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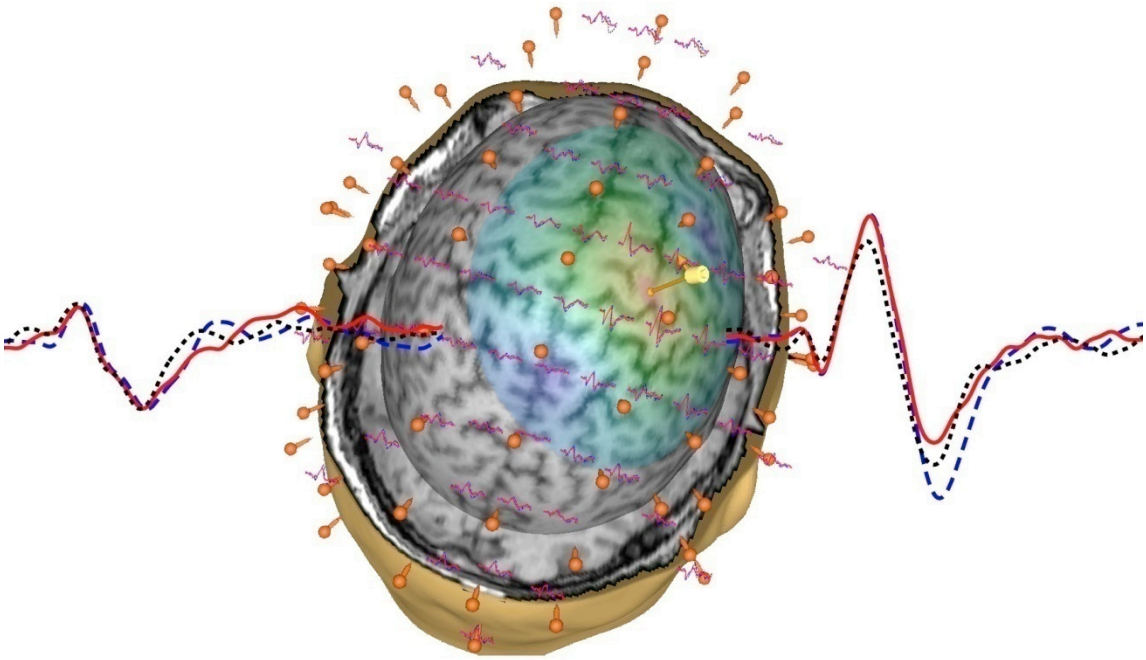
Department of Biomedical Engineering and Computational Science
Teknillisen korkeakoulun Lääketieteellisen tekniikan ja laskennallisen tieteen laitoksen julkaisuja

October, 2009 REPORT A13

PROBING CORTICAL EXCITABILITY WITH TRANSCRANIAL MAGNETIC STIMULATION

Dubravko Kičić



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PROBING CORTICAL EXCITABILITY WITH TRANSCRANIAL MAGNETIC STIMULATION

Dubravko Kičić

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Helsinki University of Technology
Faculty of Information and Natural Sciences
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Department	Department of Biomedical Engineering and Computational Science
Field of research	Applied mathematics and neuroscience
Opponent(s)	Prof. John Rothwell
Supervisor	Prof. Risto Ilmoniemi
Instructor	Dr. Vadim V. Nikulin

Abstract

This thesis, consisting of seven original publications (I–VII), explored the technical and neurophysiological plausibility of combining neuro-navigated transcranial magnetic stimulation (nTMS) with neuroimaging techniques such as multichannel electroencephalography (EEG) and magnetoencephalography (MEG). This work has focused on the interaction between the current state of neuronal activity at the targeted cortical network and the effects of TMS. We took an integrative approach, including a correlation between cortical (EEG, MEG) vs. peripheral electromyographic (EMG) measurements. TMS-evoked EEG responses were used as probes for the current functional state of the cortex during the processing of sensory stimuli and the preparation/execution of different motor activities. Contrary to standard indirect approaches utilizing peripheral EMG measures, our study directly demonstrated graded excitability in contra- and ipsilateral hemispheres during the preparation/execution of unilateral movements. The obtained data suggest that the specific balance of interhemispheric excitability is tailored for the optimal performance of unilateral movement by preventing not only mirror movements through decreased excitability of ipsilateral hemisphere, but also via pre-emptive background tonic inhibition of this hemisphere. The utility of the TMS-EEG combination was further demonstrated by providing direct evidence for cortical involvement in short-latency afferent inhibition. We found a linear correlation between the attenuation of TMS-evoked EEG responses and the attenuation of muscle responses, thus revealing how changes in cortical neuronal activity are related to changes on the periphery. The clinical feasibility of the TMS-MEG combination was demonstrated by showing that delivering trains of TMS pulses to the motor cortex of Parkinson's patients successfully modulated the spontaneous beta-range oscillations measured with MEG over the rolandic cortical regions, suggesting probable alteration of the cortico-thalamo-basal ganglia networks. The present thesis demonstrates that the spatial accuracy of localizing primary motor representational areas with both MEG and nTMS is superior to electrical cortical stimulation via subdural grids. Furthermore, this work demonstrates very high reproducibility of TMS-evoked EEG deflections after repeated stimulation of both the primary motor and prefrontal cortices. This suggests new standards in preoperative clinical workup and a wide range of studies with test-retest design. Thus, this thesis provides a new methodological and technical framework for measuring the time-resolved functional connectivity and causality of activation in the observed neural networks of human cerebral cortex.

Keywords transcranial magnetic stimulation, electroencephalography, motor cortex	
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Academic dissertation

Probing cortical excitability with transcranial magnetic stimulation

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Preface and acknowledgements

Professor Jari Karhu, a colleague and a dear friend of mine, told me several years ago: ”doctors of science are just common people who are stubborn enough to carry out the work that virtually no one would do!” Jari, thanks for putting this bug into my ears, it kept me going on all this time! However, the present thesis is not solely my personal achievement. Rather, it is the result of successful collaboration between a number of people and organizations.

I started my scientific career in the BioMag Laboratory of the Helsinki University Central Hospital. For extended period of time, this lab has been a pleasurable and stimulating place to work, where I carried out all the experiments and measurements for this thesis. I'm indebted to the director, Dr. Jyrki Mäkelä, for being truly supportive both as a supervisor and coauthor. The fact that he was always available when we needed a subject to test our wild scientific ideas, surely makes his brain one of the most TMS'd and MEG'd brains in the Helsinki brain research community! My special thanks also go to Dr. Juha Montonen, present technical director of the BioMag Lab, for being a perpetual force pushing us forward. I shall always remember his excellent running of the BioMag laboratory during the toughest phases of its existence. From BioMag, I have to mention also Dr. Juha Heiskala, Dr. Leena Lauronen, Dr. Heidi Wikström, Chris Bailey, Karen Johanne Pallesen, Lauri Lipiäinen, Kalle Kotilahti, Tommi Noponen, Dr. Milena Korostenskaja, Suvi Heikkilä, Ville Mäntynen, and Simo Monto.

With all of my heart, I would like to express my gratitude to Jussi Nurminen for being an unprecedented computer geek and a Matlab guru to me - Jussi has opened many secret doors in my perception of the world of ones and zeros.

When, in the winter of 2000, Dr. Vadim V. Nikulin told me that he has some interesting preliminary TMS-EEG data, I immediately replied: show me! ”Is that really what you want”, Dr. Nikulin was persistent. ”What else could I want?” was my answer, as well as my ticket to the most important part of my scientific career. Under the guidance of Dr. Nikulin, I was able to both crystallize my methodological approach for studying the functional aspects of the human brain, as well as to successfully integrate our results into a framework of known neurophysiological data. I'm honored and deeply thankful to Dr. Nikulin for adding a scientific essence to my (most of the times) scattered thoughts, and for being a true friend and spiritus movens of my work.

I have been extremely fortunate in being given the opportunity to collaborate with top professionals from several companies with the mission of transferring scientific expertise into solutions for both the clinics and laboratories. In world of TMS, Dr. Jarmo Ruohonen, technology director at Nexstim Oy, was the first person to instill in me in the fire of applied neuroscience. Thanks to collaborators from Nexstim - Henri Hannula, Marko Ollikainen, Tuomas Neuvonen, and Perttu Sipilä - I have learned that only a team effort between dedicated scientists excited about their work can successfully bring about development in a field.

Working as a consultant for Elekta Neuromag Oy provided me with both a very deep

insight into the processing of magnetic multichannel signals and a robust experience of working with a top-notch expert MEG group. I'm especially grateful to Dr. Jukka Nenonen, method development manager in Elekta Neuromag, for being the most responsive collaborator I have ever met; to Dr. Samu Taulu for informal discussions on mathematical aspects of the analysis of MEG data; to Dr. Veikko Jousmäki for our endless discussions about the technical solutions undelying MEG physics and Apple computers; and to Mrs. Candice Weir and Mr. Juha Virola for their support.

Professor Risto Ilmoniemi, the head of Department of Biomedical Engineering and Computational Science supervised my postgraduate studies and research from the very beginning, and his contribution to this thesis goes far beyond its scientific borders. I'm indebted to him for treating me always primarily as a human being and a friend, and then as a student. My take-for-life message from Risto is definitely: "do not blindly believe scientific results, even if they are your own!" With his unique approach to teaching and scientific conduct, Risto surely provided me with qualities that will forever remain as my own elements of style. I'm also grateful to Prof. (emer.) Toivo Katila for supervising my graduate studies and for immersing me into the world of multidisciplinary assessment of neuronal phenomena.

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The list of names of my Finnish and international collaborators would be too long to be presented here. However, several people I would like to emphasize as contributors which significantly shaped and contributed certain phases of my scientific development. I would especially like to mention Prof. Claudia Tesche, Dr. Elina Pihko, Prof. Pekka Meriläinen, Dr. Klaus Linkenkaer-Hansen, Prof. Yoshio Okada, Prof. Yoshikazu Ugawa, Nobuyuki Igarashi-san, Prof. Pedro Valdes-Sosa, Prof. Mireille Besson, Mireille Bonnard, Prof. Selma Supek, Prof. Riitta Hari, Dr. Anna Shestakova, Dr. Ilkka Nissillä, Dr. Ville Mäkinen, Prof. Hannu Tiitinen, and Dr. Patrick May.

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I love my wife Jagoda and my daughters Lucija and Tonka for being the light of creation in my life.

Helsinki, October 2009

Dubravko Kičić

Contents

List of Publications

Publications included in this thesis are:

I Nikulin V.V., Kičić D., Kähkönen S., and Ilmoniemi R.J. (2003). Modulation of electroencephalographic responses to transcranial magnetic stimulation: evidence for changes in cortical excitability related to movement. Eur J Neurosci 18(5), 1206-12.

II Kičić D., Lioumis P., Ilmoniemi R.J., and Nikulin V.V. (2008). Bilateral changes in excitability of sensorimotor cortices during unilateral movement: combined electroencephalographic and transcranial magnetic stimulation study. Neuroscience 152(4), 1119-29.

III Bikmullina R., *Kičić D., Carlson S., and Nikulin V.V. (2009). Electrophysiological correlates of short-latency afferent inhibition: combined EEG and TMS study. Exp Brain Res 194(4), 517-26.

IV Lioumis P., Kičić D., Savolainen P., Mäkelä J.P., and Kähkönen S. (2009). Reproducibility of TMS-Evoked EEG responses. Hum Brain Mapp 30(4), 1387-96.

V Raij T., Karhu J., Kičić D., Lioumis P., Julkunen P., Lin F.H., Ahveninen J., Ilmoniemi R.J., Mäkelä J.P., Hämäläinen M., Rosen B.R., and Belliveau J.W. (2008). Parallel input makes the brain run faster. Neuroimage 40(4), 1792-7.

VI Kičić D., Bikmullina R., Lioumis P., Nurminen J., Kaakkola S., Mäkelä J.P., and Pekkonen E. (2007). Effects of 10 Hz rTMS on spontaneous brain oscillations in non-demented Parkinson's patients: Preliminary results of combined MEG-rTMS study. International Congress Series 1300, 1717-20.

VII Vitikainen A.M., Lioumis P., Paetau R., Salli E., Komssi S., Metsähonkala L., Paetau A., Kičić D., Blomstedt G., Valanne L., Mäkelä J.P., and Gaily E. (2008). Combined use of non-invasive techniques for improved functional localization for a selected group of epilepsy surgery candidates. Neuroimage 45(2), 342-8.

* Dubravko Kičić and Rozaliya Bikmullina equally contributed to the study.

Author's contribution

The theoretical and experimental basis for this thesis was developed in Publication I together with the first author. Publication III was used to test the accuracy and to justify the experimental approach, which was used in Publications II–VI. Publications II, IV, and V expanded this basic theory into a more general framework and tested it in a variety of neurophysiological systems and experimental settings.

Publication I: The author performed extensive optimization measurements in order to test and establish experimental setup and to obtain reliable TMS-EEG recordings without artifact. He conducted TMS-EEG measurements, data acquisition, pre-processing, a significant amount of data analysis, and actively participated in interpreting the results as well as writing the article.

Publication II: The author designed the experimental paradigm, planned and tested the experimental setup, performed all measurements, data analysis and writing of the article. He is the principal author of the article.

Publication III: The author adapted the experimental paradigm into the TMS-EEG environment and performed optimization of the measurements and analysis methods. He supervised and monitored data analysis at all stages and participated equally with the first author in interpreting the results and writing of the manuscript. His contribution was equal to that of the first author of the article.

Publication IV: The author pointed out the methodological necessity for this study, designed the experimental paradigm and performed test measurements. He monitored the data analysis at all stages, significantly contributed to data interpretation, and wrote significant parts of the article.

Publication V: The author technically adapted the study paradigm into the experimental TMS-EEG environment and performed optimization measurements. He designed the data analysis approach and performed the initial stages of data analysis. He actively contributed in writing the article.

Publication VI: The author proposed the methodology for this clinical study. He designed, tested and evaluated the paradigm prior to actual patient measurements. He performed all MEG and rTMS measurements, data acquisition, pre-processing and data analysis, and wrote the article. He is the principal author of the article.

Publication VII: The author contributed to the TMS part of the study. He performed a technical setup of the paradigm together with the second author, performed optimization measurements, and suggested implementation strategies with results from other imaging modalities used in the study.

List of Abbreviations

CSF	Cerebro-Spinal Fluid
D2	Index Finger
DLPFC	Dorsolateral Prefrontal Cortex
EEG	Electroencephalography
EMG	Electromyography
ECD	Equivalent Current Dipole
ECS	Electrical Cortical Stimulation
EOG	Electro-oculogram
ER	Evoked Response
ERF	Event-Related Field
ERP	Event-Related Potential
fMRI	Functional MRI
GABA	γ-Aminobutyric acid
GABA-A	γ-Aminobutyric acid type A
GABA-B	γ-Aminobutyric acid type B
LTP	Long-Term Potentiation
LTD	Long-Term Depression
M1	Primary Motor Cortex
MEG	Magnetoencephalography
MEP	Motor-Evoked Potential
MRI	Magnetic Resonance Imaging
NIRS	Near-Infrared Spectroscpy
NREM	Non-Rapid Eye Movement
nTMS	Navigated TMS
PAS	Paired Associative Stimulation
PD	Parkinson's Disease
PET	Positron Emission Tomography
REM	Rapid Eye Movement
ROI	Region Of Interest
rTMS	Repetitive TMS
SAI	Short-latency Afferent Inhibition
SEF	Somatosensory Evoked Field
SP	Spectral Power
TBS	Theta-Burst Stimulation
TMS	Transcranial Magnetic Stimulation
TMS-EEG	TMS combined with EEG
UPDRS	Unified Parkinson's Disease Rating Scale

1 Aims of the study

The specific aims of Publications I–VII were as follows.

I To identify electroencephalographic (EEG) correlates of increased cortical premovement excitability using cortical response to transcranial magnetic stimulation (TMS) as a probe.

II To demonstrate the inhibitory role of the ipsilateral hemisphere in the performance of unilateral movement.

III To demonstrate the cortical origins of short-latency afferent inhibition (SAI) with direct EEG recordings.

IV To evaluate repeatable probing of cortical excitability with transcranial magnetic stimulation combined with concurrent EEG (TMS-EEG).

V To evaluate the effects of serial and parallel cortical processing in a behavioural task.

VI To validate the use of magnetoencephalography (MEG) for mapping the direct effects of rapid-rate TMS (rTMS) on specific cortical circuits in patients with Parkinson's disease (PD).

VII To evaluate the combined use of MEG and navigated TMS (nTMS) as non-invasive protocols for localization of the epileptogenic and sensorimotor cortical regions in patients with epilepsy.

2 Introduction

Transcranial magnetic stimulation is a non-invasive technique for stimulating the human brain by means of rapidly changing magnetic fields (Barker et al. 1985). The stimulating effect is achieved by induction of weak, brief intracortical currents, which depolarize the cell membranes of both cortical excitatory pyramidal cells and inhibitory interneurons. If the depolarization exceeds a threshold level, the nerve cell will discharge and, as the propagated action potential greatly outlives the electrical pulse, the effect of one TMS pulse can last tens of milliseconds. This TMS-evoked activity can be measured with a variety of electrophysiological methods and a number of parameters can be studied in the activated network. The neural impact of TMS stimulus is not determined only by the properties of that stimulus, but also by the initial state of the activated brain region, which is usually referred to as neuronal excitability (Abbruzzese and Trompetto 2002; Amassian et al. 1989).

In general terms, the neuronal excitability can be understood as the responsiveness of the neuronal population to the incoming signals. Current neuronal states of the cortex might be shaped by the sensory inputs as well as by the activity of other neuronal structures projecting into the given area. Cognitive neuroscience has predominantly focused on the cerebral cortex, which is also easily reachable by TMS. Because of the wealth of information regarding TMS impacts on the motor system, particularly due to measurable compound motor evoked potentials (MEPs) from peripheral muscles, motor cortex excitability has become the most common topic in TMS studies. However, a proper study of motor cortex excitability with TMS should clearly differentiate between the indices of the overall excitability of the corticospinal system (corticospinal excitability), and those specifically reflecting the excitability of the motor cortex (cortical excitability) and spinal cord.

MEPs caused by TMS were used routinely in research and clinical evaluation – abnormalities in the latency of amplitude of MEPs, or in the duration of the electromyographically (EMG) observed silent period were often taken as indicators of cortical pathology (Meyer 2002; Morita et al. 2008; Liepert et al. 2009). The problem with EMG in general, and with MEPs in particular, is that they are affected by a combination of cortical, subcortical, and spinal-cord mechanisms, which usually coincide in time, making their separation very difficult. If drawn exclusively on MEP recordings, conclusions about cortical pathologies, or in general about cortical involvement of the primary motor cortex (M1) in a given process might be uncertain. The present thesis provides an alternative approach, utilizing a combination of magnetic resonance image (MRI) guided TMS with both MEG and concurrent EEG to distinguish cortical involvement in a range of experimental paradigms.

