Department of Biomedical Engineering and Computational Science

Transcranial magnetic stimulation in assessment of cortical network properties

Pantelis Lioumis

Aalto University

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Pantelis Lioumis

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Aalto University
School of Science
Department of Biomedical Engineering and Computational Science

Supervising professor
Professor Risto Ilmoniemi

Thesis advisors
Docent Jyrki Mäkelä
Dr. Dubravko Kičić

Preliminary examiners
Professor Esa Mervaala, Department of Clinical Neurophysiology, Kuopio University Hospital, Finland

Assistant Professor Vasilios Kimiskidis, Department of Neurology III, Aristotle University of Thessaloniki, Greece

Opponent
Assistant Professor Marcello Massimini, Department of Biomedical and Clinical Sciences, University of Milan, Italy

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Abstract

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Abstract

This Thesis demonstrates the way to combine navigated transcranial magnetic stimulation (nTMS) with electrophysiological techniques, such as electroencephalography (EEG) and magnetoencephalography (MEG). This technical and neurophysiological possibility allows the assessment of cortical excitability and functional connectivity with the advantage of high spatiotemporal resolution. Investigation of these cortical network properties can lead in deeper understanding of sensorimotor and speech networks and bridge the gap between basic research and clinical applications by means of TMS. First, we examined whether nTMS–EEG can be used as a marker of cortical excitability changes by investigating the reproducibility of EEG after TMS. We showed that reproducibility is a feature of TMS-evoked EEG responses if the parameters of the stimulation and coil orientation are kept the same. Utilization of navigation is crucial for such test–retest paradigms. The second part of the thesis elaborated the effect of neuronal state prior to TMS on cortico–cortical excitability. We demonstrated modulation of excitability not only of the contra- but also of the ipsilateral hemisphere during preparation and execution of unilateral movements. We also tested the methodology to measure the time onset of cortical activation by grading the levels of its modulation with TMS–EEG. Next, we utilized MEG to detect sensorimotor cortical sources. nTMS was used to target these sources and modulate their activity during a motor task after a sensory stimulation. We demonstrated that stimulation of the secondary somatosensory cortex can influence the primary one and amplify somatosensory processing. By this study, we set the methodological standards on how to use nTMS and MEG in mapping the sensorimotor cortex. Therefore, we applied our experience in presurgical mapping of epileptic patients before cortical resection. By combining the nTMS and MEG advantages, we created a noninvasive methodology to map the sensorimotor cortex. The results were as accurate as electrical cortical stimulation in most patients. Thus, it may be possible to replace costly invasive standard procedures, which pose a high risk for the patient, when the epileptic focus is near sensorimotor cortex and accessible to MEG. This motivated us to create another nTMS paradigm for mapping speech-related areas. We combined an object naming paradigm and repetitive TMS to find cortical sites sensitive to interference during the task. We recorded video of the experiment to evaluate the effect of TMS on the subjects' performance. The results show that this method may map speech-related areas successfully. All in all, we show that recent advances in TMS set new standards in basic research and clinical applications, such as preoperative work- up and test–retest pharmacological studies. Cross-modal nTMS applications open new avenues in studying cortical network parameters.

Keywords transcranial magnetic stimulation, electroencephalography, magnetoencephalography, functional cortical mapping

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Preface

This work presented here is the result of teamwork that took place in BioMag Laboratory, HUS Medical Imaging Center, Helsinki University Central Hospital during the years 2004–2012. I have been extremely fortunate that my road brought me in Finland and BioMag where I had the opportunity to experience and learn how research is done, what organization is required to produce high level research and how people need to collaborate in order to achieve such standards. After this experience, my thinking is never the same again. I am grateful that I have been given this opportunity to be part of a very important scientific group and environment. Since brain plasticity is a fact and such a solid fact is as well the non-existence of "parthenogenesis" in terms of original and innovative ideas due actually to brain plasticity, I would like to thank here all people that have influenced my work, ideas and thinking.

I am grateful to my instructors Dr. Dubravko Kičić for my early and Docent Jyrki Mäkelä for my later steps as a researcher. Dubi has taught me how to convey neurophysiological measurements of high quality, and Jyrki has shown me how to think as a researcher and to write scientific articles. The useful technique cannot exist without the thinking and vice versa. I thank both of them for the huge amount of time that they have spent with and for me and for all the knowledge that they have transmitted to me. I respect both of them both as scientists and personalities and I consider it a great deal that I have met them. I would also like to thank Dr. Seppo Kähkönen for his contribution to my early steps in BioMag and research in general. The technical manager of BioMag Dr. Juha Montonen, who has been the key person for all of us to produce our research in BioMag facilities, is particularly thanked. His contribution in this Thesis is huge.

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Professor Esa Mervaala and Assistant Professor Vasilios Kimiskidis, the preliminary examiners of this Thesis, are sincerely thanked for their valuable comments and constructive crticism. I would like to warmly thank Assistant Professor Marcello Massimini for accepting the role of the opponent.

I am particularly happy having been in the same working environment in BioMag and sharing friendship with Juha Heiskala, Jussi Nurminen, Ville Mäkinen, Simo Monto, Andrey Zhdanov, Elina Pihko, Leena Lauronen, Päivi Nevalainen, Essi Marttinen-Rossi, Rozaliya Bikmullina, Ville Mäntynen, Minna Kylmälä, Katja Airaksinen, Juha Wilenius, Bei Wang, Elina Mäkelä and Jarkko Luoma. Special thanks go to our secretary Pirjo Kari and our nurses Suvi Heikkilä and Jari Kainulainen who have been making my life in the lab much easier. Many thanks go also to the colleagues and friends from BECS Ilkka Nissilä, Hanna Mäki, Julio Cesar Hernandez Pavon and especially to Matti Stenroos whose advices and friendship in the beginning of my studies have been very crucial. I would also like to thank Dr. Jussi Perkiö for our fMRI–EEG collaboration, the colleagues and co-authors from Nexstim Henri Hannula, Tuomas Neuvonen, Petri Savolainen and Jarmo Laine, the colleagues and co-authors from Elekta Neuromag Jukka Nenonen and Samu Taulu. I am happy and proud for collaborating with Drs. Eija Gaily, Liisa Metsähonkala, Ritva Paetau, Erika Kirveskari and Aki Laakso for our common presurgical project and with Drs. Markku Kaste, Nina Forss, Turgut Tatlisumak and Satu Mustanoja for the stroke project. I am particularly proud that all these highly skilled clinicians and very devoted to their patients work in the public health system. My warmest and sincere thanks go also to Dr. Tommi Raij and Professor Yoshio Okada from Harvard Medical School and to Dr. Vadim Nikulin from Charité-University Medicine Berlin. All three of them have influenced me significantly. Finally, particular thanks go to my closest collaborators during the last years, Anne-Mari Vitikainen

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Helsinki, November 13, 2012,

Pantelis Lioumis

Contents

List of Publications

This thesis consists of an overview and of the following publications which are referred to in the text by their Roman numerals.

I P. Lioumis, D. Kičić, P. Savolainen, J. P. Mäkelä, S. Kähkönen. Reproducibility of TMS-evoked EEG responses. *Human Brain Mapping*, 30, 1387–1396, 2009.

II D. Kičić, P. Lioumis, R. J. Ilmoniemi, V. V. Nikulin. Bilateral changes in excitability of sensorimotor cortices during unilateral movement: combined electroencephalographic and transcranial magnetic stimulation study. *Neuroscience*, 152, 1119–1129, 2008.

III T. Raij, J. Karhu, D. Kičić, P. Lioumis, P. Julkunen, F-H. Lin, J. Ahveninen, R. J. Ilmoniemi, J. P. Mäkelä, M. Hämäläinen, B. R. Rosen, J. W. Belliveau. Parallel input makes the brain run faster. *NeuroImage*, 40, 1792–1797, 2008.

IV A. M. Vitikainen, P. Lioumis, R. Paetau, E. Salli, S. Komssi, L. Metsähonkala, A. Paetau, D. Kičić, G. Blomstedt, L. Valanne, J. P. Mäkelä, E. Gaily. Combined use of non-invasive techniques for improved functional localization for a selected group of epilepsy surgery candidates. *NeuroImage*, 45, 342–348, 2009.

V P. Lioumis, A. Zhdanov, N. Mäkelä, H. Lehtinen, J. Wilenius, T. Neuvonen, H. Hannula, V. Deletis, T. Picht, J. P. Mäkelä. A novel approach for documenting naming errors induced by navigated transcranial magnetic stimulation. *Journal of Neuroscience Methods*, 204, 349–354, 2012.

Author's Contribution

Publication I: "Reproducibility of TMS-evoked EEG responses"

The author designed and planned the experimental paradigm and setup along with the second author. He performed all the measurements, the data analysis, and the interpretation of the results. He is the principal author of this article.

Publication II: "Bilateral changes in excitability of sensorimotor cortices during unilateral movement: combined electroencephalographic and transcranial magnetic stimulation study"

The author participated in all the pilot and main experimental measurements. He assisted the principal author in data acquisition, data analysis, and writing of the article.

Publication III: "Parallel input makes the brain run faster"

The author participated in the design, technical implementation and optimization of the TMS–EEG part of the experimental setup. He performed the TMS–EEG measurements together with the first author and assisted in the data analysis and writing of the article.

Publication IV: "Combined use of non-invasive techniques for improved functional localization for a selected group of epilepsy surgery candidates"

The author conceived, designed, and executed the TMS measurements together with the first and the second last author. He assisted in data analysis, result interpretation, and participated in writing the article.

Publication V: "A novel approach for documenting naming errors induced by navigated transcranial magnetic stimulation"

The author designed and implemented the preliminary experimental setup along with the fifth author. He designed and optimized the methodology together with the second, third, and last authors. He conducted all the measurements together with the third and last authors and assisted in data analysis. He interpreted the data and wrote the article together with the last author. He is the principal author of the article.

List of Abbreviations

AF	Arcuate fascicle
anG	Angular gyrus
APB	Abductor pollicis brevis
BA	Brodmann area
CSF	Cerebrospinal fluid
CNS	Central nervous system
DCS	Direct cortical stimulation
DLPFC	Dorsolateral prefrontal cortex
DTI	Diffusion tensor imaging
ECD	Equivalent current dipole
EcoG	Electrocorticography
ECS	Electrical cortical stimulation
EEG	Electroencephalography
EF	Evoked field
EMG	Electromyography
EOG	Electrooculogram
ERP	Event related potential
IFG	Inferior frontal gyrus
fMRI	Functional magnetic resonance imaging
GABA	γ-aminobutyric acid
MEG	Magnetoencephalography
MEP	Motor evoked potential
MI	Primary motor cortex
MM	Mirror movement
MRI	Magnetic resonance image/imaging
MT	Motor threshold

nTMS	Navigated transcranial magnetic stimulation
PMC	Premotor cortex
PET	Positron emission tomography
PNS	Peripheral nervous system
PoG	Postcentral gyrus
PrG	Precentral gyrus
ROI	Region of interest
RT	Reaction time
rTMS	Repetitive transcranial magnetic stimulation
SEF	Somatosensory evoked field
SEP	Somatosensory evoked potential
SMA	Supplementary motor area
SMG	Superior marginal gyrus
SI	Primary somatosensory cortex
SII	Secondary somatosensory cortex
STG	Superior temporal gyrus
TMS	Transcranial magnetic stimulation

1. Introduction

Transcranial magnetic stimulation (TMS) is a non-invasive method that allows cortical neural excitation by means of brief and strong magnetic field pulses [4] that induce weak intracortical currents in the tissue, resulting in membrane depolarization. The initiation of cortical activation or its modulation depends on the characteristics of the coil, its position and orientation with respect to the head [46], the waveform of the pulse generated by the coil, and on the background activation of the neurons of the cortical region to be activated [83].

TMS is an important tool to investigate cortical functions in humans by evoking motor or behavioral responses or by interrupting task-related processing. Cortico-spinal excitability can be evaluated by recording electromyographic (EMG) responses elicited by single TMS pulses over the motor cortex, whereas intracortical excitability can be measured by means of paired pulse TMS. Repetitive TMS can be used as a therapeutic tool and to disturb various cognitive processes. Furthermore, TMS combined with simultaneous EEG allows the studying of cortico-cortical excitability and connectivity. Finally, if TMS is assisted with neuronavigation (nTMS), precise test-retest paradigms can be performed, the majority of the cortical mantle can be targeted and stimulated (including those areas that do not produce measurable neurophysiological or behavioural results; "silent" cortical regions) and functional cortical mapping can be achieved.

The motivation of these publications came from previous TMS–EEG studies that were conducted in BioMag laboratory (HUSLAB, Hospital District of Helsinki and Uusimaa; [63, 89]) and by the availability of the navigation system that allowed stimulation of "silent" cortical regions as well and motor and speech functional cortical mapping in contrast to conventional TMS. Main target of this Thesis is to investigate whether TMS–EEG, nTMS and nTMS–EEG can give new information about brain excitability in comparison to conventional TMS, to elucidate further the mechanisms that underlie brain excitability and to use these findings as the basis for novel clinical applications and more advanced basic research.

1.1 Aims of the study

I To investigate whether TMS-evoked electroencephalographic (TMS–EEG) responses are reproducible. To create the background for studying the effect of neuromodulating drugs and therapeutic methods on cortical excitability in test-retest designs by means of navigated TMS (nTMS).

II To highlight the inhibitory role of ipsilateral hemisphere during unilateral movements.

III To examine the role of parallel arrangements from thalamus to primary and associative sensory areas during cortical processing by combining MEG and nTMS. To co-register anatomical information provided by different imaging methods.

IV To combine MEG and nTMS for locating epileptogenic and sensorimotor areas in preoperative planning of epilepsy surgery. To compare this non-invasive approach to the invasive standard electrical cortical stimulation (ECS) procedure.

V To create an nTMS protocol to disturb speech performance during a naming task for potential presurgical planning. To record the speech performance synchronously with the coil movement over the MRIs and the object to be named for valid off-line analysis.

2. Background

2.1 Cerebral cortex

The adult central nervous system (CNS) can be divided into the spinal cord, the medulla, the pons and cerebellum, the midbrain, the diencephalon, and the cerebral hemispheres [55]. The midbrain, the pons, and the medulla make up the brain stem. The medulla is the link between the brain and the spinal cord. The CNS is connected with the rest of the body through the peripheral nervous system (PNS). All motor, sensory and autonomic nerve cells and fibres outside the CNS are part of the PNS.

The cerebral hemispheres are by far the largest region of the brain. They consist of the cerebral cortex, the underlying white matter and the basal ganglia, the hippocampal formation and the amygdala. The cerebral cortex is the outermost surface of cerebral hemispheres, under the skull, the cerebrospinal fluid (CSF) and the meninges. It is generally organized into six distinct layers consisting of glial cells, axons, pyramidal and nonpyramidal cells. Pyramidal cells are the output cells of the cortex. The nonpyramidal cells are responsible for interconnecting local neurons of the cortex. Pyramidal neurons from layers II and III project to different cortical areas and from layers V and VI to subcortical areas and back to the thalamus. Nonpyramidal neurons receive also direct input from thalamic afferents, but they are inhibitory and use γ-aminobutyric acid (GABA) as neurotransmitter, in contrast to the pyramidal neurons which are excitatory and use glutamate or aspartate as neurotransmitters.

