UNIVERSITY OF HELSINKI REPORT SERIES IN PHYSICS

HU-P-D235

NAVIGATED TRANSCRANIAL MAGNETIC STIMULATION IN PREOPERATIVE FUNCTIONAL MAPPINGS FOR PATIENTS WITH EPILEPSY

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ACADEMIC DISSERTATION

To be presented, with the permission of
the Faculty of Science of the University of Helsinki,
for public criticism in Lecture Hall 4 of Meilahti Tower Hospital,
Haartmaninkatu 4, Helsinki
on Saturday March 19th, 2016, at 12 o'clock noon.

Helsinki 2016

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Report Series in Physics HU-P-D235
ISSN 0356-0961
ISBN 978-951-51-1574-4 (printed version)
ISBN 978-951-51-1575-1 (pdf-version)
http://www.ethesis.helsinki.fi
Unigrafia Oy
Helsinki 2016

A.-M. Vitikainen: Navigated transcranial magnetic stimulation in preoperative functional mappings for patients with epilepsy, University of Helsinki, 2016, 53 pages + appendices. University of Helsinki, Report Series in Physics, HU-P-D235

Keywords: Navigated transcranial magnetic stimulation, motor cortex, speech-related cortical areas, mapping, epilepsy

Classification (INSPEC 2004): A8730, A8760D, A8780, B7510, B7510D, C7330

Abstract

Individually navigated transcranial magnetic stimulation (nTMS) has been used to locate and map the primary motor cortical areas since the inception of the technique. Recently, it has been added to the pre-surgical routine for epilepsy and brain tumor patients. The accuracy of the mappings in healthy volunteers and brain tumor patients and their feasibility in the pre-surgical evaluation of brain tumor patients have been established. The originating causes for epilepsy are variable and affect the functional localizations in relation to conventional anatomy. A reliable and versatile pre-surgical method for the localization of the functional cortical areas is essential for pre-surgical risk-benefit assessments and it is important to the success of surgical treatments.

In this thesis, I describe an nTMS mapping protocol suitable for clinical use and evaluate the accuracy of the motor cortical mappings by comparing the results with the results of direct electrical stimulation of the primary motor cortex. The accuracy, 11 ± 4 mm for the hand and 16 ± 7 mm for the arm muscle groups, is sufficiently good for pre-surgical evaluation in patients with severe epilepsy. With this patient group, the nTMS technique enables the mapping of the abnormally excitable tissue, which has an impact on the interpretation and reliability of the mappings as well.

In addition to the mapping of the motor cortical areas, the cortical areas related to speech are of key interest in neurosurgery. The speech-related cortical areas are commonly localized noninvasively with functional magnetic resonance imaging techniques. The dominant hemisphere for language functions can be discriminated with the invasive Wada test in the pre-surgical evaluation of epilepsy patients. Recently, nTMS protocols have been introduced for localization of speech-related cortical areas. The analysis of the nTMS elicited modifications in the language task performance have commonly been analyzed manually from video recordings and the methods for the reliable determination of the nTMS elicited speech-response latencies, their categorization and analysis, have been sparse. In the last part of this dissertation, I developed a semi-automated script for the speech-response latency difference calculation based on the accelerometer signal of the speech-response elicited vibrations of the larynx. The developed script was individually optimized for speech-response detection. According to the presented results the method is capable of determining the speech-response latencies with a sensitivity of 96% and a specificity of 71%, against the manual review from the video and visual observations from the accelerometer signals.

Based on the results presented in this thesis, nTMS is a reliable method for the mapping of the functional cortical areas pre-surgically in patients with severe epilepsy. It also enables the mapping of abnormally excitable brain areas.

A.-M. Vitikainen: Navigoidun transkraniaalisen magneettistimulaation käyttö ennen leikkausta tehtävissä toiminnallisten aivokuorialueiden kartoituksissa epilepsiapotilailla, Helsingin Yliopisto, 2016, 53 sivua + liitteet. University of Helsinki, Report Series in Physics, HU-P-D235

Avainsanat: Navigoitu transkraniaalinen magneettistimulaatio, liikeaivokuori, puheeseen liittyvät aivokuorialueet, kartoitus, epilepsia

Luokitus (INSPEC 2004): A8730, A8760D, A8780, B7510, B7510D, C7330

Tiivistelmä

Yksilöllisesti navigoitua transkraniaalista magneettistimulaatiota (nTMS) on käytetty koko menetelmän olemassaolon ajan liikeaivokuoren tarkkaan paikantamiseen, ja viime vuosina menetelmää on ryhdytty käyttämään rutiininomaisesti ennen kirurgista hoitoa epilepsia- ja aivokasvainpotilailla. nTMS-kartoitusten luotettavuus terveillä koehenkilöillä on vakiintunut ja kartoitusten on todettu olevan käyttökelpoisia aivokasvainpotilailla leikkaushoidon suunnittelussa. Vaikeaa epilepsiaa sairastavilla potilailla kohtausten alkusyy voi vaihdella suuresti, millä voi olla vaikutusta aivokuoren toiminnallisten alueiden sijaintiin suhteessa tavanomaiseen anatomiaan. Riittävän monipuolinen ja luotettava toiminnallisten alueiden kartoitus ennen leikkauksen riski-hyötyarviointia ja leikkauspäätöstä on hyödyllistä hoidon onnistumisen kannalta.

Tässä väitöskirjatyössä esittelen kliiniseen työhön soveltuvan epilepsiapotilaiden liikeaivokuoren paikannusprotokollan ja osoitan protokollalla saatujen nTMS-kartoitustulosten tarkkuuden vastaavan aivokuoren pinnalta tehtyjen suorien sähköstimulaatioiden tuloksia. Menetelmän tarkkuuden voidaan todeta olevan riittävä leikkaushoidon suunnitteluun vaikeaa epilepsiaa sairastavilla potilailla. nTMS-menetelmällä on mahdollista paikantaa myös epilepsiaa sairastavien potilaiden poikkeavasti ärtyviä aivokuoren alueita. Tällä on merkitystä kartoitustuloksia tulkittaessa ja niiden luotettavuutta arvioitaessa, samoin kuin kirurgisesti poistettavan alueen laajuutta ja kohdennusta määritettäessä.

Epilepsiaa sairastavien potilaiden liikeaivokuoren paikantamisen lisäksi mielenkiinnon kohteena on puheen tuottamiseen ja käsittelyyn liittyvien aivokuorialueiden paikannus. Näitä aivokuoren alueita paikannetaan tyypillisesti toiminnallisella magneettikuvantamisella. Leikkaushoitoa suunniteltaessa kielellisesti hallitseva aivopuolisko voidaan erottaa myös Wada-testin avulla. Sarjoittaista nTMS menetelmää hyödyntäviä kielellisten alueiden paikannusprotokollia on kehitetty, mutta niissä stimulaation aiheuttamia muutoksia potilaan suoriutumiseen annetusta tehtävästä on tyypillisesti voitu analysoida vain videotallenteita katsomalla. Erityisesti saatujen puhevasteiden toistettavaan ja objektiiviseen luokitteluun ja analyysiin on ollut tarjolla vain vähän menetelmiä.

Analyysin helpottamiseksi kehitin kiihtyvyysanturisignaaliin perustuvan yksilöllisesti optimoidun puoliautomaattisen analysointirutiinin puhevasteiden viive-erojen määritykseen. Tulosten mukaan analysointirutiinin suorituskyky puhevasteiden viiveiden tunnistuksessa oli hyvä (sensitiivisyys 96 % ja spesifisyys 71 % verrattuna manuaaliseen analyysiin videolta ja suoraan signaalista).

Väitöskirjassa esitettyjen tulosten perusteella voidaan todeta nTMS-menetelmän olevan käyttökelpoinen ja luotettava tutkimusmenetelmä vaikeaa epilepsiaa sairastavien potilaiden leikkausta edeltävään toiminnallisten alueiden kartoitukseen. nTMS-menetelmällä voidaan saada myös lisätietoa poikkeavan herkästi ärtyvistä aivoalueista.

Preface and acknowledgements

This thesis is based on a research conducted at the BioMag Laboratory and in the Radiology department at the HUS Medical Imaging Center of the Helsinki University Hospital and at the Department of Physics at the University of Helsinki. I thank the previous and current heads of the Physics Department Prof. Juhani Keinonen and Prof. Hannu Koskinen for supporting my graduate studies at the University of Helsinki, and for the possibility to finish my degree in the doctoral program in Materials Research and Nanosciences (MATRENA). Thank you belong also to the managing and deputy managing directors of the HUS Medical Imaging Center, Jyrki Putkonen and Pekka Tervahartiala, for providing me with excellent research facilities and opportunities at Helsinki University Hospital. I gratefully acknowledge The Finnish Cultural Foundation, the University of Helsinki, and HUS Medical Imaging Center for financial support over the years.

I express my gratitude to the official reviewers of the thesis: Adjunct Prof. Petro Julkunen and Prof. Satu K. Jääskeläinen for their detailed review of my work, valuable comments, suggestions and criticism. I'm also thankful to Mr. Donald Smart for streamlining the language. I thank honorable Academy Prof. Risto J. Ilmoniemi for accepting the invitation to be the official opponent at my dissertation.

Special thanks go to my supervisors: Eero Salli D.Sc. (Tech.) for a kind introduction to the world of the medical image analysis, Adjunct Prof. Jyrki P. Mäkelä for endless encouragement during this long journey, and Prof. Sauli Savolainen for believing in me and gently pushing me forward with the dissertation. I am deeply grateful to you for your soft guidance and encouragement throughout this work. Without you I would not have finished this work.

A warm hug goes to my friends and colleagues at Helsinki University Hospital, especially all the co-authors appearing in this thesis. Without you this would not have happened. Pantelis Lioumis from the BioMag Laboratory deserves special thanks, for not only being a colleague, but also being a good friend over the years. Liisa Metsähonkala from the Video-EEG unit has been, not only an encouraging colleague and a co-author, but also a close mentor over the years.

I would like to thank my parents Ulla-Maija and Raimo for giving me nurturing environment to grow and freedom to pursue the things I wanted. My sisters Anu and Aino deserve thanks for providing contents in my life outside of work and research.

Most importantly, I owe my deepest gratitude to the love of my life, Topias. His patience, understanding and love have supported me all these years. Our first son, Kuura, was born during this dissertation project. Together with Kuura, I have been privileged to discover and marvel at all the things in life and the world that he has wanted to show me.

Thank you 

Torkkelinmäki Helsinki, March 2016

List of original articles

This thesis consists of a summary and four original articles, which are referred to by the Roman number numerals **I - IV** throughout the text.

I **Vitikainen, AM.**, Lioumis, P., Paetau, R., Salli, E., Komssi, S., Metsähonkala, L., Paetau, A., Kicić, D., Blomstedt, G., Valanne, L., Mäkelä, JP., Gaily, E. (2009). Combined use of non-invasive techniques for functional localization for a selected group of epilepsy surgery candidates. *Neuroimage,* 45(2):342-348.

II Mäkelä, JP., **Vitikainen, AM.**, Lioumis, P., Paetau, R., Ahtola, E., Kuusela, L., Valanne, L., Blomstedt, G., Gaily, E. (2013). Functional plasticity of the motor cortical structures demonstrated by navigated TMS in two patients with epilepsy. *Brain Stimulation*, 6(3):286-291.

III **Vitikainen, AM.**, Salli, E., Lioumis, P., Mäkelä, JP., Metsähonkala, L. (2013). Applicability of nTMS in locating the motor cortical representation areas in patients with epilepsy. *Acta Neurochirurgica* 155(3):507-518.

IV **Vitikainen AM.**, Mäkelä, E., Lioumis, P., Jousmäki, V., Mäkelä, JP. (2015). Accelerometer-based automatic voice onset detection in speech mapping with navigated repetitive transcranial magnetic stimulation. *Journal of Neuroscience Methods*, 253(1):70-77.

 The results of the study **I** are also presented in the Ph.D. theses of D. Kicić (Helsinki University of Technology, 2009) and P. Lioumis (Aalto University School of Science, 2012).

Author's contribution

The basis for this thesis was laid in article **I**, where a navigated transcranial magnetic stimulation (nTMS) mapping protocol suitable for clinical purposes was developed, and used to map the selected motor cortical regions of two patients with severe epilepsy. Important issues regarding the functional state of the brain reflected in the nTMS mapping results in patients with severe epilepsy are highlighted in article **II**. In article **III**, the nTMS mapping results were compared with the results of invasive direct electrical cortical stimulation (DECS) in surgically treated epilepsy patients. Article **IV** broadened the scope of this thesis to mappings of the speech-related cortical areas. A measurement setup with an accelerometer sensor was developed for response latency difference determination in nTMS speech mappings for objective analysis.

I The author contributed to the nTMS part of the study. The author participated in planning and performing the mappings, the analysis and interpretation of the results and was in charge of writing the article.

II The author contributed to the planning and performing the mappings, the data analysis and the interpretation of the results, as well as writing the article.

III The author planned the study, took part in the mappings, performed and developed the data analysis and was in charge of writing the article.

IV The author developed the algorithm together with the second author, performed the data analysis, interpreted the results, and was in charge of writing the article.

