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Selja Vaalto

Functional Muscle Representations in Cerebral Cortex and Use-Dependent Plasticity in Motor Cortices

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SELJA VAALTO
(née TEITTI)

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ABSTRACT

This thesis describes upper limb muscles' functional representations in contralateral cerebral cortex in healthy subjects as observed with navigated transcranial magnetic stimulation (nTMS). Local inhibitory and excitatory activity of cortical interneurons is compared in muscle representations in non-primary and primary motor areas. Learned motor skill –related plasticity is discussed based on the motor skill-specific findings in the reorganization of muscle representations. In addition to supplementing the information of neuroanatomy and neurophysiology in the healthy brain, an awareness of the distribution of pyramidal tract motoneurons originating from the motor cortices is important when one tries to estimate the recovery capacity in individuals suffering brain deficits such as those after ischemic stroke.

Study I presents muscle representations in contralateral non-primary motor areas (NPMAs), which were found to reside in dorsal premotor area (PMd) and in some subjects also within the supplementary motor area (SMA). Study II shows slightly, but significantly decreased cortical inhibition in NPMAs, which may facilitate the recruitment of motoneurons when additional innervation to the upper limb muscles is needed.

Studies III and IV examine plasticity in motor cortices related to learned motor skills. The spatially suppressed actively-used muscle representation in motor cortex and slightly increased inhibition in NPMA representations in string instrument players, i.e. fine motor skill specialists, shows that focused cortical control is an important factor in fine motor skill performance. In contrast, the larger lower limb muscle cortical representations in figure skaters suggest that the plasticity is skill-specific, perhaps even muscle task-specific. Recruitment of additional motoneuron capacity may be more beneficial in skills demanding synchronous co-activation of multiple muscles.

Overall, the four studies show that cortical motor representations are not strictly somatotopic, as classically presented, but widely distributed in the motor cortices and the functional size of the motor representation varies dynamically according to different demands. Motoneurons originating in NPMAs may be recruited when additional motoneuron capacity is needed. Muscle representations in NPMAs may have an important role in recovery after ischemic or traumatic brain lesions as well as in aiding the functional reorganization caused by brain tumors, which affect pyramidal tract fibers originating in primary motor cortex (M1).

National Library of Medicine Classification: WL 335, WL 307, WL 102
Medical Subject Headings: Brain Mapping; Evoked potentials, Motor; Learning; Motor cortex; Motor Skills; Neuronal plasticity; Transcranial magnetic stimulation

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TIIVISTELMÄ

Väitöskirjassa esitellään yläraajalihasten toiminnallisten edustusalueiden sijoittuminen kontralateraaliselle aivokuorelle terveillä koehenkilöillä. Lihasten edustusalueiden toimintaa estävää ja herkistävää aivokuoritason säätelyä verrataan primaarisella ja sekundaarisella liikeaivokuorella. Tutkimuksissa käsitellään erilaisiin motorisiin taitoihin liittyviä muutoksia liikeaivoalueilla. Sen lisäksi että väitöskirja täydentää perustietoutta motoriikan säätelystä, löydökset liikehermosolujen paikantumisesta aivokuorelle ovat tärkeitä arvioitaessa kuntoutumismahdollisuuksia erilaisten aivovammojen yhteydessä.

Ensimmäisessä osatyössä ilmenee, että yläraajalihasten edustusalueet sijoittuvat kontralateraalisen primaarisen liikeaivokuoren lisäksi sekundaariselle liikeaivokuorelle, tarkennettuna dorsaaliselle premotoriselle alueelle (PMd) ja supplementaariselle motoriselle alueelle (SMA). Toisessa osatyössä havaitaan lievästi alentunut estävien välineuronien vaikutus sekundaarisella liikeaivokuorella, mikä voi edistää tällä alueella sijaitsevien liikehermosolujen käyttöönottoa niissä tilanteissa, joissa lihasten hermotusta täytyy tehostaa. Kolmannessa ja neljännessä osatyössä käsitellään opittuihin motorisiin taitoihin liittyviä muutoksia lihasten edustusalueiden toiminnassa. Kielisoittimien soittajilla todettiin pinta-alallisesti pienemmät aktiivisesti käytetyn käsilihaksen edustusalueet ja lievästi voimistunut paikallinen estävä säätely sekundaarisella liikeaivokuorella instrumentin soittoa harrastamattomiin verrokkeihin verrattaessa. Löydös viittaa siihen, että riittävästi eriytynyt lihaksen edustusalue on yksi tärkeä tekijä hienomotorisessa suorittamisessa. Vastakkainen löydös havaittiin taitoluistelijoilla, joilla aktiivisesti käytetyn alaraajalihaksen edustusalueet olivat laajemmat kuin verrokeilla. Lihasten edustusalueiden toiminnallinen muovautuvuus voi siis olla erilaista lajista ja liikkeen vaatimuksista riippuen. Lihasten edustusalueiden laajeneminen ja uusien liikehermosolujen käyttöönotto voi olla hyödyllistä niissä lajeissa ja liikesuorituksissa, joissa vaaditaan useampien lihasten yhdenaikaista käyttöä.

Yhteenvetona voidaan todeta, että lihasten edustusalueet eivät sijoitu ainoastaan primaariselle liikeaivokuorelle, kuten klassisesti on esitetty, vaan jakautuvat laaja-alaisemmin ulottuen sekundaariselle liikeaivokuorelle. Lihasten edustusalueet ovat dynaamisesti muovautuvia erilaisten käyttövaatimusten mukaan. Sekundaariselle liikeaivokuorelle sijoittuvat liikehermosolut voivat olla tärkeitä etenkin niissä tilanteissa, joissa lihaksen hermotusta täytyy vahvistaa, kuten aivoinfarktin tai muun aivovamman jälkeisessä kuntoutumisessa.

Luokitus: WL 335, WL 307, WL 102
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List of the original publications

This dissertation is based on the following original publications:

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

II Vaalto S, Säisänen L, Könönen M, Julkunen P, Hukkanen T, Määttä S, Karhu J. Corticospinal output and cortical excitation-inhibition balance in distal hand muscle representations in nonprimary motor area. *Human Brain Mapping 32(10): 1692-1703, 2011.*

III Vaalto S, Julkunen P, Säisänen L, Könönen M, Määttä S, Karhu J. Long-term plasticity may be manifested as reduction or expansion of cortical representations of actively used muscles in motor skill specialists. *Neuroreport 24(11): 596-600, 2013.*

IV Vaalto S, Julkunen P, Säisänen L, Könönen M, Määttä S, Karhu J. Increased inhibition in non-primary motor areas of fine motor skill specialists. Submitted.

Contents

Abbreviations

ADM	Abductor digiti minimi muscle
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
aMT	Active motor threshold
BA	Brodmann area
BB	Biceps brachii muscle
BDNF	Brain-derived neurotrophic factor
CB1	Cannabinoid type 1 receptor
CoG	Center of gravity
CS	Conditioning stimulus
DTI	Diffusion tensor imaging
EF	Electric field
EMG	Electromyography
FCR	Flexor carpi radialis muscle
FDI	First dorsal interosseus muscle
FOV	Field of view
GABA	Gamma-aminobutyric acid
GABA(A)	Gamma-aminobutyric acid A-type receptor
GluR1	Glutamate receptor 1
fMRI	Functional magnetic resonance imaging
I-wave	Indirect wave
ICF	Intracortical facilitation
ISI	Interstimulus interval
LTD	Long-term depression
LTP	Long-term potentiation
M1	Primary motor cortex
MEP	Motor evoked potential
MRI	Magnetic resonance imaging
MT	Motor threshold
NBS	Navigated brain stimulation
NMDA	N-methyl-D-aspartate
NPMA	Non-primary motor area
nTMS	Navigated transcranial magnetic stimulation
OP	Opponens pollicis muscle
PAS	Paired associative stimulation
PMA	Premotor area
PMd	Dorsal premotor area
PMv	Ventral premotor area
ppMEP	Paired-pulse motor evoked potential
rMT	Resting motor threshold
rTMS	Repetitive transcranial magnetic stimulation
S1	Primary somatosensory cortex
SICI	Short-interval intracortical inhibition
SMA	Supplementary motor area
SO	Soleus muscle
SOI	Stimulation of interest
TA	Tibialis anterior muscle
TMS	Transcranial magnetic stimulation

TE	Echo time	VL	Vastus lateralis muscle
TR	Repetition time	VM	Vastus medialis muscle

1 Introduction

The motor cortex and the lower parts of pyramidal tract together with lower motor neurons are responsible for the execution of voluntary movements. The majority of corticospinal tract motoneurons originating from the motor cortex cross the midline in the medulla oblongata in a structure called the pyramidal decussation resulting in contralateral innervation of muscles. The origin of the pyramidal tract motoneurons has been classically situated in the posterior border of precentral gyrus (Brodmann area 4) based on cortex cytoarchitecture, especially the existence of gigantopyramidal cells (Betz cells) (Brodmann 1909), and physiological experiments such as cortical resections and cortical stimulations (Penfield and Boldrey 1937). According to these pioneering studies, the posterior part of precentral gyrus is named the primary motor cortex (M1), in which the muscles of different parts of the body are presented somatotopically (Penfield and Boldrey 1937; Penfield W. 1954). There is a kind of differentiating cytoarchitecture, with smaller pyramidal cells and sparser gigantopyramidal cells, and differentiating motor function producing complex limb movements in physiological experiments in more anterior cortical areas and this formed the basis for the naming the cortical areas anterior to the M1 as premotor (PMA) and supplementary motor areas (SMA) (Brodmann 1909; Fulton 1935; Penfield and Welch 1951; Penfield W. 1954).

Non-human primates have multiple muscle representations in non-primary motor areas (NPMAs) in addition to the representations in the M1 (Boudrias, Lee et al. 2010; Boudrias, McPherson et al. 2010; Dum and Strick 2002). In humans, invasive cortical stimulations in patients (Uematsu et al. 1992) and non-invasive brain imaging studies in healthy subjects (Fink et al. 1997; Partanen et al. 2000) have suggested that muscle representations may exist anterior to the M1 also in humans. More advanced imaging methods such as diffusion tensor imaging (DTI) have permitted tracking of the corticospinal tract fibers originating also from NPMAs (Johansen-Berg et al. 2004; Schulz et al. 2012).

Functional and structural plasticity are the unique characteristics of the brain tissue. Motor learning –related plasticity is one of the most widely studied forms of plasticity in healthy subjects. The major plasticity mechanisms in motor skill learning include enforcement of synaptic transmission and recruitment and formation of new synapses in actively used cortical muscle representations (Bütefisch et al. 2000; Liepert et al. 1998; Ziemann et al. 2004). The changes in cortical synaptic signaling alter the functional size of cortical muscle representations, and these are often seen as the expansion and overlapping of actively used muscle representations (Liepert et al. 1999; Pascual-Leone, Nguyet et al. 1995). The area of cortical muscle representations can be evaluated with navigated transcranial magnetic stimulation (nTMS) allowing an exploration of the functional reorganization underpinning motor skill learning.

Transcranial magnetic stimulation (TMS) was introduced in 1980's (Barker et al. 1985). TMS made it possible to examine the distribution of functional muscle representations non-invasively in healthy subjects and the first evidence appeared about the direct pyramidal tract fibers originating from motor representations outside M1 (Uozumi et al. 2004). More sophisticated versions of TMS, nTMS, with magnetic resonance -image guided stimulations, offer a tool to explore adjacent cortical areas such as M1 and NPMAs independently (Ilmoniemi et al. 1999; Krings et al. 2001; Miranda et al. 1997; Paus and Wolforth 1998; Ruohonen and Karhu 2010; Ruohonen et al. 1996). The focus of this thesis was to study the distribution of pyramidal tract motoneurons in cerebral cortex and observe the plasticity in motor cortices in different well-learned motor skills with the aims of nTMS.

This thesis describes functional muscle representations in motor cortices and adds the information about the use-dependent cortical plasticity, which is related to high-level motor performance. The studies show that depending on the demands of the motor skill, cortical reorganization may be directed towards either recruitment or suppression of motoneurons. Widely distributed muscle representations may be beneficial when additional motoneuron capacity is needed as in motor learning or in recovery from a stroke or some other brain lesion affecting the motor cortices or pyramidal tract fibers.

2 Review of the literature

2.1 CLASSIFICATION OF PRIMARY AND NON-PRIMARY MOTOR AREAS

2.1.1 Histology and cytoarchitecture based classification

Cerebral cortex may be classified according to histology and cytoarchitecture to distinctive areas. The neurologist, A.W. Campbell, explored the histology of functionally different areas in cerebral cortex in humans by comparing the cortical histology of human subjects with the cortical histology of non-human primates who had undergone electrical cortical stimulations earlier for identifying the function of different cortical areas. Campbell found that in humans the cortex anterior to Rolandic fissure with giant cells of Betz corresponded histologically to the area responsible for motor function in other mammals (Campbell 1905). The anatomist, K. Brodmann, classified and numbered cortical areas based on cytoarchitectural organization of neurons (Brodmann 1909) (Figure 1).

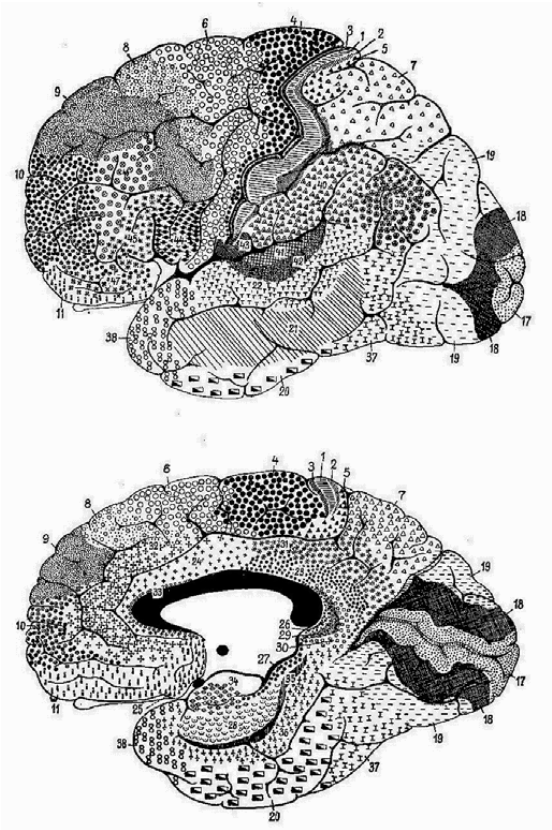

Figure 1. Cytoarchitectural subdivisions of the human cerebral cortex (Brodmann 1909). The upper picture represents the lateral view of the left hemisphere and the lower picture the medial view of the right hemisphere. Frontal lobe is directed to left and occipital lobe to right.