The motivation for the studies in this thesis came from multichannel EEG mapping of cortical responses to TMS (Ilmoniemi et al. 1997; Komssi et al. 2002) and multi-modal stimulation experiments (Nikouline et al. 1999; Schürmann et al. 2001; Tiitinen et al. 1999) conducted in the BioMag Laboratory (HUSLAB, Hospital District of Helsinki and Uusimaa). Those studies showed on one side that TMS-evoked EEG responses can be reliably mapped over the whole scalp, and on the other side

that the TMS-EEG technique is suitable for detection of subtle changes in cortical excitability. Questions concerning intersensory facilitation and cross-modality suppression raised in a study by Nikouline et al. (1999) encouraged the idea to further investigate functionally-specific modulation of TMS-evoked EEG responses. In particular, local interaction between TMS-induced activity and the neural activation caused by peripheral somatosensory stimulation, as well as an indicated relationship between evoked responses (ER) and spontaneous EEG (Schürmann et al. 2001), encouraged the idea to develop a methodological framework to further study changes in the cortical excitability of healthy subjects and patients. For this purpose, we utilized the unique characteristic of TMS to interfere with ongoing neural processes of the living human brain.

Using a multitude of brain mapping techniques, we established and empirically tested a novel framework for probing the subtle, functionally specific, and importantly, transient changes in cortical excitability.

All Publications (I–VII) in this thesis used TMS as a probe of cortical excitability.

Anatomical structures seen in MRI were utilized for the selection of cortical TMS targets in Publications III–VII. We named this technology navigated TMS (nTMS). Additional accuracy in TMS targeting was gained from activation sites determined by MEG inverse solutions (Publications V and VII). Publication I identifies the EEG correlates of increased cortical excitability related to the preparation and execution of movement, while Publication II represents its methodological extension to the role of the ipsilateral hemisphere in the control of unilateral movements. Publication III presents the first demonstration of a correlation between the EEG and MEP manifestations of the short-latency afferent inhibition phenomenon. The very important issue of the reproducibility of TMS-evoked EEG responses was evaluated in Publication IV. Of special interest in that study is the introduction of cortical excitability probing of non-motor areas, which was further developed in Publication V. Based on our interest in the use of rTMS for treatment of neurological diseases, Publication VI is pioneering an offline combination of rTMS and MEG for monitoring rTMS effects on spontaneous cortical oscillations in Parkinsonian patients. Publication VII evaluates the use of nTMS as an additional tool in preoperative motor mapping in patients with epilepsy.

2.1 Cerebral cortex

The cerebral cortex is a greatly convoluted sheet of neural cells on the outer surface of the brain, just under the skull and the cerebrospinal fluid (CSF). It is about 3 mm thick, consisting of small folds called sulci, large grooves called fissures, and bulges between them called gyri (Fig. 2.1). Approximately two-thirds of the cortical surface is located in the sulci and fissures. The cortex is grossly divided into three functionally separate groups: sensory, motor and association cortices. On the same spatial scale, the cortex in each hemisphere is anatomically divided into the four lobes: the frontal, temporal, parietal and occipital lobe (Fig. 2.1). The central sulcus separates the frontal lobe from the parietal lobe, and the lateral (or Sylvian)

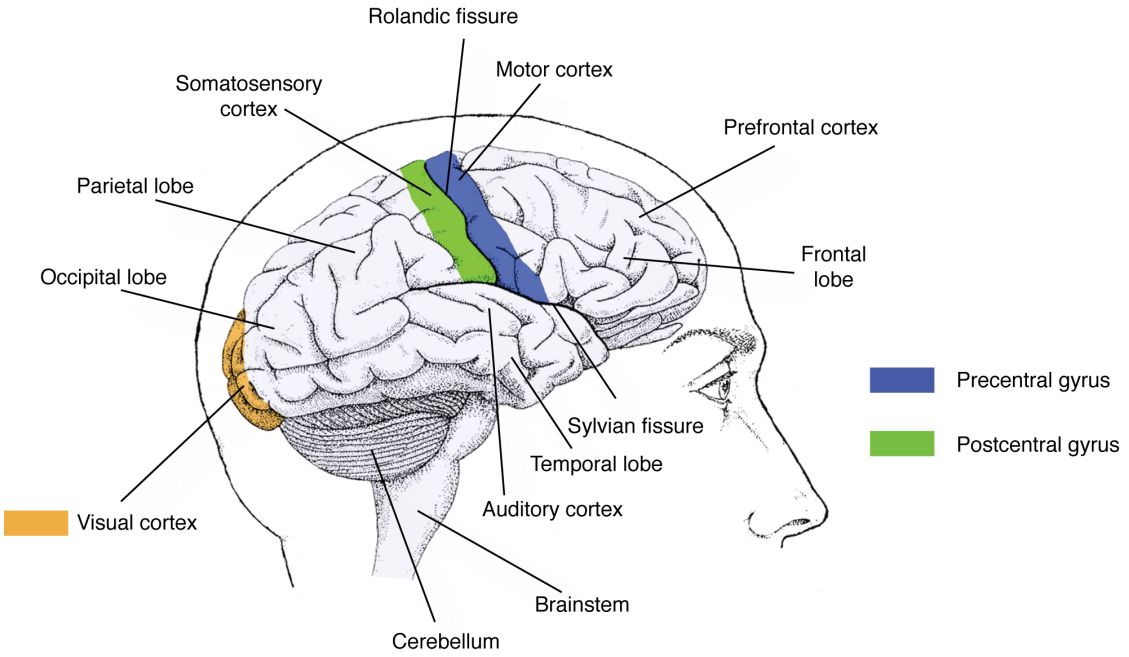

Figure 2.1: Gross functional and anatomical divisions indicated on the right lateral view of the human brain. Some of the important structural landmarks and special areas of the cerebral cortex are highlighted.

fissure separates the temporal lobe from the overlying frontal and temporal lobes (Fig. 2.1). The motor cortex controls the movement and is located in the precentral sulcus of the frontal cortex, just opposite to the somatosensory cortex. The visual cortex occupies most of the occipital lobe but stretches into the temporal lobe. The auditory cortex lies in the temporal sulcus, while the somatosensory cortex is situated in the postcentral gyrus and receives an input from the sensory systems via the thalamus. The associative cortex includes parts of the parietal and the frontal cortex and plays an important role in performing higher cognitive functions, such as memory and learning. Roughly, cortical neurons can be subdivided into the interneurons and the pyramidal cells. The interneurons project locally, while the pyramidal cells might also project globally into remote cortical structures. The cortical neurons are massively interconnected. A single pyramidal neuron has been estimated to receive around 60 000 synaptic inputs and may directly contact around 5000 other neurons. A volume of 1 mm^3 contains the axons corresponding in length to approximately 1–4 km.

The cortex of the cerebral hemispheres is a six-layered mixture of cell bodies and local fibres that varies in size and configuration from one cortical region to the other (Fig. 2.2). In general, the upper four cortical layers receive input projections from other cortical areas, the brainstem, and the subcortical nuclei (*e.g.,* basal ganglia and thalamus), whereas the lower two layers comprise the output projection layers. Layer 5 (called internal pyramidal layer, or ganglion cell layer, Fig. 2.2) is particularly prominent in the motor cortex, where it contains large pyramidal Betz cells that give rise to a portion of the descending pyramidal motor tract. Layer 1

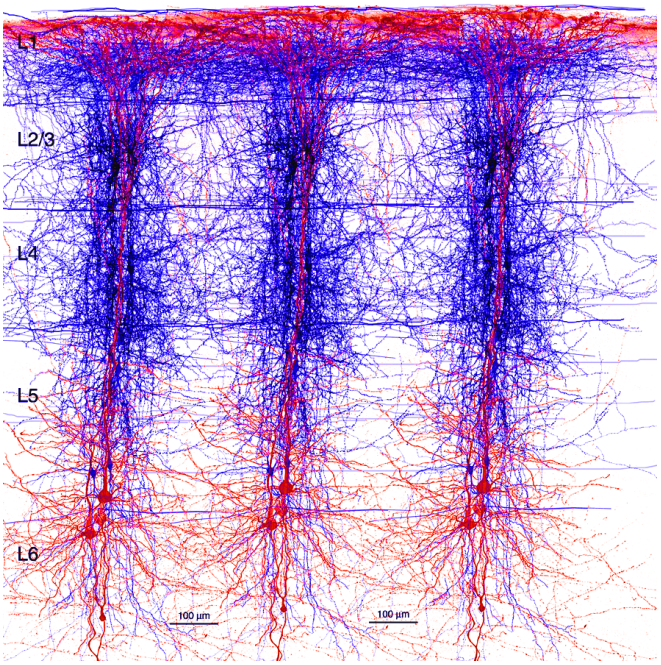

Figure 2.2: The six layers of the cerebral cortex. Note the large layer V and VI pyramidal neurons (in red), with their apical shafts ascending to layer I. The inhibitory fibres (in blue) wrap around these apical shafts in order to control the level of excitability in the cortex. Figure adapted with permission from The Blue Brain Project (http://bluebrain.epfl.ch/).

has a sparse abundance of neurons, being thus less important from the aspect of TMS-evoked activity. Even though layer 4 is very thin in the motor cortex (Gatter et al. 1978), it is rich in inhibitory fibres (blue traces in Fig. 2.2), which control the level of excitability in the cortex.

2.2 Neural basis of TMS, EEG, and MEG

Bioelectric activity studied with MEG or EEG is described in terms of a primary or source current:

$$\mathbf{J}^p(\mathbf{r}) = \mathbf{J}(\mathbf{r}) - \mathbf{J}^v(\mathbf{r}), \tag{2.1}$$

which results from activation of cortical cells. The primary current alters distribution of charges in the surrounding tissue, thus generating an electric field $\mathbf{E}(\mathbf{r})$, which in turn drives the ohmic volume current:

$$\mathbf{J}^v(\mathbf{r}) = \sigma(\mathbf{r})\mathbf{E}(\mathbf{r}), \tag{2.2}$$

which is determined by the conductivity of the tissue σ. Total current distribution at point $\mathbf{r}$ is $\mathbf{J}(\mathbf{r})$, representing the sum of the primary and the volume currents. EEG measures the voltage distribution on the scalp that arises from the altered charge distribution. Synchronous activation of neurones in a number of cortical columns is required to generate dipole moments in the order of 10 nAm. Such dipole moments

are associated with magnetic fields large enough to be detected by the MEG sensors and correspond to typical event-related potentials (ERP) and event-related fields (ERF) (Chapman et al. 1984).

MEG is particularly sensitive to superficial and tangentially oriented sources. On the other hand, EEG measures both tangential and radial sources, where the major source of primary neuronal currents originates at the apical dendrites that are oriented perpendicularly to the surface of the cortex (Proverbio and Zani 2003).

A stimulation effect of TMS in the cortex is due to the induced electric field, which affects the transmembrane potential of the neuronal cell by opening its voltage-sensitive ion channels. Since the cell membrane behaves as a leaky capacitor, faster and stronger changes in the electromagnetic environment are more effective for excitation (Panizza et al. 1992; Nagarajan et al. 1993). The gradient of a TMS-induced electric field along a distal axon has been considered as the primary mechanism of activation (Basser et al. 1992), though perpendicular electric field components have also been shown to change the membrane potentials of neurones (Ruohonen et al. 1996). Bends and other non-uniformities of the neural structure have been determined as locations of increased excitability for magnetic stimulation (Maccabee et al. 1993; Ilmoniemi et al. 1997).

2.3 Theory of TMS is the converse of MEG

The volume current $\mathbf{J}^v$ is passive and results from the macroscopic electric field on charge carriers in the conducting medium. Everything else is represented as the primary current $\mathbf{J}^p$ (Ilmoniemi et al. 1999):

$$\mathbf{J}(\mathbf{r}) = \mathbf{J}^p(\mathbf{r}) + \sigma(\mathbf{r})\mathbf{E}(\mathbf{r}) = \mathbf{J}^p(\mathbf{r}) - \sigma(\mathbf{r})\nabla V(\mathbf{r}). \tag{2.3}$$

Neural activity gives rise to primary current mainly inside or within the vicinity of a cell, whereas the volume current flows passively everywhere in the medium (Hämäläinen et al. 1993). By finding the primary current, we can locate the source of brain activity, as described by a current dipole.

The (equivalent) current dipole $\mathbf{Q}$ is a theoretical, infinitely small current element. It is a convenient building block for constructing mathematically equivalent models of electrical activity patterns in the brain. Current dipole is an approximation of the localized primary current and is a widely used concept in neuromagnetism. Let us consider the concentration of $\mathbf{J}^p(\mathbf{r})$ to a single point $\mathbf{r}_Q$:

$$\mathbf{J}^p(\mathbf{r}) = \mathbf{Q}\delta(\mathbf{r} - \mathbf{r}_Q), \tag{2.4}$$

where $\delta(\mathbf{r})$ is the Dirac delta function (Arfken and Weber 1995). In EEG and MEG applications, a current dipole is used as an equivalent source for the unidirectional primary current that may extend over several square centimetres of cortex.

The theory of lead fields is very important for spatial analysis of EEG and MEG signals. It yields a measure of the sensitivity of sensors for electromagnetic field

quantities, depending on lead configuration, source location and conductivity distribution. The existence of the lead field is a direct consequence of the linearity (principle of superposition) of electromagnetic fields (Hämäläinen and Ilmoniemi 1994). This principle predicts that a measurement of an electromagnetic scalar entity - be it the electric potential or the components of the magnetic field - must be proportional to the magnitude of each of the components of the current source - in this case the primary currents. This can be written as:

$$B = \mathbf{L}(\mathbf{r}') \cdot \mathbf{J}^p(\mathbf{r}'\ ), \tag{2.5}$$

where $\mathbf{L}(\mathbf{r}$') is termed the lead vector and B is the amplitude of the sensor. Note that the sensor can be either a magnetometer or an electrode pair and that the lead field is specific for each sensor. The flux in a magnetometer coil

$$\Phi = \int_{\text{coil i}} \mathbf{B} \cdot \mathrm{d}\mathbf{A} \tag{2.6}$$

depends linearly on the primary current distribution. Therefore, we can define a sensitivity function $\mathbf{L}_i(\mathbf{r}')$ called lead field for each sensor i. Integrating 2.5 over a volume containing sources yields:

$$B_i = \int \mathbf{L}_i(\mathbf{r}') \cdot \mathbf{J}^p(\mathbf{r}')\ dv'\ , \tag{2.7}$$

where $B_i = \Phi_i / A_i$, (A_i is the coil area) is the magnetic field in the detection coil of magnetometer i. The lead field depends on the coil geometry and its location and orientation with respect to the head as well as on the tissue conductivity distribution $\sigma = \sigma(\mathbf{r})$ (Ilmoniemi et al. 1999).

The lead field of a TMS coil is the same as the lead field of a magnetometer coil of the same size, shape, location, and orientation. This allows us to summarize: if $\mathbf{L}_i(\mathbf{r}')$ is the lead field of coil i and current $I_i = I_i(t)$ is fed into the coil, the total electric field, induced directly and caused by charges at conductivity boundaries, is

$$\mathbf{E}(\mathbf{r}') = -A_i \frac{\mathrm{d}I_i}{\mathrm{d}t}\ \mathbf{L}_i(\mathbf{r}'). \tag{2.8}$$

The complicated part here is the precise calculation of $\mathbf{L}_i(\mathbf{r}')$, which not only depends on the stimulator coil, its location, but also on the minute local conductivity distribution of the head.

3 TMS as a tool for probing cortical excitability

3.1 Methodological aspects: review of literature

TMS is unique in that it offers a non-invasive, painless method for stimulating the brain. The stimulating effect depends on several important factors, including the geometry of the stimulating coil (circular, figure-of-eight, cone-shaped), the waveform of the current pulse driven through the coil (monophasic or biphasic), or the cytoarchitectonic structure of the stimulated area. With commonly used stimulation parameters and focal figure-of-eight coils (Ueno et al. 1988), the superficial cortical structures are activated within the cone-shaped volume of few cube centimetres, extending approximately 2–3 centimetres in depth from the surface of the human skull (Bohning et al. 1997).

Pulses of sufficient intensity can evoke a sequence of descending cortico-spinal volleys (Day et al. 1989). They can be measured with peripheral EMG in the form of MEPs to provide information on the anatomical and functional organization of the motor system, useful for precise mapping of motor cortex representations (Kammer et al. 2005; Bestmann et al. 2008; Julkunen et al. 2009). After it was shown that abnormal central motor conduction could be associated with neuronal deficit (Barker et al. 1987), TMS methodology was widely introduced to patient studies, demonstrating excitability alterations in various diseases, including Parkinson's disease (Pascual-Leone et al. 1994b; Lefaucheur 2005; Fisher et al. 2008), dystonia (Edwards et al. 2003; Sohn and Hallett 2004; Bütefisch et al. 2005; Quartarone et al. 2005), Huntington's disease (Meyer et al. 1992; Lorenzano et al. 2006), Tourette's syndrome (Ziemann et al. 1997; Berardelli et al. 2003; Gilbert et al. 2004), and essential tremor (Romeo et al. 1998; Modugno et al. 2002).

Delivering two consecutive TMS pulses to the motor cortex (paired-pulse TMS, Kujirai et al. 1993) with independently adjusted stimulus intensities and a short inter-stimulus interval (1–200 ms) allows modulation of M1 excitability to be investigated by local circuits, as well as the study of inhibition and facilitation within the motor pathway (Di Lazzaro et al. 2000; Kujirai et al. 1993; Manganotti et al. 2002; Shimizu et al. 1999; Tamburin et al. 2004; Valls-Solé et al. 1992). If a conditioning stimulus is given to the brain areas other than M1, an area-to-area facilitation and inhibition can be estimated by observing changes in the size of conditioned MEPs relative to test MEPs alone (double-pulse TMS: Bajbouj et al. 2004; Daskalakis et al. 2002; Di Lazzaro et al. 1999; Kujirai et al. 1993; Meyer et al. 1998; Ridding et al. 2000). In general, modulating inputs from conditioning pulses elicit inhibitory or facilitatory effects on the motor cortex trough intracortical (Kujirai et al. 1993; Orth et al. 2003; Ziemann et al. 1996; Chen et al. 1998a), intrahemispheric (Bajbouj et al. 2004; Hanajima et al. 1996; Strafella et al. 2000; Pierantozzi et al. 2002; Buhmann et al. 2004), or interhemispheric connections (Ferbert et al. 1992; Boroojerdi et al. 1999; Cracco et al. 1989; Di Lazzaro et al. 1999; Wilkins et al. 1984; Hanajima et al. 2001; Chen et al. 2003).