Symbols and abbreviations

3-D	Three-dimensional
$\boldsymbol{A}$	Vector potential field
ADM	Abductor digiti minimi muscle
AH	Abductor halluces muscle
AMT	Active motor threshold
APB	Abductor pollicis brevis muscle
$\boldsymbol{B}(\boldsymbol{r}, t)$	Magnetic field at position $\boldsymbol{r}$ and at time t
BB	Biceps brachii muscle
CT	Computed tomography
DE	Deltoideus muscle
DECS	Direct electrical cortical stimulation
$DECS_{COG}$	The arithmetic mean of the coordinates of the electrode centers weighted by the inverse of the stimulating current
$DECS_G$	The arithmetic mean of the coordinates of the electrode centers
$DECS_{MIN}$	The center location of the electrode eliciting motor response with the lowest current
$dist(nTMS_G, DECS_{COG})$	3-D Euclidian distance between $nTMS_G$ and $DECS_{COG}$
$dist(nTMS_G, DECS_G)$	3-D Euclidian distance between $nTMS_G$ and $DECS_G$
$dist(nTMS_G, DECS_{MIN})$	3-D Euclidian distance between $nTMS_G$ and $DECS_{MIN}$
$\boldsymbol{E}$	Total electric field
$\boldsymbol{E}_1$	Primary electric field
$\boldsymbol{E}_2$	Secondary electric field
EDC	Extensor digitorum communis muscle
EEG	Electroencephalography
EMG	Electromyography
FBP	Flexor pollicis brevis muscle
FCD	Focal cortical dysplasia
FCR	Flexor carpi radialis muscle
FH	Flexor halluces muscle
fMRI	Functional magnetic resonance imaging
$I(t)$	Current pulse
μ_0	Permeability of free space
MEG	Magnetoencephalography
MEP	Motor evoked potential
MR	Magnetic resonance
MRI	Magnetic resonance imaging
msop	Maximum stimulator output
MT	Motor threshold
nTMS	Navigated transcranial magnetic stimulation
$nTMS_G$	The arithmetic mean of the stimulation site coordinates projected to the brain surface
PET	Positron emission tomography
Φ	Electrostatic potential
RF	Rectus femoris muscle
RMT	Resting motor threshold
rTMS	Repetitive transcranial magnetic stimulation
σ	Electrical conductivity
SO	Soleus muscle
SP	Silent period
TA	Tibialis anterior muscle
TMS	Transcranial magnetic stimulation

Contents

1 Introduction

Epilepsy is the fourth most common neurological disorder with an approximately 1% prevalence worldwide and in Finland [Suomalaisen Lääkäriseuran Duodecimin ja Suomen Neurologinen Yhdistys ry:n asettama työryhmä 2013; Suomalaisen Lääkäriseuran Duodecimin ja Suomen Neurologinen Yhdistys ry:n asettama työryhmä 2014; World Health Organization 2015]. The disorder is associated with elevated mortality [Neligan et al. 2011] especially with childhood-onset epilepsy [Sillanpää et al. 2010]. The mortality rate depends on the control of seizures. With varying causes for the disorder, up to 70% of children and adults can be successfully treated with anti-epileptic medication. In the remaining patients, the response to medication stays unsatisfactory. The multiplicative effects of medication resistant epilepsy such as handicap and restricted education or working capabilities are significant for the individual and for the community as well [Lindsberg et al. 2014]. Some of these patients benefit from surgical treatment, which is considered to be very cost-effective especially for children [Silfvenius 1999].

In the majority of the patients, no cause for the disorder can be identified. The functional organization or the excitability of the affected cortex may be altered [Janszky et al. 2003]. Approximately one fifth of the candidates for surgical treatment require invasive intracranial electroencephalography (EEG) to delineate the epileptic focus in addition to preoperative noninvasive imaging, electrophysiological and functional studies [Adelson et al. 1995; Jayakar 1999; Rosenow et al. 2001; Snead 2001]. The traditional methods for the localization for motor functions include direct electrical cortical stimulation (DECS) via semi-permanent subdural electrodes or directly during the surgery. For the evaluation of the lateralization of the language functions, the intracarotid amobarbital test (the Wada test) is used [Wada 1949]. However, the use of intracranial electrodes as well as the Wada test is associated with considerable risks for complications [Loddenkemper et al. 2008; Taussig et al. 2015], although the DECS performed while the intracranial electrodes are already implanted, adds only slightly to the risk. This emphasizes the need for adequate noninvasive methods for assessing the spatial relationship between function, anatomy and pathology before surgery.

The transcranial magnetic stimulation technique (TMS) was adopted for the study of central motor pathways after its first demonstration in 1985 [Barker et al. 1985; Amassian et al. 1989; Levy et al. 1991]. The addition of individual magnetic resonance imaging (MRI) based navigation to TMS (navigated TMS (nTMS)) in the late 2000s advanced the technique's accuracy and feasibility in preoperative functional mappings [Julkunen et al. 2009b; Picht et al. 2009; Säisänen et al. 2010; Picht et al. 2012; Frey et al. 2014]. TMS mapping of cortical areas is based on the idea of the stimulating a region of the brain and measuring the motor response, or observing the behavioral effects [Pascual-Leone et al. 1991; Wilson et al. 1993b]. With individual MRI-based navigation, the region of the stimulation can be referenced to individual anatomy. It has been suggested that the TMS method only stimulates regions with corticospinal projections, making it more precise for functional localizations than functional MRI (fMRI) where all sensorimotor cortical areas are activated by the motor task [Macdonell et al. 1999]. This might be also nTMS' disadvantage when the mapping of higher

cortical function is indicated.

Preoperative nTMS functional motor mappings have proven to be useful and sufficiently reliable, and thus the method has been adopted into wide clinical use. The use of nTMS to map the speech-related cortical areas is still work in progress [Picht et al. 2013], as the parameters of the protocols have not been fully optimized for clinical use yet. The usefulness of the speech mappings might be increased when combined with online MRI diffusion tensor imaging based fiber tracking during stimulation [Sollmann et al. 2015] for superior individual nTMS stimulation targeting, and objective means to detect and categorize the obtained results.

This thesis was designed to develop a clinical nTMS protocol for mapping of motor cortical areas in patients with severe epilepsy in the course of their pre-surgical workup and evaluate the technique's accuracy against the DECS method, currently the gold standard in functional localizations. The last part of the thesis focused on developing an objective and repeatable analysis method for speech-response latency difference calculation that could be used in the nTMS mapping of speech-related cortical areas.

2 Background

2.1 Methods for mapping functional cortical areas

The organization of the functional cortical regions and their correlation with the cortical anatomy has troubled scientists and medical doctors for well over a century, ever since the first documentation of a specialized region involving speech control by Broca in 1861. In the early years of epilepsy research and surgery, the functionality of the cortex was studied by DECS in patients and a map of the functional organization of the brain was outlined [Foerster 1936; Penfield et al. 1937; Penfield et al. 1950], creating the well-known maps of human sensory and motor homunculi.

DECS, either by implantable electrode grids or directly during the surgery, has been the gold standard for the functional localizations of the sensorimotor cortex ever since. In electrical stimulation mapping a short train of alternating current pulses is driven through the electrodes to the surface of the cortex [Lesser et al. 1987; Jayakar 1993; Nathan et al. 1993b]. The produced electric field stimulates the underlying neuronal axons directly [Ranck 1975]. For motor cortex localization the electromyography (EMG) is recorded intramuscularly from selected muscles in anesthetized patients [Taussig et al. 2015]. For language localizations, the stimulation needs to be used with the conscious patients.

The Wada test was introduced more than 50 years ago as a technique to determine the hemispheric lateralization of language functions prior to surgical resection [Wada 1949]. The technique was later modified to evaluate memory functions and predict the risk of the loss of memory following resective surgery on the temporal lobe [Milner et al. 1962]. The Wada test is still the gold standard for language lateralization in pre-surgical evaluation of epilepsy. In the test, the patient is awake and an anesthetic agent is introduced into one hemisphere at a time via the intracarotid arteries, thus inhibiting the ipsilateral hemisphere. The idea is to shut down any language-related functions in that hemisphere and to test the other hemisphere's involvement with these functions using a series of language-related tests. One major practical limitation of the Wada test is that it is a lateralizing test and further localization of the language functions can not be made [Abou-Khalil 2007].

The need for noninvasive methods for the assessment of the functional organization led to the introduction of positron emission tomography (PET) with oxygen-15 labeled water [Fox et al. 1987], magnetoencephalography (MEG) [Gallen et al. 1995], fMRI [Mueller et al. 1996], and TMS [Barker et al. 1985; Amassian et al. 1989; Levy et al. 1991] for mapping the sensorimotor and language-related cortical regions. The clinical use of PET in functional localizations did not receive much interest as the mapping of multiple cortical sites required a considerable amount of time and a radiation dose, the spatial resolution in the early days was modest and the equipment was not widely available.

In MEG the tiny magnetic fields produced by the natural electrical activity of the brain are picked up by the extremely sensitive sensor setup in a magnetically shielded room

[Hämäläinen et al. 1993]. For sensorimotor cortex localization, median nerve stimulation is used [Korvenoja et al. 2006]. For the language localizations language stimuli are used, the corresponding event-related field patterns are identified and their sources are localized [Papanicolaou et al. 2004]. Also correlation of the sensorimotor spontaneous activity patterns with motor unit firing recorded with surface EMG during voluntary contraction or with a motor task can be used [Salenius et al. 1997; Mäkelä et al. 2001]. The anatomical landmarks and head-positioning indicator coils are located in the reference system of the measurement setup and later co-registered with the individual MRIs. The accuracy of the presurgical cortical MEG localizations have been established in the primary somatosensory cortex [Sutherling et al. 2001; Castillo et al. 2004; Korvenoja et al. 2006] by comparing the results with the invasive mappings. Based on the state-of-the-art practices, an 8 mm confidence interval has been recently suggested around the estimated source location in preoperative median nerve stimulation paradigms [Solomon et al. 2015], resulting in reasonable spatial accuracy. MEG can also be used for the localization of epileptic foci. The most prominent limiting factor for the method seems to be the small number of laboratories performing MEG.

The fMRI approach rapidly gained a broad degree of interest as it could be done with clinical MR devices, already widely available. The key assumption is the existence of a causal relationship between neural function and cerebral blood flow. Most often the effects of deoxyhemoglobin on the magnetic resonance (MR) signals and the difference between the oxygenated and deoxygenated blood flow is used [Ogawa et al. 1992]. The changes in the blood flow dynamics are supposed to reflect the task-related changes in the local neuronal activity. One advantage of fMRI localization is its ability to represent all the areas contributing to the functional network studied, including the areas located more deeply in the brain [Rutten et al. 2010]. On the other hand, it is difficult to separate the primary cortical areas from the secondary or non-essential activations, and there are no standardized user-independent protocols for functional localizations. The method is not limited to only some functional entities, but any sensorimotor or higher cognitive function can be studied. fMRI is currently used routinely for sensorimotor and language localization worldwide although its accuracy compared with DECS or nTMS has been criticized [Giussani et al. 2010].

2.2 Navigated transcranial magnetic stimulation

After its introduction in 1985, the TMS method and techniques applying it for functional mappings have evolved quickly. Especially the innovation of adding individual MRI-based online frameless navigation to the TMS stimulation has opened a new era for the method [Herwig et al. 2001] and enabled its use in presurgical planning with adequate accuracy.

2.2.1 Physics

The TMS rests on the principle of inducing a current flow in an individual's brain by magnetic induction. The desired effect, the localized excitation of neuron population, is generated by driving an intense time dependent current pulse $I(t)$ through a stimulation coil placed over the individual's head. The current pulse circling in the coil windings C generates a time varying magnetic field $\boldsymbol{B}(\boldsymbol{r}, t)$ around it according to the Biot-Savart

Law (2.1), where $\boldsymbol{r}$ denotes the position and t the time point at which the magnetic field is calculated. This, in turn, induces a primary electric field $\boldsymbol{E}_1$ following the Maxwell–Faraday equation (2.2) inside the individual's brain leading to a current flow and charge accumulation on the conductivity boundaries or gradients of conductivity on the path of the flow. These accumulated charges create an electrostatic potential Φ, giving rise to a secondary electric field $\boldsymbol{E}_2$ (2.3). As the $\boldsymbol{B}$ can be rewritten with the vector potential field $\boldsymbol{A}$ as $\boldsymbol{B} = \nabla \times \boldsymbol{A}$, an equation for the total electric field $\boldsymbol{E}$ can be written (2.4). The μ_0 in the equations is the permeability of free space and $d\boldsymbol{l}(\boldsymbol{r}')$ is the vector along the windings of the coil. [Barker et al. 1987; Cohen et al. 1990; Roth et al. 1991]

$$\boldsymbol{B}(\mathbf{r}, \mathrm{t}) = \frac{\mu_0 \, C \, I(t)}{4\pi} \oint_C \frac{d\boldsymbol{l}(r') \times (\boldsymbol{r} - \boldsymbol{r}')}{|\boldsymbol{r} - \boldsymbol{r}'|^3} \tag{2.1}$$

$$\nabla \times \boldsymbol{E}_1 = -\frac{\partial \mathbf{B}}{\partial \mathrm{t}} \tag{2.2}$$

$$\boldsymbol{E}_2 = -\nabla \Phi \tag{2.3}$$

$$\boldsymbol{E} = \boldsymbol{E}_1 + \boldsymbol{E}_2 = -\frac{\partial \mathbf{A}}{\partial \mathrm{t}} - \nabla \Phi \tag{2.4}$$

The eventual shape and magnitude of the electric field in the brain depend on the shape and size of the stimulation coil and stimulation parameters [Thielscher et al. 2004], the location, orientation and the tilting of the coil in respect to the individual's head, the heterogeneous and anisotropic electrical structure and characteristics of the brain and the surrounding tissues [Miranda et al. 2003; Toschi et al. 2009; Chen et al. 2010]. The TMS-generated magnetic field strength decreases exponentially with the distance from the coil [Ruohonen et al. 1999; Stokes et al. 2007].

