairs signed rank test. To analyze the categorical outcome of “positive” spots, we performed a Chi-square test. For all tests a p-value <0.05 was considered significant (GraphPad Prism 6.0, La Jolla, CA, USA).

3 RESULTS

3.1 Mapping characteristics

We determined a mean RMT of 34.9 ± 8.9% maximal stimulator output for the left hemisphere and of 34.5 ± 8.2% for the right hemisphere (p=0.9274; Table 2). Due to reported pain, we reduced the stimulation intensity after RMT determination in two cases (marked with an asterisk). Yet, the electric field strength on cortical level was higher than 55 V/m at all times and we did not observe any effect on error occurrence or frequency in these subjects compared to the whole collective as observed in previously (Picht et al., 2013). All subjects tolerated the mapping well; mean discomfort was comparable for both hemispheres. During baseline testing 94.3 ± 4.1% of the pictures were answered correctly, and the individual mapping task set consisted of 68 pictures on average. The number of baseline errors did not correlate to the number of errors during mapping conditions.

3.2 Sum of errors

First, we looked at the error category “sum of errors.” It contains all errors in summary without regard to the particular type of error.

3.2.1 Comparison of the two hemispheres

Error occurrence for the two hemispheres was comparable (p=0.2314). Pooled across all subjects, 5122 stimulations of the left hemisphere could elicit 163 errors, equivalent to a mean total ER of 3.2 ± 1.6%. Concerning the right hemisphere, we observed 182 errors during 5126 stimulations (ER of 3.6 ± 1.7%). Subject rates per cortical spot ranged from 0 to 6 positive out of 10 stimulated subjects within the left hemisphere and from 0 to 5 within the right hemisphere (p=0.6445; Table 3 & 4).

3.2.2 Left hemisphere

Referenced to cortical spots, we observed a mean total ER (pooled across all subjects) between 0% and 7%. Best ER were obtained for the aSMG (spot no. 32) and the dLOG (spot no. 49), for the SPL (spot no. 48) and for the vPrG (spot no. 23) (Fig. 3a, Online Resource 1). Subject rates are presented separately (Fig. 3c, Online Resource 1). The most convenient co-occurrence of a high ER on average and a high subject rate (i.e., a high number of subjects contributing to the error count) was observed for cortical spots within the aSMG and the dLOG (Fig. 3a & 3c).

3.2.3 Right hemisphere

Mean total ER ranged from 0% to 8%. The highest rates (pooled across all subjects) occurred within middle frontal and pre-central gyri (spots no. 13, 17, and 21), within the opIFG (spot no. 10), the pMTG (spot no. 43), and the polLOG (spot no. 51) (Fig. 3b, Online Resource 2). Subject rates are presented respectively (Fig. 3d, Online Resource 2), and they coincide best with high ER spots in the frontal lobe.

3.3 Distribution of leftward and rightward errors

To differ between leftward and rightward attention processing, we looked at the particular types of error. Particular ER tend to be relatively small; however, some differences show statistical significance.

3.3.1 Comparison of the two hemispheres

We observed left- and rightward deficits during the stimulation of both hemispheres. The number of leftward errors was comparable for the two hemispheres (p=0.3877; Fig. 4a & 4c, Table 3 & 4). Pooled across all subjects, we obtained a mean leftward ER of 2.0 ± 1.3% for the left hemisphere and a mean leftward ER of 1.7 ± 1.3% for the right hemisphere (Table 3 & 4). Subject rates for leftward errors varied for cortical spots of both hemispheres comparably (p=0.1292; Fig. 4c & 4d, Table 3 & 4). Rightward errors occurred significantly more often during stimulation of the right hemisphere than during stimulation of the left hemisphere (ER 1.6 ± 1.3% vs. 1.0 ± 1.0%, p=0.0141; Fig. 5a & 5b, Table 3 & 4). Yet, subject rates for rightward errors were comparable between both hemispheres (p=0.5034; Fig. 5c & 5d, Table 3 & 4).

3.3.2 Left hemisphere

After stimulation of the left hemisphere, we observed predominantly leftward errors (p=0.0005; Fig. 6a, Table 3, Online Resource 1). In addition, some cortical spots presented higher rightward ER, especially in anterior parietal regions (spots no. 32, 33, 36, 40, and 44; Fig. 5a & 6a).

3.3.3 Right hemisphere

Stimulation of the right hemisphere elicited leftward and rightward errors to a similar extent (p=0.6836; Fig. 6b, Table 4, Online Resource 2). ER of both types varied from 0% to 5%. Although not statistically significant, we observed a noticeable trend of rightward errors being cumulatively distributed to the frontal lobe (Fig. 5b & 6b).

4 DISCUSSION

4.1 nTMS-based mapping of visuospatial attention function

The first goal of this study was to show that rTMS can mimic visual neglect in healthy volunteers (Duecker et al., 2014; Fierro, 2000; Sack, 2010); we successfully evoked visual neglect-like deficits in all examined subjects. The observed effects equate contralesional, or rather ipsilesional, visual neglect depending on the combination of stimulated (i.e., thus virtually lesioned) hemisphere and elicited type of error. Leftward errors (equal to right-sided visuospatial attention deficits) during stimulation of the left hemisphere correspond to classical contralesional visual neglect, as do rightward errors (or left-sided deficits) for stimulation of the right hemisphere. Leftward errors during stimulation of the right hemisphere and rightward errors during stimulation of the left hemisphere, on the other hand, are in line with ipsilesional visual neglect. In this study, rTMS could imitate contralesional and ipsilesional visual neglect (Figs. 4 & 5, Tables 3 & 4) and we were able to link the effects accurately to cortical areas by means of the neuronavigation system which is—at least to our knowledge—the first time to be reported.

4.2 Landmark task design and tachistoscopic testing

In recent years, neuroscientists entered into a discussion about the term of visuospatial attention and neglect (Bartolomeo et al., 2007; Corbetta et al., 2011; de Haan et al., 2012; Karnath et al., 2012). They require the separation of particular components of attention processing (spatial vs. non-spatial, goal directed vs. stimulus driven, subject centered vs. object centered, etc.) and call on researchers to distinguish between tasks demanding these components to a different extent. Besides, in a review on visuospatial tasks for diagnosing visual neglect patients, Bonato et al. discusses a couple of compensation mechanisms (fixation, reorienting, etc.) masking existent deficits; they consequently propose the construction of tasks more demanding and sensitive than paper-and-pencil-tasks (Bonato, 2012). In this study, we therefore tested visuospatial, object-centered attention processing by embedding an adapted version of the landmark task into a tachistoscopic test setting, as already used before (Fierro, 2000). The short display time of 50 ms prevents eye scanning and fixation, thus increasing sensitivity. Generally, we can rate our setup as feasible and effective. However, ER during baseline and mapping conditions were considerably small; hence, one should consider increasing difficulty by minimizing the differences between left and right line segments. At the same time, we should keep in mind that this study examined a cohort of young and healthy subjects; a patient study might not be feasible at a higher difficulty level, which is what we are basically aiming for. The chosen combination provided an adequate visuospatial task design for this study and made it possible to sensitively map visuospatial object-centered attention.

4.3 Results in comparison to the current literature

There are several theories about the functional mechanisms of visuospatial attention processing. Kinsbourne (1977) and Heilman (1980) were the first to outline the role of parietal regions and interhemispheric differences and interactions; over time, more and more studies put frontal and temporal regions into play: Corbetta and Shulman (2002, 2011) concluded a dynamic model of frontoparietal intrahemispheric circuits. They distinguished between a dorsal network including superior and posterior parietal and superior frontal regions (represented in both hemispheres to a similar extent) and a ventral network including the temporoparietal junction (TPJ) and inferior frontal regions (represented dominantly within the right hemisphere).

Literature on the hemispheric asymmetries is very rarely balanced; most studies on visuospatial attention focus on the right hemisphere (Sack, 2010). The prevalence of visual neglect might be higher after damage to the right rather than the left hemisphere, but the severity after left hemispheric damage shows comparable sequelae (Suchan et al., 2012). To paint a total picture of the underlying mechanisms, though, it is crucial to examine both hemispheres in a comparable way. Besides, apparent from case reports on visual neglect in its diverse shapes and coherences, we have to assume that the network shows highly individual differences (Kwon et al., 2011; Sacchetti et al., 2015; Shinoura et al., 2009). This study included a considerably homogenous cohort with no participants driving the results; hence we could show good agreement in particular regions. In the following paragraphs, we will discuss these findings in relation to the current literature.

4.3.1 General error occurrence and cortical distribution

In contrast to other studies, we tested cortical spots of the whole left and right hemisphere (Fig. 1), and observed effects during stimulation over all lobes (Fig. 3) (Brighina et al., 2002; Fierro, 2000). Between both hemispheres, we found regional differences. Within the left hemisphere, we especially want to point to anterior parietal spots (aSMG) and more posterior parietal or rather occipital spots of the SPG and the dLOG (Figs. 3a & 3c, Table 3). The role of parietal spots corresponds well with previous (non-navigated) TMS studies (Duecker et al., 2014; Fierro, 2000; Salatino et al., 2014), and with the original theories in general, as described above (Heilman, 1980; Kinsbourne, 1977). Frontal positive spots were observed in the SFG, IFG, and vPrG (Figs. 3a & 3c, Table 3). Referring to Corbetta superior spots within the human frontal eye field (FEF) might be part of a dorsal network (Corbetta et al., 2002).

Within the right hemisphere, parietal spots were slightly more common in superior and middle parietal regions; i.e. the dorsal parts of the anG and the aSMG, as well as the mPoG (Fig. 3b & 3d, Table 4). Additionally, one occipital spot showed an unexpected high ER (pooled across all subjects), which might be explained as a direct effect on the visual cortex. Particularly striking were posterior temporal spots of the pSTG and pMTG and frontal spots of the MFG, the mPrG, and the opIFG (Figs. 3b & 3d). Again referring to Corbetta, these regions accord especially well with their proposed right-lateralized ventral network, including right TPJ and right ventral frontal areas (Corbetta et al., 2002; Corbetta et al., 2011).

4.3.2 Distribution of leftward and rightward errors

Overall, reports on ipsilesional neglect are less common than those on classical contralesional neglect. In this study, we were able to mimic both types of attention shift by stimulation of both hemispheres (Fig. 6, Tables 3 & 4); and yet, rightward errors (or left-sided neglect) occurred significantly more often during stimulation of the right hemisphere, according to a contralesional neglect (Figs. 5b & 5d), than during stimulation of the left hemisphere (that would parallel ipsilesional neglect, Figs. 5a & 5c).

The observed rightward errors within the left hemisphere (corr. to ipsilesional neglect) were mainly distributed to anterior parietal regions (Figs. 5a & 5c); interestingly, Salatino et al. found the same in a TMS study on parietal hot spots (Salatino et al., 2014). Apart from that, during stimulation of the left hemisphere, we elicited primarily leftward errors and thus contralesional neglect (Figs. 4a & 4c, Fig. 6a, Table 3), well in accordance with all major theories (Corbetta et al., 2002; Heilman, 1980; Kinsbourne, 1977).

For the right hemisphere, it was more difficult to differentiate between higher leftward or rather rightward error occurrences (Fig. 6b, Table 4). Generally, we observed both, a finding that Roux et al. (2011) also confirmed in a patient study by direct cortical stimulation. However, rightward errors (corr. to contralesional neglect) had a particular share in ventral frontal regions (Figs. 5b & 5d, Fig. 6b), while leftward errors (corr. to ipsilesional neglect) were spread over all lobes (Figs. 4b & 4d, Fig. 6b).