A new approach to TMS paradigms was introduced by showing that a subject's

performance in a character identification task was transiently impaired when single TMS pulses were administered to the occipital cortex at specific latency after onset of the visual stimulus (Amassian et al. 1989). Disruption of the ongoing cortical processing was named the lesion paradigm, and is broadly used in cognitive neuroscience with the objective of interfering in the neural activity associated with cognitive processes. TMS applied in healthy subjects during a cognitive process most commonly leads to disruptions in task performance (Cowey 2005; Walsh and Pascual-Leone 2003). Nevertheless, there is a growing number of reports indicating that TMS can also facilitate behaviour if single TMS pulses are applied shortly before the onset of a cognitive process (*e.g.,* Töpper et al. 1998; Grosbras and Paus 2003). Some of these 'paradoxical' facilitatory effects of TMS can be accounted for by a disinhibition of an unstimulated brain area whose function is normally suppressed by the TMS target region (Walsh and Pascual-Leone 2003). Such functional release suggests that TMS-induced neuronal activity can spread beyond the directly stimulated area to anatomically connected sites (Fox et al. 1997; Ilmoniemi et al. 1997; Komssi et al. 2002; Paus et al. 1997; Paus et al. 2001; Strafella et al. 2001).

An important development in TMS technology was the introduction of rapid-rate TMS (mode of stimulation with frequency higher than 1 Hz; Cadwell Laboratories Inc., Kennewick, USA, 1988), showing that rTMS of language areas in the dominant hemisphere can arrest the speech production (Pascual-Leone et al. 1991; Jennum et al. 1994; Stewart et al. 2001). This sparked immediate interest among clinical researchers because TMS avoids systemic side effects and stimulates the brain with a spatial and temporal specificity that currently cannot be achieved pharmacologically or via electroconvulsive therapy. At the same time, rTMS makes it possible to test behavioural effects of brain stimulation in healthy volunteers. To be of lasting benefit beyond the period of stimulation, enduring changes in the functioning of the target pathways would need to be invoked. The duration of the after effects can last for 30–60 minutes, depending on parameters such as the number of pulses applied, the rate of application, and the intensity of each stimulus. One of the possible mechanisms for such rTMS effects can be long-term potentiation (LTP). However, the above-mentioned plasticity effects are often weak, highly variable between individual subjects, and rarely last longer than 30 minutes. Because rTMS of the cortex has the potential to induce epileptic activity even in healthy subjects, safety instructions have to be followed (Wassermann 1998).

To enhance LTP effects, new protocols, such as theta burst stimulation (TBS), have been introduced (Huang et al. 2005). In TBS, the 50-Hz bursts are repeated at a frequency of 5 Hz (theta range) and the protocol holds promise as a powerful LTP inducer. TBS has been applied to the primary motor cortex, tending to result in improved motor recovery following stroke (Talelli et al. 2007), as well as to brain regions outside the M1, with evidence of lasting inhibition demonstrated in the frontal eye field (Nyffeler et al. 2006), and the occipital cortex (Franca et al. 2006). With advanced technical solutions, new protocols and paradigms are continuously being tested and explored: paired associative stimulation (PAS) produces long-term plasticity effects, measured by an increase of MEPs in the target muscle for more than 30 minutes (Stefan et al. 2000; Meunier et al. 2007), triple-pulse TMS (Komissarow et al. 2004; Sacco et al. 2009) exerts a facilitatory effects on MEP

amplitude, quadripulse TMS (Hamada et al. 2007b) induces long-lasting locally restricted facilitation of motor cortex excitability for up to 75 minutes (Hamada et al. 2007a), which is considered to be a cortical event (Hamada et al. 2008).

In recent years TMS has been combined with EEG (Ilmoniemi et al. 1997; Esser et al. 2006; Massimini et al. 2005; Komssi et al. 2002; Kähkönen and Wilenius 2007), positron emission tomography (PET: Fox et al. 1997; Paus et al. 1997; Strafella et al. 2003; Ko et al. 2008), functional magnetic resonance imaging (fMRI: Bohning et al. 1997; Bestmann et al. 2006; Kemna and Gembris 2003; Siebner et al. 2003; Denslow et al. 2005), near-infrared spectroscopy (NIRS: Nissilä et al. 2002; Mochizuki et al. 2006), and MEG (Tamura et al. 2005). A combination of TMS with these methods offers an opportunity to localize the target of stimulation, to measure local and distal responses to the stimulation (*i.e.,* to study reactivity and connectivity the stimulated brain areas), to assess long-term (hours, days, weeks) effects of rTMS, and to investigate the pathophysiology of neuropsychiatric disorders.

TMS holds great promise in therapeutic and clinical settings. In addition to studying alterations of cortical excitability in neurological diseases (Di Lazzaro et al. 2004b; Kühn et al. 2004; Fisher et al. 2008) and task-related cortical excitability changes (Bestmann et al. 2002; Nixon et al. 2004; Ellison and Cowey 2008; Gallasch et al. 2009), the treatment of psychiatric disorders have been the focus of many studies (Cohen et al. 2004; Fitzgerald et al. 2003; Amiaz et al. 2009; Baumer et al. 2009; Kleinjung et al. 2008; Thickbroom et al. 2008). Even though it is unlikely that rTMS will restore function to specific sets of synaptic connections affected by the disease, it may be possible for rTMS to confer compensatory interaction with the normal processes of brain plasticity that accompany damage or chronic disease (Ridding and Rothwell 2007).

3.2 Physical aspects of TMS

Magnetic brain stimulation follows the fundamental physical principles of electromagnetic induction: if the conducting medium (*e.g.,* brain) is adjacent to a rapidly changing magnetic field, the current will be induced in that conducting medium. According to the Lenz's law, the flow of the induced current will be parallel but opposite in direction to the current in the coil (Fig. 3.1). The magnetic field pulse is generated by driving a current pulse $I(t)$ through an induction coil (Polson et al. 1982; Cadwell 1990; Barker et al. 1991; Jalinous 1991). Even though a TMS pulse must have a peak amplitude of up to 10 000 amperes within less than 100 microseconds, the basic electrical circuit of the magnetic stimulator is simple (Fig. 3.2). It consists of a capacitor (capacitance C), a thyristor (switch S), and the stimulating coil (inductance L). The circuit forms an RLC oscillator with a series resistance R in the coil, cables, thyristor, and a capacitor. The capacitor, charged to several kilovolts, is discharged through the coil by gating the thyristor into the conducting state (left panel in Fig. 3.2). In case of rapid-rate stimulators, during the second-half cycle of the oscillation (right panel in Fig. 3.2), the current in the circuit flows in the opposite direction, thus returning the charge to the capacitor through the diode D. If the thyristor gating is terminated during the second half-cycle, the oscillation ends

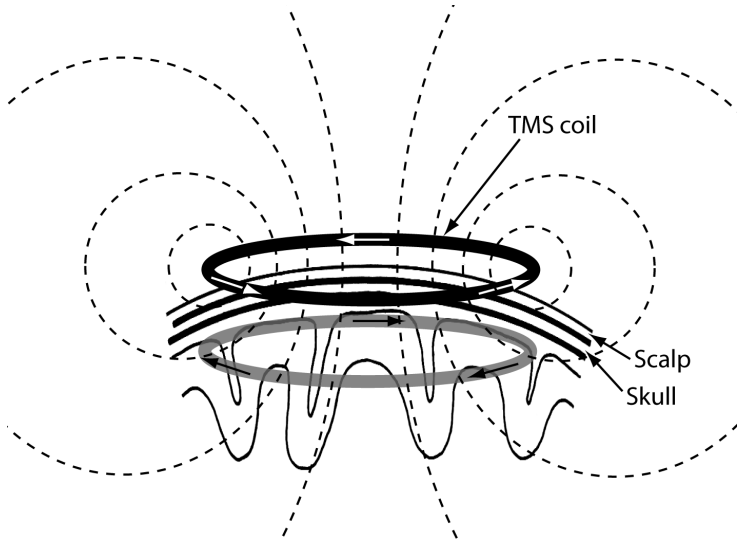

Figure 3.1: Lenz's law: when strong current flows through the magnetic coil placed over the scalp, as a consequence of electrochemical events, underlying cells generate weak electrical currents. Currents induced in the tissue obey Lenz's law - they are parallel to, but in a direction opposing the current flow in the coil.

when the cycle is completed.

Both the electric field **E** and current density **J**=ρ**E** (ρ being conductivity) induced in the neural tissue are proportional to dI/dt:

$$\mathbf{E}(\mathbf{r}) \sim \mathbf{J}(\mathbf{t}) \sim \frac{dI}{dt} = \frac{U_0}{L\omega} e^{\alpha t} = (\omega cos\omega t - \alpha sin\omega t). \tag{3.1}$$

When the electrostatic energy stored in a capacitor bank is discharged, it is transformed into the coil's magnetic energy - the peak energy is dependent on the coil's

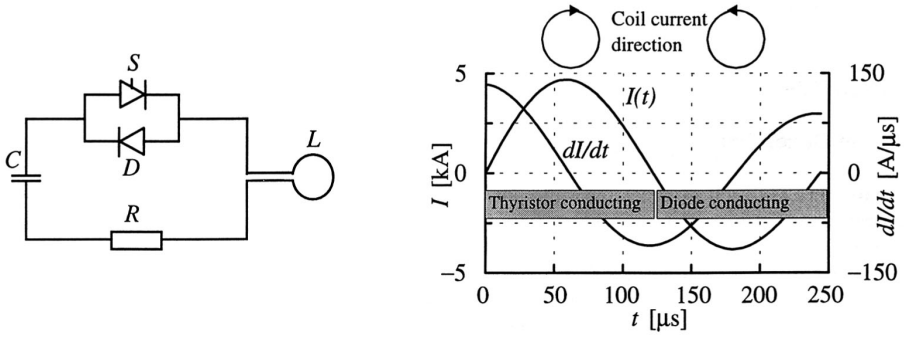

Figure 3.2: Left: basic electrical circuit of the magnetic stimulator. Right: when capacitor is discharged, the oscillating RLC circuit sets up a brief exponentially decaying sinusoidal current pulse I(t). The energy is returned through the diode D from the coil back to the capacitor, which reduces coil heating and power consumption (biphasic pulse). Without D or with great R, the current polarity reversal is absent or suppressed (monophasic pulse). Figure adapted from Ilmoniemi et al. 1999.

inductance L and the peak current in the coil:

$$W = \frac{1}{2} L I_{max}^2. \tag{3.2}$$

The efficacy of the coil can be improved if the inductance and the peak current can be lowered without affecting the strength of the induced electric field. After the electronic sequence of firing the TMS pulse is initiated, the energy is dissipated as a Joulean heating in the coil, cables and electronic components. Most of the circuit's total resistance is in the coil (*e.g.,* 15 out of 20 mΩ); hence most of the heat dissipation is on the coil. This brings into focus coil warming, which is limited by the Safety Standards for Medical Equipment (IEC-601) to temperatures below 41° Celsius. The optimal temperature rise should be limited to about 0.1° per pulse.

The electric field vector $\mathbf{E}$ and magnetic field vector $\mathbf{B}$ can be determined from a scalar potential Φ and a vector potential $\mathbf{A}$ (Jackson 1975; Reitz et al. 1980):

$$\mathbf{B} = \nabla \times \mathbf{A} \tag{3.3}$$

$$\mathbf{E} = -\frac{\partial \mathbf{A}}{\partial t} - \nabla \Phi \tag{3.4}$$

The scalar potential Φ is the same as voltage $\mathbf{V}$ and its source is the charge, while the source of vector potential $\mathbf{A}$ is the current. The vector potential only contributes to the induced electric field if it changes with time (coming from the changing current in the coil and changing magnetic field $\mathbf{B}$). The change of current in the stimulating coil is so rapid that kilo-amperes of current are driven in typically 100 μs, so $\mathbf{A}$ must be considered. Total electric field induced in the tissue, $\mathbf{E}(\mathbf{r}, t)$, is the sum of two terms: $\mathbf{E}_\mathrm{A}$ due to the current integrated over the coil, and $\mathbf{E}_\Phi$ due to the charge integrated over the tissue surface, denoted as primary and secondary electric fields, respectively. The primary electric field $\mathbf{E}_\mathrm{A}$ is induced directly by the changing magnetic field. The electric field produced by magnetic induction forms closed loops concentric with the coil (see Fig. 3.1). In response to this field, charged ions in the tissue move, following the electric field lines until they reach the surface of the tissue or the skull. Thus, $\mathbf{E}$ causes a flow of current according to Ohm's law, $\mathbf{J}{=}\rho\mathbf{E}$, with ρ being conductivity. Since air is an isolator, the charge accumulates on the surface of the skull, *e.g.,* a non-uniform conductivity along the path of the current results in an uneven distribution $\rho{=}\rho(\mathbf{r})$ of electric charges (Ilmoniemi et al. 1999). These charges produce their own electric field, the secondary field $\mathbf{E}_\Phi$, according to Gauss's law, $\nabla{\cdot}\mathbf{E}{=}\rho/\epsilon_0$. The total electric field is then the sum of the fields due to the charge and magnetic induction (Roth and Basser 1990):

$$\mathbf{E} = \mathbf{E}_\mathrm{A} + \mathbf{E}_\Phi = -\frac{\partial \mathbf{A}}{\partial t} - \nabla \Phi \tag{3.5}$$

The induced electric field strength for brain stimulation should be in the order of 100 mV/mm to elicit sufficient motor-cortex activation that would lead to measurable peripheral EMG responses (Ilmoniemi et al. 1999).

3.3 Electrophysiology of excitation in TMS

The activated region under the coil is defined by the strength and direction of the induced electric field with respect to neuronal structures (Komssi and Kähkönen 2006). Macroscopically, the locus of TMS-induced activity is most likely at the maximum of the induced electric field (Krings et al. 1997). Based on experimental evidence in humans (Garnham et al. 1995), it is likely that high effective gradients of the induced electric field ($\partial \mathbf{E}_x/\partial x$) are achieved at axonal bends even in homogeneous $\mathbf{E}$ (Abdeen and Stuchly 1994).

At the cellular level, TMS is thought to excite mostly the corticospinal axons (in M1) close to the axon hillock (Baker et al. 1995; Rothwell 1997), rather than other parts of the neurons (Maccabee et al. 1996). This suggests the pyramidal neurons are activated predominantly transsynaptically, via interneurons in superficial cortical layers (Fig. 2.2; Day et al. 1989; Di Lazzaro et al. 2001a; Nakamura et al. 1996; Sakai et al. 1997; Mills 1991). According to this view, the action potentials are initiated at the initial segment of the axon, close to the cell body (soma) of the neuron and travel both orthodromically and antidromically (Stuart et al. 1997). The most efficient direction of induced current for activation of corticospinal neurons is one along the axis of the neuron (parallel to the apical dendrite) towards the cell body and the initial segment.

However, this view partially contradicts with findings showing that different neuronal structures seem to be preferentially targeted by the different coil orientations (Brasil-Neto et al. 1992; Fox et al. 2004; Mills et al. 1992; Pascual-Leone et al. 1994a; Sakai et al. 1997; Werhahn et al. 1994). It has been hypothesized that these differences may be attributable to different populations of fibres being excited by anterior-posterior (AP) versus posterior-anterionr (PA) directed currents (Di Lazzaro et al. 2001b). It is possible that large afferent axons from premotor and somatosensory areas, which constitute the main cortical input to the motor cortex (DeFelipe et al. 1986; Sutor et al. 2000), may be especially sensitive to AP currents. There, afferents bend into motor cortex (Rockel et al. 1980), and it is known from modelling and peripheral nerve stimulation studies that axonal bends in large fibres have a low threshold for TMS activation (Abdeen and Stuchly 1994; Maccabee et al. 1993; Esser et al. 2005).

Response of the motor cortex to TMS is complex and consists of two major stages. In the first stage, the motor cortical system responds with waves of activity that can last for 5–10 ms after the pulse (Day et al. 1987; Esser et al. 2005). These waves are typically recorded with electrodes positioned in the epidural space in the form of compound action potentials from the axons descending from the motor cortex originating in layer 5 (Fig. 2.2; Di Lazzaro et al. 1998a; Di Lazzaro et al. 2001b; Edgley et al. 1997). The volleys are called direct (D) and indirect (I) waves (Patton and Amassian 1954). D-waves are generated by direct stimulation of corticofugal axons in the white matter, whereas later I-waves come from indirect or trans-synaptic activation of the same corticospinal neurons (Amassian et al. 1990; Edgley et al. 1990; 1997; Burke et al. 1990; 1993; Di Lazzaro et al. 1998b; Houlden et al. 1999).

The second stage of the motor cortical response to TMS is characterized by a longer

period of suppression of ongoing voluntary activity in the EMG, lasting 100–200 ms, which most probably comes from long-lasting inhibitory input mediated by γ-aminobutyric acid (GABA) neurotransmitters responsible for regulating neuronal excitability throughout the nervous system (Ridding and Rothwell 2007; Werhahn et al. 1999; Di Lazzaro et al. 2007; Florian et al. 2008).

3.4 Electrophysiological state-dependency of TMS

One of the fundamental concepts in brain physiology is the functional state of the cortex, which has important electrophysiological consequences for neuronal activity during TMS. Both D- and I-waves were shown to be affected by the current state of the cortex. Since the D-waves arise from the initial segment, their generation will be affected by the overall excitability of the neuron. Hence, D-wave response is likely to be affected by factors influencing the cortical excitability - a fact demonstrated in numerous studies (*e.g.,* Di Lazzaro et al. 2003; Di Lazzaro et al. 2004a). Similarly, the number and the amplitude of the I-waves increase with the level of neuronal activity, showing that they are also strongly influenced by the overall level of excitability (*e.g.,* Cash et al. 2009; Di Lazzaro et al. 2008). This result was expected, because I-waves require transmission through a larger network of neurons (Bohning et al. 2000). The important point here is that any neuronal processes affecting the cortical excitability are likely to be reflected in the efficacy of TMS to stimulate neuronal networks. Indeed, an initial functional neuronal state plays a major role in the modulation of the MEP amplitude, being specific for the type of performed task (Cracco et al. 1999; Nielsen et al. 1999; Bestmann et al. 2004; Tamburin et al. 2005; Gallasch et al. 2009; Bikmullina et al. 2009).

TMS-induced neuronal activity spreads beyond the directly stimulated area to anatomically connected sites (Bohning et al. 2000; Ilmoniemi et al. 1997; Komssi et al. 2002; Paus et al. 2001; Strafella et al. 2001). This implies an important reverse: namely, the anatomically connected sites can equally exert an exogenous influence on the stimulated cortical area, thus making the effect of TMS a function of the activity in anatomically interconnected sites (not the case, though, it could be unidirectional connections). To support this, there is growing electrophysiological evidence also from stimulation of cortical areas other than motor, indicating that the neural impact of TMS is not determined only by the properties of the stimulus, but also strongly by the initial state of the activated interconnected brain regions (Amassian et al. 1989; Ramos-Estebanez et al. 2007; Silvanto et al. 2007; Silvanto and Muggleton 2008).