Subsequently, these cytoarchitectural areas have been correlated closely to diverse cortical functions. The agranular cortex with giant pyramidal cells (Betz cells) in cortical layer V was numbered to Brodmann area 4 (BA 4) corresponding to the motor cortex classified by Campbell. Later on BA 4 was named as primary motor cortex (M1), and this is the region which is functionally responsible for muscle movements (Fulton 1935).

The agranular cortex anterior to BA 4 has smaller pyramidal cells and fewer giant pyramidal cells when compared to BA 4. This agranular cortex was numbered as BA 6 and it correlated to the area producing complex motor movements when stimulated and it was later named as the premotor cortex (PMA) (Fulton 1935). Brodmann area 8 anterior to area 6 has a diffuse granular layer (Brodmann 1909). This area corresponds to the anterior portion of supplementary motor area (SMA) (Lee et al. 1999).

2.1.1.1 Probability maps of non-primary motor areas

The exact boundaries of cytoarchitectural and histological cortical areas vary between individuals and, unfortunately, there are no precise anatomical landmarks which can be used to distinguish between separate cytoarchitectural areas. Geyer and co-workers have created probabilistic maps of non-primary and primary motor areas corresponding to BA 6 and BA 4 based on post-mortem examinations of individual cortex histology supplemented with magnetic resonance imaging (MRI) of post-mortem brains (Geyer et al. 1996; Geyer 2004). These probabilistic population maps were created by superimposing individual three-dimensional cortical maps. According to the probabilistic maps, the rostral border of area 6 lies medially rostral to anterior commissure, laterally on the precentral gyrus near the sylvian fissure, and caudally on anterior part of precentral gyrus. Thus, probabilistic maps of NPMAs (BA 6) can be used to locate functional findings according to histological classification of cortex.

2.1.2 Functional classification

The functional classification of motor cortices in humans was originally conducted by electrically stimulating the cortex during neurosurgery. The neurologist and neurosurgeon O. Foerster was one the first scientists who studied the motor areas in the human frontal lobe and discerned differences in the motor responses when the posterior part of precentral gyrus and the more anterior cortical areas were electrically stimulated (Foerster 1936). The most famous classification of motor cortices was made by the neurosurgeon W. Penfield and the neurophysiologist H. Jasper. They localized cortical muscle representations to posterior part of precentral gyrus corresponding to BA 4 and created a topographic map, the so-called motor homunculus (Penfield and Boldrey 1937) (Figure 2). This part of the precentral gyrus was responsible for single muscle movements. In the motor homunculus, the lower limb muscle representations are situated near the interhemispheric fissure in the precentral gyrus, while upper limb muscles are situated more laterally and the face muscles located most laterally in the precentral gyrus near the temporal lobe. The areas anterior to posterior part of precentral gyrus elicited also motor responses with the higher electricity threshold and usually with the longer latencies. The motor responses could be elicited from the medial and superior frontal gyri as well as from the mesial part of the superior frontal gyrus, which is restricted to gyrus cingulum. The excitable area corresponded to BA 6. The responses from these premotor areas were more like movements or postures consisting of activation of multiple muscles (Penfield and Welch 1951; Penfield W. 1954). These areas represented higher order motor functions. Stimulations of mesial and superior part of frontal lobe evoked variety of responses including face responses, vocal responses and inhibition of movements in addition to multiple responses of limb movements (Figure 2). Many of these movements were bilateral. Stimulations also produced very often rhythmic movements or repetitive voice responses. This area was named as the supplementary motor area (SMA) (Penfield and Welch 1951). After the resection of M1, the movements could still

be elicited from SMA and from more lateral parts of PMA indicating that there were some direct connections to the lower motor neurons.

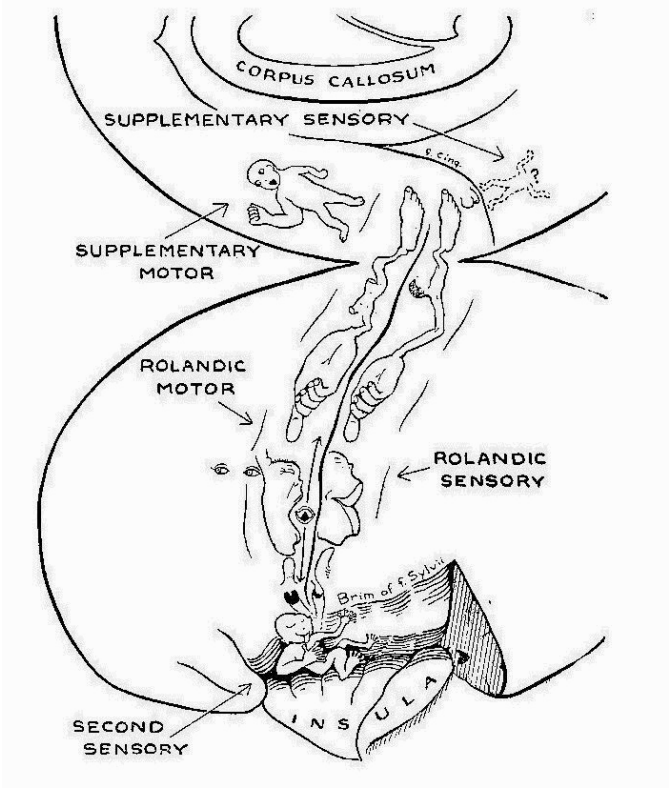

Figure 2. Functionally distinct motor and sensory areas in the human cerebral cortex (Penfield and Jasper 1954). The lower part of the picture represents the lateral aspect of the left hemisphere and the upper part of the picture the medial aspect of the same hemisphere turned upside down. Frontal lobe is directed to left and occipital lobe to right.

Subsequently the distinct role of SMA, more lateral parts of PMA and M1 in initiation, execution, and control of movements was clarified. Intracortical recordings of movement-related cortical potentials have shown that since 1.0–1.5s before movement onset spatially and temporally different components of cortical potentials, the so-called readiness potentials (Bereitschaftspotential), can be recorded from SMA, PMA and M1. The first component arises from SMA, often bilaterally, and is followed by a component from lateral PMA also bilaterally and at about 400 ms prior to movement onset one can detect the component arising from the contralateral M1 and the contralateral PMA (Chiarenza 1993; Kornhuber and Deecke 1965; Shibasaki et al. 1980; Shibasaki 2012). Early potentials are larger with mere complex movements than those elicited for simple movements emphasizing the important role of SMA especially in the preparation of complex movement sequences. Readiness potentials in SMA and in the lateral PMA are somatotopically organized although the somatotopy is not as strict as in M1 (Ikeda et al. 1992; Shibasaki 2012). In addition, non-invasive regional cerebral blood flow experiments have revealed the

important role of SMA in the preparation and control of complex movement sequences and demonstrated functional somatotopy in SMA and in PMA (Cunningham et al. 2013; Orgogozo and Larsen 1979; Roland et al. 1980).

Multiple non-primary motor areas could be distinguished in a movement-related positron emission tomography study conducted by Fink et al. (1997). Motor-related activations were observed in areas corresponding to dorsal premotor area (PMd) and ventral premotor area (PMv) in non-human primates as well as SMA and three separate regions in cingulate sulcus. Later functional studies have demonstrated the presence of separate activations in anterior and posterior parts of PMA and SMA (Picard and Strick 2001). The activations in anterior areas are related to cognitive, sensory, and motivational inputs to motor behavior, whereas activations in posterior areas are more concretely associated with motor patterns. The anterior part of SMA, pre-SMA, is activated when sensory-motor associations are established or retrieved and also in preparation for undertaking complex movement sequences (Kurata et al. 2000; Lee et al. 1999; Sakai et al. 1999), while the posterior part, SMA-proper, is active in controlling movement execution (Lee et al. 1999). Activation of posterior PMd is observed in the preparation phase of forthcoming actions (Picard and Strick 2001; Pochon et al. 2001) and anterior PMd in movement imagination, conditioned visuo-motor associations, and in response selection (Gerardin et al. 2000; Grafton et al. 1998; Toni et al. 1999). The posterior PMv is involved in reaching and grasping movements, while anterior PMv is active during the manipulation of objects, as well as in imaging, observation, and imitation of movements and actions (Binkofski et al. 1999; Buccino et al. 2001; Nishitani and Hari 2000; Rizzolatti et al. 2002). The anterior PMv is most probably situated in BA 44 while SMA and PMd are located in BA 6 (Binkofski et al. 1999; Nishitani and Hari 2000; Picard and Strick 2001). Movement-related activations can also be observed in cingulate areas (Picard and Strick 2001). Posterior part of cingulate sulcus is active during movement execution, whereas more anterior areas are active in conflict monitoring (Botvinick et al. 1999) and in action selection (Petersen et al. 1988) .

In M1, latest functional MRI (fMRI) studies have revealed representations of differently directed arm movements (Cowper-Smith et al. 2010; Eisenberg et al. 2010; Toxopeus et al. 2011). Differing neuronal activation patterns corresponding to the direction of arm movements were first reported in monkeys (Georgopoulos et al. 1986). These findings indicated that motoneurons in limb muscle representations in M1 were directionally organized. In addition to M1, there are studies demonstrating that directional organization of movements is represented in non-human primates and in humans also in NPMAs (Kakei et al. 2001; Tankus et al. 2009).

2.1.3 Classification based on anatomical connections

Neural tracts connecting different cortical and subcortical areas form the basis for functional connectivity. Thus, functionally different areas may be divided based on connection profiles. Connection profiles also offer insights into the possible function of different areas. Combined studies of DTI and fMRI have revealed differences in anatomical connection profiles between pre-SMA and SMA-proper and also between the anterior and posterior parts of PMv and PMd (Johansen-Berg et al. 2004; Leh et al. 2007; Schubotz et al. 2010). The more anterior parts of SMA and PMA are interconnected to other prefrontal regions, which is compatible with the more cognitive role of these areas, while the more posterior parts are connected to M1 and to spinal cord (Johansen-Berg et al. 2004; Picard and Strick 2001; Schubotz et al. 2010; Seo and Jang 2013).

2.2 MUSCLE REPRESENTATIONS IN NON-PRIMARY MOTOR AREAS

2.2.1 Muscle representations in non-human primates

In contrast to the situation in the human motor homunculus locating in precentral gyrus, studies of macaque monkeys have revealed six separate fore- and hindlimb muscles representations in NPMAs in addition to M1 (Dum and Strick 1991, 2002; He et al. 1993, 1995). These studies were conducted by injecting retrograde transported tracer into cervical and lumbosacral segments of the spinal cord. Separate representations located in each non-primary motor area including PMv, PMd, SMA, and cingulate areas. The connections of axons originating from NPMAs with neurons in spinal cord were studied by injecting an anterograde tracer into each representation area and mapping the corticospinal terminals in cervical segments of spinal cord (Dum and Strick 1996). The terminations were quite similar to that of M1. The densest terminations were located in the intermediate zone of spinal cord but there were also terminations in the ventral horn providing evidence for direct connections to lower motor neurons in addition to connections to spinal interneurons. The terminations of neurons originating from NPMAs were not as dense as the terminations originating from M1. The densest terminations originating from NPMAs were located in the lower cervical segments, which project their axons to distal hand muscles.

Functional studies of multiple motor representations in monkeys have shown that there are direct projections from NPMAs to lower motoneurons but the functional connectivity is much weaker when compared to the functional connectivity between upper motoneurons originating from M1 and the lower motoneurons (Boudrias, Lee et al. 2010; Boudrias, McPherson et al. 2010).

2.2.2 Muscle representations in humans

Corticospinal tract fibers originating from NPMAs as well as those from the parietal lobe were described in humans in 1960's in a post-mortem study of the pyramidal tract of a patient who had undergone two ablations of precentral gyrus due to involuntary movements since early childhood (Jane et al. 1967). They found that the volume of the pyramidal tract fibers originating from operated hemisphere were 40% from the volume of fibers originating from the intact hemisphere and concluded that 60% of fibers had originated from M1 (Jane et al. 1967). Thereafter DTI studies have detected corticospinal tract fibers originating from M1, SMA, PMd and PMv in healthy humans and in patients with brain lesions (Johansen-Berg et al. 2004; Newton et al. 2006; Schulz et al. 2012; Seo and Jang 2013). The volumes of the tracts originating from SMA and PMA are smaller than the tract volume originating from M1 (Seo and Jang 2013).

TMS and electrical cortical stimulations of patients with brain lesions have demonstrated corticospinal tract fibers originating from cortical areas anterior to M1 (Fridman et al. 2004; Mikuni et al. 2007; Mäkelä et al. 2012; Uematsu et al. 1992). Fridman et al. (2004) showed that after ischemic stroke and damage of corticospinal tract fibers the motor-evoked potentials (MEPs) could be elicited from PMA of the affected hemisphere. In the study of Uematsu et al. (1992) the electrical cortical stimulations of epilepsy patients evoked muscle responses more than 10 mm anterior from central sulcus. In the studies of Mikuni et al. (2007) and Mäkelä et al. (2012), the corticospinal tract fibers originating from cortical areas anterior to M1 were identified both functionally and anatomically.

The challenge has been to identify the function of muscle representations outside M1 in healthy human subjects. The findings in patients with brain lesions do not correspond to unaffected human brain due to lesion-related plasticity, and the anatomical connections visualized by DTI do not reveal the function of the fibers. In the study of Partanen et al. (2000), the function of corticospinal tract was monitored during surgery in scoliosis patients by recording pyramidal tract potentials antidromically from the cortex. The field distribution of potentials identified a wide area of motor neurons anterior to M1 (Partanen

et al. 2000). Kim et al. (2004) showed that after intensive motor practice, the responses of hand muscles were evoked from a larger area, especially from more anterior areas, corresponding to NPMAs, than before the practice period. The finding was interpreted as reflecting learning-related plasticity in NPMAs. In the study of Uozumi et al. (2004), hand muscle responses could be elicited anterior to M1 by stimulations of BA 44 on the lateral convexity of hemisphere. Fast-latency MEPs were postulated to represent direct corticospinal projections from BA 44 corresponding to the posterior part of speech-related cortical areas.