4.4 Limitations

Despite these encouraging results and the accordance to current literature, we should also consider limitations of this study. First of all, this study was designed as a pilot study to evaluate general feasibility. With our main focus on the wide-ranged examination of both hemispheres and the analysis of summary data, we had to simplify our stimulation protocol and accept a number of basic limitations. The use of a fixed mapping template and the strictly anterior-posterior coil orientation need to be particularly mentioned. As confirmed by Sollmann et al., variations in stimulation site or coil angulation certainly could have changed our results; yet, anterior-posterior orientation is the current standard for rTMS examinations since it has shown reliable results in navigated and non-navigated rTMS studies on language, neglect and calculation function (Sollmann et al., 2015b). In addition, we had to reduce the stimulation intensity in two of our subjects. Yet, the electric field strength on cortical level was above 55 V/m at all times, which is known to be sufficiently effective in rTMS language mapping (Picht et al., 2013). Accordingly we did not find any effect on mapping performance and error occurrence in these subjects compared to the other subjects of the cohort.

One could question the significance of our results in respect to a rather small and obviously young cohort and small ER. A low mean age minimizes the generalizability without question; the examination of a larger diverse collective would be appropriate to investigate the general applicability. Yet, all our subjects were healthy, without any medication, and without any neurological pathology (e.g. subcortical ischemic changes), and thus beneficially homogenous. Certainly, there is a discrepancy between the assumption of highly individual distribution of cortical networks (and their suggestibility) and the analysis of individual data in summary. Furthermore, our stimulation protocol did not include any specific test-retest evaluation of positive spots. However, we observed good accordance of ER and subject rates in particular regions. With a number of 10 subjects, this study took a first step of evaluation. So, we should consider the general results with this background, and we should pay special attention to the significant ones.

As one final crucial point, we want to address the missing controls. We cannot answer if any errors were due to other effects than the local disturbance of neuronal tissue by rTMS; for example, impaired concentration, eye movements, etc. To filter these unintended effects, a control trial by sham stimulation or inclusion of an eye tracking device should be considered in future studies. Furthermore, some studies raise the issue whether rTMS also has remote effects on functional networks; i.e. cortical structures that are connected to the site of stimulation via subcortical fiber tracts. Better understanding of these interactions might explain—among others—the discrepancy between leftward and rightward attention processing within one hemisphere. For example, combined fMRI/TMS studies allow the visualization of local and distal rTMS effects by concurrent use of fMRI, a design that has already been used before (Ricci et al., 2012; Ruff et al., 2008).

4.5 Future implications and challenges

This study may be considered a pilot study for further research. For example, it would be interesting to design a comparative study with different stimulation frequencies to further analyze inhibiting vs. exciting rTMS effects (Epstein, 1996; Hauck et al., 2015b; Miranda, 2013). Apart from that, investigations on visuospatial attention and visual neglect increasingly focus on subcortical network components; i.e., intra- and inter-hemispheric white matter fiber tracts. Diffusion tensor imaging (DTI) affords an opportunity to visualize changes of these network structures in patients over the course of post-stroke recovery or chronification (Lunven et al., 2015; Umarova et al., 2014). On the other hand, DTI fiber tracking (DTI FT) in healthy subjects can visualize regular connections and interactions (Suchan et al., 2014). A promising outlook for future analysis afford latest approaches in nTMS-based DTI FT (Sollmann et al., 2015a); the idea here is to use nTMS-mapped cortical spots as specific origins for the visualization of fiber tracts. However, apart from basic research, rTMS mapping of visuospatial attention may also have clinical benefits, such as accurate preoperative cortical maps in brain tumor patients undergoing neurosurgical resection. Additionally, several studies already successfully used therapeutic rTMS to reduce visual neglect in stroke patients (Brighina et al., 2003; Fierro et al., 2006; Koch et al., 2012). Corbetta et al. (2005) described neglect as the combination of "structural changes at the locus of injury" and supplementary "physiological changes in distant but functionally related brain areas"; the aim of rehabilitation treatment, therefore, is a rebalancing of the partially damaged network. Previous approaches broadly targeted the parietal cortex. rTMS mapping could provide more accurate cortical maps and thus specific sites for therapeutic rTMS application.

CONCLUSIONS

To finally answer our hypotheses, we may say that rTMS is a feasible tool to evoke visual neglect-like deficits in healthy volunteers. Based on our task setting, we could specifically locate cortical components of the visuospatial attention network, and our results accord well to the current scientific literature.

CONFLICT OF INTEREST

SK is a consultant for BrainLab AG (Feldkirchen, Germany). Yet, the study was completely financed by institutional grants from the Department of Neurosurgery and the Section of Neuroradiology, and all authors declare to have no conflict of interest affecting this study, nor the materials or methods used, nor the findings specified in this paper.

INFORMED CONSENT

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, and the applicable revisions at the time of the investigation. Informed consent was obtained from all patients for being included in the study.

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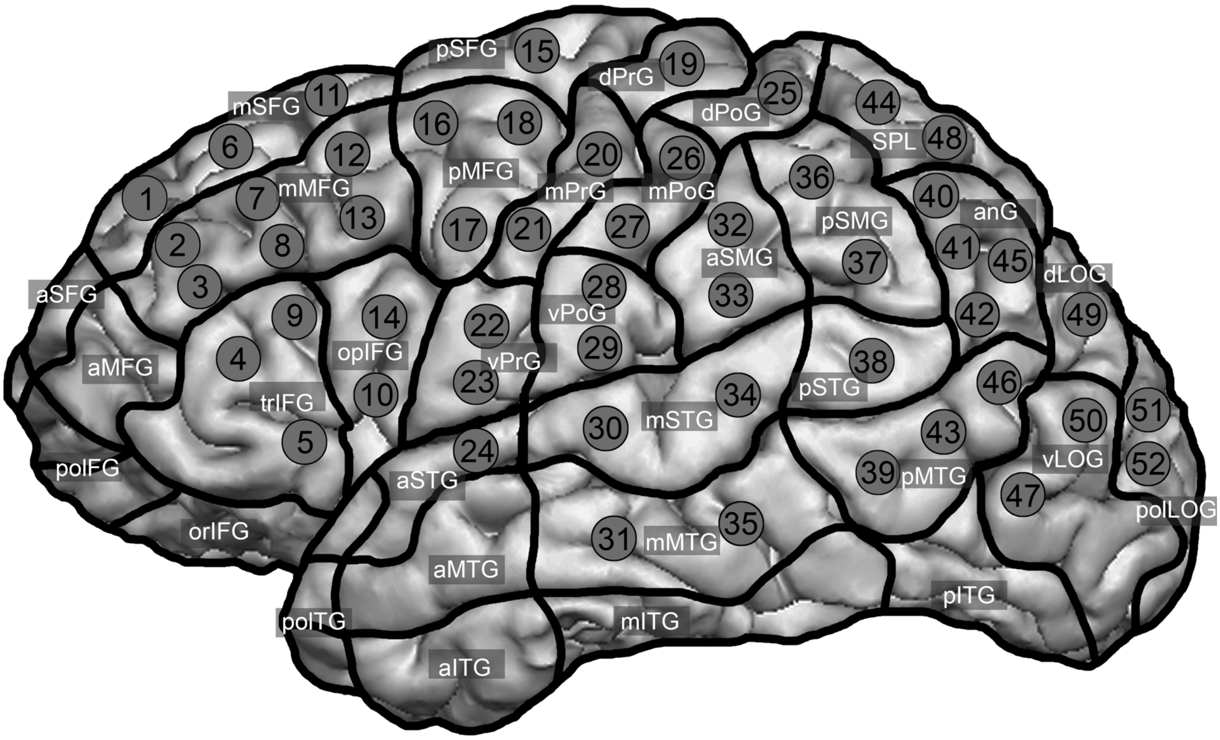
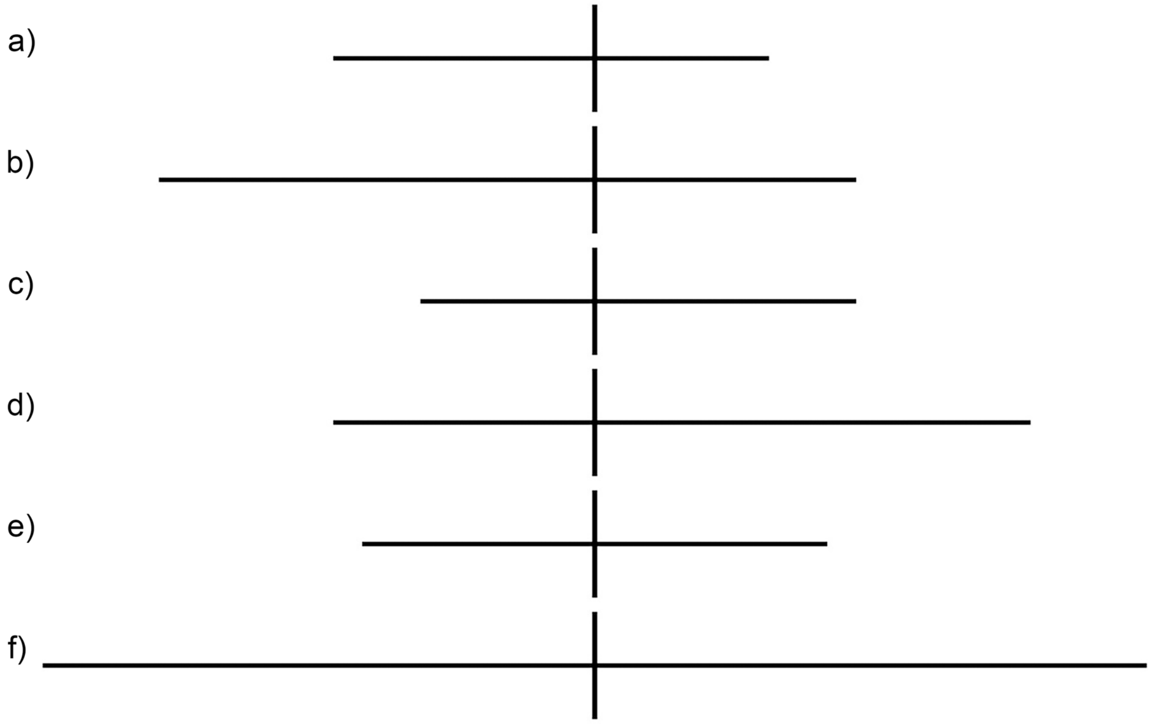
FIGURES

