Dept. of Biomedical Engineering and Computational Science

Studying the cortical state with transcranial magnetic stimulation

Hanna Mäki

Aalto University

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Studying the cortical state with transcranial magnetic stimulation

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Supervisor
Professor Risto Ilmoniemi

Instructor
Professor Risto Ilmoniemi

Preliminary examiners
Professor Christoph Herrmann, Carl von Ossietzky University, Germany
Professor Pasi Karjalainen, University of Eastern Finland, Finland

Opponent
Assistant Professor Pedro Miranda, University of Lisbon, Portugal

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Abstract

Cortical excitability and connectivity describe the state of the cerebral cortex. They reflect the ability of neurons to respond to input and the way information flows in the neuronal networks. These properties can be assessed with transcranial magnetic stimulation (TMS), which enables direct and noninvasive modulation of cortical activity. Electrophysiological or hemodynamic recordings of TMS-evoked activity or behavioral measures of the stimulation effect characterize the state of the cortex during and as a result of the stimulation. In the research reported in this Thesis, the ability of TMS to inform us about the cortical state is studied from different points of view. First, we examine the relationships between different measures of cortical excitability to better understand the physiology behind them; we show how cortical background activity is related to motor cortical excitability and how the evoked responses reflect the excitability. Second, this study addresses the questions whether the TMS-evoked responses include stimulation-related artifacts, how these artifacts are generated, and how they can be avoided or removed. Specifically, we present a method to remove the artifacts from TMS-evoked electroencephalographic (EEG) signals arising as a result of cranial muscle stimulation. The use of TMS–EEG has been limited to relatively medial sites because of these artifacts, but the new method enables studying the cortical state even when stimulating areas near the cranial muscles, especially lateral sites. Finally, this work provides new information about brain function. The mechanisms how the brain processes visually guided timed motor actions are elucidated. Moreover, we show that cortical excitability as measured with TMS-evoked EEG increases during the course of wakefulness and decreases during sleep, which contributes to our understanding of what happens in the brain during wakefulness that makes us feel tired and why the brain needs sleep. The study also shows the sensitivity of the TMS–EEG measurement to changes in the state of the cortex. Accordingly, we demonstrate the power of TMS in studying the cortical state.

Keywords transcranial magnetic stimulation, electroencephalography, electromyography, near-infrared spectroscopy

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Tiivistelmä

Aivokuoren tilaa voidaan kuvata sen reaktiivisuuden ja konnektiivisuuden avulla. Nämä parametrit heijastavat hermosolujen kykyä reagoida ärsykkeisiin ja kytkeytymistä toisiinsa, mikä ohjaa informaation kulkua hermoverkoissa. Transkraniaalisen magneettistimulaation (TMS) avulla aivokuorta voidaan aktivoida suoraan ja kajoamattomasti, mikä mahdollistaa näiden ominaisuuksien tutkimisen. Aivokuoren tilaa stimulaation aikana ja seurauksena voidaan mitata sähköfysiologisten tai verenkierrollisten rekisteröintien avulla tai tutkimalla TMS:n vaikutusta suoriutumiseen erilaisissa tehtävissä. Tässä tutkimuksessa selvitetään eri näkökulmista, miten TMS:ää voidaan hyödyntää aivotutkimuksessa ja mitkä ovat sen haasteet ja mahdollisuudet. Ensin tutkimme aivokuoren reaktiivisuuden mittareiden keskinäisiä suhteita selvittääksemme niiden taustalla vaikuttavia fysiologisia mekanismeja: näytämme miten aivokuoren tausta-aktiivisuus on kytköksissä liikeaivokuoren reaktiivisuuteen ja miten reaktiivisuus vaikuttaa TMS:n synnyttämiin vasteisiin. Toiseksi tässä työssä tutkitaan, sisältävätkö TMS:n synnyttämät vasteet fysiologisia häiriökomponentteja, jotka heijastavat muuta kuin aivotoimintaperäistä aktivaatiota, miten nämä häiriöt syntyvät ja miten ne voidaan välttää tai poistaa mitatuista signaaleista. Erityisesti esittelemme uuden menetelmän, jonka avulla TMS:n synnyttämistä aivosähkökäyrämittauksista (EEG) voidaan poistaa kallon lihasten aktivaation aiheuttamat häiriöt. Lisäksi tämä työ tuottaa uutta tietoa aivojen toiminnasta. Selvennämme niitä mekanismeja, joiden avulla aivot käsittelevät näköärsykkeen avulla ohjattuja ajastettuja liikesarjoja. Lisäksi näytämme, että TMS–EEG:n avulla mitattu aivokuoren reaktiivisuus kasvaa hereilläolon aikana ja pienenee unen seurauksena, mikä auttaa ymmärtämään paremmin sitä, miksi uni on aivojen toiminnalle välttämätöntä. Samalla tutkimus todistaa TMS–EEG-mittauksen herkkyyden aivojen tilassa tapahtuville muutoksille. Näin ollen tämä työ osoittaa, että TMS:ää voidaan käyttää menestyksekkäästi aivokuoren tilan tutkimiseen.

Avainsanat transkraniaalinen magneettistimulaatio, elektroenkefalografia, elektromyografia, lähi-infrapunakuvantaminen

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Preface

For me, the human brain is definitely the most intriguing system that exists. I have been fortunate to explore the field of neuroscience during my doctoral studies at Aalto University, Department of Biomedical Engineering and Computational Science (BECS). I am deeply grateful to the head of department, my supervisor Prof. Risto Ilmoniemi, for this opportunity. I also want to express my gratitude to Dr. Jyrki Mäkelä, the head of BioMag Laboratory, for being able to conduct the experiments with the state-of-the-art equipment.

This work would not have been possible without my colleagues and coauthors. During these years, Prof. Ilmoniemi has introduced me to the world of science and taught me scientific thinking and writing. I want to thank him for being an inspiring and supportive supervisor and a coauthor with extensive knowledge of TMS. Prof. Marcello Massimini from University of Milan, Department of Clinical Sciences, has been another mentor for me, providing the perspective of a neurologist on the TMS studies. I am very thankful for having the opportunity to visit his laboratory and to collaborate in the extremely fascinating sleep deprivation study. I also want to thank Prof. Reto Huber from the Children's Hospital, University of Zürich, for collaboration in this project.

It has been a pleasure to work and share the office with my friend Tiina Näsi. Our cooperation in the TMS–NIRS studies has been extremely efficient in all the phases of the work. I am also thankful to Dr. Petri Haapalahti for providing his expertise in blood circulation as well as to the NIRS gurus Dr. Ilkka Nissilä and Kalle Kotilahti. Dr. Irene Ruspantini and Reeta Korhonen deserve my compliments for the cooperation in the study of visuomotor synchronization.

I am happy to note that our TMS research group has come a long way since its foundation in summer 2006. For that, I want to express my gratitude to the past and present members of the group. Especially, Prof. Risto Ilmoniemi, Prof. Jukka Sarvas, Johanna Metsomaa, Julio César

Hernández Pavón, Tuomas Mutanen, and Reeta Korhonen have done excellent work in tackling the TMS-evoked muscle artifacts. Siina Pamilo deserves a special thank-you for helping to carry out a number of experiments. Our group would not be here without the preceding work done at the BioMag laboratory and the valuable advice of its TMS researchers, especially Pantelis Lioumis and Dr. Dubravko Kičić. I am also grateful to all my colleagues at BECS for making it a pleasant place to work.

I thank the preliminary examiners Prof. Christoph Herrmann and Prof. Pasi Karjalainen for taking the time to comment on this manuscript. The valuable feedback from these experts on this interdisciplinary field has further improved this Thesis.

Last but definitely not least, I want to acknowledge the support of my dearest. My beloved friends Riikka, Liisa, Maarit, Meri, Hanna, my brothers Tuomas, Miika, Teemu, and Lauri, thank you for the pleasant moments, the discussions, the adventures, and the hysterical laughs. Panu, thank you for being there during the highs and lows of this dissertation project and for the great time together. Especially, with all my heart, I thank my mom and dad for the love and support throughout my life.

Helsinki, May 26, 2011,

Hanna Mäki

Contents

List of Publications

This Thesis consists of an overview and the following Publications, which are referred to in the text by their Roman numerals.

I H. Mäki and R. J. Ilmoniemi. The relationship between peripheral and early cortical activation induced by transcranial magnetic stimulation. *Neuroscience Letters*, 478, 24–28, 2010.

II H. Mäki and R. J. Ilmoniemi. EEG oscillations and magnetically evoked motor potentials reflect motor system excitability in overlapping neuronal populations. *Clinical Neurophysiology*, 121, 492–501, 2010.

III R. Huber*, H. Mäki*, M. Rosanova, S. Casarotto, P. Canali, A. Casali, G. Tononi, and M. Massimini. Human cortical excitability increases with time awake. Submitted.

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

V T. Näsi*, H. Mäki*, K. Kotilahti, I. Nissilä, P. Haapalahti, and R. J. Ilmoniemi. Magnetic-stimulation-related physiological artifacts in hemodynamic near-infrared spectroscopy signals. Submitted.

VI I. Ruspantini, H. Mäki, R. Korhonen, A. D'Ausilio, and R. J. Ilmoniemi. The functional role of the ventral premotor cortex in a visually paced finger tapping task: a TMS study. *Behavioral Brain Research*, 220, 325–330, 2011.

* The first two authors contributed equally to these studies.

Author's Contribution

Publication I: "The relationship between peripheral and early cortical activation induced by transcranial magnetic stimulation"

The author planned and executed the experiments, analyzed the data, and interpreted the results. She is the principal writer of the article.

Publication II: "EEG oscillations and magnetically evoked motor potentials reflect motor system excitability in overlapping neuronal populations"

The author designed and conducted the experiments, analyzed the data, and interpreted the results. She is the principal writer of the article.

Publication III: "Human cortical excitability increases with time awake"

The author performed all the data analysis except the analysis of the sleep EEG. She actively participated in interpreting the results and wrote the article together with the first and last authors.

Publication IV: "Projecting out muscle artifacts from TMS-evoked EEG"

The author designed and executed the experiments and analyzed the data. She implemented the method to reduce the large muscle artifacts. She is the principal writer of the article.

Publication V: "Magnetic-stimulation-related physiological artifacts in hemodynamic near-infrared spectroscopy signals"

The author, together with the first author, designed and executed the experiments, analyzed the data, interpreted the results, and wrote the article.

Publication VI: "The functional role of the ventral premotor cortex in a visually paced finger tapping task: a TMS study"

The author planned the TMS part of the experiments. Together with the first and third authors, she conducted the experiments. She analyzed the data and participated in interpreting the results and writing the article.

List of Abbreviations

AMT	Active motor threshold
BOLD	Blood oxygen level dependent
DLPFC	Dorsolateral prefrontal cortex
DPF	Differential pathlength factor
dPMC	Dorsal premotor cortex
ECG	Electrocardiogram
EEG	Electroencephalography
EMG	Electromyography
EOG	Electrooculogram
fMRI	Functional magnetic resonance imaging
GMFA	Global mean field amplitude
HbO_2	Oxygenated hemoglobin
HbR	Deoxygenated hemoglobin
HbT	Total hemoglobin
M1	Primary motor cortex
MEG	Magnetoencephalography
MEP	Motor evoked potential
MRI	Magnetic resonance image/imaging
MT	Motor threshold
NBS	Navigated brain stimulation
NIRS	Near-infrared spectroscopy
NREM	Non-rapid-eye-movement sleep
PC	Principal component
PCA	Principal component analysis
PET	Positron emission tomography
PPG	Photoplethysmogram
Process C	Circadian component of sleep regulation
Process S	Homeostatic component of sleep regulation
PTT	Pulse transit time
PVT	Psychomotor vigilance task
rCBF	Regional cerebral blood flow
RMT	Resting motor threshold
rTMS	Repetitive transcranial magnetic stimulation
S1	Primary somatosensory cortex

SEP	Somatosensory evoked potential
SSP	Signal-space projection
std	Standard deviation
SWA	Slow wave activity
TES	Transcranial electrical stimulation
TMS	Transcranial magnetic stimulation
TSE	Temporal spectral evolution
VEP	Visual evoked potential
vPMC	Ventral premotor cortex

List of Symbols

$\mathbf{A}$	Magnetic vector potential
A_{I}	Damping of light intensity in tissue
$a_i(t)$	The amplitude of source i of muscle artifact
$b_i(t)$	The amplitude of source i of brain activity
$\mathbf{B}$	Magnetic flux density
d	EEG signal dimension
d_{SD}	Distance between NIRS source and detector
$\mathrm{d}\mathbf{l}$	Vector along the TMS coil winding
$\mathbf{E}$	Total electric field
$\mathbf{E}_{\mathrm{A}}$	Induced primary electric field
$\mathbf{E}_{\mathrm{V}}$	Secondary electric field
f_{th}	Frequency threshold
G	Background absorption and scattering of light
I	Current in the TMS coil
I_{m}	Measured light intensity
I_0	Original light intensity
$\mathbf{J}$	Induced current density
$\mathbf{J}^{\mathrm{p}}$	Primary current produced by activity of neurons
$\mathbf{J}^{\mathrm{v}}$	Volume current
$\mathbf{m}(t)$	Measured EEG signal
$\mathbf{m}_{\mathrm{corr}}(t)$	Corrected EEG signal
$\mathbf{n}(t)$	Noise
s_i	Eigenvalue of principal component i
$\mathbf{x}_i$	The topography of source i of muscle artifact
$\mathbf{y}_i$	The topography of source i of brain signal
α	Specific absorption coefficient
$\alpha_j(t)$	Time-varying amplitude of principal component j
ϵ_0	Vacuum permittivity
μ_0	Magnetic permeability in vacuum
μ_j	Principal component j
ρ	Charge density
σ	Tissue conductivity

1 Introduction

The human brain has intrigued philosophers, scientists, and the public alike for a long time. This amazingly complex system, which controls our actions and makes us conscious of ourselves and the world around us, still remains a mystery in many respects. During the past hundred years, however, we have started to gain understanding of this most intricate organ of ours, thanks to a multitude of methods revealing features of the anatomy, the connections, and the functioning of the brain. One of the most recent brain research methods is transcranial magnetic stimulation (TMS), which allows us to stimulate the cerebral cortex safely, noninvasively, directly, and in a controlled manner [14]. By examining the stimulation-evoked reactions of the brain with electrophysiological or hemodynamic recordings or with behavioral measures, we get information about the properties of the neuronal networks at the time of the stimulation: the TMS-evoked reactions inform us about the excitability and effective connectivity of the brain. TMS is a very promising method with potential applications in many areas of clinical and scientific research.

Since TMS and especially its combinations with different neuroimaging techniques such as electroencephalography (EEG) and near-infrared spectroscopy (NIRS) are relatively new, many aspects of them still need to be clarified. A thorough understanding of the methods is necessary to be able to interpret the TMS-evoked responses and behavioral changes — especially before they can be applied clinically.

The main goal of this work is to contribute to our understanding of the mechanisms of TMS and the responses evoked by it. With the insight gained, I want to provide answers to the question how powerful a method TMS is in studying the cortical state. In particular, this Thesis aims at showing the sensitivity of the combined TMS–EEG measurement to changes in the state of the brain, pointing out some remaining challenges, and presenting solutions to them. In addition, it provides new insights into how the brain functions.

1.1 Aims of the study

To elucidate the mechanisms of and relationships between different measures of cortical excitability (*Publications I* and *II*)
We aimed at a better understanding of the methods to probe cortical excitability by assessing to what extent spontaneous EEG oscillations, TMS-evoked peripheral muscle responses and TMS-evoked EEG responses reflect the fluctuations of excitability in the same neuronal population. In addition, our objective was to elucidate the physiology of the TMS-evoked responses.