2.3 MECHANISMS OF CORTICAL PLASTICITY

The cerebral cortex has the capability to react to different demands not only by modifying function of neurons but also by altering the structure of neurons and routes of neuronal pathways. Cortical plasticity consists of various forms of functional and structural plasticity.

2.3.1 Functional plasticity

Functional plasticity refers to mechanisms of plasticity which alter the function in synapses. Functional plasticity may be divided into rapid, long-lasting, Hebbian synaptic plasticity, and to slower, non-Hebbian synaptic plasticity (for a review see Feldman 2009; Hebb 1949). Functional plasticity has been extensively studied in cortical sensory neurons and, so far, some forms of plasticity have been described only in visual, auditory, and sensory cortices.

Hebbian plasticity refers to spike-timing -dependent plasticity, in which temporally strongly correlated pre- and postsynaptic activity leads to an increase in the strength of synaptic transmission whereas weakly correlated pre- and postsynaptic activity is followed by a decrease in the strength of synaptic transmission (Hebb 1949). Long-term potentiation (LTP) and long-term depression (LTD) refer to use- and activity-dependent rapid, long-lasting synaptic plasticity. LTP and LTD are also mediators of Hebbian synaptic plasticity. LTP is characterized by a long-term increase in synaptic strength and is usually preceded by a temporally strongly correlated pre- and postsynaptic activity (for a review see Feldman 2009; Malenka et al. 1989). Most often LTP is expressed in excitatory synapses in different cortical areas including motor, visual, and sensory cortices (Castro-Alamancos et al. 1995; Hess and Donoghue 1994; Kirkwood and Bear 1994), and it is especially important in the reinforcement of actively used synapses (Rioult-Pedotti et al. 2000). In LTP, synaptic strengthening usually occurs via N-methyl-D-aspartate (NMDA) receptors. The increase in intracellular calcium levels occurring after postsynaptic NMDA receptor stimulation and other sources activates many kinases, which lead to phosphorylation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and insertion of GluR1-containing AMPA receptors into synapses (Malinow and Malenka 2002). Long-lasting LTP leads to altered gene expression (for a review see Feldman 2009). Another form of LTP is expressed presynaptically and is mediated by nitric oxide signaling leading to an increase in release probability in the presynaptic terminals (Hardingham and Fox 2006).

LTD is described as a rapid, long-lasting decrease in synaptic strength and is usually induced by poorly correlated pre- and postsynaptic activity (for a review see Feldman 2009). LTD is the inverse of LTP and usually associated with synapses with deprived inputs. LTD has been detected in motor cortex in addition to cortical areas processing perceptual information (Hess and Donoghue 1996). Various forms of LTD exist: NMDA receptor-dependent LTD leads to dephosphorylation of the AMPA receptor GluR1 subunit and the internalization of AMPA receptors (Feldman et al. 1998), in cannabinoid type 1 – LTD (CB1-LTD) the postsynaptic calcium level increase leads to endocannabinoid synthesis and increased endocannabinoid signaling to presynaptic CB1 receptors decreasing the

release probability in the presynaptic terminals (Chevaleyre et al. 2006). The metabotropic glutamate receptor-dependent LTD is a third major form of LTD (Barbara et al. 2003).

Homeostatic plasticity represents a slower, non-Hebbian synaptic plasticity. Homeostatic plasticity balances synaptic strength towards the baseline and is also called synaptic scaling (for a review see Feldman 2009; Turrigiano and Nelson 2004). Cortical scaling of excitatory synapses is most often mediated by AMPA receptors similarly to NMDA-LTP and NMDA-LTD. An elevated neuronal activity is followed by synaptic scaling towards a decrease in activity and vice versa (for a review see Feldman 2009; Turrigiano and Nelson 2004). It is not clearly understood how homeostatic plasticity is activated but the secretion of the cytokine, tumor-necrosis factor-α, has been claimed to be a one potential mediator (for a review see Feldman 2009; Stellwagen and Malenka 2006).

Metaplasticity refers to the type of plasticity, which alters the synaptic capability to produce LTP and LTD. While deprived inputs induce LTD in synapses, metaplasticity increases the capability of the same synapses to produce LTP in response to forthcoming signals (Bear et al. 1987; for a review see Feldman 2009; Murakami et al. 2012).

Gamma-aminobutyric acid (GABA) is a major inhibitory neurotransmitter in the central nervous system. Mature GABAergic neurons form inhibitory synapses with target cells. In addition to excitatory synapses, also GABAergic synapses are capable of undergoing activity-dependent long-term plasticity (for a review see Feldman 2009; Gaiarsa et al. 2002). The plasticity in GABAergic synapses mediates the expression of plasticity in target neurons. In M1, blockade of GABA(A) receptors by receptor antagonist bicuculline methiodide has enhanced the induction of LTP in excitatory synapses (Hess et al. 1996). In primary somatosensory cortex (S1), the overuse of sensory pathways is followed by increased activation and formation of GABAergic synapses in cortical target area showing that plasticity in GABAergic synapses is important in maintaining the excitatory-inhibitory balance in cortex (for a review see Feldman 2009; Knott et al. 2002).

2.3.2 Structural plasticity

Structural plasticity may be divided into the formation of new synapses and axonal sprouting. The formation of spines, which is followed by synaptogenesis, may be observed after hours, even days of increased cortical activation. Axonal sprouting represents a slower form of structural plasticity and is observed usually after several days or weeks of the onset of continuous, increased, cortical activity. Classically it is thought that structural plasticity follows functional plasticity (for a review see Feldman 2009) and is related to the consolidation of repetitively active neuronal networks (Kleim et al. 2004).

New dendritic spines continuously appear and disappear while most of the stabilized spines persist for months. The formation of dendritic spines precedes the formation of synapses. Knott et al. (2006) observed that new dendritic spines which persisted for at least four days had developed new synapses whereas the spines disappearing in less than four days lacked synapses. Holtmaat et al observed that altered sensory information stabilized new spines and destabilized previously persistent spines, providing evidence that the stabilization of dendritic spines and the formation of new synapses is experience-dependent (Holtmaat et al. 2006). In M1, synaptogenesis is preceded by functional plasticity and is detected after one week of practice of a new motor skill (Kleim et al. 2004).

Axonal sprouting refers to the formation of new axon collaterals and projections to novel targets. Similar to synaptogenesis, axonal sprouting is also experience-dependent (Hihara et al. 2006). Axonal sprouting is mediated by several neurotrophins (for a review see Feldman 2009; Grasselli and Strata 2013).

2.4 MOTOR LEARNING -RELATED PLASTICITY

2.4.1 Plasticity related to different types of motor training

Motor training may be classified into skill, strength, and endurance training. Skill training, which is characterized as training of complex movement sequences, induces plasticity mainly at the cortical level (for a review see Adkins et al. 2006). Skill training -related cortical plasticity may be observed as synaptic strengthening (Rioult-Pedotti et al. 2000; Ziemann et al. 2004), synaptogenesis (for a review see Adkins et al. 2006; Kleim et al. 2004), reorganization of cortical representations of actively used muscles (for a review see Adkins et al. 2006; Kleim et al. 2004; Liepert et al. 1999; Pascual-Leone, Nguyet et al. 1995),and increased corticospinal excitability (Pascual-Leone, Nguyet et al. 1995). Synaptogenesis and reorganization of muscle representations are dependent on cortical protein synthesis, in which brain-derived neurotrophic factor (BDNF) plays an important role (Kleim et al. 2006). Skill training induces plasticity also at the spinal level, which can be observed as altered spinal stretch reflexes while acquiring a new motor skill (for a review see Adkins et al. 2006). Usually actively used muscles spinal stretch reflexes decrease as individual acquires a new skill. Progressive adaptation of reflexes is thought to be mediated by enhanced presynaptic inhibition of spinal motoneurons (Ung et al. 2005). In addition to motor cortex and spinal cord, skill training related plasticity has been observed in cerebellum (Boyden et al. 2004; Kleim et al. 1998; Park et al. 2009) and basal ganglia (for a review see Adkins et al. 2006; Hamzei et al. 2012; Yin et al. 2009).

Strength training does not alter cortical representations of actively used muscles and decrease the cortical excitability in actively used muscle representations (for a review see Adkins et al. 2006; Jensen et al. 2005; Remple et al. 2001). Instead, strength training induces synaptogenesis in spinal excitatory synapses (Remple et al. 2001) and an increase in the amplitude of the spinal stretch reflexes (Aagaard et al. 2002), highlighting the important role of spinal plasticity in strength training (for a review see Adkins et al. 2006).

Endurance training induces angiogenesis and an increase in blood flow in motor cortex (for a review see Adkins et al. 2006; Kleim et al. 2002). Endurance training also increases protein synthesis including elevations in BDNF levels (Klintsova et al. 2004). In contrast to skill training, endurance training does not alter cortical representations of actively used muscles (Kleim et al. 2002). Angiogenesis, increased blood flow, and increased protein synthesis possibly create a more supportive environment for cortical neurons (for a review see Adkins et al. 2006). Endurance training has also effects at the spinal level, usually increasing spinal stretch reflexes (for a review see Adkins et al. 2006; Koceja et al. 2004).

2.4.2 Plasticity in motor skill learning

Skill learning –related plasticity may be divided into the fast initial plasticity observed within minutes after practicing a new skill, and slower plasticity related to the consolidation of the skill and which requires hours or days after continuous practice. The initial plasticity is mainly manifested as functional plasticity such as an increase in the strength of synaptic transmission in the cortical representations of actively used muscles, whereas plasticity related to the consolidation of a skill is associated in structural changes in the cortical representations of actively used muscles (Karni et al. 1995; Karni et al. 1998; Kleim et al. 2004; Ziemann et al. 2004).

2.4.2.1 Initial plasticity in skill learning

In the initial phase of a new motor skill learning, GABAergic inhibition decreases and excitatory synapses strengthen via LTP in M1 in the representation area of actively used muscles (Bütefisch et al. 2000; Floyer-Lea et al. 2006; Rioult-Pedotti et al. 2000; Ziemann et al. 2004). If the practiced motor skill demands simultaneous activation and relaxation of adjacent muscles, then cortical inhibition is decreased in actively used muscle

representation and increased in effortlessly relaxed muscle representation (Liepert et al. 1998). The changes in GABAergic inhibition and the strengthening of synapses via LTP occurs and may be observed in minutes after the onset of intensive training such as fast thumb movements in a certain direction (Liepert et al. 1998; Ziemann et al. 2004). If two muscles are used synchronously, the short-lasting reorganization of muscle representation towards a greater overlap occurs in minutes (Liepert et al. 1999) and the cortical area evoking muscle responses in actively used muscle rapidly enlarge due to increased excitation (Karni et al. 1995; Pascual-Leone, Nguyet et al. 1995).

In addition to M1, rapid functional changes occur in multiple brain regions in the initial learning phase of a new motor skill. The locations of decreased and increased activations in subcortical areas, cortical areas, and cerebellum differ depending on the practiced skill. In the initial learning phase, wider cortical networks display either increased or decreased activations when compared to long-term learning related activation patterns, in which increased activity is observed, especially in S1 and M1 as well as in subcortical structures (Floyer-Lea and Matthews 2005).

2.4.2.2 Consolidation of the skill

Continuous training leads to the consolidation of the skill. It is related to synaptogenesis and the long-term reorganization of actively used muscle representations. Synaptogenesis is observed in rodents M1 after one week of practice onset (Kleim et al. 2004). In humans, cortical gray matter volume increments have been observed after a few days of practice in relation to the improvement occurring in a skill (Draganski et al. 2004; Gaser and Schlaug 2003; Gryga et al. 2012; Taubert et al. 2010). Depending on the skill, the increments or decrements in the gray matter volumes are observed in different cortical areas such as M1, PMA, and SMA (Gaser and Schlaug 2003; Gryga et al. 2012; Taubert et al. 2010). After days of practice, changes in the white matter structure are also observed in the cortical areas related to the acquired motor skill (Scholz et al. 2009; Taubert et al. 2010). Animal studies have also revealed an extension of corticocortical axons into new areas, which are crucial in a trained motor skill (Hihara et al. 2006).

Functional studies have shown that a representation area of an acquired movement sequence in M1 is larger than the representation area of an unskilled sequence even if performed using the same muscles as in a skilled sequence (Karni et al. 1995; Karni et al. 1998). In contrast, after years of practice, activation of cortical and subcortical areas becomes more focused during performance of a skilled movement as compared to less adapted controls indicating that a diminished neuronal network is needed for correct movement performance after there has been a consolidation of a skill (Hund-Georgiadis and von Cramon 1999; Jancke et al. 2000; Krings et al. 2000; Lotze et al. 2003; Milton et al. 2007). Cortical areas evoking muscle responses in actively used muscles have been found to be larger in motor skill specialists when compared to the representation areas of less used muscles or control subjects (Pascual-Leone et al. 1993; Schwenkreis et al. 2007). Even after consolidation of a skill, dynamic changes have been observed in the size of the representation area depending on the latency from the last practice session indicating that rapid changes still occur in neuronal excitability due to practice (Pascual-Leone, Wassermann et al. 1995).

2.5 TRANSCRANIAL MAGNETIC STIMULATION

2.5.1 Basics of transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) is a non-invasive method capable of activating neurons in the cerebral cortex. Since 1980's (Barker et al. 1985), TMS has been extensively used for exploring the function of corticospinal tract in the clinic. TMS is widely used in the

determination of central motor conduction velocity, which is affected by demyelination or axonal loss of upper motoneurons.