Figure 1: Stimulated cortical spots



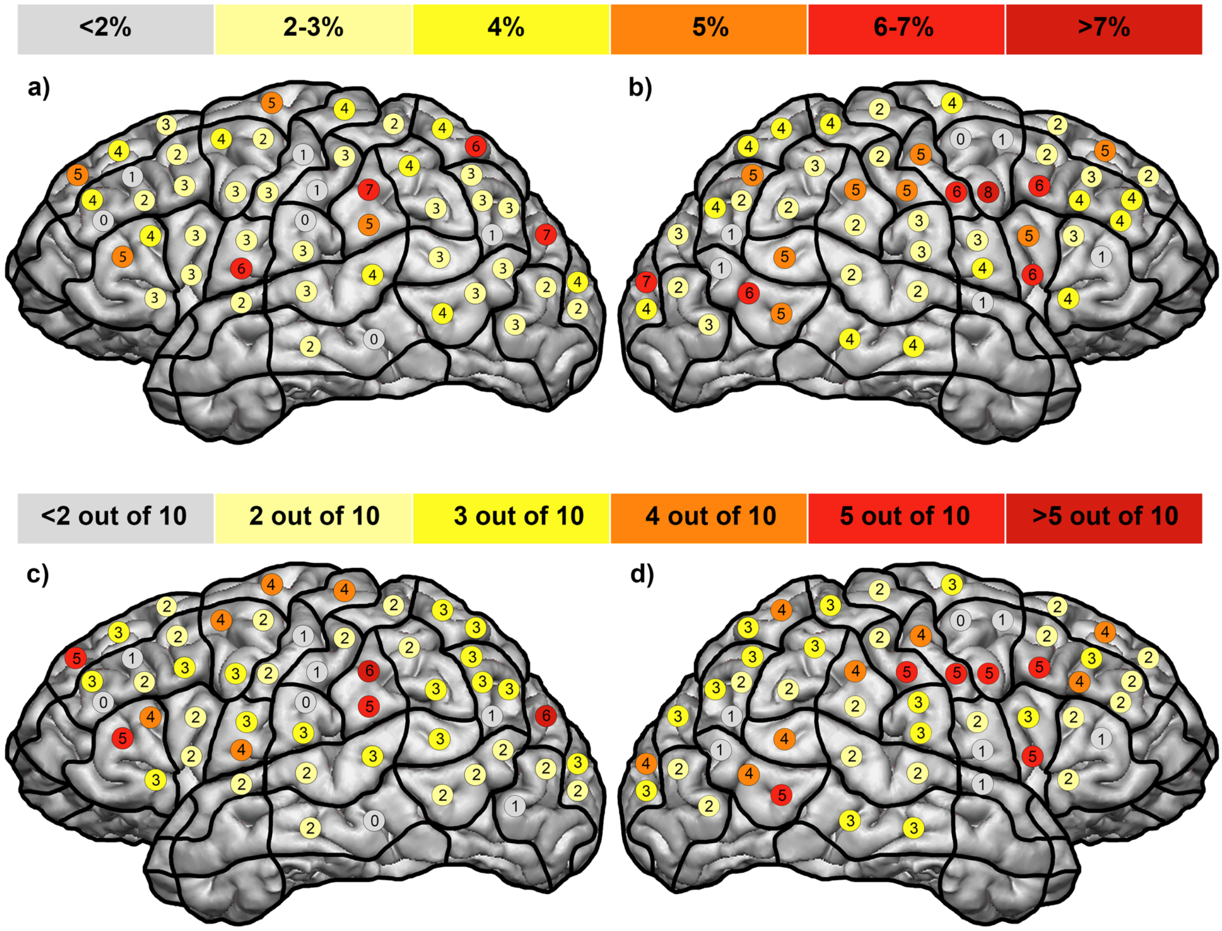
Cortical spots were distributed to brain areas by use of the cortical parcellation system (Table 1; Corina et al., 2005) and thus providing a mapping template.

Figure 2: Sample pictures from the landmark task



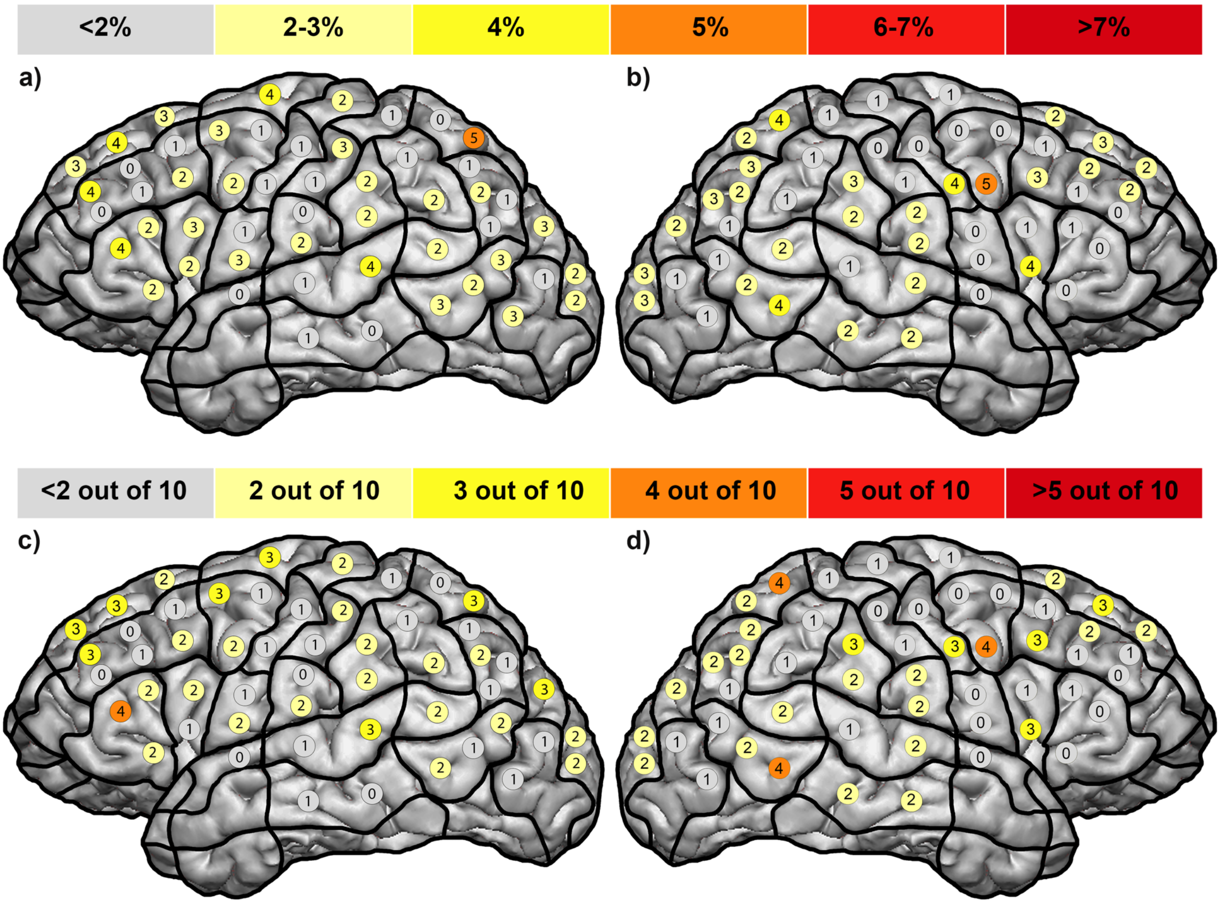
Six sample pictures from the landmark task. On each picture, the subject was asked to report whether the presented line appeared to be longer left (a, b), longer right (c, d), or equal in length (e, f).

Figure 3: Sum of errors



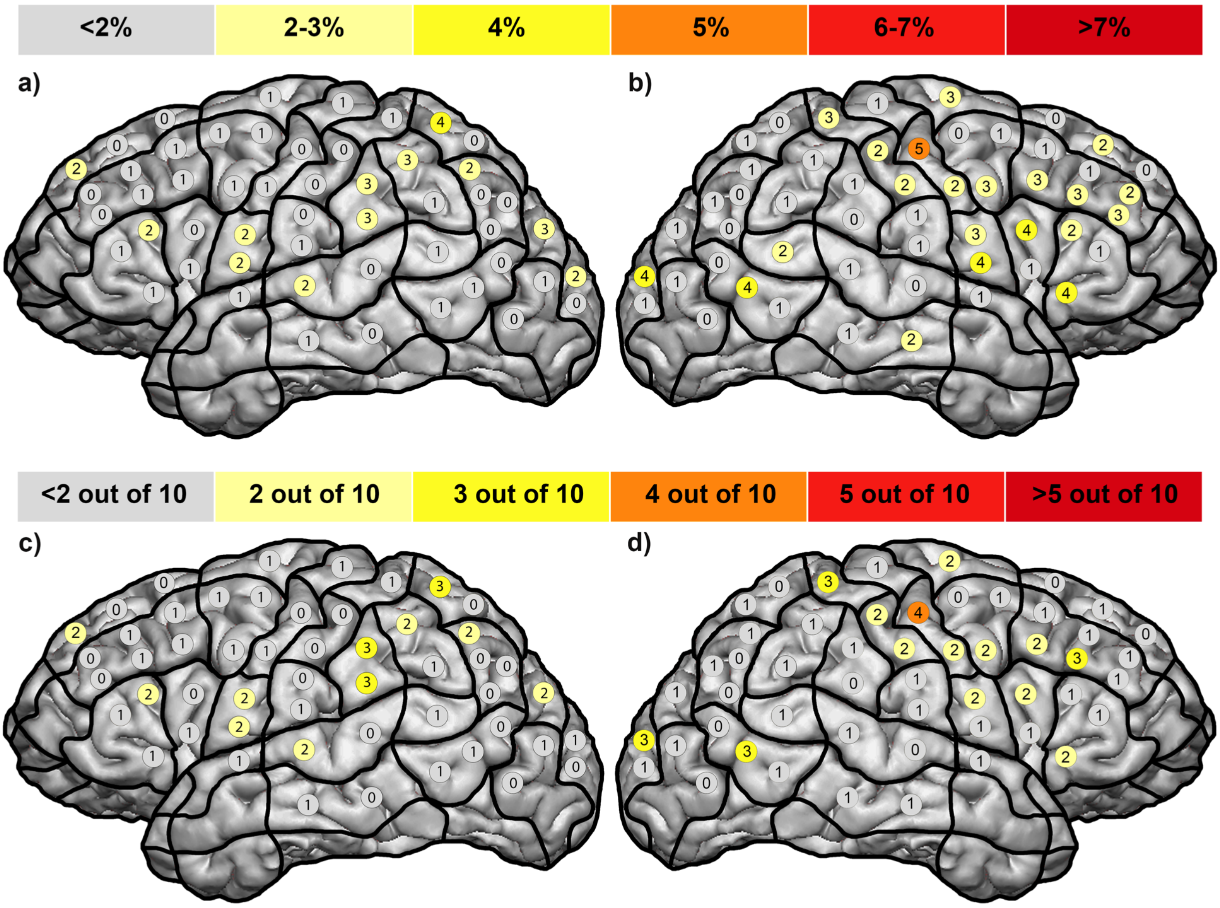
This figure illustrates the distribution of error rates per stimulated cortical spot (on average, pooled across all subjects) for the left (a) and the right hemisphere (b). Respective subject rates (number of positive subjects out of 10 stimulated subjects) are presented separately, for the left (c) and the right hemisphere (d).

Figure 4: Leftward errors



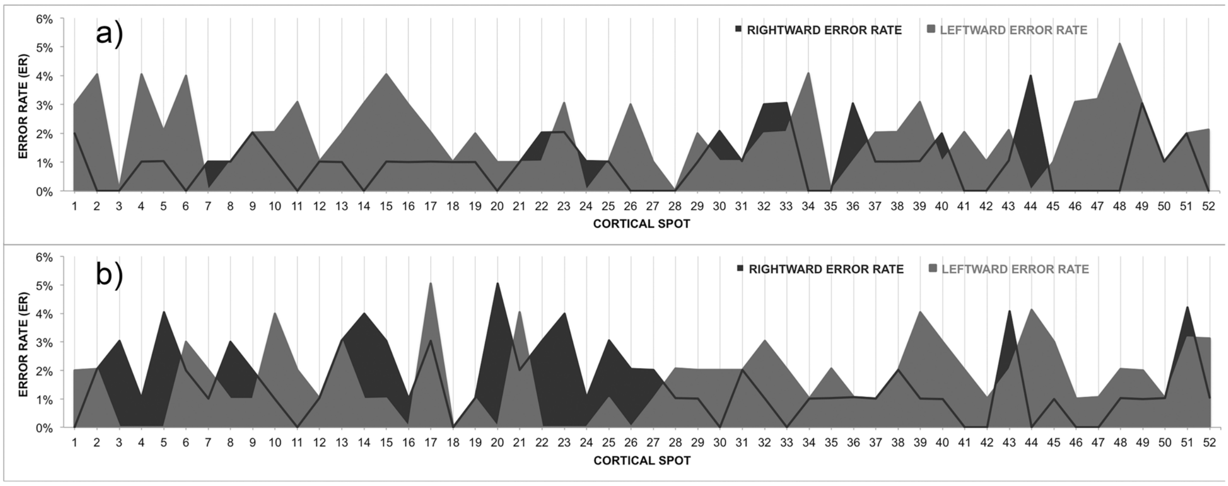
Distribution of leftward error rates per cortical spot (on average, pooled across all subjects) within the left (a) and the right hemisphere (b). Respective subject rates (number of positive subjects out of 10 stimulated subjects) are presented separately, for the left (c) and the right hemisphere (d).