To elucidate the role of sleep and the changes occurring in human neuronal circuits during wakefulness (*Publication III*)
What happens in the brain during wakefulness that causes the need for sleep is poorly known. Our objective was to show sleep- and wake-dependent changes in the cortical circuits of awake humans with TMS–EEG. By this means, we aimed at contributing to our understanding of sleep function. In addition, our objectives included demonstrating the sensitivity of TMS–EEG to study the cortical state.

To develop a muscle artifact removal method for TMS-evoked EEG (*Publication IV*)
As is shown in this Thesis, stimulation of certain parts of the head activates the cranial muscles and, consequently, produces very large muscle artifacts in the evoked EEG signals masking the brain signals. To allow probing the cortical areas in the vicinity of cranial muscles with TMS–EEG, we aimed at developing and testing the applicability of a signal processing method to remove the muscle artifacts from the signals.

To characterize stimulation-related physiological artifacts in TMS-evoked NIRS signals (*Publication V*)
The NIRS method is applied increasingly to study the changes in hemoglobin concentrations due to TMS. Our objective was to show whether the TMS-evoked NIRS signals include stimulation-related physiological artifacts due to the activation of other types of tissue than cerebral neurons. In addition, we aimed at characterizing these artifacts and elucidating their origin.

To understand the role of ventral premotor cortex (vPMC) in visually paced motor timing tasks (*Publication VI*)

Timing of motor actions is an essential skill in everyday life. Our objective was to clarify how motor timing is processed in the brain and to show that TMS is a suitable tool for studying these processes; specifically, we aimed at elucidating the involvement of the vPMC, an area thought to play a role in visuomotor transformation, in a visually paced finger-tapping task by disturbing its functioning with TMS.

2 Cerebral cortex

The cerebral cortex is the 2–4-mm-thick outermost layer of the brain containing most of the somas of the cerebral neurons. The two primary types of cortical neurons are excitatory pyramidal cells and inhibitory interneurons. Pyramidal neurons are oriented, on average, perpendicular to the cortical surface, while inhibitory interneurons do not have a preferred orientation. The excitatory and inhibitory cells form complex neuronal networks in which the information processing takes place. The cerebral cortex has an important role in higher functions such as perception, movement planning and execution, language, memory, attention, and conscious thought. Transcranial magnetic stimulation provides us the possibility to directly interfere with these and other cortical functions.

The cerebral cortex is divided into frontal, temporal, parietal and occipital lobes that contain functionally distinguished areas such as motor, somatosensory, and visual areas and a multitude of their subdivisions. The cortex is folded so that it forms grooves (sulci) and ridges (gyri). Although there are small interindividual variations, each cortical area has its typical location in terms of the sulci and gyri (see Fig. 2.1); e.g., the primary motor cortex (M1) is located on the precentral gyrus anterior to the central sulcus while many visual areas are located in the occipital lobe. The areas mainly responsible for language production and understanding, Broca's and Wernicke's areas, are located laterally: Broca's area in the inferior frontal gyrus, and Wernicke's area in the posterior part of the superior temporal gyrus. In most people, these language areas are activated more strongly in the left hemisphere.

2.1 Cortical excitability and connectivity

The electrical state of a neuron can be characterized by its instantaneous membrane potential. It depends on the net input the neuron receives

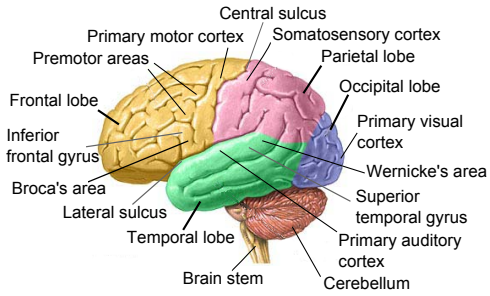

Figure 2.1: The human brain from the left: cortical lobes, cerebellum and brain stem, some sulci, gyri, and sensory, motor, and language areas. Modified from [64].

from other cells; each neuron receives both excitatory (depolarizing) and inhibitory (hyperpolarizing) signals from other neurons resulting in excitatory and inhibitory postsynaptic potentials, respectively. The net input determines the output of the neuron: if the membrane potential exceeds a certain threshold, an action potential is generated. Thus, cortical excitability is related to the membrane potential distribution of the neuronal population, as also a model for the intensity dependence of the TMS-evoked neuronal activity presented by Komssi et al. [117] suggests. Other factors affecting cortical excitability include the geometry of the stimulated tissue, such as the orientation and density of the neurons, the availability of neurotransmitters delivering signals between neurons, and the strength of synapses. The connections in the neuronal networks are modulated as a result of learning, as the strengths of the synapses are altered and new synapses are formed. In addition, the activity of neurons is fluctuating, e.g., according to the task being performed and as a function of vigilance. Excitability and connectivity describe the state of a neuronal population: excitability reflects the ability of the neurons to respond to input and connectivity is a measure of the linking between the cells. In addition to anatomical connectivity, which refers to the hard-wiring between neurons, the connectivity between two sites needs to be described in terms of effective connectivity, which reflects the transmission of signals from one brain area to another. Effective connectivity depends, e.g., on the momentary excitability of the neurons and the availability of neurotransmitters. Excitability and effective connectivity are thus closely related.

2.2 Sleep function

Many aspects of the functioning of the cerebral cortex are still to be clarified. One puzzling question is: why do we sleep? The role of sleep seems to be to restore the ability of the brain to function properly: lack of sleep causes cognitive problems (see [62] for a review) and prolonged sleep deprivation can have severe consequences such as hallucinations [13] or increase seizure risk [77]. On the other hand, sleep deprivation ameliorates depressive symptoms in some depressed patients [79]. It is not well known what happens in the brain during wakefulness that causes the need of sleep and makes us feel tired, or what is the mechanism recovering the functional capacity of the brain during sleep.

According to the two-process model [30, 31], sleep is regulated by homeostatic and circadian processes, referred to as processes S (synaptic homeostasis) and C (circadian factors), respectively. Process C regulates sleep propensity according to the time of day and is independent of preceding waking or sleep, whereas process S describes the increase in sleep propensity during wakefulness and decrease during sleep. Process S is related to EEG slow wave activity (SWA; 1–4.5 Hz spectral power) during non-rapid-eye-movement (NREM) sleep; SWA increases as a function of prior wakefulness and decreases during sleep [35, 235, 57, 58, 59]. Thus, SWA provides an electrophysiological marker of tiredness related to prior sleep and wakefulness, which can be measured during sleep. During wakefulness, EEG undergoes changes related to both processes S and C; the oscillatory activity especially in theta band (4–8 Hz) increases with the time spent awake and shows circadian modulation as well [222, 4, 5, 38, 39, 69]. These measures do not, however, explain the processes occurring during wakefulness and sleep that make sleeping necessary.

It has been hypothesized that, during wakefulness, plastic processes result in synaptic potentiation and a net increase in synaptic strength, while during sleep, synaptic depression downscales the synaptic strengths [219, 220]. According to this hypothesis, synaptic downscaling is the role of sleep, making plasticity possible; a constant increase in synaptic strength would be energetically unfavorable, require a growing amount of space, and eventually saturate the ability to learn. The sleep homeostasis hypothesis also states that slow oscillations in the membrane potentials of cortical neurons during sleep, reflected as SWA, are closely related to the synaptic potentiation: increased synaptic strength increases their

amplitude, which then decreases during the night along with decreasing net synaptic strength. Furthermore, the SWA is hypothesized to cause the synaptic downscaling. After waking up, what has been learned is still preserved in the relative strengths of the synapses, while the net strength has been scaled to a lower level for efficiency. Electrophysiological and molecular evidence from animal studies supports this hypothesis [80, 132, 231], but we lack a neuronal correlate of tiredness and evidence for the role of sleep in the synaptic homeostasis in humans. The changes in synaptic strengths are related to cortical excitability, which makes it possible to study them in humans with the combination of TMS and EEG. We took advantage of TMS–EEG to study the changes in cortical excitability as a result of wakefulness, sleep deprivation, and sleep in *Publication III*.

3 Tools for studying the cortical state

TMS modulates the functioning of selected neuronal populations directly and the reactions of the brain are measured in different ways, for example, with EEG or with methods measuring brain hemodynamics. In this chapter, TMS and its combinations with other methods to study the cortical state are presented.

3.1 Transcranial magnetic stimulation (TMS)

TMS, introduced in 1985, is a method to modulate brain function [14]. It is generally considered noninvasive, because the stimulation is mediated through changing magnetic fields, which penetrate the skull. Initially, TMS was used to test the integrity of motor pathways from M1 to the muscles. The muscle responses measured following stimulation of M1 and phosphenes (flashes of light perceived when the visual cortex is stimulated) were the only measured excitatory effects to TMS. Later, TMS has been combined with different neuroimaging techniques such as EEG [94], which measures the electrical activity of neurons with a millisecond time resolution, as well as PET [170], fMRI [22], and NIRS [165], which measure hemodynamic changes in the brain coupled to neuronal activity. These multimodal approaches have opened novel avenues in brain research; it is possible to alter brain function in a direct and controlled manner and to study the reactions of the brain to the perturbation both at the stimulated and at the interconnected sites. As opposed to sensory-evoked methods, direct stimulation allows probing the brain without peripheral contribution. The controllability means that the stimulation parameters, including the location, amplitude, and direction of the induced current can be accurately determined. With repetitive TMS (rTMS), i.e., by delivering several TMS pulses in a row to the same site, brain function can be altered for periods outlasting the stimulation [233, 41, 169]. Depending

on the stimulation frequency and duration, the effect can be excitatory or inhibitory and last for several seconds, minutes, or even longer times.

3.1.1 The physics of TMS

The mechanisms of TMS are well understood on the macroscopic level; the brain is activated through electromagnetic induction. However, although TMS has been used for more than 25 years, it is still not clear what the exact activation mechanisms are at the cellular level.

The operating principle of a magnetic stimulator is rather simple: a large capacitor is discharged through a stimulation coil when a thyristor is gated into conducting state. The current pulse $I(t)$ in the coil generates a fast-changing magnetic field $\mathbf{B}(\mathbf{r},t)$ around the coil according to the Biot–Savart law:

$$\mathbf{B}(\mathbf{r},t) = \frac{\mu_0}{4\pi} I(t) \oint_C \frac{\mathrm{d}\mathbf{l}(\mathbf{r}') \times (\mathbf{r}-\mathbf{r}')}{|\mathbf{r}-\mathbf{r}'|^3}, \tag{3.1}$$

where $\mathrm{d}\mathbf{l}$ is the vector along the coil winding C. The magnetic field penetrates the skull unattenuated and induces a primary electric field $\mathbf{E}_\mathrm{A}$ in the brain according to Faraday's law:

$$\nabla \times \mathbf{E}_\mathrm{A} = -\frac{\partial \mathbf{B}}{\partial t}. \tag{3.2}$$

The induced electric field can be expressed in terms of the magnetic vector potential $\mathbf{A}$:

$$\mathbf{E}_\mathrm{A} = -\frac{\partial \mathbf{A}}{\partial t}. \tag{3.3}$$

The electric field puts electric charges into motion. The current induced inside the brain flows parallel to the head surface and, according to Lenz's law, in the opposite direction to the rate of change of the current in the coil. The distribution of the current depends on the conductivity distribution (structure) of the brain; the induced current density $\mathbf{J}$ is directly proportional to the conductivity σ and the total electric field according to Ohm's law $\mathbf{J} = \sigma\mathbf{E}$. Because of nonuniform conductivity in the brain, the induced current produces a nonuniform charge distribution, which produces a secondary electric field $\mathbf{E}_\mathrm{V}$ according to Gauss's law:

$$\nabla \cdot \mathbf{E}_\mathrm{V} = \frac{\rho}{\epsilon_0}, \tag{3.4}$$

where ρ is the charge density.

The total electric field caused by TMS is the sum of the primary and the secondary electric fields:

$$\mathbf{E} = \mathbf{E}_{\mathrm{A}} + \mathbf{E}_{\mathrm{V}}. \tag{3.5}$$

When charge accumulates at cellular membranes so that the membranes are depolarized, neurons are activated. Simulations and experimental evidence suggest that the stimulation is most effective when there are strong electric field gradients along the longitudinal axis of the neuron [15, 76]. As a result, a neuron is most easily activated in locations where it bends or terminates [134, 9, 2]. Also electric fields perpendicular to the cell axis are able to excite the cell, but stronger stimulation is needed [196]. More accurate models for the activation of neurons are needed to better understand the mechanisms of TMS at the cellular level.

Fast changes in charge distribution are most effective in activating neurons because current leaks through cellular membranes [166, 154]. Thus, for effective stimulation, a current in the stimulation coil of several kiloamperes needs to be generated in a very short time ($\sim$100 μs), producing a changing magnetic field with a peak strength of the order of 1 T. An induced electric field of around 100 V/m about 2 cm beneath the scalp is needed to activate pyramidal motor neurons to such an extent that measurable motor responses are evoked in the target hand muscles [65, 194, 117]. Still, EEG responses to TMS have been recorded at a stimulation intensity of only 40% of the motor threshold [118], showing that the threshold for activating neurons is much lower. The effective stimulation area depends on the coil shape, which is usually round or figure-of-8-shaped. Compared to a round coil, a figure-of-8 coil produces a more focused effective stimulation area, typically a few cm^2.

The induced electric field ($\mathbf{E}_{\mathrm{A}}$) is always strongest near the surface of the head and it falls rapidly as a function of the distance from the surface (as r^{-4} in case of a figure-of-8 coil and as r^{-3} in case of a round coil). The total electric field ($\mathbf{E}$) falls off even more rapidly. Thus, superficial neurons are most effectively stimulated. Other factors affecting the stimulation efficacy include the relative orientation of the neurons and the induced current. It has been shown that neurons are more easily activated when the electric field is parallel to the cell's longitudinal axis than perpendicular to it [197, 50]. As a result, pyramidal neurons are activated most easily when the stimulus is delivered over a sulcus and the induced current

is oriented perpendicular to it [74, 34]. Other types of neurons such as inhibitory interneurons are activated as well, both directly and transsynaptically. In the case of M1 stimulation, the most effective stimulation is achieved when the induced current is perpendicular to the central sulcus between anterior and medial directions, in about 45° angle compared to the midline.

3.1.2 TMS of the motor cortex

Stimulation of M1 with appropriate parameters results in peripheral muscle activity, which can be measured with electromyography (EMG). The response seen in the EMG, called motor evoked potential (MEP), reflects the excitability of the corticospinal tract leading from the cortex to the motor neurons. Because of this easily measurable response to stimulation, TMS was earlier mostly applied on M1. Therefore, most of what is known about the neural mechanisms of TMS has been learned from M1 stimulation studies. TMS has been used clinically to study the integrity of motor pathways since its introduction.

Measurements of TMS-evoked responses after M1 stimulation in the epidural space of the spinal cord have revealed that TMS activates the pyramidal cells of the motor tract mainly transsynaptically but also directly [156, 63, 56]. The direct activation produces shorter-latency responses called direct (D) waves in the epidural recording, while the longer-latency responses due to transsynaptical activation are called indirect (I) waves. The threshold for evoking I waves is more variable than the D-wave threshold [63] and the variability of MEPs elicited by transcranial electrical stimulation (TES), which preferably evokes D waves, is smaller than that of TMS-evoked MEPs [36]. This evidence shows that the effect of TMS at the stimulation site does indeed depend on cortical excitability, which would not necessarily be the case if TMS stimulated mainly the pyramidal cell axons in the white matter.