An example of an electric field induced by a single pulse in a homogeneous spherical model through a figure-of-eight coil is presented in Figure 1. The current pulse can have

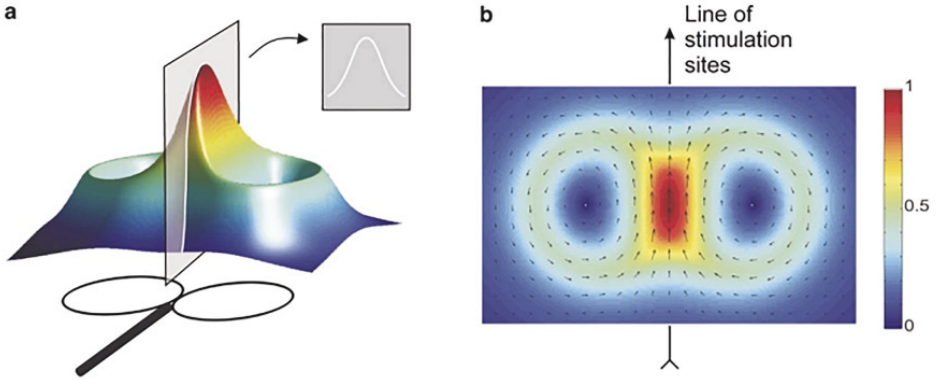

Figure 1. a) Electrical field strength calculated on a plane 1 cm above the coil plane. The field strength is coded as both color and height. The inset depicts the bell-shaped form of the field strength along the axis parallel to the coil handle. b) The 2D plot of the electrical field on the same plane. The strength is color-coded. The arrows indicate the direction of the induced currents. For the same current direction to be maintained over various target sites, these sites have to lie on the indicated line. The figure is reprinted from [Thielscher et al. 2002], with permission from Elsevier.

essentially one phase (monophasic) resembling the first quarter of a sine-wave and then decaying slowly to zero, two phases (biphasic) being a full sine wave or multiple phases (polyphasic) having multiple sine waves. Stimulation with monophasic pulses is more focused, but also less effective [Sommer et al. 2006; Salvador et al. 2011]. Biphasic stimuli produce more complex activation in the cortex reducing the focality but increasing the effectiveness [Kammer et al. 2001; Di Lazzaro et al. 2004].

The pulses can be delivered independently, in pairs or repetitively. Single pulse can be used to elicit responses from the motor circuitry. Paired pulses which are delivered via two consecutive single pulses of the varying intensity and time between the pulses to the same cortical area, can be used to study the excitability in human motor cortex [Kujirai et al. 1993]. Repetitive stimulation (rTMS) delivered via repeated single pulses of the same intensity to the same cortical area can have suppressing or enhancing effects depending on the frequency used for the repetition [Pascual-Leone et al. 1994a] as well as the spreading of the activation from the target area [Terao et al. 2002; Di Lazzaro et al. 2008]. The lower frequencies in rTMS tend to suppress the excitability [Pascual-Leone et al. 1994a; Pascual-Leone et al. 1998], whereas higher frequencies of the stimulation train seem to increase the excitability temporarily [Pascual-Leone et al. 1998; Yozbatiran et al. 2009]. Short 5 to 10 pulse trains of repeated single stimuli with frequency of 5 to 10 Hz can also be used in mappings of higher functions, such as language.

In the navigation, the individual's anatomic head MRI is registered with three external anatomical landmark pointers obtained from the MRIs and from the individual's skin. The initial registration is defined by pointing to an additional set of surface points on the skin around the head [Herwig et al. 2001]. The identification of the landmark points is performed with a stylus with infrared reflectors attached to it and to the tracker headband worn by the individual, enabling free movement of the head during the study. The stimulation coil is equipped with a rigidly attached set of similar trackers to enable online tracking of the coil location. An infrared camera locates these trackers during the registration and during the whole experiment. The coil location, its orientation, and the subsequently calculated estimate of induced electric field can be visualized online during the experiment, the stimulation sites can be planned ahead, repeated, and the evoked responses linked to the stimulation sites and documented [Ilmoniemi et al. 1999; Ruohonen et al. 2010].

2.2.2 Physiology

The neurophysiological mechanism and the corresponding site of brain activated by TMS are not fully comprehended. In the magnetic stimulation of peripheral nerves, the gradient of the electric field along the nerve plays the most important role [Roth et al. 1990; Nilsson et al. 1992; Maccabee et al. 1993]. Cortical neurons have a variety of different orientations in relation to the induced electric field due to the differences between cortical regions, the gyral folding, and the differences in the substructure of the neurons and their axons. This likely leads to variations in stimulation sites and mechanisms [Roth 1994; Silva et al. 2008; Salvador et al. 2011].

The effects of the stimulation of the motor cortex have been widely studied by

theoretical and model-based calculations. The results can be compared with experimental evidence since the resulting peripheral effect can be measured. With single pulses delivered to the motor cortex, the current interpretation is that neurons are excited most preferably when the induced electric fields are oriented perpendicular to the central sulcus creating a natural-like current flow in the crown of the precentral gyrus where the axons are longitudinally oriented and bending downwards (Figure 2) as well as in the axonal terminations [Rushton 1927; Maccabee et al. 1993; Nagarajan et al. 1993; Abdeen et al. 1994; Pascual-Leone et al. 1994b; Maccabee et al. 1998; Salvador et al. 2011]. The optimal orientation of the coil and thus the orientation of the induced electric field depend also on the selected intensity and pulse shape [Patton et al. 1954; Di Lazzaro et al. 2001; Terao et al. 2002].

According to the current view, in the transsynaptic activation the most probable site of depolarization is the axon terminals of the long-range intracortical interneurons or axon collaterals located at the crown of the gyrus [Esser et al. 2005; Salvador et al. 2011]. The pyramidal tract neurons located at the lip of the sulcus seem to be stimulated directly at the bend of the axon in the border of grey and white matter, but with a higher threshold than the interneurons [Roth 1994; Ruohonen 1998; Salvador et al. 2011]. The mechanism of activation is always the charge accumulation either at axonal termination or at the bend. The activation in the cell originates from the high concentration of the voltage-gated sodium channels in the membrane of these cell segments [Catterall 1981], opened by the accumulated charges modulating the membrane potential. An action potential is fired when the membrane potential exceeds a threshold value.

The coil is oriented with relation to the central sulcus and thus the orientation of the induced electric field in the motor cortex is significant for generation of motor evoked responses [Janssen et al. 2015]. The motor evoked potentials (MEPs) consist of multiple components that can be studied epidurally from the spinal cord [Amassian et al. 1989]. The first component (named the D-wave) with a short latency is thought to be generated at the direct depolarization of the initial axon segment of the corticospinal neuron and the subsequent components (named the I-waves) with approximately 1.5 ms periodicity

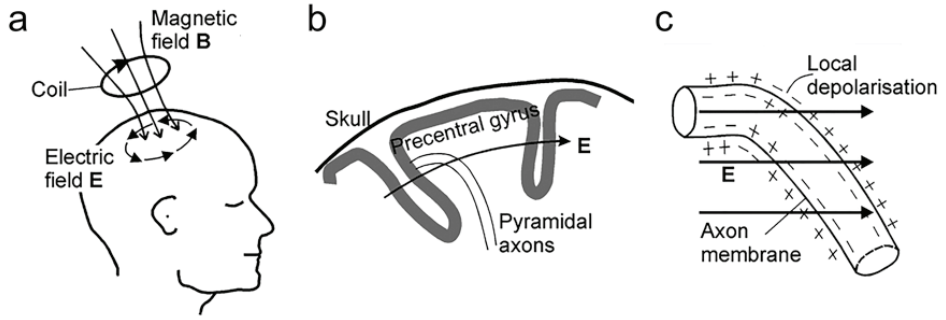

Figure 2. Principles of TMS. a) Current I(t) in the coil generates a magnetic field **B** that induces an electric field **E**. b) A schematic illustration of a lateral view of the precentral gyrus in the right hemisphere. Two pyramidal axons are shown, together with a typical orientation of the intracranial **E**. c) The induced electric field affects the transmembrane potential, which may lead to local membrane depolarization and axon potential firing of the neuron. Pyramidal axons are likely stimulated near bends. Figure adapted from [Ruohonen 1998].

are thought to be generated in the transsynaptic activation [Patton et al. 1954; Di Lazzaro et al. 1998; Di Lazzaro et al. 2004].

The intensity and the waveform of the stimulation have also been found to have an impact on the mechanism of activation: With intensities around the threshold and with a current oriented posterior-to-anterior the pyramidal cell activation is thought to be transsynaptic [Patton et al. 1954; Di Lazzaro et al. 2001; Terao et al. 2002; Di Lazzaro et al. 2004] with both a monophasic and biphasic pulse shapes generating indirect I-waves. With intensities which are double the threshold a direct corticospinal compound contributes to the activation when a monophasic pulse shape is used [Di Lazzaro et al. 1998] generating a D-wave. With a monophasic pulse shape and the current oriented in the antero-posterior direction, or with a biphasic pulse shape with very high intensities the mechanism is twofold representing both the transsynaptic and direct components [Di Lazzaro et al. 2001]. With the intensities just above the resting motor threshold (RMT), a value used commonly in the mappings, the most likely scenario of activation is through the transsynaptic activation at the crown of the gyrus. The stimulating area and mechanisms in language area stimulations are more difficult to evaluate than in the motor cortex due to the complicated neural network of underlying higher cognitive functions.

2.2.3 Cortical mapping

By measuring the evoked response with EMG from the desired muscles, a detailed map of stimulation sites evoking excitatory or inhibitory responses can be drawn [Amassian et al. 1989; Levy et al. 1991; Wassermann et al. 1992; Wassermann et al. 1993; Wilson et al. 1993b]. With the modern online navigation, the induced electric field pattern can be estimated to target the stimulation and the evoked EMG response can be linked to the stimulated site [Krings et al. 1997; Ettinger et al. 1998; Kammer et al. 1998; Herwig et al. 2001; Ruohonen et al. 2010].

In the tradition of mapping studies, the term (primary) motor cortex mapping refers to the mapping of the areas that elicit observable movements or recordable response in the muscle of interest. The primary motor cortex in the precentral gyrus appears to hold the large scale somatotopic organization of the body parts but also to encode movements and kinematic parameters explaining the overlap in the representation areas of adjacent body parts [Penfield et al. 1950; Schieber et al. 1993; Hluštík et al. 2001]. It is still unclear, how these other parameters are represented in the primary motor cortex and how the final fine motor commands are generated [Kalaska et al. 1992; Desmurget et al. 1998; Lacquaniti et al. 1998; Kakei et al. 2003]. The resulting map represents not only the underlying corticospinal and kinematic maps, but also the ongoing cortical and spinal activity and the stimulation parameters all at the same time [Najib et al. 2011]. The stimulation of nonprimary motor areas may also produce MEPs indistinguishable from those induced by stimulation of the primary motor cortex [Vaalto et al. 2011].

In clinical settings, nTMS has been used with brain tumor patients with tumors close to their sensorimotor cortices [Picht et al. 2009; Krieg et al. 2012] or close to the hand and/or facial motor cortices [Säisänen et al. 2015]. The accuracy of nTMS compared with the freehand DECS has been established in this patient group to be on a scale of

few millimeters [Picht et al. 2009; Picht et al. 2011; Krieg et al. 2012]. nTMS mappings were found to be beneficial for surgical planning in three-fourths of the patients [Picht et al. 2012], changing the treatment plan in six out of eleven patients with gliomas non-enhancing in MRI [Picht et al. 2013], and impacting the planned surgical treatment in 79% of 250 patients with brain tumors in the motor eloquent regions [Frey et al. 2014].

nTMS preoperative mapping of the motor cortical areas of epilepsy patients, have been found to be a feasible tool for planning in six out of 10 patients aged from 2 to 55 years [Säisänen et al. 2010]. nTMS has been reported to enable the mapping of abnormally excitable epileptogenic areas as well [Schmidt et al. 2010]. Commonly used antiepileptic medications increase the motor threshold (MT) [Ziemann et al. 2015], and this can be dose-dependent [Danner et al. 2013]. The underlying neuronal condition with this modulated cortical excitability, resulting from possibly multiple concurrent antiepileptic medications, complicate the interpretation of the results and might even hinder the elicitation of the TMS motor responses [Ziemann et al. 2015].

The mapping of language-related cortical areas has recently received growing attention. nTMS mapping with navigated rTMS has been tested with patients with brain tumors near their classical cortical language areas [Picht et al. 2013; Tarapore et al. 2013; Krieg et al. 2014; Rösler et al. 2014]. The nTMS mapping results were compared with the results from the awake craniotomy with DECS and a good concordance of the results was found [Picht et al. 2013; Tarapore et al. 2013; Krieg et al. 2014; Ille et al. 2015]. There are many useful protocols and paradigms for speech area mapping and the technique is still being developed. Nevertheless, nTMS mapping has been found to have an impact on reducing the extent of surgical craniotomy and diminishing postoperative deficits [Sollmann et al. 2015].

The TMS mapping results have been projected from the skin to the cortical surface in the pre-navigation era to localize results in relation to the cortical anatomy and to enable comparison of TMS results with PET and fMRI results [Wassermann et al. 1996; Classen et al. 1998; Herwig et al. 2002; Lotze et al. 2003]. In these studies, the projections of the TMS results were made along the line of the head surface normal. The location of the induced electric field maxima is theoretically located along the surface normal in the spherical head model if the stimulation coil is held exactly tangential to the scalp [Cohen et al. 1990; Thielscher et al. 2004]. This approach is reasonably accurate in the motor cortex when compared with more realistic head models [Nummenmaa et al. 2013].