4 Electrophysiological assessment of cortical excitability

4.1 Concurrent TMS with EEG

Measuring the neuronal electrical activity elicited by TMS is a relatively new modality of functional brain mapping. It enables experimenters to stimulate many regions of the cortical mantle, thus providing real-time information about the state of the cortex (the state of the cortex is usually understood as the distribution of chemicals in intra- and extracellular spaces, membrane potentials, and overall configuration of the cells at the time of stimulation). With an excellent time resolution at a millisecond level, TMS-EEG provides a measurement and mapping of cortical excitability and reactivity (Publications I–IV), monitors how brain oscillatory activity is modulated by targeted stimulation (Publication VII), measures functional connectivity between brain areas and between central and peripheral parts of the nervous system (Publication III), monitors the effects of rTMS during and after treatment, or monitors the safety of magnetic stimulation and alerts if epileptiform activity appears in the EEG (Publication VII). In order to effectively measure the EEG response induced by the TMS, it is necessary to consider several major technical challenges. A successful solution will require various aspects of engineering, combined with electrophysiological and anatomical knowledge, and even electrochemical reactions. TMS-EEG was utilized in Publications I–V of this thesis.

4.1.1 Technical aspects

Figure 4.1 describes the general technical setup that was used for acquisition of all TMS-EEG data sets for this thesis. The central hardware units consisted of an *Experiment-controlling computer* and *Stimulus generation device*, since the whole experimental paradigm is programmed using these two devices, and they control the rest of the hardware. An important aspect of our protocols is integration of peripheral and central responses within TMS paradigms studying the primary motor cortex. Some parts of the data presented here combine both types of activity by using EEG and EMG recordings obtained concurrently with the TMS of the motor cortex. For these measurements, it is important that event-triggers in all recording devices are registered for later off-line data analysis. Fig. 4.1 also schematically describes the triggering scheme between the devices. It is important to note that the output triggers from the magnetic stimulator were collected (for indication that TMS pulse was actually fired) in both the EEG and EMG recording devices (in Fig. 4.1 denoted as 'ST2' and 'EMG trigger collector' inputs, respectively). This is essential in faster oddball paradigms in which events (*i.e.,* stimuli) are interchanged rapidly, and the TMS pulse accompanies only some of these events.

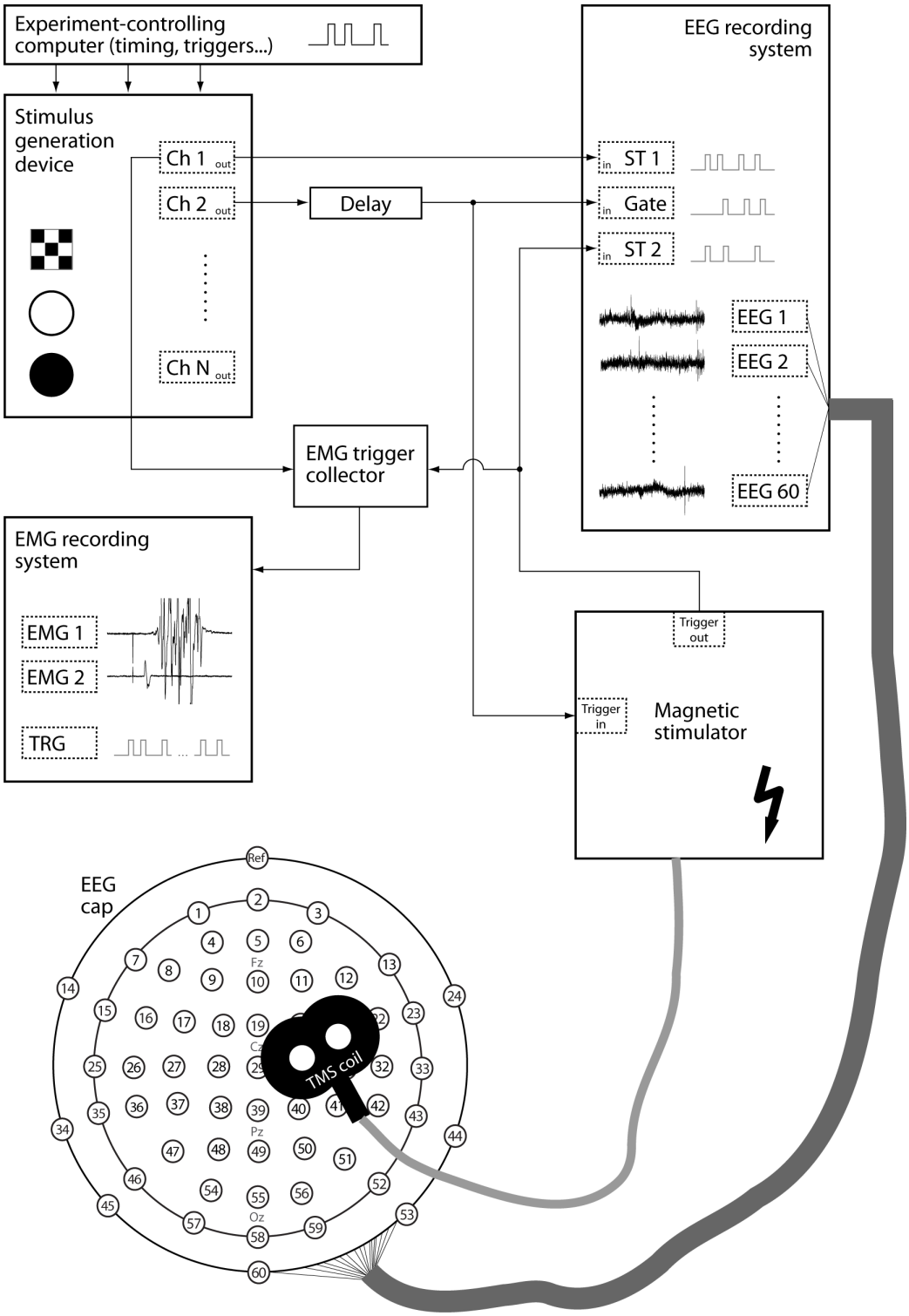

Figure 4.1: A comprehensive experimental setup for recoding the EEG responses to TMS, with parallel recording of the peripheral MEPs.

Because of the fairly long recharging periods of some of the TMS devices, it might happen that the TMS pulse might fail to fire 'on time' within the sequence of other

stimuli. In such cases, the input trigger from the *Experiment-controlling computer* would indicate this as a 'TMS event', even though the TMS was actually not delivered. If present in abundance, such epochs could substantially influence the results. Recording output TMS triggers overrides this problem.

4.1.2 TMS-evoked EEG responses

The first measurement of complete scalp distribution of ERPs following TMS was reported by Ilmoniemi et al. (1997) with an EEG amplifier that was specifically designed to operate in the harsh electromagnetic environment of TMS pulses (Virtanen et al. 1999). Similarly to MEPs, the TMS-evoked EEG responses had until that time mostly been investigated in the motor cortical system (Ilmoniemi et al. 1997; Komssi et al. 2002; Bender et al. 2005a; Massimini et al. 2005; Esser et al. 2006). In this thesis, EEG (with concurrent TMS) was measured with 60 electrodes covering the whole scalp (see Figs. 4.1 and 4.2). A typical topographical plot of TMS-evoked

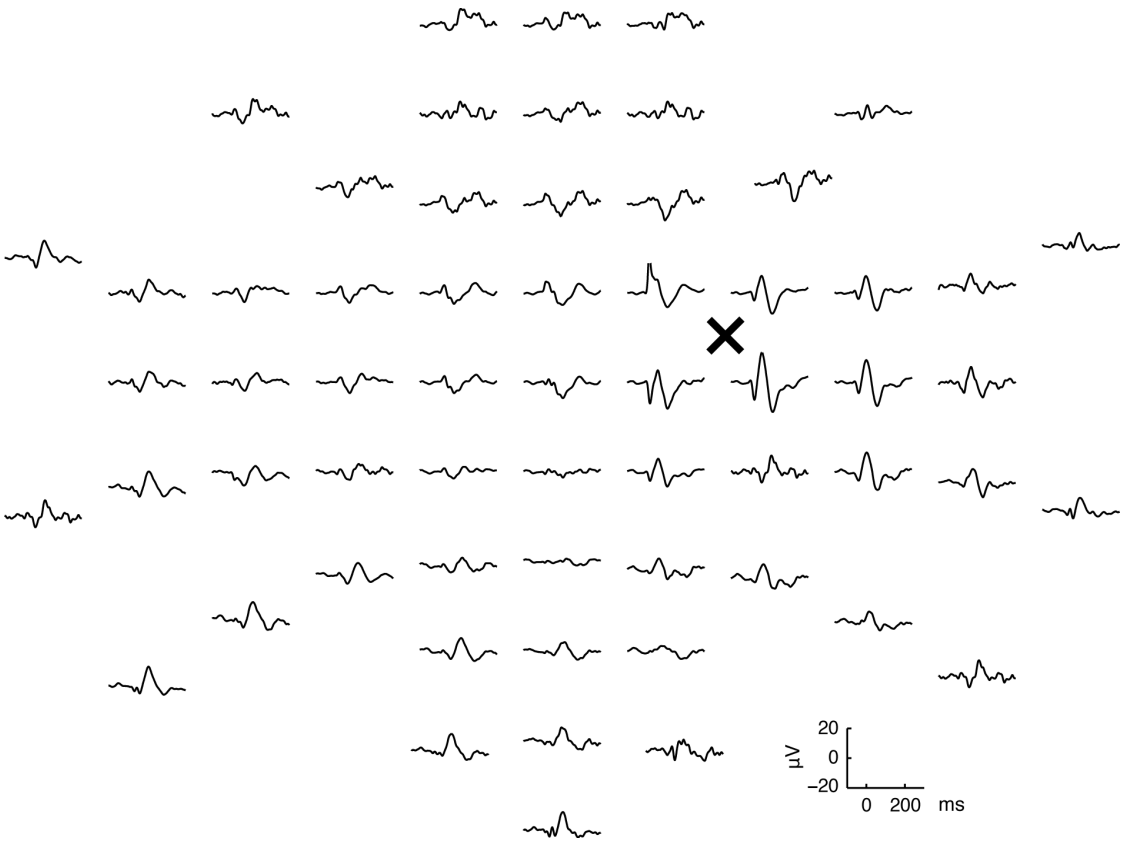

Figure 4.2: Averaged responses evoked by the TMS in one subject. The signals are arranged according to the layout of the electrodes (the view is from the top of the head, nose pointing upward). Prominent response amplitudes at latencies of approximately 50 to 100 ms are dominant in the vicinity of the stimulated point (denoted with 'X'). Note the lateralization of responses: in the vicinity of the stimulated site, the amplitudes are the highest, attenuating with increasing distance from the coil.

EEG responses after stimulation of the right motor cortex is shown in Fig. 4.2. The purpose of such a measurement is to detect both the local and distal effects of TMS: both to measure local excitability of the stimulated patch of the cortex, as well as to assess the spreading of TMS-evoked activity in a broader cortical network.

Fig. 4.2 also shows that the overall responses amplitudes are the highest right under the coil, diminishing with increasing distance from the stimulation point. An important feature of TMS-evoked EEG topography is that even though only one cortical hemisphere was stimulated, clearly bilateral EEG responses are evoked with different features. This confirms interhemispheric connectivity, which was proposed previously to be transcallosal (Ilmoniemi et al. 1997; Komssi et al. 2002; 2004). Locally, within one hemisphere, an increased EEG activity can be seen in a number of neighbouring electrodes, suggesting the spread of TMS-evoked activity to anatomically interconnected cortical areas (Bohning et al. 2000; Fox et al. 1997; Ilmoniemi et al. 1997; Komssi et al. 2002; Paus et al. 1997; 2001; Siebner et al. 2000; Strafella et al. 2001).

The averaged response of approximately 60 single trials from a single channel in the immediate vicinity of the stimulating coil is shown in Fig. 4.3. The investigators have been able to identify several components of the EEG response to a single-pulse TMS in the motor cortex: N15 (negative EEG deflection peaking approximately 15 ms post-stimulus), P30 (positive EEG deflection, 30 ms post-stimulus), N45, P55, N100, P200 (Komssi et al. 2002; 2004; Nikouline et al. 1999; Paus et al. 2001; Bender et al. 2005b; Massimini et al. 2005; Esser et al. 2006). However, it should be noted that the component structure may vary depending on the subjects (*e.g.,*

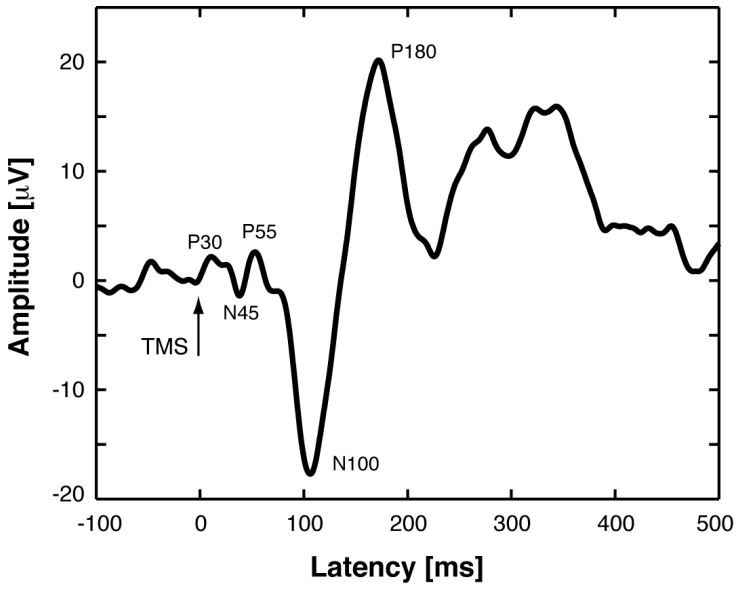

Figure 4.3: TMS-evoked EEG response from the motor cortex: single channel response in the vicinity of the stimulated cortical site. The names of the components relate to the polarities and latencies. The structure and latencies of the peaks may vary slightly between subjects and measurements.

healthy volunteers vs. patients), experimental setup (*e.g.,* no-task or performing the task), or pharmacological manipulation. Indeed, several reports have indicated large variability in the responses at latencies from 0 to 70 ms (Komssi et al. 2002; Bonato et al. 2006; Kähkönen et al. 2004).

In our measurements, the most pronounced and reproducible component across subjects and conditions was the TMS-evoked N100 component (Fig. 4.3), in agreement with other reports (Paus et al. 2001; Bender et al. 2005a; Massimini et al. 2005). This component peaks at about 100 ms after the TMS, with channels having the highest N100 amplitudes being located in the vicinity of the stimulated cortical site. This component was shown to be a robust TMS-evoked EEG response sensitive to subtle changes in cortical excitability (Bender et al. 2005a; Kähkönen and Wilenius 2007), and was suggested to represent the inhibitory response after activation of inhibitory interneurons, reflecting the activation of GABA-B receptors (Connors et al. 1988; Werhahn et al. 1999; Tamas et al. 2003; Markram et al. 2004). In order to maintain compatibility with the large pool of TMS-MEP studies, the EEG responses are also typically referred to as TMS intensity during their recording (*e.g.,* 90% MT). Importantly, it has been shown that clear EEG responses were elicited even at subthreshold TMS intensities, when no peripheral muscle activity was observable (Komssi et al. 2004; Kähkönen et al. 2005). These findings have been previously indicated by combined TMS and fMRI measurements (Bohning et al. 1999; Nahas et al. 2001) and confirm the TMS-EEG as a sensitive method for assessment of cortical excitability.

4.1.3 Reliability of TMS-EEG recordings

The amplitude of EEG signals is typically within a 1–100 microvolt range. Their quality and reliability in the harsh electromagnetic environment of TMS is not an easily achievable goal. Electric disturbances arising from the electronics or the subject may appear in parallel with responses reflecting the real neuronal activity, making the analysis and the interpretation of results difficult. Amplifier saturation is the greatest technical challenge for recording the EEG concurrent with TMS (Izumi et al. 1997; Virtanen et al. 1999; Fuggetta et al. 2005). For example, if the distance between two EEG electrodes on the scalp (*e.g.,* mounted on the EEG-cap) is approximately 20 mm, the induced voltage caused by applied magnetic TMS pulse is in the order of 50 V (Virtanen et al. 1999). An effective TMS-compatible EEG amplifier has to recover from the 50-V pulse fast enough to record the six orders of magnitude smaller ERPs (measured in microvolts) following the pulse.

EEG electrodes have a general purpose of establishing good electrical contact between the skin and the amplifier input, via an electrolyte. The resistance of the electrode contact should be low compared to the input impedance of the amplifier, and sufficiently low to avoid thermal noise in the contact resistance. Heating of the electrodes is caused by the eddy currents induced by the changing magnetic field and is proportional to the square of TMS intensity and the square of the electrode diameter, but independent of the thickness (Roth et al. 1992). The most commonly used electrodes in modern commercial TMS-EEG systems are small Ag/AgCl pellet

electrodes, which exhibit less electric noise than equivalent metallic Ag electrodes (Geddes and Baker 1980). Ag/AgCl pellet electrodes are electrically very stable and can also efficiently remove the direct-current shift that may appear in signals recorded just under the coil (Virtanen et al. 1999). However, they are not without defects. For example, an electro-deposited chloride coating can be relatively easily removed by abrasion - then the level of exhibited noise is far higher than with the AgCl layer. Moreover, Ag/AgCl is photosensitive, *i.e.,* changes its potential slightly when exposed to light (Geddes and Baker 1980).

Sources of disturbances in the EEG signal are numerous. Movement of the electrodes due to TMS coil vibration causes a disturbance of the electrical double layer at the skin-electrode interface, reflected usually as a DC shift in the recorded signal. This event is in the frequency range of many bioelectrical events (Geddes and Baker 1980) and may have a decay constant as high as 300 ms (Virtanen et al. 1999). It has been quite problematic (Paus et al. 2001; Komssi et al. 2004), though the filtering may be employed with success (Komssi et al. 2002). Electrical stability of an electrode in TMS recording is considerably enhanced by stabilization of the electrode-electrolyte (*i.e.,* skin) interface (Virtanen et al. 1999). Preparing impedances for all electrodes in an array to an equal level minimizes coupling of the mains voltage to the recording circuitry. It is useful to place the reference electrode into a relatively electrically inactive position, such as forehead, nose or mastoids.

A very common and strong artefact (at the millivolt scale) may result from direct stimulation of cranial muscles. This usually occurs when the coil is held above the lateral aspects of the head, or near the neck for stimulation of directly underlying cortical neurons. These artefacts are very strong and may last tens of milliseconds, masking the real neuronal activity. Scalp movements can also cause disturbances and are transferred to the EEG signal through electrode contacts (Paus et al. 2001).

Each TMS pulse is associated with a loud click (up to120 dB), which inevitably activates the subject's auditory system, giving rise to an auditory-evoked potential. These middle-latency auditory evoked potentials, such as P30 or P55, usually demonstrate a fronto-central distribution (Cohen 1982; Woods et al. 1987; Deiber et al. 1988) and may partially arise from auditory activation due to the coil click (Komssi and Kähkönen 2006). Sometimes, good hearing protection may be sufficient to deal with the coil click, but one has to be aware that a large part of the effect may be due to bone-conducted sound (Nikouline et al. 1999), which is difficult to mask. More complete suppression of the auditory activation due to coil click can be obtained by playing acoustic noise through headphones during TMS (auditory masking) in addition to hearing protection (Paus et al. 2001; Fuggetta et al. 2005; Massimini et al. 2005).