With paired-pulse stimulation, the connectivity of the local circuitry at M1 can be probed: a conditioning pulse delivered to the M1 before the test pulse results in intracortical inhibition or facilitation, depending on the interstimulus interval and manifested as a decrease or an increase in MEP amplitude [68, 123, 226]. The MEPs are also modulated after repetitive TMS [41, 169, 233]. The effect of a conditioning pulse and preceding rTMS, both of which can alter cortical excitability transiently, show fur-

ther evidence that the effect of TMS indeed depends on the cortical state. Moreover, a conditioning stimulus delivered to the opposite M1 is much more effective in modulating the amplitude of MEP evoked by TMS, resulting mainly from indirect waves, than that evoked by TES, resulting mainly from direct waves [68].

TMS-evoked MEPs are also modulated during several actions that alter motor cortical excitability such as movement preparation [91], observation [67], and imagery [108], as well as tasks nonspecific in terms of target muscle control like sticking out the tongue and counting aloud [92], thinking emotional thoughts [221], and nonmotor linguistic tasks [167]. Studying cortical excitability modulations provides interesting possibilities to assess information processing during different tasks. For example, a TMS study [109] showed evidence for the involvement of a right-hemisphere network in self-awareness; it was demonstrated that MEPs evoked by right M1 stimulation were facilitated when subjects recognized their own face in a picture compared to recognizing other faces.

Cortical excitability probing may prove useful in the diagnosis and assessment of progression of neuronal diseases. It has been shown that motor cortical excitability as measured with TMS-evoked MEPs is altered in Alzheimer's disease, correlating with cognitive severity [51, 6, 55, 174], in multiple sclerosis as a function of the clinical stage [45], and in Huntington's disease already in its preclinical stage [202].

The excitatory effect of the stimulus manifested as MEP after M1 stimulation is followed by an inhibitory phase at least in case of M1 stimulation. This is seen as suppression of voluntary muscle activity lasting about 100 ms after the pulse [147, 1]. This so-called silent period is believed to reflect cortical inhibitory processes activated as a consequence of the cortical excitation.

MEP amplitudes in response to identical consecutive stimuli vary largely. In addition to cortical excitability fluctuations, also fluctuations in spinal excitability and varying synchronization between action potentials descending from the brain to the muscle affect the trial-to-trial variability of MEP amplitudes [136, 193].

The stimulation intensity is commonly related to the motor threshold (MT), defined as the intensity producing 5 out of 10 MEPs larger than 50 μV in amplitude. MT is usually determined during rest (resting motor threshold; RMT); when determined during slight voluntary contraction,

it is called active motor threshold (AMT). Since the contraction increases the excitability of the motor tract, AMT is lower than RMT.

3.1.3 Repetitive TMS

Delivering TMS in trains of pulses is called repetitive TMS, or rTMS. rTMS interferes with the functioning of the neurons stimulated directly and indirectly. Studying the behavioral effects of rTMS provides a way to assess various brain functions including higher cognitive processes such as language skills [168, 232], memory retrieval [141], and the sense of time [164].

rTMS can alter the excitability of the stimulated [224, 223, 81, 135] and interconnected [234, 78, 151] sites for periods outlasting the stimulation. The net effect depends on the stimulation parameters. In general, stimulation at 1 Hz leads to decreased cortical excitability [233, 41], whereas rTMS at frequencies of 5 Hz and higher tends to increase excitability [169, 135]. The stimulation-parameter-dependent modulation can be explained by the fact that the effect of each pulse depends on the state of the stimulated neuronal network, which is modulated by the preceding TMS pulses. rTMS delivered in an attempt to affect cortical function within minutes or longer from the stimulation is called offline rTMS, whereas online rTMS refers to stimulation during task performance.

The possibility of modulating brain function for longer periods suggests that rTMS could be used for therapeutic purposes. Accordingly, there has been growing interest in applying rTMS with a large number of pulses as a treatment for several disorders. High-frequency rTMS over the left dorsolateral prefrontal cortex (DLPFC) or low-frequency rTMS over the right DLPFC provides significant benefits for some patients with medically intractable depression (see, e.g., [203, 204] for a review). Although rTMS appears to be superior to sham stimulation in the treatment of depression, the response rate is relatively low and more studies are needed to test whether the treatment provides long-lasting results [125]. rTMS is also under investigation for the treatment of a number of other conditions such as auditory hallucinations in schizophrenia (see [7] for a review) and obsessive-compulsive disorder (e.g., [195]). The long-term effects of rTMS probably result from plastic synaptic changes due to repeated TMS-induced synaptic activations.

3.2 Electroencephalography (EEG)

In the 1920s, Hans Berger, the inventor of the EEG, recorded changes in the oscillatory EEG activity of the brain as the subjects opened or closed their eyes [18]. After these first noninvasive measurements of the functional state of the brain, EEG has become a popular method and is nowadays widely used in clinical studies.

3.2.1 Origins of the EEG signal

EEG measures the electrical activity of the brain with a temporal resolution of the order of milliseconds by electrodes placed on the scalp. Synchronized activity of groups of similarly oriented (i.e., pyramidal) neurons can be recorded as electric potential difference changes on the head surface. The electric field produced by action potentials, which behave as current quadrupoles [177], falls off rapidly as a function of distance (r^{-3}), whereas that produced by postsynaptic potentials behaving as current dipoles falls off less rapidly (r^{-2}). As a result, action potentials, which are also very brief (1–2 ms) and lack synchrony, are not easily detected with EEG. Thus, EEG signals reflect mainly the slower (10–200 ms) postsynaptic potentials, both excitatory and inhibitory, generated in pyramidal neurons when they receive input from other neurons [114, 46, 47]. Because of this relatively slow synchronous postsynaptic activity of neurons and the difficulty in detecting the high-frequency action potentials, information about neuronal activity in the EEG signal is mainly restricted to frequencies below 100 Hz.

Activation of neurons produces a primary current $\mathbf{J}^{\mathrm{p}}(\mathbf{r})$ mostly inside and in the vicinity of the neuron, which affects the charge distribution and produces an electric field $\mathbf{E}(\mathbf{r})$. The return current, also called volume current, $\mathbf{J}^{\mathrm{v}}(\mathbf{r})$, flows passively in the conducting medium and is generated as a result of $\mathbf{E}(\mathbf{r})$:

$$\mathbf{J}^{\mathrm{v}}(\mathbf{r}) = \sigma \mathbf{E}(\mathbf{r}). \tag{3.6}$$

EEG measures the changes in potential V between measurement points 1 and 2 associated with $\mathbf{E}(\mathbf{r})$:

$$V_{1,2} = \int_1^2 \mathbf{E}\left(\mathbf{r}\right) \cdot \mathrm{dl}. \tag{3.7}$$

In contrast to the good temporal resolution, the spatial resolution of EEG is compromised because the volume conductor effects, i.e., the inhomogeneous electrical conduction properties of the tissue, blur the potential distribution seen on the scalp; especially the skull, which has much lower conductivity than other tissues, makes a significant contribution.

EEG can be used to measure the spontaneous activity of the brain or evoked potentials. Evoked potentials reflect the activity associated with and time-locked to stimuli or other events. Spontaneous EEG signals show oscillations at various frequency ranges including delta (1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz), and gamma (30–60 Hz), which have a characteristic distribution over the head and reflect synchronous activity of neuronal networks; in other words, synchronous fluctuations in the membrane potentials of groups of neurons. Spontaneous oscillations are often considered to indicate idling states of brain areas. In healthy adults, delta oscillations are only seen during slow wave sleep and theta oscillations are related to drowsiness and lapses in vigilance [222, 38, 138]. Posterior alpha oscillations are associated with a resting state of visual areas [3]; they emerge when eyes are closed or during relaxation. Alpha and beta oscillations measured over the sensorimotor cortex (also called Rolandic alpha and beta oscillations according to their origin in the Rolandic fissure, i.e., the central sulcus) reflect idling states of the somatosensory and motor cortices, respectively [122, 101, 175, 199, 213, 188]. On the contrary, for example gamma and frontal beta oscillations are associated with increased activation, as they can be measured during some cognitive tasks.

An EEG system amplifies the voltage measured between each electrode and a reference, filters the signals to prevent aliasing, and converts the analog signal to digital form. Conducting paste is used to create a contact after scraping the skin in order to reduce its impedance. The electrodes are often attached to an elastic cap to facilitate their positioning.

3.2.2 TMS-evoked EEG

The introduction of TMS-compatible EEG devices has greatly expanded the possibilities to probe the cortical state with TMS. Like neuronal activity evoked by sensory stimulation, also activity elicited by and time-locked to TMS can be measured with EEG [94]. In addition to enabling cortical excitability probing in areas other than M1 [48, 71, 107, 106, 142, 191],

TMS–EEG also provides the chance to study cortical connectivity by examining the signals arising from areas connected to the stimulated area [116]. For example, the breakdown of cortical effective connectivity during sleep was demonstrated with TMS–EEG [142]. With paired-pulse stimulation and EEG, intracortical inhibition and facilitation can be studied at brain sites other than M1 as well [48, 71]. When the stimulation is targeted with an MRI-guided neuronavigation system, responses averaged over trials are highly repeatable between similar experiments performed on the same subject [130, 40]. The repeatability enables reliable studies of treatment or other effects on TMS-evoked EEG responses.

Combining TMS with simultaneous EEG is challenging because TMS induces currents in the electrode leads. This type of electromagnetic artifact can be eliminated with an EEG system using gain-control and sample-and-hold circuits [230] or largely reduced by slew-rate-limited amplifiers that do not become saturated during the pulse [95]. TMS also sets special requirements for the electrodes so that they will not overheat or move as a result of forces due to induced currents. Even when using a TMS-compatible EEG system, electromagnetic artifacts can arise: especially with high stimulation intensities and bad electrical contacts, the electrode–electrolyte interface may polarize, which produces a baseline shift and an exponentially decaying artifact lasting tens of milliseconds.

In addition, stimulation of the lateral parts of the head and areas near the neck or forehead activates the cranial muscles, which produces an artifact lasting tens of milliseconds and masking the early components of the evoked EEG signal. Examining brain areas near cranial muscles with TMS–EEG has been restricted, because the early components of the evoked signals are of greatest interest with respect to cortical excitability and connectivity. Even though there are no muscles over the motor cortex, temporal scalp muscles of some subjects may still be activated during M1 stimulation depending on the individual motor threshold and anatomy; if the coil location, orientation and stimulation intensity required to activate the pyramidal cells controlling the target muscle are also favorable in terms of cranial muscle stimulation, muscle artifacts may arise. Nonetheless, EEG signals without or with only moderate muscle artifacts have been successfully recorded following stimulation of the M1 [94, 116, 117, 66, 118, 160, 172, 112, 21], the dorsolateral prefrontal cortex [107, 106, 105, 130], the primary somatosensory cortex (S1) [183], premotor areas [142, 191], the parietal cortex [191], and the asso-

ciative visual area [191]. To enable studying brain areas near the cranial muscles, a method to reduce the large muscle artifacts was developed in *Publication IV*.

The stimulus is accompanied by a loud click as a result of electromagnetic forces in the coil, which produces an auditory response in the EEG signal [158, 218]. Part of the sound is conducted through air and part through the skull [158]. The auditory response can be reduced with hearing protection, although it is usually not sufficient to completely block the sound. A more efficient way to prevent the perception of the click is to play masking noise from headphones [172, 142, 75]. In addition, a thin piece of foam plastic can be placed between the coil and the head to reduce the conduction of coil vibrations to the head and thus the bone-conducted sound [142].

TMS–EEG is a tool with great potential, since cortical excitability and connectivity are altered in a range of circumstances. For example, TMS-evoked EEG responses are modulated by a conditioning TMS pulse [48, 71], rTMS [66], movement preparation and execution [29, 160, 112], cutaneous stimulation [21], the sleep or waking state [142], and the intake of alcohol [104]. Thus, TMS–EEG might have a wide variety of clinical and scientific applications, e.g., monitoring the effect of pharmaceuticals, diagnosing different neuronal diseases, and studying the involvement of different brain areas in cognitive tasks.

TMS-evoked EEG responses vary between subjects, stimulation and electrode sites, and experimental conditions. Fig. 3.1 shows a typical averaged EEG response following M1 stimulation measured between an electrode near the stimulation site and a reference electrode behind the contralateral ear. The deflections are named according to their polarity (negative = N, positive = P) and typical latency in milliseconds. N15 possibly reflects activation of the premotor cortex on the stimulated (ipsilateral) hemisphere [66, 131]. The estimated origin of P30 is inconsistent between different studies, as it has been suggested to reflect activity around ipsilateral sensorimotor/premotor cortex border [66], in the superior wall of the ipsilateral cingulate gyrus or in the supplementary motor area [131], and in the nonstimulated (contralateral) cortex [116]. The N45 component is believed to reflect activity in the ipsilateral sensorimotor cortex [172, 66]. Unless proper hearing protection and auditory masking are used, part of the N100–P180 complex is a result of the auditory stimulation [158, 218], but N100 is also believed to reflect inhibitory mech-

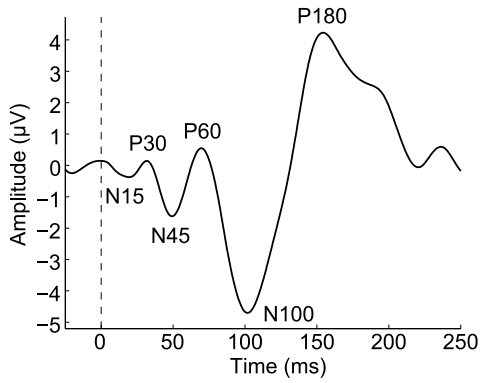

Figure 3.1: A typical TMS-evoked EEG response after M1 stimulation measured with one channel near the stimulation site referenced to an electrode behind the contralateral ear. The deflections are named according to their polarity and typical latency.

anisms in the cortex as it is attenuated during movement preparation [160, 17]. This interpretation is supported by the coincidence of N100 in time with the long intracortical inhibition [226], the silent period [147, 1], and long-lasting inhibitory postsynaptic potentials [121, 192]. As the conduction time between the cortex and small hand muscles is about 20 ms, in case of M1 hand area stimulation with intensities at or above the motor threshold, components peaking approximately 40 ms after the stimulus and later may be affected by the somatosensory responses arising from S1 and higher somatosensory areas as a result of the target muscle activation. Moreover, signals around 30–40 ms after the stimulus may be slightly affected by somatosensory components (P9 and P14) originating in subcortical structures, although these components are spatially too widespread to be easily detected when the reference electrode is placed on the head [126].

TMS–EEG studies suggest that also subthreshold stimulation can evoke activation spreading to distant cortical areas: stimulation of the premotor cortex at 90% of MT [142] and subthreshold stimulation of the M1 and the visual cortex [94] produced activation spreading to the contralateral hemisphere, and intensities as low as 60 or even 40% of MT produced measurable responses to TMS of the M1 [117, 118], including deflections believed to originate elsewhere than in M1. There is evidence that auditory stimulation alone does not explain the responses to subthreshold TMS of the

M1: responses to stimuli at different intensities recorded with and without auditory masking did not differ markedly [117]. In addition, when hearing protection suppressed the air conduction of the sound, stimulation with the coil against the head and raised above the head with intensities producing an electric field of similar strength in the brain produced similar responses [118]. In this context, it has to be taken into account that the motor threshold may not describe the excitability of other brain areas sufficiently, because the distance between the head surface and the cortex, cortical folding, and neuronal level structure vary between areas. Thus, the stimulation of other brain areas with intensities below the motor threshold may have a different effect than the stimulation of the M1 with the same intensities.

3.3 Relationships between measures of cortical excitability

As spontaneous EEG oscillations, TMS-evoked MEPs, and TMS-evoked EEG responses all reflect cortical excitability, they might correlate. The relationships between different measures of cortical excitability have been assessed in a few studies with controversial results.