In TMS devices, magnetic stimulation coil is connected to stimulator. The circuit in the stimulator contains a discharge capacitor, which is connected in series with a coil via a thyristor. Stimulator generates a short current pulse in a coil by discharging a charged capacitor via the change in the thyristor conductivity (Ruohonen 2003). The generated waveform of a current is sinusoidal with a peak value of 5−10 kA. Depending on the coil properties, the waveform may be monophasic, biphasic or polyphasic. The duration of a current pulse varies between 200-600 μs depending on the coil (Ruohonen 2003). A current pulse in a coil generates a rapidly changing magnetic field that induces an electric field under the coil. When a coil is placed on the scalp, the magnetic field penetrates skin and bone tissues and transient electric field is induced on the cerebral cortex. The induced electric field generates electric currents in non-homogenous brain tissue. These currents can depolarize neurons' cell membranes and trigger an action potential. When stimulations are targeted to the motor cortex, the action potentials in the upper motoneurons may depolarize lower motoneurons transsynaptically in the spinal cord. Generated action potentials in lower motoneurons depolarize muscle cell membranes and elicit a brief activation of a muscle observed as a muscle response in the electromyography (EMG) recording.

TMS elicited MEPs have usually about 2 ms longer latencies than muscle responses evoked by transcranial electrical stimulation, which indicates that with TMS upper motoneurons are mostly depolarized transsynaptically via excitable cortical interneurons (Amassian et al. 1989; Day et al. 1989). However in certain coil orientations also equal latencies have been measured suggesting that direct axonal activation of motoneurons is also possible (Amassian et al. 1989; Day et al. 1989). The most efficiently activated cortical area is the area with the strongest electric field (Ruohonen 2003). TMS can depolarize curved and short axons more easily than straight and longer axons (Maccabee et al. 1993). Curved axons are most easily depolarized near to the bends (Maccabee et al. 1993). The majority of upper motoneuron axons curve in a caudal direction from the posterior wall of precentral gyrus, which is buried in a central sulcus, and thus the optimal activation of upper motoneurons is achieved with the coil orientation inducing an electric field and current perpendicular to the central sulcus.

The shape of a coil determines the shape of an induced electric field on the cortex (Ruohonen 2003). In circular coils, the induced electric field mimics the form of a coil and is wide-spread over a circular cortical area. In a figure-of-eight coil, two circular coils are attached and the electric field maximum is induced below the center of the coil where the two wings join. The figure-of-eight coil induces focal electric field and is more accurate in stimulations of discrete cortical areas.

2.5.2 Navigated transcranial magnetic stimulation

Navigated transcranial magnetic stimulation (nTMS) combines TMS and neuronavigation. In nTMS, coil location is visualized on the three-dimensional head model based on individual MRIs during TMS examination enabling accurate positioning of the coil above certain cortical areas (Ilmoniemi et al. 1999; Krings et al. 2001; Miranda et al. 1997; Paus and Wolforth 1998; Ruohonen et al. 1996). Navigated brain stimulation (NBS) system (Nexstim Ltd., Helsinki, Finland) calculates the induced electric field and displays the location and direction of the strongest electric field on the cortex in addition to providing information about the coil location (Hannula et al. 2005; Ruohonen and Karhu 2010) (Figure 3).

By using the navigation tool, stimulations can be repeated to previously stimulated targets. The repetition of stimulations to precise targets minimizes the spatial error when focal cortex function is being studied (Danner et al. 2008; Julkunen et al. 2009; Säisänen et al. 2008) or it can assess the spread of cortical activation from a focal stimulation target

(Lioumis et al. 2009; Massimini et al. 2005). Functionally different cortical areas may be stimulated with equal voltages based on the calculations of the estimated electric field in the different distances of cerebral cortex from the scalp (Lioumis et al. 2012).

The accuracy in NBS is based on co-registration of the subject head to the three-dimensional head MRIs, and co-registration of the coil with respect to the subject's head. The mismatch is usually restricted to 4 mm enabling reasonable accuracy in the positioning of the coil, provided that placement of coil trackers is ideal. The subject wears an optically tracked eye frame. In the co-registration the external landmarks of the head, usually nasion and ear tragus bilaterally, are marked on MRI in navigation software; and the same landmarks on subject's head are pointed by using optically tracked pointer. Additional nine scalp points on subject's head are pointed to improve the accuracy.

The calculation of the electric field distribution in the three-dimensional reconstructed MRIs is based on a spherical model (Sarvas 1987; Tarkiainen et al. 2003). The most probable stimulation site is the area where an electric field is at its strongest (Ravazzani et al. 1996; Ruohonen 2003; Thielscher and Kammer 2002). The computed electric field does not account for details of geometry or material- and tissue-specific conductivity differences but it will account for the stimulation intensity, coil parameters (the shape of copper wiring inside the coil, three-dimensional position and orientation of the coil) as well as local head curviture (Hannula et al. 2005).

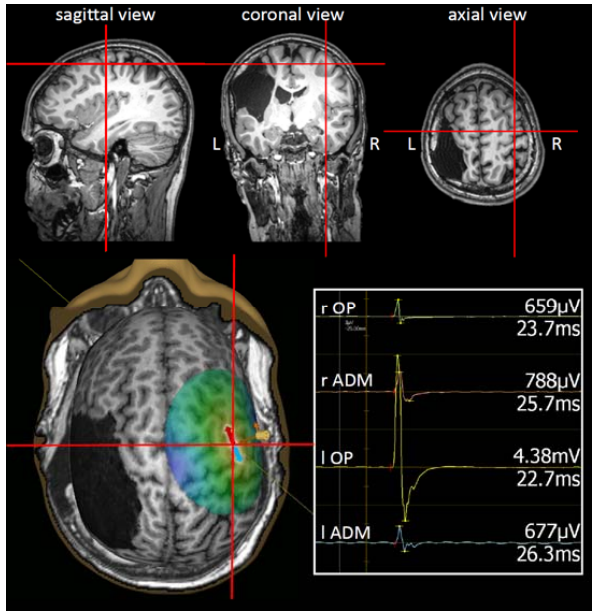

Figure 3. Navigated brain stimulation (NBS) in cerebral palsy patient shows overlapped left and right hand muscle representations in the right hemisphere. The right hand is innervated by ipsilateral corticospinal tracts from the right hemisphere and left hand by contralateral tracts from the right hemisphere to left hand muscles. Sagittal, coronal, and axial projections of the MRIs are shown in the upper row. The picture in the lower left corner visualizes the coil position on the scalp as yellow cylinder and the area of the strongest electric field in the junction of blue and red arrow. The arrow in the cylinder and the red arrow on the scalp show the direction of the stimulating current. The window in the lower right corner shows triggered EMG episodes and motor evoked potentials in hand muscles. r OP = right opponens pollicis; r ADM = right abductor digiti minimi; l OP = left opponens pollicis; l ADM = left abductor digiti minimi.

The advantage of nTMS in the mapping of motor representations is the direct activation of corticospinal tract neurons when compared with other non-invasive imaging methods. The accuracy of nTMS is ≤ 1 cm in comparison with direct cortical stimulation (Takahashi et al. 2013). This is the reason why NBS and other forms of nTMS are commonly used in presurgical mappings of motor representations (Picht et al. 2009; Picht et al. 2012; Säisänen et al. 2010; Takahashi et al. 2013; Vitikainen et al. 2009) (Figure 4).

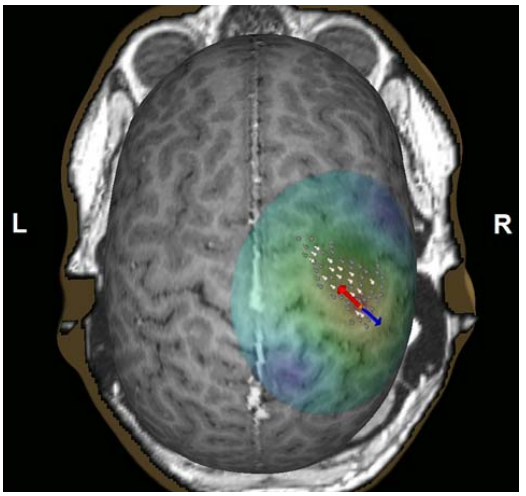

Figure 4. The presurgical mapping of left hand motor representation from the right hemisphere in brain tumor patient. The cerebral cortex is viewed from above (L, left side of the head; R, right side of the head). White dots visualize the stimulation points eliciting muscle responses in the selected left hand muscle and grey dots the stimulation points without responses. In this patient, the cortical representation of a hand muscle (white dots) is located in the affected right hemisphere in a tumor area.

2.5.3 TMS variables

Navigated TMS can be used to study local cortical functions, cortico-cortical connections (Baumer et al. 2006; Ferbert et al. 1992; Lioumis et al. 2009; Massimini et al. 2005), upper and lower motoneuron functions as well as the functional connections between sensory and motor cortices (Chen et al. 1999; Sailer et al. 2003; Tokimura et al. 2000).

TMS may be used to measure and produce cortical plasticity (Bütefisch et al. 2000; Rosenkranz et al. 2007; Stefan et al. 2000; Ziemann et al. 2004). Paired associative stimulation (PAS), in which peripheral nerve electrical stimulation precedes cortical TMS, produces LTP or LTD in cortical synapses depending on the interstimulus interval of the electrical stimulation and the TMS pulse, in other words, the time interval between sensory afferent signal and activation of cortical neurons by the TMS pulse (Stefan et al. 2000). If the LTP-type functional plasticity already exists in synapses, the PAS protocol does not produce LTP. By the means of PAS, motor learning related LTP-type plasticity has been demonstrated by TMS (Ziemann et al. 2004). Repetitive stimulations delivered at low (≤ 1 Hz) frequencies will inhibit but at high (≥ 5 Hz) frequencies will excite the function of underlying neurons; this forms the basis for the therapeutic use of repetitive TMS (rTMS) (Khedr et al. 2005; Lefaucheur et al. 2011; Schutter 2009, 2010; Ziemann et al. 2008).

Depending on the aim of a study or therapy different paradigms and variables can be chosen. The variables presented below have been used in separate studies of this thesis and they depict the methods which are often used in studies of local motor cortex function.

2.5.3.1 Motor evoked potentials

Motor evoked potential (MEP) is a muscle response elicited by motor cortex stimulation and activation of the motor pathway from the cortex to the muscle. Usually both MEP amplitudes and latencies from the stimulation moment to the beginning of MEP are measured. MEPs may be elicited by cortical, spinal nerve root, brachial plexus, and peripheral nerve stimulations. A comparison of MEP latencies between cortex and spinal nerve root stimulations can allow an estimation of central conduction velocity and localization of motor tract damage (Barker et al. 1986; Segura et al. 1990). The size of MEPs is usually described as the peak-to-peak amplitudes measured from a selected muscle and expressed either as milli- or microvolts. MEP amplitudes describe motor pathway integrity and in addition, the efficiency of synaptic transmission at the neuromuscular junction (Brouwer and Ashby 1990; Oh et al. 1996). In addition to longer MEP latencies, a reduction in cortically elicited MEP amplitudes has been related to pyramidal tract damage such as that occurring after stroke or in motoneuron disease (Bembenek et al. 2012; Eisen et al. 1990). The appearance of MEPs after pyramidal tract injury points to a better prognosis when estimating the recovery potential after brain injury (Bembenek et al. 2012; Stinear et al. 2007). The increase of MEP amplitude is observed shortly after motor skill training reflecting the recruitment of new synapses (Liepert et al. 1998), more efficient synaptic transmission (LTP) (Ziemann et al. 2004) and possibly the recruitment of additional motoneurons (Liepert et al. 1999). MEP amplitudes are higher when muscle activation is increased (Säisänen et al. 2008). Imaging and observation of movements also increase MEP amplitudes (Bucchioni et al. 2013; Facchini et al. 2002; Li et al. 2009). MEP amplitudes are sensitive to minor changes in the strength of the stimulating electric field in the cortex (Julkunen et al. 2009). In TMS studies, MEP characteristics are usually measured by applying stimulation intensity higher than MT i.e. 120% of individual motor threshold (MT) of selected muscle.

2.5.3.2 Motor thresholds

The motor threshold (MT) is used to describe the level of motor pathway excitability. In TMS studies, MT is usually defined as a percent of maximal stimulator intensity producing muscle responses with the amplitude equal or higher than 50 μV in at least half of the stimulations when the optimal cortical representation area of the selected muscle is stimulated (Rossini et al. 1994). If nTMS device provides estimate calculation of electric field, MT can be depicted also as an electric field value (V/m) (Danner et al. 2012; Julkunen et al. 2012; Ruohonen and Karhu 2010). MT can be determined separately for resting muscles and slightly activated muscles. Muscle activation increases motor pathway excitability, most probably at both cortical and spinal levels (Brouwer et al. 1989; Datta et al. 1989) and decreases MT, which means that the active MT (aMT) is lower when compared to resting MT (rMT). Individual MT can serve as a reference value when selecting stimulation intensities for other TMS tests described often as the percent of MT.

TMS activates upper motoneurons most probably transsynaptically, which means that MT reflects excitability in intracortical interneurons in addition to the upper motoneurons, lower motoneurons and muscle fibers. At the cellular level, MT expresses membrane excitability (Ziemann et al. 1996 b). Membrane excitability is decreased in cortical neurons and MT increased by the kinds of antiepileptic drugs which block sodium- and calcium-channels in presynaptic terminals and cause a decrease in excitatory postsynaptic potentials (Ziemann et al. 1996 b). MT is also altered in certain type of epilepsies (Danner et al. 2013). In addition to membrane excitability, MT reflects the effectiveness of motoneurons in the

pyramidal tract (Brouwer and Ashby 1990). MT is lower for muscles with the densest connections from the upper motoneurons to the lower motoneurons and higher for muscles with weaker connections (Brouwer and Ashby 1990). Pyramidal tract damage increases MT (Butler et al. 2005; Caramia et al. 1991; Tallus et al. 2012). The recruitment of the upper motoneurons during motor skill learning has been related to a decrease in MT values but results differ depending on the skill being trained (Pascual-Leone et al. 1993; Pearce et al. 2000).

MT is to some extent affected by drowsiness as seen in the elevated MT values observed after sleep deprivation (De Gennaro et al. 2007). It is not significantly affected by caffeine (Cerqueira et al. 2006). It is also not significantly affected by positive allosteric modulators of GABA(A) receptors, benzodiazepines, and other antiepileptic drugs, which increase the magnitude of GABA and enhance intracortical inhibition (Ziemann et al. 1996 a, 1996 b).