The cerebral cortex is a greatly convoluted sheet of neurons that consists of sulci and gyri. Its average 2.5-mm thickness does not vary significantly across regions [30]. Some sulci have a relatively consistent position in all human brains so they are used as landmarks to divide the brain into four lobes, the frontal, temporal, parietal and occipital lobes (Fig. 2.1). Cytoarchitecturally, the cortex can be divided into Brodmann areas (BA; [13]). The cortex is important in processing and executing perceptual, cognitive, and higher sensorimotor functions, but also emotions and memory [55]. The central sulcus separates the frontal lobe from the parietal lobe. In

the middle part of the central sulcus a structure with a shape of inverted omega or epsilon [142], is easily recognizable and is used as a landmark for stimulation of the hand muscles when nTMS is applied (Publications I, III, and IV). The Sylvian fissure separates the temporal lobe from the parietal and frontal lobes. It is also easily recognizable and therefore used as a landmark for speech mapping purposes as in Publication V. The motor cortex is located in the precentral gyrus and the somatosensory cortex in the postcentral gyrus. The visual cortex resides in the occipital lobe and the auditory cortex in the temporal lobe. Speech functions are distributed in an extensive network involving fronto-temporo-parietal regions in the human cortex.

2.1.1 Sensorimotor system

The primary motor (MI) and somatosensory (SI) cortices are organized somatotopically (homunculus; [94]; Fig. 2.1). Specific regions in the motor cortex are responsible for directing movements of specific muscle groups in the periphery. Axons from MI project directly to motor neurons in the spinal cord via the corticospinal tract. The fibers that synapse directly on these motor neurons derive from cortical layer V. The descending corticospinal tract on each side of the brain stem crosses to the opposite side of the spinal cord. Most of the fibers cross the midline at the medulla, whereas 10 % of fibers continue on the same ipsilateral side. The corticospinal axons end on groups of motor neurons in the spinal cord associated with specific limb muscles and on interneurons associated with the motor neurons. The corticospinal tract controls distal muscles specialized on precise movements [55]. The ascending somatosensory system is organized in a similar manner.

The highest level in the hierarchy of motor control is directed by the motor cortex. The motor cortex consists of MI, the premotor cortex (PMC) and the supplementary motor area (SMA). Each of them projects directly to the spinal cord through the corticospinal tract and indirectly via the brain stem. PMC and SMAs also project to MI. MI is located in the precentral gyrus and it corresponds to BA 4. SMA is located in the superior and medial part of the hemisphere, whereas PMC is on the lateral surface of the hemisphere (Fig. 2.1). The two areas are important for coordinating and planning complex sequences of movements. The cytoarchitecture of the three motor areas differs from that of the somatosensory areas. Layer IV, although it is thin, it is rich in inhibitory fibers [57]. Layer V in MI

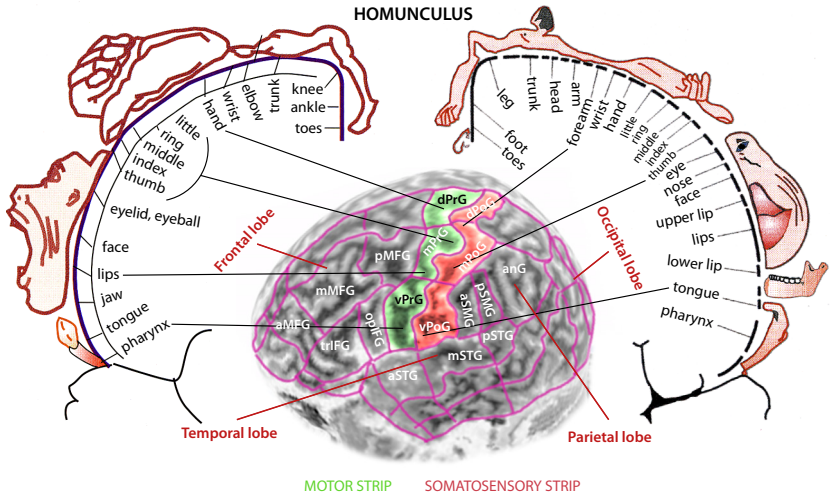

Figure 2.1. Left lateral view of the human brain with the motor and sensory functions indicated for the motor and somatosensory strip. The purple lines divide the brain in different anatomic areas. The brain areas that were mainly stimulated in the Publications of this Thesis are: anG = Angular gyrus, opIFG= Opercular inferior frontal gyrus, trIF= Triangular inferior frontal gyrus, aMFG = Anterior middle frontal gyrus, mMFG = Middle middle frontal gyrus, pMFG = Posterior middle frontal gyrus, dPoG = Dorsal postcentral gyrus, mPoG = Middle postcentral gyrus, vPoG = Ventral postcentral gyrus, dPrG = Dorsal precentral gyrus, mPrG = Middle precentral gyrus, vPrG = Ventral precentral gyrus, aSMG = Anterior supramarginal gyrus, pSMG = Posterior supramarginal gyrus, aSTG = Anterior superior temporal gyrus, mSTG = Middle superior temporal gyrus, pSTG = Posterior superior temporal gyrus.

contains a distinct population of giant pyramidal neurons (Betz cells) and it is particularly prominent in the motor cortex. The axons of these cells run in the corticospinal tract, but they represent only one of several populations of nerve cells that contribute to the corticospinal tract. The tract originates from neurons of all sizes in layer V. Half of the axons of the tract originate from MI and most of the others come from the supplementary motor area. A smaller portion comes from the premotor cortex and the SI [55]. nTMS is a tool that can be used to investigate and further confirm such pathways [129].

The somatosensory system plays an important role in processing all somatosensory inputs. It consists of the SI, the secondary somatosensory cortex (SII) and parts of posterior parietal lobe that receive also somatic inputs. SI is located in the postcentral gyrus and it consists of BA 1, 2, 3a, and 3b (Fig. 2.1). Projections from the thalamus to SI arise mainly from the ventral posterolateral nucleus and transmit information from the contralateral side of the body in somatotopically organized manner. SII is located laterally and a bit posteriorly from SI in the upper bank of

lateral sulcus. SII receives input primarily from SI and in turn projects to the somatosensory fields in the insular region. However, direct thalamocortical inputs to SII exist in non-human primates [143] and probably also in humans as proposed in Publication III. The parts in the posterior parietal lobe consist a region of higher-order sensory cortex, which relates sensory and motor processing and is focusing in integrating the different somatosensory modalities that are necessary for perception [55].

2.1.2 Speech network

Traditionally, the left hemisphere is considered dominant for speech functions. The main components responsible for the process and execution of speech are the inferior frontal gyrus (IFG; Broca area), the angular gyrus in the parietal lobe, Wernicke's area in the vicinity of superior temporal gyrus (STG), and their interconnections by the arcuate fascicle (AF; [35, 80]; Fig. 2.1). Some recent studies support this organization of speech-related areas [17, 105]. The trajectory of the fronto-parieto-temporal fiber pathway has been detected by means of diffusion tensor imaging (DTI) tractography [17]. However, some other studies suggest a dual pathway system to connect temporal and frontal cortices for speech processing [26, 44, 137]. A ventral pathway is involved in mapping sound into meaning and a dorsal pathway mapping sound into articulatory based representations [43]. This dual stream model has been supported by new studies (for review, see [44, 80, 102, 116]; Fig. 2.2).

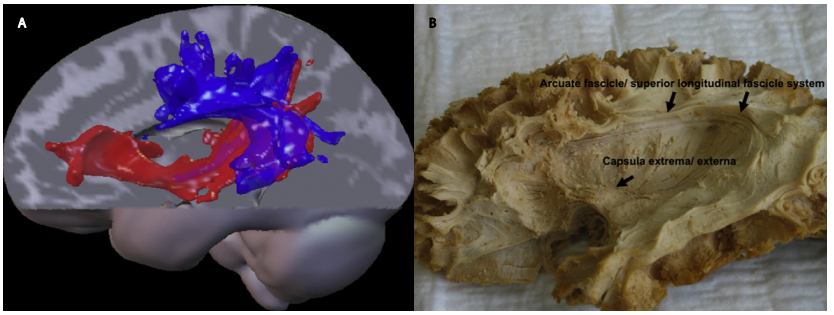

Figure 2.2. The dual stream model. **A:** A diagram of the ventral (red) and the dorsal (blue) pathways based on the DTI trackings from several studies. **B:** Anatomical proofs of the the dual pathway system. Adapted from [137].

However, already Wernicke in 1868 had suggested that a sensorimotor integration is needed for language production and speech learning and an integration of representations in the sensory and motor centres with non-linguistic representations is needed for comprehension [137, 138, 139]. He

recognized that two routes for normal language are required, one to connect the concept center to the center for imaging the movements for sound production and another one for automated corrections. Recent anatomical studies, mainly in monkeys, provide evidence for a ventral connection with two individual pathways, the extreme capsule and the uncinate fascicle, connecting temporal with frontal areas (for review, see [137]). The dorsal system has been investigated mainly with DTI. In humans there is evidence for a dichotomy in dorsal routes, with the classical arcuate pathway connecting Broca's and Wernicke's areas directly and another indirect pathway passing through inferior parietal cortex [17].

Speech is lateralized to the left hemisphere for 95 % of right-handed people and to the right hemisphere for 15 % of left-handed ones [33]. In addition, there is a left-side dominance in the volume of Broca's area, the planum temporale and in the degree of the anatomical connectivity for the AF. Most of these studies have combined functional magnetic resonance imaging (fMRI) and DTI (for review, see [33]). Evidence for parallel pathways involved in speech recognition are also provided by studies on split brain patients, patients with unilateral damage of either hemisphere and by Wada tests [7, 86], indicating that there is at least one pathway in each hemisphere that can process speech sounds sufficiently [43]. Functional imaging has also shown bilateral organization of speech recognition. Listening to speech activates STG bilaterally, including the dorsal STG and the superior temporal sulcus. Moreover, phonological networks in both hemispheres have been identified in several studies (for review, see [44]). In addition, awake intraoperative language mapping prior to tumor resection and epilepsy surgery in the right hemisphere in patients with right dominance or bilateral dominance, as indicated by Wada test, has suggested that language processing in the right hemisphere is enabled by the same general connectivity and anatomical layout as when the left hemisphere is dominant [18]. Moreover, in most right-handed individuals, even though the left hemisphere is crucial for language production and comprehension, the nondominant right hemisphere plays an important role in the prosody and paralinguistic aspects of normal speech [18]. Patients with right perisylvian lesions lack prosodic modulation and are unable to judge emotional tone of the speech [93]. Finally, damage of the nondominant hemisphere impairs the ability of integrating, contextualizing and inferring meaning from language [81].

2.2 TMS

2.2.1 Physics of TMS

TMS is governed by the fundamental principles of electromagnetic induction. The Faraday law states that a time-varying electric current in the stimulation coil (primary coil) produces a changing magnetic field that induces a flow of electric current in nearby conductors (scalp, skull, cortical tissue; secondary coil; Fig. 2.3). In TMS, the excitation of the neurons is achieved by generating intense pulses of current $I(t)$ through a coil placed over the head. The neurons are activated by currents resulting from the induced electric field in the tissue, $\mathbf{E}$, given by Faraday's law:

$$\nabla \times \mathbf{E} = -\frac{\partial \mathbf{B}}{\partial t}, \tag{2.1}$$

where $\mathbf{B}$ is the magnetic field produced by the stimulating coil that obeys the Biot–Savart law:

$$\mathbf{B}(\mathbf{r}, t) = \frac{\mu_0}{4\pi} I(t) \oint_C \frac{\mathrm{d}\mathbf{l}(\mathbf{r}') \times (\mathbf{r} - \mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|^3}, \tag{2.2}$$

where μ_0 is the free space permeability and $\mathrm{d}\mathrm{l}$ the vector along the windings of the coil C.

The total electric field in the tissue is the sum of the primary electric field $\mathbf{E}_1$, the one induced directly from the coil, and the secondary field $\mathbf{E}_2$. Due to the non-uniform conductivity in the brain tissue, the current produced by $\mathbf{E}_1$ runs through the conductor (tissue). This creates an uneven distribution of electric charges ($\rho = \rho(\mathbf{r})$, ρ is the charge density), which in turn results in the secondary field, which can be given by Maxwell's equation: $\nabla \cdot \mathbf{E}_2 = \frac{\rho}{\epsilon_0}$. It can be expressed as the gradient of the potential V: $\mathbf{E}_2 = -\nabla \mathrm{V}$. The varying magnetic field $\mathbf{B}(t)$responsible for $\mathbf{E}_1$ can be expressed as vector potential $\mathbf{A}$ as follows: $\mathbf{E}_1 = -\frac{\partial \mathbf{A}}{\partial t}$. The total field is then [108]:

$$\mathbf{E} = \mathbf{E}_1 + \mathbf{E}_2 = -\frac{\partial \mathbf{A}}{\partial t} - \nabla \mathrm{V}. \tag{2.3}$$

2.2.2 Neurophysiology of TMS

The total electric field in the tissue moves charges in both the intracellular and extracellular spaces, depolarizing or hyperpolarizing the cell membranes. Simultaneous depolarization of many neurons in the region

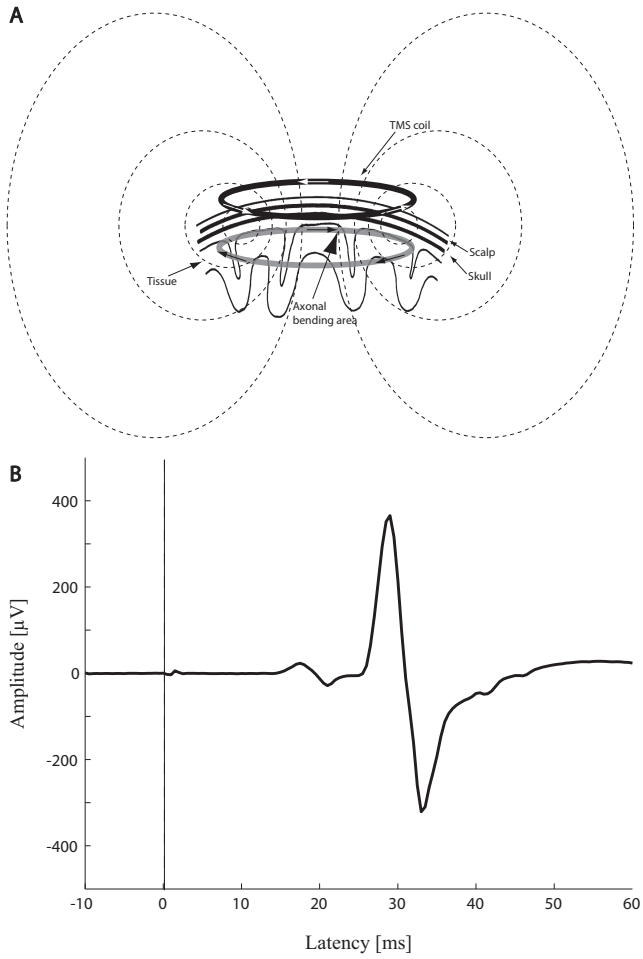

Figure 2.3. A: The law of induction. When a strong current flows through the TMS coil placed over the scalp, a magnetic field is generated, which induces a current parallel but in opposite direction to the current flowing in the coil. Maximum activation of the axons take place at axonal bends. When the TMS coil is placed over MI in the hand representation area, an MEP (**B**) is evoked at about 25 ms after the stimulation.

under the coil generates simultaneous action potentials. If for example, the TMS coil is situated over the motor cortex, a membrane depolarization exceeding a threshold generates action potentials evoking a twitch of the corresponding peripheral muscle. This can be recorded as an electromyographic (EMG) response in the form of a motor evoked potential (MEP; Fig. 2.3).

It is known that in a homogeneous medium, an axon is activated at places where $\partial E_x/\partial t$ is maximum. E_x is the component of the electric field along the axon [1, 5]. Therefore, such gradients can be achieved best at axonal bends or (Fig. 2.3, [46, 107]) endings. Although $\partial E_x/\partial t$ is the major

factor of activation, the component of the field transverse to the axon may play a role as well [110]. Besides the various geometrical factors that influence neuronal activation, such as axon terminal, bending, branching, tapering, and volume-conductor inhomogeneities, the important quantity of cortical excitation is the amplitude of the field. Equally important are the coil geometry and orientation [2, 75].