Even though spontaneous alpha-frequency oscillations measured over the sensorimotor cortex are expected to reflect somatosensory rather than motor cortical state [199, 213, 188], in some studies, prestimulus Rolandic alpha power measured with EEG, but not beta power, has been found to correlate negatively with TMS-evoked MEP amplitudes measured from a resting small hand muscle [240, 200]; larger-amplitude alpha oscillations are associated with smaller-amplitude MEPs and vice versa. Considering the numerous anatomical connections and functional relevance of interplay between sensory and motor areas, the correlation is not surprising. On the contrary, in another study, negative but nonsignificant correlation coefficients were reported between Rolandic alpha power and MEP amplitudes with the target muscle in rest, as well as during movement observation, imagery and execution, while an exploratory analysis (not corrected for multiple comparisons) suggested a relationship between Rolandic low-to-midrange beta (12–18 Hz) oscillations and MEP amplitudes in the rest and execution conditions [128]. During a precision grip task known to promote Rolandic beta oscillations, no significant correlation was found between beta oscillations and MEPs [148].

A similar approach has been taken to study the relationship between posterior prestimulus alpha oscillations and phosphene perception following TMS delivered to visual areas. During periods of low-amplitude alpha EEG oscillations, the probability for perceiving a phosphene was higher than during periods of high-amplitude alpha oscillations [189]. In addition, the individual threshold for evoking phosphenes correlated with the individual posterior alpha oscillation power [190].

The relationship between MEP amplitudes and spontaneous EEG oscillations at different frequencies measured above different brain areas was studied in *Publication II*. Although the relationship between MEP and spontaneous oscillation amplitudes has been studied before, the previous controversial results require further clarification. In addition, considering that spontaneous oscillations reflect alterations in the membrane potentials and thus the excitability of groups of neurons, also the phase of oscillations might be related to evoked responses [115]. To our knowledge, *Publication II* is the first study addressing the relationship between MEP amplitudes and spontaneous oscillation phase. In addition, analogously to [190], the relationship between individual motor threshold and individual average oscillation amplitude was studied in *Publication II*.

TMS-evoked MEP and EEG responses can be assumed to correlate when stimulus strength is altered between stimuli, for example, by changing the stimulation intensity or moving the coil so that the neurons experience a different electric field. However, even if the stimulation parameters stay virtually the same, a correlation can still be expected; during periods of high excitability of the target neurons, both MEP and EEG responses are likely to be larger than during periods of low excitability. In one study, a significant correlation was shown between MEP and N100 amplitudes [172], whereas in another study no such relationship was found [160]. N100, like any other component measured more than 40 ms after M1 hand area stimulation, may include a somatosensory component resulting from target muscle contraction. Thus, the early deflections including N15 and P30 (see Fig. 3.1) in the evoked EEG serve as more direct measures for studying the excitability of the stimulated area. Nonsignificant correlation coefficients r = 0.13 and r = 0.46 were reported between the average amplitude of MEPs and the average amplitude of N15 and P30 deflections, respectively, using the average values of five series of responses of all the six subjects averaged over 100 trials and all the 19 channels [28]. To our knowledge, the correlation between MEPs and the early deflections of the

TMS-evoked EEG response has not been studied before at the single-trial level within subjects. This relationship was assessed in *Publication I*.

The relationship of EEG oscillations with evoked responses or with perception has also been studied with sensory stimulation modalities. In most studies, as expected, a negative correlation has been found between oscillation amplitudes and evoked responses including visual evoked potentials (VEP) [32, 180], somatosensory evoked potentials (SEP) [176], and auditory evoked potentials [181] or between oscillation amplitudes and visual perception [217, 88, 227]. In some studies, oscillation amplitudes have been reported to correlate positively with VEP [33] and SEP [159]. In addition, a positive correlation was found between optical signals reflecting the prestimulus membrane potentials of a neuronal population and visually evoked local field potentials [11]. This positive correlation is not, however, comparable to the aforementioned findings in studies of spontaneous oscillations and evoked responses; rather than reflecting the oscillations in the background activity, these optical signals reflect the instantaneous membrane potentials of neurons and are thus more closely related to oscillation phase. With this type of optical imaging, a positive correlation is actually expected as higher membrane potentials indicate higher excitability.

Also the relationship between spontaneous oscillation phase and evoked responses has been studied with sensory stimulation. The traditional approach is to average the evoked responses over trials with the prestimulus oscillation in a certain phase and compare the evoked responses between phase groups. The problem with this kind of analysis is that the background oscillations will not average to zero, but instead affect the evoked responses. A similar problem occurs when prestimulus oscillation phase is estimated using Fourier or wavelet transform with the poststimulus data included: the poststimulus data affects the estimated phase and misleading correlations may be detected [139]. No relationship was found between prestimulus alpha phase and VEP when these problems were avoided with methods to subtract the ongoing activity from the evoked responses [113, 187], but visual perception was shown to depend on occipital alpha phase [37, 143].

The correlations between different measures of cortical excitability are only likely to apply within some limits; for example, the expected negative correlation between oscillation and evoked response amplitudes does not

extend to a situation where both are (close to) zero, such as in case of a severe brain injury.

3.4 Hemodynamics-based neuroimaging

Neuronal activity increases the need for oxygen and nutrients in the active cells and, consequently, blood flow is increased at the activated areas through a mechanism called neurovascular coupling, which is not understood in all the details. The increased consumption of oxygen is overcompensated by the increased blood flow so that the concentration of oxygenated hemoglobin (HbO_2) and total hemoglobin (HbT) increases and the concentration of deoxygenated hemoglobin (HbR) decreases at the site of activation. This so-called hemodynamic response is slow compared to neuronal activity, reaching its peak about 5 s after the onset of the activation and returning even more slowly back to baseline, typically in less than half a minute. The hemodynamic response reflects postsynaptic activity rather than action potentials [144, 133]. Hemodynamics-based neuroimaging methods reflect the neuronal activity indirectly by measuring the changes in blood flow or hemoglobin concentrations. For example, fMRI is based on a blood oxygen level-dependent (BOLD) signal, related to the decreased HbR concentration, while PET measures changes in regional cerebral blood flow (rCBF).

The BOLD response is in many cases positive, reflecting a typical hemodynamic response during which the HbR concentration decreases. In many studies, however, negative BOLD responses (increasing HbR concentration) and decreased rCBF have been reported [54, 85, 207]. This kind of responses have been suggested to result from inhibition of neuronal activity at the brain areas in question [182]. A competing hypothesis proposes that the negative responses are of vascular and not neuronal origin, resulting from the increased need of blood flow in other parts of the brain [89]. One reason why this subject is still under debate is that inhibition mediated through synaptic activity demands blood flow increase [102]. However, even though inhibition requires activation of inhibitory neurons, the net synaptic activity within a brain area may decrease. Indeed, growing evidence suggests that inhibited neuronal activity can produce negative hemodynamic responses (e.g., [210, 206]).

3.4.1 TMS-evoked fMRI and PET

TMS combined with hemodynamics-based neuroimaging techniques enables the study of the vascular response of the brain to the stimulation. These combinations of methods can, e.g., shed light on neurovascular coupling and its malfunctions in some diseases [93]. Because the evoked hemodynamic responses to single TMS pulses are relatively weak, rTMS trains have been used in most studies, although BOLD responses to single pulses have been reported as well [27, 86].

TMS–fMRI and TMS–PET studies have shown modulation of blood flow and oxygenation at the stimulated and interconnected sites, elucidating the local hemodynamic effects of TMS and connectivity patterns between brain areas. Generally, TMS–fMRI studies have shown BOLD signal increases at the stimulated motor cortex with suprathreshold intensities [27, 26, 25, 23, 16, 19, 20, 53, 111, 86], while responses to subthreshold stimulation have not been detected at the site of stimulation [24, 16, 19, 20]. The increases as a response to suprathreshold stimulation of M1 may at least partly result from the somatosensory feedback due to the contracting target muscle [16, 19]. Following M1 stimulation, on the contralateral M1, both BOLD signal decreases [19, 20, 53, 111] and increases [155, 23, 27] have been reported. TMS–PET studies have mostly shown increased rCBF at the site of the stimulation with both sub- and suprathreshold intensities [72, 170, 208, 211, 212, 73], while decreased rCBF has been reported as well [171]. On the contralateral hemisphere, rCBF has been found to decrease [72, 212, 73].

In the TMS–fMRI literature, it has been proposed that subthreshold stimulation would not be able to evoke activity at remote sites, but the response seen at interconnected sites evoked by subthreshold TMS would result from altered pattern in the ongoing activity due to the changed excitability of the stimulated area [20]. One evidence suggested to indicate this is the reported higher threshold for inducing transcallosal inhibition compared to the motor threshold: in one study, half (3) of the subjects had a transcallosal inhibition threshold comparable to MT, and half (3) needed a conditioning pulse at around 120% of MT to induce inhibition [68]. This evidence is not sufficient, however, to draw conclusions about the relative thresholds for exciting different neuronal populations: the optimal stimulation parameters between transcallosal and other types of cortico-cortical or cortico-subcortical neurons may vary and the stimulation parameters

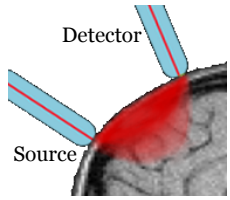

Figure 3.2: Propagation of near-infrared light in the tissue.

in [68] may not be optimal for inducing inhibition. In addition, evidence from TMS–EEG studies shows spread of activation to interconnected sites following subthreshold TMS (Chapter 3.2.2). The distant hemodynamic changes recorded following TMS may thus reflect the TMS-evoked activity mediated by cortico-cortical neurons between the stimulated and the interconnected sites.

3.4.2 Near-infrared spectroscopy (NIRS)

NIRS utilizes near-infrared light to measure hemodynamic changes in the brain. The light, transmitted to the tissue via an optical fiber placed on the scalp, is absorbed and scattered in the tissue. Because of the strong scattering, light that has traversed the tissue can be measured with a detection fiber placed a few centimeters apart from the source (Fig. 3.2). If NIRS signals are recorded with several source–detector pairs, topographic information of brain activity can be extracted.

HbO_2 and HbR have different absorption spectra, so when light at two different wavelengths is used, the hemoglobin concentration changes can be derived from the modified Beer–Lambert law

$$A_{\mathrm{I}} = \log_{10} \frac{I_0}{I_{\mathrm{m}}} = (\alpha_{\mathrm{HbO_2}} \cdot c_{\mathrm{HbO_2}} + \alpha_{\mathrm{HbR}} \cdot c_{\mathrm{HbR}}) \cdot d_{\mathrm{SD}} \cdot \mathrm{DPF} + G \qquad (3.8)$$

written separately for both wavelengths, where A_{I} is the attenuation of the measured light intensity I_{m} compared to the reference intensity I_0, c_i and α_i are the concentration and the specific extinction coefficient of hemoglobin type i, d_{SD} is the distance between the source and the detector, DPF is the differential pathlength factor, i.e., $d_{\mathrm{SD}} \cdot$ DPF gives the mean pathlength traveled by photons in the tissue, and G describes the background absorption and scattering.

All the light travels through the surface tissue (Fig. 3.2), which makes NIRS susceptible to interference due to changes in superficial circulation. These changes are typically systemic and may be related to the brain activation triggering event. Common methods to separate the surface component utilize the fact that NIRS channels with different source-to-detector distances measure the contribution of superficial and brain signals in different proportions [70, 198, 241] or that systemic changes are seen in all the measurement channels [242, 229].

3.4.3 TMS-evoked NIRS

The combination of TMS and NIRS is advantageous compared to TMS–fMRI and TMS–PET in some regards: With TMS–NIRS it is possible to calculate both HbO_2 and HbR concentrations, NIRS measurement is not disturbed by TMS electromagnetically, the time resolution is good enough to obtain the shape of the hemodynamic response, and the subjects are not exposed to ionizing radiation. In addition, NIRS can be used for long-term monitoring of TMS effects.

TMS-evoked hemodynamic changes have been measured with NIRS following stimulation of M1 [165, 149, 150, 163, 161, 97, 83, 120, 216], DLPFC [10, 120, 87], dPMC [149], as well as the anterior frontal region [165]. The signals have been measured above the stimulated (ipsilateral) [165, 150, 163, 83, 216] or contralateral [149, 161, 97, 87, 10] hemisphere, or bilaterally [120]. On the stimulated hemisphere, both increases [165, 150, 163] and decreases of HbO_2 [83, 120] as well as decreases of HbT and HbR concentrations [149] have been reported. The differences cannot be clearly attributed to the stimulation parameters, since single-pulse stimulation [150, 163, 150] and relatively low-frequency (0.25–2 Hz) rTMS [165, 83, 120] have induced both ipsilateral signal increases and decreases. Neither the stimulation intensities show a consistent effect on the NIRS responses. Thus, based on the TMS–NIRS studies, it is unclear how TMS affects brain hemodynamics. In contrast, mostly HbO_2 decreases have been measured on the contralateral hemisphere [149, 97, 87, 120, 10], while in one study, increased absorption, plausibly reflecting increased HbT concentration, was detected [161].

NIRS signals may contain artifacts due to altered surface circulation, and TMS-evoked NIRS is no exception. Quite the contrary, TMS induces currents in all the excitable tissues under the coil and the induced electric

field on the surface is stronger than further away from the coil: TMS may induce local circulatory changes unrelated to cerebral neuronal activity near the stimulation site, which can be reflected in the NIRS signals. The excitable surface tissues include cranial and arterial muscles as well as the nerves innervating them. In addition to surface effects, TMS might also activate vascular smooth muscles and sympathetic nerve fibers in the brain. The role of stimulation-related artifacts in TMS–NIRS signals has not been studied before; it is possible that some of the reported hemodynamic changes do not reflect the hemodynamics related to cerebral neuronal activity but rather the local direct effects of TMS on circulation. These artifacts were studied in *Publication V*.

3.5 Finger-tapping tasks and TMS in motor timing studies

Temporal information is crucial in sensory processing such as speech recognition and motor coordination. How the human brain processes time in the 10–1000-ms range required in these tasks is not well known. Earlier work suggested the existence of a centralized clock (see, e.g., [8]), but a lot of experimental data support the view that temporal processing is distributed across different neuronal structures (see [145] for a review) depending on the context [100]. It has also been suggested that, rather than engaging specialized mechanisms, timing is an inherent property of neuronal function, bound to the processing of neuronal signals [145].

Timing is an essential component of motor function, which requires fine-tuned sequential contractions of different muscles and adaptation to sensory information. The mechanisms of motor timing at a subsecond time scale have been studied with finger-tapping tasks in which subjects either have to synchronize their tapping rate to an external pacer or to perform the tapping in the absence of a pacer. Neuroimaging and lesion studies have shown the involvement of a network of areas including the cerebellum [96, 173] and parietal, premotor, and supplementary motor areas [236, 98] in these tasks.

TMS, being able to temporarily distract brain function, is a potential tool for studying the functioning of this network. Single TMS pulses administered to M1 during the tapping was shown to increase intertap-interval variability [228] and to alter movement kinematics without the subjects noticing [129]. In addition, offline rTMS to M1 distracted the synchrony

between the taps and the external pacer [61] and decreased the maximal tapping speed [99]. The intertap-interval variability was increased also after rTMS to the cerebellum [52, 215] and to the left dPMC [52], and offline rTMS to dPMC [179] and superior temporal–parietal area [140] affected the synchronization accuracy, supporting the view that these areas are involved in the networks processing timed motor actions.

Whether the ventral and dorsal aspects of the premotor cortex have different roles in motor timing tasks has not been studied extensively and the few results are partly contradictory. Especially, the role of vPMC has not been elucidated. Based on an MEG study, it has been suggested that vPMC is mainly activated when the subjects synchronize their tapping to a visual pacer, while dPMC is more involved with tasks including an auditory pacer [178]. Supporting this finding, one study with offline rTMS on vPMC failed to show a significant effect on performance in an auditory-cued tapping task [140]. On the contrary, other evidence based on fMRI measurements during finger tapping proposes that vPMC is more strongly engaged during auditory than visual cueing while there is no difference in dPMC activation between the modalities [98]. In general, dPMC is thought to receive a combination of sensory information of different modalities to guide motor actions, while vPMC is considered to be more involved in utilizing visual information required for hand movements and in observation–execution matching (see [42] for a review). In *Publication VI*, the roles of vPMC and dPMC were studied by perturbing these areas during a visually guided finger-tapping task with online rTMS.