2.5.3.3 Cortical motor output maps

Cortical motor output maps are used to represent the location and size of cortical muscle representation areas. The size of cortical muscle representation areas has been usually measured by stimulating the cortex at standard distances using the grid and constant intensity, and after the stimulations quantifying the area in two-dimensional space. The number of active locations in the grid has been counted or volume maps have been computed by summing up all stimulus responses (Foltys et al. 2003; Gagne et al. 2011; Hetu et al. 2011; Kesar et al. 2012; Malcolm et al. 2006; Triggs et al. 1999).The location of muscle representations can be defined by the center of gravity (CoG), in which the location of the stimulation is weighted with the height of MEP amplitude (Wassermann et al. 1992). The area producing the highest MEPs represents the densest and optimal muscle representation and there is gradual decrease in MEP amplitudes in surroundings with weaker corticospinal connections (Wassermann et al. 1992). Motor learning -related cortical plasticity can be displayed as changes in cortical motor output maps or displacements in CoGs (Pascual-Leone et al. 1993; Pascual-Leone, Nguyet et al. 1995; Pascual-Leone, Wassermann et al. 1995; Pearce et al. 2000; Schwenkreis et al. 2007; Tyc et al. 2005). It has also been shown that pathological brain processes change cortical motor output maps (Forster et al. 2012; Säisänen et al. 2010).

2.5.3.4 Short interval intracortical inhibition (SICI) and intracortical facilitation (ICF)

TMS activates upper motoneurons transsynaptically. Therefore the function of inhibitory and excitatory cortical interneurons can be examined with TMS (Claus et al. 1992; Di Lazzaro et al. 1998; Kujirai et al. 1993; Ziemann et al. 1996 b; Ziemann, Rothwell et al. 1996). Cortical interneurons can be activated by lower stimulation intensities than those needed to activate motoneurons. The inhibitory or facilitatory effect on cortical motoneurons can be measured locally by using paired-pulse measures, in which the first pulse (conditioning stimulus, CS) is delivered at a intensity lower than MT and the following second pulse (test pulse) is delivered at the suprathreshold stimulation intensity. Depending on the interstimulus interval (ISI), the inhibitory or facilitatory effect may be more pronounced seen as decrease or increase in MEP amplitude. The effectiveness of inhibitory and facilitatory interneurons can be estimated by comparing the paired-pulse MEP (ppMEP) amplitude to the single-pulse MEP amplitude. Changes in intracortical inhibition and intracortical facilitation are crucial in activity-dependent cortical plasticity and are related to pathological brain processes (Beck et al. 2008; Bütefisch et al. 2000; Bütefisch et al. 2003; Liepert et al. 1998; Ridding et al. 1995; Ridding and Rothwell 1995; Rosenkranz et al. 2007). Paired-pulse measures may be used in pharmacological studies to observe the effect of drugs affecting the central nervous system on cortical inhibition and facilitation and, vice versa, to study the role of different neurotransmitters in intracortical inhibition and

facilitation when the drugs with well-known pharmocodynamics are used (Di Lazzaro et al. 2006; McDonnell et al. 2006; Ziemann et al. 1996 a, 1996 b).

In paired-pulse measurements, interstimulus intervals shorter than 6 ms induce a decrease in MEP amplitudes. This fast inhibitory effect presents short-interval intracortical inhibition (SICI), which was first demonstrated by Kujirai et al. in 1993 (Kujirai et al. 1993). SICI is mostly mediated by GABA(A)ergic interneurons (Ziemann et al. 1996 a) and at the receptor level by GABA(A) α2- and α3-receptor subunits (Di Lazzaro et al. 2006). ISI has an effect on SICI. The most pronounced SICI has been observed with 1 and 2.5 ms interstimulus intervals (Fisher et al. 2002; Roshan et al. 2003) and different indirect waves (I-waves), produced by transsynaptic cortical activation of motoneurons, are inhibited at 1 and 3–5 ms ISIs (Hanajima et al. 2003), which reflect the activity of separate inhibitory circuits in the cerebral cortex. SICI is also affected by short-interval cortical facilitation, which has been observed in various ISIs between 1.5–4.5 ms (Peurala et al. 2008). The CS intensity has also an effect on inhibition. The SICI intensity curve is typically U-shaped. CS intensities which are substantially lower than MT as well as high, near MT, CS intensities produce less inhibition than CS intensities in the midrange of MT intensity (Chen et al. 1998; Schafer et al. 1997; Ziemann, Rothwell et al. 1996). Since the threshold for activation of facilitatory interneuronal circuits is higher than the threshold for activation of inhibitory circuits, the decreased SICI in stronger CS intensities may be due to an increased effect of facilitation (Ziemann, Rothwell et al. 1996). Very strong CS intensities may facilitate motoneuron axons non-synaptically and induce an increase in MEP amplitudes even when an inhibitory ISI (1–6 ms) is used (Ilic et al. 2002).

Intracortical facilitation (ICF) and MEP amplitude increase may be observed with ISIs over 7 ms (Claus et al. 1992; Kujirai et al. 1993; Nakamura et al. 1997; Valls-Sole et al. 1992; Ziemann, Rothwell et al. 1996). The excitatory effect on MEP is mediated mainly by glutamatergic synapses (Hanajima et al. 1998; Schwenkreis et al. 1999; Ziemann et al. 1998). GABAergic synapses have also an effect on ICF. The use of bentzodiatzepines, allosteric activators of GABA(A) receptors, can increase ICI and reduce ICF (Ziemann et al. 1996 a). As mentioned above, the CS intensity needed to elicit ICF is higher than the CS required to elicit ICI (Chen et al. 1998; Ziemann, Rothwell et al. 1996).

2.6 PLASTICITY OBSERVED BY TMS AND OTHER NON-INVASIVE IMAGING METHODS IN PROFESSIONALS WITH DIFFERENT MOTOR SKILLS

2.6.1 Plasticity in professional musicians

Playing a musical instrument demands seamless control of upper extremity muscles. Intrinsic hand muscles are especially important when playing certain instruments such as string instruments or the piano. Thus professional string instrument and piano players may be considered as fine motor skill specialists because they make continuous repetitive and complex hand movement sequences. Professional musicians have been used as subjects in studies examining the long-term functional and structural plasticity occurring in brain after years of fine motor skill practice.

Functional and structural studies have shown larger motor and sensory representations of the actively used muscles and fingers in right-handed string instrument players in right, non-dominant, hemisphere when compared to left, dominant, hemisphere or control subjects (Elbert et al. 1995; Gaser and Schlaug 2003; Schwenkreis et al. 2007). In right-handed string instrument players, the fingers in left hand are more actively used explaining hemispheric differences in plasticity. When compared with controls, professional musicians show increased recruitment of upper motoneurons in actively used muscle representations when stimulating M1 with gradually intensified stimulations (Rosenkranz et al. 2007). In addition, musicians demonstrate also stronger cortical inhibition towards stronger impulses

denoting more efficient recruitment of inhibitory interneurons as compared to control subjects (Rosenkranz et al. 2007). Enhanced excitatory and inhibitory capacity are believed to reflect the increased volume of excitatory and inhibitory cortical synapses in actively used muscle representation due to the years of practice. Increased recruitment of inhibitory interneurons may be essential in avoiding unwanted spread of cortical activation while local motoneurons are still efficiently recruited (Rosenkranz et al. 2007). Professional musicians demonstrate greater increase and decrease in MEP amplitudes when the effect of artificially induced LTP and LTD are compared with controls indicating enhanced synaptic plasticity (Rosenkranz et al. 2007). Musicians show also altered sensorimotor integration in cortical hand representations. In control subjects, a vibration of a hand muscle decreases cortical inhibition in the corresponding muscle representation, but in musicians, the decrease in motor cortex inhibition is also detected in the adjacent muscle representations (Rosenkranz et al. 2005). Altered sensorimotor integration may be essential in performance of movement sequences demanding the synchronous use of intrinsic hand muscles. Certain muscle representations show less altered cortical inhibition after vibration of an adjacent muscle in a hand; this may be due to the more independent role of these muscles in music performance (Rosenkranz et al. 2005).

Musician's dystonia is a pathological condition in which multiple hand muscles activate simultaneously preventing the performance of correct movements. An excessive decrease in motor cortex inhibition and significantly altered sensorimotor integration are detected in musicians with musician's dystonia (Rosenkranz et al. 2005).

When fMRI studies have been conducted in musicians more focused or even diminished brain activation patterns have been observed during performance or even the imagining of complex hand movement sequences when compared with controls (Hund-Georgiadis and von Cramon 1999; Jancke et al. 2000; Krings et al. 2000; Lotze et al. 2003). This suggests that spatially reduced neuronal activity is needed for the performance of correct movement sequences in musicians.

2.6.2 Plasticity in athletes

Athletes have been extensively studied in attempts to characterize the effects of different sports in plasticity in cortical and spinal cord regions (for a review see Adkins et al. 2006). Almost all sports include some level of strength, endurance, and skill training, which makes it challenging to study the pure skill training effect on plasticity in the central nervous system.

Ball games such as volleyball demand the synchronous use of the proximal and distal upper limb muscles. Volleyball players demonstrate enlargements in the dominant hemisphere in the actively used muscle representations as well as a greater overlap of proximal and distal upper limb muscle representations when compared to control subjects or non-dominant hemisphere (Tyc et al. 2005). A greater overlap is interpreted as being beneficial in movements demanding synchronous activation of proximal and distal muscles. Professional badminton players show increased motor cortex excitability in the dominant hemisphere in the representation of actively used muscles as well as altered topography of the actively used muscle representation when compared with controls and less-adept players. Increased motor cortex excitability was observed as a decrease in the MTand increase in MEPs, indicating that excitatory synapses are more efficiently used or additional motoneurons are being recruited in response to practice (Pearce et al. 2000). Similar to musicians, professional golf players demonstrate more focused brain activation patterns than controls when studied with fMRI when they are imagining their swings (Milton et al. 2007).

3 Aims of the Study

The aims of this thesis were to localize muscle representations in cerebral cortex in healthy subjects and to examine long-term motor task –specific plasticity in motor cortices. The main objective was to augment understanding of spatial extent of muscle representations. The knowledge of motor task-specific reorganizational changes in muscle representations may be brought into practice in rehabilitative therapy of patients suffering motor impairment. The specific aims of the studies were:

I To localize cortical hand muscle representations in cerebral motor cortex.

II To characterize the functional properties of muscle representations in M1 and NPMA.

III To study long-term use-dependent cortical plasticity in the motor cortices and to compare the reorganization of muscle representations with different motor skills.

IV To characterize the cortical control of muscle representations in M1 and NPMA in fine motor skill specialists.

4 Subjects and Methods

4.1 SUBJECTS

A total of 15 healthy adults were recruited into the studies. All the subjects participated in studies I and III. Eleven of the 15 subjects participated also in studies II and IV. None of the subjects had any history of neurological disorders or continuous use of medications affecting the central nervous system. Five subjects had a long practice history of string instrument playing, another five had a long practice history of figure skating and five had no practice history of long-term systematic motor skill training. Handedness and footedness was determined for each subject with the revised and reduced form of the Waterloo questionnaire (Elias et al. 1998).

All experiments were conducted in Kuopio University Hospital. Subjects participating in all four studies made three visits to the hospital. The first visit was for the MRI, the second and third visits for the nTMS measurements. The first nTMS for studies I and III was performed on a single day and data was collected for both studies from the same experiment. The second nTMS for studies II and IV was performed one year after the first nTMS. Subjects participating only in studies I and III made two visits to hospital. The first visit was for the MRI and second for the nTMS. The demographics of the subjects in studies I–IV are summarized in Table 1.

Table 1. Subjects in studies I–IV. Handedness / Footedness: R= right, L= left.

	Number of subjects	Gender (Males/Females)	Handedness (H) / Footedness (F) (R/L)	Age range (yrs) (mean ± S.D.)
Study I	Healthy volunteers 15	5/10	H: 14/1	20–37 (25.3 ± 4)
Study II	Healthy volunteers 11	4/7	H: 10/1	21–31 (25.3 ± 2.9)
Study III	String instrument players 5	1/4	H: 5/0, F: 5/0	21–26 (23.8 ± 2.2)
	Figure skaters 5	1/4	H: 5/0, F: 3/2	22–27 (24.2 ± 2.2)
	Control subjects 5	2/3	H: 4/1, F: 4/1	20–36 (27.8 ± 5.9)
Study IV	String instrument players 5	1/4	H: 5/0	21–26 (23.8 ± 2.2)
	Control subjects 6	3/3	H: 5/1	21–31 (24.3 ± 3.7)

4.1.1 Subjects in studies I and III

In studies I and III, 15 adults were examined. All the subjects formed a one group of healthy adults in study I. In study III, there were three groups representing string instrument players (5 subjects), figure skaters (5 subjects) and non-trained individuals as control subjects (5 subjects).

4.1.2 Subjects in studies II and IV

In studies II and IV, 11 adults were examined. All five string instrument players, four figure skaters and two control subjects participated in these studies. In study II, all 11 subjects formed a single group of healthy adults. In study IV, two groups were studied: string

instrument players and a control group formed by figure skaters and non-trained individuals.

4.1.3 Motor skill specialists

String instrument players and figure skaters were selected for studies to represent motor skill specialists. String instrument players actively use intrinsic hand muscles especially in the hand, which is responsible for tightening the strings in achieving the right tones (left hand in right-handed string players). Some of the intrinsic hand muscles are used more synchronously with adjacent muscles and some have a more independent role (Kim et al. 2004; Mozart 1948). Figure skating requires synchronous use of proximal and distal lower limb muscles. The co-activation of proximal and distal leg muscles is especially important in the jumps. The leg responsible for take-off varies but the landing is always performed on the same foot.

None of the string instrument players or figure skaters had practiced on the day of TMS examinations.

4.1.3.1 String instrument players

In a string instrument group, two players were recruited from the local music conservatory and the other three were recruited from the students of Kuopio University and personnel of Kuopio University Hospital. Four string instrument players played the violin and one was a guitar player. All violin players had completed national basic level examinations (levels 1/3- 3/3). Three of them had completed also higher examinations: one subject had passed the music institute level (level D), one subject had completed the second level (level B) in the music conservatory and one subject had passed the highest level (level A) in the music conservatory (examination criteria: www.musicedu.fi; www.siba.fi). The guitar player played regularly but had not completed any national examinations. All of the string instrument players continued their regular practice at the time of the study. Detailed information about the levels of practice is summarized below (Table 2).