Cortical nerve fibers align either perpendicularly or tangentially to the cortical surface. Pyramidal cells that represent 75 $\%$ of all neurons in the cortex are oriented perpendicularly. Moreover, the most abundant group of the stellate cells, the spiny ones, have their axons perpendicularly. Therefore, most neurons align perpendicular to the cortical surface [120]. It is well established by electrical stimulation experiments that neurons are excited at lower intensities when the induced currents are oriented longitudinally along the axon and they are most effectively excited when the currents are simulating the depolarizing post-synaptic current flow [23]. Similar dependence on orientation has been found during TMS, where the maximum responses have been recorded when the induced current was oriented 45^o to the antero-posterior plane, probably because the induced current was perpendicular to the central sulcus [11, 87]. This orientation is optimal because of the columnar organization of the cortex and stimulation becomes most effective when combined also with orthodromic current flow (posterior–anterior direction). Thus, optimal aligning with a cortical column excites the maximum number of available neurons and produces action potentials in or near the soma [101].

Recent modelling studies have investigated the probability of several mechanisms involved in TMS [120]. It appears that these mechanisms depend on the type and position of neurons and the orientation and geometry of the induced electric field [114]. At low stimulation intensities, TMS acts transsynaptically, whereas at high stimulation intensities, both transsynaptic and axonal pathways are probably excited. This should be considered when evaluating nTMS results for cortical mapping. In nTMS, it is possible to take into account all these factors and orient the electric field perpendicularly to the corresponding sulcus [109].

The initial state of the neurons of the interconnected brain regions is also important for TMS efficacy [122, 123]. In a single-motor-neuron modelling study [83], the response of the system to a TMS pulse depended not only on the TMS intensity but also non-linearly on the synaptic noise and on the background tonic firing. In simple terms, the effect depends on

the background activity, or it can be modified by a conditioning stimulus and even by a pathology such as focal cortical dysplasia in patients with epilepsy.

2.2.3 Navigated TMS

Conventional TMS has a somewhat limited use in clinical applications and in basic research. It can be utilized to stimulate areas that can produce measurable neurophysiological (e.g., MEP) or behavioural results. In addition, any other cortical site can be identified by external anatomical landmarks, as has been done in many TMS studies. But even in the motor cortex, where MEP responses can be easily generated, it is not known where the targeted site is on the cortex. Moreover, different cortical regions or hemispheres of the same brain have different distances from the skull. Hence, the induced electric field is not the same, although the stimulator output is kept fixed. The variability of different brains in shape, size, and location and orientation of anatomical structures produces unspecificity for the selection of the stimulation site. As a result, reproducibility studies targeting exactly the same cortical site, cortical functional mapping and stimulations of "silent" areas cannot be implemented reliably with the traditional TMS methodology [109].

In nTMS, individual MRIs are co-registered with the subject's head. For this purpose, an infra-red camera locates the tracker tools that are attached on the coil and on goggles that are worn by the subject. In order to align the 3-D MRI head model and the head, landmarks that have been set on the MRIs are chosen manually on the head with a digitizing pen, which serves as a tracker tool. After this procedure, the coil can be visualized over the 3-D MRI head model. In this way, the stimulation site, the coil orientation, and the calculated estimate of the induced electric field can be visualized and reproduced in different measurements of the same subject, as long as the registration error remains the same [109]. The navigation system has been essential in this thesis. Navigated TMS allows the operator to plan, perform, monitor, and document the experiments in an accurate and reproducible manner [46].

2.3 Electroencephalography (EEG)

2.3.1 Neural basis of EEG

EEG measures noninvasively the electrical activity of the brain with temporal resolution of the order of milliseconds [8]. The EEG electrodes are placed on the scalp and the electric potential differences between them can then be measured. It is widely used both in basic and clinical research to investigate the functional state of the brain.

Neural activation gives rise to a primary current $\mathbf{J}^{\mathrm{p}}(\mathbf{r})$. $\mathbf{J}^{\mathrm{p}}(\mathbf{r})$ is generated by the movement of the ions in and out through the cell membranes due to a change in the chemical balance . $\mathbf{J}^{\mathrm{p}}(\mathbf{r})$ affects the charge distribution and potential difference, which produces an electric field $\mathbf{E}(\mathbf{r})$, which in turn produces another current due to the passive ohmic currents in the surrounding medium, the volume current $\mathbf{J}^{\mathrm{v}}(\mathbf{r})$. EEG signal measures actually the difference potential between two points on the scalp that result from the generation of this electric field.

EEG is used by inspecting the deflections visually, by calculating the spectral power of brain spontaneous activity, and by measuring the evoked potentials that are time locked to an external stimulus or an event (ERP). EEG has an excellent temporal resolution, but its spatial resolution is in the order of centimetres. This is because of many reasons but mainly due to the fact that the EEG signal is a projection on the skull, the summation of brain activity around the focus of $\mathbf{E}(\mathbf{r})$. If EEG is combined with imaging methods (e.g., MRI) or with functional tools (e.g., fMRI or TMS), spatial resolution can be clearly improved.

2.3.2 TMS-evoked EEG

TMS-evoked EEG detects the brain electrical activity elicited by the magnetic stimulus. Conventional TMS studies are able to investigate the cortico-spinal pathway and the cortical excitability by means of EMG, or to study cognitive functions with behavioural tests. However, neither the functional cortico-cortical connectivity nor the instantaneous state of the brain can be assessed [63, 82]. TMS-compatible EEG systems have been developed for these purposes.

The TMS-induced electric currents produce action potentials that activate synapses. The distribution of the postsynaptic currents are recorded

by the EEG [47]. These signals can be used for locating and quantifying synaptic current distributions by dipole modelling [117] or minimum-norm estimation [40], provided that multichannel EEG is used and that the conductivity structure of the head is taken into account. Alternatively, the activation of different regions and hemispheres of the brain can be located at different time points after stimulation in terms of functional connectivity [47, 82]. Finally, the signals can simply be just filtered and averaged (Fig. 2.4). Regions of interest (ROIs) can then be selected to address the role or the behaviour of specific cortical areas [89].

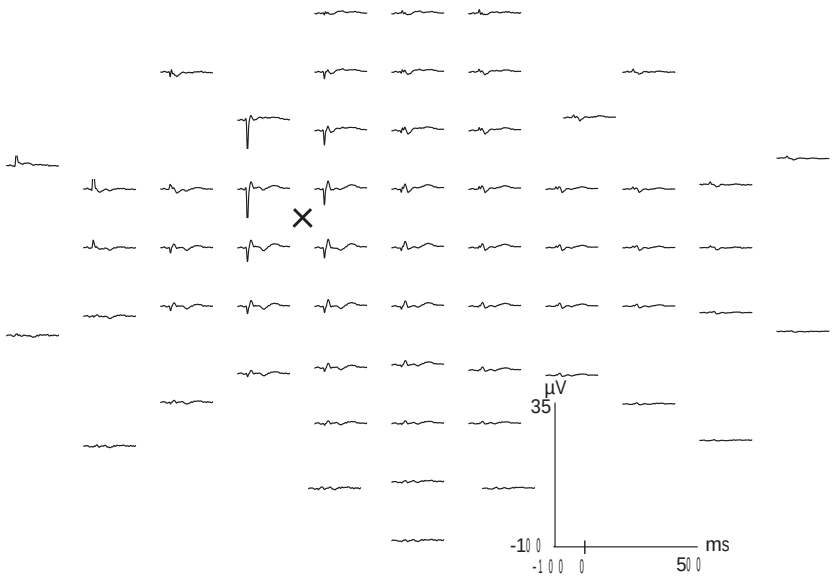

Figure 2.4. Averaged EEG responses evoked by TMS in one subject. The signals are arranged according to the layout of the electrodes (the view is from the top of the head, and the nose points upwards). Stronger responses are located in the vicinity of the stimulation point , marked with "X". Responses attenuate with increasing distance from the stimulation site.

The first efforts to combine TMS–EEG suffered from strong electromagnetic artifacts [22]. The advancement in TMS-compatible EEG amplifiers has boosted the use of TMS-evoked EEG studies [45]. However, even with amplifiers that either recover after a delay [49, 133] or are unsaturated by the TMS pulses [50], artifacts remain. Artifacts can be generated by eye movements or blinks, by cranial muscles close to the EEG electrodes, by electrode movements and their polarization, and by the coil click or somatic sensation. Careful subject preparation guaranteeing electrode impedances below 5 kΩ, immobilization of coil over the electrodes and, if possible, a small sponge between coil and electrodes to reduce vibrations,

earplugs and even masking sound through headphones should be used to minimize the artifacts. The magnetic stimulation needs to be repeated in tens of pulses to increase the signal-to-noise ratio of the TMS-evoked EEG responses. Moreover, various methods such as averaging, independent and principal component analysis, subtraction methods and projection operators can be utilized to extract the brain responses [45].

TMS–EEG can be utilized in studying cortico-cortical and interhemispheric interactions, cortical inhibitory processes, cortical plasticity, and oscillations. When used with navigation, it can probe excitability changes during motor or cognitive tasks and be used for monitoring pharmacological effects as suggested in Publication I. So far, TMS–EEG has been applied in the assessment of the general brain state under alcohol influence [53], during deep sleep and wakefulness [82], and during minimum cognitive and persistant vegetative states [104]. TMS–EEG can also give insights in the interaction of different brain areas during sensory processing or motor control (Publications II and III, [9, 89]). Analysis of how activity in a specified area affects the ongoing activity in remote areas [121] can be studied as well. Moreover, TMS–EEG can be used to investigate the plastic reorganization of the cortical circuitry after repetitive TMS (rTMS; [27, 131]). Finally TMS–EEG is used to alter the spectral content of the EEG signal [12, 34, 92] and to correlate specific frequency bands with distinct functions [64].

2.4 Magnetoencephalography (MEG)

2.4.1 General

TMS and MEG can be considered as converse to each other in terms of their physical properties [47]. The magnetic field of the brain is generated by both $\mathbf{J}^{\mathrm{p}}(\mathbf{r})$ and $\mathbf{J}^{\mathrm{v}}(\mathbf{r})$. If the primary source and the surrounding distribution are known, then the magnetic field (MEG) can be calculated by Maxwell's equations (forward problem; [39]). A current dipole approximates the source of a localized primary current $\mathbf{J}^{\mathrm{p}}(\mathbf{r})$. Once the solution for the elementary current dipole that derives from the linearity of Maxwell's equations is known, the fields of more complex brain sources can be calculated by superposition. MEG measures mainly activity from the cortical fissures, because it detects only currents that have

a component tangential to the surface of a spherically symmetric conductor, such as the human head. This can simplify the interpretation of the data. In MEG as in EEG, the interpretation of the data is part of the inverse problem which has no unique solution [134]. The current dipole is a popular source model in MEG and is valid if the activated cortical region is small. The optimal solution is achieved by fitting the theoretical and measured field patterns by the least-squares method (equivalent current dipole (ECD); [39]). This procedure has been followed in Publications III and IV.

2.4.2 TMS and MEG

TMS and MEG can be used in a complementary manner. MEG can be applied before and after rTMS, which is claimed to have therapeutic effects [99]. By comparing spectral amplitudes of the brain activity with MEG before and after rTMS application, specific rhythms of the brain can be correlated with therapeutic effects, e.g. in Parkinson's disease [58]. This setup can be expanded to several diseases that seem to be treated by rTMS, such as depression, stroke, chronic pain, and tinnitus. In addition, MEG can be used to locate the generators of evoked fields (EF). The time and site of the activated brain areas can be then utilized to identify target brain areas for subsequent TMS, as we show in Publication III. MEG and TMS can also be used for presurgical evaluation, as suggested in Publication IV.

2.5 Functional cortical mapping in brain surgery

2.5.1 Invasive cortical mapping

Functional eloquence of brain areas based on anatomical landmarks is unpredictable due to anatomical, functional, and pathology-related variability [100]. Neuroimaging and intraoperative brain mapping should be applied to patients individually in order to preserve eloquent cortex and to optimize the extend of resection while preserving the quality of life [36]. Resection without intraoperative or extraoperative invasive mapping should not be considered in lesions estimated to be close to functionally crucial areas [100]. Invasive functional cortical mapping (Fig. 2.5) prior to resection is achieved by means of electrical cortical stimulation

(ECS). Intraoperatively is applied by direct cortical stimulation (DCS) to tumor patients utilizing monopolar or bipolar electrode probes [61]. Extraoperative stimulation is done by operative insertion of a subdural grid of electrodes. Recordings and stimulations are then performed outside the operation room. Grids are applied usually to patients with intractable epilepsy both for functional mapping and to locate epileptic foci [71]. This requires a diagnostic surgery and is associated with a non-trivial risk of complications [41]. Invasive functional cortical mapping is considered the gold standard for patients to be operated due to its ability to localize accurately the primary motor cortex [130]. It has also been well validated for localizing speech-related areas [21, 115] during awake craniotomy and it can also be used for mapping of visuospatial and cognitive functions [25].

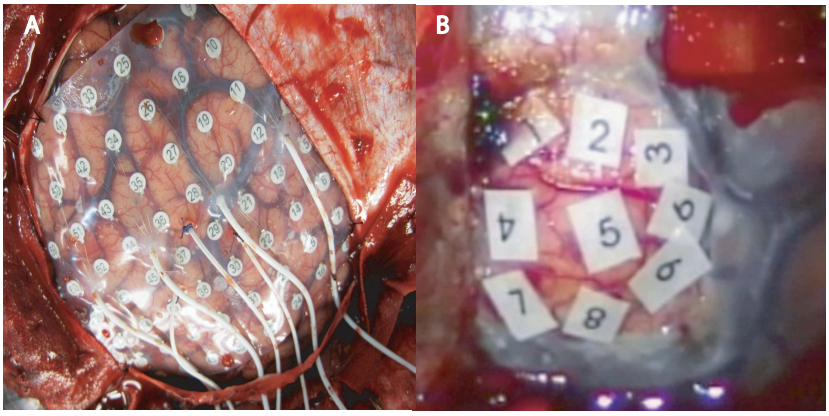

Figure 2.5. Examples of invasive cortical mapping. **A:** Subdural grid of electrodes. The grid is placed over a part of the cortex. The electrodes are labelled. The electrode leads pass through the skull to allow subsequent stimulations for localizing sensorimotor cortex and epileptogenic area, before the final resection. The stimulations are done during the week separating the two operations. **B:** DCS mapping of motor cortex. During the stimulation of motor cortex, EMG is also recorded from the muscles under investigation. When a response is observed in the EMG, a numbered tag is placed over the site that evoked responses. Resection takes place immediately after the mapping.

Laterilization of speech is necessary if the to-be resected area is estimated to be near speech related areas. The standard procedure for the identification of cerebral speech dominance is the WADA test [135]. During the WADA test, sodium amytal is injected in one of the carotid arteries to induce temporary functional loss of one hemisphere. The WADA test, although an efficient way to identify speech lateralization, has constraints and risks [6]. Therefore, noninvasive preoperative neuroimaging methods are of high interest.

2.5.2 Neuroimaging in preoperative cortical mapping

Utilization of neuroimaging has increased during the last decade. MRI, fMRI, DTI, and MEG are used for preoperative mapping [76, 77, 111]. It has been suggested that preoperative mapping should include at least fMRI [100] since other methods like MEG and PET [124] are usually found in specialized centres only.

Anatomical MRI is crucial in localizing tumors and in general lesions, but does not reveal the epileptic foci. It can be also used in neuronavigation in the operation theatre to guide the neurosurgeon to the cortical site of interest [141]. fMRI is used for localization of motor functions. It has been widely used also for speech-dominant hemisphere identification, although with variable results. Some studies have compared also fMRI to DCS results for localization of speech-related areas (for a review, see [111]). fMRI produces more false positive activations than DCS, but still can offer valuable information about the sensitivity of different tasks in the demonstration of eloquent cortical speech areas [96]. DTI can image the white-matter fiber tracts that connect different speech regions (for reviews, see [33, 137]). It can illustrate the different connections in the speech network, important information for neurosurgeons [111].