4 Methods

The EEG (*Publications I–IV*), EMG (*Publications I–II*), and NIRS (*Publication V*) signals were recorded continuously. The measurement was controlled with a computer sending triggers to each device allowing analysis of synchronous events in each signal. The subjects were instructed to keep their eyes open and hands relaxed (*Publications I–V*) or to perform a task (*Publication VI*) during the stimulation. In studies *I, II*, and *IV–VI*, the subjects participated in a single stimulation session, whereas in study *III*, the subjects participated in stimulation sessions during a baseline day after normal sleep, after one night of sleep deprivation, and after a night of subsequent recovery sleep.

4.1 TMS

In *Studies I–II*, TMS was targeted at left M1 hand area in order to evoke MEPs in the target muscle. The left M1 hand area was also stimulated in *Study V* to evoke NIRS responses comparable to most published TMS–NIRS studies. In addition, in *Study V*, TMS was delivered to the left shoulder to elucidate the role of stimulation-related hemodynamic changes not related to cerebral neuronal activation. As stimulation of Broca's area is known to evoke large muscle artifacts in the EEG signals, TMS was targeted there in *Study IV*, where a method to remove those artifacts was studied. In *Study III*, TMS was applied to a frontal (superior frontal cortex/supplementary motor area, Brodmann area 6/8) site to measure the changes in the evoked EEG responses as a function of previous wakefulness and sleep; since the frontal cortex has a significant role in sleep physiology [69], it was chosen as a target to emphasize the sleep-induced changes. In *Study VI*, the vPMC, the dPMC as a functionally related control, and another control site (above the interhemispheric sulcus where

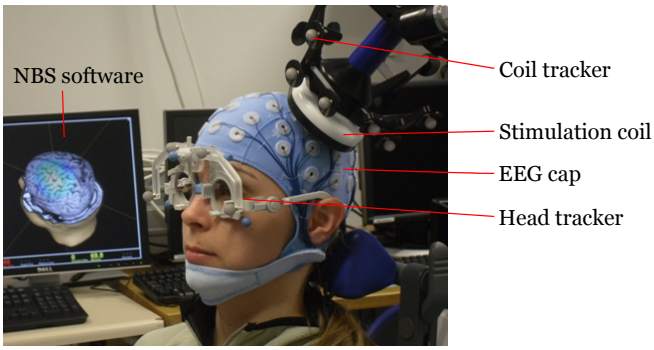

Figure 4.1: Trackers and visualization of the tracking in the NBS software.

the central sulci end) were stimulated with the aim of elucidating the role of the vPMC in finger-tapping tasks requiring visuomotor transformation.

TMS was delivered with a Nexstim eXimia stimulator (Nexstim Ltd., Helsinki, Finland) and its figure-of-8 coil, which produces a relatively focused effective stimulation area of a few cm^2. Stimulation targets were chosen from the individual magnetic resonance images (MRI) according to anatomical landmarks. The stimulation was targeted above and perpendicular to a sulcus to optimally activate the pyramidal neurons in all the experiments, except when the control site in *Study VI* was stimulated (current directed anteriorly). In *Studies I, II*, and *V*, the coil position was further adjusted to maximize the MEP amplitudes measured from the targeted small hand muscle. MRI-based targeting was done with Nexstim eXimia navigated brain stimulation (NBS) system. Trackers equipped with reflecting markers attached to the coil and the head reflect infrared light emitted from and measured with a tracking unit. After registering the position of the head with respect to the head tracker, it was possible to track the relative position of the head (brain) and the coil in real time. Coregistration of the head and MRI was done by pointing at sites on the head surface chosen from the MRI with a tracker pen also seen by the tracking unit. Fig. 4.1 shows parts of the tracking system.

The NBS software calculates the induced electric field in the brain with the spherical head model, allowing the investigator to see in advance which brain areas are stimulated. As the spherical head model assumes homogeneous conductivity inside the brain, inhomogeneities in brain conductivity result in small inaccuracies in the estimate of the stimulation

site. The position of each reflecting marker is tracked with an accuracy of about 0.5 mm, but the precision of the targeting is also affected by errors in coregistration of the head and the MRI and possible movements of the head tracker with respect to the head. Provided that head tracker movements are carefully avoided, the accuracy within an experimental session is probably better than between sessions when a new coregistration is needed. The software records the position of the coil with respect to the head at the time of each stimulus. The coil position was tracked with the NBS system during the experiments and stimuli were only delivered when the coil location deviated less than 2 mm from the initially defined site. Accurate and reproducible positioning of the coil was important in all the experiments, but especially in *Studies I–III*; keeping the coil position as constant as possible reduced variations in brain reactions due to stimulus-related factors, which might mask the effect of changes in cortical excitability on the evoked responses.

Several single TMS pulses were delivered in *Studies I–IV* to obtain the TMS-evoked EEG response as an average over the trials, while in *Studies V* and *VI*, online rTMS was applied. Since NIRS responses to single pulses may be very hard to detect, 8-s trains of pulses at 0.5, 1, and 2 Hz were delivered to evoke measurable hemodynamic changes. In *Study VI*, three pulses at 5 Hz were delivered every fourth finger tap interval to disrupt cortical processing related to the tapping task.

The stimulation intensity was chosen based on the individual motor threshold of each subject (*Publications I–II*: 100% MT, *V*: 75% MT, *VI*: 90% MT) or on the induced electric field on the cortical surface (120–130 V/m in *Publication III*). In *Publication IV*, where Broca's area was stimulated, the intensity was adjusted to produce an electric field on the cortical surface of the same magnitude as was produced on the surface of M1 when 100% MT intensity was used. This way, the stimulation effect at these two sites can be assumed to be approximately the same even though the distance between the coil and the cortex varies.

The subjects listened to masking noise to attenuate the perception of the coil click. The noise also prevented the subjects from hearing the sound of the finger tapping (*Publication VI*). In addition, a piece of foam plastic was added between the coil and the head to reduce the vibrations of the coil mediated to the head and thus the bone-conducted sound (*Publications I–II*). These procedures aimed at reducing the auditory component in the evoked responses and the interference of the coil click with the task.

The origins of TMS-induced artifacts in the EEG signals were studied in separate experiments (unpublished data), in which TMS was delivered to 16 different sites around the left hemisphere of 3 subjects, 30 pulses to each site (above electrodes AF1, CZ, C3, CP1, FZ, F5, FC1, FC5, FPZ, FT9, OZ, PZ, P3, P9, PO3, and TP7) at 100% of MT with the induced current oriented anteriorly.

4.2 EEG

A 60-channel TMS-compatible Nexstim eXimia EEG device recorded the reactions of the brain to the stimuli (*Publications I–IV*), prestimulus oscillatory activity (*Publication II*), and spontaneous EEG before each stimulation session and during sleep (*Publication III*). The reference electrode was placed behind the right ear, which is relatively far away from the stimulation coil as the left hemisphere was stimulated in all the experiments. The ground electrode was placed on the right cheek bone. Since eye movements produce a large component in the EEG signal, the electrooculogram (EOG) was measured with electrodes placed above the left eye and on the right side of the right eye to detect eye movements.

TMS-compatibility of the Nexstim EEG device is based on sample-and-hold and gain-control electronics, which limit the amplifier gain and keep the signal input constant during the stimulus pulse, and on small Ag/AgCl pellet electrodes, which are not heated excessively and do not move, which may happen with conventional electrodes because of currents induced in the electrodes. With this system it is possible to measure EEG signals free of artifacts induced in the electrode leads even a couple of milliseconds after the pulse. To reduce other electromagnetic artifacts including the electrode polarization artifact, the electrode contact was carefully prepared to obtain an impedance smaller than 5 kΩ.

4.3 EMG

A Medtronic Keypoint EMG device (Medtronic, Inc., Minneapolis, Minnesota, USA) recorded the MEPs evoked by TMS (*Publications I–II*). One electrode was placed on the target muscle and the other one on a distal tendon next to the muscle (muscle-belly–tendon montage). The ground

electrode was placed on the back of the hand. Hand relaxation was monitored by visually inspecting the EMG signal during the measurement.

4.4 NIRS and circulatory parameters

A frequency-domain instrument with two laser diodes of different wavelengths recorded the NIRS signals [162] (*Publication V*). The source fiber and detector fiber bundles were attached to a probe comprising two sources and seven detectors (brain experiments) or one source and three detectors (shoulder experiments). The fibers were arranged in three different source-to-detector distances (short: 1.3 cm, intermediate: 2.8 cm, and long: 3.8 cm) to measure the signals originating in different depths in different proportions. The probes were positioned above the M1 hand areas of both hemispheres with the help of the NBS system in the brain experiments. In the shoulder experiments, the probes were positioned above the proximal end of the left humerus according to anatomical landmarks. A movement sensor was attached to the head or to the shoulder to measure subject movements.

Signals reflecting changes in blood circulation were measured as well to elucidate the changes caused by TMS that might be reflected in the NIRS signals. A pulse oximeter was attached to the left index finger to measure the heart rate and the photoplethysmographic (PPG) signal amplitude, which reflects the amount of blood that is pulsating in the blood vessels of the finger. In addition, the electrocardiogram (ECG) was measured in the shoulder experiments.

4.5 Measures of vigilance

In *Study III*, subjects' vigilance was monitored with a visuomotor tracking task [137] during an additional stimulation session. The subjects had to keep a tracker ball close to a target while the tracker position was constantly deviated in different directions. Task performance was characterized by the distance of the tracker from the target. This way it was possible to study whether momentary lapses in vigilance affected the evoked responses. In addition, the subjects performed a psychomotor vigilance task (PVT) in which they had to respond to a flash of light with a button

press [60], a commonly used measure of sleepiness, before each stimulation session.

4.6 Finger tapping and visual pacers

In the finger-tapping experiments (*Publication VI*), the subjects tried to synchronize their right index finger tapping rate to a periodic continuous visual pacer, either a movie of a tapping finger or a hinged bar (Fig. 1 in *Publication VI*), with a period of 800 ms and a contact time of 40 ms with the ground. The times when the subject pressed the key and lifted their finger from the key were recorded. The tapping hand was covered so that the subjects did not see it. The three TMS pulses at 5 Hz were given every fourth tapping interval, 100, 300, and 500 ms after the pacing stimulus.

4.7 Data analysis

Offline analysis was performed with MATLAB (The Mathworks, Inc., Natick, Massachusetts, USA). First, the data were visually inspected; trials containing eye blinks as revealed by the EOG, artifacts, increased EMG baseline activity showing contraction of the target muscle, or subject movement as revealed by the movement sensor data were omitted.

4.7.1 Comparison of measures of cortical excitability

TMS-evoked MEPs were compared with brain activity measured with EEG before (*Publication II*) and after (*Publication I*) the TMS pulse. As a measure of TMS-evoked peripheral activity, the peak-to-peak MEP amplitudes were determined for the accepted trials.

The EEG data were bandpass filtered to obtain the frequency components of interest. In *Study I*, the data were filtered with a passband of 2–80 Hz to reduce high-frequency noise and slow drifts, resulting in a time resolution of about 6 ms in the filtered signal defined as the full-width at half maximum of the filter in the time domain. In *Study II*, only prestimulus EEG traces were filtered; filtering reduces the time resolution of the signal, and therefore the poststimulus data would affect the filtered prestimulus data if included. Since prestimulus oscillations were of in-

terest in *Study II*, the data were filtered separately at different frequency ranges including alpha (8–12.5 Hz), low-beta (12–15 Hz), midrange-beta (15–18 Hz), and high-beta (18–30 Hz). The beta range was divided into subranges, because Rolandic oscillations at beta frequencies are known to originate in the motor cortex and are thus of special interest when studying motor cortical excitability.

The TMS-evoked filtered EEG data were divided into trials from -100 to +500 ms with respect to the stimuli (*Publication I*). The peak-to-peak amplitude of the N15–P30 complex was chosen for further analysis since, based on visual inspection, these deflections seemed free of stimulus-related artifacts and at their latencies the somatosensory feedback from the target muscle has not had time to reach the cortex. The N15–P30 amplitudes were averaged over channels showing largest amplitudes at the average latencies of N15 and P30.

The temporal spectral evolution method (TSE) [199] was used to find the time course of the prestimulus oscillation amplitude (*Publication II*); the prestimulus traces filtered to a desired frequency range were rectified and smoothed. To compare oscillations originating in different brain areas, the TSE waveforms were averaged separately over four channel groups: left Rolandic (above the stimulated motor cortex), right Rolandic (above the contralateral motor cortex), occipital (above the visual cortex), and frontal. The oscillation phase (*Publication II*) at the time of the stimulus was estimated by fitting a sinusoid at the individual dominant frequency at each frequency range to the filtered prestimulus signals and correcting for the known phase shift introduced by the filter.

The relationship between MEP amplitudes and EEG oscillations (*Publication II*) as well as evoked EEG responses (*Publication I*) was studied at the single-trial level and between groups of trials divided according to the MEP amplitude, i.e., trials corresponding to 1/3 of the smallest and 1/3 of the largest MEPs. In *Study II*, correlation coefficients were calculated between the individual average oscillation amplitudes at different frequency ranges and motor thresholds. The statistical analysis between MEP size groups in *Study II* was done with Bonferroni-corrected paired t-tests separately for each channel-group–frequency-range pair and, to study the specificity of the t-test results and time dependency, with ANOVAs.

Even though the trials with increased prestimulus EMG activity clearly indicating contraction of the target muscle were omitted, in *Study I*, we assessed if more subtle changes in background EMG had an effect on the

evoked responses (MEP and N15–P30 amplitudes). The correlation coefficients between prestimulus root-mean-square EMG activity and the evoked responses were calculated.

Although the position of the coil was controlled, very small changes in the distance of the coil from the head might affect the evoked responses a lot. To check whether the distance changed markedly and affected the evoked responses in *Study I*, the coil coordinates projected to the axis of the coil normal were determined. Spearman's correlation coefficient was calculated between the distance of the coil from the head along the coil normal axis and the evoked response (N15–P30 and MEP) amplitudes.

4.7.2 Analysis of the effects of sleep and wakefulness

The effect of sleep and sleep deprivation on the TMS-evoked EEG responses was evaluated in *Study III*. The data were filtered (2–80 Hz) and averaged over trials ($-80\ldots+300$ ms). The slope between the earliest deflections peaking at 10 ± 1 and 20 ± 2 ms (mean $\pm$ s.d. over subjects), defined as the peak-to-peak amplitude divided by the difference in latencies, was chosen for further analysis. The evoked EEG responses were averaged over those channels in which the response showed a clear negative-to-positive deflection and over trials. The slope was determined from the averaged response and the single-trial values of the slope were determined automatically from responses averaged over the region of interest channels but not over trials. To see whether the slope differed between sessions, Bonferroni-corrected t-tests were used.

The effect of momentary fluctuations in vigilance on the evoked EEG was evaluated by determining task performance during the stimuli (tracker ball distance from target at $-1\ldots2$ s around the TMS pulses). Pearson's correlation coefficients were calculated between the slope and task performance values. In addition, a few parameters known to correlate with tiredness were evaluated: the power of theta-band activity during each session as well as the SWA during the first NREM sleep episode during baseline and recovery sleep were determined from the spontaneous EEG recordings. The average of the 10th percentile of the longest reaction times in the PVT was determined.