4.1.3.2 Figure skaters

Figure skaters were recruited from figure skating clubs in Eastern Finland. All of them had finished regular practicing at the time of studies (mean latency from active practice 3 ± 2.3 years). After regular practicing three of them were coaching younger skaters on a weekly basis. All of them had competed at the national junior level, two also at the national senior level. All fulfilled skill requirements for competing in international junior competitions as delineated in the rules of the International Skating Union (www.ISU.org, ISU rules). Detailed information about the levels of practice is summarized below (Table 2).

4.1.4 Control subjects

Control subjects were recruited from the personnel of Kuopio University Hospital and their relatives. None had a history of any long-term systematic motor skill training.

Table 2. Individual and group-specific information of string players and figure skaters. Magnitude of practice is presented as a magnitude in every 5 year age-period (age 5–9 yrs, 10–14 yrs, 15–19 yrs, ≥ 20 yrs). Gender: F = female, M = male; Handedness/Footedness: R = right, L = left.

	subject ID, gender (F/M)	age (yrs)	handedness (string players)/footedness (figure skaters)	instrument	age at practice onset (yrs)	practice duration (yrs)	magnitude of practice (hours/week)			
							5–9 yrs	10–14 yrs	15–19 yrs	≥ 20 yrs
string players	1, F	25	R	violin	5	20	1.5	5	14	14
	2, F	26	R	violin	5	21	1.5	5	10	10
	3, M	25	R	guitar	9	16	1	7.5	17.5	17.5
	4, F	21	R	violin	7	14	1.5	4	18	18
	5, F	22	R	violin	5	17	2.5	6	5	2
mean ± SD		**24 ± 2**			**6 ± 2**	**18 ± 3**	**2 ± 1**	**5.5 ± 1.3**	**12.9 ± 5.5**	**12.6 ± 11.3**
figure skaters	1, F	27	L	-	5	15	8	12	15	1
	2, M	25	R	-	5	18	8	12	15	18
	3, F	22	R	-	5	14	7.5	10	12	-
	4, F	22	L	-	3	17	6	15	21	-
	5, F	25	R	-	5	19	6	10	18	18
mean ± SD		**24 ± 2**			**5 ± 1**	**17 ± 2**	**7 ± 1**	**11.8 ± 2.0**	**16.2 ± 3.4**	**7.4 ± 9.7**

4.2 ETHICAL CONSIDERATIONS

Studies were performed in compliance with the Declaration of Helsinki and approved by the Ethics Committee of the Hospital District of Northern Savo (Kuopio, Finland). The experiments were conducted with the understanding and the written consent of each subject.

Each subject was asked about contraindications to MRI and TMS before experiments; none had any contraindications such as metal objects in head area or ongoing pregnancy.

A neuroradiologist analyzed MR images; no pathological abnormalities were found.

TMS is a rather painless method for the subjects and has few side-effects. The most common side-effect is a mild headache following the TMS examination, which is most probably the tension type caused by sitting in the same position (Machii et al. 2006). TMS may provoke epileptiformic discharges when repetitive pulses with high-frequency are used. We used single- and paired-pulses which have not been reported to provoke epileptiformic discharges in healthy subjects (Wassermann 1998). Furthermore, anticonvulsive medication was available in the examination room during the procedures.

4.3 METHODS

4.3.1 Magnetic resonance imaging

A three-dimensional individual head MRIs is needed for nTMS. The MRIs must be extended to cover external landmarks such as a nose and ears to allow later registration in the navigation software. The MRIs was performed with a 1.5T Siemens Magnetom Avanto (Erlangen, Germany) using a 3D Magnetization Prepared Rapid Acquisition GRE T1-weighted sequence (repetition time, TR=1980 ms; echo time, TE= 3.93 ms; field of view, FOV= 256 mm; slice thickness 1.0 mm, inplane resolution 1x 1.4 mm^2, 176 (or 192) sagittal slices).

4.3.2 Navigated TMS

In the nTMS experiments, the navigation system (Nexstim Ltd., Helsinki, Finland) was connected to a stimulator (Magstim BiStim 200^2, Magstim Company Ltd., Whitland, Wales, UK) and monophasic pulses were delivered via a 70-mm figure-of-eight coil. The navigation software version eXimia 2.1 was used in studies I and III and the software version eXimia 2.2.0 in studies II and IV. The cortex in the peeled 3D head MRI at a depth of 25 mm from the scalp was used as the mapping surface. At this depth, sulci and gyri are easily identified.

4.3.3 Electromyographic recordings

Surface EMG (ME 6000, Mega Electronics Ltd., Kuopio, Finland) was recorded and monitored on-line during nTMS. Continuous EMG and stimulation triggered MEPs were visualized in separate windows on a computer screen. In stimulation triggered MEPs, the recorded, and visualized pre-stimulation time was 50 ms and post-stimulation time 100 ms. The EMG signals were filtered (8–500 Hz), amplified, displayed and stored for off-line analyses.

Disposable, circular, pre-gelled Ag-AgCl electrodes (diameter 9 mm) were used for EMG recordings. In studies I and III the EMG signals were recorded from four upper limb muscles and four lower limb muscles bilaterally. The selected muscles were opponens pollicis (OP), abductor digiti minimi (ADM), flexor carpi radialis (FCR) and biceps brachii (BB) in the upper limbs, and vastus lateralis (VL), vastus medialis (VM), tibialis anterior (TA) and, soleus (SO) in the lower limbs. In studies II and IV, the electrodes were placed on OP and ADM muscles. OP and ADM muscles were selected because left OP muscle is one

of the less used whereas ADM muscle is one of the most extensively used muscles in right-handed string instrument players (Mozart 1948). The active electrodes were positioned on the skin above the muscles. Reference electrodes were positioned on the skin as follows: above the bone in the 1st metacarpophalangeal joint (for OP), above the bone in the 5th metacarpophalangeal joint (for ADM), above the bone in the elbow for FCR, above the biceps brachii tendon (for BB), above the patella bone (for VL and VM), above the tibia bone (for TA), and above the achilles tendon (for SO). Before the electrode placements, the skin was rubbed and brushed with alcohol around the electrode sites.

During nTMS experiments, the subjects were instructed to relax the muscles and to avoid any upper and lower limb movements. If motor unit potentials were visualized in continuous EMG, the stimulations were stopped and subject was informed to relax muscles more completely.

4.3.4 Research protocol in studies I and III

Motor threshold (MT)

In studies I and III, rMT were determined for OP and TA muscles bilaterally from precentral gyrus (M1) and for OP muscles from NPMAs anterior to M1. First, posterior border of contralateral precentral gyrus was mapped in about 2 mm steps to find the optimal OP target (interstimulus interval ~ 5 sec, direction of induced current perpendicular to central sulcus), which elicited repeatedly highest peak-to-peak amplitudes in OP muscle. The optimal direction for induced current was determined in the appropriate target by rotating the coil at 45° intervals. The estimate of OP rMT was determined with ten steps with the use of the threshold-hunting paradigma of Awiszus (Awiszus 2003). Subsequently, the rMT was defined as the minimum stimulation intensity and electric field value (V/m) eliciting at least four MEPs (≥ 50 μV) out of 10 stimulations.

NPMAs, including SMA and PMAs, were stimulated with 100% M1 OP rMT and 120% M1 OP rMT intensities along the precentral sulcus, and sulci between superior and medial, and medial and inferiol frontal gyri as well as along the gyri anterior to M1 (distance between stimulation targets ~2 mm, interstimulus interval ~5 sec). The coil orientation and induced current were kept perpendicular to the nearest sulcus. The optimal target was chosen from the stimulation targets producing repeatedly highest peak-to-peak amplitudes. The OP rMT was measured as in M1. The electric field value in M1 was estimated simultaneously and if the estimated electric field value remained lower than the electric field of OP rMT value in M1, the NPMA target was chosen as the optimal OP target. Thereafter, the optimal target in M1 was stimulated with the intensity inducing corresponding electric field value in M1 while stimulating the optimal target in NPMA with the NPMA rMT intensity to verify that the induced electric field in M1 was not eliciting muscle responses.

The optimal TA target in M1 was searched from the medial part of precentral gyrus near to the interhemispheric fissure. The coil orientation and induced current was kept perpendicular to the interhemispheric fissure and the direction of current towards the contralateral hemisphere. The target producing repeatedly highest peak-to-peak amplitudes in contralateral TA muscle was selected as the optimal target. The rMT was measured as for OP representations.

Areas anterior to precentral gyrus were stimulated with 100% and 120% M1 TA rMT intensities to determine the optimal target from NPMAs. If optimal NPMA targets for TA could be found outside M1, the corresponding rMT values for TA targets were measured with simultaneous control of electric field value in M1.

Motor mapping

Precentral gyrus (M1), postcentral gyrus (S1) and NPMAs were stimulated in both hemispheres with 100% and 120% of local M1 OP and TA rMT intensities. In the mapping

of upper limb muscle representations, stimulations were targeted to the posterior border of the precentral gyrus when stimulating M1 and to the posterior border of the postcentral gyrus in S1 stimulations (coil orientation and induced current perpendicular to central and postcentral sulci, distance between stimulations ~2 mm, interstimulus interval 5 sec). The stimulated areas in NPMAs included SMA and PMAs. Stimulations were targeted to the precentral sulcus and the sulci between superior and medial, and medial and inferior frontal gyri (coil orientation and induced current perpendicular to the nearest sulci). In the mapping of lower limb muscle representations, the medial part of precentral gyrus, postcentral gyrus and NPMAs were stimulated. Coil orientation and induced current were perpendicular to the interhemispheric fissure and sulci between superior and medial frontal gyri.

In the mapping of upper and lower limb muscle representations, the stimulations were targeted distinctly in lateral-medial and anterior-posterior directions until MEPs could no longer be detected. All the stimulation points which elicited muscle responses (≥ 50 μV) were visualized on the mapping surface. In study I, all the stimulation points evoking MEPs in recorded muscles outside M1 were visualized and the electric field value in M1 was controlled with each stimulation to check that M1 OP rMT electric field values were not exceeded when stimulating cortical areas outside M1. In study I, stimulation points outside M1, which could be verified to elicit MEPs without simultaneous stimulation of M1 and preceding muscle activity, were accepted for further analyses. In study III, all the stimulation points eliciting MEPs (≥ 50 μV) in recorded muscles without preceding muscle activity were accepted for further analyses.

4.3.5 Research protocol in study II and study IV

Motor threshold (MT)

In studies II and IV, rMTs were measured for OP muscle from non-dominant M1 and NPMA. In the search for the optimal target from M1 and NPMAs one year after the previous examination, the mapping intensity was adjusted to be ~15% higher than the previously determined MT value. Stimulations were targeted to the area eliciting the highest MEPs in the previous examination and the mapping was thus more restricted than in studies I and III. As in studies I and III, the coil orientation and induced current were kept perpendicular to the nearest sulci and the distance between stimulation points was ~2 mm and interstimulus interval was ~5 sec. In the optimal target in M1 and in NPMA, the estimate of OP rMT was determined with ten steps using the threshold-hunting paradigm (Awiszus 2003) and the final rMT was defined as the stimulation intensity eliciting at least five MEPs (≥ 50 μV) out of 10 stimulations. As in the previous examination, the electric field value in M1 was controlled and had to remain below the M1 rMT value when stimulating the optimal target in NPMA with NPMA rMT intensity.

Suprathreshold motor evoked potentials (single-pulse MEPs)

Suprathreshold MEPs were recorded from optimal OP targets in M1 and in NPMA. Ten stimulations were delivered to optimal targets with 120% of local OP rMT intensities (interstimulus interval ~5 sec).

Paired-pulse MEPs (ppMEPs)

Paired-pulses were delivered to optimal OP targets in M1 and in NPMA with four different ISIs and four different CS intensities. The effect of the different ISIs on SICI and ICF were examined with the conditioning stimulus intensity set to 80% of local rMT and the test stimulus intensity to 120% of local rMT and ISIs set to 2 ms, 3 ms, 10 ms and 15 ms. Ten trials were conducted with each ISI (intertrial interval ~5−10 sec) with the order of trials being randomized. The effects of different CS intensities on SICI and ICF were examined with standard 2 ms ISI and the CS intensities set to 30% rMT, 50% rMT, 70% rMT and 90%

rMT. The test pulse intensity was set to 120% of local rMT. Ten trials were conducted with each CS intensity in a randomized order.

4.4 DATA ANALYSIS

4.4.1 Electromyography

In the off-line analyses, all MEPs with preceding muscle activity in prestimulation period were excluded.

4.4.1.1 Study I

In study I, upper limb muscle MEPs elicited outside M1 were accepted for analyses and named as "SOI" (stimulation of interest) if the electric field value in M1 stayed below the M1 rMT value when stimulating the cortical area outside M1. The fastest MEP latencies from M1 optimal OP target stimulations (100% rMT intensity) and the fastest MEP latencies elicited by NPMA stimulations (100% M1 rMT intensity) were selected for further analyses. The number of MEPs detected from each upper limb muscle after NPMA stimulations was normalized to the total number of upper limb muscle MEPs after NPMA stimulations. Lower limb muscles MEPs were not included in the analysis because the existence of hand muscle representations in NPMAs was more pronounced.

4.4.1.2 Study II

In study II, in ppMEP analysis the highest and lowest single- and ppMEP amplitudes were excluded from each trial, and the mean amplitudes for OP muscle were calculated from the remaining eight responses from each trial. In addition, MEPs with amplitudes lower than 50 μV were accepted for analysis. In the case of very small uncertain responses, the amplitude was marked as 0 μV in the average calculation. Mean ppMEP amplitudes were normalized to single-pulse MEP amplitudes. Furthermore the mean single-pulse MEP latencies were calculated for OP muscle from M1 and NPMA from eight responses.

4.4.1.3 Study III

In study III, all the stimulation points eliciting MEPs (≥ 50 μV) in OP, ADM or TA muscles were accepted for further analysis.

4.4.1.4 Study IV

In study IV, the highest and lowest single- and paired-pulse MEP amplitudes were excluded from each trial and the mean amplitudes for OP and ADM MEPs were calculated from the remaining eight responses from each trial.

4.4.2 Stimulus locations

The navigation software makes it possible to use the MRIs for localization. Co-registration is based on external landmarks of the subject's head in MRI and on actual head pointed with optically traced pointer.