MEG is unique in depicting somatomotor cortical function and detecting sources and the spread of epileptic activity [77]. Functional localizations of MEG have been confirmed by intraoperative mapping and appear more accurate than fMRI localizations [48, 66]. In addition, mapping of speech-related areas can be useful for presurgical planning. Recent studies show that fMRI depicts better than MEG the frontal speech-related activity, but MEG is more useful in detecting temporoparietal speech-related cortices. MEG combined with fMRI may give valuable and accurate results for localizing speech functions [54]. Finally, MEG can locate accurately epileptiform spikes as confirmed by electrocorticography (EcoG). MEG may turn out to be indispensable in diagnosis and surgical resection for epilepsy to locate accurately the epileptogenic zone [119]. However, MEG availability is low and it requires high expertise for the data analysis and interpretation, in contrast to fMRI [77].

2.5.3 TMS in preoperative mapping

TMS has been used efficiently for preoperative mapping both in brain tumor [32, 97] and epilepsy (Publication IV, [113]) patients. Although good

results have been obtained earlier in locating motor cortex [68], nTMS has been only recently utilized extensively for preoperative mapping. In mapping of motor functions, nTMS is more accurate than fMRI [32, 67] and agrees well with DCS [67, 97]. These studies suggest that nTMS mapping improves the surgical planning [98] and increases surgeons' confidence during resection [67]. In speech mapping, early studies [91] inspired several attempts producing variable results [24]. Nevertheless, the utilization of nTMS may open new avenues in speech mapping as well, as we propose in Publication V. However, extensive comparisons with the gold standard DCS recordings are needed.

3. Material and methods

3.1 Stimulators

Single-pulse TMS in Publications I, II and III was performed with a Magstim 200 (The Magstim Company Ltd.) device connected to a co-planar figure-of-eight coil (NP 9925) with an average diameter of 70 mm for each wing. In Publications IV and V, a Nexstim stimulator (Nexstim Oy, Finland) with a monophasic or biphasic (when rTMS was applied) figure-of-eight coil of 70 mm outer diameter for each wing was used.

3.2 Navigation

The navigation system used for the Publications I, III, IV, V is based on the principles of frameless stereotaxy. It is an optical tracking system [140] that consists of a light-emitting camera and several light-reflecting optical elements attached to the head (reference tracker) and the coil as shown in Fig. 3.1. The accuracy of coil localization depends on the 3-D localization technique, on movement of the reference tracker and on errors in alignment of anatomical MRIs to the real head of the subject.

The principles of navigation and the extra features it offers, such as saving the coil's location and orientation, and digitization of the locations of the EEG electrodes, were vital for test–retest design and in accurate stimulation of the dorsolateral prefrontal cortex in Publication I, for cross-modal study in Publication III, and for careful cortical on-line mapping in Publications IV and V.

3.3 TMS–EEG

TMS–EEG enables the direct study of cortical excitability. This advantage can be used to study functional connectivity, state-dependent excitability and to investigate cortical areas that have no specific behavioral or peripheral activity markers. The huge artifacts that arise from the electric

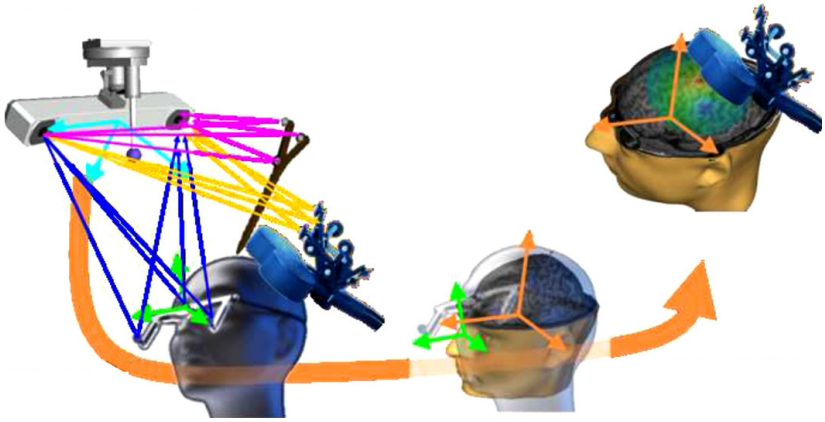

Figure 3.1. Navigated TMS. The infra-red light is emitted by the tracking system (camera). It is reflected from the digitizing pen, the coil and the head trackers back to the camera. The position of the coil is monitored after co-registration between the 3-D MRI head model and the real head. This procedure is done by aligning the cardinal points chosen on the 3-D MRI head reconstruction with the real anatomic structures on the head by the digitizing pen. Thereafter, both the coil projection on the individual's cortex and the induced field over the particular cortical site can be visualized in real time. Adapted from [109].

field induction by the stimulus pulses can be dealt with by using TMS-compatible EEG amplifiers (for reviews, see [31, 45]).

We utilized a TMS-compatible EEG amplifier based on gain-control and sample-and-hold circuits (Fig. 3.2; [133]). In this electronic set-up, the artifact does not pass through the circuits, and a considerable part of it is blocked. The blocking is externally triggered and takes place during the "gating period", i.e., 50 μs before and 2–8 ms after the delivery of the TMS pulse.

The EEG responses to TMS were recorded with sixty Ag/AgCl sintered (Publications I and III) or C-shaped electrodes (Publication II) especially designed for TMS–EEG measurements to avoid overheating by eddy currents induced by TMS (Nexstim Ltd.). The EEG sampling rate was 1450 Hz, the bandwidth was 0.1–350 Hz (Publications I and III) or 0.1-500 Hz (Publication II), and 16-bit AD conversion resolution was applied (eXimia, Nexstim Ltd.).

In Publication I, TMS–EEG was applied twice to each subject with one week separation between the two experiments. Three different intensities (90, 100, and 110 % of MT) over MI and DLPFC were applied and a hundred pulses for each intensity were given with 3.3-s interstimulus interval (ISI). In the first experiment, the site of stimulation over cortical representation of APB in MI was found by optimizing location and

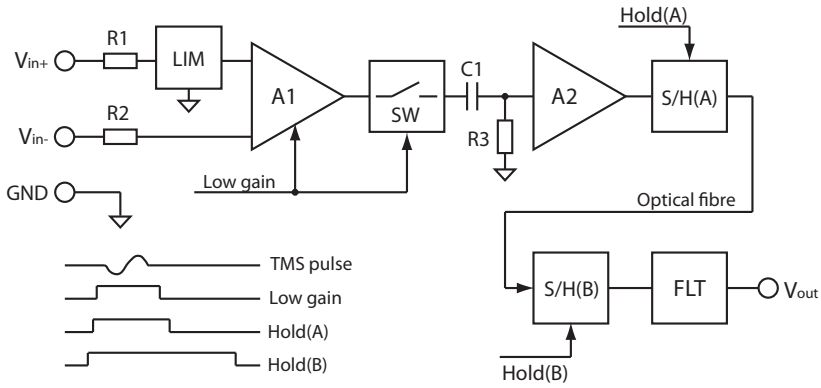

Figure 3.2. Block diagram of the TMS–EEG amplifier. After the signals are high-pass filtered (f>0.1 Hz) and amplified, they are light-intensity modulated and transferred to a light receiver unit with optical fibres. Then, the analog signals are low-pass filtered, with cut-off frequency of 350/500 Hz. The sampling rate during A/D conversion is 1450 Hz. The gain of the first amplifier stage A1 is reduced during the TMS pulse. At the same time, the semiconductor switch SW, following A1, opens the signal path during the TMS pulse: the input voltage of the second amplifier stage A2 drops to zero and the voltage over capacitor C1 remains constant. To block large voltage peaks before the optical isolator, the sample-and-hold circuit S/H(A) latches the signal from A2 prior to the TMS pulse and keeps the output at this level during the pulse. S/H(B), located in the non-isolated section of the amplifier, prevents any residual artifact from the stimulus from being stored in the subsequent filters (FLT). To keep the differential input voltage of the preamplifier A1 in the linear operating range, the signal in the positive input terminal Vin+ is limited to $\pm$9 V (LIM), and the voltage between the negative terminal Vin- and the amplifier ground is kept smaller than $\pm$1 V by attaching the reference and ground electrodes close to each other. If the voltage exceeds these values, the 20-kΩ resistors R1 and R2 limit the current to a safe level in accordance with standards. The sample-and-hold circuit S/H(B) is controlled by the Hold(B) signal, which is activated about 50 μs before the TMS pulse and is released after the pulse. Adapted from [45].

orientation of the coil with the assistance of the navigation system. The motor threshold was determined by evoking contralateral MEPs of minimum 50 μV in 5 out of 10 stimuli [106]. The site of stimulation in the DLPFC was found by means of anatomical landmarks seen on the individual MRIs. The location was double-checked by transforming the head coordinates of the site to Talairach coordinates [126]. The coil was placed with lateral–medial direction towards the middle frontal gyrus. For both MI and DLPFC sites, coil positioning was kept stable with a targeting tool provided by the software of the navigation system (eXimia, Nexstim Ltd.). The locations of the EEG electrodes were digitized so that their projection to the stimulated cortical sites of the 3-D head MRI reconstruction for each subject was visible. The exactly same location for stimulation sites and electrodes were used in the second experiment by applying the

special features of the navigation system.

In Publication II, TMS was applied time–locked to a visual stimulus Fig. 3.3, which transiently modulated cortical excitability at the targeted cortical network. EEG was recorded immediately after the TMS pulse. The visual stimulus was followed by a TMS pulse in two conditions, with or without a voluntary movement of the thumb. ISI was 3.3-4 s.

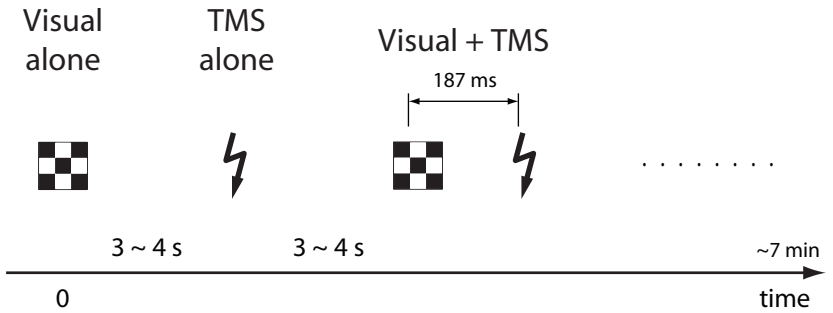

Figure 3.3. Experimental setup of Publication II.

In Publication III, TMS–EEG was recorded over several locations (iMI, cSI, cSII, iSII) 15–210 ms after electrical stimulation of the median nerve of the dominant hand of each subject. 40 electrical stimuli were given with ISI 1.5–21 s. The stimulation sites were chosen from source localizations of prior MEG experiments. The navigation system allowed accurate stimulation of the predetermined targets and digitization of the EEG electrode sites.

3.4 MEG

Magnetoencephalography maps magnetic fields generated by neuronal activity in the brain. A 306-channel MEG device (Elekta Neuromag Ltd.) was used to measure somatosensory evoked fields (SEFs) to median (Publications III and IV) and tibial nerve stimulation (Publications IV) and spontaneous ictal and interictal brain activity (Publication IV). Spontaneous ictal and interictal brain activity was recorded with frequency band of 0.03-172 Hz and sampling frequency of 600 Hz. In Publication III, the somatosensory stimuli were 120 electrical 0.2-ms pulses with variable ISI (range 1.5–21 s). SEFs were recorded at 0.01–330 Hz. In Publication IV, SEFs were elicited by 100 electrical pulses to the wrist, and 500 to the ankle using stimulus intensity above the motor threshold. ISI was kept constant at 2 s. The data were band-pass filtered at 0.3–90 Hz for off-line

analysis. All measurements were performed in a magnetically shielded room (Euroshield, ETS Lindgren, Eura, Finland).

3.5 Speech mapping setup

During speech mapping, the subjects named pictures of objects presented every 2.5 s for 700 ms on a computer screen with or without nTMS. During the nTMS sessions, trains of 5 pulses at 5 Hz were applied by nTMS 300 ms after the presentation of each picture. The nTMS and stimulus presentation screens were cloned. A commercial digital camera was utilized to record the subject's performance and the screen clones. Delays between presentation, audio and video signals were eliminated by carefully tested combination of displays and camera (Fig. 3.4).

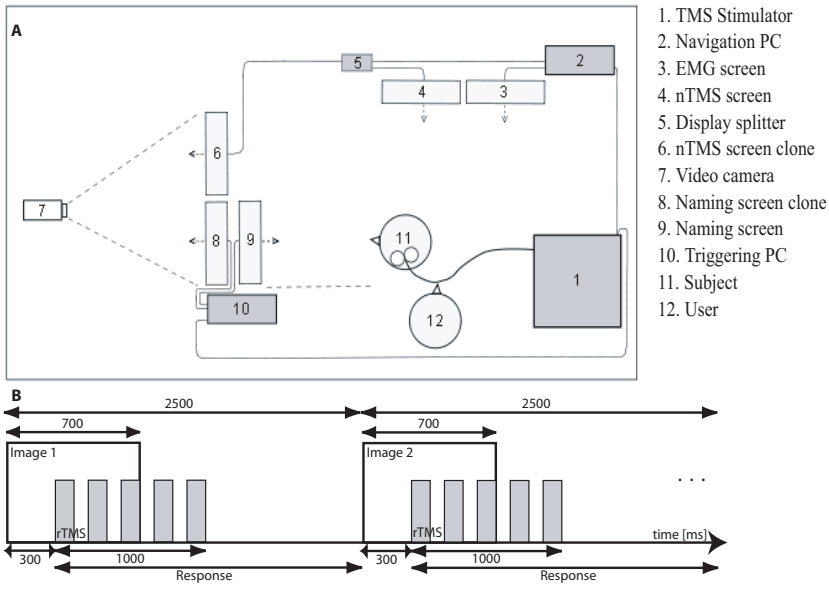

Figure 3.4. A: A scheme of experimental setup of speech mapping from above. **B:** Timeline of events. Naming response took place in variable times after the image presentation.

3.6 Analysis methods

3.6.1 TMS–EEG

In Publications I, II, and III, the ERPs were obtained by recording the EEG signals locked to the TMS stimulus. The analysis of the multichan-

nel TMS–EEG ERPs was focused on selected ROIs and on time segments from 100 ms before TMS up to 500 ms after TMS. Before averaging, the raw EEG was inspected for artifacts caused by eye movements, muscle activity and mechanical disturbances. Epochs with signals larger than 50 μV were excluded from further analysis. Four to ten electrodes near the vicinity of the stimulation site were selected as ROI in the stimulated hemisphere. An analogous ROI was selected also from the contralateral to TMS hemisphere to investigate inter-hemispheric differences (Fig. 3.5).

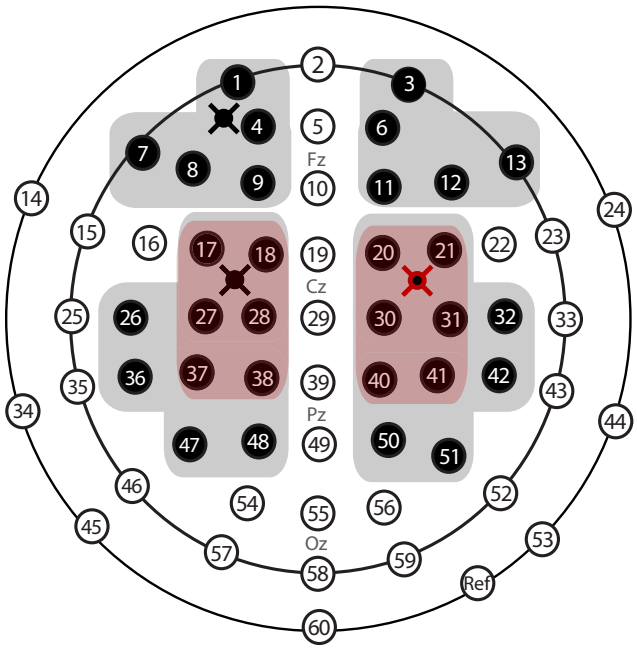

Figure 3.5. ROIs of Publications I (grey areas) and II (red areas). The black crosses represent the stimulation sites of Publication I and the red cross the stimulation site of Publication II.