4.7.3 Analysis and removal of the muscle artifact

The EEG responses evoked by stimulating 16 different sites around the left hemisphere in a separate set of experiments (unpublished) were analyzed to evaluate the origins of TMS-evoked artifacts. The responses were averaged over trials and the global mean field amplitude (GMFA) [127], i.e., the root-mean-square sum over average-referenced signals, reflecting the overall evoked EEG-response over time, was calculated. The overall artifact size associated with each stimulation site was calculated as the maximum value of the GMFA between 0 and 30 ms after the stimulus. To analyze the frequency content of the muscle artifact and the brain signal, the TMS-evoked averaged EEG data recorded after Broca's area stimulation (the data of subject S3 reported in *Publication IV*) were short-time Fourier transformed using a 128-sample Hamming window with an overlap of 120 samples between adjacent windows.

Brain and muscle signals have generally different frequency contents, which can be made use of to separate their contributions. While the brain signal is mainly restricted to frequencies below 100 Hz, the surface EMG signal, which reflects the summed motor unit action potentials, is manifested at frequencies up to 400–500 Hz [43, 146]. Since muscle activity is also present at lower frequencies, simple lowpass-filtering is not adequate to separate the signals, whereas signals highpass-filtered with an appropriate cutoff frequency resulting in data containing only muscle activity and no brain signal can be utilized. Given that the low-frequency muscle activity is produced in the same muscles as the high-frequency muscle activity, they originate in similar current distributions and thus produce topographically similar signals in multichannel EEG. Thus, projecting out the topographies of the high-frequency data should also remove the contribution of the low-frequency muscle activity, as was reasoned in *Publication IV*.

The method can be described mathematically as follows: The TMS-evoked d-dimensional EEG signal is a weighted sum of signals originating from the brain and from the muscles and noise. Both brain and muscle signals can be divided into high- and low-frequency components according to a frequency threshold f_{th}. Let $\mathbf{x}_i$ and $\mathbf{y}_i$ represent the d-dimensional time-independent topographies (vectors in the signal space) of muscle and brain source activity, respectively, describing the relative signal amplitudes measured with each electrode as a result of respective source acti-

vation. $a_i(t)$ and $b_i(t)$ are the time-varying amplitudes of the muscle artifact and brain sources, respectively. Thus, a signal $\mathbf{m}(t)$ can be described as a sum of N^{L} low-frequency and N^{H} high-frequency muscle components as well as M^{L} low-frequency and M^{H} high-frequency brain components and noise $\mathbf{n}(t)$:

$$\mathbf{m}(t) = \sum_{i=1}^{N^{\mathrm{L}}} a_i^{\mathrm{L}}(t)\mathbf{x}_i^{\mathrm{L}} + \sum_{i=1}^{N^{\mathrm{H}}} a_i^{\mathrm{H}}(t)\mathbf{x}_i^{\mathrm{H}} + \sum_{i=1}^{M^{\mathrm{L}}} b_i^{\mathrm{L}}(t)\mathbf{y}_i^{\mathrm{L}} + \sum_{i=1}^{M^{\mathrm{H}}} b_i^{\mathrm{H}}(t)\mathbf{y}_i^{\mathrm{H}} + \mathbf{n}(t), \quad (4.1)$$

where superscripts L and H refer to low- and high-frequency components.

If f_{th} is chosen so that the high-frequency EEG signal originating from the brain is negligible ($\sum_{i=1}^{M^{\mathrm{H}}} b_i^{\mathrm{H}}(t)\mathbf{y}_i^{\mathrm{H}} \approx 0$), highpass-filtering the signal with a cutoff frequency f_{th} results in a signal that consists mainly of the high-frequency components of the muscle activity and noise:

$$\mathrm{H}(\mathbf{m}(t)) \approx \sum_{i=1}^{N^{\mathrm{H}}} a_i^{\mathrm{H}}(t)\mathbf{x}_i^{\mathrm{H}} + \mathrm{H}(\mathbf{n}(t)), \quad (4.2)$$

where H represents the highpass-filter operator. If the low-frequency muscle components belong to the signal subspace spanned by the high-frequency muscle components ($\{\mathbf{x}_1^{\mathrm{L}},\ldots,\mathbf{x}_{N_{\mathrm{L}}}^{\mathrm{L}}\} \in \mathrm{span}(\mathbf{x}_1^{\mathrm{H}},\ldots,\mathbf{x}_{N_{\mathrm{H}}}^{\mathrm{H}})$), projecting out the topographies of the highpass-filtered data also removes the low-frequency muscle components.

Principal component analysis (PCA) transforms the highpass-filtered data to a new coordinate system of orthogonal components

$$\boldsymbol{\mu}_j = [\mu_{j,1}\ \mu_{j,2}\ldots\mu_{j,d}]^{\mathrm{T}}, \quad (4.3)$$

each being a linear combination of the original variables, with respective eigenvalues s_i and time-varying amplitudes $\alpha_j(t)$:

$$\mathrm{H}(\mathbf{m}(t)) = \sum_{j=1}^{d} \alpha_j(t)\boldsymbol{\mu}_j. \quad (4.4)$$

Each principal component (PC) $\boldsymbol{\mu}_j$ is the signal-space vector orthogonal to PCs $\boldsymbol{\mu}_k$ ($k < j$) explaining the largest amount of remaining variance in the data. Since noise is present in all the signal-space directions, the highpass-filtered data consists of d orthogonal components. Therefore, projecting out all the topographies of the highpass-filtered data from the original signal would remove all the data. Since the PCs with the largest eigenvalues reflect the largest amount of variance in the data, they presumably reflect the muscle artifacts at least in cases where the artifacts

are much larger than the noise. Accordingly, projecting out N PCs ($N < d$) with the largest eigenvalues using signal-space projection (SSP) [225] reduces the muscle artifact:

$$\mathbf{m}_{\mathrm{corr}}(t) = \mathbf{m}(t) - \sum_{j=1}^{N} \boldsymbol{\mu}_j \boldsymbol{\mu}_j^{\mathrm{T}} \mathbf{m}(t), \tag{4.5}$$

where $\mathbf{m}_{\mathrm{corr}}(t)$ is the corrected signal and T stands for transpose.

The muscle artifact reduction method was applied on the data recorded following the stimulation of Broca's area (*Publication IV*). The effect of the projections was evaluated after projecting out 1–30 PCs. The GMFAs of the original unfiltered data as well as of the data obtained after the projections were calculated and the amplitudes and latencies of the GMFA peaks were determined. The signal-to-artifact ratio was defined as the amplitude of each GMFA peak appearing later than 50 ms divided by the amplitude of the first artifact peak in the GMFA. The signal-to-artifact improvement factor was calculated to describe the increase in the ratio as a result of the projections. The 95% confidence intervals Bonferroni-corrected with factor 5 (number of peaks after 50 ms in the original signals) of the GMFAs were calculated. A GMFA peak was considered statistically significant if its confidence interval did not overlap with that of the baseline.

4.7.4 Analysis of NIRS and circulatory data

The NIRS amplitude signals were filtered (0.015–0.5 Hz) and converted to HbO_2, HbR, and HbT concentrations with the modified Beer–Lambert law (Eq. 3.8). The heart rate and the PPG peak-to-peak amplitude were determined from the pulse oximeter signal. The pulse transit time (PTT), i.e., the time it takes for the pulse pressure wave to travel from the heart to the finger, thus reflecting arterial stiffness [157], was calculated as the time difference between the R peak in the ECG and the corresponding PPG pulse wave peak. The inverse of PTT, which correlates with blood pressure [157], was then calculated. The hemoglobin concentrations, heart rate, PPG amplitude, and 1/PTT were averaged over trials (-2...25 s). The hemoglobin concentrations recorded in the brain experiments were also averaged over channels with same source-to-detector distances within both hemispheres. The PPG amplitudes were normalized

with the average value of each subject. Each of the signals was averaged over subjects.

To test whether the responses were statistically significant, the amplitudes of the average responses at the end of the TMS pulse train (6...8 s) were compared with the corresponding baseline amplitudes ($-2...0$ s) with t-tests corrected for multiple comparisons with the false discovery rate method for positively correlated tests. To test for similarity between different responses (brain vs. shoulder responses, NIRS vs. circulatory responses), Pearson's correlation coefficients were calculated between the waveforms of the responses at 0...25 s.

4.7.5 Analysis of finger-tapping data

The synchronization error (the time when the key was pressed with respect to the pacer onset) and the contact time (the time the key was held down) were determined for each tap. The taps, named t_0–t_3 according to their proximity to the previous TMS pulse (TMS, t_0, t_1, t_2, t_3, TMS, etc.), were divided in two groups, early (t_0, t_1) and late (t_2, t_3). The mean and standard deviation of the synchronization error and contact time were calculated for each stimulation site (vPMC, dPMC, control), pacer (finger, bar), and tap latency (early, late). The differences between these groups were studied with three-way repeated-measures ANOVAs.

5 Results and Discussion

The results revealed aspects of the ability of TMS to inform us about the cortical state. On one hand, the sensitivity of the measures to changes in cortical excitability was elucidated. On the other hand, to assess the reliability of TMS-evoked responses in determining the excitability and connectivity, the nature of the stimulation-related artifacts was clarified and the feasibility of the TMS–EEG muscle artifact removal method was shown. In addition, we learned about the sleep- and wakefulness-related excitability changes in cortical circuits and about motor-timing processing in the brain.

5.1 TMS-evoked responses

We measured electrophysiological and hemodynamic reactions to TMS to better understand the mechanisms of the stimulation and the physiology of the evoked responses.

5.1.1 TMS-evoked MEPs

Since cortical excitability fluctuates, MEPs can be expected to vary in amplitude also with unchanging stimulation parameters. The amplitudes were indeed highly variable even though the stimulation intensity was kept constant and the coil position with respect to the head was strictly controlled to avoid changes in the electric field experienced by the target neurons (*Publications I* and *II*). Fig. 5.1 shows the distribution of typical MEP amplitudes evoked by stimulation at 100% of MT.

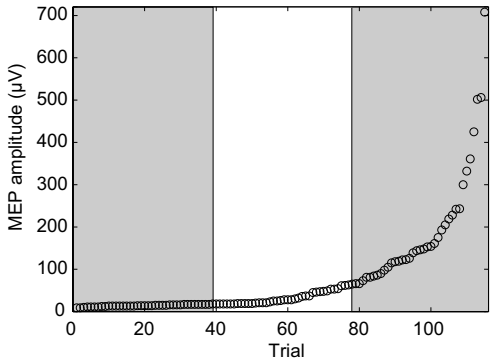

Figure 5.1: The stimulus effect varied between trials although the conditions were kept constant. MEP amplitudes evoked with M1 stimulation at the intensity of 100% of MT. The trials are sorted according to the amplitudes. The grey areas indicate 1/3 of the smallest and 1/3 of the largest MEPs.

5.1.2 TMS-evoked EEG responses

The evoked EEG responses following M1 stimulation in *Study I* were consistent with those reported in previous studies [28, 66, 116, 117, 142, 158, 172]; deflections identified as P5, N15, P30, N45, P60, and N100 were present. Stimulation of the premotor cortex (*Publication III*) evoked responses in accordance with those reported by Rosanova et al. [191]: the response oscillated in the high-beta frequency range producing deflections at 3±1, 10±3, 19±2, 41±3, 59±3, and 77±3 ms (mean±std latencies of the vertex responses over subjects on the baseline day).

The stimulation of Broca's area (*Publication IV*) produced a two-phasic fast muscle artifact (Fig. 5.2) peaking at around 5 and 10 ms in the unfiltered data. The second peak decayed slowly to the baseline level at around 60 ms after the stimulus. The amplitude of the artifact in the filtered (2–80 Hz) signal was at least 100 μV in most channels and up to 1000–1500 μV in the channels near the stimulation site, i.e., 1–3 orders of magnitude larger than typical brain responses (Fig. 5.2). In the filtered data, the latency of the second peak was shifted to 13±1 (mean±std over channels), because the fast initial component was affected by the filtering more than the slow decay. The time–frequency analysis (Fig. 5.3) of the unfiltered data revealed that the signal just after the stimulus consisted

of both high- and low-frequency components, whereas after some tens of milliseconds the signal was mainly restricted to frequencies below 50 Hz.

The dependency of the artifact on the stimulation site as revealed by the additional experiments strongly supports the view that the artifact originates at least partly in the muscles: the artifact was clearly largest when areas close to cranial muscles were stimulated (Fig. 5.4). Especially, stimulation of the lateral parts of the head produced large artifacts. In addition, stimulation of areas close to but not directly under cranial muscles produced largest artifact peaks in channels above the nearby muscles and not above the stimulation site (Fig. 5.5). However, a similar two-phasic artifact with an amplitude and duration comparable to those measured in our experiments, evoked and measured by similar equipment as used here, was deduced to originate in the skin as the stimulus-induced charge decayed over it; mini-puncturing the skin under the electrodes decreased the artifact amplitude to about half [103]. It is possible that, in addition to muscle-activity-related electric fields, muscle movements contribute to the artifact: when the muscles move, they produce a movement artifact on the signal, which may result from both electrode movement and changes in skin potential when the skin stretches. The combination of electrical activity and movement of muscles explains both the involvement of the muscles and the skin in the artifact generation; the mini-puncturing, with the effect of short-circuiting the epithelium, reduces the movement-related changes in skin potential which have been shown as a major cause of movement artifacts [214]. When the stimulation evokes a large artifact, it is seen in all the channels and not just in those under the muscle, which indicates that the artifact is not solely a result of the movement, but also the electrical activity of the muscles plays a role.

Because of the nonspherical shape of the head, the electrode cap sits more firmly on the top of the head than above the lateral and posterior parts, which may result in worse electrode contacts and in larger electrode polarization in the lateral and posterior channels. This factor alone cannot, however, explain the stimulation-site dependency of the artifact: if this was the case, the artifact would only be present in the channels with worse electrical contacts. In contrast, in cases where the stimulation evokes a very large artifact, it is seen in all the channels, also in those on the other side of the head. If the coil is moved to more central sites, the stimulation produces seemingly high-fidelity data. Nonetheless, the polarization of the electrode contact may contribute to the artifact.

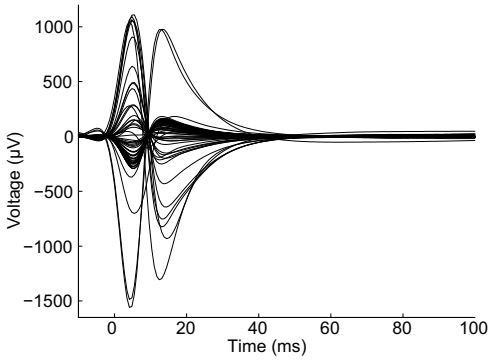

Figure 5.2: Filtered (2–80 Hz) data of all the channels after the stimulation of Broca's area. The artifact is 1–3 orders of magnitude larger than typical brain responses.

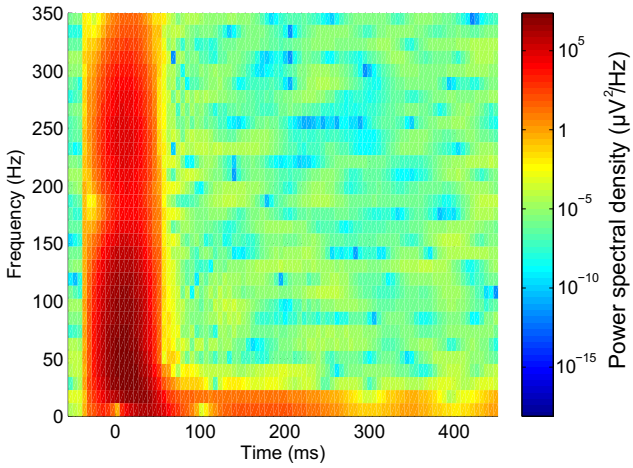

Figure 5.3: The power spectral density of the EEG data of channel FC1 evoked by stimulation of Broca's area as calculated with the short-time Fourier transform.