Figure 5: Rightward errors



Distribution of rightward error rates per cortical spot (on average, pooled across all subjects) within the left (a) and the right hemisphere (b). Respective subject rates (number of positive subjects out of 10 stimulated subjects) are presented separately, for the left (c) and the right hemisphere (d).

Figure 6: Comparison of leftward and rightward errors



This figure compares leftward and rightward error rates per cortical spot (on average, pooled across all subjects) within the left (a) and the right hemisphere (b).

TABLES

Table 1: Anatomical names and abbreviations of the cortical parcellation system

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

Anatomical names and abbreviations of the cortical parcellation system as used for anatomical description of the stimulated cortical areas and as outlined in Figure 1 (Corina et al., 2005).

Table 2: Subject-related characteristics and mapping parameter

Subject	RMT (% stimulator output)		Pain Temporal (VAS)		Pain Convexity (VAS)		Correct baseline pictures (out of 72 pictures, in %)
	Left hemisphere	Right hemisphere	Left hemisphere	Right hemisphere	Left hemisphere	Right hemisphere	
1	45*	42*	5	3	3	2	88.9
2	26	27	2	2	1	1	98.6
3	32	31	5	5	1	1	97.2
4	44	41	4	4	1	1	93.1
5	36	35	6	6	1	1	95.8
6	28	26	2	2	0	0	86.1
7	51*	52*	3	3	1	1	95.8
8	33	32	4	6	2	2	94.4
9	28	28	4	3	3	1	98.6
10	26	31	7	7	4	4	94.4
mean	34.9	34.5	4.2	4.1	1.7	1.4	94.3
SD	8.9	8.2	1.6	1.8	1.3	1.1	4.1
MIN	26	26	2	2	0	0	86.1
MAX	51	52	7	7	4	4	98.6
	p = 0.9274		p = 0.8686		p = 0.6431		-

Mapping characteristics per subject. Resting motor threshold (RMT) as % stimulator output, in two subjects (*) we reduced stimulation intensity due to reported pain. The pain score was used according to the visual analogue scale (VAS). Correct baseline pictures as % of all 72 pictures.

Table 3: Summary of errors induced by rTMS of the left hemisphere

	no response error		leftward error		rightward error		sum of errors	
	error rate	subject rate	error rate	subject rate	error rate	subject rate	error rate	subject rate
mean	0.2%	0/10	2.0%	2/10	1.0%	1/10	3.2%	3/10
SD	0.5%	0/10	1.3%	1/10	1.0%	1/10	1.6%	1/10
median	0.0%	0/10	2.0%	2/10	1.0%	1/10	3.1%	3/10
MIN	0.0%	0/10	0.0%	0/10	0.0%	0/10	0.0%	0/10
MAX	2.0%	2/10	5.1%	4/10	4.0%	3/10	7.1%	6/10

Average data for stimulation of the left hemisphere. Error rates (on average, pooled across all subjects) and subject rates (number of positive subjects out of 10 stimulated subjects). We defined four categories: no response error, leftward error, rightward error and sum of errors. Additional data (distribution per cortical spots) is given in Online Resource 1.

Table 4: Summary of errors induced by rTMS of the right hemisphere

	no response error		leftward error		rightward error		sum of errors	
	error rate	subject rate	error rate	subject rate	error rate	subject rate	error rate	subject rate
mean	0.2%	0/10	1.7%	2/10	1.6%	1/10	3.6%	3/10
SD	0.5%	1/10	1.3%	1/10	1.3%	1/10	1.7%	1/10
median	0.0%	0/10	2.0%	2/10	1.0%	1/10	4.0%	3/10
MIN	0.0%	0/10	0.0%	0/10	0.0%	0/10	0.0%	0/10
MAX	2.1%	2/10	5.1%	4/10	5.1%	4/10	8.1%	5/10

Average data for stimulation of the right hemisphere. Error rates (on average, pooled across all subjects) and subject rates (number of positive subjects out of 10 stimulated subjects). We defined four categories: no response error, leftward error, rightward error and sum of errors. Additional data (distribution per cortical spots) is given in Online Resource 2.

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10.2. Mapping visuospatial attention – the greyscales task in combination with repetitive navigated transcranial magnetic stimulation

Mapping visuospatial attention – the greyscales task in combination with repetitive navigated transcranial magnetic stimulation

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ABSTRACT

Background: Visuospatial attention is executed by the frontoparietal cortical areas of the brain. Damage to these areas can result in visual neglect. We therefore aimed to assess a combination of the greyscales task and repetitive navigated transcranial magnetic stimulation (rTMS) to identify cortical regions involved in visuospatial attention processes. This pilot study was designed to evaluate an approach in a cohort of healthy volunteers, with the future aim of using this technique to map brain tumor patients before surgery. Ten healthy, right-handed subjects underwent rTMS mapping of 52 cortical spots in both hemispheres. The greyscales task was presented tachistoscopically and was time-locked to rTMS pulses. The task pictures showed pairs of horizontal rectangles shaded continuously from black at one end to white at the other, mirror-reversed. On each picture the subject was asked to report which of the two greyscales appeared darker overall. The responses were categorized into "leftward" and "rightward," depending on whether the subject had chosen the rectangle with the darker end on the left or the right. rTMS applied to cortical areas involved in visuospatial attention is supposed to affect lateral shifts in spatial bias. These shifts result in an altered performance on the greyscales task compared to the baseline performance without rTMS stimulation.

Results: In baseline conditions, 9/10 subjects showed classic pseudoneglect to the left. Leftward effects also occurred more often in mapping conditions. Yet, calculated rightward deviations were strikingly greater in magnitude ($p < 0.0001$). Overall, the right hemisphere was found to be more suggestible than the left hemisphere. Both rightward and leftward deviation scores were higher for the rTMS of this brain side ($p < 0.0001$). Right hemispheric distributions accord well with current models of visuospatial attention [1]. We observed leftward deviations triggered by rTMS within superior frontal and posterior parietal areas and rightward deviations within inferior frontal areas and the temporoparietal junction (TPJ).

Conclusion: The greyscales task, in combination with rTMS, yields encouraging results in the examination of the visuospatial attention function. Future clinical implications should be evaluated.

Keywords: cortical mapping; greyscales task; neglect; repetitive navigated transcranial magnetic stimulation; tachistoscopic testing; visuospatial attention

1. BACKGROUND

Visuospatial attention is processed in particular brain areas and fiber tract connections [2, 3]. The complexity of interactions becomes apparent by regarding the corresponding pathology at malfunction: visual neglect. Visual neglect describes a neurological syndrome of various forms, degrees, and recovery potential, accompanied by a significantly reduced functional outcome [4-6]. Classically observed as a consequence of right hemispheric parietal lesions, it has also been reported after left hemispheric, frontal, temporal, subcortical, and combined brain lesions [7, 8]. Research on detecting and understanding the underlying mechanisms is essential. In tumor patients, mapping prior to resection may prevent functional deficits [9, 10]. In stroke patients, mapping and timely counteraction may prevent chronification [1, 11-13].

To learn more about the visuospatial attention function, it proved insightful to study the conditions of healthy adults. As frequently reported, and also meta-analyzed by Jewell and McCourt in 2000, neurologically healthy individuals show slight but significant leftward errors in line bisection tasks [14-19]. Bowers and Heilman described this phenomenon first, calling it “pseudoneglect” [20]. Common models ascribe this observation to a right-hemispheric dominance in spatial attention processing. Imaging studies show preferential activity of the right hemisphere during visuospatial task performance [16, 21]. Other projects have examined the effect of inactivating the right hemisphere and have reported both activity shifts to the left hemisphere and a resultantly reduced leftward bias [14, 22, 23]. In 2011, Thiebaut de Schotten et al. confirmed anatomical correlates. They were able to link pseudoneglect to a larger network of frontoparietal fiber tracts within the right hemisphere compared to the left hemisphere [24]. Conclusively, Varnava et al. studied the predictability of visuospatial deficits depending on the extent and direction of pseudoneglect in the initial state. Reasoning from their findings, pseudoneglect and neglect originate from common or at least coupled mechanisms [25].

Conventional neglect screening in patients is usually undertaken using paper-and-pencil tests (e.g., line bisection). However, to measure biases in perceptual attention sensitively, task and setting must be selected appropriately [26]. As for measuring pseudoneglect in healthy volunteers, the greyscales task by Mattingley et al. consistently obtained promising results. First describing the test in 1994, they proved its sensitivity in several studies and developed an electronic version [27-30]. The task consists of tachistoscopic forced-choice decisions on the luminance of two greyscales. Analysis results in a score reflecting the spatial bias. The score ranges from -1.00, reflecting a maximal leftward bias, to 1.00, for the right side, respectively.

Repetitive navigated transcranial magnetic stimulation (rTMS) affords an opportunity to accurately and non-invasively detect cortical areas. rTMS pulses applied to an eloquent cortical spot effect a so-called virtual lesion and thus temporary inactivation. As a result, we can observe performance changes on concurrently conducted neuropsychological tasks. The method is increasingly used to map neuropsychological functions such as language and calculation; recently, our group also reported its usefulness for the mapping of visuospatial attention [31-37]. To further pursue this objective, we combined rTMS with the aforementioned greyscales task in the same cohort of healthy volunteers as investigated before [36]. We assumed our subjects present with a basic spatial bias that reflects their individual processing balance between the left and the right hemisphere. This bias might be indexed by the greyscales task. In the presence of pseudoneglect, we would obtain leftward baseline scores. Our next thought was that temporary inactivation of eloquent cortical spots ought to effect an inter-hemispheric misbalancing and therefore drive lateral shifts in spatial bias. These again might be indexed by the greyscales task. We expected particularly significant effects for rTMS applied to cortical spots of the right hemisphere. Based on the idea of a dominantly active right hemisphere in healthy adults with pseudoneglect, we supposed that inactivation of spots within this hemisphere would reduce the basic leftward bias. Hence we would obtain rightward deviation scores on the greyscales task.

Summarizing, the presented pilot study aims to assess a combination of the greyscales task and rTMS in healthy volunteers by examining the following hypotheses:

4) The greyscales task in tachistoscopic test conditions is appropriate and sensitive for testing visuospatial attention function via rTMS.
5) The resulting brain maps are in accordance with current models of visuospatial attention.

2. MATERIAL AND METHODS

2.8 Subjects

The study included five women and five men. All subjects were healthy at state and without any history of neurological or neuropsychological deficit. Their ages ranged from 21 to 31 years (median age: 24 years). Inclusion criteria were pure right-handedness (Edinburgh inventory score >40) and German as a first language. Exclusion criteria were general TMS and MRI exclusion criteria (pacemaker, cochlea-implant, deep brain stimulation) [38]. As mentioned in the introduction, this cohort has been examined before [36].