In Publication I, EEG signals were low-pass filtered with 45-Hz cut-off frequency. Statistical comparison between the TMS–EEG evoked responses that were obtained with one week difference was performed by means of paired two-tailed t tests with Bonferroni correction. In Publication II, EEG signals were low-pass filtered with 40-Hz cut-off frequency. The responses to visual stimuli alone were subtracted from the responses to the combined presentation of visual stimuli and TMS stimulation. A statistical comparison by means of a 2x2 ANOVA was utilized to reveal influences of different cortical functional states on the TMS–EEG evoked potentials. Finally, in Publication III, no additional filters were used. The EEG responses were averaged with respect to the somatosensory stimuli

to reveal ERPs separately for each TMS location and latency.

3.6.2 Motor mapping and source analysis of the epileptiform activity and the evoked fields

In Publication IV, the MEPs to TMS were evaluated off-line. The area where nTMS evoked MEPs of 50 μV peak-to-peak or larger, or a clear silent period [59, 127] within the preactivated target muscle, was determined as motor representation area of the target muscle. Epileptiform activity during nTMS was monitored with EEG, but no increased activity or seizures were observed.

All individual MEG traces were screened visually for epileptiform activity according to traditional EEG criteria, and for corresponding dipolar magnetic field patterns, both during and between seizures. The ECDs were fitted to sensor locations covering the magnetic field pattern of interest. The center of this pattern was focused at the largest gradiometer signal of interest, and a sufficient number of sensor locations (36-40) to cover both magnetic field extrema were selected. The overall spatial distribution of the field pattern rather than the signal from specific sensor location was used as a criterion of dipole selection giving over 80 % goodness-of-fit values. When testing the dipole with all the 306 channels for residual signal of interest, we accepted also lower goodness-of-fit values, but required a good visual congruity between the measured signal and the waveform predicted from the estimated dipole.

3.6.3 Speech mapping

In Publication V, the speech mapping data were analysed off-line. A neuropsychologist with expertise in analysis of effects of electrical cortical stimulation during subdural recordings on speech reviewed the videos and compared the baseline naming with that during nTMS. During the video analysis, the screen showing the stimulation sites was obscured. No-response errors (anomia), performance errors, neologisms, semantic and phonologic paraphasias, and circumlocutions [21] were searched for from the videos. If one pulse train induced an error, the site was marked up as speech-related. Then speech-error-related maps for each individual were made, as shown in Fig. 3.6.

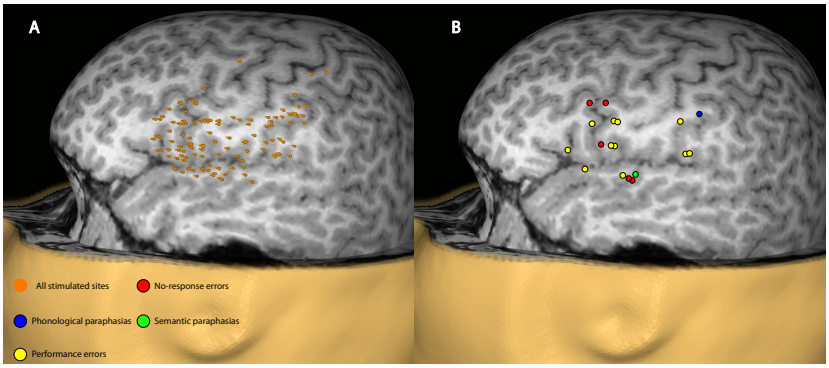

Figure 3.6. Results of an nTMS speech mapping shown over the 3-D MRI reconstruction of one subject's head. **A:** All the stimulated cortical sites. **B:** The cortical sites where speech errors were induced.

3.7 Summary of the experimental setup

Altogether 23 subjects and 2 patients participated in the experiments that constitute Publications I–V. All study protocols were approved by the Ethical Committee of the Helsinki University Central Hospital and all participants gave their informed written consent. Table 3.1 summarizes the setup of the experiments.

Publ.	Subjects/Patients (Age range)	Site	TMS type	Intensity	Recording
I	7 S. (23-34)	left MI+DLPFC	SP	90, 100, 110% MT	nTMS–EEG
II	9 S. (23-32)	left and right MI	SP	120% MT	TMS–EEG
III	3 S. (26-41)	left SI and SII, Right MI and SII	SP	120% MT	nTMS–EEG, MEG
IV	2 P. (16-22)	left and right hand, arm, foot and leg MI representations	SP	105–110% MT	nTMS–EMG, spont. EEG
V	4 S. (22-55)	left and right frontal, parietal and temporal lobes	5Hz rTMS	80–100 % MT	nTMS, video

Table 3.1. Overview of all publications.

4. Results and discussion

4.1 Reproducible cortical excitability

In Publication I, we performed nTMS–EEG in seven healthy subjects at three different intensities at and around MT. The stimulation sites were over left MI and DLPFC and were repeated with an 1-week interval. We found high overall ($r > 0.83$) reproducibility of peak ERP amplitudes elicited by nTMS over both hemispheres for both MI and DLPFC stimulations. In all subjects, six peaks from the ERPs were identified after MI and DLPFC nTMS in ROIs over both hemispheres (Fig. 4.1). Exceptionally, Peak I was not identified in the ipsilateral prefrontal ROI after DLPFC nTMS stimulation, because the residual TMS electrical artifact covered it. The amplitudes of peak II elicited by MI nTMS and peak VI elicited by DLPFC nTMS were significantly less repeatable than the other deflections. In the contralateral hemisphere the correlation coefficients were lower than in the ipsilateral hemisphere for the MI stimulation, probably because of signal fluctuations originating from the transcallosal connections. Test-retest correlations of response peak latencies were in general high and similar for all ROIs. Generally, significantly higher nTMS–EEG ERPs were recorded over MI than DLPFC confirming previous results that have suggested the different reactivity of the two regions [52]. Additionally, high correlation of MTs of both hemispheres were found between repeated measurements.

In line with previous studies, we identified N15, P35, N45, P55, N100, and P180 deflections [10, 62]. The origins of these deflections are not clear. N100 is the most discriminable and reproducible peak in TMS-evoked ERPs. It is possibly a marker of cortical inhibition [9]. If it is so, these data enhance its importance as cortical marker, because of its high reproducibility. Nevertheless, one should be careful in interpretation of N100 results, since the N100–P180 complex may contain auditory activity due to the TMS sound click conducted through the skull bones [88].

The results presented in Publication I show that reproducibility is a feature of the combined nTMS–EEG method. This feature can be a valuable

tool when investigating the potential role of medications on movement and degeneration disorders, or to explain on solid electrophysiological basis the beneficial role of rTMS over DLPFC in patients with depression. Vice versa, knowing the mediating effect of a drug or of some other therapeutic technique (*e.g.*, rTMS) on neuroreceptors/neurotransmitters that have a known inhibitory or facilitatory role, such a reproducible test–retest paradigm can elucidate the origins of the TMS-evoked EEG deflections.

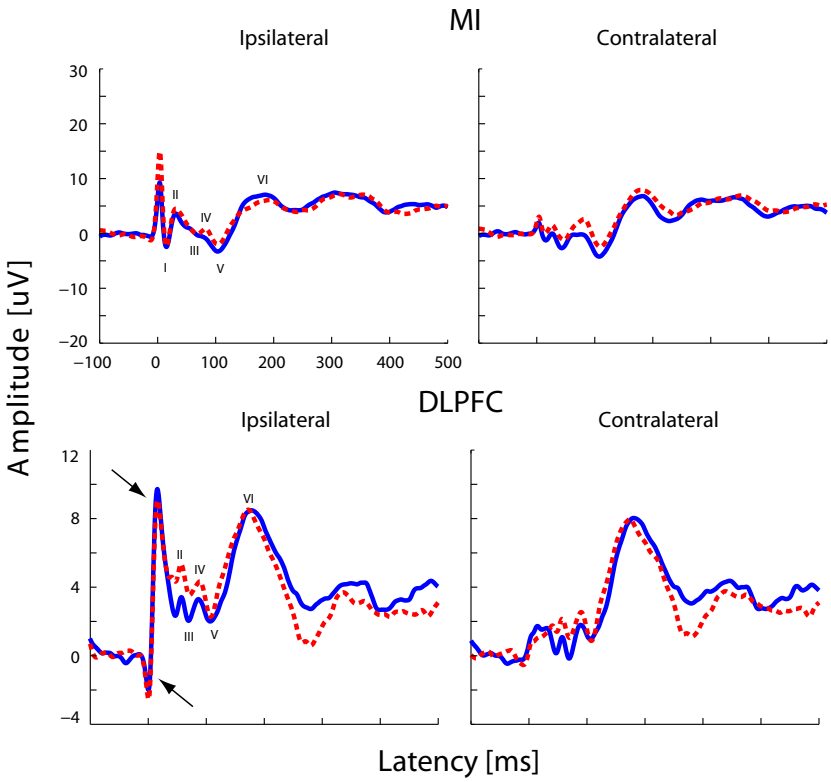

Figure 4.1. Grand average waveforms of the two measurements from ROI electrodes after primary motor (MI) and dorsolateral prefrontal cortex (DLPFC) stimulation at 90 % of MT. The dashed lines illustrate the first and the solid lines the second recordings separated by one week. The arrows indicate the residual TMS artifact. The signals were low-pass filtered with a cut-off frequency of 45 Hz. Note different amplitude scales for MI and DLPFC responses. The variability of the response peaks is larger than the baseline noise.

4.2 The role of ipsilateral hemisphere in movements

The motivation for Publication II comes from an earlier work of our group [89] where it was hypothesized that the TMS-evoked N100 component

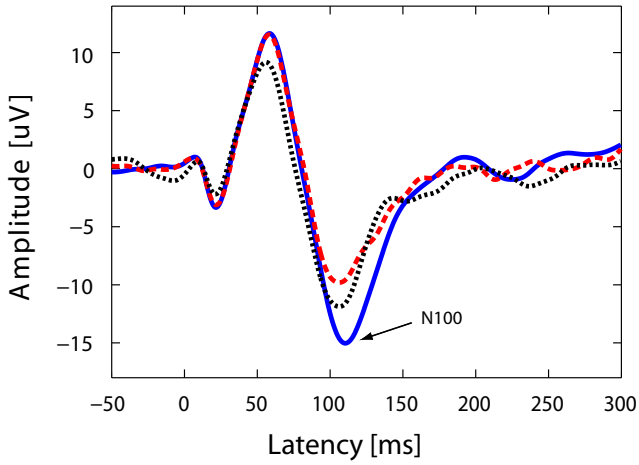

Figure 4.2. Grand average nTMS-evoked EEG responses of three measurements from the right MI ROI. Responses to TMS are illustrated with the blue trace. TMS-evoked N100 was more attenuated during the contralateral (red trace) than the ipsilateral (black trace) hand movement.

represents an inhibitory response following the TMS. Similarly, we simultaneously recorded both central (TMS-evoked EEG) and peripheral (EMG) responses to investigate the role of the ipsilateral sensorimotor cortex during unilateral movements. In this study, we showed that the TMS-evoked N100 component exerts task-related differences between the hemispheres, being attenuated to a greater degree during contralateral movements (36 %) compared to ipsilateral movements (25 %). This higher attenuation of contralateral hemisphere might be due to the elevated neuronal activity which is associated with the preparation and generation of motor performance. This association between cortical and peripheral muscle response modulation was observed only for the contralateral hemisphere. On the other hand, in the ipsilateral hemisphere such association was not observed. Instead, we found that while subjects were moving their thumb in response to the visual cue, an unevenly distributed EMG activity was occasionally registered in the homologous muscle of the opposite hand. This pointed to a probable additional inhibitory mechanism in the ipsilateral hemisphere responsible for suppression of (unwanted) motor output discharges and may control the EMG activity of the opposite hand. This EMG activity might be a remainder of mirror movements (MMs) that usually occur in childhood [20] or are associated to developmental disorders [19, 84] but are not abundant in normal subjects.

Our results demonstrate a bilateral activation of sensorimotor cortices

that occurs during execution of unilateral movements [85, 132]. This activation could be responsible for facilitating or suppressing the MMs [69, 70, 95]. It is suggested in this study that in ipsilateral hemisphere there is a mechanism initiating undesired MMs and another one that suppresses them [60, 95]. Indeed, MM-related excitatory activity is counterbalanced by inhibitory activity and this is reflected as a smaller decrease of the ipsilateral N100 than in the contralateral one, as shown in Fig. 4.2.

4.3 Mapping the interaction of motor and sensory cortical areas

In publication III, we applied nTMS–EEG 15–210 ms after electrical somatosensory median nerve stimulation in three healthy volunteers. The TMS latencies were chosen for each individual based on the individual SEF response latencies. During TMS, the task was to respond with the hand contralateral to somatosensory stimulation as quickly as possible, while reaction times (RT) were measured. By this setup, we investigated the cortico–cortical communication between primary sensory cortex and the hierarchically higher-order cortical areas that receive parallel inputs directly from the thalamus, bypassing the primary sensory cortices. The possible advantage of such inputs was also examined, by studying the effect of TMS on RTs when performed over different cortical sites and at different latencies after the somatosensory stimulus.

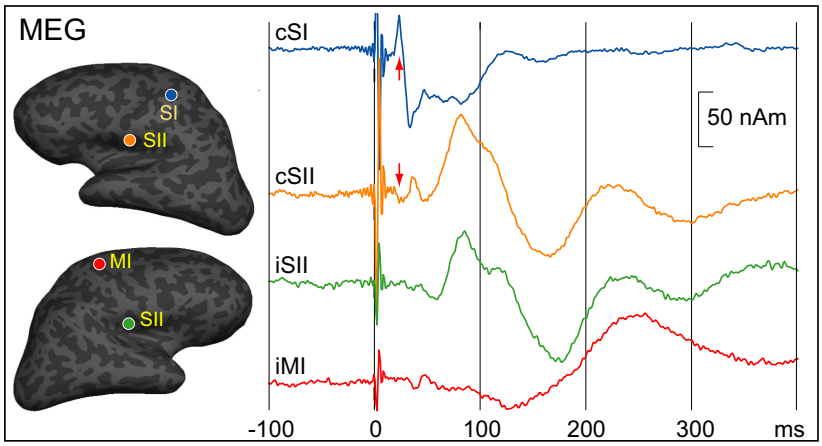

Figure 4.3. Source locations and source strengths of MEG responses to the right median nerve stimulation and their time courses.

The SEF locations and their time courses were identified by MEG by utilizing multidipole modelling (Fig. 4.3; [40]). The main finding from the

MEG experiment was that cSII was activated several milliseconds earlier than cSI, suggesting that higher-order cortices may become activated earlier than primary sensory cortices, in line with previous reports [3, 29, 56], but contrary with many others (for review, see [42]). In other words, it should be an early parallel input directly into SII, completely independent to the pathway via SI [56]. Our nTMS stimulation further supported this view. nTMS to cSII resulted in significantly faster RTs than when nTMS was delivered over cSI or iSII. Largest facilitation was observed when nTMS was delivered to cSII 20 ms after the electrical stimulus. In general, TMS pulses speeded up RTs when applied 15–40 ms after the somatosensory stimulus.

Our data suggest that faster RTs due to TMS can be explained by a top-down influence of SII to SI that facilitates the reciprocal SI to SII pathway. As TMS is highly state-dependent, we have probably activated an already existing mechanism for brain-speeding, by positioning our coil on the correct cortical site by means of navigation and triggering it on the time that the cortical sites were activated by the somatosensory stimulus.