2.3 Direct electrical cortical stimulation

DECS is based on the concept of stimulating a local area of the cortex by directly introducing a current flow in the cortex. The localized excitation of neurons is generated by driving a train of current pulses through the electrodes located on the cortical surface. The electrode pair generates an electric field $\boldsymbol{E}$ in the brain. The field can be presented with the electrostatic potential Φ and electrical conductivity σ and written as (2.5) [Nathan et al. 1993a; Nathan et al. 1993b]. The addition of the relevant boundary conditions (the known applied voltage at the electrode contact, the current permanence in the model, and at least piecewise continuous conductivity) reduces the equation (2.5)

to a Laplace equation (2.6), which can be solved analytically for simple geometries. For complex geometries modelling can be used [Nathan et al. 1993b].

$$\vec{\nabla} \cdot \left(\sigma \vec{\nabla} \Phi\right) = 0 \tag{2.5}$$

$$\nabla^2 \Phi = 0 \tag{2.6}$$

The current density is estimated to have its maximum in the tissue underneath the electrodes and to decrease rapidly with depth from the electrodes on the cortical surface [Nathan et al. 1993b]. The selection of adjacent electrodes produces more focused stimulation than the selection of electrodes distant from each other [Phillips et al. 1962; Stark et al. 1962; Nathan et al. 1993b]. In practice, the same electromyographic response was obtained with DECS from locations within 11 ± 1 mm distance [Schiffbauer et al. 2002]. The stimulation parameters, such as the frequency [Jayakar 1993], the pulse duration, as well as the electrical structure and characteristics of the brain and the surrounding tissues, including the thickness of the cerebrospinal fluid between the cortex and the electrodes [Manola et al. 2005], have an impact on the eventual shape and magnitude of the electric field.

The physiology of DECS is only partially understood [Borchers et al. 2012]. The stimulation is focused on the most excitable elements in the cortex, the large fibers of the pyramidal cells [Tehovnik et al. 2006]. Based on extracellular recordings, the activation is currently thought to take place in the axon of the pyramidal neuron [Rattay 1999], either in the initial segment or in the axonal collaterals [Gustafsson et al. 1976; Nowak et al. 1998; Rattay 1999; MacIntyre et al. 2002]. This mechanism generates mainly the direct D-waves [Di Lazzaro et al. 1998]. The action potential generation in the cellular level is similar to that induced by TMS.

2.4 Motor evoked potential responses

The eventual target of the stimulation of TMS and DECS is to elicit action potentials in motor cortex neurons that project to the targeted muscles. The success of the stimulation can be evaluated by observing the target muscle twitch, or by measuring the electrical activity burst of the muscle with a pair of electrodes placed on the skin above the muscle and its tendon or intramuscularly. MEP responses are commonly used to evaluate the level of cortical excitability, whereas the silent period (SP) responses after the MEP can be used to evaluate the inhibitory aspects. Both response types can be used in functional mappings. Examples of the responses are given in Figure 3. The MT represents the lowest stimulus intensity required to elicit a MEP response of a predefined size in 50% of the trials in the target muscle. Due to the variable nature of the MEP responses [Brasil-Neto et al. 1992; Kiers et al. 1993; Nielsen 1996] a statistical method for MT determination is used [Rossini et al. 1994] either at rest (RMT) or during a controlled contraction of the muscle (active motor threshold (AMT)).

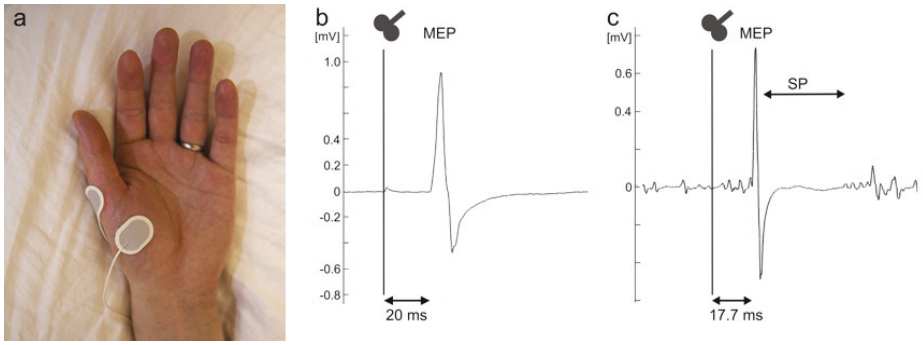

Figure 3. An example of surface EMG electrode placement in the left APB, b) a MEP response and c) a post MEP SP response elicited by nTMS.

During relaxation, the MEPs tend to be smaller than during a slight contraction [Kischka et al. 1993; Mazzocchio et al. 1994], as the constant activation changes the excitability both at the cortical and spinal levels [Mazzocchio et al. 1994]. Mapping in the relaxed state may thus be complicated by excitability fluctuations not measured by EMG. On the other hand, mapping during a controlled steady contraction requires online monitoring of the level of contraction either by the EMG activity or by the applied force [Lim et al. 1992; Nielsen 1994] complicating the measurement setup.

The post-MEP SP, a period of minimal EMG activity in an activated muscle after the stimulus and concurrent MEP response, reflects intracortical inhibition [Inghilleri et al. 1993; Wilson et al. 1993c]. The center of the map based on the duration of the post-MEP SP has been shown to be similar to that of map based on the amplitude of the MEPs [Wilson et al. 1993a; Cruccu et al. 1997], but the area of the SP maps is slightly larger [Wilson et al. 1993a]. In mappings, the SP response can be useful, when MEPs cannot be elicited with the available stimulator output, as a slight preactivation of the target muscle lowers the MT and may enable the SP response recordings.

2.5 Speech response

In contrast to the motor cortex stimulation, the efficacy of the stimulation of the speech-related areas cannot be directly measured, but behavioral responses elicited or inhibited by the stimulation can be registered. In the object naming paradigm, suitably located and correctly timed stimulations may produce “errors” in the naming process [Corina et al. 2010; Pouratian et al. 2010]. Errors such as being unable to name an object (no-response), variations in the performance, the use of words that have meaning only to the individual independent of their common meaning (neologism), the substitution of a word with a related one (semantic error), the substitution of a word with a non-word resembling the correct one (phonemic error), or the use of many words instead of the correct one (circumlocutions) can be elicited [Corina et al. 2010].

2.6 Combining results from different modalities

Each method used in the mapping of functional organization as well as imaging the

anatomy has its limitations and a combination of modalities is commonly used in preoperative workup, during the surgery, and when the outcome is evaluated. For convenient visualization of the results from different modalities and techniques the results are registered into a common coordinate system and viewed relative to the patient's anatomy [Risholm et al. 2011]. The segmentation, registration and fusion of the data, especially in the case of pre-, intra-, and postoperative imaging data and neuronavigation, inevitably contains some degree of uncertainty [Shamir et al. 2009]. Medical image analysis aiming to extract clinically useful information from the multiple images, including the segmentation, registration and fusion components is a rapidly growing discipline outside the scope of this dissertation.

3 Aims and scope of the study

The scope of this thesis was to establish the nTMS method as a clinical tool to be used with epilepsy patients and advance its application in preoperative speech area localization. The studies were designed in order to:

1 Develop a clinical nTMS protocol for preoperative motor cortex mappings, and depict the functional plasticity of the motor cortex and the subsequent issues in the interpretation of the mapping results associated with epilepsy.

2 Evaluate the reliability and feasibility of the preoperative nTMS motor cortex mappings for patients with epilepsy.

3 Develop an accelerometer sensor-based speech response onset detection and latency determination setup to facilitate nTMS speech area mapping.

4 Materials and methods

All nTMS measurements involving patients in this series of studies were performed at the BioMag Laboratory of the HUS Medical Imaging Center in Helsinki University Hospital, Helsinki, Finland as part of their clinical preoperative care and the procedures were supervised by medical doctors. The research projects were approved by the Ethics Committee of the Hospital District of Helsinki and Uusimaa.

DECS were performed at the Video-EEG unit in the Children's Castle Hospital in Helsinki University Hospital, Helsinki, Finland during the period of the intracranial EEG study. The stimulations were performed and the results evaluated by medical doctors and the data were collected for clinical purposes.

In this thesis I present the results for 24 individual patients, 6 tumor and 18 epilepsy patients of ages 9-39 years. The patient characteristics are outlined in Table 1. The measurements were performed during 2007-2015.

Table 1. The patients presented in this thesis, according to the articles in which they appear. * denotes patients whose data were lost due technical difficulties.

Article	Patient no. in the article	Age [years]	Sex [F/M]	Condition [Epilepsy/Tumor]
I	1	22	F	Epilepsy
	2	16	F	Epilepsy
II	1	9	M	Epilepsy
	2	19	M	Epilepsy
III	1 (same as Pat 1 in article **I**)	22	F	Epilepsy
	2 (same as Pat 2 in article **I**)	16	F	Epilepsy
	3	14	F	Epilepsy
	4	12	F	Epilepsy
	5	12	M	Epilepsy
	6	14	M	Epilepsy
	7	35	M	Epilepsy
	8 (same as Pat 1 in article **II**)	9	M	Epilepsy
	9	17	M	Epilepsy
	10	25	F	Epilepsy
	11	29	F	Epilepsy
	12	16	M	Epilepsy
	13	19	F	Epilepsy
IV	1	31	F	Tumor
	2	39	F	Tumor
	3	36	M	Tumor
	4	39	M	Tumor
	5	12	M	Epilepsy
	6	17	F	Epilepsy
	7	37	M	Tumor
	8	15	F	Epilepsy
	9	17	M	Tumor
	10	17	M	Epilepsy
	11*	14	M	Epilepsy
	12*	9	F	Epilepsy

4.1 Instrumentation

In this dissertation, different nTMS infrastructures were used. The eXimia NBS and EEG (Nexstim Ltd., Helsinki, Finland) was used for the TMS stimulus navigation and delivery, and for the concurrent EEG recordings. A figure-of-eight stimulation coil was used in all studies.

The MEP responses were recorded with a Keypoint EMG device (Keypoint, Medtronic, Minneapolis, USA), ME6000 EMG device (ME6000, Mega Electronics Inc., Kuopio, Finland), or Nexstim EMG (Nexstim, Helsinki, Finland).

For the speech paradigm setup and stimulus delivery, the NBS speech mapping module (NexSpeech, Nexstim Ltd., Helsinki, Finland) was used. For the accelerometer setup a purpose-built three-axis accelerometer (ADXL330 iMEMS® Accelerometer, Analog Devices, Norwood, MA), similar to that used by [Bourguignon et al. 2013], was used. The accelerometer was attached to the skin on the left side of the patient's throat, over the larynx site where palpable vibrations during vocalization could be clearly felt. The accelerometer signals were connected to the EMG channels of the NBS system.

The nTMS mapping results were compared with stimulations performed via intracranial subdural grid electrodes. The instrumentation at the Video-EEG unit in the Children's Castle Hospital was used. The implanted electrode grids were chosen by clinical and individual needs. A constant current stimulator (Grass S-12 biphasic stimulator, Grass Instrument Co., Quincy, MA, USA; Osiris NeuroStimulator, Inomed, Teningen, Germany; Micromed SD LTM STIM, Micromed, Mogliano Veneto, Italy) was used to deliver the direct electrical stimulation.

4.2 Preoperative nTMS mappings

In this dissertation a protocol was developed to enable the mapping of the primary motor cortex of patients referred to the study with a clinical indication. The cortical area controlling the thumb abduction and extension (abductor pollicis brevis muscle (APB)) in the hand was first located by stimulating the presumed hand area based on the individual MRI (the hand knob if distinguishable [Yousry et al. 1997]) from the hemisphere affected by epilepsy. The stimulation intensity used in the beginning of this search phase was clearly over the RMT to locate the site producing the maximal MEP responses. At this location the most favorable orientation of the stimulation was searched for and the RMT was determined as the lowest stimulation intensity at which five out of ten stimuli evoked a MEP of at least 50 μV peak-to-peak [Rossini et al. 1994; Rossini et al. 1999]. The corresponding electric field strength at the individual cortical depth was recorded. This initial phase of the mapping was performed in articles **I-IV**. An example of the nTMS measurement setup is shown in Figure 4.