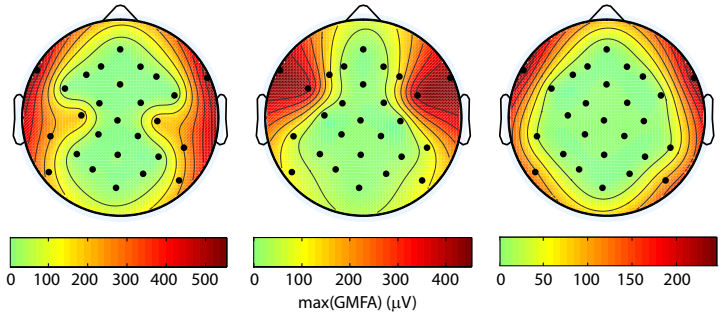

Figure 5.4: The maximum amplitude of the GMFA as a function of the stimulation site in three subjects. The values have been mirrored to the right hemisphere, as only the left hemisphere up to the midline was stimulated. The stimulation sites and the corresponding locations at the right hemisphere have been marked with dots. Modified from [153].

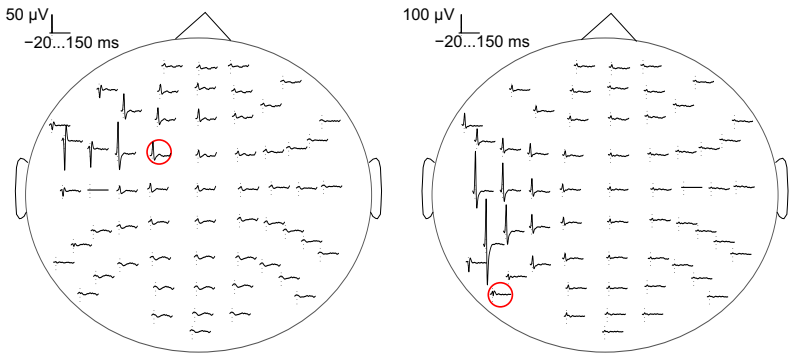

Figure 5.5: The largest artifact peaks appeared above the nearest cranial muscles instead of above the stimulation site (marked with the circle).

5.1.3 TMS-evoked NIRS responses

In *Publication V*, we showed that stimulation of the brain and the shoulder produced similar decreases in HbT concentrations measured with NIRS above the stimulated site (Fig. 5.6), suggesting that the TMS-evoked NIRS signal does indeed include a component that does not directly reflect cerebral neuronal activity. On the contralateral hemisphere, HbT decreases were measured as well, but on the contralateral shoulder, HbT increases appeared. The difference in the responses measured from different shoulders implies that the shoulder responses are not solely caused by global changes in blood circulation but the stimulation-related artifact in the NIRS signal includes local effects of TMS. In addition, the PPG amplitude (reflecting local vascular compliance) and the heart rate increased as a result of both brain and shoulder stimulations and 1/PTT (reflecting blood pressure) increased as a result of shoulder stimulation indicating that also global changes in the circulation occur. The local artifact might result from a direct effect of TMS on the vascular smooth muscles or activation of sympathetic vasoconstrictor nerve fibers, either directly or indirectly through systemic sympathetic outflow.

When TMS is combined with NIRS to probe the cortical state, these physiological artifact components may mask the hemodynamic response to TMS-evoked neuronal activity. Therefore, careful control measurements of the artifacts are needed.

5.2 Relationships between the measures of cortical excitability

Spontaneous EEG is an established clinical tool. To understand what TMS-evoked responses tell us about the cortical state, it is useful to relate them to the information spontaneous EEG gives us. Furthermore, as TMS-evoked MEPs have been measured since the introduction of magnetic stimulation, while TMS-evoked EEG responses are relatively new and not as well known, it is essential to understand how these two are related. The mechanisms of these measures of cortical excitability were studied by assessing their mutual relationships.

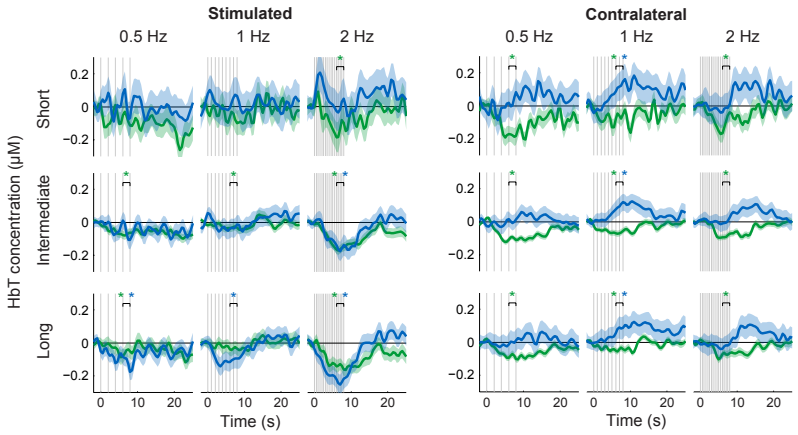

Figure 5.6: The HbT concentration measured above the stimulation site decreased both after M1 (green) and shoulder (blue) stimulation. HbT concentration decreased also on the contralateral hemisphere, whereas it increased on the nonstimulated shoulder. The vertical lines indicate the TMS pulses. The asterisks (* $p < 0.05$) indicate significant response amplitudes at the end of the TMS pulse train as compared to baseline (t-tests).

5.2.1 TMS-evoked EEG responses and MEPs

In *Publication I*, we demonstrated that MEP amplitudes and the peak-to-peak amplitudes of the N15–P30 complex of the evoked EEG responses correlated significantly at the single-trial level (Fig. 5.7). The result supports the view that fluctuations in both MEP and evoked EEG responses reflect cortical excitability; the state of the cortex at the time of the stimulus affects the level of initial activation at the stimulation site. The amount of initial activation affects both subsequent cortical activation at the stimulated and interconnected sites and peripheral muscle activation. The result also gives further evidence that these deflections reflect magnetically evoked cortical activation.

Because the amplitudes of the evoked EEG responses were determined within 40 ms after the stimulus, at the time period when the somatosensory signal resulting from target muscle contraction has not had time to reach the cortex, the correlation was not likely to be caused by an MEP-amplitude-dependent somatosensory evoked potential. Contraction of the target muscle would result in increased spinal and cortical excitability

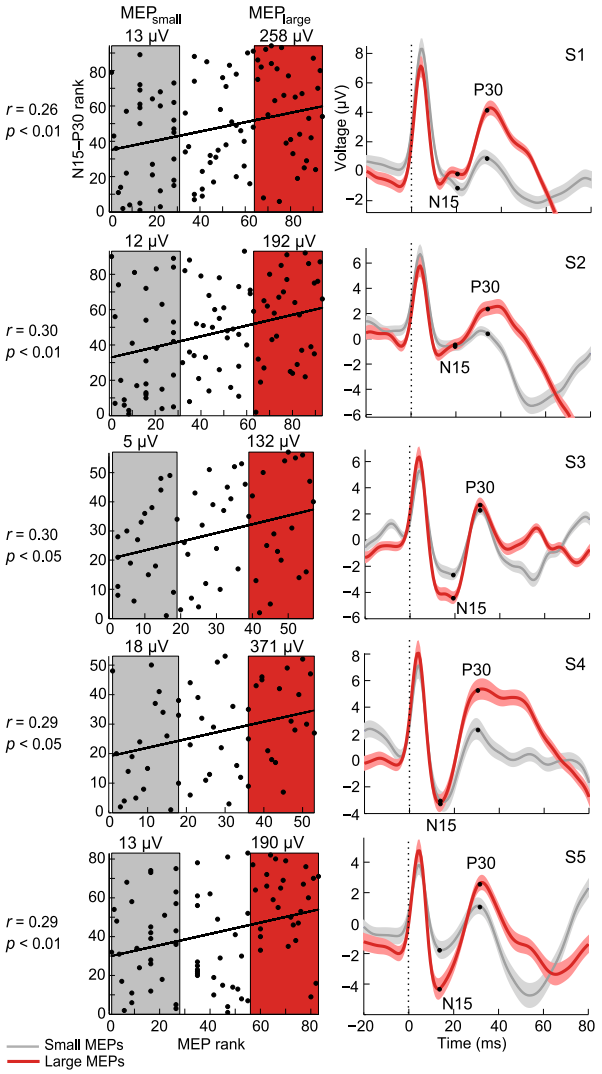

Figure 5.7: The rank correlation plot between MEP and N15–P30 amplitudes (left) and the evoked EEG responses (±s.e.m.) averaged separately over small- and large-amplitude-MEP trials (right) of each subject (S1–S5). The MEP and N15–P30 amplitudes were ordered from smallest to largest and the correlation coefficient was calculated between the ranks. The correlation coefficients (r) and the respective p-values of each subject are shown on the left side of the correlation plots. The $\mathrm{MEP}_{\mathrm{small}}$ and $\mathrm{MEP}_{\mathrm{large}}$ values on top of the correlation plots show the average MEP amplitude of 1/3 of the smallest and 1/3 of the largest MEPs.

and fluctuations in contraction level could thus explain the observed correlation. This is not likely, however, since there was no correlation between the prestimulus EMG activity and the evoked responses.

Movements of the stimulation coil with respect to the head might affect the evoked responses and thereby the observed correlation. If the coil moved away from the initially defined stimulus site so that the electric field experienced by the target neurons was reduced, both MEP and EEG amplitudes would be reduced and the coil movement would result in increased correlation. On the contrary, if the coil moved away from the representation area of the target muscle towards the representation area of another muscle, EEG responses would not necessarily decrease, whereas MEPs would, and the observed correlation would decrease. Neither case is likely in this study, because the coil movements were small (1–2 mm) compared to the stimulated area, which is of the order of a few cm^2. On the contrary, even small changes in the distance between the coil and the head could change the evoked responses a lot. However, coil movements in the direction of the normal of the coil (approximately normal to the head surface) were less than 0.5 mm in 4/5 subjects, and the evoked responses did not correlate with the distance in these subjects. In one subject (S5), coil movement normal to the head was 1.9 mm and correlated with both N15–P30 ($r = -0.23, p = 0.034$) and MEP amplitudes ($r = -0.41, p = 0.0001$). In this subject, coil movements can explain the observed correlation between the MEP and N15–P30 amplitudes, whereas in the others it is not likely.

5.2.2 EEG oscillation amplitudes and MEPs

In *Study II*, we showed that, between groups of small and large MEPs, there was a difference in oscillation amplitudes at midrange-beta frequencies measured above the stimulated (left) motor cortex (Fig. 5.8); smaller oscillation amplitudes were associated with larger MEP amplitudes and vice versa. However, at the single-trial level, there were no correlations between MEP and EEG oscillation amplitudes measured above any area at any frequency range tested. Temporal analysis showed that the difference in left Rolandic midrange-beta oscillation amplitudes between the size groups of MEPs was the larger the closer in time to the stimulus it was evaluated; significant differences were only observed during a few

hundred milliseconds before the stimulus indicating that the fluctuations in excitability occur on a subsecond timescale.

The result supports the view that Rolandic beta oscillations reflect the state of the motor cortex. However, the lack of a single-trial correlation indicates that either one or both measures are affected by other factors than the excitability of the cortical target neurons to the extent that the underlying correlation is masked. Indeed, MEP amplitudes are affected by spinal excitability changes and fluctuations in the synchrony of action potentials. EEG, for its part, reflects the activity of a large neuronal population, the neurons controlling the target muscle being only part of it. Since a large part of variation in MEPs reflects the excitability of the target neurons (*Publication I*), the lack of a strong correlation between EEG oscillations and MEPs seems to result from the fact that EEG oscillations reflect the excitability of a neuronal population which is much larger than the overlapping population.

Based on the ANOVA, we could not show that the relationship between MEP amplitudes and midrange-beta oscillations would be specific to left Rolandic sites. Indeed, Fig. 5.8 shows a similar time course in midrange-beta amplitudes measured above the nonstimulated (right) motor cortex and above the frontal areas as above the stimulated motor cortex. However, because a significant relationship was not found between MEP and midrange-beta amplitudes measured above these sites, further studies are needed to clarify whether such relationships exist. In fact, a recent study showed a link between MEP amplitudes and rolandic beta oscillations both above stimulated and nonstimulated motor cortices during voluntary target muscle contraction [205], extending our finding to the contralateral hemisphere and to the muscle preactivation state.

We found no correlation between the resting motor threshold and the average amplitudes of spontaneous oscillations at any frequency range. Previously, a correlation has been found between the individual threshold for evoking phosphenes and occipital alpha power [190]. As was noted in [190], other factors such as skull thickness and cortical folding affect the excitability as probed with TMS, and these factors may mask the possible relationship between individual oscillations and excitability.

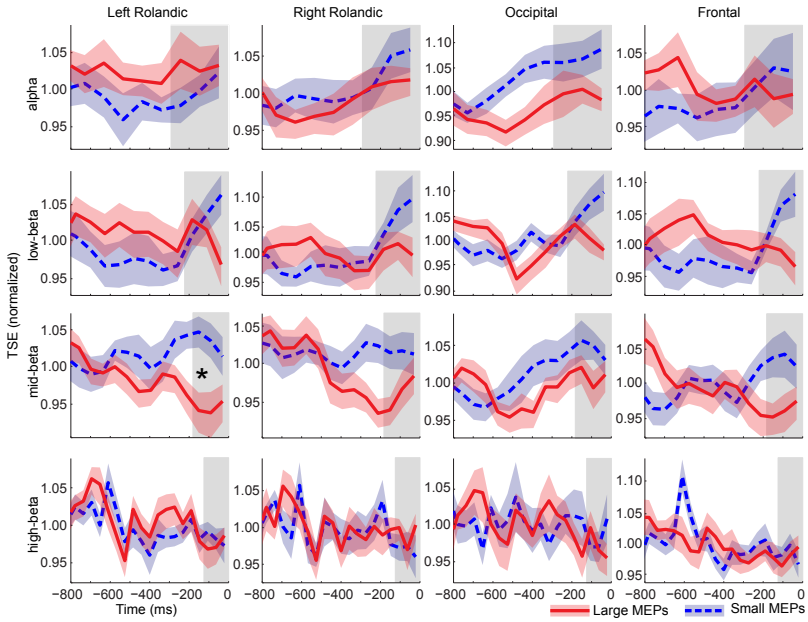

Figure 5.8: Grand averages of the TSE curves normalized by the average value of the subject in question in the shown time range before averaging. TSE indicates the temporal evolution of spontaneous oscillation amplitudes at each frequency range before the stimuli. The curves are averages over two groups of trials: those with small- and those with large-amplitude MEPs. The shaded areas indicate the s.e.m. over subjects. The grey area shows the time period over which the TSE value was averaged for statistical analysis. * = significant ($p < 0.05$) difference between the small- and large-MEP groups.

5.2.3 EEG oscillation phase and MEPs

In *Publication II*, the relationship between spontaneous oscillation phase and MEP amplitude was studied. While the oscillation phase measured above the stimulation site was not found to be associated with MEP amplitudes, midrange-beta oscillations measured above the occipital area were weakly related to MEPs; the oscillation slope was negative rather than positive during the time of the stimuli producing large-amplitude MEPs. The relationship was found when comparing groups of trials with small- and large-amplitude MEPs, whereas there were no single-trial correlations.