4.4.2.1 Study I

In study I, the locations of optimal OP targets in M1 and the furthest SOIs were determined in the navigation coordinate system (x,y,z) and the distances between the targets in M1 and in NPMA were calculated as Euclidean distances between coil locations and distances between centers of maximal electric fields at the mapping depth (25 mm). All the SOIs were visualized on the cortex in the MR image.

4.4.2.2 Study II

In study II, the locations of optimal OP targets in M1 and in NPMA were determined in the navigation coordinate system (x,y,z) and the distances between optimal targets were calculated as Euclidean distances between coil locations and distances between centers of maximal electric fields at the mapping depth (25 mm). For one subject, the distances could not be determined because of a technical failure in the TMS log data.

4.4.2.3 Study III

In study III, the locations of all stimulation points eliciting MEPs (≥ 50 μV) in OP, ADM or TA muscles were determined in the navigation coordinate system (x,y,z), fitted to an ellipsoid surface and converted into two dimensions. The transformed coordinates were used to compute the cortical area at different MEP amplitude thresholds confined by a convex hull. The threshold amplitude for a MEP was increased systematically to determine the location specificity for the different MEP amplitudes and to create representation area curves of the different MEP amplitudes. The cortical amplitude areas were determined for each muscle separately.

4.4.2.4 Study IV

In study IV, the locations of optimal targets in M1 and in NPMA were the same as in study II.

4.5 STATISTICAL ANALYSES

Non-parametric tests were used because the parameters were not normally distributed. In studies I and II, the statistical tests were performed with SPSS 16 (SPSS Inc., Chicago, Illinois, USA). In study IV the statistical tests were performed with SPSS 19 (SPSS Inc., Chicago, Illinois, USA). In study III, the statistical tests were performed with Matlab 7.4 (MathWorks Inc., Natick, Massachusetts, USA).

4.5.1 Study I

The 2-tailed Wilcoxon signed ranks test was used to compare M1 and NPMA rMT values in both hemispheres (n=15 in analyses of the dominant hemisphere, n=13 in the analyses of the non-dominant hemisphere), to compare rMT values between hemispheres (n= 13 in analyses of NPMA rMT values, n= 15 in analyses of M1 rMT values), and to compare the furthest SOIs between hemispheres in 100% rMT and 120% rMT stimulation intensities. The Mann-Whitney test (1-tailed) was used in the analyses of differences in rMTs and in locations of the furthest SOIs between genders (n=13, 4 male, 9 female, in analyses of NPMA rMT values, and n=15, 5 male, 10 female, in all other analyses).

4.5.2 Study II

The Wilcoxon signed ranks test was used to compare single- and ppMEP amplitudes, to compare M1 and NPMA rMT values, and to compare single-pulse MEP latencies between M1 and NPMA.

4.5.3 Study III

The results of OP and ADM representations were compared between string instrument players and controls, and the results of the TA representations compared between figure skaters and controls. The linear mixed model was used to estimate between-group and within-group variations from the data of different MEP thresholds. The group and the stimulated hemisphere were used as fixed factors and the subject identifier was used as a random factor. The full interaction model was evaluated. Wilcoxon signed ranks test was

used to compare pairwise differences between hemispheres and Mann-Whitney U-test to compare differences between groups.

4.5.4 Study IV

OP and ADM single- and ppMEP amplitudes were compared between M1 and NPMA, and between string instrument players and controls. Wilcoxon signed ranks test was used in the comparison of rMT, single- and ppMEP amplitudes between M1 and NPMA. Mann-Whitney U-test was used in the comparison of the results between the groups.

5 Results

5.1 Upper limb muscle representations outside M1 proper (Study I and II)

MEPs could be elicited in the upper limb muscles from contralateral superior frontal gyrus and from stimulations of sulcus between superior and medial frontal gyri in two separate examinations conducted in consecutive years in all subjects (Figure 5). The areas evoking MEPs correspond to BA 6 and in some subjects also BA 8. Functionally these areas correspond to PMd and in case of some subjects also SMA (Geyer et al. 2004).

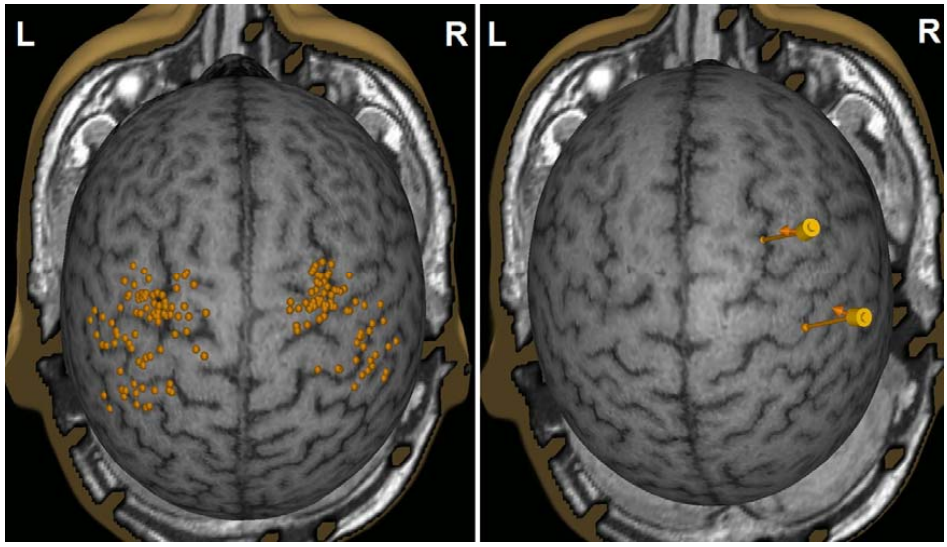

Figure 5. All the stimulation points, indicated with orange dots, evoking responses in OP muscles (left) and the optimal left OP muscle representations in M1 and in NPMA in the non-dominant hemisphere of one subject (right). Yellow cylinders show coil locations and small arrows direction of induced current. Three-dimensional head MRI is peeled and cerebral cortex is shown from above. L = left, R = right.

NPMA stimulations evoked usually MEPs in two to four upper limb muscles. MEPs could be elicited bilaterally from anterior to precentral gyrus from all subjects with the stimulation intensity of 120% of individual M1 OP rMT, and from 13/15 subjects with a stimulation intensity of 100% of individual M1 OP rMT. In the second examination (n=11) which took place one year after the first, the locations of optimal targets differed from the locations mapped in the first examination by 2.0 ± 2.8 mm in M1 and 9.7 ± 5.6 mm in NPMA when the centers of maximal electric fields were compared in the non-dominant hemisphere. In the second experiment, the distance between optimal targets in the non-dominant M1 and in NPMA was 32.9 ± 4.2 mm when defined as the distance between locations of maximal electric fields and 30.1 ± 6.5 mm when defined as the distance between the coil locations. The average MEP latencies were shorter for NPMA stimulations than for M1 stimulations in the non-dominant hemisphere (22.4 ± 1.3 ms in M1 vs. 21.8 ± 1.4 ms in

NPMA, $p < 0.01$). The average amplitudes evoked by stimulation of the optimal target in NPMA elicited higher MEP amplitude than stimulation of the optimal M1 target with 120% of local rMT intensity in the non-dominant hemisphere (1201 ± 750 μV in NPMA vs. 924 ± 791 μV in M1, $p < 0.01$)

The average rMT values were a few percentages higher in the optimal target in NPMA than in M1. In the first examination, both hemispheres were stimulated and the average rMT was 44 ± 9 % in NPMA and 37 ± 6 % in M1 in the dominant hemisphere ($p = 0.001$), and 43 ± 6% in NPMA and 38 ± 6 % in M1 in the non-dominant hemisphere ($p= 0.011$). There were no significant differences in rMT values between hemispheres or genders. In the second experiment (n=11), one year after the first, the non-dominant hemisphere was stimulated and the rMT value was 46 ± 6 % in NPMA and 37 ± 5% in M1.

The average distances between optimal targets in M1 and furthest SOIs are summarized in Table 3.

Table 3. The distances between M1 target and the furthest stimulation eliciting MEPs from NPMAs presented as mean ± SD. EF = electric field.

	hemisphere	
	dominant (maximum EF distances/coil location distances) (mm)	**non-dominant** (maximum EF distances/coil location distances) (mm)
100% rMT	35 ± 9 / 26 ± 7	37 ± 9 / 28 ± 11
120% rMT	45 ± 7 / 39 ± 8	42 ± 8 / 38 ± 11

The distances varied from 22 mm to 53 mm when stimulated with 100% of rMT and from 28 mm to 57 mm when stimulated with 120% of rMT, the distance difference was statistically significant. The furthest SOIs detected with 120% rMT stimulations were located more frontally from the M1 target than the furthest SOIs detected with 100% rMT stimulations in both hemispheres (in dominant hemisphere: $p=0.005$ when the distances of maximal electric fields were compared, and $p= 0.001$ when the distances of coil locations were compared; in non-dominant hemisphere: $p=0.027$ when the distances of maximal electric fields were compared and $p=0.017$ when the distances of coil locations were compared).

5.2 Cortical inhibition and excitation balance in upper limb muscle representations in NPMA and M1 (Study II)

Paired-pulse MEPs displayed a clear SICI both in M1 and in NPMA with 2 ms and 3 ms ISIs and CS set at 80% of rMT. Furthermore, ICF was shown with 10 ms and 15 ms ISIs (80% rMT CS intensity) in both locations. The normalized ppMEP amplitude was inhibited more in M1 than in NPMA at an ISI of 2 ms ($p< 0.05$) (Figure 6). There were no other statistically significant differences in SICI and ICF between M1 and NPMA with other ISIs. When the effect of CS intensity was examined, SICI was observed in M1 and in NPMA with 70% and 90 % rMT CS intensities. In NPMA, a significant decrease in ppMEP amplitudes was also detected with 30% and 50% stimulation intensities ($p < 0.05$). There were no significant differences in SICI or ICF between M1 and NPMA when variable CS intensities were used. The normalized ppMEP amplitudes are summarized in Table 4.

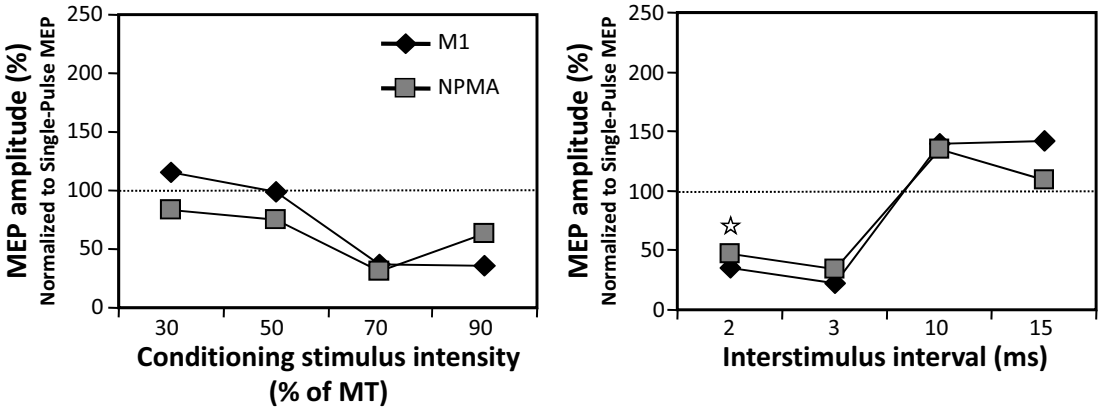

Figure 6. SICI curves. Diagram on the right shows reduced SICI in NPMA in optimal OP muscle representation with 2 ms ISI when compared to M1. Significant differences were not observed in SICI between the muscle representations when the effect of different CS intensities was studied (diagram on the left). Asterisk indicates significant difference in the normalized ppMEP amplitude between M1 and NPMA.

Table 4. Normalized ppMEP amplitudes (% of average single-pulse MEP amplitudes; mean ± SD) in M1 and NPMA elicited with different ISIs and CS intensities. CS = conditioning stimulus; ISI = interstimulus interval; rMT = resting motor threshold.

	CS 80% rMT, ISI (ms) variable				**ISI 2 ms, CS (% of rMT) variable**			
	2	**3**	**10**	**15**	**30**	**50**	**70**	**90**
M1	35.3 ± 31.3	22.9 ± 15.3	140.1 ± 58.0	141.7 ± 59.7	115 ± 151.2	98.7 ± 90.4	37.1 ± 40.7	36.3 ± 44.4
NPMA	47.1 ± 34.8	34.1 ± 25.4	134.6 ± 126.0	109.7 ± 52.0	83.2 ± 58.1	74.6 ± 57.0	30.9 ± 20.0	62.5 ± 52.9

5.3 Plasticity in upper and lower limb muscle representations induced by motor skill training (Study III)

5.3.1 Plasticity in intrinsic hand muscle representations in string instrument players

The string instrument players had significantly smaller cortical representation area of ADM muscle evoking MEPs higher than 100 μV in the non-dominant hemisphere (contralateral to string hand) when compared with controls ($p < 0.05$, pairwise comparison and group x hemisphere interaction effect on the mixed model; Figure 7). In addition, the string players had significantly smaller ADM representation areas in the non-dominant hemisphere than in the dominant hemisphere evoking MEPs 70–270μV ($p<0.05$, post-hoc analysis with least significant difference (LSD) adjustment). The representation areas did not differ in the dominant hemisphere. The string instrument players had also smaller OP representation areas than the controls evoking MEPs < 130 μV as indicated by the main effect on the mixed

model (no effects of hemispheres and no interaction effects). The resting MT values did not differ between the groups (Table 5).

5.3.2 Plasticity in lower limb muscle representations in figure skaters

The figure skaters had significantly larger cortical representations of TA muscles than controls evoking the smallest MEPs (50–60 μV in the pairwise comparison and 50-100 μV in the mixed model) in the dominant hemisphere ($p < 0.05$) (Figure 7). No main effect of hemisphere and no interaction effects were observed between group and hemisphere. The average rMT was higher in figure skaters than in controls in the non-dominant hemisphere (Table 5).