TMS also activates the sensory terminals at the scalp, giving rise to a somatosensory brain response, which may affect data interpretation. The latency of the N45 response coincides with that involving the conduction of a motor command to the hand muscles and the return of subsequent sensory afferent to the cortex (Tokimura et al. 2000). The potential pattern of N45 remains unchanged regardless of sub- or suprathreshold TMS intensities, strongly indicating that N45 is not generated by afferent input from peripheral muscles (Nikouline et al. 1999; Paus et al. 2001).

4.2 TMS combined with MEG

Recent years have seen enormous interest in the use of rTMS for both clinical research (treatment of neurological and psychiatric disorders) and basic brain research. This has sparked methodological and technical investigation in an effort to find paradigms that could induce strong, long-lasting effects using lower stimulation intensity and a shorter period of stimulation compared to conventional rTMS protocols (Cardenas-Morales et al. 2009). Here, MEG becomes increasingly relevant for mapping the effects and efficacy of rTMS protocols, since it offers far better time resolution than conventionally used techniques, such as fMRI, or PET. Furthermore, advanced source localization methods combined with artifact removal solutions (Taulu et al. 2004) enable the recording of subjects with implants and even life support and other assisting devices (Taulu and Simola 2006) - the patient groups that were up to several years ago unthinkable as participants in MEG studies.

Technically, the only possible combination of TMS and MEG at present is that in which the two measurements are separated in time, usually referred to as 'TMS combined with off-line MEG'. Figure 4.4 describes the off-line MEG protocol for mapping the effects of a single rTMS treatment, utilized in Publication VI of this thesis. With TMS applied first, off-line MEG imaging is usually used to study the

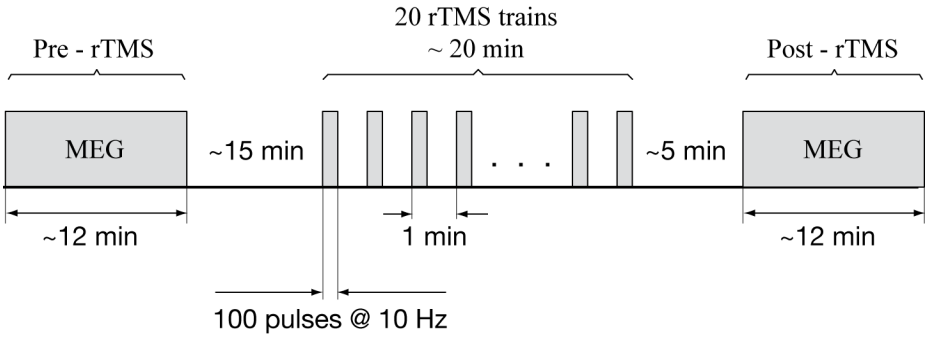

Figure 4.4: Technical setup of TMS-MEG combination. Spontaneous brain oscillations were recorded with MEG before and after the rTMS treatment in which 20 blocks of 100 TMS pulses were delivered to the patient's motor cortex.

long-lasting effects of rTMS on brain function, or spontaneous brain oscillations. If MEG measurement precedes the TMS, it is most probably used to define appropriate cortical sites to be targeted by TMS. Although the neurobiological mechanisms of rTMS are not fully understood at present, they may involve long-term potentiation (LTP)- and depression (LTD)-like processes, as well as inhibitory mechanisms modulated by GABA-ergic activity. The development of optimized rTMS protocols for directing the effects to specific cortical circuits, such as the thalamo-cortical motor loop of interest in Parkinsonian patients, and afterwards utilizing MEG to precisely track the time course of excitability fluctuations in a studied neuronal network have been the focus of contemporary rTMS-MEG studies (Tamura et al. 2005). Obtained data can be subsequently used to further study functional aspects of selected cortical networks.

5 General methods

5.1 Instrumentation and methodology of TMS

5.1.1 Magnetic stimulators

Single pulse TMS in Publications I, II, and IV was performed with Magstim 200 (The Magstim Company Ltd, Whitland, UK) device connected to a coplanar figure-of-eight coil (NP 9925) with an average diameter for each wing of 70 mm. In Publications III and VII, the Nexstim stimulator (Nexstim Oy, Helsinki, Finland) was used in combination with a figure-of-eight coil with a 70-mm outer diameter for each wing. Publication V utilized the Magstim Rapid stimulator.

Rapid rate TMS was used only in Publication VI. Twenty trains consisting of 100 pulses at 10 Hz were delivered at 1-min inter-train intervals. A coplanar figure-of-eight coil was used to deliver trains of rTMS pulses produced by the Magstim Rapid Stimulator.

Sham TMS for control conditions was systematically performed in Publication I and Publication VI in order to check the effect of auditory stimulation alone, and to measure the auditory responses associated with the residual coil click.

5.1.2 Navigated TMS

At the micro-level, the motor cortex consists of spatially discrete clusters of neurons primarily responsible for activation of specific lower motor neurons (Asanuma et al. 1976; Cheney and Fetz 1984). Thus, even small errors in coil placement might lead to a difference in the neurons excited in cortical neuronal clusters, and thereby contribute to variation in the MEPs. Therefore, precise targeting of the TMS coil is needed to accurately repeat the cortical stimulation. This is possible by tracking the location and orientation of the TMS coil relative to the subject (Fig. 5.1).

The navigated TMS targeting system should provide essential information regarding the relationship between the functional aspects of the stimulated cortex, cortical surface anatomy and/or pathological lesions as they exist in individual subjects/patients. The work described in this thesis benefits from the use of navigated TMS (eXimia, Nexstim Ltd., Helsinki, Finland) for enhanced precision and reproducibility of the stimulation. Relative positions of the subject's head and the TMS coil are determined and tracked in real-time by means of an optical locating system, which has a precision of less than 1 mm. In practice, however, this precision can be affected by imperfect registration of the subject's head (with her/his MRI), fixation of the trackers on the coil, errors in optical tracking, and possible head movements. The nTMS system also takes into account the stimulation intensity, coil parameters, and the individual brain anatomy. The intracranial electric field calculation based on the spherical model (Sarvas 1987) is visualized and matched to the 3D reconstruction of individual subject's brain MRIs. The induced electric field is visualized on a colour-coded map based on individual MRIs, enabling the operator to see in

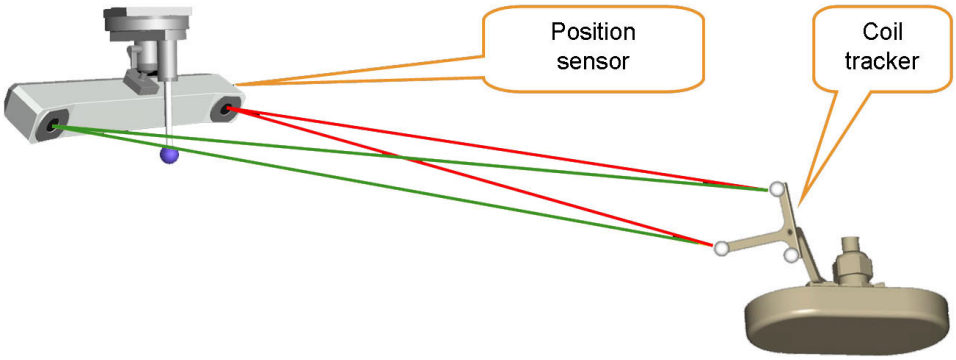

Figure 5.1: Navigation system for the TMS coil. The beam of light is emitted from the emitting diode to be reflected from the coil trackers back to the coil position sensor. The same principle works for the tracking of the subject's head movement. Figure courtesy of Jarmo Ruohonen, Nexstim Oy - Helsinki, Finland.

advance the exact cortical location being stimulated (see, Fig. 1A in Publication III and Fig. 1 in Publication IV). Using this system, the cortical target as well as the coil position, direction, and the angle of the stimulator were monitored in real time throughout the sessions. The device also allows the user to digitize the locations of the EEG electrodes for each subject (see, the lower panel of Fig. 1 in Publication V). The system records the orientation of the coil, its location, and induced electric field for every stimulus pulse. These recorded parameters can be recalled to reproduce the location and orientation (direction and angle) of the coil in subsequent stimulation sessions.

5.1.3 Cortical targets

Classical studies involving direct electrical stimulation of the cortex (Penfield and Boldrey 1937) consistently and repeatedly showed a defined myotopic organization of M1 where stimulation of a small cortical patch leads to activation of a specific effector. Surprisingly, a recent anatomical study (Rathelot and Strick 2006) showed that direct corticomotor neuron monosynaptic connection has a wide distribution in M1 for a specific muscle, *e.g.,* finger muscles. One should note, however, that direct monosynaptic cortico-spinal (CS) projections constitute only a minor part of the CS tract. When electric or magnetic stimulation of the cortex is used, a large number of output pyramidal cell are activated which have mono- and oligosynamptic connections with alpha-motor neurons in the spinal cord. It appears that such heterogeneous activation of the CS tract has the virtue of activating distinctly specific muscle groups. Specifically, muscle representations in M1 were the stimulation targets in the present thesis. For the hand area, they are localized in the anterior bank of the central sulcus, approximately between the two junctions - one is between the precentral and superior frontal sulcus, and the other is between the postcentral and intraparietal sulcus (Rumeau et al. 1994; Sastre-Janer et al. 1998) - and are distinguished by a knob-like form (Yousry et al. 1997) that resembles the letter 'omega' (present in 90% of population), or 'epsilon' (present in 10% of population). This

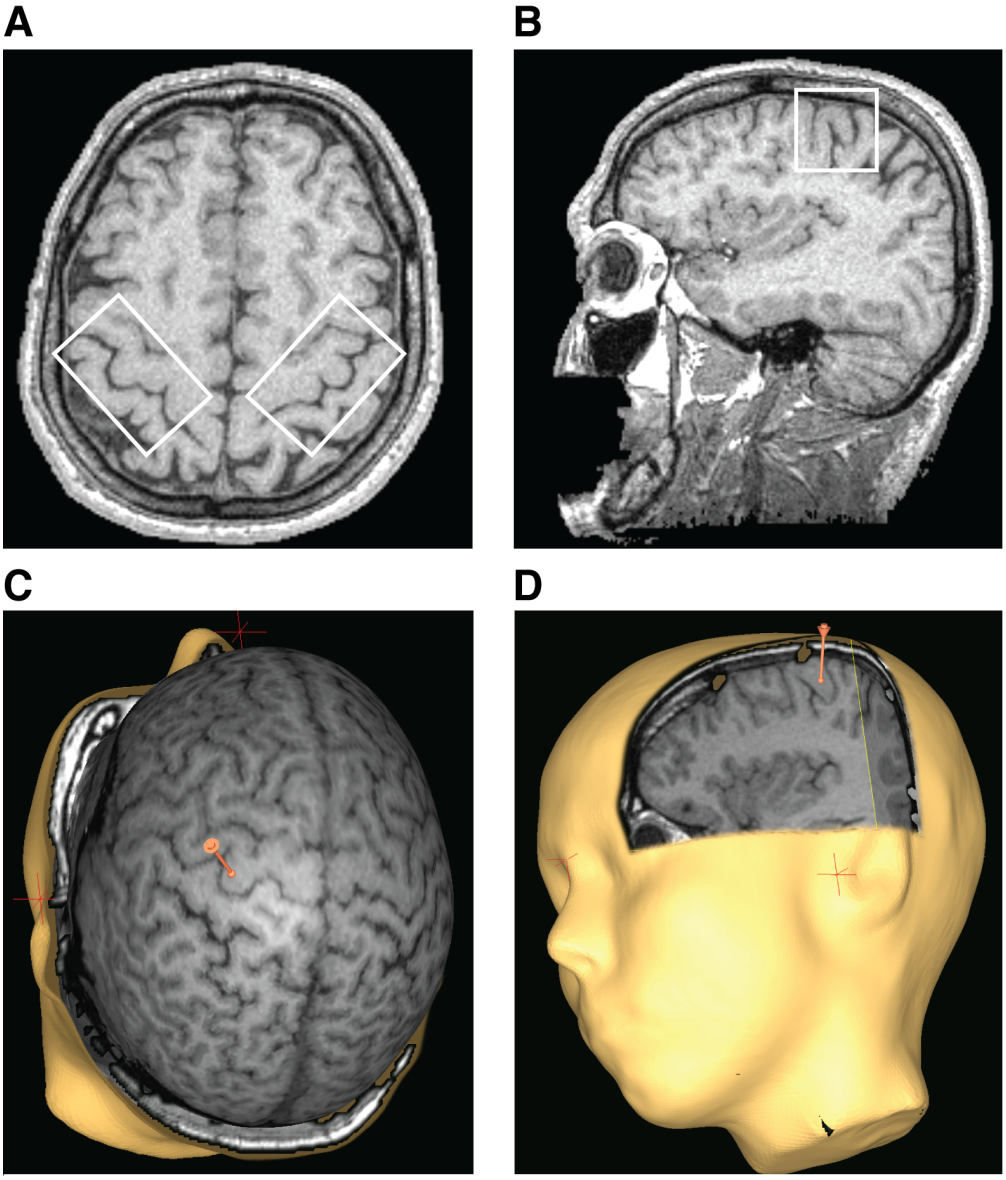

Figure 5.2: Localization of the functional hand area in the motor cortex. A) An omega-shaped segment on the anterior bank of the central sulcus containing hand projections on the motor strip in coronal MRI slices. C) The same structure in 3D nTMS visualization. B) The specific hook-like form of the precentral gyrus within the hand area in saggital MRI slices. D) The same structure in 3D nTMS visualization.

form was evident in the axial slices visualized by the neuronavigational system, as shown in Fig. 5.2. In saggital slices, the precentral gyrus within the hand area has a specific hook-like form (Fig. 5.2B). These cortical forms could be distinguished in all of our subjects and patients. A practical procedure for targeting the motor cortex consisted of two steps: (i) using MR images, we identified the hand area on the anterior bank of the central sulcus (Fig. 5.2A); and (ii) in the vicinity of the hand area, we performed a search for the optimal position where TMS evokes the

strongest MEPs.

The primary motor cortex was stimulated in all studies (I–VII), with the coil being placed tangentially to the scalp and the handle pointing backward and laterally at approximately a 45-degrees angle away from the midline in order to achieve the strongest stimulation of the motor cortex (Thielscher and Kammer 2002; Ziemann et al. 1999). Thus, the current induced in the brain had a posterior-to-anterior orientation, approximately perpendicular to the orientation of the central sulcus (Brasil-Neto et al. 1992).

Apart from motor cortical representations, Publication IV included magnetic stimulation of the dorsolateral prefrontal cortex (DLPFC) in the left middle frontal gyrus, located from a 3D MRI reconstruction, based on anatomical sketches (Yousry et al. 1997). In Publication V, targets other than the primary motor cortex were selected according to source locations (and their time courses) as identified by MEG modelling after electrical somatosensory stimulation of the median nerve of the dominant hand.

5.1.4 Protocol: functionally specific cortical excitability

Figure 5.3 presents the general design of the experimental setup used for investigating functionally specific changes in cortical excitability in this thesis.

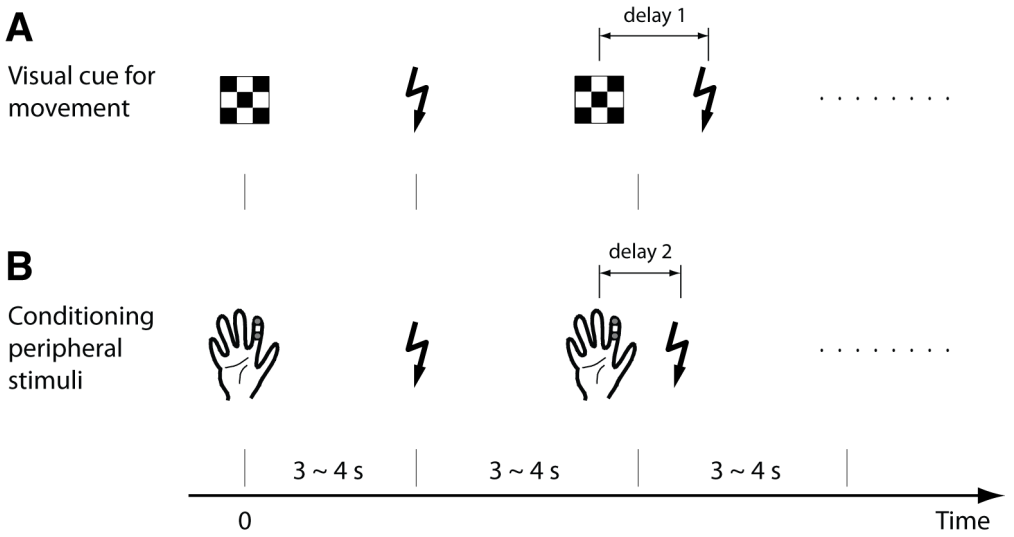

Figure 5.3: General experimental setup for assessing functionally specific cortical excitability. In the presented examples, transient modulation of cortical excitability was achieved prior to TMS by: A) brisk finger movements in response to the visual cue, or B) peripheral electrical stimuli.

The subjects were seated comfortably in an armchair, fully relaxed, with eyes opened with a fixed gaze. TMS was applied time locked to a specific event, which transiently modulated cortical excitability at the target cortical network, such as the instruction to make a brisk unilateral finger movement triggered by a visual cue (Fig. 5.3B,

Publications I and II), the peripheral somatosensory electrical stimulus (Publicatoin III), or a unilateral motor reaction to the peripheral somatosensory electrical stimulus (Publicatoin IV). Both EEG and EMG were recorded continuously and simultaneously during the whole duration of each session.

Depending on the exact experimental paradigm, there were several stimulation categories (normally 2 or 3) distributed across several measurement sessions and conditions. For example, Publication II (see Fig. 5.3A) used three categories of stimuli (visually-cued movements alone, TMS alone, and visually-cued movements followed by TMS) separated into three conditions (ipsilateral motor response, contralateral motor response, and no motor response), each repeated in two sessions. We took special care to balance between overall duration of the sessions and the total number of epochs in order to prevent the measurements from becoming biased by the subject's fatigue or unwanted peripheral tonic muscle activity.