4.4 Functional mapping of motor cortex in clinical applications

In Publication IV, we applied nTMS and MEG on two patients with drug-resistant epilepsy with sensory auras that progressed into motor seizures. nTMS was used for mapping the primary motor cortex and MEG for the localization of the epileptogenic and the somatosensory cortical regions. These two protocols were used in addition to the invasive cortical mapping by means of ECS, which is conventionally required as a preoperative work-up for epilepsy surgery.

For both patients, nTMS-evoked MEPs revealed excellent correspondence to the MEPs elicited by preoperative and subdural stimulation (Fig. 4.4). Localization of epileptogenic regions was also successful. Histological studies of the resected cortex revealed a microscopic focal cortical dysplasia, not visible in 3-T MRI in one of them. Both patients have remained seizure free.

The combination of nTMS and MEG in these two patients was useful in planning the placement of the subdural electrodes. nTMS mapped accurately the hand and leg motor cortical representations. For these two patients, nTMS mapping was spatially more precise than that of ECS, whose spatial resolution is limited to the 1-cm inter-electrode distance of

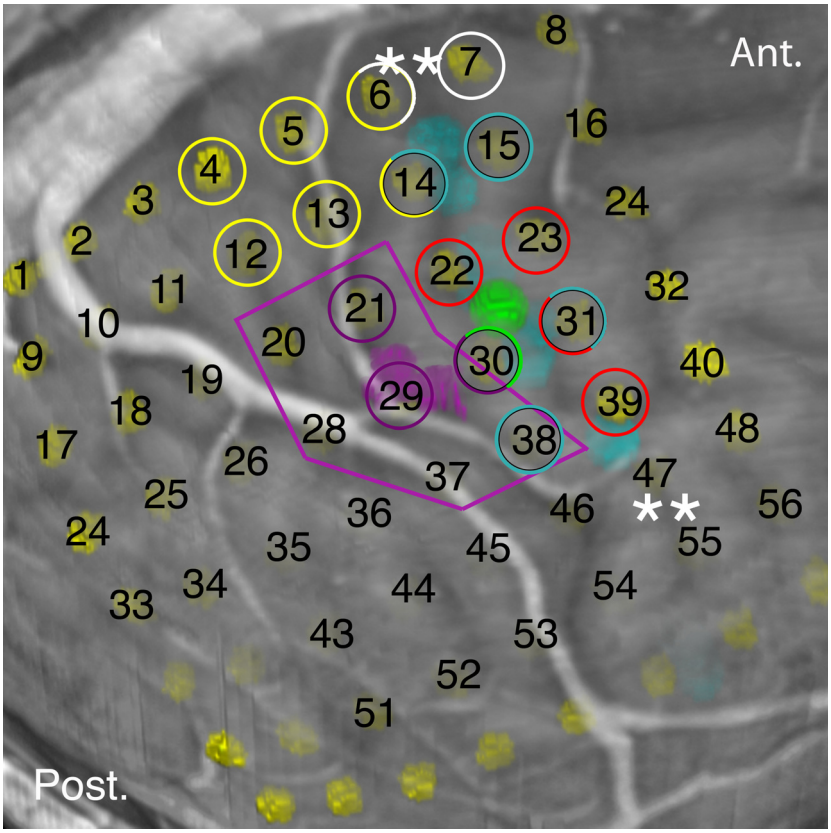

Figure 4.4. A 3-D MRI reconstruction of a patient in epilepsy surgery planning. The results from all the techniques used preoperatively and intraoperatively are presented. ECS grid electrodes are shown in yellow and are numbered. MEG ictal source area is depicted by purple and SEF ECD-sources of left median nerve responses by green colour. Stimulations of grid electrodes marked with purple circle elicited habitual and those marked with red circles non-habitual seizures. nTMS activations of hand and arm muscles are depicted by turquoise. The resected area is delineated by a purple line. The double asterisks (⋆⋆) indicate the location of the central sulcus. Ant. stands for anterior and Post. for posterior view.

the electrode grid (Fig. 4.4). MEG is superior to surface EEG in locating the interictal epileptic discharges [118] and in satisfactory concordance with ECS in localizing SI [77]. Additionally, MEG can localize SI more reliably than fMRI [66]. Finally, during the nTMS mapping no seizures were observed, whereas during the subdural stimulation mapping several seizures occurred, suggesting that single-pulse TMS is a safe tool for epilepsy patients. Our data suggest that the combination of nTMS and MEG may have the potential to replace ECS in a subgroup of patients with epilepsy who have the suspected epileptic zone near the sensorimotor cortex and seizures frequent enough for ictal MEG.

4.5 Categorizing speech errors elicited by nTMS

In Publication V, we mapped speech-related areas of four healthy volunteers by means of navigated rTMS. The stimulations revealed three cortical regions in individual subjects where a complete anomia was elicited by the applied rTMS. These were the inferior frontal gyrus (IFG), the superior temporal gyrus (STG), and the supramarginal gyrus (SMG). Although the variability of these sites was considerable between subjects, anomia was more reproducible in IFG. Moreover, performance errors and paraphasias were observed in SMG, IFG, STG and precentral gyrus (PrG) regions in individual subjects (Table 4.1). Semantic paraphasias were more reproducibly elicited from SMG. Most stimulation sites did not affect naming. The navigated rTMS was also applied to the right hemisphere in all four subjects, but it did not elicit disturbances. The baseline naming of all four subjects was performed without errors.

	No-response errors				Semantic paraphasias				Phonological paraphasias				Performance errors				Total errors
Areas/Subjects	S1	S2	S3	S4	S1	S2	S3	S4	S1	S2	S3	S4	S1	S2	S3	S4	
anG				2				1								1	4
IFG		3	3	3						1	1	1					12
PoG	1										1						2
PrG				3				1			1						5
SMG	8	2		2	3	3		1			2	2					23
STG	3		1						1								5
Total errors	12	5	4	10	3	3		3	1	1	5	3				1	51
	31				9				10				1				

Table 4.1. Different error types induced by rTMS in different cortical areas. Subject and number of specific error for each cortical area are presented. anG = Angular gyrus, IFG = Inferior frontal gyrus, PoG = Postcentral gyrus, PrG = Precentral gyrus, SMG = Supramarginal gyrus, STG = Superior temporal gyrus.

The experimental setup of Publication V provides a high-fidelity report of the experiment testing the feasibility of nTMS in mapping speech related cortical areas. It allows detailed information about the effective stimulation sites to be displayed and documented, e.g., in the planning of surgery. Some of the errors, especially the semantic and performance errors, were detected only during the video analysis. The results display a clear individual variation in stimulation sites producing speech disturbances, as described previously in direct cortical stimulations [21, 38, 90, 115].

The clinical usefulness of the obtained reproducible and non-reproducible sites, in terms of surgical decision making, needs to be verified versus the effects of direct cortical stimulation in patients with intracranial grid electrodes or stimulation sites producing speech disturbances during awake

craniotomy.

5. General discussion

The combination of nTMS with EEG allows direct and noninvasive stimulation of almost any cortical area and the subsequent recording of the resulting neuronal activity with very good spatio-temporal resolution. The advantage of this technological achievement is based on the fact that the TMS-evoked EEG signal originates from the electrical neural activity and it is an index of cortico-cortical excitability. As any other method, limitations and problems exist in TMS with or without navigation, arising mainly from the TMS focality, depth of penetration, and the targeting precision of the navigation systems. In particular, in commercial nTMS systems, the models used for the estimation of the actual stimulation intensity are simplified, based mainly on spherical head models. Thus, these models ignore subject-specific electromagnetic field–tissue interactions and can be inaccurate in regions of cortical inhomogeneity [136]. Nevertheless, nTMS methodology improves and models that include more realistic geometries and tissue anisotropies (for review, see [136]) may give solutions in clinical applications (Publication IV), where lesion pathology can potentially mislead the TMS mapping. However, in a recent study of our research group [78], it seems that although the spherical model is simple, it is fairly good in taking into account the conductivity structure and in localizing eloquent cortex at the borders with lesion cavities.

Despite the TMS-compatible EEG amplifiers, residual TMS artifacts remain in TMS–EEG methodology. Artifacts from cranial muscles, particularly when lateral sites over the skull are stimulated, can contaminate the EEG signal. These artifacts are larger than the TMS–EEG signal, last for several milliseconds and cover early EEG deflections. Thus, studying the cortico–cortical excitability and connectivity of areas like Broca and Wernicke can be challenging [79]. Similar problems can be found when stimulating prefrontal areas as in Publication I, where eye blinks can contaminate the TMS–EEG signal. Recently, various artifact rejection methods have been applied [65, 79] with quite promising results, opening the road for setups like in Publication II to be applied to speech-related areas.

An additional problem in nTMS–EEG is that the inverse problem has

many unknowns. Thus, it is very difficult to characterize the sources of the brain responses to TMS only [14], but also to verify the modelling techniques to solve the inverse problem [37]. In order to overcome these difficulties, efforts on source modelling such as minimum norm least squares or weighted minimum norm have been performed on different nTMS–EEG studies [15, 28, 82]. These methods are used to locate the distribution of neuronal activation. Then, in order to control for false positive sources of activation, non parametrical statistical analysis has to be applied. This procedure is described in [14]. This kind of approach seems to be very important and a safe way for nTMS–EEG studies on cortical excitability and functional connectivity. Manual ways of constructing multiple source models, like an ECD model, can give significant results as well [73]. All these approaches require high-density electrode arrays (>60) and also registration of the EEG electrodes to the brain anatomy, which is allowed by means of navigation. However, these models have located so far only early sources (10–30 ms). Later sources, like the source of N100 that is supposed to reflect cortical inhibitory processes and is the most pronounced and reproducible deflection (but also may contain an auditory response to the TMS coil click; for review, see [45]), are not yet well understood.

MEG is very efficient in localizing epileptogenic zones in the cortical surface, but it cannot detect reliably epileptic activity in the mesial temporal cortex and deep orbitofrontal cortices (for review, see [77]). This is because gradiometers that are insensitive to noise sources are also insensitive to deep sources. Use of magnetometers can hold some promise, despite the fact that they are more sensitive to noise [77]. Nevertheless, technological development in MEG such as signal space separation [128] can help in removing a wide range of interference signals. Thus, this technology may be extremely valuable in detecting of deep epileptic regions by means of magnetometers, which are currently used in commercial MEG systems.

nTMS alone or combined simultaneously with other methods can noninvasively probe and transiently alter neural processing in the working brain, giving unique information and new applications [103]. Casarotto *et al.* [15] have extended the results from Publication I. They concluded that TMS-evoked EEG responses are sensitive to changes in the stimulation parameters and repeatable over time. They further showed [16] that TMS–EEG responses over the left superior frontal cortex are not affected by physiological ageing but only due to cognitive impairment, as in

Alzheimer's disease. These three studies suggest that TMS–EEG can be used to detect and track pathological modifications of cortical excitability.

A study with fMRI driven rTMS on congenital hemiparesis patients [74] supports the suggestion from Publication II that ipsilateral MI is needed for optimal performance of unilateral movements. We recently showed the relation of ipsilateral hemisphere excitability and recovery from stroke [72]. In addition, basic research with paired-pulse nTMS [112] has shown how to optimize short-interval intracortical (SICI) inhibition and intracortical facilitation (ICF). SICI and ICF can be correlated with neurological motor task tests during recovery from stroke and other pathologies [72, 125]. Optimizing such parameters and knowing the effect of navigation on MT and MEP [51] can lead in better understanding of the role of each hemisphere during recovery of neurological disorders affecting the sensorimotor cortex. Moreover, combination of these results with the knowledge obtained from basic research with TMS–EEG may pave the way for new and more effective rehabilitation strategies.

Crossmodal studies, as introduced by Publication III, can be further elaborated clinically in presurgical evaluation of sensorimotor cortex, shown in Publication IV. In parallel with our efforts, other groups have applied nTMS prior to epilepsy [113] and tumor resection surgeries [32, 67, 97] with very good results when compared to DCS and fMRI. fMRI, DTI and MEG should be used in a complementary way along with nTMS during motor and speech mapping. For example, fMRI depicts several activated areas and DTI detects white-matter tracts between different cortical areas. nTMS can demonstrate the functional role of an area or a pathway that have been pinpointed by fMRI and DTI [78].

Crossmodal applications may help minimize the use of procedures like subdural cortical grid installation that have risk of complications and require a lot of resources. In speech mapping, especially as the speech network is quite wide-spread, information obtained by fMRI, DTI, and MEG can guide the nTMS mapping and make the procedure faster and more efficient. nTMS speech mapping, proposed in Publication V, can be applied in different populations such as bilinguals and cerebral palsy (CP) patients. In the CP patients, speech may be organized in the right hemisphere due to pathology in the left one. Nevertheless, in these two groups, speech organization can differ from the normal and a priori information obtained by other neuroimaging methods can guide the nTMS mapping. DTI can also be used as a marker for functional connectivity between

cortical areas. Thereafter, their activity and causality can be confirmed by nTMS–EEG. All these examples illustrate the possibilities of different studies that can be done with clinical impact as well by using the methods demonstrated in this Thesis. Publications I–V introduce advanced and novel ways of using TMS technology and suggest that nTMS can be a very important clinical tool in preoperative functional mapping.

6. Summary and Conclusions

I EEG responses evoked by TMS are highly reproducible when neuronavigation is utilized, suggesting that nTMS–EEG is a reliable tool for evaluating the effect of therapeutical methods or drugs in test-retest design paradigms.

II The ipsilateral hemisphere plays an active role during unilateral movement by exerting an inhibitory control.

III Parallel inputs in human brain can be utilized for facilitating distant cortico-cortical connections. Navigation allows co-registration of multimodal information.

IV nTMS can reliably localize primary motor cortex. MEG can successfully localize epileptogenic activity of some patients. For this patient group, combination of nTMS and MEG can provide a noninvasive functional mapping and potentially replace the standard invasive procedure.

V nTMS combined with synchronized video recording provides an accurate monitoring tool of behavioral TMS experiments. This experimental setup can be particularly useful for high-quality cognitive paradigms and for presurgical planning.

References

[1] M.A. Abdeen and M.A. Stuchly. Modeling of magnetic field stimulation of bent neurons. *Biomedical Engineering, IEEE Transactions On*, 41:1092–1095, 1994.

[2] V.E. Amassian, L. Eberle, P.J. Maccabee, and R.Q. Cracco. Modelling magnetic coil excitation of human cerebral cortex with a peripheral nerve immersed in a brain-shaped volume conductor: the significance of fiber bending in excitation. *Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section*, 85:291–301, 1992.

[3] C. Barba, M. Frot, and F. Mauguiere. Early secondary somatosensory area (SII) SEPs. Data from intracerebral recordings in humans. *Clinical Neurophysiology*, 113:1778–1786, 2002.

[4] A.T Barker, Jalinous R., and Freestone I.L. Non-invasive magnetic stimulation of the human motor cortex. *Lancet*, 1:1106–1107, 1985.

[5] P.J. Basser, R.S. Wijesinghe, and B.J. Roth. The activating function for magnetic stimulation derived from a three-dimensional volume conductor model. *Biomedical Engineering, IEEE Transactions On*, 39:1207–1210, 1992.

[6] S. Baxendale. The Wada test. *Current Opinion in Neurology*, 22:185–189, 2009.

[7] D. Benson and E.E. Zaidel. *The dual brain: Hemispheric specialization in humans.* Guilford Press, 1985.

[8] H. Berger. Über das Elektrenkephalogramm des Menschen. *European Archives of Psychiatry and Clinical Neuroscience*, 87:527–570, 1929.

[9] R. Bikmullina, D. Kičić, S. Carlson, and V.V. Nikulin. Electrophysiological correlates of short-latency afferent inhibition: a combined EEG and TMS study. *Experimental Brain Research*, 194:517–526, 2009.