2.9 Navigated rTMS

2.9.1 MRI dataset

For MR imaging, we used a 3 Tesla MRI scanner with eight-channel phased-array head coil (Achieva 3T, Philips Medical Systems, Amsterdam, The Netherlands B.V.). Our protocol was comprised of two sequences: a T2-weighted FLAIR sequence (TR: 12,000 ms, TE: 140 ms, voxel size: 0.9 × 0.9 × 4 mm^3, acquisition time: 3 min) and a T1-weighted 3D gradient echo sequence (no intravenous contrast administration, TR: 9 ms, TE: 4 ms, 1 mm^3 isovoxel covering the whole head, acquisition time: 6 min 58 s). The 3D dataset was transferred to our rTMS system by DICOM standard.

2.9.2 Mapping setup

For rTMS mapping, we used a Nexstim eXimia System Version 4.3 with NEXSPEECH® module (Nexstim Plc., Helsinki, Finland). This system uses a stereotactic camera to link the subject’s 3-D MRI dataset with its head via anatomical landmarks and a registered “tracker” headband. This meant we were able to visualize the stimulation coil's real-time position or, rather, the induced electric field in the 3D MRI reconstruction and to selectively and accurately stimulate the brain regions [33, 34, 39, 40]. Through the use of NEXSPEECH software, we were able to stimulate the selected brain regions and time-locked present task pictures on a video screen [41].

2.9.3 Mapping parameter

In each subject we determined resting motor thresholds (RMT) for the right and left abductor pollicis brevis muscles and individually adjusted the stimulation intensity for the respectively contralateral hemisphere [42]. Mapping was performed at 100% RMT. rTMS pulses were applied as a train of 10 stimuli at a repetition frequency of 5 Hz, equaling stimulation trains of 1800 ms. To reach a maximal field induction, we placed the coil in anterior-posterior field orientation strictly tangentially to the skull, as previously reported [36, 41, 43].

2.9.4 Mapping targets

We tested 52 cortical spots on each hemisphere and distributed them to brain areas using the cortical parcellation system created by Corina (CPS; Fig. 1, Table 1) [44]. We anatomically identified the spots in each subject's 3D MRI reconstruction and marked them as stimulation targets. First we selected the targets of the left hemisphere. We probed each target five times in a block. The order of selecting was randomly chosen by the examiner. Next we examined the right hemisphere, respectively. We redid this procedure once. According to this protocol each target was probed 10 times in total. Though, due to difficulties in adjusting the stereotactic camera during the mapping, some spots got addressed more, some less frequent. Certain brain areas had to be omitted: Stimulation of the polar and anterior frontal gyri (polFG, aSFG, aMFG), the orbital part of the inferior frontal gyrus (orIFG), the polar temporal gyri (polTG), and the anterior middle temporal gyrus (aMTG) is known to be too painful to provide reliable results due to muscle contractions. Stimulation of the inferior temporal gyrus (ITG) is known to be incomparably effective because the increased range between the skull and brain tissue causes decreased stimulation intensities [39, 45].

2.10 The greyscales task

2.10.1 Task setup

During rTMS mapping, the subjects had to perform a visuospatial attention task. More specifically, they had to handle one task picture during each rTMS stimulation train. A video screen (38,1 cm in diameter) was placed at viewing distance (about 60 cm nose to screen) in front of the examination chair. As evaluated before, we delivered rTMS pulses and task pictures synchronously and without delay between rTMS-stimulus-onset and picture-display [46]. The inter-picture interval was set to 3000 ms.

2.10.2 Task design

Our visuospatial attention task follows the greyscales task by Mattingley et al. [30]. Task pictures were conceived as pairs of horizontal rectangles arranged vertically, one above another (Fig. 2). They were shaded continuously from black at one end to white at the other, shown on a grey background, and framed by a black line of 0.7 mm. The rectangles of each pair were identical in length and shading, solely depicted as mirror images. Uniformly 30 mm in height, the rectangles varied in length from 180 mm to 330 mm (in 30 mm steps). Six lengths per two shading orientations each made a task set of 12 different task pictures. Pictures were displayed tachistoscopically for 50 ms, as reported earlier [18, 36, 47]. The order of presentation was randomized by the software. On each picture the subject was asked to report which of the two greyscales appeared darker overall by saying aloud “top” or “bottom.” There was no third option to select “no difference.” The responses were categorized into “leftward” and “rightward,” depending on whether the subject had chosen the rectangle with the darker end on the left or the right. Subjects performed a baseline session of 72 pictures without stimulation prior to the rTMS mapping session. Both sessions were videotaped for later analysis [41, 48].

2.11 Evaluation of discomfort

After rTMS mapping, the subjects were asked to evaluate discomfort, separately for the temporal muscle area (“temporal”) and for the remainder of the head surface (“convexity”). The meter was the visual analogue scale (range 0-10): 0 signifying no pain and 10 signifying maximal pain.

2.12 Data analysis

Data analysis comprised several steps. First we went over the subject’s video records and labeled each response as “leftward” or “rightward” (as outlined in 2.4.2). Next we related responses and stimulated cortical spots. For each spot we counted the number of effective rTMS stimulations and, among these, the number of leftward and rightward responses. Stimulation was deemed effective if a complete train of 10 rTMS pulses had been applied and if the electric field strength at the cortical level had been above 55 V/m the entire time [34]. Then scores were computed as the difference between the rightward and leftward responses divided by the number of effective stimulations (between a range of -1.00 and 1.00). The subject’s task performance in baseline conditions was documented as the baseline score. Their performance in mapping conditions was documented for each particular spot as the particular deviation score (i.e., the spot's computed score minus the subject's baseline score). The deviation scores, in turn, were categorized as “leftward” or “rightward,” depending on whether the scores were negative or positive. Then we pooled the information of all the subjects per cortical spot as follows:

1) We calculated the number of subjects with leftward deviation scores and the mean of their scores, i.e., the mean of all leftward deviation scores.
2) We calculated the number of subjects with rightward deviation scores and the mean of their scores, i.e., the mean of all rightward deviation scores.

For clearer comparison, we handled all mean deviation scores in terms of their magnitude.

2.13 Statistics

The results are listed as mean ± standard deviation plus median and range where applicable. Inter-spot comparisons were made by the Mann-Whitney U test for independent samples. For single-spot analysis (concerning “leftward” vs. “rightward” effects), we used the Wilcoxon matched-pairs signed rank test. All tests were regarded as significant at a p-value < 0.05 (GraphPad Prism 6.0, La Jolla, CA, USA).

3. RESULTS

3.1 Subject characteristics

The subject characteristics are listed in Table 2. We determined a mean RMT of 33.1 ± 6.4% maximal stimulator output, in terms of the left hemisphere, and of 32.9 ± 5.9%, in terms of the right hemisphere ($p = 0.9564$). Without stimulation, 9 out of 10 subjects presented with a leftward basic bias; one subject showed a rightward basic bias. Taken together, the baseline score averaged -0.59 ± 0.51. rTMS mapping was tolerated well, and discomfort was comparable for both hemispheres. All subjects were purely right-handed and showed left-hemispheric dominance.

3.2 Number and size of deviations

Tables 3 and 4 provide all computed deviation scores on mapping conditions. Additional subject-related scores are available as an online resource (ESM 1 & 2). First we had a look at the number and size of leftward and rightward deviations.

3.2.1 Leftward deviations

Regarding the frequency, leftward deviations occurred significantly more often than rightward deviations within both the left ($p = 0.0077$) and the right hemisphere ($p < 0.0001$). Analyzing the results of both hemispheres together, we found that inter-hemispherically, their number was comparable ($p = 0.6397$). Regarding the effect size, rTMS of the right hemisphere elicited significantly stronger leftward deviations than rTMS of the left hemisphere ($p < 0.0001$; Fig. 3). Altogether, i.e. for both hemispheres, the mean leftward deviation scores ranged from 0.06 to 0.40 in magnitude.

3.2.2 Rightward deviations

Consequently, rightward deviations were more rarely observed than leftward deviations. Their number was comparable for the two hemispheres (*p* = 0.6352). However, rightward deviations were strikingly greater in magnitude, namely, compared to leftward deviations (*p* < 0.0001) and according to inter-hemispheric comparison of the right rather than the left hemisphere (*p* < 0.0001; Fig. 3). The mean rightward deviation scores ranged from 0.06 to 1.26 in magnitude.

3.3 Cortical distribution of deviations

In what follows we outline the cortical distribution of deviations. Figure 4 depicts the leftward deviations in blue color and the rightward deviations in red.

3.3.1 Leftward deviations

Regarding the left hemisphere, we observed strong leftward effects within parietal areas (vPoG, anG; spots no. 28, 40; Fig. 4a). Regarding the right hemisphere, the parietal areas (SPL, anG; spots no. 41, 45, 48) were as prominent as the middle middle temporal gyrus (mMTG; spot no. 35), and as a wide frontal area (mSFG, mMFG, pMFG; spots no. 8, 11, 13, 16-18, Fig. 4b).

3.3.2 Rightward deviations

Rightward deviations within the left hemisphere were distributed to the posterior superior frontal gyrus (pSFG; spot no. 15) and to occipital areas (dLOG, vLOG; spots no. 49-50; Fig. 4c). The right hemisphere showed a number of striking spots, including the posterior supramarginal gyrus (pSMG; spot no. 37), the ventral lateral occipital gyrus (vLOG; spots no. 47, 50), temporal areas (mSTG, pMTG; spots no. 34, 43, 46), and frontal areas (mMFG, trIFG, opIFG; spots no. 4, 5, 9, 13-14; Fig. 4d).

3.4 Raw data

We provide our subjects' raw data as an online resource (ESM 3 & 4). Cortical spots of the left hemisphere were stimulated 9.8 ± 0.2 times on average, and cortical spots of the right hemisphere were stimulated 9.7 ± 0.3 times. The number of effective stimulations per spot ranged from 5 to 15 for the left hemisphere and from 4 to 12 for the right hemisphere.

4. DISCUSSION

4.1 General aims and limitations

We have already reported on the usability of navigated rTMS to mimic visual neglect and map corresponding cortical areas in another study [36]. While searching for preferably sensitive visuospatial tasks, we also came across literature on the greyscales task and, thus, designed the pilot study presented in this manuscript. We mainly focused on general feasibility and the broad-ranging examination of both hemispheres, which involved accepting a number of limitations. To assess new setups and to understand the anatomical correlates of pathologies, it is crucial to examine healthy subjects. Our volunteers formed a small and homogenous healthy cohort, which may be seen as a benefit [49]. At the same time, it may be seen as a restriction, and the generalizability of our findings certainly must be further assessed in relation to a higher number of subjects of all ages. Moreover, we should be aware of limitations due to our rTMS protocol. We tested a wide range of brain areas using a fixed mapping template. We stimulated at a frequency of 5 Hz and with strict anterior-posterior field orientation. Several protocol changes, for example, varying coil angulations, could have modified our results [50]. However, we proceeded comparably to all current mapping standards that have been used before [36, 37, 45]. Some cortical spots showed a quite small number of effective stimulations. However, the mean number of stimulations per spot was over 9.1 for all subjects with a consistently small variance. As a last point, we can neither offer any test-retest evaluation in the form of a second examination, nor any sham-stimulation controls to exclude factors such as concentration deficits or unintended remote rTMS effects. This should be the next step following this feasibility study. With all this in mind, our findings should clearly be carefully considered. Nevertheless, as a first step in an evaluation, we may rate them as useful and encouraging for a further pursuit of this approach.