5.1.5 Analysis of TMS-evoked neuromodulation in EEG

In Publications I–V, the ERPs were obtained from the electrophysiological recordings of brain potentials synchronized with delivery of TMS. The analysis of multichannel ERPs focused on time segments from –100 ms up to +500 ms with respect to the TMS. The N100 component was emphasized, since it was hypothesized to reflect functionally specific changes in cortical excitability. In Publications I and II, the modulation of cortical excitability was achieved by performing a unilateral

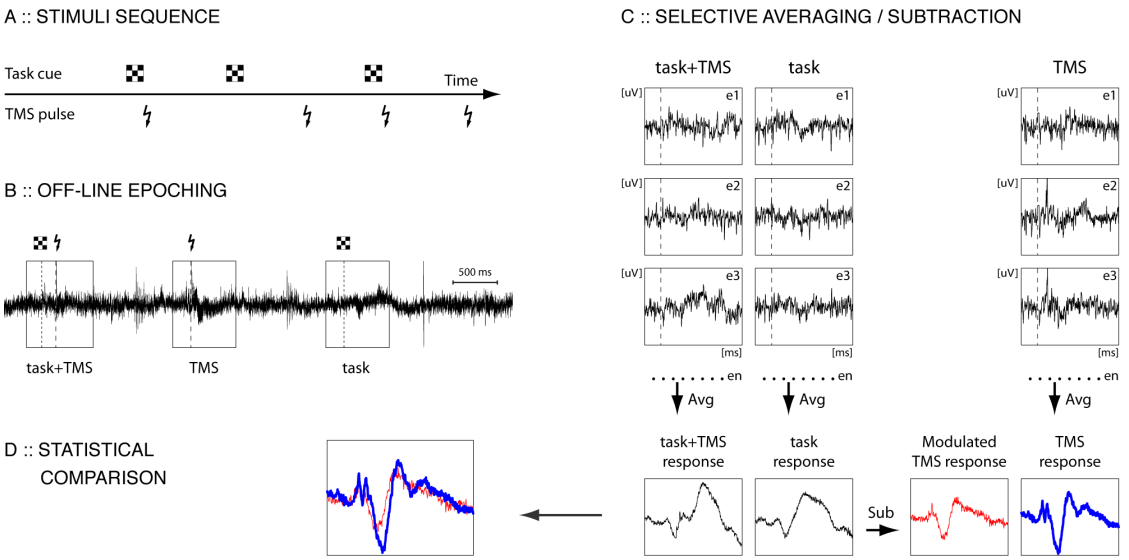

Figure 5.4: Results revealing functionally specific changes in cortical excitability. A) During the data acquisition, stimuli are presented in a specific order. B) Post-processing starts with a grouping of epochs and continues with C) their selective averaging. Averaged potentials for TMS alone, and for a combined presentation of TMS with other stimuli (visual or somatosensory) are calculated separately. D) Statistical comparison of the results reveals the influence of functional states of the cortex on the measured TMS-evoked EEG signals.

movement in response to a visual cue presented on a computer screen, while in Publications III and V, modulation was obtained by delivering peripheral electrical stimuli prior to TMS. In an offline analysis, the EEG data were re-referenced with respect to the common average potential. Data processing is schematically described in Fig. 5.4. After the rejection of the EEG segments containing mechanical and muscle artefacts, responses were grouped into several sets according to their experimental protocol (Fig. 5.4B) and selectively averaged (Fig. 5.4C). Then, the amplitude and latency of the modulated N100 response were obtained from a difference curve (Fig. 5.4C) as follows. In Publications I and II, the responses to visual stimuli alone were subtracted from the responses to the combined presentation of visual stimuli and TMS. Similarly, in Publication III, evoked responses to D2 stimuli alone were subtracted from the evoked responses to a combined presentation of TMS and D2 stimuli. Finally, statistical comparison revealed the influence of the functional states of the cortex on the measured TMS-evoked EEG signals (Fig. 5.4D). The cortical regions of interest (ROI) were sensorimotor areas in both hemispheres. With the goal of investigating local cortical excitability changes, we selected a ROI covered by several electrodes (ranging from 4 to 10) in the vicinity of the point of stimulation. A similar ROI was also selected from the homologous area of the opposite hemisphere in order to demonstrate interhemispheric differences. An average trace was obtained from these electrodes, and the amplitude and latency characteristics of N100 were assessed from it. The amplitude of N100 integrated in the time window of ± 5 ms around the peak latency was calculated separately for each session and condition.

It is important to note that EEG epochs were inspected by taking into account EMG activity, *i.e.,* whether an EMG epoch was rejected, the corresponding EEG epoch was rejected from further analysis as well, and vice-versa.

5.2 MEG instrumentation, data acquisition and analysis

In Publications V–VII, the 306-channel MEG data were recorded with an Elekta neuromagnetometer (Elekta Neuromag Ltd, Helsinki, Finland) in a magnetically shielded room (Euroshield, ETS Lindgren, Eura, Finland). During the MEG recording of spontaneous interictal and ictal brain activity and somatosensory evoked fields (SEFs) to median and tibial nerve stimulation in Publication VII, the head movements were continuously monitored by four coils on the scalp (Medvedovsky et al. 2007; Uutela et al. 2001). This setup provided very accurate ictal recordings, which is important for clinical study. MEG was recorded at a 0.03–172 Hz frequency band and sampled at 600 Hz. MEG data in Publication V were recorded at frequency band of 0.01–330 Hz and sampled at 1 kHz.

In order to reveal ERFs, MEG data in Publication V were averaged with respect to the somatosensory stimuli. Epochs of activity containing electro-oculogram (EOG) signals exceeding ± 150 μV were discarded. The generators of the ERFs were located using dipole modeling. The dipole amplitudes were allowed to vary in a multidipole model as a function of time while keeping their locations and orientations fixed. This resulted in millisecond-accuracy time courses of the activated brain areas. These

time courses were utilized to identify target brain areas for subsequent magnetic stimulation.

In Publication VII, in two epilepsy patients, single equivalent current dipoles (ECD) were first computed for the separate dipolar fields (with limited number of sensors) at different post-stimulus time points. Subsequently, these dipoles were used as initial guesses for a single- or multi-dipole fit using all 306 channels. Finally, the analysis period was extended to cover the entire signal of interest, and the optimal dipole strengths were computed by assuming fixed dipoles. The used dipole had to explain the signal of interest (most commonly, a spike), but not other MEG signals (*e.g.,* posterior alpha activity). Thereafter, the MEG results were co-registered with MRI data and compared with nTMS and the electro-cortical stimulation (ECS) results.

6 Results and discussion

6.1 Time course of movement-related cortical excitability

Publication I demonstrated that EEG responses to TMS are modulated by preparation and execution of visually cued unilateral movements compared to responses when TMS was delivered alone, and subject was not performing any task (Fig. 6.1).

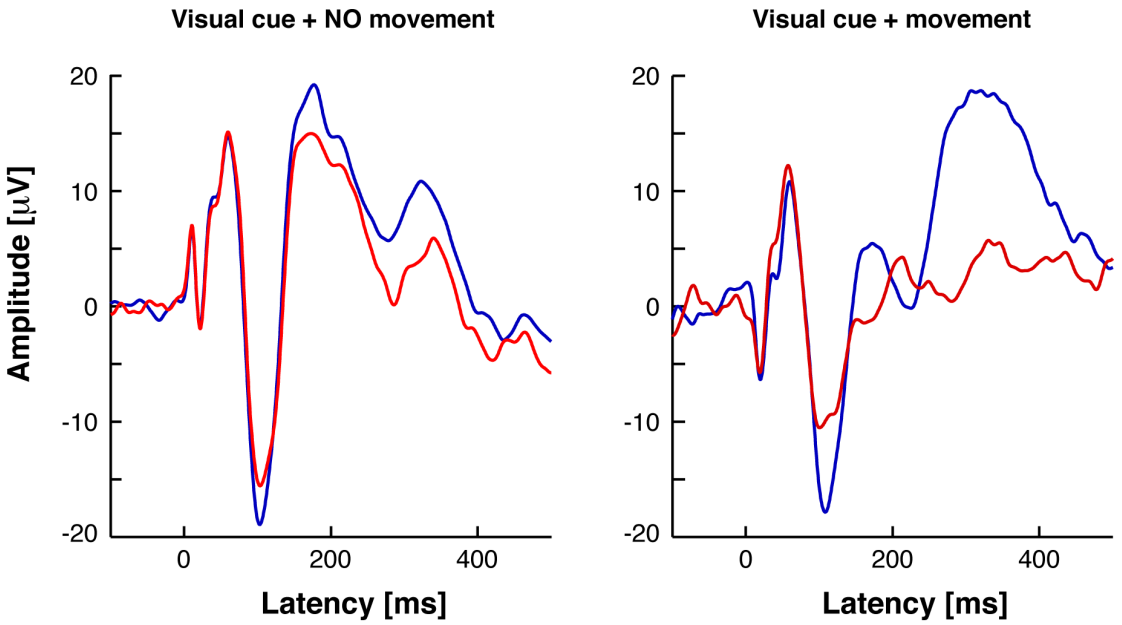

Figure 6.1: Comparison of the EEG responses evoked by TMS pulses delivered alone (blue traces) vs. the TMS-evoked N100 response modulated by observing the visual cues (red trace, left panel) and visually-cued motor cortical processing (red trace, right panel). The right panel shows that modulation is markedly stronger when the subject was reacting to visual cues with brisk thumb twitches. All signals were recorded over the motor cortex contralateral to the moving hand.

At the same time, the amplitude of MEPs was clearly modulated during the movement condition, showing a significant increase. These results are in agreement with accumulated published data suggesting that the time interval immediately before the onset of the movement, during, and immediately after the movement is characterized by the highest cortical excitability, which is seen as lowered motor thresholds to TMS (Rossini et al. 1988; Starr et al. 1988), and/or increased MEP amplitudes (Chen et al. 1998b; Leocani et al. 2000). During that time window, there is an increased rate of neuronal firing in the motor cortex (Evarts 1966; 1974; Fetz and Finocchio 1971; Gribova et al. 2002) corresponding to increased cortical excitability. The experimental paradigm was designed so that the visual cue preceded the TMS by 180 ms. Taking into consideration that the average reaction time of our subjects ranged from 150 to 200 ms (using the onset of the EMG of the moving muscle), the

observed effect of MEP facilitation also covers the increase in motor cortex excitability by approximately 50–80 ms before the voluntary movement had commenced, *i.e.,* pre-movement excitability. The highest MEP facilitation was previously reported in this interval (Starr et al. 1988). The time course of facilitation approximates that found in monkey pyramidal neurons of primary and supplementary areas, which begin to discharge between 120 and 50 ms before movement onset and show increasing rate of firing as the interval to the onset of movement shortens (Evarts 1966; Brinkman and Porter 1979; Kubota and Hamada 1979). Publication I demonstrates that the increasing discharge rate of pyramidal neurons found in animals also occurs in humans (Lee et al. 1986) and is accompanied by lowered neuronal thresholds to TMS applied over the scalp projection of primary motor cortex.

MEP responses could be detected reliably in each individual trial. This was not possible to do for the EEG responses, since signal-to-noise ratio (SNR) was very low (as is the case for practically all EEG studies with or without TMS). Therefore, a detailed temporal dynamics of the responses, with respect to the movement onset, was only feasible for MEPs. However, for Publication I, we subdivided all EEG responses into two groups - fast and slow with respect to the median value of RTs. The results of this analysis are described as a peripheral aspect of the temporal evolution of increased cortico-spinal excitability related to the preparation and execution of movement, as presented in Fig. 6.2. This figure shows the MEP amplitude changes as a function of the speed of the motor response in latency bins of 70 ms. Amplitudes of the MEPs associated with fast reactions up to approximately

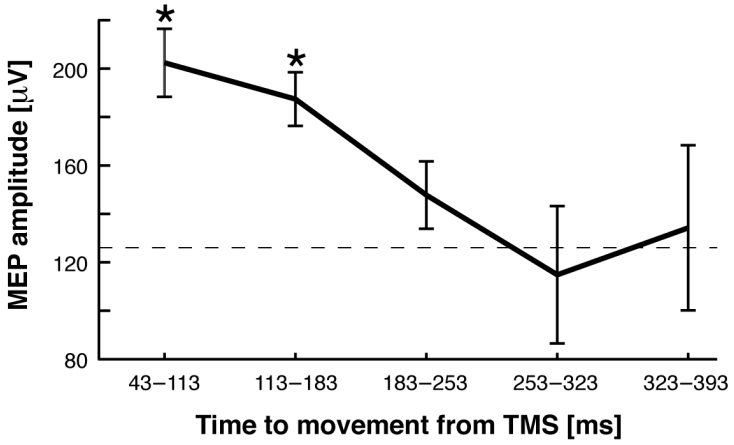

Figure 6.2: Amplitudes of the MEPs as a function of time from the TMS to the onset of motor response. The time on the x-axis indicates the beginning of the movement with respect to the TMS pulse (adding 180 ms to numbers in the horizontal axis gives the reaction time after the visual stimulus). The MEPs were grouped with a bin of 70 ms. The horizontal dashed line shows the average amplitude of the MEPs to the TMS alone. The asterisks indicate a significant enhancement of the MEPs preceding the movement with respect to the MEPs produced by the TMS alone.

200 ms after the TMS were enhanced, while MEPs associated with slower reactions remained unchanged. Enhancement of the 'fast MEPs' is likely to come from an increased amount of synchronously descending impulses along the fast propagating

corticospinal tracts as both the number of pyramidal tract neurons engaged by the stimulus and their firing rates increase. We have related the presented peripheral manifestations of motor cortico-spinal excitability to its EEG (central) counterpart of changes in neuronal activity by selectively averaging the EEG epochs according to the speed of reaction to a visual cue. The EEG epochs were, however, grouped into only two bins: according to whether the reaction time was shorter or longer than the median value. This procedure allows correlating the specific stage of the cortical motor processing with the parameters of the EEG response. According to the literature (Evarts 1966; 1974; Fetz and Finocchio 1971; Gribova et al. 2002; Gottlieb et al. 1970; Hayes and Clarke 1978; Ruegg and Drews 1991), the slow group N100 responses would be associated with the less pronounced cortico-spinal excitability, compared with the fast-group N100 responses. However, the modulation of N100 was similar in both groups, indicating that EEG can detect the onset of excitability modulations even earlier than MEPs. It is important to note that the N100 component was also diminished significantly when TMS was preceded by the visual stimulus, and no motor response was executed (left panel in Fig. 6.1). The origin of this change in motor cortex excitability is not entirely clear, and at least two mechanisms have been suggested to explain this. One scenario is that visual stimuli alone could produce this modulation, since anatomical studies suggest only two synaptic connections from the eye to the motor cortex through the mesencephalic reticular formation (MRF): one form retina to MRF and one from MRF to the motor cortex (Leichnetz 1986; Nakagawa et al. 1998). The second scenario suggests that modulation of N100 might have occurred due to previous association of visual stimuli with the motor reactions. Here, visual stimuli would trigger subthreshold (for generation of motor output) processes in the motor cortex, which

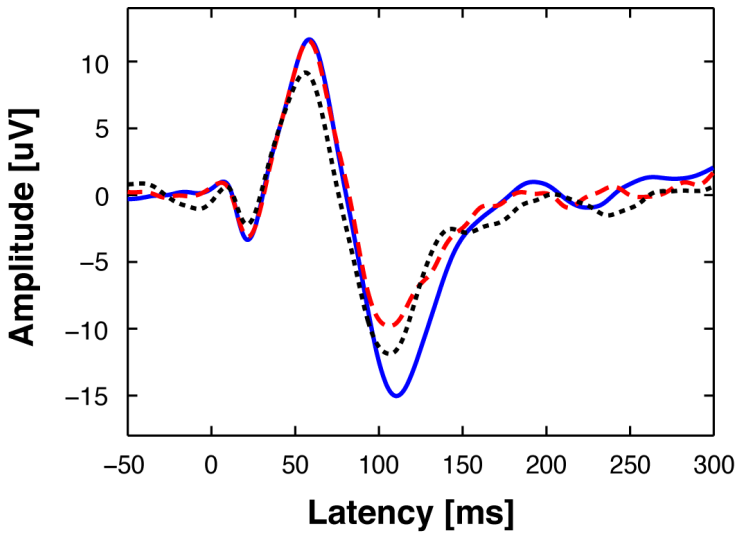

Figure 6.3: Functionally specific modulation of TMS-evoked N100 component. During movements with hand contralateral to the stimulated hemisphere (red trace), the attenuation was stronger compared to the condition when the response was given with ipsilateral hand (black trace). Blue trace represents responses to TMS pulses alone, without visual cue or motor response.

would modulate the N100 amplitude. Future experiments will determine which of these scenarios is more plausible.