Occipital beta oscillations have been associated with visual attention [238] and visuomotor processing: in visuomotor tasks, decrease in lower beta range (<20 Hz) amplitudes has been related to decreased response times [243] and increased preparatory attention [82]. In addition, during visuomotor tasks the coherence between visual and motor cortex in the lower beta range (13–21 Hz) has been found to increase [44]. Since visual attention is mainly associated with occipital alpha oscillations [237, 201, 110, 185, 186, 209, 239, 217], processes related to visuomotor integration are more likely to explain the result in *Study II*. As in these experiments the subjects were at rest, the result suggests that the mechanisms responsible for visuomotor processes are active to some extent also during rest and activity at visual areas is weakly related to motor cortical excitability; visual areas may modulate motor areas or they may have a common modulator. This coupling during rest is rather surprising, but as visuomotor integration is extremely important in controlling action, the connections between visual and motor areas are likely to be strong.

According to ANOVA, the effect is not necessarily specific to occipital sites. In fact, if there was a phase coupling between occipital and motor oscillations, the oscillation phase measured above the motor sites would also be expected to be related to MEP amplitudes. We could not, however, show such a relationship, and it remains to be clarified whether it exists. It is possible that the phase of oscillations is altered in such a small neuronal population in the motor cortex that the relationship between the Rolandic oscillation phase and MEP amplitudes is masked by oscillations originating elsewhere.

5.3 The effects of sleep and wakefulness on TMS-evoked EEG

In *Publication III*, we were able to clarify the cortical processes occurring during wakefulness that cause the need for sleep. We showed sleep- and wakefulness-related changes in cortical excitability in a frontal area: slope of the early TMS-evoked EEG response increases during sleep deprivation and decreases during subsequent recovery sleep (Fig. 5.9). A similar excitability modulation was seen from morning to evening on the baseline day after normal sleep; only one out of six subjects did not show an increase in slope. In addition, in line with previous studies, the subjects showed changes in the behavioral and electrophysiological measures of tiredness during the course of the experiment: the error rate in the visuomotor task, the reaction time in the PVT, the theta power, and the SWA increased after sleep deprivation compared to the baseline period.

Although the subjects experienced lapses in vigilance after sleep deprivation as shown by the worsened and strongly fluctuating task performance, the performance in the task during the stimuli did not correlate with the slope. Thus, the observed modulation of the slope is not likely to reflect the momentary lapses in vigilance, but rather a more stable effect on cortical excitability. One possible explanation for the increased excitability comes from the synaptic homeostasis hypothesis; the wake- and sleep-related changes in synaptic strengths might be reflected as the observed changes in excitability.

The electrophysiologically measured effects of sleep deprivation, i.e., the increase in TMS-evoked EEG slope, theta power, and SWA, may be interlinked; presumably, they all reflect the same increase in cortical excitability, which may result from the synaptic homeostasis phenomenon. However, as opposed to theta and SWA, the slope is the only direct marker of the excitability; it provides a neuronal correlate of tiredness related to preceding time awake in awake humans. In addition, the other negative effects of sleep deprivation may be linked to the increased excitability: for example, the increased risk for seizures is probably a direct consequence of it.

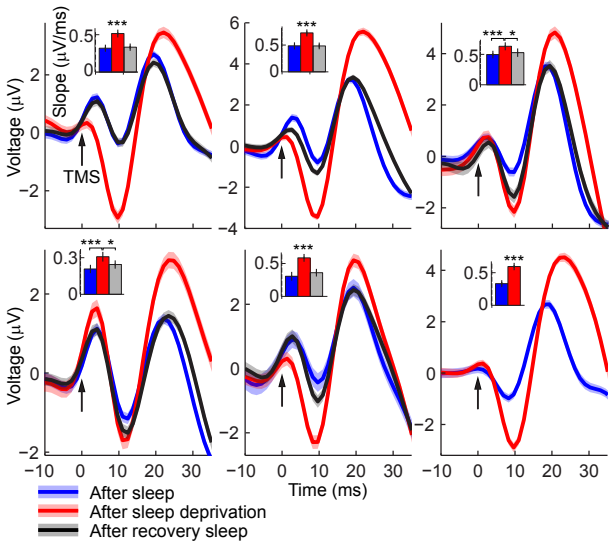

Figure 5.9: The slope (peak-to-peak amplitude divided by difference in latencies) of the early TMS-evoked EEG response (10±1...20±2 ms) increased as a result of sleep deprivation and returned back to the baseline level after recovery sleep in all subjects (one subject did not participate in the session after recovery sleep). The shaded areas indicate the s.e.m. over trials. * $p < 0.05$, *** $p < 0.001$.

5.4 Muscle artifact reduction with the projection method

In *Publication IV*, we presented a method to remove muscle artifacts from TMS-evoked EEG signals. Thanks to the new method, the large artifacts no longer prevent applying TMS–EEG when cortical areas under or near cranial muscles are stimulated.

Projecting the topographies derived from the high-frequency data out of the EEG signals recorded after the stimulation of Broca's area reduced the large muscle artifact remarkably. The increase in the signal-to-artifact ratio was of the order of 10–100 depending on the number of projections. The original data and the data after projecting out 30 high-frequency topographies are shown in Fig. 5.10.

As can be expected, the data in the channels near the stimulation site were attenuated the most. Several peaks appearing in the GMFA were statistically significant after the projections. Whether the data remaining after the projections still contains useful information and where the re-

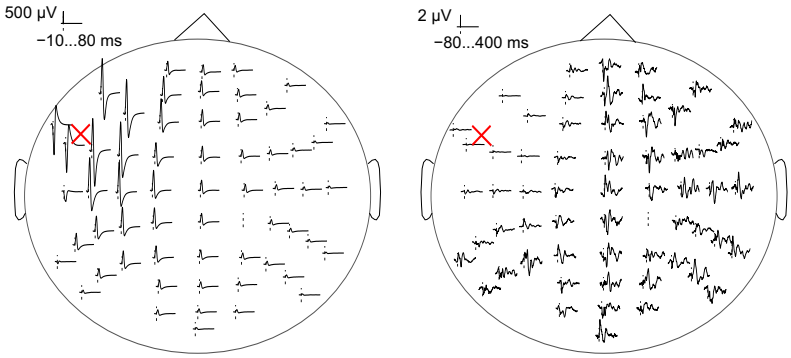

Figure 5.10: The filtered (2–80 Hz) data recorded following the stimulation of Broca's area before (left) and after (right) projecting out 30 high-frequency topographies. The cross marks the stimulation site.

maining data originates in needs to be confirmed in future studies. This can be done with source localization techniques, e.g., the minimum norm estimate [84]; the SSP method is advantageous in comparison to some other artifact removal methods in that it allows source localization despite the distortion of the original data if the projections applied are taken into account when solving the forward problem [225]. Brain activity sources near the muscle probably produce topographies nearly parallel to those produced by the muscles and are likely to be attenuated as well, whereas brain sources further away are better preserved. The more projections are applied, the more brain data dimensions are lost as well. Therefore, the optimal number of projections, which depends on the paradigm, needs to be evaluated individually in each study.

The method is based on the assumption that the artifact results from the electrical activity of the muscles. As was discussed in chapter 5.1.2, this assumption holds at least partially, although part of the artifact may also result from muscle movement or polarization of the electrode contact. It can be expected that these phenomena affect mostly the channels close to the muscle and the stimulation site, respectively. As the method attenuates the signal in these channels — especially if a large number of topographies is projected out — it seems to remove also these types of artifact components if they are present in the original data, even if they appeared only at low frequencies. The new method presented in *Publication IV* combined with some other method designed to remove these other types of artifacts might be even more effective.

5.5 Ventral premotor cortex in finger-tapping tasks

In *Publication VI*, we clarified the role of vPMC in motor timing tasks requiring visuomotor transformation.

In all the finger-tapping experiments, the subjects tapped their finger in somewhat earlier phase than the pacer. This phenomenon called negative asynchrony has been reported in most finger-tapping studies (see [12, 184] for reviews). Stimulation of the vPMC disturbed the negative asynchrony of the taps just after the TMS pulse (tap latency 'early') when the bar pacer was used: the subjects tapped their finger closer to the pacer onset and the synchronization error was reduced consequently. To our knowledge, this is the first evidence from a TMS study suggesting the involvement of the vPMC in a visually guided finger-tapping task. No such significant effect was found when the more natural finger pacer was used or when the dPMC was stimulated. The contact time did not change between conditions.

The observed difference between vPMC and dPMC can be understood in terms of the specific role of vPMC in visually guided hand motor control: it has been suggested to be involved in visually cued finger-tapping tasks [178] and in the control of distal movements [49], especially in matching visual information to hand movements [152]. dPMC, being involved in motor preparation [124] and implementation of associations between arbitrary sensory information and motor responses [90], could also be assumed to be involved in the task. Indeed, the synchronization error values following dPMC stimulation were intermediate between those measured after vPMC and control site stimulation, but they did not differ significantly from the control. Thus, the role of dPMC in visually guided finger tapping still needs clarification. It is possible that the stimulation was not sufficient to disturb the function of dPMC significantly or that stimulation of a slightly different site could have been more effective.

The result emphasizing the different role of vPMC during bar and finger pacer cued tapping is somewhat surprising: the vPMC, known to have a role in the execution–observation of hand movements, could be assumed to be more involved in the condition where the finger pacer was used. It is, however, possible that the finger pacer activates a more distributed network of areas than the bar pacer and the task performance is thus less affected during the finger condition.

Even though the TMS click sound was masked with the noise, the sensory effect resulting from scalp sensory nerve and muscle activation might disturb the task performance. The standard deviation of the synchronization error did indeed increase in the early taps compared to the late taps regardless the stimulation site and pacer. As the vPMC stimulation activates the cranial muscles the most, it might have the largest disturbing effect. However, the difference between the bar and finger conditions cannot be explained by sensory disturbance, and the result is thus likely to reflect the effects of TMS on brain function.

6 Overall discussion and conclusions

In the research reported in this Thesis, we evaluated TMS as a method to study the cortical state, in particular cortical excitability. Based on the results, when the stimulation site is chosen to avoid muscle artifacts, TMS–EEG tracks changes in the excitability reliably, both short-term fluctuations within seconds and natural changes occurring at the time scale of a day. We also show that spontaneous EEG combined with TMS-evoked responses can reveal aspects of cortical excitability and connectivity. Here, we showed the feasibility of spontaneous EEG with MEP measurement, but in the future, the combination of spontaneous and TMS-evoked EEG recordings may prove useful in studying the cortical state. The reliability of TMS-evoked responses is compromised by different types of artifacts: the evoked muscle activity produces a large component in the EEG signals when areas near cranial muscles are stimulated and TMS-evoked NIRS signals are contaminated with physiological circulatory artifacts. These artifacts need to be carefully controlled to measure cortical excitability and connectivity reliably. Although the muscle artifacts are better avoided, they can be reduced with signal processing methods. In addition, methods to remove the physiological artifacts from NIRS signals are needed in the future. Altogether, we demonstrate the ability of TMS to reveal new characteristics of brain function. Particularly, we show that TMS can interfere with the complex visuomotor integration and demonstrate the effect of sleep and wakefulness on cortical excitability.

Studies I and *II* improve our understanding of different measures of cortical excitability, which helps in planning and interpreting scientific and clinical studies related to cortical excitability. We were able to elucidate how the activity of stimulated and interconnected brain regions affect the excitability of the stimulated site and how the activation induced at the stimulation site is mediated to the interconnected sites. On one hand, we show how the background oscillatory activity is related to motor cortical excitability. On the other hand, we elucidate how the excitability of

the stimulated motor cortex affects the resulting evoked responses. Since changes in cortical structure and function are in many cases reflected as changes in cortical excitability, the methods studied here have great potential. Especially, TMS-evoked EEG provides an accurate and flexible tool for cortical probing. The results of *Publication I* inform us about the physiology of TMS-evoked EEG responses, showing that they reflect cortical excitability reliably. The finding provides a basis for future investigation of the early TMS-evoked EEG deflections, e.g., to study the effect of drugs or progression of neurological diseases.

The otherwise flexible TMS–EEG tool suffers from the large muscle artifacts evoked by stimulation of some parts of the head, which mask the early brain signal. We showed that stimulation of the lateral parts of the head produces especially large artifacts and somewhat smaller artifacts arise from the posterior and frontal regions, whereas stimulation of more central parts provides seemingly high-fidelity data. We also present evidence that at least part of this artifact indeed reflects the electrical activity of the cranial muscles, although part of it seems to result from muscle movement and the electrode contact polarization may contribute as well. To overcome these problems, in *Study IV*, we developed an artifact removal method based on the different frequency contents of brain and muscle signals. The method seems to work reasonably well, judged by the relative amplitudes of the artifact and later responses believed to originate in the brain. It remains to be clarified whether the corrected signals can be utilized, for example, to analyze TMS-evoked signals originating from the sites neuronally connected to the stimulation site and how large artifacts it can eliminate without suppressing the brain signals excessively. The method is, in any case, likely to extend the area of use of TMS–EEG to those brain areas whose stimulation produces small muscle artifacts. The novel method presented here might need to be combined with other methods (e.g., [119]) to obtain optimal results.

In *Publication V*, we show that also TMS-evoked NIRS responses contain physiological artifact components, which challenges the assumption that the previously reported NIRS responses to TMS reflect merely the cerebral hemodynamic response. The results suggest that the signals reflect both local and global effects of TMS on blood circulation. Therefore, the traditional methods to remove artifacts from NIRS signals are probably not sufficient to remove them from TMS-evoked NIRS responses, as these methods are designed to remove systemic signal components which

are not localized to the stimulation site. Consequently, new efficient methods to remove the artifacts are needed. For example, a denser measurement grid might help in separating the brain signal from the artifacts, for example, by enabling independent component analysis. Nonetheless, TMS–NIRS studies need to be carefully controlled for artifacts and the results have to be interpreted with caution.

Despite the challenges, we were able to provide new insights into brain function and therefore also to demonstrate the power of TMS in studying the cortical state. In *Publication VI*, we show that TMS can interfere with visuomotor synchronization. By means of this interference, we provide new information about the processing of timed motor actions: the vPMC seems to play a role in the visual transformation related to visually cued motor timing. In addition, we show that biological and non-biological visual cues are processed in a different way.

Publication III sheds light on the questions 1) what happens in the brain during wakefulness that causes the need for sleep? and 2) why do we sleep? We show that cortical excitability increases during wakefulness. The increase may be related to the cognitive and other negative effects of sleep deprivation; higher excitability does not imply higher functional capacity of the cortex, but may rather increase noise in cortical processing. Restoring the excitability to normal level may be one of the functions of sleep. The observed effect of wakefulness and sleep on cortical excitability may result from altered synaptic strengths, as the synaptic homeostasis hypothesis states. In addition, as sleep deprivation alleviates the symptoms in some depressed patients [79], the result suggests that synaptic strengths may be decreased in these patients and that sleep deprivation may restore them to normal levels. The TMS-evoked EEG responses show incredible sensitivity to the altered cortical state due to sleeping history on the single-subject level. Also the repeatability of the responses between experiments made in comparable conditions, which has also been shown in previous studies [130, 40], is evident when comparing the responses recorded after normal sleep and after recovery sleep.

All in all, this Thesis shows that TMS can be used successfully to probe the cortex, bringing us closer to understanding how our minds work. TMS enables interference with complex functions such as the visuomotor integration, which helps better understanding these processes. In addition, TMS combined with EEG is a repeatable and sensitive method to measure changes in the cortical state, both spontaneous and those related to

prior sleep and wakefulness. Although the region that can be stimulated without artifacts in the evoked EEG is restricted by stimulation-related activation of cranial muscles, it can be extended with signal processing methods that reduce the muscle artifacts. Thereby, it is also possible to probe the effective connectivity from brain areas near cranial muscles to other sites. The TMS-induced circulatory changes not related to the hemodynamic response cause a challenge in TMS-evoked hemodynamic measurements, particularly in the TMS–NIRS measurement, which is important to take into account in future studies. In conclusion, when certain limitations related to the artifacts are taken into account, TMS is a powerful tool for studying the cortical state.

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