4.2 The greyscales task

Neglect patients are known to develop various mechanisms to compensate for existent pathologies. Hence, a true diagnosis requires precise and challenging task selections [26]. The greyscales task serves as a sensitive tool to measure perceptual biases in healthy subjects and in patients and has even been used to uncover deficits in patients without apparent visual neglect in conservative testing [27, 30]. In this study we chose a computerized and tachistoscopic application and conclusively can approve this setting. It proved to be applicable and highly sensitive. Tachistoscopic task display prevents effects such as fixation or eye scanning. As originally conducted, our subjects had to respond verbally. We had to take into account the fact that left-hemisphere-activation by speaking might affect the inter-hemispheric processes of visuospatial attention. On the other hand manual demands have also been reported as affecting results—for example, depending on the hand being used to perform [18]. A key advantage of the greyscales task is that there are no errors to make or be detected, but each response contributes to the overall result, representing the subject's fully individual tendency with regard to visuospatial attention processing. By determining a basic bias prior to the rTMS examination and considering all subsequent results in relation to this value, there is no usability limitation accompanying the already existent deficits. Here we examined a collective of healthy men, but our setting may be applied to patients as well. Moreover, the adaptability does not depend on the presence or form of pseudoneglect. Our baseline findings are consistent with reports on the prevalence of pseudoneglect among young adults: 9 out of our 10 subjects naturally tended to the left rather than the right [18, 20, 22, 27]. With advancing age, pseudoneglect is known to shift rightwards [51, 52]. This fact should be kept in mind for future analysis of patient data, but as stated above, it does not restrict the applicability. Besides, we should mention that Friedrich et al. analyzed the age factor of pseudoneglect by means of the greyscales task and found that healthy elderly people presented with an even stronger leftward bias than their younger participants [53].

4.3 rTMS mapping

Across the literature, visuospatial attention is described as highly individually distributed, balanced, and suggestible [1, 54-56]. However, we assume that a scaffold of cortical spots exists connected anatomically, that they are thus available by order of visuospatial function, and that they are at least available to be recruited if necessary. As already addressed in 4.1, our rTMS results certainly should not be considered absolute. There were cortical spots with outstanding deviation scores averaged over less than half of our subjects; the other subjects were either not suggestible (but by chance showed small deviation scores in the opposite direction) or alternatively were suggestible but, as a matter of fact, in the opposite direction (Tables 3 & 4; ESM 1-4). One more factor we should mention is the experiment’s fairly long time span. A natural leftward bias on baseline performance is known to decline in the course of visuospatial task demands. Due to diminished alertness and neural fatigue, biases shift rightward naturally over time [57-59]. We examined the two hemispheres in the order left-right-left-right, i.e., in two turns. To prevent a time-on-task effect, we took breaks after every examination of one hemisphere, and we periodically animated our subjects to maintain concentration for the time span in between. An increasing rightward shift over time should have resulted in a higher total number of rightward deviations for the right hemisphere compared to the left hemisphere. Fortunately, we could not find any pattern of time-effects. The number of rightward deviations was comparable for both hemispheres (see 3.2.2).

To get a better measure of our findings, we performed a principal analysis of deviation numbers and sizes, as outlined in 3.2. Leftward deviations were recorded significantly more often and were significantly smaller in magnitude than rightward deviations. The higher frequency may be based on pre-existent pseudoneglect and might solely reflect right hemisphere activity during visuospatial task demands, especially as the score values tended to be small. On the other hand, an already leftward baseline score limited the attainable magnitude of negative deviation scores per se. In contrast, rightward deviations were found to be strikingly great in magnitude and significantly stronger than leftward deviations (Fig. 3; Tables 3 & 4). Once more referring to the baseline performance, we could categorize these rightward deviations as a reduction or cancellation of the natural leftward bias, i.e., of pseudoneglect. This pseudoneglect "ceiling effect" has been described before [14, 17]. Furthermore these rightward deviations parallel the classic symptom of left visual neglect. In clinical routine, visual neglect is described as being both the most common and most pronounced phenomenon after right hemispheric damage [7, 8, 27, 60]. Accordingly, we found the right hemisphere to be significantly more suggestible by rTMS than the left hemisphere (Figs. 3 & 4). This is also in line with our initial assumption that rTMS of the right hemisphere ought to strikingly misbalance the base state of processing in which the right hemisphere takes the dominant part. To summarize, we may reaffirm that rTMS affords a useful opportunity to map visuospatial attention function at the cortical level, most convincingly for the right hemisphere and—when examining healthy men with pseudoneglect—for attention processing to the right.

4.4 Cortical distributions with reference to the current literature

The unquestionably best-known form of visual neglect is the combination of right hemispheric parietal damage followed by contralesional left deficits. Notwithstanding, there are more and more reports of other lesion locations and clinical manifestations, up to reports on the concurrent occurrence of ipsi- and contralesional deficits [47, 61-64]. As a side note, the greyscales study by Mattingley et al. also included two right-parietal patients with an extreme leftward bias and thus ipsilesional neglect [27]. As introduced above, studies on pseudoneglect in healthy adults have additionally helped to explain processing mechanisms [14-18, 20, 22-25]. However, a comparative discussion of results proves difficult because of the heterogeneity of approaches. Studies use different tasks to measure visuospatial deficits, focus on different locations, and interpret their results from different angles. One fact upon which they all agree, which has persisted over the course of decades, is that the right hemisphere at least plays a somewhat special role, whether dominant or controlling [65, 66]. This idea also provides the basis for explaining the high prevalence of pseudoneglect in healthy adults [15, 16, 21-24, 51]. Regarding cortical distributions, there is the widely accepted idea of subcortical fiber tracts connecting frontal areas with parietal areas and the temporoparietal junction (TPJ) [2, 3, 24, 54, 55, 65, 67]. Corbetta and Shulman assume two networks: a dorsal network including superior parietal and frontal areas represented on both hemispheres, and a ventral network including the TPJ and inferior frontal areas represented dominantly on the right hemisphere and supervising the dorsal network [3]. To class our findings with these models, we have to differentiate between the left and the right hemisphere. Within the left hemisphere occasional spots of frontal, parietal, and lateral occipital areas presented with strong deviation effects (Fig. 4a & c), though we cannot distribute them distinctly to the stated networks and must suggest forming careful conclusions from these findings. Yet, rTMS-lesioning of the right hemisphere detected cortical spots that accorded well with the introduced models. Interestingly, we found leftward deviations (corresponding to ipsilesional neglect) to mainly be distributed to posterior parietal and superior frontal areas, according to the proposed dorsal network (Fig. 4b; Table 4). The observation of leftward instead of rightward deviations does not go in line with the basic responsibilities Corbetta and Shulmann intended for their networks [3]. However, supposing equal neuronal structures and thus rTMS-effects for dorsal or ventral brain regions, we should contemplate subtler task allocations within the dorsal network. There are several publications on the occurrence of ipsilesional neglect after right-hemispheric damage [62, 63, 68, 69]. Chokron et al. even reported right visual neglect in patients with left hemianopia plus neglect [70]. Especially the role of frontal and subcortical areas is discussed, albeit, so far, there is no generally accepted explanation that could be integrated into the model of Corbetta and Shulmann [61, 64]. On the contrary, rightward deviations (corr. to contralesional neglect) could be triggered best at inferior frontal spots and at a pool of spots within the area of the TPJ (Fig. 4d; Table 4). In turn, these observations comply with both localization and function of a ventral network.

At this point we also want to mention our group's first work on neglect, which was a combination of rTMS and a classical landmark task [36]. We successfully showed the feasibility of mapping visuospatial attention, yet the landmark task solely provided information in the form of right-or-wrong answers, and the resulting error rates among our healthy volunteers tended to be rather small. The study presented here can be seen as a second approach to gather more and better comparable data using the greyscales task. As already outlined, the greyscales task takes into account any recorded answer and allows interpretations independently from any existent deficits. Since the two tasks use quite different ways of measuring visuospatial attention and respectively different forms of analysis, and since both approaches conformed to pilot studies' inclusive limitations, we decided not to compare single results. However, we may summarize that the findings of both go well together, embedded in the generally acknowledged model of visuospatial processing. Regarding the right hemisphere, we found consistent distributions in the area of the TPJ and for spots of the middle frontal gyrus. For clinical purposes the greyscales task design stands out by being quite easily applicable and bearable while achieving sensitive results. To reach similar sensitivity for the landmark task, we would have had to increase its difficulty, for example, by shortening the line differences between the left and right segments. Yet, all our healthy subjects reported the landmark task as being particularly demanding, which is why we seriously doubt its feasibility at a higher difficulty level, let alone in elderly patients.

4.5 Future prospects

Obviously, the acting and interacting of networks responsible for visuospatial attention has not yet been understood to the fullest extent. Research increasingly concentrates on the subcortical level [71-73]. However, several options are conceivable to integrate cortical mapping using rTMS. For example, a combination with fMRI enables the detection of unintended remote stimulation effects and potentially accountable white matter connections [74]. Furthermore, seminal approaches are made by diffusion tensor imaging fiber tracking. The combination of diffusion tensor imaging fiber tracking and rTMS language mapping recently obtained highly promising results for the imaging of subcortical language pathways and may be assessed similarly for the rTMS-mapped visuospatial attention function [75-78]. Basic research naturally aims to yield a clinical advantage. It could be shown that neurosurgeons profit by presurgical maps by preventing functional deficits while allowing maximal resection [9, 79]. In patients with certain tumor locations, we should consider adding maps of visuospatial attention function to the individual preoperative assessment. On the other hand, dealing with already existent deficits, neurologists currently develop new treatment regimes. In light of visual neglect being the result of damage accompanied by a misbalancing of large-scale brain networks, recovery correlates with rebalancing [1, 11, 80]. Once more, the presented combination of the greyscales task and rTMS may be advantageous in terms of generating individual and accurate cortical maps for therapeutic interventions.

5. CONCLUSION

Referring to our initial hypotheses, we can conclude that the greyscales task on tachistoscopic test conditions, in combination with rTMS, is appropriate, sensitive, and accurate in mapping visuospatial attention function on a cortical level.

ABBREVIATIONS

fMRI	functional magnetic resonance imaging
ESM	Electronic supplementary material
MRI	magnetic resonance imaging
RMT	resting motor threshold
rTMS	repetitive navigated transcranial magnetic stimulation
TMS	transcranial magnetic stimulation
TPJ	temporoparietal junction

6. DECLARATIONS

6.1 Ethics approval and consent to participate

Our experimental protocol is in accord with the Declaration of Helsinki. It was authorized by the local ethics committee (Ethikkommission der Fakultät für Medizin der Technischen Universität München, Ismaninger Straße 22, 81675 Munich, Germany; registration number: 223/14). All subjects gave written informed consent to participate prior to the navigational MRI scan.

6.2 Consent for publication

All subjects gave written informed consent for publication of the gathered data.

6.3 Availability of data and material

All data analyzed during this study are included in this published article and its supplementary information files.

6.4 Competing interests

All authors declare that they have no conflict of interest affecting this study, the materials or methods used, or the findings specified in this paper. SK is a consultant for Brainlab AG (Munich, Germany) and for Nexstim Plc. (Helsinki, Finland).

6.5 Funding

This study was funded by institutional grants from the Department of Neurosurgery and the Section of Neuroradiology.

6.6 Authors' contributions

KG was responsible for the recruitment of participants, data acquisition and analysis, literature research and manuscript draft. SM performed pretests, participated in interpreting the data and corrected the final manuscript. CZ and BM were part of the conception planning and critically revised the final manuscript. SK is responsible for concept and design of the study, performed literature research, handled the acquired data and drafted the manuscript. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

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6.8 Authors' information

KG is a medical student, SM is a neurosurgical resident. They are performing a high number of rTMS studies in healthy subjects and brain tumor patients. CZ is chairman of the section of neuroradiology. BM is chairman of the department of neurosurgery. SK is attending neurosurgeon. BM and SK are involved in the treatment of brain tumors in a specialized neurooncological center, including preoperative mapping, intraoperative neuroimaging and awake surgery.