6.2 Role of the ipsilateral hemisphere in motor control

Neurophysiological correlates of unilateral movement in sensorimotor areas of both hemispheres were explored in Publication II, with an emphasis on the role of the ipsilateral hemisphere. We aimed at studying bilateral activation of motor areas during the performance of unilateral movements (Kristeva et al. 1991; Rao et al. 1993; Salmelin et al. 1995; Kim et al. 2004). For this purpose, we contrasted the MEP and EEG results and closely analyzed the mirror movements in healthy subjects occurring during unilateral movements. This study successfully repeated the results of Publication I showing that the TMS-evoked N100 component is significantly attenuated during performance of unilateral movements. Furthermore, we demonstrate that a similar attenuation occurs in the ipsilateral hemisphere during the same motor action. Both of these results are shown in Fig. 6.3. Then, we compared the degree of attenuation between the sessions in terms of the percentage of N100 decrease: during contralateral movements, the attenuation was 36%, while during the ipsilateral movements it was 25%. To evaluate the spatial extent of N100 attenuation, we calculated it for each of the 60 recorded EEG channels and plotted a topographical plot (Fig. 6.4). It can be seen that during unilateral movements, the attenuation of N100 is strongest in contralateral hemisphere (left panel in Fig. 6.4), most likely due to the elevated neuronal activity associated with the preparation and generation of motor output

However, only in the contralateral hemisphere were these changes associated with modulation of peripheral muscle responses, as shown earlier in Publication I. This dissociation implies the presence of additional inhibitory mechanisms in the ipsilateral hemisphere responsible for the suppression of motor output discharges. This,

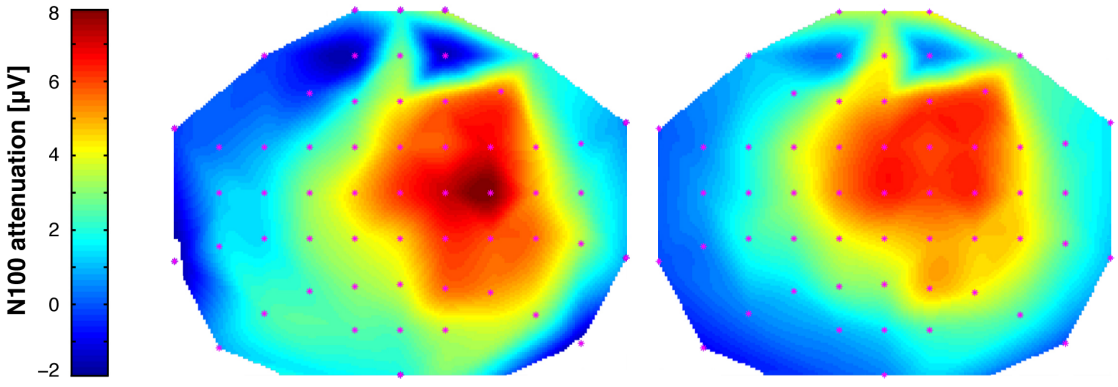

Figure 6.4: Topographical plot of attenuation of the TMS-evoked N100 component during movements with contralateral (left panel) and ipsilateral (right panel) hand. Attenuations of TMS-evoked N100 in both hemispheres have very similar spatial character, being stronger in the hemisphere contralateral to the moving hand.

for example, could be the mechanism that controls the occurrence of mirror movements (Fig. 6.5), which were indeed present in all subjects, at a rate comparable with known literature (Verstynen et al. 2007). These results point to the possibil-

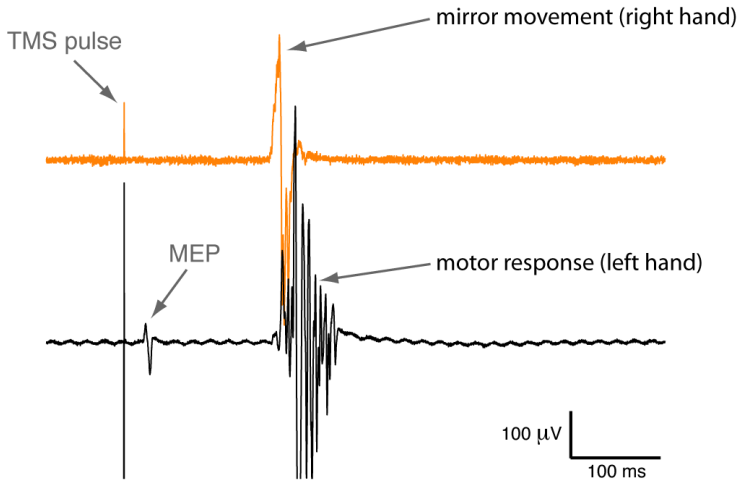

Figure 6.5: An example of EMG recording of a mirror movement. Subject responded with the left hand, but the EMG was clearly recorded also in the right hand, the so-called mirror movement. The MEP response is clearly visible at about 22 ms after the TMS. Vertical lines on the left side of the plot indicate the TMS pulse.

ity of bilateral activation of sensorimotor cortices during the execution of unilateral movements, most probably related to the occurrence of mirror movements (Mayston et al. 1999; Verstynen et al. 2007), or to its suppression (Kristeva et al. 1991; Leocani et al. 2000; Perfiliev 2005). Both processes are possible and might lead to the generation of undesired MMs, which should, nevertheless, be suppressed. The likely mechanism of suppression is transcallosal inhibition from the contralateral hemisphere (Ferbert et al. 1992; Wassermann et al. 1994; Mayston et al. 1999; Ziemann et al. 1999). Publication II shows that most probably these two processes are occurring concurrently in the ipsilateral hemisphere, one being related to the initiation of the unwanted MMs, and another to its suppression (Kobayashi et al. 2003; Perfiliev 2005). By this scenario, the amplitude of N100 in the ipsilateral hemisphere should demonstrate a smaller decrease compared to N100 decrease in the contralateral hemisphere, since MMs-related excitatory activity is to be counterbalanced by inhibitory activity. These are exactly the results of Publication II presented in Fig. 6.3 on page 47.

6.3 Central reflections of periphery

Short-latency afferent inhibition refers to the attenuation of upper limb MEPs evoked by TMS due to preceding stimulation of peripheral digital nerves or the median nerve at the wrist. Based on previous suggestions that SAI reflects primarily cortical processing (Classen et al. 2000; Tamburin et al. 2001), Publication III aimed to further investigate its cortical mechanisms using experimental tools

already tested in Publications I and II. In accordance with previous TMS studies on SAI (Tokimura et al. 2000; Cucurachi et al. 2008; Nardone et al. 2008), we show that MEPs to TMS applied 25 ms after index finger (D2) stimulation (see Fig. 5.3 on page 41) were significantly attenuated. Moreover, the attenuation of MEPs due to SAI is associated with the amplitude attenuation of the TMS-evoked N100 EEG component. We demonstrate for the first time that the attenuation of MEPs is positively correlated with the amplitude attenuation of the N100 response, shown in Fig. 6.6. In that figure it can be seen that even small individual changes in periph-

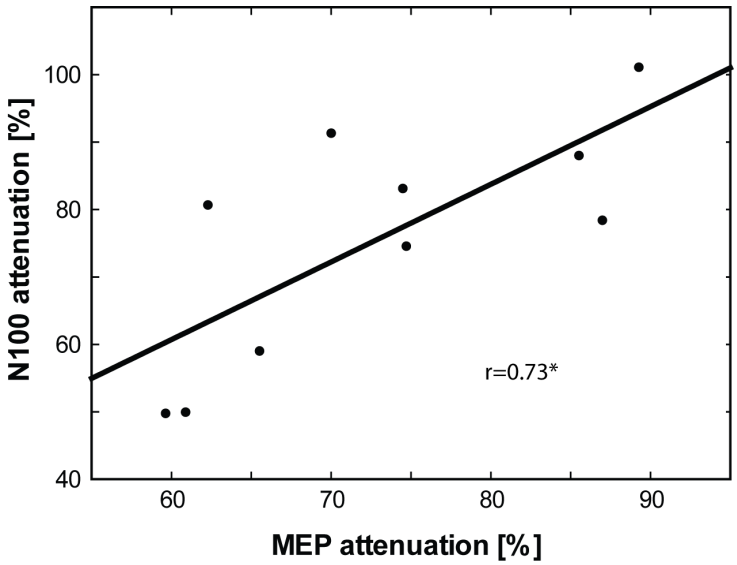

Figure 6.6: Demonstration of a positive correlation between central and peripheral manifestation of the SAI phenomenon. Correlation plot of the amplitude attenuation of the TMS-evoked N100 vs. the amplitude of MEPs due to D2 electrical stimulation. The black line represents the least-squares fit to the data. An important message of this plot is that even small individual changes in the amplitude of peripheral responses are paralleled by amplitude changes in cortical responses.

eral activity are paralleled by changes in cortically probed excitability. This is most probably achieved through an interaction between two inhibitory processes, partially coinciding over time. The first inhibition, due to incoming peripheral electrical stimulus (SAI), is directed at pyramidal cells and should produce hyperpolarization of the neuronal membrane, thus leading to a decrease in the MEP amplitude (the same mechanism can also lead to a decrease in I-waves recorded epidurally, Tokimura et al. 2000). At the time when the second, TMS-induced, inhibition starts, the neurons are already hyperpolarized due to SAI, resulting in a smaller amplitude of N100. Conclusions about probable neuronal assemblies responsible for manifestation of later stages of inhibitory influences of SAI were drawn based on analysis of early EEG responses to TMS. Negativity peaking at 15 ms (N15) indicates initial recruitment of neurons directly activated by TMS, which as such have to be located superficially, where the induced electric field is strongest. The N15 was not affected by D2 stimulation, thus leaving the deeply located pyramidal cells as the most likely candidates responsible for the late inhibitory influences of SAI.

Pursuing further the influences of peripheral stimulation on cortical circuits in combination with TMS-probing of cortical excitability, Publication V studied cortico-cortical communication between the areas receiving parallel sensory input from one side of the thalamus to primary projection areas, and from the other side directly to hierarchically higher-order cortices, bypassing the primary sensory cortices. This Publication utilizes an integrative multimodal approach for studying this effective connectivity. Source locations (together with their time courses) identified by MEG,

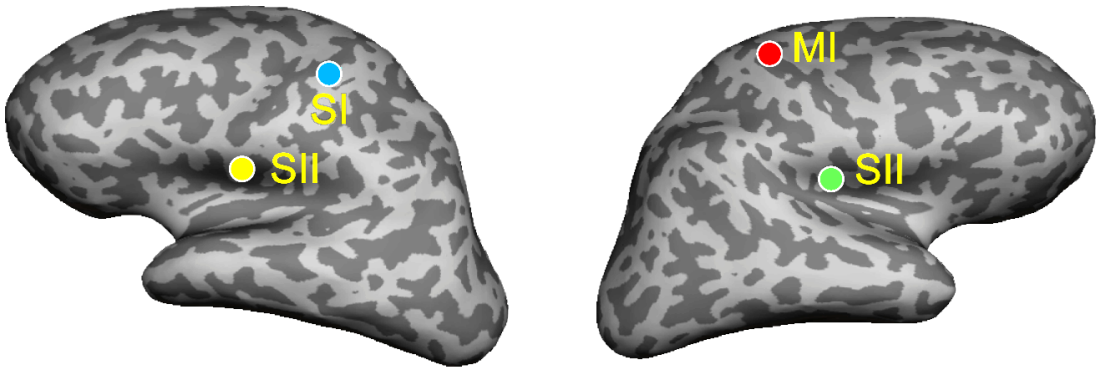

Figure 6.7: MEG source locations used as TMS targets in Study V. During MEG measurement, the subject was instructed to respond to right median nerve stimuli with the left index finger. This resulted in four evoked MEG responses: 1) the primary somatosensory cortex in the hemisphere contralateral to the median nerve stimulus (SI, blue dot), 2) the secondary somatosensory cortices bilaterally (SII, yellow and green dots), and 3) the primary motor cortex contralateral to the motor response, but ipsilateral to the median nerve stimulus (MI, red dot).

after electrical somatosensory median nerve stimulation with a reaction time task, were used in a subsequent session as targets to be modulated with TMS at different latencies after the somatosensory stimulus. As shown on the inflated cortex in Fig. 6.7, these included the contralateral primary somatosensory cortex (cSI), bilateral secondary somatosensory cortices (cSII and iSII), and the ipsilateral primary motor cortex (iMI). Interestingly, MEG data showed the activation of cSII several milliseconds earlier than cSI, confirming previous reports that higher-order cortices may become activated even earlier than primary sensory cortices (Barba et al. 2002; ffytche et al. 1995; Karhu and Tesche 1999). This is inconsistent with serial processing and suggests that SII receives a direct, early parallel sensory input independent of the pathway via SI (Karhu and Tesche 1999). The rest of our results supported this view. First, RT was significantly faster when TMS was given to cSII, than to cSI, or to iSII, with the largest facilitatory effects being observed when the TMS pulse was targeted at the contralateral SII at about 20 ms post-stimulus. Second, peak latency analysis of the TMS-evoked responses revealed that TMS pulses at 15–40 ms speeded up the 140-ms ERP component by 8±8 ms compared to the no-TMS condition, as shown in Fig. 6.8.

Publication V proposes that the speeded RTs could be best explained if the somatosensory-evoked physiological SII activation at about 20 ms normally exerts a top-down SII → SI influence that facilitates the reciprocal SI → SII pathway. TMS

to SII at a latency of approximately 20 ms appears to facilitate the natural brain-speeding mechanism already in place. It appears that fast thalamocortical parallel sensory inputs to multiple cortical sites could decrease the activation thresholds of the cortico-cortical connections between the areas (Ullman 1995).

6.4 Background oscillations and cortical excitability

In addition to the role of the ipsilateral hemisphere in unilateral movement control, Publication II also investigated the fine-tuning of background (*i.e.*, ongoing spontaneous) neuronal activity related to performance of a specific task. The classification as 'ongoing spontaneous' or 'background' implies that the neuronal activity is not evoked or induced by the stimuli. The main idea of this approach is that neurophysiologic TMS-evoked EEG responses during time intervals in which the subject is not performing any task, but merely sitting relaxed, should reflect specific fine-tuning of the neuronal activity broadly related to an experimental condition. When TMS pulses were delivered alone (without preceding visual stimuli) the N100 component

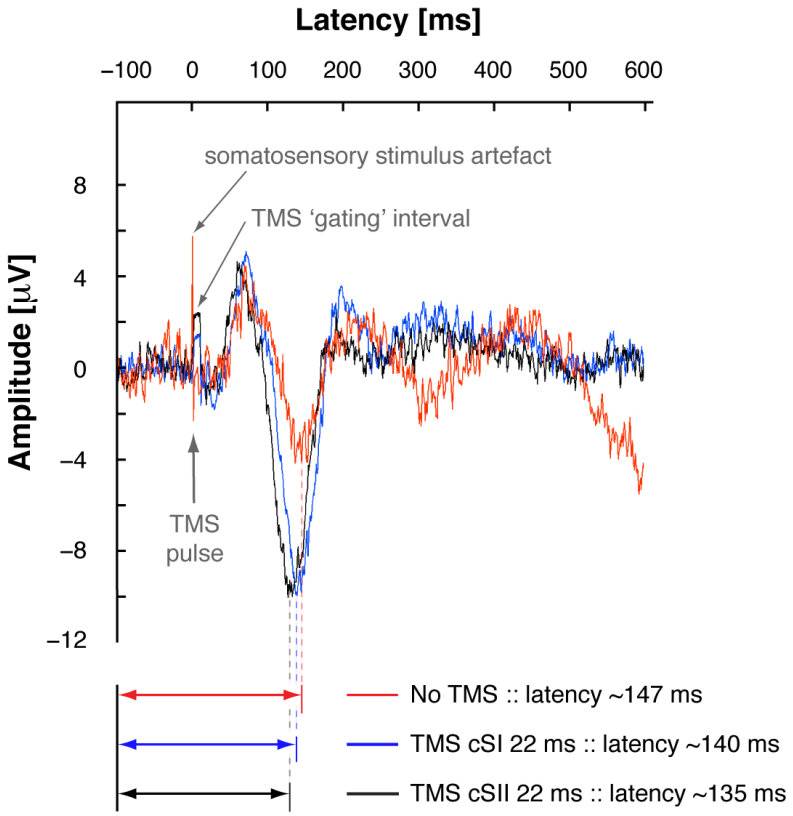

Figure 6.8: Somatosensory ERPs recorded when the subject responded to right median nerve stimuli with the left index finger (unfiltered averaged traces in one subject). Compared to the condition without TMS (red trace), conditions with TMS (blue and black traces) show earlier and stronger SII activity at latencies around 140 ms. The ERP peak shifts appear to correspond to faster RTs.

was significantly larger in sessions requiring a motor response with the ipsilateral hand than in sessions with contralateral responses. This finding may reflect an involvement of inhibitory processes implemented already at the level of spontaneous activity, which are functionally fine-tuned in the ipsilateral hemisphere to prevent the occurrence of MMs during unilateral movements. This is supported by animal studies showing that effective performance in motor tasks is related to a specific fine-tuning of ongoing neuronal firing in the motor cortex (Favorov et al. 1988; Cisek et al. 2003; Perfiliev 2005). In experiments with cats, Perfiliev (2005) demonstrated that background neuronal firing in the ipsilateral hemisphere might contribute to correct selection of the unilateral response. For the first time, here we provide electrophysiological evidence for the existence of a similar mechanism in human sensorimotor cortices. In our TMS-EEG demonstration, the N100 receives a larger contribution from already pre-activated tonic inhibitory processes recruited for the suppression of undesired MMs, indicating that being engaged in a specific motor task differently affects the ongoing background neuronal activity in the contra- and ipsilateral sensorimotor cortices.

Another aspect in the assessment of spontaneous activity in humans is to perturb

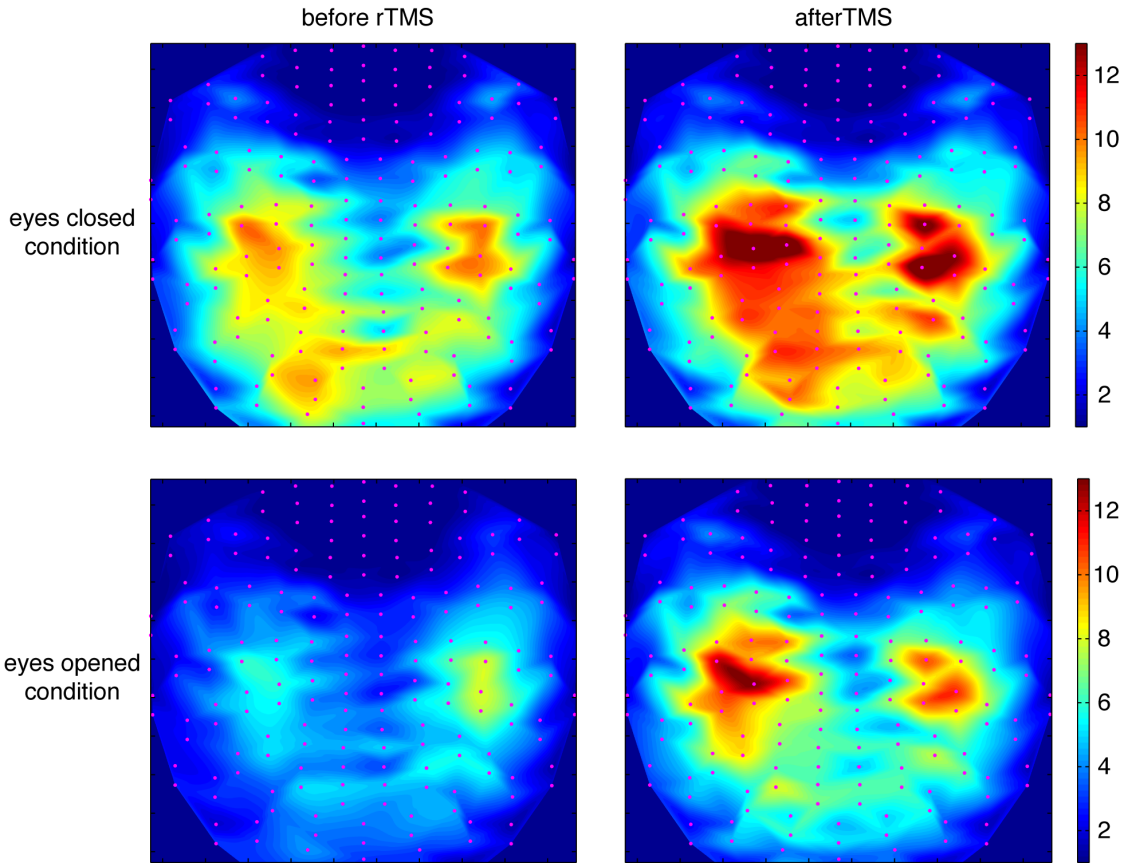

Figure 6.9: An example of changes in 22 Hz beta oscillations after rTMS treatment in one PD patient. A clear bilateral enhancement of the oscillation power over rolandic regions is visible.

its dynamics and observe the changes occurring in response to that perturbation. This approach was utilized in Publication VI, in which we investigated whether a single treatment with subthreshold rTMS to M1 affects the spontaneous cortical oscillations in PD patients. Furthermore, we wanted to explore the correlation between observed features of spontaneous oscillations and improvements in the motor symptoms of PD. A broader goal of this study was to contribute to the development of rTMS protocols that could affect specific cortical circuitry. Based on the basal ganglia–thalamocortical circuit model (Alexander et al. 1990), we targeted the network responsible for functional deafferentation of the primary motor cortex.