[10] C. Bonato, C. Miniussi, and P-M. Rossini. Transcranial magnetic stimulation and cortical evoked potentials: a tms/eeg co-registration study. *Clinical Neurophysiology*, 117:1699–1707, 2006.

[11] J.P. Brasil-Neto, L.M. McShane, P. Fuhr, M. Hallett, and L.G. Cohen. Topographic mapping of the human motor cortex with magnetic stimulation: factors affecting accuracy and reproducibility. *Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section*, 85:9–16, 1992.

[12] D. Brignani, P. Manganotti, P.M. Rossini, and C. Miniussi. Modulation of cortical oscillatory activity during transcranial magnetic stimulation. *Human Brain Mapping*, 29:603–612, 2008.

[13] K. Brodmann. Vergleichende Lokalisationslehre der Großhirnrinde des Menschen. *Barth, Leipzig*, 1909.

[14] A.G. Casali, S. Casarotto, M. Rosanova, M. Mariotti, and M. Massimini. General indices to characterize the electrical response of the cerebral cortex to TMS. *NeuroImage*, 49:1459–1468, 2010.

[15] S. Casarotto, L.J.R. Lauro, V. Bellina, A.G. Casali, M. Rosanova, A. Pigorini, S. Defendi, M. Mariotti, and M. Massimini. EEG responses to TMS are sensitive to changes in the perturbation parameters and repeatable over time. *PloS One*, 5:e10281, 2010.

[16] S. Casarotto, S. Määttä, S.K. Herukka, A. Pigorini, M. Napolitani, O. Gosseries, E. Niskanen, M. Könönen, E. Mervaala, M. Rosanova, H. Soininen, and M. Massimini. Transcranial magnetic stimulation-evoked EEG/cortical potentials in physiological and pathological aging. *NeuroReport*, 22:592–597, 2011.

[17] M. Catani, D.K. Jones, and D.H. Ffytche. Perisylvian language networks of the human brain. *Annals of Neurology*, 57:8–16, 2005.

[18] E.F. Chang, D.D. Wang, D.W. Perry, N.M. Barbaro, and M.S. Berger. Homotopic organization of essential language sites in right and bilateral cerebral hemispheric dominance. *Journal of Neurosurgery*, 114:893–902, 2011.

[19] L.G. Cohen, J. Meer, I. Tarkka, S. Bierner, D.B. Leiderman, R.M. Dubinsky, J.N. Sanes, B. Jabbari, B. Branscum, and M. Hallett. Congenital mirror movements. *Brain*, 114:381–403, 1991.

[20] K. Connolly and P. Stratton. Developmental changes in associated movements. *Developmental Medicine & Child Neurology*, 10:49–56, 1968.

[21] D.P. Corina, B.C. Loudermilk, L. Detwiler, R.F. Martin, J.F. Brinkley, and G. Ojemann. Analysis of naming errors during cortical stimulation mapping: Implications for models of language representation. *Brain and Language*, 115:101–112, 2010.

[22] R.Q. Cracco, V.E. Amassian, P.J. Maccabee, and J.B. Cracco. Comparison of human transcallosal responses evoked by magnetic coil and electrical stimulation. *Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section*, 74:417–424, 1989.

[23] B.L. Day, D. Dressler, A. Maertens de Noordhout, C.D. Marsden, K. Nakashima, J.C. Rothwell, and P.D. Thompson. Electric and magnetic stimulation of human motor cortex: surface EMG and single motor unit responses. *The Journal of Physiology*, 412:449–473, 1989.

[24] J.T. Devlin and K.E. Watkins. Stimulating language: insights from TMS. *Brain*, 130:610–622, 2007.

[25] H. Duffau. Awake surgery for nonlanguage mapping. *Neurosurgery*, 66:523–528, 2010.

[26] H. Duffau, P. Gatignol, E. Mandonnet, P. Peruzzi, N. Tzourio-Mazoyer, and L. Capelle. New insights into the anatomo-functional connectivity of the semantic system: a study using cortico-subcortical electrostimulations. *Brain*, 128:797–810, 2005.

[27] S.K. Esser, R. Huber, M. Massimini, M.J. Peterson, F. Ferrarelli, and G. Tononi. A direct demonstration of cortical LTP in humans: a combined TMS/EEG study. *Brain Research Bulletin*, 69:86–94, 2006.

[28] F. Ferrarelli, M. Massimini, S. Sarasso, A. Casali, B.A. Riedner, G. Angelini, G. Tononi, and R.A. Pearce. Breakdown in cortical effective connectivity during midazolam-induced loss of consciousness. *Proceedings of the National Academy of Sciences*, 107:2681–2686, 2010.

[29] D.H. Ffytche, C.N. Guy, and S. Zeki. The parallel visual motion imputs into areas V1 and V5 of human cerebral cortex. *Brain*, 118:1375–1394, 1995.

[30] B. Fischl and A.M. Dale. Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proceedings of the National Academy of Sciences*, 97:11050–11055, 2000.

[31] P.B. Fitzgerald. TMS–EEG: A technique that has come of age? *Clinical Neurophysiology*, 121:265–267, 2010.

[32] M.T. Forster, E. Hattingen, C. Senft, T. Gasser, V. Seifert, and A. Szelényi. Navigated transcranial magnetic stimulation and functional magnetic resonance imaging: Advanced adjuncts in preoperative planning for central region tumors. *Neurosurgery*, 68:1317–1324, 2011.

[33] A.D. Friederici. Pathways to language: fiber tracts in the human brain. *Trends in Cognitive Sciences*, 13:175–181, 2009.

[34] G. Fuggetta, A. Fiaschi, and P. Manganotti. Modulation of cortical oscillatory activities induced by varying single-pulse transcranial magnetic stimulation intensity over the left primary motor area: a combined EEG and TMS study. *NeuroImage*, 27:896–908, 2005.

[35] N. Geschwind. Language and the brain. *Scientific American*, 226:76–83, 1972.

[36] S. Gil-Robles and H. Duffau. Surgical management of world health organization grade II gliomas in eloquent areas: the necessity of preserving a margin around functional structures. *Neurosurgical Focus*, 28:E8, 2010.

[37] R. Grech, T. Cassar, J. Muscat, K.P. Camilleri, S.G. Fabri, M. Zervakis, P. Xanthopoulos, V. Sakkalis, and B. Vanrumste. Review on solving the inverse problem in EEG source analysis. *Journal of Neuroengineering and Rehabilitation*, 5:25–58, 2008.

[38] M.M. Haglund, M.S. Berger, M. Shamseldin, E. Lettich, and G.A. Ojemann. Cortical localization of temporal lobe language sites in patients with gliomas. *Neurosurgery*, 34:567–576, 1994.

[39] M. Hämäläinen, R. Hari, R.J. Ilmoniemi, J. Knuutila, and O.V. Lounasmaa. Magnetoencephalography — theory, instrumentation, and applications to noninvasive studies of the working human brain. *Reviews of Modern Physics*, 65:413–496, 1993.

[40] M.S. Hämäläinen and R.J. Ilmoniemi. Interpreting magnetic fields of the brain: minimum norm estimates. *Medical and Biological Engineering and Computing*, 32:35–42, 1994.

[41] H.M. Hamer, H.H. Morris, E.J. Mascha, M.T. Karafa, W.E. Bingaman, M.D. Bej, R.C. Burgess, D.S. Dinner, N.R. Foldvary, J.F. Hahn, P. Kotagal, I. Najm, E. Wyllie, and H.O. Lüders. Complications of invasive video-EEG monitoring with subdural grid electrodes. *Neurology*, 58:97–103, 2002.

[42] R. Hari and N. Forss. Magnetoencephalography in the study of human somatosensory cortical processing. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences*, 354:1145–1154, 1999.

[43] G. Hickok and D. Poeppel. Dorsal and ventral streams: a framework for understanding aspects of the functional anatomy of language. *Cognition*, 92:67–99, 2004.

[44] G. Hickok and D. Poeppel. The cortical organization of speech processing. *Nature Reviews Neuroscience*, 8:393–402, 2007.

[45] R.J. Ilmoniemi and D. Kičić. Methodology for combined TMS and EEG. *Brain Topography*, 22:233–248, 2010.

[46] R.J. Ilmoniemi, J. Ruohonen, and J. Karhu. Transcranial magnetic stimulation: a new tool for functional imaging of the brain. *Critical reviews in Biomedical Engineering*, 27:241–284, 1999.

[47] R.J. Ilmoniemi, J. Virtanen, J. Ruohonen, J. Karhu, H.J. Aronen, R. Näätänen, and T. Katila. Neuronal responses to magnetic stimulation reveal cortical reactivity and connectivity. *NeuroReport*, 8:3537–3540, 1997.

[48] T. Inoue, H. Shimizu, N. Nakasato, T. Kumabe, and T. Yoshimoto. Accuracy and limitation of functional magnetic resonance imaging for identification of the central sulcus: comparison with magnetoencephalography in patients with brain tumors. *NeuroImage*, 10:738–748, 1999.

[49] K. Iramina, T. Maeno, Y. Nonaka, and S. Ueno. Measurement of evoked electroencephalography induced by transcranial magnetic stimulation. *Journal of Applied Physics*, 93:6718–6720, 2003.

[50] J.R. Ives, A. Rotenberg, R. Poma, G. Thut, and A. Pascual-Leone. Electroencephalographic recording during transcranial magnetic stimulation in humans and animals. *Clinical Neurophysiology*, 117:1870–1875, 2006.

[51] P. Julkunen, L. Säisänen, N. Danner, E. Niskanen, T. Hukkanen, E. Mervaala, and M. Könönen. Comparison of navigated and non-navigated transcranial magnetic stimulation for motor cortex mapping, motor threshold and motor evoked potentials. *NeuroImage*, 44:790–795, 2009.

[52] S. Kähkönen, J. Wilenius, S. Komssi, and R.J. Ilmoniemi. Distinct differences in cortical reactivity of motor and prefrontal cortices to magnetic stimulation. *Clinical Neurophysiology*, 115:583–588, 2004.

[53] S. Kähkönen, J. Wilenius, V.V. Nikulin, M. Ollikainen, and R.J. Ilmoniemi. Alcohol reduces prefrontal cortical excitability in humans: a combined TMS and EEG study. *Neuropsychopharmacology*, 28:747–754, 2003.

[54] K. Kamada, F. Takeuchi, S. Kuriki, T. Todo, A. Morita, and Y. Sawamura. Dissociated expressive and receptive language functions on magnetoencephalography, functional magnetic resonance imaging, and amobarbital studies. *Journal of Neurosurgery*, 104:598–607, 2006.

[55] E.R. Kandel, J.H. Schwartz, and T.M. Jessell. *Principles of neural science*, volume 4. McGraw-Hill New York, 2000.

[56] J. Karhu and C.D. Tesche. Simultaneous early processing of sensory input in human primary (SI) and secondary (SII) somatosensory cortices. *Journal of Neurophysiology*, 81:2017–2025, 1999.

[57] D. Kičić. *Probing cortical excitability with transcranial magnetic stimulation*. PhD thesis, Helsinki University of Technology, Espoo, 2009.

[58] D. Kičić, R. Bikmullina, P. Lioumis, J. Nurminen, S. Kaakkola, J.P. Mäkelä, and E. Pekkonen. Effects of 10 Hz rTMS on spontaneous brain oscillations in non-demented Parkinson's patients: Preliminary results of combined MEG-rTMS study. In *International Congress Series*, volume 1300, pages 717–720. Elsevier, 2007.

[59] V.K. Kimiskidis, S. Papagiannopoulos, K. Sotirakoglou, D.A. Kazis, A. Kazis, and K.R. Mills. Silent period to transcranial magnetic stimulation: construction and properties of stimulus–response curves in healthy volunteers. *Experimental brain research*, 163:21–31, 2005.

[60] M. Kobayashi, S. Hutchinson, G. Schlaug, and A. Pascual-Leone. Ipsilateral motor cortex activation on functional magnetic resonance imaging during unilateral hand movements is related to interhemispheric interactions. *NeuroImage*, 20:2259–2270, 2003.

[61] T. Kombos and O. Süss. Neurophysiological basis of direct cortical stimulation and applied neuroanatomy of the motor cortex: a review. *Neurosurgical Focus*, 27:E3, 2009.

[62] B.S. Komssi, H.J. Aronen, J. Huttunen, M. Kesäniemi, L. Soinne, V.V. Nikouline, M. Ollikainen, R.O. Roine, J. Karhu, S. Savolainen, and R.J. Ilmoniemi. Ipsi- and contralateral EEG reactions to transcranial magnetic stimulation. *Clinical Neurophysiology*, 113:175–184, 2002.

[63] S. Komssi. *Electroencephalographic responses to transcranial magnetic stimulation*. PhD thesis, University of Helsinki, 2004.

[64] S. Komssi and S. Kähkönen. The novelty value of the combined use of electroencephalography and transcranial magnetic stimulation for neuroscience research. *Brain Research Reviews*, 52:183–192, 2006.

[65] R.J. Korhonen, J.C. Hernandez-Pavon, J. Metsomaa, H. Mäki, R.J. Ilmoniemi, and J. Sarvas. Removal of large muscle artifacts from transcranial magnetic stimulation-evoked EEG by independent component analysis. *Medical and Biological Engineering and Computing*, 49:397–407, 2011.

[66] A. Korvenoja, E. Kirveskari, H.J. Aronen, S. Avikainen, A. Brander, J. Huttunen, R.J. Ilmoniemi, J.E. Jääskeläinen, T. Kovala, J.P. Mäkelä, E. Salli,

and M. Seppä. Sensorimotor Cortex Localization: Comparison of Magnetoencephalography, Functional MR Imaging, and Intraoperative Cortical Mapping. *Radiology*, 241:213–222, 2006.

[67] S.M. Krieg, E. Shiban, N. Buchmann, J. Gempt, A. Foerschler, B. Meyer, and F. Ringel. Utility of presurgical navigated transcranial magnetic brain stimulation for the resection of tumors in eloquent motor areas. *Journal of Neurosurgery*, 116:994–1001, 2012.

[68] T. Krings, B.R. Buchbinder, W.E. Butler, K.H. Chiappa, H.J. Jiang, B.R. Rosen, and G.R. Cosgrove. Stereotactic transcranial magnetic stimulation: correlation with direct electrical cortical stimulation. *Neurosurgery*, 41:1319–1325, 1997.

[69] R. Kristeva, D. Cheyne, and L. Deecke. Neuromagnetic fields accompanying unilateral and bilateral voluntary movements: topography and analysis of cortical sources. *Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section*, 81:284–298, 1991.

[70] L. Leocani, L.G. Cohen, E.M. Wassermann, K. Ikoma, and M. Hallett. Human corticospinal excitability evaluated with transcranial magnetic stimulation during different reaction time paradigms. *Brain*, 123:1161–1173, 2000.

[71] R.P. Lesser, H. Lüders, G. Klem, D.S. Dinner, H.H. Morris, J.F. Hahn, and E. Wyllie. Extraoperative cortical functional localization in patients with epilepsy. *Journal of Clinical Neurophysiology*, 4:27–53, 1987.

[72] P. Lioumis, S. Mustanoja, R. Bikmullina, A.M. Vitikainen, D. Kičić, O. Salonen, T. Tatlisumak, M. Kaste, N. Forss, and J.P. Mäkelä. Probing modifications of cortical excitability during stroke recovery with navigated transcranial magnetic stimulation. *Topics in Stroke Rehabilitation*, 19:182–192, 2012.

[73] V. Litvak, S. Komssi, M. Scherg, K. Hoechstetter, J. Classen, M. Zaaroor, H. Pratt, and S. Kähkönen. Artifact correction and source analysis of early electroencephalographic responses evoked by transcranial magnetic stimulation over primary motor cortex. *NeuroImage*, 37:56–70, 2007.