The primary motor cortex in the precentral gyrus was mapped with an intensity of 105-110 % RMT of the APB [Macdonell et al. 1999] to maintain the focality of the stimulation. The purpose of the mapping was to delineate the cortical extent from where MEPs could be elicited from the target muscle. Additionally, the representation areas of other hand muscles (abductor digiti minimi (ADM)) could be mapped with the same

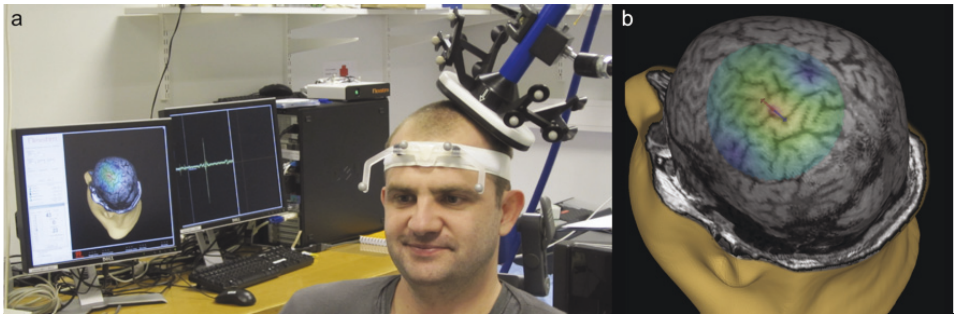

Figure 4. The measurement setup for nTMS motor cortex mapping. a) The subject is comfortably seated in a slightly reclined chair and he is wearing a headband with the navigation tracker balls attached to it. The stimulation coil with the rigidly attached tracking device is positioned over his left motor cortex. The EMG electrodes are attached to the desired target muscles in his right hand. In the background, the two computer screens are showing the estimated electric field distribution overlaid on the 3-D reconstruction of the subject's head, and the elicited EMG response from the selected muscle. b) The estimated electric field distribution of a single stimulation location over the hand motor area in the left hemisphere is shown. The colors are indicative of the field strength (red denoting the largest and blue the smallest estimated electric field strength), In the 3-D reconstruction the tissues are peeled off to a surface just below the cortical surface for convenient navigation of the stimuli locations in respect to the gyral anatomy.

stimulation intensity. For the lower extremity muscle representations, a new RMT was determined from the foot dorsiflexor and inverter muscle (tibialis anterior (TA)). The stimulation intensity was increased in small steps for other muscles in the upper or lower extremities (extensor digitorum communis (EDC), flexor carpi radialis (FCR), biceps brachii (BB), deltoideus (DE), rectus femoris (RF), flexor pollicis brevis (FPB), abductor hallucis (AH), flexor hallucis (FH), soleus (SO)), if the stimulation with 105-110% RMT of the APB or TA was not enough to elicit MEPs. The stimulation sites evoking 50 μV peak-to-peak or higher were considered as positive response sites [Rossini et al. 1994]. If no such responses were elicited, a SP response from a pre-activated muscle was used [Tataroglu et al. 2004]. The mappings presented in articles **I-III** followed this scheme.

For the mappings of speech-related areas in article **IV**, an object-naming paradigm was used, as it had previously been found to be useful [Lioumis et al. 2012; Picht et al. 2013; Sollmann et al. 2013]. In this paradigm, an image of an object is shown to the patient for 700 ms and the patient is advised to name it as fast as possible. An example of the nTMS measurement setup for the speech mapping is shown in Figure 5. Either a subset out of a set of 84 color images depicting everyday objects [Lioumis et al. 2012], or a subset out of a set of 92 images from a standardized image bank [Brodeur et al. 2010] was used. The selection from the sets was chosen to represent frequently used items in Finnish everyday life, whose names are common in the Finnish language and have only a few commonly used synonyms and which are suitable and familiar to the patient's age group. The accelerometer sensors have previously been used in the recordings of the fundamental frequency of the voice in similar types of demanding settings [Bourguignon et al. 2013] and they have been found to be accurate compared with microphone recordings [Hillman et al. 2006] and the binaural method with microphone recordings [Lindstrom et al. 2009].

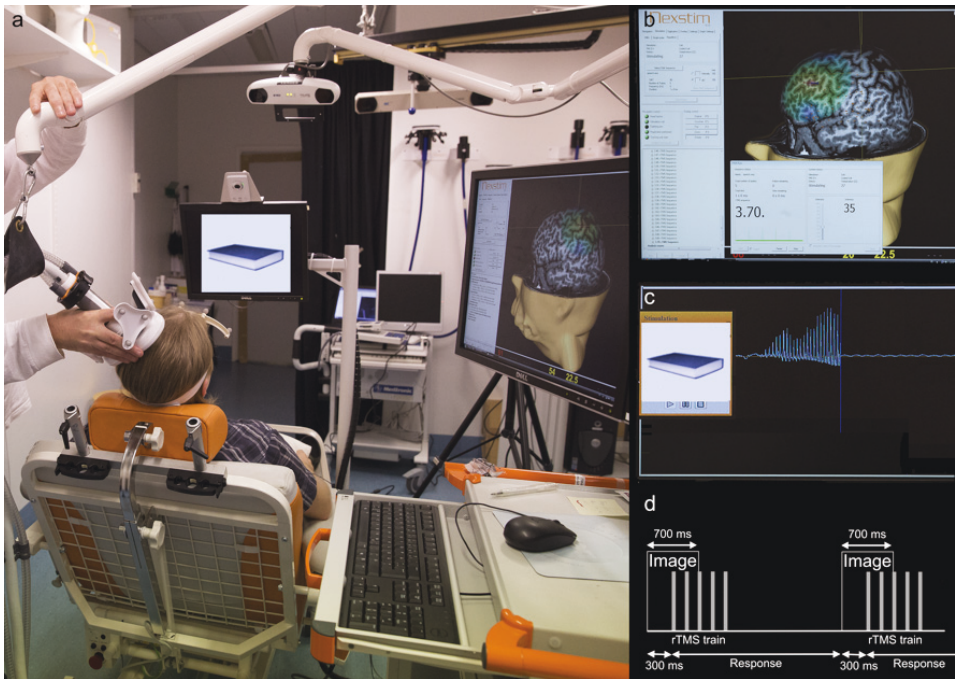

Figure 5. The measurement setup for nTMS mapping of speech-related areas. a) The subject is seated in a chair wearing a headband with the attached navigation tracker balls. The stimulation coil with the rigidly attached tracking device is positioned over his left parietal cortical areas. The accelerometer is attached over the larynx. Visual stimuli are presented on the screen in front of him. b) The stimulation is targeted with the aid of the estimated electric field distribution. The stimulation parameters are also shown on the screen. c) The visual stimuli as well as the accelerometer signal during the measurement is shown in one of the EMG channels. d) Schematics for the object-naming paradigm are outlined.

During the baseline session, the patient named the presented images to get acquainted with the setup. All the images that were not named correctly, associated with performance difficulty or trouble in pronunciation were discarded from the subsequent sessions. After the baseline, trains of 5 or 7 biphasic TMS pulses at 5 or 7 Hz were added to the paradigm at 300 ms after the image onset in order to disrupt the naming. In the first session, the rTMS trains were delivered with a stimulation coil near the patient's head and with 0-1% of stimulation intensity in order to get the baseline without the rTMS but with the stimulus train triggers for the analysis. For the rest of the sessions, an intensity inducing electric field of a strength similar to the MT of APB cortical area was used for the stimulation. If this was not tolerable, the intensity was reduced in 5-10% decrements until it was bearable. The stimulation was targeted to the expected speech-related cortical areas at the frontal, parietal and temporal cortices [Corina et al. 2010; Pouratian et al. 2010]. The whole stimulation session with the images and the patient's responses were recorded on video. The timing parameters for the paradigm were the same as in [Lioumis et al. 2012].

Based on these measurements recorded with the accelerometer, a semi-automated script was developed for analysis of the response latencies. The script's feasibility in speech rTMS paradigms was evaluated by its ability to correctly identify the rTMS trains and

the response onsets. The evaluation was performed against the visual determination of the accelerometer signal shapes and the patient's performance from the video.

4.3 Direct electrical cortical stimulation mappings

The motor cortex was mapped with 5 s trains of 50-Hz 300-μs biphasic square-wave pulses increasing the current in a stepwise manner from 1.0 mA until stimulation elicited a motor response, afterdischarges in the EEG, or when the predetermined maximum current of 13.5 mA was reached [Lesser et al. 1984; Lesser et al. 1987; Lesser et al. 1994]. The stimulation was always delivered between two electrodes, mainly in a stimulation montage in which one of the electrodes was located on the cortical area of interest and the other, on the cortical area not eliciting responses.

A clearly visible localized movement of the contralateral side of the body while the patient was at rest was defined as a motor response. If the response was unclear, the stimulation was repeated. A continuous video of the stimulation and the behavior and the responses of the patient, linked to the EEG, were recorded. The responses were reviewed from the video after the stimulation.

4.4 Comparison of the mappings

In article **III**, the nTMS mapping results were compared with the results from DECS. To be able to make an appropriate comparison, both results were categorized into two muscle groups consisting of muscles of the same part of the upper extremity: The hand area including the muscles distal to wrist and arm area including the muscles in between shoulder and wrist.

The nTMS mapping results were projected from the level of visualization used during the stimulations to the cortical surface to enable more relevant comparison. To account for any possible non-tangentiality of the stimulations in our patients, the projections were made for each stimulation site individually, from the electric field maximum to the segmented brain surface via the stimulation coil normal provided by the navigation software. The nTMS results were re-calculated to a visualization surface as near to the cortical surface as visually possible in the navigation software before the projections were calculated to minimize the errors. The projections were calculated with custom scripts.

The positions of subdural electrodes can be determined accurately from post-operative computed tomography (CT) images based on their high Hounsfield units (Figure 6). The opacity transfer function was adjusted to show the objects with high Hounsfield units. Finally, to enable the comparison, the CT images showing the locations of the subdural electrodes were registered with the preoperative anatomical MR images including the nTMS mapping results by using mutual information metrics [Viola et al. 1997; Van Leemput et al. 2004]. The centers of the relevant electrodes were manually pointed from the three dimensional (3-D) volume rendered images for the distance parameter calculations.

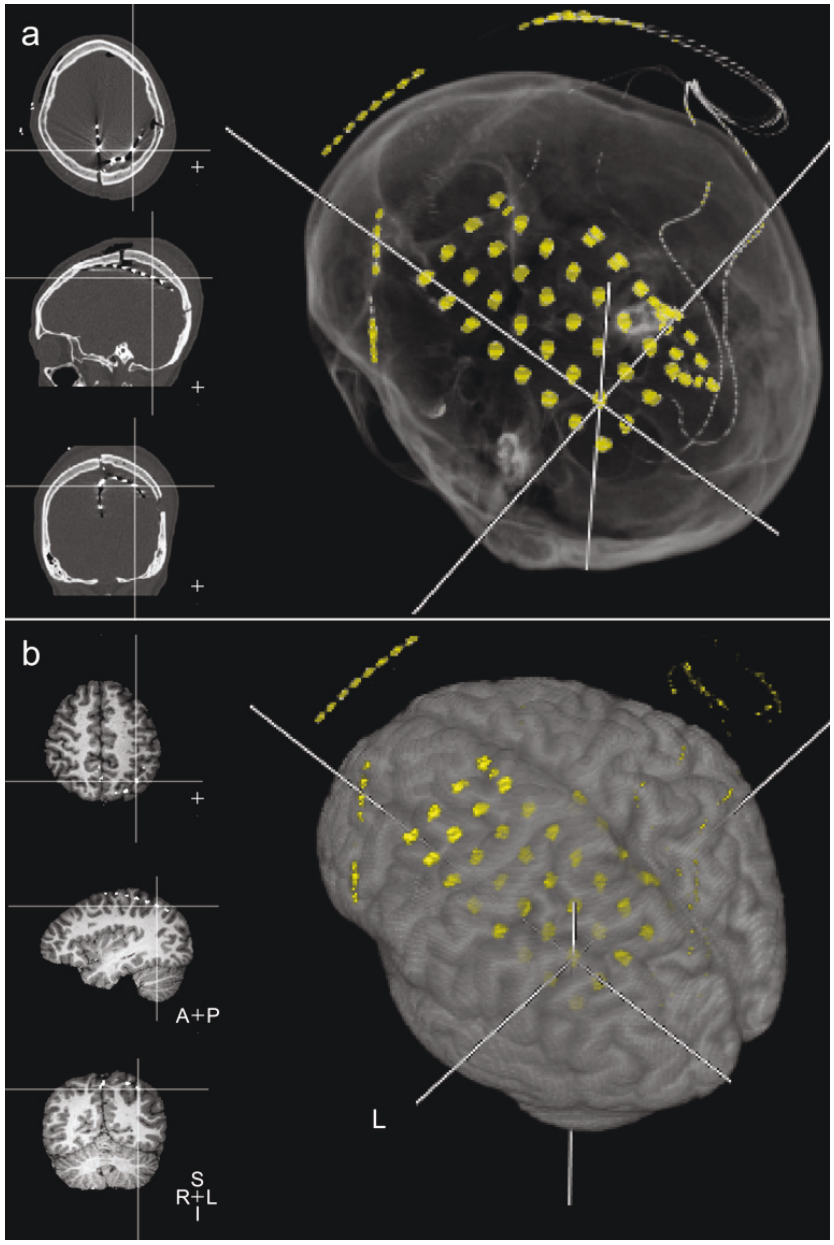

Figure 6. a) An example of the localization of the subdural electrodes from post-operative CT images, in different orientations and in 3-D volume rendering. The opacity transfer function is adjusted to show the electrodes in the 3-D reconstruction, which are also highlighted with yellow in the 3-D volume rendering. b) The preoperative cortical MR segmentation in different orientations and in 3-D volume rendered image. The CT is registered to the preoperative MR and the electrodes are transferred to it as high intensity objects (highlighted with yellow in the 3-D volume rendering). The centers of relevant electrodes (one shown with a crosshair in the images) were manually pointed from the 3-D volume rendered images for the distance parameter calculations.

Three distance parameters were calculated to represent the correspondence between the two mappings. In all of them, the average nTMS site ($nTMS_G$), the arithmetic mean of the stimulation site coordinates projected to the brain surface, was used. Three different parameters were calculated from the DECS results: the arithmetic mean of the coordinates of the electrode centers ($DECS_G$), the center of the electrode eliciting motor response with the lowest current ($DECS_{MIN}$) and the arithmetic mean of the electrode locations weighted by the inverse of the stimulating current ($DECS_{COG}$). The 3-D Euclidian distances were calculated between $nTMS_G$ and the DECS parameters: $dist(nTMS_G, DECS_G)$, $dist(nTMS_G, DECS_{MIN})$ and $dist(nTMS_G, DECS_{COG})$.