After two daily subthreshold rapid rate stimulations of the motor cortex in the hemisphere contralateral to the more affected limb, the total unified Parkinson's disease rating scale (UPDRS) scores were significantly improved, both after first-day and second-day treatments. Specifically, improvements were observed in rigidity and hypokinesia. Hypokinesia, however, led to significant improvement only after the second rTMS treatment. MEG beta spectral power (SP) was calculated over a broad range (14–30 Hz). Measurements performed approximately 20 minutes after the rTMS treatment showed significantly increased beta SP in Rolandic regions, as shown in Fig. 6.9.

The post-stimulation elevated power of oscillatory activity in the beta range demonstrates primarily the effectiveness of rTMS to excite thalamocortical circuits (Rothwell 2007). It has been proposed that beta oscillations are related to a resting (idling) state of the motor cortex (Pfurtscheller 1992; Stancak and Pfurtscheller 1995). The observed beta SP changes may reflect positive alterations in the abnormal synchronization of spontaneous activity generated by the thalamocortical-basal ganglia circuitry in Parkinson's disease (Pollok et al. 2004, Timmermann et al. 2003).

In contrast to studies reporting the placebo effects of rTMS (Strafella et al. 2006), the MEG results were consistent with total UPDRS motor scores, which generally improved only after the first treatment. However, no general significant correlation was detected between these two measures. Relief of rigidity suggests that beta oscillations may be related to akinetic features of PD. Because of the short duration of the measurement sessions (total approximately 2 h), it is unlikely that the observed changes could have been caused by medication withdrawal effects.

Although this is the first study investigating subthreshold TMS stimulation on the motor symptopms in PD patients, the results encourage further studies to determine optimal parameters for effective stimulation. Such parameters could include the intensity and the frequency of TMS pulses, as well as the total amount of stimulation.

6.5 Mapping precision and response repeatability

In Publication VII, the nTMS was used to determine the location and the extent of the primary motor cortical representations for preoperative surgical motor mapping. The novelty of the approach is that it combines nTMS with MEG for use in guiding subdural grid deployment, as well as subsequent comparison with results from ECS and validation by an actual surgery outcome. Furthermore, this study revisited the

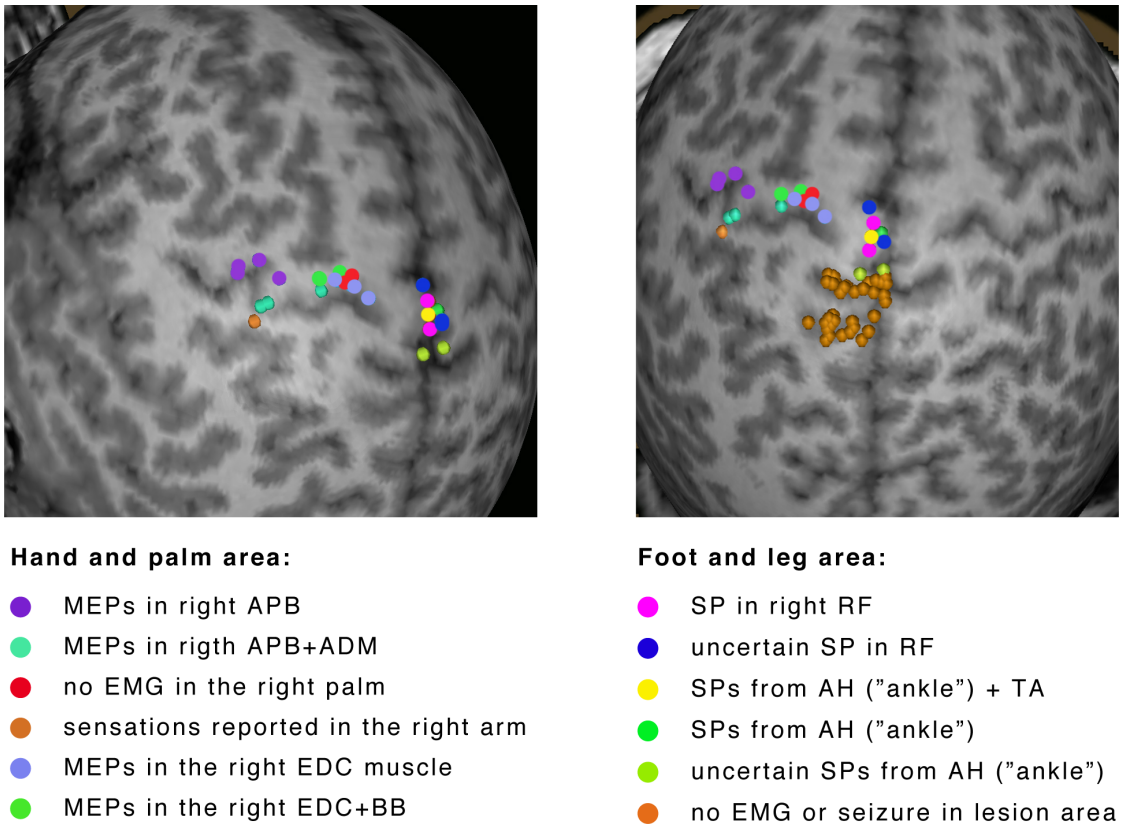

Figure 6.10: Outcome of clinical motor mapping in one epilepsy patient. Left panel (hand and palm area): lilac - MEP response from right hand APB; turquoise - MEP responses from right hand APB and ADM muscles at the same time; red - no EMG responses from the right palm (medial limit); orange - feeling sensation in the right arm reported by the patient (could not be repeated); blue - MEP response from the right extensor digitorum communis (arm); green - MEP response from the right extensor digitorum communis (arm) and biceps muscles at the same time. Right panel (foot and leg area): pink - silent period (SP) and MEP-like wave form in the EMG response from the right side rectus femoris muscle (thigh); blue - unsure SP response from the rectus femoris muscle; yellow - SP response from the abductor hallucis ("ankle") and tibialis anterior muscles at the same time; green - SP response from the abductor hallucis musle alone; light green - unsure SP response from the abductor hallucis muscle; orange - the patient had small lesion in the left medial parietal lobe, close to foot S1, visible in the 3-T MRI (lesion not shown here). Orange dots represent all the locations stimulated over the lesion area, eliciting no leg or foot EMG responses, nor any other responses or seizure activity.

safety issues in the use of single-pulse TMS for epilepsy patients - at intensities close to the MT, epileptiform or ictal EEG activity was not elicited in either of our two studied patients, even though the stimulated sites occasionally overlapped with the MEG-estimated localizations of the epileptogenic cortical region or lesion. Figure 6.10 shows the nTMS mapping results of the foot and leg cortical representations in one epilepsy patient. The orange points below the motor representations in the right panel are those points that produced no measurable response in peripheral muscles. Some of these points lie within the 'lesion' area of this patient, and are

valuable in seizure induction assessment.

This figure is especially important in terms of spatial accuracy, since it gives an impression of how accurately nTMS can distinguish the motor representations. MEG is superior to EEG in locating the interictal epileptic discharges (Shibasaki et al. 2007) and generally in satisfactory agreement with both the intraoperative localizations (for references see Mäkelä et al. 2001), and fMRI-localized primary activation areas (Korvenoja et al. 2006). However, neither MEG nor fMRI can reliably detect the extent of the motor representation provided by nTMS, thus advancing nTMS as a potentially new useful tool for preoperative surgical planning. Indeed, in this study, nTMS produced spatially more precise mapping than ECS (ECS having spatial separation limited by a 1-cm inter-electrode distance). The obtained representations were in line with MEG results adding a new dimension of reliability to the preoperative localization of the primary motor and somatosensory cortices.

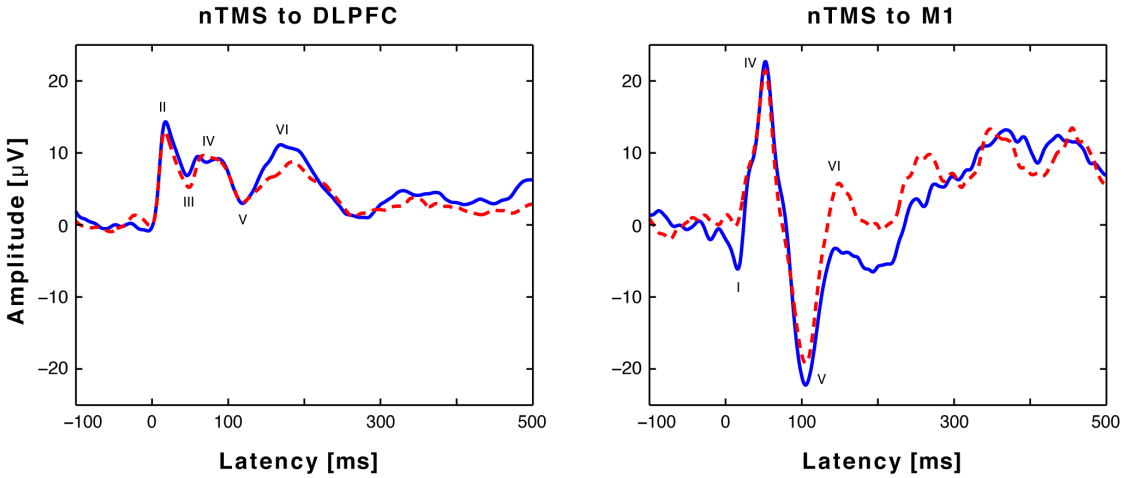

Figure 6.11: Averaged EEG TMS-evoked responses from ROI electrodes after stimulation of DLPFC (left) and the M1 cortex (right) in one subject. Note the difference in general shape of the response and higher amplitudes after stimulation of M1.

An electrophysiological extent of nTMS-based cortical mapping was done in Publication IV, which also investigated mapping precision in term of the repeatability of nTMS EEG measurements. In addition to motor cortical representations and motor threshold, the repeatability of prefrontal TMS-evoked EEG responses was assessed as well. The reproducibility of the TMS-evoked EEG responses is an essential prerequisite for studies with test-retest design. TMS evokes a specific pattern of EEG activity - averaged EEG responses after TMS to primary motor cortex were already presented in Fig. 4.2 on page 33. The amplitudes of responses demonstrated high interhemispheric asymmetry, being most pronounced in the vicinity of the stimulated site. Generally, the response amplitudes were significantly smaller for magnetic stimulation of the prefrontal cortex than M1, indicating the different reactivity of the two regions (Kähkönen et al. 2003; 2004). We have also repeated the results of previous studies by showing that subthreshold TMS to M1 elicits clear EEG responses in healthy humans (Komssi et al. 2004; Kähkönen et al. 2005).

In all subjects, six peaks from the averaged responses were identified after both M1 (right panel in Fig. 6.11) and DLPFC (left panel in Fig. 6.11) nTMS in ROIs over both hemispheres, at all three applied stimulation intensities. Amplitudes of peak II elicited by M1 nTMS, and peak VI elicited by DLPFC nTMS were less replicable than the other deflections. Caution is needed in signal analysis and interpretation of results for peak I (negativity at 15 ms), since it might be considerably contaminated with remains of the stimulus artefact. A very important result within the scope of this work is the high repeatability of both the amplitude and the latency of the TMS-evoked N100 component, enhancing its value as a marker of cortical (inhibitory) processing for both basic and clinical brain research. However, cautious interpretation of N100 results is also needed, especially when analyzing the N100-P180 complex, since it may contain a significant auditory contribution due to bone-conducted sounds (Nikouline et al. 1999). A high correlation was found between repeated measurements of motor thresholds.

7 Summary and conclusions

The main findings of Publications I–VII are:

I The combination of nTMS and EEG provides a sensitive tool for studying changes in cortical excitability related to motor preparation and execution. The increase in pre-movement cortical excitability, manifested by enlarged MEPs, is associated with an amplitude decrease in the N100 component.

II The ipsilateral hemisphere exerts inhibitory control in the human sensorimotor system during the performance of unilateral motor action.

III The attenuation of peripheral MEPs by cutaneous stimulation has its counterpart in the attenuation of the TMS-evoked cortical N100 response, thus providing further support for the cortical origin of SAI.

IV The fact that it offers high overall reproducibility of responses over both hemispheres makes the combination of nTMS and EEG a reliable tool for studies implementing test-retest designs.

V The human brain may utilize direct thalamo-cortical parallel inputs to facilitate long distance cortico-cortical connections, resulting in accelerated processing and faster reaction times.

VI rTMS in Parkinsonian patients modulates spontaneous brain activity, probably by altering cortico-thalamo-basal ganglia networks.

VII Preoperative MEG and nTMS localizations of primary motor representational areas were highly consistent with ECS results and provided improved spatial precision.

7.1 Scientific value of results

This thesis presents an integrative technological and methodological account of a multimodal approach to problems in modern system neuroscience. The most important result is the demonstration that the TMS-EEG approach might be a complementary method for evaluating the cortical effects of TMS, being the only method allowing us to measure TMS-induced neuronal activation at the millisecond time scale. We hypothesized and experimentally proved the combination of TMS with high-resolution multichannel EEG as a very precise and sensitive tool to study transient and fast changing alterations in cortical excitability related to specific functional cortical processing. The presented studies of the motor system in humans bring into focus the recordings of macroscopic cortical neuronal responses to TMS, which, in combination with peripheral measures such as MEPs, allow a more direct evaluation of the cortical excitability without additional contributions from the spinal cord processes. Additionally, we show that this approach produces highly

repeatable results - test-retest correlation of all mapped peak amplitudes ipsilateral to nTMS for both an M1 and DLPFC stimulation exceeded factor of 0.83, revealing a highly significant correlation between repeated measurements. Another very important aspect of this thesis is that it provides an electrophysiological correlate for the state dependency of TMS: the TMS effects were measured and correlated at the level of interaction between the applied stimulus and the functional states of both the central and peripheral neuronal networks under investigation. Together with co-workers, I have been able to raise and at least partially answer important physiological questions, such as which (local and remote) brain areas are affected by TMS over a particular site, or how does TMS over a particular brain area affect interconnected areas, in relation to a particular cortical processing or clinical pathology? Even though the concept of the state dependency of TMS has a very strong spatial basis, this thesis provided important answers in its temporal domain. Probing the functional cortical excitability with TMS requires delivering it at the correct time during the cortical processing of interest. Here, we demonstrated how the TMS could be effectively assisted through prior MEG imaging of the subject performing the same task that will be performed in a subsequent TMS experiment, and how the source time courses and dipole locations delineated by MEG provide precise TMS targeting at the millisecond time scale and millimetre spatial scale. The neural basis of effects induced by rTMS is likely to be very different from those of online single-pulse stimulation. rTMS has evidently a prolonged effect on brain activity, exerting effects on cortical excitability lasting for up to 30–60 minutes (Ridding and Rothwell 2007; Rothwell 2007). Considering the tremendous interest in using rTMS for clinical treatment, as well as the present trend in clinical neuroscience toward finding optimized rTMS protocols able to affect specific cortical circuitry, the new technological solutions and paradigms are more than welcome in this arena. The present thesis has explored a new technological and methodological approach for clinical assessment of rTMS-induced plastic changes in a group of Parkinson's patients (Rothwell 2007), by introducing the MEG as a far more precise temporal monitor compared to standards such as fMRI, or PET. Last but not least, another contribution of this thesis is to show that concurrent TMS-EEG can be reliably mapped outside the motor areas, in repeatable sessions. Almost all studies involving electrophysiological assessment of cortical excitability using TMS with a test-retest design will benefit from our findings, as an essential prerequisite. Response changes elicited by, *e.g.,* rTMS over the dorsolateral prefrontal gyrus in healthy subjects or patients with depression, as well as changes elicited by M1 TMS in patients with movement and degenerative disorders, can be tracked precisely in test-retest designs to gain information on the pathophysiological mechanisms of the disease.

7.2 Clinical relevance of the study and future avenues

Publication VII clearly showed the practical clinical need for detailed nTMS mapping in epilepsy patients in cases when the epileptogenic focus is located near the sensorymotor cortex, or in cases when the malformation might alter the anatomical organization of the motor representation. This brings nTMS close to one of its

potential key applications - pre-surgical mapping of the cortical areas that should be preserved (Picht et al. 2009). In addition to improved surgical planning and mapping of the motor cortical representations in a range of patient groups, nTMS might also be effectively used for non-invasive detection and verification of eloquent cortical areas that should be protected during surgery. A potentially very important clinical application might emerge from stroke neurodiagnostics. There, nTMS can be used to rapidly assess the status of the human central nervous system (central and peripheral) to reveal changes in the acute phase of a stroke. If the peripheral hand or leg MEPs could be observed and evoked by nTMS during this acute stroke phase, it might provide an indication of an elevated chance of good motor recovery (for example, Peurala et al. 2008). This very early indication of the state of the human motor system after stroke might be very useful in rehabilitation planning and follow up. Increased interest has focused on assessment and functional basis of sleep disorders, such as insomnia, restless leg syndrome, and narcolepsy. Thus far, nTMS has successfully been utilized for studying sleep by providing evidence for a breakdown of transcallosal and long-range effective connectivity during NREM sleep (Massimini et al. 2005), which was explained as a transient impairment in the brain's ability to integrate information among specialized thalamocortical modules. For example, it would be important to determine whether cortical effective connectivity recovers in part during late-night sleep, especially during the REM phase - a time at which conscious reports become long and vivid (Stickgold et al. 2001) - and relate these electrophysiological measurements to general sleep quality. Thus, probing the brain's effective connectivity directly with nTMS-EEG may become useful in determining the optimal pattern of sleep stages and contribute to better clinical assessment/therapy of sleep disorders. Finally, an important contribution of the present work is that it provides empirical confirmation of the TMS-evoked N100 component as an inhibitory process induced by the TMS, as well as several important implications for basic brain research and clinical applications arising from this knowledge. First, our findings offer a plausible neurophysiological interpretation of activity during TMS. TMS effectively activates the inhibitory interneurons whose activity is associated with a long-lasting inhibition. These evoked inhibitory processes last up to a few hundred milliseconds and reflect the activation of the GABA-B receptors (Connors et al. 1988; Werhahn et al. 1999; Tamas et al. 2003; Markram et al. 2004). GABA-B receptors can be activated by repetitive firing of interneurons or their cooperative co-activation (Tamas et al. 2003). Simultaneous activation of many neurons can be easily achieved with TMS, with the net effect being a long-lasting inhibition, such as that observed in the present experiments. Second, this thesis has opened up new possibilities for basic brain research in the study of the cortical mechanisms underlying interaction between cognitive and motor functions in the living brain. For example, one could investigate the relation between the anticipatory changes in cortical excitability (Bender et al. 2005b; Brunia and van Boxtel 2001) and the cortical inhibitory processes as revealed by the TMS-evoked N100 component. Third, the known electrophysiological data and proposed phenomenology of TMS-evoked N100 component can provide a sound basis for studies with pharmacological agents modulating GABA-B and/or GABA-A receptors.

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