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8. FIGURE AND TABLE LEGENDS

Table 1: Anatomical names and abbreviations of the cortical parcellation system

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
poIFG	polar frontal gyri
poITG	polar temporal gyri
poILOG	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

Anatomical names and abbreviations according to the cortical parcellation system [44].

Table 2: Subject characteristics

Subject	RMT		Pain score temporal		Pain score convexity		Greyscales task baseline score
	Left hemisphere	Right hemisphere	Left hemisphere	Right hemisphere	Left hemisphere	Right hemisphere	
1	29	29	2	3	1	1	-0.61
2	34	29	2	2	1	1	0.78
3	29	33	3	6	1	1	-0.81
4	43	39	4	4	1	1	-0.94
5	36	35	3	3	1	1	-0.94
6	30	28	2	2	0	0	-0.97
7	45	45	6	6	1	1	-0.75
8	31	36	4	6	1	3	-0.47
9	28	26	4	2	3	1	-0.67
10	26	29	2	4	1	3	-0.53
Mean	33.1	32.9	3.2	3.8	1.1	1.3	-0.59
SD	6.4	5.9	1.3	1.7	0.7	0.9	0.51
Median	30.5	31	3	3.5	1	1	-0.71
MIN	26	26	2	2	0	0	-0.97
MAX	45	45	6	6	3	3	0.78
	$p = 0.9564$		$p = 0.5493$		$p = 0.8375$		

Subject characteristics. Resting motor threshold (RMT) as % of stimulator output. Pain score according to the visual analogue scale (VAS), range from 0 (no pain) to 10 (maximal pain). Greyscales task baseline score determined on 72 pictures without stimulation, range from -1.00 (leftward bias) to 1.00 (rightward bias).

Table 3: Deviation scores per cortical spot for the left hemisphere

cortical spot	"leftward" deviation scores		"rightward" deviation scores	
	number of subjects	mean of these subjects' scores	number of subjects	mean of these subjects' scores
1	2	-0.06	8	0.26
2	5	-0.13	5	0.15
3	2	-0.09	8	0.27
4	2	-0.06	8	0.40
5	3	-0.23	7	0.34
6	4	-0.11	6	0.33
7	5	-0.22	5	0.30
8	2	-0.26	8	0.34
9	5	-0.19	5	0.29
10	3	-0.24	7	0.33
11	4	-0.13	6	0.28
12	4	-0.16	6	0.31
13	5	-0.13	5	0.23
14	7	-0.17	3	0.31
15	7	-0.26	3	0.88
16	6	-0.16	4	0.52
17	7	-0.15	3	0.36
18	4	-0.14	6	0.25
19	7	-0.12	3	0.40
20	5	-0.22	5	0.42

21	6	-0.19	4	0.46
22	7	-0.18	3	0.06
23	6	-0.22	4	0.20
24	9	-0.23	1	0.55
25	8	-0.23	2	0.29
26	7	-0.24	3	0.17
27	9	-0.20	1	0.47
28	5	-0.38	5	0.13
29	6	-0.31	4	0.20
30	6	-0.15	4	0.52
31	6	-0.29	4	0.21
32	5	-0.18	5	0.36
33	7	-0.26	3	0.78
34	6	-0.21	4	0.58
35	5	-0.32	5	0.61
36	4	-0.22	6	0.33
37	6	-0.28	4	0.81
38	4	-0.22	6	0.46
39	6	-0.15	4	0.62
40	6	-0.36	4	0.71
41	6	-0.15	4	0.39
42	7	-0.22	3	0.44
43	7	-0.29	3	0.42
44	5	-0.18	5	0.67

45	8	-0.18	2	0.44
46	8	-0.18	2	0.45
47	7	-0.24	3	0.38
48	7	-0.18	3	0.81
49	7	-0.18	2	0.88
50	7	-0.24	3	0.85
51	8	-0.22	2	0.48
52	6	-0.18	4	0.14
Mean	6	-0.20	4	0.42
SD	2	-0.07	2	0.20
MIN	2	-0.06	1	0.06
MAX	9	-0.38	8	0.88

Results for stimulation of the left hemisphere. Number of subjects with negative deviation scores (“leftward”) and mean of their scores. Number of subjects with positive deviation scores (“rightward”) and mean of their scores. Outline per cortical spot (no. 1-52) plus mean, standard deviation (SD), minimum (MIN), and maximum (MAX).

Table 4: Deviation scores per cortical spot for the right hemisphere

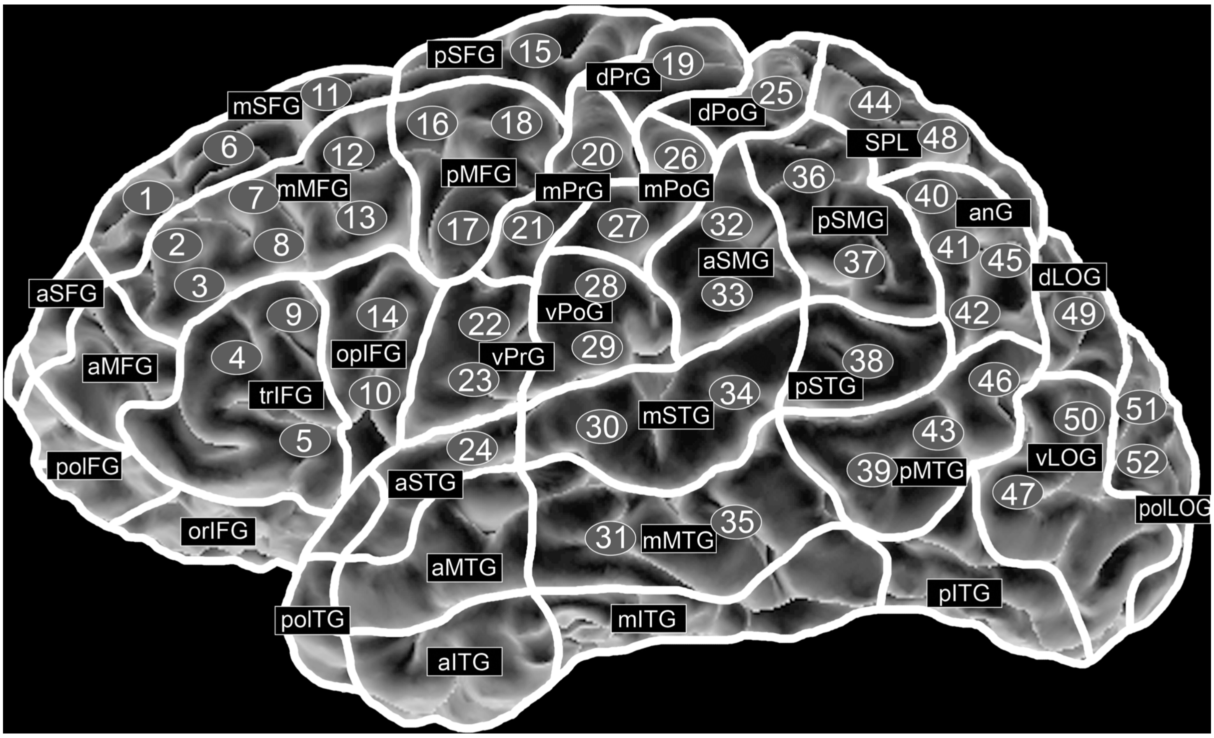
cortical spot	"leftward" deviation scores		"rightward" deviation scores	
	number of subjects	mean of these subjects' scores	number of subjects	mean of these subjects' scores
1	4	-0.21	6	0.56
2	6	-0.29	4	0.63
3	7	-0.22	3	0.73
4	7	-0.24	3	0.96
5	7	-0.18	3	0.93
6	7	-0.17	3	0.62
7	7	-0.24	3	0.33
8	5	-0.40	5	0.32
9	7	-0.26	3	1.15
10	6	-0.28	4	0.72
11	6	-0.38	4	0.73
12	7	-0.27	3	0.44
13	7	-0.34	3	1.15
14	7	-0.26	3	0.95
15	6	-0.23	4	0.48
16	7	-0.33	3	0.52
17	6	-0.34	4	0.43
18	5	-0.40	5	0.73
19	6	-0.23	4	0.58
20	4	-0.30	6	0.44

21	4	-0.23	6	0.44
22	5	-0.26	5	0.80
23	4	-0.18	5	0.72
24	6	-0.21	4	0.68
25	3	-0.19	6	0.57
26	5	-0.22	5	0.58
27	5	-0.25	5	0.65
28	5	-0.21	5	0.46
29	5	-0.27	5	0.61
30	4	-0.23	6	0.80
31	5	-0.23	5	0.65
32	4	-0.28	6	0.49
33	4	-0.26	6	0.63
34	6	-0.20	4	1.04
35	4	-0.35	6	0.41
36	5	-0.20	5	0.73
37	7	-0.24	3	0.90
38	7	-0.18	3	0.77
39	4	-0.21	6	0.43
40	6	-0.23	4	0.53
41	4	-0.36	6	0.59
42	5	-0.21	5	0.38
43	6	-0.15	4	1.04
44	6	-0.24	4	0.79

45	7	-0.33	3	0.58
46	6	-0.19	4	0.87
47	7	-0.26	3	1.26
48	5	-0.38	5	0.65
49	7	-0.22	3	0.56
50	7	-0.26	3	0.91
51	7	-0.27	3	0.59
52	4	-0.16	6	0.41
Mean	6	-0.25	4	0.67
SD	1	-0.06	1	0.22
MIN	3	-0.15	3	0.32
MAX	7	-0.40	6	1.26

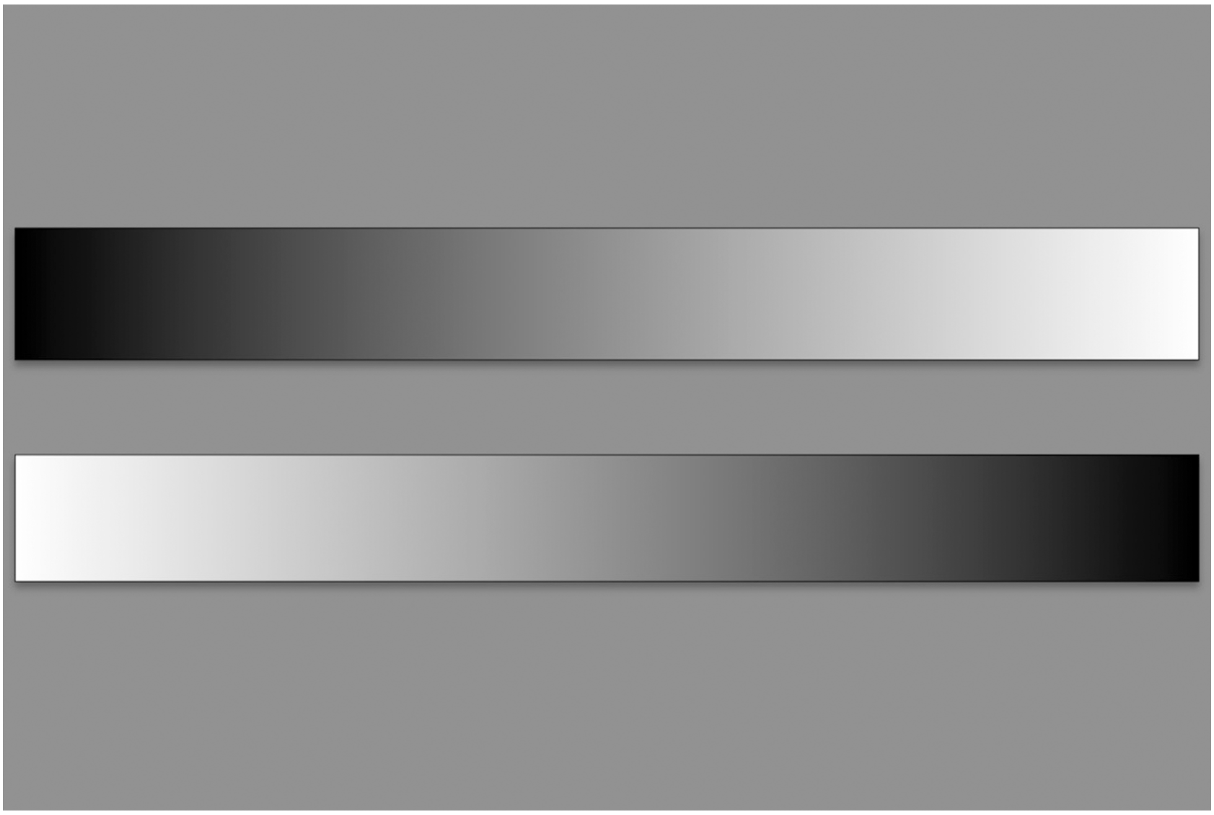
Results for stimulation of the right hemisphere. Number of subjects with negative deviation scores ("leftward") and mean of their scores. Number of subjects with positive deviation scores ("rightward") and mean of their scores. Outline per cortical spot 1-52 plus mean, standard deviation (SD), minimum (MIN), and maximum (MAX).