4.5 Statistical methods

In articles **I** and **II**, the results for individual patients are presented. In articles **III** and **IV**, the basic descriptive statistical methods were used. In article **IV** the performance of the developed algorithm was demonstrated by comparing its capability to correctly detecting the rTMS trains, the response onsets, and the no-response events with a visual onset determination from the accelerometer signal and from the video. The speech response onset latencies could not be directly compared, since the latencies are not provided by the current system with the manual review of the responses viewed from the video.

Sensitivity and specificity measures (equations 4.1 and 4.2) were used to describe the performance of the algorithm. Tables of confusions denoting the number of false positive, false negative, true positive, and true negative detections were used to aid the sensitivity and specificity calculations (Tables 2, 3 and 4).

$$sensitivity = \frac{true\ positive}{true\ positive + false\ negative} \tag{4.1}$$

$$specificity = \frac{true\ negative}{true\ negative + false\ positive} \tag{4.2}$$

The sensitivity of the developed script to correctly detect the rTMS trains actually occurring was calculated with the proportion of the occurring rTMS train sequences detected as such and the events showing absence of the trigger signal despite the rTMS pulse train occurrence and the corresponding specificity was calculated with the proportion of the rTMS trains not occurring and identified as such (Table 2).

The script's sensitivity to correctly detect the speech response onset was calculated with the proportion of the correctly and incorrectly detected speech responses actually occurring and the specificity was calculated from the speech onset detections related to the extraneous triggers and the events of no-responses detected as responses (Table 3).

The script's sensitivity and specificity to correctly identifying no-responses were calculated with the proportions of the correctly and incorrectly identified no-responses (Table 4). The sensitivity and specificity measures of no-response identification were calculated for the sessions combined and for the baseline sessions and the rTMS sessions separately.

Table 2. The table of confusion used in the sensitivity and specificity calculation for the automatic routine's ability to correctly detect the rTMS pulse train.

	Total number of rTMS trains	Manually reviewed from the video recording	
		rTMS train sequence occurred	rTMS train sequence did not occur
Automatic routine's ability to detect the rTMS pulse train	Occurrence was detected	True positive: rTMS trains was identified correctly	False positive: An extra detection was identified
	Occurrence was not detected	False negative: Trigger signal was missing and rTMS train was not detected	True negative: The picture stimulus was shown but no rTMS train occurred and the rTMS train was not detected

Table 3. The table of confusion used in the sensitivity and specificity calculation for the automatic routine's ability to correctly detect the speech-response onset.

	Total number of speech-response onsets	Manually reviewed from the video recording	
		Speech-response occurred	Speech-response did not occur
Automatic routine's ability to detect the speech-response onset	Speech-response onset was detected	True positive: Speech-response onset was identified correctly	False positive: An extra rTMS train was detected leading to subsequent incorrect speech-response onset identification, no-response was identified as speech-response
	Speech-response onset was not detected	False negative: Speech-response was incorrectly identified	True negative: No-response

Table 4. The table of confusion used in the sensitivity and specificity calculation for the automatic routine's ability to correctly detect the no-responses.

	Total number of no-response responses	Manually reviewed from the video recording	
		No-response response occurred	No-response response did not occur
Automatic routine's ability to detect the no-responses	No-response was detected	True positive: No-response was identified correctly	False positive: No-response response was identified, when there was a real speech-response occurring
	No-response was not detected	False negative: No-response was not identified	True negative: Speech-response was identified

5 Results

5.1 Mappings of the primary motor cortex

The primary motor cortex in the precentral gyrus was mapped for 14 surgery candidates with severe epilepsy. The muscles were selected for the mappings on the basis of clinical needs. Motor cortex mapping characteristics for each patient are presented in Table 5.

For 11 patients presented in the articles **I-III**, the RMT could be determined with the monophasic pulse shape and the mapping was performed with the monophasic stimuli. For three patients (patients 1 in article **II**, patients 4 and 9 in article **III**), the RMT was higher than the maximum stimulator output (msop) and the RMT could not be determined with the monophasic pulse shape. If the SP responses were elicited with the monophasic pulses, the mapping was performed with the SP responses, otherwise biphasic stimuli were used. The RMTs were lower with the biphasic than with the monophasic stimuli.

In article **I**, the first two patients were presented. They had an expected organization of the representation of the selected muscles. The results of patient 2 are presented in Figure 7. For both patients, the nTMS results were concordant with other noninvasive methods and they were confirmed with DECS. nTMS results were spatially more precise than DECS results.

In article **II**, two patients with an atypical organization of the representations were presented. A repeated mapping was performed to one of them six months after the resective surgery. In patient 1, biphasic pulses needed to be used, and the largest MEPs were elicited over the lesion area, anterior to the expected precentral gyrus, anatomically corresponding to the premotor area. The SP responses were elicited from the anatomically estimated motor cortex. The healthy hemisphere was not mapped. The nTMS results differed from the sites eliciting positive responses in DECS, and less weight was given to the noninvasive results. The mapping was repeated six months post-operatively, revealing not only modified AMT but also representation of motor areas more posteriorly than in the preoperative mapping. The area producing MEPs was still larger and more scattered than in healthy subjects. In patient 2, who had a large post-infarct cavity in the left hemisphere, the nTMS mapping result was unexpected. Responses to both hands could be elicited from the same locations in the right hemisphere. The left leg representation was found to be located at the predicted site of the right hemisphere close to the interhemispheric fissure, but the representation of the right leg was found in the remaining anterior cortical area of the left hemisphere.

Table 5. The motor cortex mapping characteristics of patients presented in this thesis, divided by the articles in which they first appear. For the article **IV** (mapping of speech-related areas) only the resting motor thresholds (RMTs) are presented. msop is the maximum stimulator output, APB abductor pollicis brevis, ADM adbuctor digiti minimi, EDC extensor digitorum communis, FCR flexor carpi radialis, BB biceps brachii, DE deltoideus, RF rectus femoris, TA tibialis anterior, FPB flexor pollicis brevis, FH flexor hallucis, AH abductor hallucis, SO soleus, MEP motor evoked potential and SP silent period.

Article	Patient no.	Pulse shape used	RMT of APB [% msop]	Muscles to which nTMS evoked responses in the mapping	Response type acquired	Number of positive responses
I	1	monophasic	62	APB, ADM, FCR, EDC, BB	MEP	64
	2	monophasic	72	APB, ADM, FCR, BB	MEP	17
II	1	monophasic	pre-op. > 100	APB, ADM, BB	SP	23
		biphasic	pre-op. 70	APB, ADM, BB	MEP	20
		monophasic	post-op. 81	APB, ADM, BB	MEP	54
		biphasic	post-op.	APB, ADM	MEP	26
	2	monophasic	69 (left hem.)	APB, TA, BB	MEP	102
		monophasic	68 (right hem.)	APB, TA, FPB	MEP	32
III	1 (same as Pat 1 in article **I**)					
	2 (same as Pat 2 in article **I**)					
	3	monophasic	90	APB, ADM, EDC, BB	MEP, SP	67
	4	monophasic	> 100	APB, ADM, EDC, BB, RF, TA, AH	SP, MEP	109
	5	monophasic	86	APB	MEP	4
		biphasic	76	APB, TA, AH, SO	MEP	121
	6	monophasic	82	APB, ADM, BB, DE	SP	24
		biphasic	73	APB, ADM, BB, DE	MEP	14
	7	monophasic	83	APB, ADM, FCR	MEP	63
	8 (same as Pat 1 in article **II**)					
	9	monophasic	> 100	APB, TA, FH	SP	29
		biphasic	> 100	APB, BB, TA, FH	SP	37
	10	monophasic	92	APB, TA, AH	MEP	45
	11	monophasic	80	APB, EDC, TA	MEP, SP	48
	12	monophasic	73	APB, FCR, TA, AH	MEP	79
	13	monophasic	57	APB, EDC	MEP	114
IV	1	biphasic	50	APB	-	-
	2	biphasic	25	APB	-	-
	3	biphasic	25	APB	-	-
	4	biphasic	39	APB	-	-
	5	biphasic	63	APB	-	-
	6	biphasic	38	APB	-	-
	7	biphasic	25	APB	-	-
	8	biphasic	63	APB	-	-
	9	biphasic	62	APB	-	-
	10	biphasic	36	APB	-	-

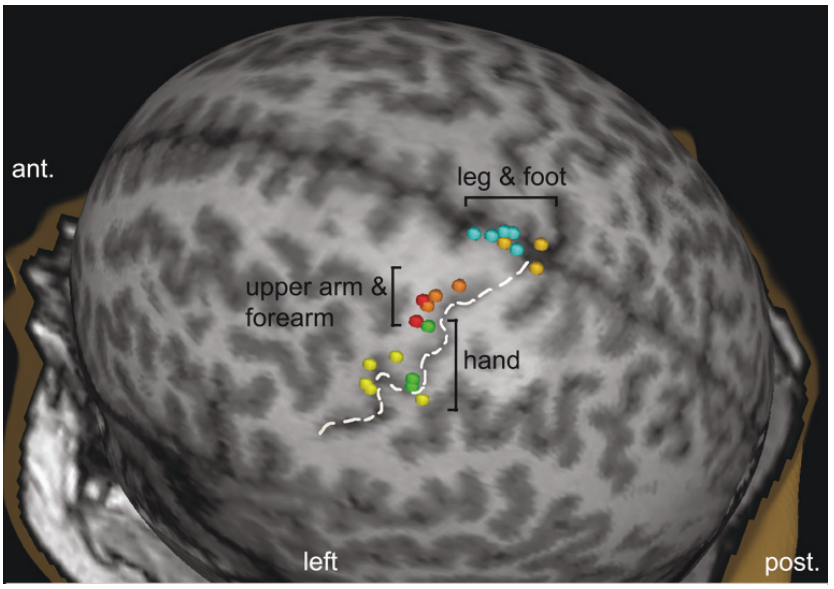

Figure 7. The nTMS mapping results of patient 2 from article **I**: The colored dots represent the stimulation sites eliciting EMG responses from different muscles. For the hand and arm area, red indicates MEPs from biceps brachii and extensor digitorum communis muscles, orange only from the biceps, green from the abductor digiti minimi and APB muscles, and yellow only from APB. Responses from the leg and foot area are represented with turquoise (rectus femoris muscle) and from tibialis anterior and abductor hallucis muscles with light orange [figure adapted from eXimia NBS]. The central sulcus is depicted with a white dashed line. Figure modified from article **I**.

5.2 Reliability of the primary motor cortex mappings

In article **III**, the data of 11 additional patients were presented and the accuracy of the mapping procedure was evaluated with mapping data from hands, forearms and upper arms of altogether 13 patients. The location of the DECS electrode grids restricted the analysis to the upper extremity muscle sites as responses of foot muscles by both DECS and nTMS were not available. An example of a mapping result for an arm muscle group and the corresponding projected results is shown in Figure 8. The comparison was made with the spatial centers of the nTMS maps and the electrode locations eliciting positive motor responses during DECS. Both responses were first categorized to muscle groups and the nTMS locations eliciting responses were projected to the cortical surface for a more meaningful comparison. Three distance parameters were calculated to reflect the mutual agreement between the maps. The main results are summarized in Tables 6 and 7 for the different muscle groups. For the hand muscle group, the average 3-D distance $dist(nTMS_G, DECS_G)$ was 11 ± 4 mm. For the forearm and upper arm muscle group the corresponding 3-D distance was 16 ± 7 mm. Both results are calculated from the nTMS data where monophasic stimuli were used. In four patients (patients 4, 6, 8 and 9) the mapping was done only either with the aid of SP responses or biphasic pulses. Anatomically, the nTMS locations eliciting positive motor responses were located on the same gyrus as the DECS ones.