[74] M. Lotze, P. Sauseng, and M. Staudt. Functional relevance of ipsilateral motor activation in congenital hemiparesis as tested by fMRI-navigated TMS. *Experimental Neurology*, 217:440–443, 2009.

[75] P.J. Maccabee, V.E. Amassian, L.P. Eberle, and R.Q. Cracco. Magnetic coil stimulation of straight and bent amphibian and mammalian peripheral nerve in vitro: locus of excitation. *The Journal of Physiology*, 460:201–219, 1993.

[76] K. Majchrzak, B. Bobek-Billewicz, M. Tymowski, P. Adamczyk, H. Majchrzak, and P. Ladziński. Surgical treatment of insular tumours with tractography, functional magnetic resonance imaging, transcranial electrical stimulation and direct subcortical stimulation support. *Neurologia i Neurochirurgia Polska*, 45:351–362, 2011.

[77] J.P. Mäkelä, N. Forss, J. Jääskeläinen, E. Kirveskari, A. Korvenoja, and R. Paetau. Magnetoencephalography in neurosurgery. *Neurosurgery*, 59:493–511, 2006.

[78] J.P. Mäkelä, A.M. Vitikainen, P. Lioumis, R. Paetau, E. Ahtola, L. Kuusela, L. Valanne, G. Blomstedt, and E. Gaily. Functional plasticity of the motor cortical structures demonstrated by navigated TMS in two patients with epilepsy. *Brain Stimulation*, 2012.

[79] H. Mäki and R.J. Ilmoniemi. Projecting out muscle artifacts from TMS-evoked EEG. *NeuroImage*, 54:2706–2710, 2011.

[80] N. Makris and D.N. Pandya. The extreme capsule in humans and rethinking of the language circuitry. *Brain Structure and Function*, 213:343–358, 2009.

[81] A. Marini, S. Carlomagno, C. Caltagirone, and U. Nocentini. The role played by the right hemisphere in the organization of complex textual structures. *Brain and Language*, 93:46–54, 2005.

[82] M. Massimini, F. Ferrarelli, R. Huber, S.K. Esser, H. Singh, and G. Tononi. Breakdown of cortical effective connectivity during sleep. *Science*, 309:2228–2232, 2005.

[83] P.B.C. Matthews. The effect of firing on the excitability of a model motoneurone and its implications for cortical stimulation. *The Journal of Physiology*, 518:867–882, 1999.

[84] M.J. Mayston, L.M. Harrison, R. Quinton, J.A. Stephens, M. Krams, and P.M. Bouloux. Mirror movements in X-linked Kallmann's syndrome. I. A neurophysiological study. *Brain*, 120:1199–1216, 1997.

[85] M.J. Mayston, L.M. Harrison, and J.A. Stephens. A neurophysiological study of mirror movements in adults and children. *Annals of Neurology*, 45:583–594, 1999.

[86] J. McGlone. Speech comprehension after unilateral injection of sodium amytal. *Brain and Language*, 22:150–157, 1984.

[87] K.R. Mills, S.J. Boniface, and M. Schubert. Magnetic brain stimulation with a double coil: the importance of coil orientation. *Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section*, 85:17–21, 1992.

[88] V. Nikouline, J. Ruohonen, and R.J. Ilmoniemi. The role of the coil click in TMS assessed with simultaneous EEG. *Clinical Neurophysiology*, 110:1325–1328, 1999.

[89] V.V. Nikulin, D. Kičić, S. Kähkönen, and R.J. Ilmoniemi. Modulation of electroencephalographic responses to transcranial magnetic stimulation: evidence for changes in cortical excitability related to movement. *European Journal of Neuroscience*, 18:1206–1212, 2003.

[90] G.A. Ojemann, O. Creutzfeldt, E. Lettich, and M.M. Haglund. Neuronal activity in human lateral temporal cortex related to short-term verbal memory, naming and reading. *Brain*, 111:1383–1403, 1988.

[91] A. Pascual-Leone, J.R. Gates, and A. Dhuna. Induction of speech arrest and counting errors with rapid-rate transcranial magnetic stimulation. *Neurology*, 41:697–702, 1991.

[92] T. Paus, P.K. Sipilä, and A.P. Strafella. Synchronization of neuronal activity in the human primary motor cortex by transcranial magnetic stimulation: an EEG study. *Journal of Neurophysiology*, 86:1983–1990, 2001.

[93] M.D. Pell. Judging emotion and attitudes from prosody following brain damage. *Progress in Brain Research*, 156:303–317, 2006.

[94] W. Penfield and T. Rasmussen. The cerebral cortex of man; a clinical study of localization of function. 1950.

[95] S. Perfiliev. Bilateral processing of motor commands in the motor cortex of the cat during target-reaching. *Journal of Neurophysiology*, 93:2489–2506, 2005.

[96] N.M. Petrovich Brennan, S. Whalen, D. de Morales Branco, J.P. O'Shea, I.H. Norton, and A.J. Golby. Object naming is a more sensitive measure of speech localization than number counting: Converging evidence from direct cortical stimulation and fMRI. *NeuroImage*, 37:S100–S108, 2007.

[97] T. Picht, S. Schmidt, S. Brandt, D. Frey, H. Hannula, T. Neuvonen, J. Karhu, P. Vajkoczy, and O. Suess. Preoperative functional mapping for rolandic brain tumor surgery: Comparison of navigated transcranial magnetic stimulation to direct cortical stimulation. *Neurosurgery*, 69:581–588, 2011.

[98] T. Picht, J. Schulz, M. Hanna, S. Schmidt, O. Suess, and P. Vajkoczy. Assessment of the influence of navigated transcranial magnetic stimulation on surgical planning for tumors in or near the motor cortex. *Neurosurgery*, 70:1248–1257, 2012.

[99] T. Platz and J.C. Rothwell. Brain stimulation and brain repair–rTMS: from animal experiment to clinical trials — what do we know? *Restorative Neurology and Neuroscience*, 28:387–398, 2010.

[100] N. Pouratian and S.Y. Bookheimer. The reliability of neuroanatomy as a predictor of eloquence: a review. *Neurosurgical Focus*, 28:E3, 2010.

[101] J.B. Ranck. Which elements are excited in electrical stimulation of mammalian central nervous system: a review. *Brain Research*, 98:417–440, 1975.

[102] J.P. Rauschecker and S.K. Scott. Maps and streams in the auditory cortex: nonhuman primates illuminate human speech processing. *Nature Neuroscience*, 12:718–724, 2009.

[103] J. Reithler, J.C. Peters, and A.T. Sack. Multimodal transcranial magnetic stimulation: Using concurrent neuroimaging to reveal the neural network dynamics of noninvasive brain stimulation. *Progress in Neurobiology*, 94:149–165, 2011.

[104] M. Rosanova, O. Gosseries, S. Casarotto, M. Boly, A.G. Casali, M.A. Bruno, M. Mariotti, P. Boveroux, G. Tononi, S. Laureys, and M. Massimini. Recovery of cortical effective connectivity and recovery of consciousness in vegetative patients. *Brain*, 135:1308–1320, 2012.

[105] E.D. Ross. Cerebral localization of functions and the neurology of language: Fact versus fiction or is it something else? *The Neuroscientist*, 16:222–243, 2010.

[106] P.M. Rossini, A.T. Barker, A. Berardelli, M.D. Caramia, G. Caruso, R.Q. Cracco, M.R. Dimitrijevic, M. Hallett, Y. Katayama, C.H. Lucking, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. *Electroencephalography and Clinical Neurophysiology*, 91:79–92, 1994.

[107] B.J. Roth. Mechanisms for electrical stimulation of excitable tissue. *Critical Reviews in Biomedical Engineering*, 22:253–305, 1994.

[108] B.J. Roth and P.J. Basser. A model of the stimulation of a nerve fiber by electromagnetic induction. *Biomedical Engineering, IEEE Transactions On*, 37:588–597, 1990.

[109] J. Ruohonen and J. Karhu. Navigated transcranial magnetic stimulation. *Neurophysiologie Clinique/Clinical Neurophysiology*, 40:7–17, 2010.

[110] J. Ruohonen, M. Panizza, J. Nilsson, P. Ravazzani, F. Grandori, and G. Tognola. Transverse-field activation mechanism in magnetic stimulation of peripheral nerves. *Electroencephalography and Clinical Neurophysiology/Electromyography and Motor Control*, 101:167–174, 1996.

[111] G.J. Rutten and N.F. Ramsey. The role of functional magnetic resonance imaging in brain surgery. *Neurosurgical Focus*, 28:E4, 2010.

[112] L. Säisänen, P. Julkunen, E. Niskanen, T. Hukkanen, E. Mervaala, J. Karhu, and M. Könönen. Short-and intermediate-interval cortical inhibition and facilitation assessed by navigated transcranial magnetic stimulation. *Journal of Neuroscience Methods*, 195:241–248, 2011.

[113] L. Säisänen, M. Könönen, P. Julkunen, S. Määttä, R. Vanninen, A. Immonen, L. Jutila, R. Kälviäinen, J.E. Jääskeläinen, and E. Mervaala. Non-invasive preoperative localization of primary motor cortex in epilepsy surgery by navigated transcranial magnetic stimulation. *Epilepsy Research*, 92:134–144, 2010.

[114] R. Salvador, S. Silva, P.J. Basser, and P.C. Miranda. Determining which mechanisms lead to activation in the motor cortex: A modeling study of transcranial magnetic stimulation using realistic stimulus waveforms and sulcal geometry. *Clinical Neurophysiology*, 122:748–758, 2011.

[115] N. Sanai, Z. Mirzadeh, and M.S. Berger. Functional outcome after language mapping for glioma resection. *New England Journal of Medicine*, 358:18–27, 2008.

[116] D. Saur, B.W. Kreher, S. Schnell, D. Kümmerer, P. Kellmeyer, M.S. Vry, R. Umarova, M. Musso, V. Glauche, S. Abel, W. Huber, M. Rijntjes, J. Hennig, and C. Weiller. Ventral and dorsal pathways for language. *Proceedings of the National Academy of Sciences*, 105:18035–18040, 2008.

[117] M. Scherg and J.S. Ebersole. Models of brain sources. *Brain Topography*, 5:419–423, 1993.

[118] H. Shibasaki, A. Ikeda, and T. Nagamine. Use of magnetoencephalography in the presurgical evaluation of epilepsy patients. *Clinical Neurophysiology*, 118:1438–1448, 2007.

[119] H. Shiraishi. Source localization in magnetoencephalography to identify epileptogenic foci. *Brain and Development*, 33:276–281, 2011.

[120] S. Silva, P.J. Basser, and P.C. Miranda. Elucidating the mechanisms and loci of neuronal excitation by transcranial magnetic stimulation using a finite element model of a cortical sulcus. *Clinical Neurophysiology*, 119:2405–2413, 2008.

[121] J. Silvanto, N. Lavie, and V. Walsh. Stimulation of the human frontal eye fields modulates sensitivity of extrastriate visual cortex. *Journal of Neurophysiology*, 96:941–945, 2006.

[122] J. Silvanto, N. Muggleton, and V. Walsh. State-dependency in brain stimulation studies of perception and cognition. *Trends in Cognitive Sciences*, 12:447–454, 2008.

[123] J. Silvanto and N.G. Muggleton. A novel approach for enhancing the functional specificity of TMS: revealing the properties of distinct neural populations within the stimulated region. *Clinical Neurophysiology*, 119:724–726, 2008.

[124] S.B. Sobottka, J. Bredow, B. Beuthien-Baumann, G. Reiss, G. Schackert, and R. Steinmeier. Comparison of functional brain PET images and intraoperative brain-mapping data using image-guided surgery. *Computer Aided Surgery*, 7:317–325, 2002.

[125] O.B.C. Swayne, J.C. Rothwell, N.S. Ward, and R.J. Greenwood. Stages of motor output reorganization after hemispheric stroke suggested by longitudinal studies of cortical physiology. *Cerebral Cortex*, 18:1909–1922, 2008.

[126] J. Talairach and P. Tournoux. *Co-planar stereotaxic atlas of the human brain: 3-dimensional proportional system: an approach to cerebral imaging*. Thieme, 1988.

[127] C. Tataroglu, S. Ozkiziltan, and B. Baklan. Motor cortical thresholds and cortical silent periods in epilepsy. *Seizure*, 13:481–485, 2004.

[128] S. Taulu and R. Hari. Removal of magnetoencephalographic artifacts with temporal signal-space separation: Demonstration with single-trial auditory-evoked responses. *Human Brain Mapping*, 30:1524–1534, 2009.

[129] S. Teitti, S. Määttä, L. Säisänen, M. Könönen, R. Vanninen, H. Hannula, E. Mervaala, and J. Karhu. Non-primary motor areas in the human frontal lobe are connected directly to hand muscles. *NeuroImage*, 40:1243–1250, 2008.

[130] S. Tharin and A. Golby. Functional brain mapping and its applications to neurosurgery. *Neurosurgery*, 60:185–201, 2007.

[131] Y.D. Van Der Werf and T. Paus. The neural response to transcranial magnetic stimulation of the human motor cortex. I. Intracortical and corticocortical contributions. *Experimental Brain Research*, 175:231–245, 2006.

[132] T. Verstynen, R. Spencer, C.M. Stinear, T. Konkle, J. Diedrichsen, W.D. Byblow, and R.B. Ivry. Ipsilateral corticospinal projections do not predict congenital mirror movements: A case report. *Neuropsychologia*, 45:844–852, 2007.

[133] J. Virtanen, J. Ruohonen, R. Näätänen, and R.J. Ilmoniemi. Instrumentation for the measurement of electric brain responses to transcranial magnetic stimulation. *Medical and Biological Engineering and Computing*, 37:322–326, 1999.

[134] H. von Helmholtz. Über einige Gesetze der Vertheilung elektrischer Ströme in körperlichen Leitern mit Anwendung auf die thierisch-elektrischen Versuche. *Ann. Phys. Chem*, 89:353–377, 1853.

[135] J. Wada and T. Rasmussen. Intracarotid injection of sodium amytal for the lateralization of cerebral speech dominance. 1960. *Journal of Neurosurgery*, 106:1117–11130, 2007.

[136] T. Wagner, J. Rushmore, U. Eden, and A. Valero-Cabre. Biophysical foundations underlying TMS: setting the stage for an effective use of neurostimulation in the cognitive neurosciences. *Cortex*, 45:1025–1034, 2009.

[137] C. Weiller, T. Bormann, D. Saur, M. Musso, and M. Rijntjes. How the ventral pathway got lost — and what its recovery might mean. *Brain and Language*, 118:29–39, 2011.

[138] C. Wernicke. *Der aphasische Symptomencomplex: eine psychologische Studie auf anatomischer Basis*. Cohn & Weigert, 1874.

[139] C. Wernicke. The symptom-complex of aphasia. *Diseases of the Nervous System. New York: Appleton*, pages 265–324, 1908.

[140] A.D. Wiles, D.G. Thompson, and D.D. Frantz. Accuracy assessment and interpretation for optical tracking systems. In *Proceedings SPIE*, volume 5367, pages 421–432, 2004.

[141] P.W.A. Willems, J.W.B. van der Sprenkel, C.A.F. Tulleken, M.A. Viergever, and M.J.B. Taphoorn. Neuronavigation and surgery of intracerebral tumours. *Journal of Neurology*, 253:1123–1136, 2006.

[142] T.A. Yousry, U.D. Schmid, H. Alkadhi, D. Schmidt, A. Peraud, A. Buettner, and P. Winkler. Localization of the motor hand area to a knob on the precentral gyrus. A new landmark. *Brain*, 120:141–157, 1997.

[143] H.Q. Zhang, G.M. Murray, G.T. Coleman, A.B. Turman, S.P. Zhang, and M.J. Rowe. Functional characteristics of the parallel SI-and SII-projecting neurons of the thalamic ventral posterior nucleus in the marmoset. *Journal of Neurophysiology*, 85:1805–1822, 2001.

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