Figure 1: Mapping targets



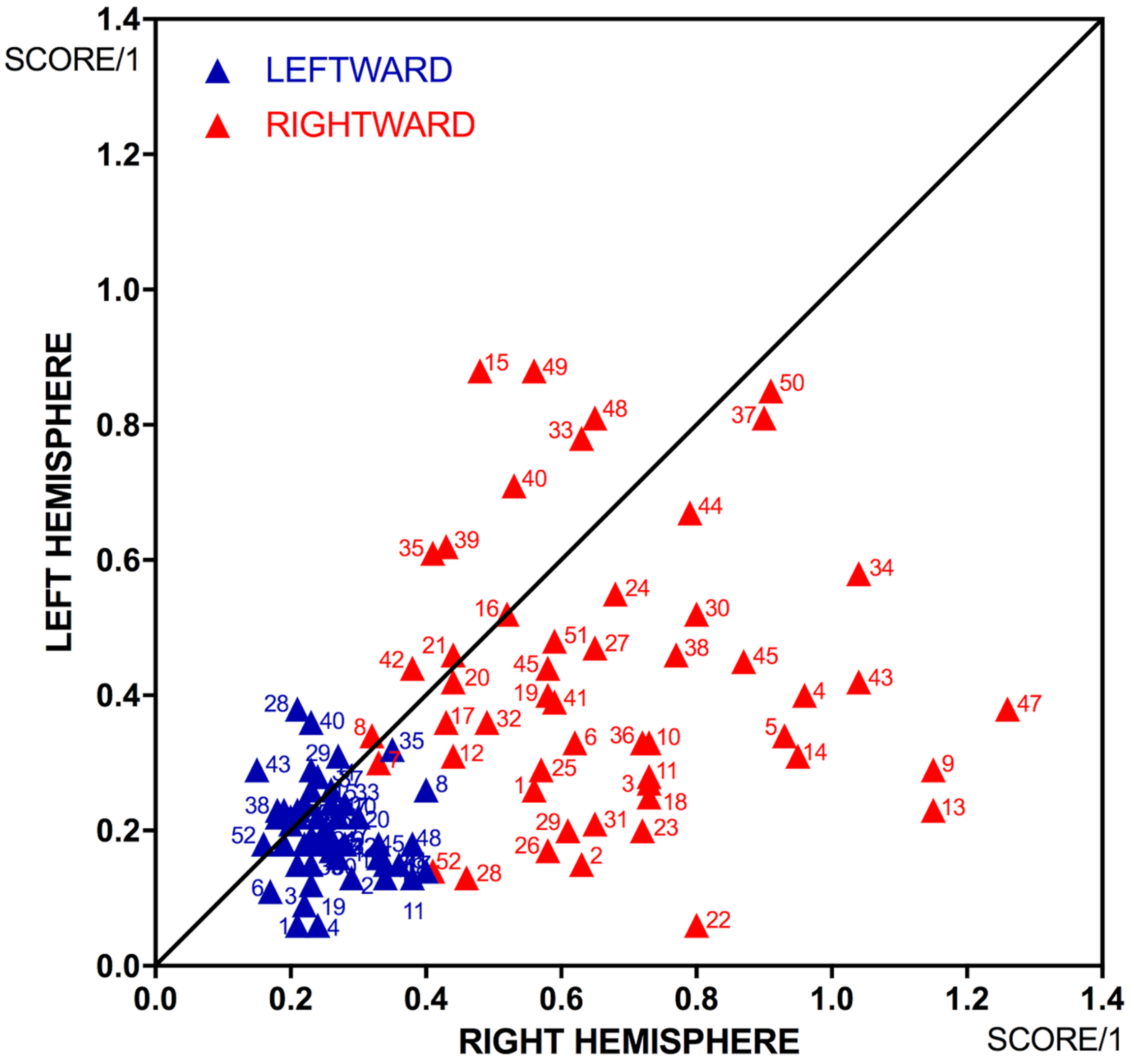
Brain areas and cortical spots no. 1-52 according to the cortical parcellation system [44].

Figure 2: Sample picture from the greyscales task



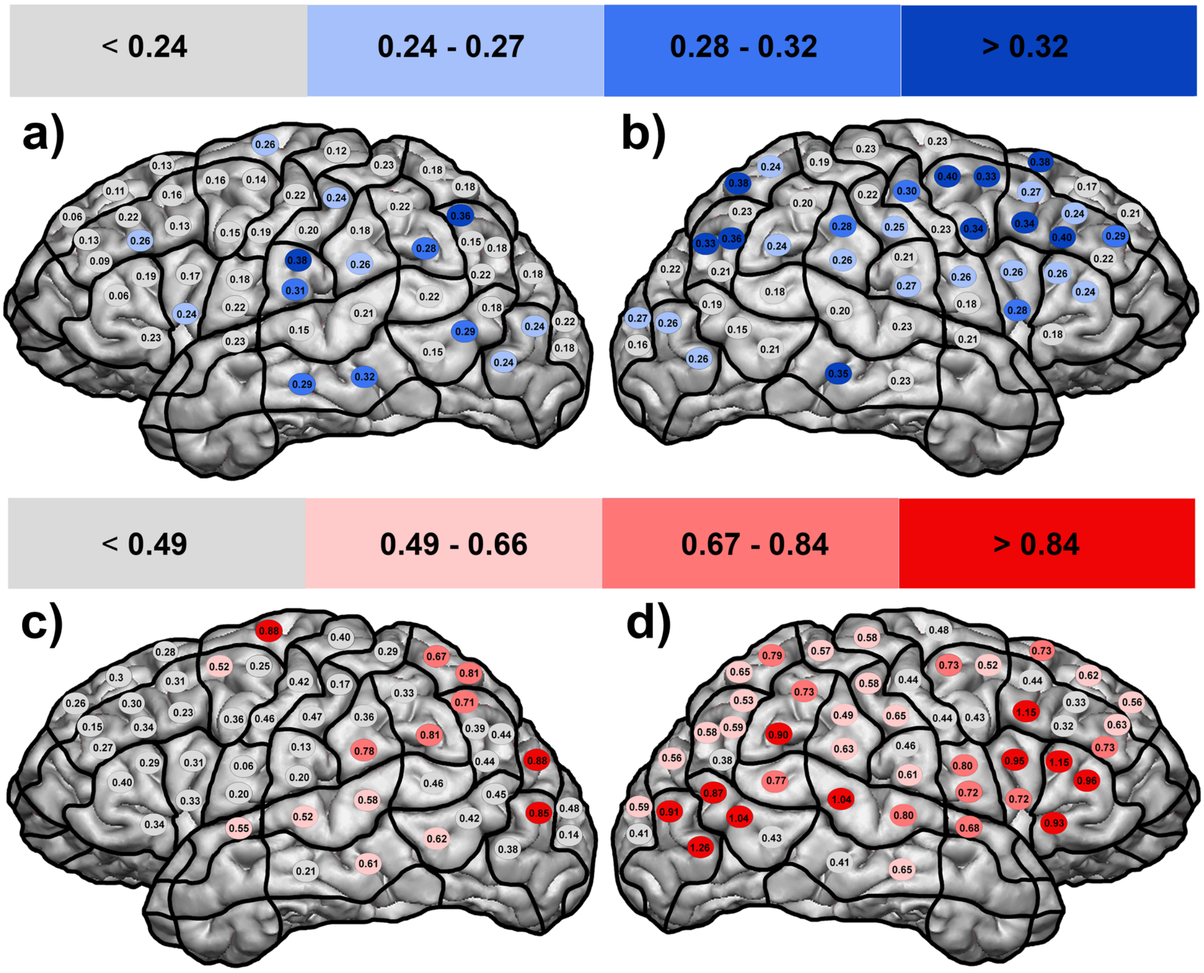
Greyscales task sample. For each picture the subject was asked to report which of the two greyscales appeared to be darker overall. The responses were categorized into “leftward” and “rightward,” depending on whether the subject had chosen the rectangle with the darker end on the left or the right, as first described by Mattingley et al. [30].

Figure 3: Inter-hemispheric comparison of deviations



Deviation sizes in comparison. Plotted are mean deviation scores per cortical spot (no. 1-52), as always, for the left hemisphere (y-coordinate; Table 3) and the right hemisphere (x-coordinate; Table 4). Leftward deviations in blue, rightward deviations in red.

Figure 4: Cortical distribution of deviations



Cortical distributions within the left hemisphere (a, c) and the right hemisphere (b, d). Presented are the mean deviation scores (Tables 3 & 4). Leftward deviations in blue, rightward deviations in red.

9. *ADDITIONAL FILES*

Electronic supplementary material (ESM)

ESM 1: Subject-related deviation scores per cortical spot for the left hemisphere

Results for stimulation of the left hemisphere. Deviation scores of subject 1-10. Number of subjects with negative deviation scores (“leftward”) and mean of their scores. Number of subjects with positive deviation scores (“rightward”) and mean of their scores. Outline per cortical spot (no. 1-52) plus mean, standard deviation (SD), minimum (MIN), and maximum (MAX).

ESM 2: Subject-related deviation scores per cortical spot for the right hemisphere

Results for stimulation of the right hemisphere. Deviation scores of subject 1-10. Number of subjects with negative deviation scores (“leftward”) and mean of their scores. Number of subjects with positive deviation scores (“rightward”) and mean of their scores. Outline per cortical spot (no. 1-52) plus mean, standard deviation (SD), minimum (MIN), and maximum (MAX).

ESM 3: Raw data per cortical spot for the left hemisphere

Results for stimulation of the left hemisphere. Raw data of each subject. Number of effective stimulations, “leftward” answers and “rightward” answers. Outline per cortical spot (no. 1-52) plus mean, standard deviation (SD), minimum (MIN), and maximum (MAX).

ESM 4: Raw data per cortical spot for the right hemisphere

Results for stimulation of the right hemisphere. Raw data of each subject. Number of effective stimulations, “leftward” answers and “rightward” answers. Outline per cortical spot (no. 1-52) plus mean, standard deviation (SD), minimum (MIN), and maximum (MAX).