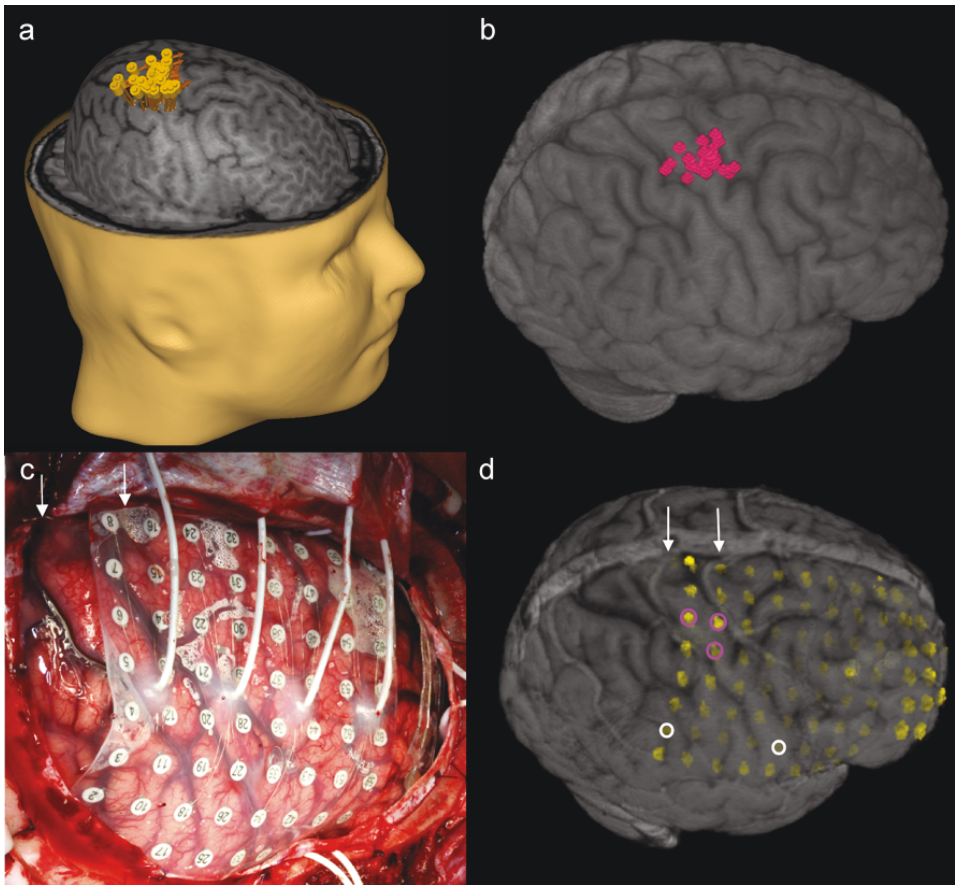

Figure 8. a) The nTMS map of the upper arm muscle group of patient 11. The locations of the estimated induced electric field maxima at each stimulation point are visualized as a small sphere on the peeled brain surface (peeling depth 19.8 mm from the skin surface), the tilt and the orientation of the stimulation coil are visualized as a stick, and the direction of the induced field is shown as a small arrow on top of each stick (screen capture from the eXimia NBS software). b) The same result shown on a 3-D volume rendering of the brain. The individual response locations are projected along the normal vector of the stimulation coil to the MR brain surface segmentation [induced electric field maxima were projected 3±1 mm (mean±SD, range 1– 5 mm) from the peeling depth to the segmented brain surface]. Note the slight orientation difference between figures. c) A digital photograph of the placement of an intracranial EEG electrode grid before skull closure. Note the cortical veins indicated with white arrows. d) Localization of the EEG electrode grid (yellow) registered on the gadolinium enhanced preoperative MRI brain segmentation with visualized cortical veins. The electrodes eliciting motor responses of stimulations from the upper arm area are marked with solid pink circles and reference electrodes with solid white circles on top of the electrode. The pointed cortical veins correspond to those depicted in c. Note the error of a few millimeters in the placement of electrodes between c and d (the locations of the white arrows and the electrode grid). The brain is made partly transparent, and the objects may be located deeper than they appear in the image. Figure adapted from article **III**.

Table 6. The summary of the mappings with monophasic pulse shape and MEP responses viewed with different distance parameters for the hand muscle group [mm].

	$dist(nTMS_G, DECS_G)$	$dist(nTMS_G, DECS_{COG})$	$dist(nTMS_G, DECS_{MIN})$
mean	11.3	11.6	12.6
SD	3.6	3.7	4.2
range	7.4 - 17.2	7.8 - 18.5	7.8 - 21.7

Table 7. The summary of the mappings with monophasic pulse shape and MEP responses viewed with different distance parameters for the arm muscle group [mm].

	$dist(nTMS_G, DECS_G)$	$dist(nTMS_G, DECS_{COG})$	$dist(nTMS_G, DECS_{MIN})$
mean	15.9	15.8	15.6
SD	6.9	6.9	6.9
range	6.3 - 23.2	6.4 - 23.2	6.7 - 23.2

For both muscle groups, the distance parameters gave similar results. This reflects mainly the characteristics of DECS with the fixed 10 mm inter-electrode distance and the variable number of active electrodes (for the hand muscle group the average was 3.6 electrodes and for the arm muscle group the average was two electrodes).

The mapping studies were well tolerated. With the first six patients, a concurrent 60-channel EEG was recorded to monitor possible epileptiform activity during the mappings. No such events were detected and the EEG recording was removed from the examination protocol for simplicity.

5.3 Speech response onset detection and latency difference determination

In article **IV** a semi-automated algorithm for speech-response latency difference between the baseline and the rTMS conditions was developed and its performance was evaluated. The rTMS train sequence was correctly detected with the semi-automated script in 98% of the 4904 trains confirmed visually from the data, from the speech stimulation software of the delivered pulse trains, and from the video. The sensitivity of the developed script to correctly detect the actually occurring rTMS trains was 99%. The specificity was 86%. This reflects the script's ability to correctly detect the not occurring rTMS trains, in situations such as a presented image without the rTMS train or extra trigger signals of unknown origin.

The performance of the speech response detection was evaluated as the proportion of the correctly detected speech response onsets compared visually with the accelerometer signal shape and the patients' performance reviewed from the video. The script's sensitivity was 96% and the specificity 71%. An example of a baseline - rTMS stimulus pair is shown in Figure 9, depicting a delayed response onset in the rTMS condition.

The script was able to correctly detect 88% of the no-response errors including the no-response errors occurring during the baseline sessions, which were removed from the image sets before the rTMS sessions. For the baseline condition the sensitivity was 100%, meaning that none of the true no-response events were missed. The specificity of the no-response detection was also 100% for the baseline condition, meaning that the script correctly identified all true speech responses. In the rTMS condition the

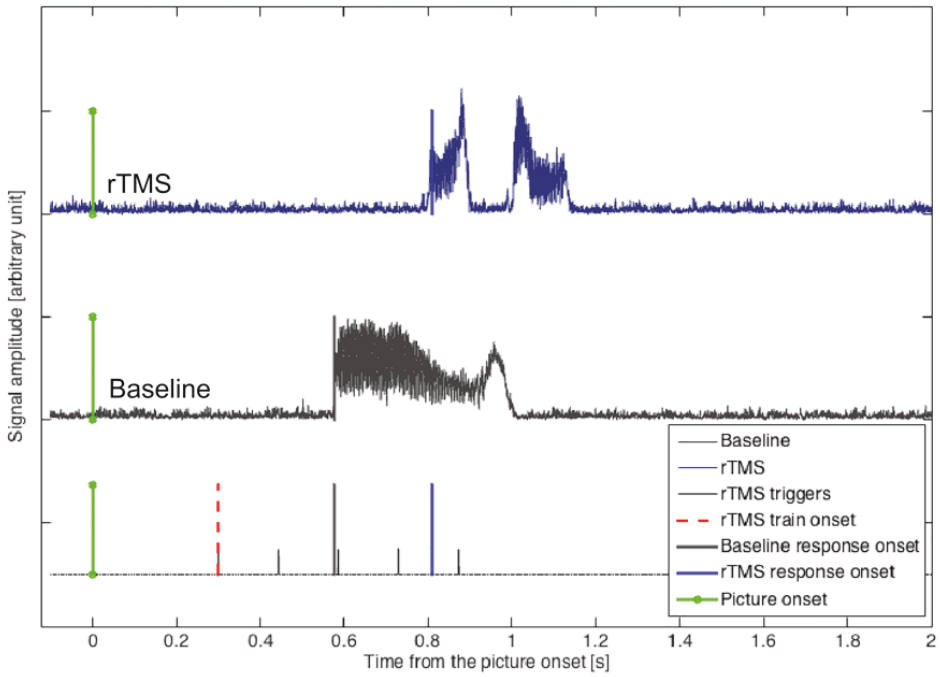

Figure 9. An example of a response pair comparison from patient 1 in article **IV**. The voice onset is delayed when rTMS is applied, and there is a semantic error of the response as well ("pullo" (bottle) in the baseline session vs. "kokis" (coke) in the rTMS session), which can also be seen as a different shape of the accelerometer signal. The figure is adapted from article **IV**.

sensitivity of the semi-automated detection algorithm was 82% and the specificity 100%.

Delayed naming of an image during the rTMS was rare. Only 0.8% of all presented image stimuli (41 events altogether) were tagged as delayed in the manual review from the video with an average delay of 719 ± 329 ms. With the developed script, altogether 463 responses had a latency delay exceeding 100 ms during the rTMS, constituting 9.2% of all presented stimuli.

6 Discussion

6.1 Preoperative protocol for the primary motor cortex mappings

The described mapping protocol enabled the successful mapping of the hand, arm and foot motor cortical areas for all patients reviewed in this thesis. In these patients, the nTMS mappings were performed with the antiepileptic medication held unchanged. The possible effect of medication elevating the RMT [Ziemann 2004; Solinas et al. 2008; Li et al. 2009; Ziemann et al. 2015], or the effect of epileptic activity on elevating the surround inhibition ipsilaterally [Hamer et al. 2005] did not hamper the mappings. The MTs have been reported to be repeatable also in epilepsy patients [Badawy et al. 2012].

Focal epileptogenic areas may be abnormally excitable. This may have an impact on the functional localizations as well [Labyt et al. 2007; Nardone et al. 2008; Danner et al. 2009]. Especially focal cortical dysplasias (FCDs) may elevate ambient cortical inhibition leading to detectable changes in DECS and nTMS [Matsumoto et al. 2005; Schmidt et al. 2010]. Indeed, one patient in article **II** showed an elevated RMT and an atypical representation of the upper extremity overlapping the area of the FCD, confirming the effects described in the literature. Moreover, in MRI tractography, this patient had bifurcated corticospinal tracts, also described to be related to FCD [Preul et al. 1997; Gondo et al. 2000; Mikuni et al. 2007]. The presented plasticity of the motor cortex between pre- and postoperative mappings is probably due to the epileptic focus in the vicinity of the precentral motor cortex increasing the overall inhibition of the surrounding cortex [Matsumoto et al. 2005; Pilato et al. 2009].

The mappings were well tolerated and no adverse effects were observed. The multichannel EEG has been included in the nTMS protocol also by others [Danner et al. 2013] although increased epileptiform activity has not been reported. TMS with single pulses and with rTMS is a safe technique also for patients with severe epilepsy as long as general safety guidelines [Wassermann 1998; Bae et al. 2007; Rossi et al. 2009; Lefaucheur et al. 2014] are followed [Tarapore et al. 2015]. In the course of this study the concurrent EEG recording was removed from the protocol, making the examinations shorter and technically simpler. The EEG electrode cap has been shown to increase the MT due to the increased coil to cortex distance [Julkunen et al. 2009a], thus possibly affecting the apparent cortical excitability measures.

6.2 Reliability of the primary motor cortex mappings

Reliability of the nTMS mappings in patients with epilepsy was evaluated against the intracranial DECS. The locations of individual nTMS stimulation points eliciting motor responses were compared with their anatomical locations and the location of the positive motor responses acquired during the DECS. In addition, the arithmetic centers of the maps were calculated. Analogously, the center of the maps with and without the weighting with the inverse of the stimulating current were calculated for the results acquired with DECS. The location of active electrode producing the positive response with minimum current was identified as well. The accuracy of the nTMS mappings was also reviewed against the presence of an FCD. The reliability of the nTMS mappings

have been established with brain tumor patients against intraoperative direct freehand cortical stimulation [Krings et al. 1997; Finke et al. 2008; Picht et al. 2009; Forster et al. 2011; Picht et al. 2011; Picht et al. 2012; Picht et al. 2013]. The correspondence between the nTMS mappings and freehand guided DECS of the motor cortex during surgery match the results for epilepsy patients presented in this thesis. The main difference between the mappings of patients with tumor or epilepsy is the use of freehand DECS during surgery with the brain tumor patients. As the patients with epilepsy often require intracranial EEG recordings to localize the epileptogenic area the DECS mappings can be performed preoperatively via the intracranial electrode grids with a fixed inter-electrode distance.

The exact physical size and shape of the induced electric field is not known with either of these methods although they seem at least in part to activate the same neuronal structures in the cortex. It is estimated that a TMS pulse could activate a cortex area within 1-2 cm^2 [Cohen et al. 1990; Levy et al. 1991; Thielscher et al. 2004]. The mean accuracy of the used TMS system is 5.7 mm [Ruohonen et al. 2010], including the accuracy of the optical tracking, the movement of the head trackers during experiments, the computational model used for the electric field estimation and the registration error of the MRIs. This means that the distance from the visualized hotspot to the true stimulated region of neurons can vary within the stated value in any direction. The projection of the nTMS results to the cortical surface which enabled the comparison with the DECS results may have produced a small error in the locations of the stimuli, but compared with the estimated area of one TMS stimulus these imprecisions seem acceptable. The pre- and postoperative results always have some differences, due to the surgery, the methodological differences, as well as all the various stages of results analysis needed for the comparison.

The reliability of the motor cortex mapping has been confirmed with non-navigated TMS methods [Wilson et al. 1993b; Mortifee et al. 1994; Thickbroom et al. 1999; Uy et al. 2002; Wolf et al. 2004] as well as with nTMS [Zdunczyk et al. 2013]. In addition, there is an apparent symmetry between the maps of the two hemispheres [Wilson et al. 1993b; Byrnes et al. 1998] with healthy volunteers. The test-retest reproducibility is assessed with non-navigated TMS from the areas of the scalp. The map area and the center of gravity of the maps of three instrinsic hand muscles [Uy et al. 2002] or the extensor digitorum communis [Wolf et al. 2004] did not change significantly between mappings done repeatedly during 24 h to two week time periods. A 67-68% overlap of APB and ADM muscle representation maps between mappings with 21-132 days of separation is reported [Mortifee et al. 1994]. The variability of the center of gravity of the map is estimated to be 4 mm with nTMS, with a 5 mm inter-examiner variability [Zdunczyk et al. 2013].

Some variability related to the map parameters can be attributed to the technical parameters such as the orientation of the stimulating coil, to the mapping intensity, to the pulse shape(s) applied, to issues specific to the targeted muscle groups, to the cortical characteristics and to the MEP variability. In the stimulation protocol presented in this thesis, the targeted area was stimulated with several coil orientations and the optimal orientations eliciting the largest MEP responses were searched for. This most favorable orientation in the upper extremity muscles was typically perpendicular to the

central sulcus, creating an electric field perpendicular to the sulcal wall, as expected [Janssen et al. 2015]. In the leg and foot area the largest EMG responses were elicited with the field perpendicular to the interhemispheric fissure creating a medio-lateral current flow, as expected [Rösler et al. 1989].

The mapping intensity has an effect on the map area, especially when the MEP response threshold is held unchanged. Typically, an MEP amplitude of at least 50 μV peak-to-peak is considered sufficient in mapping studies [Rossini et al. 1994; Rossini et al. 1999] and was used in this thesis, but also lower threshold values have been used [Lotze et al. 2003]. Increased nTMS intensity spreads the induced electric field, eliciting responses from larger cortical area, and very high intensities may be uncomfortable for the patient.

In this thesis, monophasic pulses were preferably used to optimize the focality of the stimulation [Macdonell et al. 1999]. The mapping intensity was adjusted to 105-110% RMT to ensure the generation of EMG responses and minimizing patient discomfort . The map extent was used only visually in this thesis and in relation to the underlying anatomy, as the map area depends at least on the individual MT, the mapping intensity, the MEP amplitude threshold, the mapped cortical extent and precision, the number of positive responses acquired and also on the natural variability of the MEPs.

The so-called surround inhibition in the motor cortex, thought to aid in the selective execution of desired fine movements in healthy humans [Beck et al. 2011], may impact the mappings as well. While MEPs from the targeted muscle are elicited, the MEPs from the neighboring muscles are simultaneously reduced, favoring a randomized approach [van de Ruit et al. 2015] to the mappings. With epilepsy patients, antiepileptic medication may alter the surround inhibition [Ziemann 2004; Ziemann et al. 2015] and it may be altered in the cortex surrounding the epileptic focus following frequent epileptic discharges [Matsumoto et al. 2005] thus, at least complicating the interpretation of the results.

MEPs have been shown to vary with attention [Rossini et al. 1991; Kiers et al. 1993; Rosenkranz et al. 2004; van de Ruit et al. 2015], due to the phase cancellation of the action potentials within the corticospinal tract or at the spinal cell level [Magistris et al. 1998], the physical aspects of the stimulation and the induced electric field. In addition, the antiepileptic medication may increase or decrease MEP amplitudes as well as SP durations [Ziemann et al. 2015]. These factors need to be taken into account if repeated mappings are planned. The motor cortex mapping of both hemispheres could be used in the mapping protocol to accentuate the differences between healthy and affected hemispheres, but this would almost double the examination time and might not reveal significant additional information, as the affected hemisphere is often known from the clinical workup.

6.3 Speech response onset detection and latency difference determination

Accelerometer based measurement protocol developed in study **IV** enables not only recordings of the patient's vocal responses to the visual image stimuli, but also simplifies the further analysis of the content of the signal compared with the

microphone recordings [Hillman et al. 2006]. As the accelerometer sensor records the vibrations on the skin just above the larynx, it is practically immune to environmental noises present during TMS studies, such as the coil clicks during stimuli, noise from the cooling of the stimulation coil, and personnel's advice, all issues complicating the analysis of microphone recordings [Popolo et al. 2005; Hillman et al. 2006]. However, there might be some patient related artifacts introduced to the accelerometer signal, such as skin borne muscle vibrations due to movements before the actual response (swallows, jaw movements, muscle stimulation, grimaces elicited by the stimulation, moving of the head). These movements are related to misdetections of the speech response onset constituted approximately one fourth of the misdetections in our data in spite of careful pre-rehearsal and advice given to the patients.

The speech response onset detection and latency determination were accomplished with the developed scripts. The data was collected during clinical examinations and the performance measures reflect real life situations with demands and challenges. The good preliminary performance results suggest that the speech response onsets and latency differences can be reliably determined in an object-naming paradigm with and without rTMS. The script was developed and tested with the Finnish language. There are no silent letters in Finnish, but words may start with stop consonants that do not produce enough vibrations to be picked up by the accelerometer on the skin. In the developed setting the latency difference of the speech response to the same visual stimulus is the essential outcome. It reflects the effect of the rTMS compared with the baseline, and the possibly slightly fluctuating absolute beginnings between different words do not matter. The loudness variation of the speech responses during the experiment may also introduce difficulties in the analysis. Monitoring the accelerometer signal strength during the experiment and advising the patients to adjust their voice loudness when needed can alleviate the problem.

With the developed script, the speech-related mappings can be analyzed with increased precision and objectivity as the numerical latency differences are available when reviewing the video recording. In our study, the manual scoring of the observed delays in the naming ranged from 300 ms to 1200 ms. This probably partly reflects the patients' natural rhythm of producing the responses and the analyzers' ability to habituate to this rhythm when reviewing the videos. The absolute latencies of the responses in the naming paradigm have a natural variance depending on the paradigm and setup [Indefrey 2011] and occasional word retrieval failures may happen to healthy people as well [Evrard 2002]. What is a significant latency difference in patients has yet to be determined. For research purposes a difference of 30 ms is thought to be significant when comparing paradigms with and without TMS stimuli [Wheat et al. 2013]. With the developed script, the latency differences can be listed at a chosen millisecond threshold and several magnitudes of delays can be analyzed, enabling individualization if required. Patients with temporal lobe epilepsy have frequent difficulties in finding words [Piazzini et al. 2001; Lomlomdjian et al. 2011], which might also affect the latency variation in the object-naming paradigm [Condret-Santi et al. 2014].

6.4 Methodological considerations

The original articles presented in this thesis were retrospective (**I-III**) and prospective (**IV**), and constituted altogether 24 individual patients. In articles **I-III** some of the same patients were presented. Considering the laborious presurgical workup with this heterogeneous patient group and the small number of patient eligible for these types of studies per year, the retrospective study design seems justifiable. For article **IV** a prospective series of 12 consecutive patients referred to the speech-related area mapping with nTMS was enrolled. The accelerometer-based method for speech response latency difference determination could have been first evaluated with a large number of healthy volunteers, but as the patients can be more challenging than healthy young adults, this approach might not have given the necessary evidence of feasibility with clinical reality. Furthermore, the addition of the accelerometer sensor to the measurement setup brings no added labor, but the obtainable results might significantly aid in the analysis of these challenging patients. As the purpose of this series of studies were development and preliminary validation of the methods, the relatively small number of patients was sufficient to provide the preliminary results we wanted to obtain.

In article **III**, the nTMS mapping results of upper extremity representations were compared with the results obtained with DECS. The nTMS mappings were performed in advance during the presurgical evaluation, and the patients' medication was held unchanged. During the intracranial recording, the patients' medication was reduced in order to obtain a sufficient amount of ictal activity for the precise localization of the epileptogenic cortical regions. These changes in antiepileptic medication might have also had an impact on the results via altered surround inhibition of the cortex. The patient 1 presented in article **II** is an eligible example of this phenomenon. The amount of ictal activity during the nTMS was not monitored in this study, as the concurrent EEG was monitored only from the six first patients during nTMS mapping. When the epileptic cortical area is located very close to the precentral sulcus, it might be reasonable to perform the mapping bilaterally for comparison, if the patient is co-operative. In addition, the inhibitory and excitatory aspects could be studied with paired pulse nTMS for an extensive view of the state of the cortex [Säisänen et al. 2011].

In article **III**, the MEP responses elicited by nTMS were compared with the visual movements observed during the DECS. To enable more precise comparison, the EMG responses from the same muscles need to be recorded during the DECS. In the comparison, distance parameters were used. Commonly a center-of-gravity of the nTMS maps is used in comparison studies. A spatial analog to this was used in this thesis. This was due to technical issues with the equipment used for the surface EMG recordings during the study. With the first five patients, the responses were monitored on-line and recorded, but the elicited responses could not be reliably related to the nTMS stimuli later on, hampering the precise analysis of the MEP or SP response details. With the subsequent patients, the responses were recorded and stored in a setup where the response and stimuli could be linked for off-line analysis. These differences could partly explain the slightly larger differences between nTMS and DECS presented in this thesis compared with the results from the freehand DECS reported earlier [Krings et al. 1997; Finke et al. 2008; Picht et al. 2009; Forster et al. 2011; Picht et al. 2011; Picht et al. 2012; Picht et al. 2013].

In the accelerometer-based speech-response latency difference determination the main reasons for the misdetections in the rTMS train identification and in the speech response detection were technical problems during the navigation. These included issues such as loss of the stimulation coil or the head-tracker worn by the patients from the field of view of the navigation camera, problems in trigger signal relay or reasons specific to the patients. The visual stimuli are presented continuously irrespective of whether the stimulation coil and the patient's head are in the navigations field of view, which is essential for the TMS system to deliver the stimuli. There were also instances of mistimed extraneous single or multiple trigger signals of unknown origin. The data of one patient were not analyzable due the lack of the baseline recording with the accelerometer, which was due to a human error. The data of one were lost during the measurement due to technical difficulties with the signal and equipment connections. The integration of the measurement setup and the sensor into a commercial system would alleviate these technical problems. Patient-related reasons for the misdetection of the speech response onset or the no-responses were related to visible throat movements before the response, to extra voices before responding, or delayed naming of the previous image although the patients were instructed to avoid such instances. The attachment of the accelerometer sensor must be done with care.

6.5 Advantages and limitations of the current series of studies of nTMS in functional cortical mappings

nTMS has advantages over the other methods used for functional localizations, some of them already mentioned in the introduction. Most importantly, nTMS enables the mapping of the extent of the representation of selected muscles in the motor cortex. With the freehand navigation, the precision can be selected and the scale of the mapping is not limited in advance. The neurophysiological effect of the stimulation is fairly similar to that of DECS, although the activated neuronal elements may differ. This helps in the interpretation and comparison of the results with DECS. Also, the functional plasticity of the cortical regions, a feature often intrinsic in epilepsy, may be mapped as well.

The functional mapping of the motor cortex is a challenging task in young patients, especially in children under three years of age, with possible epilepsy associated developmental delay. nTMS has the advantage of not requiring the patient's co-operation or immobility during the mapping, thus making it superior to the other commonly used techniques, such as fMRI or MEG [Narayana et al. 2015]. Also the results can be transferred to the hospital's data networks, such as picture archiving and communication systems [Mäkelä et al. 2015], for reliable and fast retrieval and subsequent use.

The limitations of the nTMS mappings involve the same contraindications as MRI, including patients having implanted ferromagnetic or electronically, magnetically or mechanically operated objects, such as programmable shunts, pacemakers or cochlear implants.

In the mappings of the cortical areas involved in speech production, the accelerometer

based measurement setup enables objective speech-response onset detection and latency difference determination, offering reliable means to categorize and systematically analyze hundreds of responses. The latency difference which would be clinically significant is still under investigation, but it may depend on the patient group or age as well. The standardization of the stimulation parameters in the speech mapping protocols is a challenging task, as there are differences between laboratories.

6.6 Future prospects

The described mapping protocols of the primary motor cortex and the speech-related areas enable individual detailed modelling of the induced electric field and thus a more precise view of the activation of the underlying cortex. The need for the individual modelling and computational estimation of the resulting fields and representational maps is pertinent in epilepsy patients with varying cortical anatomy [Opitz et al. 2011; Thielscher et al. 2011; Windhoff et al. 2013]. The conductivity differences between tissue interfaces (such as skin-skull, skull-cerebrospinal fluid, cerebrospinal fluid-grey matter, grey matter-white matter) and charge accumulation at tissue boundaries have been shown to significantly affect the TMS induced electric fields in the brain [Toschi et al. 2008; Salinas et al. 2009; Chen et al. 2010; Thielscher et al. 2011]. With the individual modelling, the characteristics of the visible epileptogenic region can be more precisely taken into account.

The time allocated for the nTMS is limited in clinical practice, and long mapping protocols can be demanding both for the patient and the staff. Usually, the mere mapping of motor cortical regions takes anything from 30 minutes to a couple of hours excluding preparation times. Recently, the time between the pulses and the number of the stimuli have been optimized [van de Ruit et al. 2015] with healthy volunteers, and a recommendation of 80 stimuli at pseudorandom locations and a 1.5 s time between the stimuli have been suggested. This reduced the mapping time to approximately two minutes while preserving the quality of the map. While this may be an extreme example of an efficient mapping protocol with healthy volunteers, there are many stimulation parameters that need a thorough optimization for clinical work.

The accelerometer sensor based speech response onset detection and latency difference determination in mappings could be further automated to detect deviant naming automatically by using, for example, form parameters or shape recognition. The experiences from other laboratories testing similar accelerometer sensor based setups will provide further knowledge of the reliability of the method. A closer integration of the method to commercial equipment would alleviate the problems related to purely technical difficulties with triggers and make the measurement setup and analysis easier for a wider group of end users.

7 Conclusions

In this thesis a clinical nTMS protocol for preoperative motor cortex mappings was developed and tested with patients with severe focal epilepsy. The first results with patients showed good correspondence with other noninvasive and invasive methods used in the preoperative workup for these patients. The underlying causes for epilepsy often are unknown and the functional plasticity of the brain in this disorder may differ from the norm. The nTMS method's ability to excite the abnormally excitable and connected tissue in addition to the targeted motor cortex needs to be taken into careful consideration when interpreting the results.

The reliability of preoperative motor cortex mappings was demonstrated by comparing the results with the current gold standard, the invasive DECS. The correlation between these methods was found to be sufficient for planning the surgical treatment and assessment of the risks and benefits that are associated with epilepsy surgery.

To advance the methodological progress of the nTMS speech mappings a measurement and analysis setup was developed for the speech response onset detection and latency calculation. The performance of the semi-automated analysis was evaluated against the current standard of manually reviewing and categorizing the responses from the video recordings of the stimulation experiment. The use of the semi-automated analysis enables precise and objective analysis of the speech-response latency differences, even on a millisecond time scale.

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