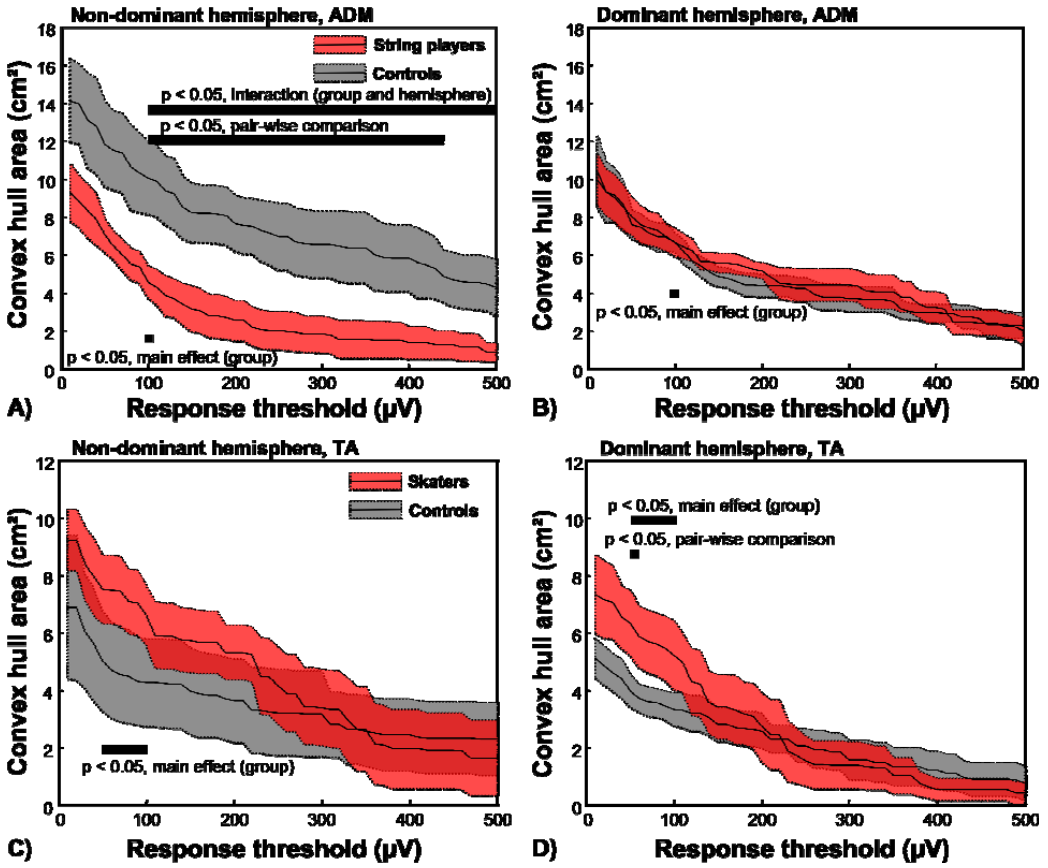

Figure 7. Spatial distribution according to MEP amplitudes. ADM muscle representation area is significantly smaller in the non-dominant hemisphere in string instrument players when compared to controls. TA muscle representation is significantly larger in the dominant hemisphere in figure skaters when compared to controls when the spatial distribution of the smallest amplitudes was compared.

Table 5. Motor threshold (MT) values (per cents of maximum stimulator intensity) of different subject-groups (mean ± SD). Asterisk indicates significantly higher MT in figure skaters when compared to controls. * p<0.05, as compared to controls; OP = opponens pollicis; TA = tibialis anterior.

	MT (OP)		**MT (TA)**	
	dominant hemisphere	non-dominant hemisphere	dominant hemisphere	non-dominant hemisphere
string players	40 ± 6	40 ± 8	-	-
figure skaters	-	-	56 ± 10	59 ± 7 *
controls	35 ± 7	36 ± 7	50 ± 7	46 ± 6

5.4 Cortical excitation and inhibition balance in NPMA and M1 in string instrument players (Study IV)

Single-pulse MEP amplitudes measured from OP and ADM muscles did not differ between string instrument players and control group nor were any major differences found within the groups. In the control group, the MEP amplitude measured from OP muscle was higher with NPMA stimulation than that with M1 stimulation (1167 ± 867 μV versus 951 μV ± 956 μV, *p=0.046*).

In paired-pulse measurements, SICI was reduced in the ADM representation in M1 in the string instrument players with 3 ms ISI and 80% rMT CS intensity when compared with controls (*p=0.028*) (Figure 8). In NPMA, SICI was increased in the ADM representation in the string instrument players with 2 ms ISI and 50% rMT CS intensity when compared with controls (*p=0.045*) (Figure 8). No other differences were observed between the groups in SICI and ICF.

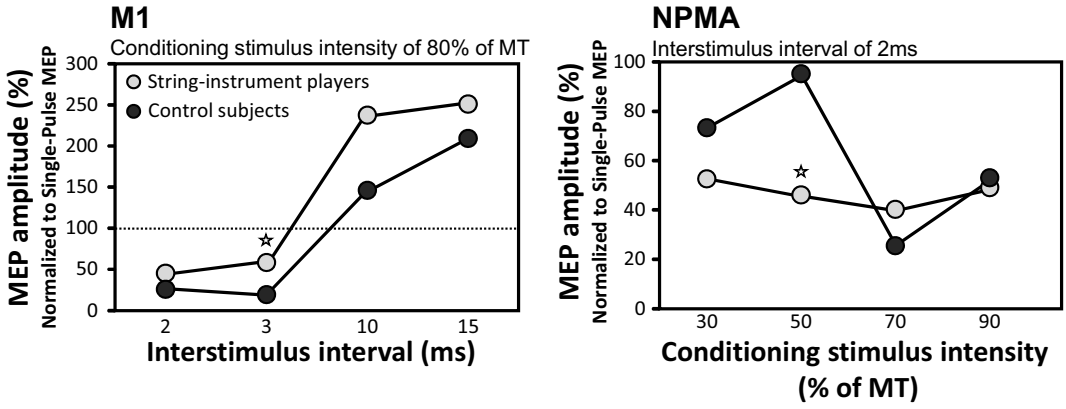

Figure 8. SICI curves show significantly weaker SICI in ADM muscle representation in M1 with 3 ms ISI and significantly stronger SICI in ADM muscle representation in NPMA with 50% CS intensity in string instrument players when compared to controls. Asterisks indicate significant differences between string-instrument players and controls.

When SICI and ICF were compared within groups, string instrument players had stronger ICF in the ADM representation in M1 with 10 ms ISI when compared with NPMA

(*p=0.043*), and stronger SICI in the ADM representation in NPMA with 30% CS intensity when compared with M1 (*p=0.043*). In control subjects ICF was stronger in the ADM representation in M1 with 15 ms ISI when compared with NPMA (*p=0.046*), SICI was weaker in ADM representation in NPMA with 3 ms ISI when compared with M1 (*p=0.046*) and ICF was stronger in M1 in the ADM representation with 15 ms ISI when compared with OP representation *(p=0.046*).

6 Discussion

6.1 DISTRIBUTION OF PYRAMIDAL TRACT MOTONEURONS IN CEREBRAL CORTEX

In this study, the aim was to localize muscle representations composing contralateral innervation of limb muscles. Ipsilateral M1 and NPMA were not systematically examined. Fast-latency MEPs could be evoked repeatedly in upper limb muscles from stimulation of contralateral superior frontal gyrus and by stimulations of sulcus between superior and medial frontal gyri in addition to the precentral gyrus in all subjects. Functionally, the areas eliciting MEPs correspond to M1, PMd, and in some subjects also to SMA-proper. If one considers them as Brodmann areas, then MEPs were being evoked mainly from BA4 and BA6 (Geyer 2004). When the optimal representation in M1 was explored, the precentral gyrus was stimulated along central sulcus and posterior part of precentral gyrus, which corresponds anatomically to M1 (Brodmann 1909; Fulton 1935; Geyer 2004; Penfield and Boldrey 1937; Penfield W. 1954). Stimulations evoking MEPs from precentral sulcus and from more anterior areas were interpreted as being produced by activation of motoneuron populations originating in NPMAs according to histological and functional classification of cortical areas (Brodmann 1909; Fulton 1935; Geyer 2004; Penfield and Boldrey 1937; Penfield W. 1954), if the estimated electric field value remained below MT in posterior part of precentral gyrus. Additional support is obtained by acknowledging that even an appropriate electric field will not induce a response, if the direction of the stimulation is not favorable for the underlying neuronal structure in the cortex (Hannula et al. 2005), such as when determining the MT. This means that the stimulation protocol was somewhat different than in mappings of optimal muscle representations i.e. presurgically, in which the stimulation target producing highest MEPs is defined as optimal muscle representation or functional M1 regardless of its exact location in precentral gyrus or other cortical areas (Säisänen et al. 2010; Vitikainen et al. 2009). In this present study, the locations of optimal targets in M1 and in NPMAs were mapped and determined according to the earlier defined boundaries of these areas.

Simultaneous stimulation of primary motor representation in M1 was excluded before stimulation targets producing MEPs in NPMAs were accepted for analysis, which strongly point to an independent activation of motoneuron populations in NPMAs. Similar or even faster MEP latencies after stimulations of NPMAs does not support polysynaptic activation of motoneurons in M1 via corticocortical connections because polysynaptic activation should produce longer latencies (Tokuno and Nambu 2000). In addition, the optimal direction of stimulating current differed between M1 and NPMAs. In M1, the optimal direction of stimulating current was from the posterior to anterior direction whereas in NPMAs it was mediated in a lateral to medial direction.

In M1 and in NPMAs, the optimal direction of stimulating current was perpendicular to the nearest sulci, which may indicate that the most excitable site of pyramidal cells is located in the wall of sulci also in NPMAs as in M1. The pyramidal cell axons bend near to the anterior wall of the central sulcus. Since axons are most excitable when the electric field is orientated in parallel to the axon and perpendicularly to a bend of an axon, the pyramidal cells in the sulcal areas are most sensitive for direct activation by TMS (Maccabee et al. 1993; Ruohonen 2003; Rushton 1927). Accordingly one could speculate that the pyramidal cells are architecturally arranged in the sulcus between superior and medial frontal gyrus similarly as in the posterior border of precentral gyrus where there are known to be giant pyramidal cells. In NPMAs, posterior to anterior directed stimulations induced

more probably higher electric field values to M1 and were more often excluded than those in the lateral to medial directed stimulations. This explains why the arrangement of pyramidal cells in NPMAs must be discussed carefully.

Non-human primates have multiple upper limb muscle representations in frontal lobe in addition to M1 and the strongest connections from NPMAs to lower motoneurons originate in medial part of the frontal lobe corresponding to superior frontal gyrus (Dum and Strick 1991). The functional connections between muscle representations in NPMA and lower motoneurons are much weaker when compared to connections originating in M1 (Boudrias, Lee et al. 2010; Boudrias, McPherson et al. 2010). In the present studies, the MT was higher in NPMAs which could indicate less dense connections from NPMAs than from M1 (Brouwer and Ashby 1990). On the other hand, single-pulse MEP amplitudes stimulated with 120% rMT stimulation intensity were higher after stimulations of optimal target in NPMAs than in M1 indicating that a large number of motoneurons have been recruited in NPMAs with strong stimulation intensities. Taken together, we may speculate that upper limb muscle representations in NPMAs are less dense than the representations in M1 but more widely spread. The lower MT in M1 means that suprathreshold MEPs were stimulated with lower absolute stimulation intensity and this explains why the activated cortical area was also smaller in surroundings of optimal target in M1 than in NPMA.

Stimulations targeted to NPMAs elicited MEPs more often in multiple upper limb muscles simultaneously than stimulations targeted to M1. In both areas, MEPs were most frequently elicited in distal hand muscles. Since the direction of the stimulating current differed in M1 and in NPMA, the interpretation of simultaneous activation of multiple muscles must be discussed cautiously. Muscle representations are situated along the precentral gyrus in M1 and if stimulated from lateral to medial directed currents MEPs could have been evoked more often in multiple muscles also in M1 than with posterior to anterior directed stimulations. Nevertheless, the present results may indicate that muscle representations in NPMAs are more overlapping than the representations in M1. Another possible explanation for the simultaneous activation of the multiple muscles could be that the pyramidal cell axons originating in NPMAs diverge and terminate in proximal and distal parts of cervical spinal cord innervating proximal and distal muscles. In humans, complex limb movements have been elicited by electrical stimulations of SMA and PMA after resection of M1 (Penfield and Welch 1951; Penfield W. 1954). The reticulospinal tract connects to propriospinal premotoneurons in upper cervical segments and premotoneurons diverge to several cervical segments. This reticulo-/propriospinal pathway operate in multiple joints and possibly produce simultaneous activation in the proximal and distal muscles (Baker 2011; Mazevet and Pierrot-Deseilligny 1994; Mazevet et al. 2003; Pierrot-Deseilligny 1996; Stinear and Byblow 2004; Ward 2011). If multiple muscle movements would have been produced in this study by polysynaptic activation of reticulospinal tract and propriospinal premotoneurons, MEP latencies should have been longer than by stimulations of M1. Nevertheless, together with results of earlier examinations these findings may indicate that connections from NPMAs to lower motoneurons have a greater role in the generation of movements demanding simultaneous activation of proximal and distal muscles than activation of single muscles.

It remains uncertain whether the muscle representations in NPMAs are separate clusters from M1 with independent muscle representations, or distant motoneurons of continuous "muscle representation mat" extending from M1 to NPMAs with some denser centers in NPMAs. Stimulation targets evoking MEPs between optimal representation in M1 and most posterior targets eliciting MEPs in NPMAs had to be excluded if the electric field value exceeded MT value in M1. The difference in optimal direction of stimulating currents and the finding that multiple muscles activated from the same stimulation targets in NPMAs suggest that motoneurons and muscle representation have at least architectural differences in M1 and in NPMAs. In DTI studies, separate motoneuron clusters have been

found from M1, PMd, PMv, and SMA (Schulz et al. 2012), which support the interpretation that MEPs evoked from NPMAs are produced by the activation of independent muscle representations locating in NPMAs .

Although not reported in the separate studies of this thesis, MEPs could be evoked in lower limb muscles also in other regions, mainly anterior to precentral gyrus without simultaneous activation of optimal leg muscle representation in M1. This means that probably also leg muscle representations exist in NPMAs as have been observed in non-human primates (He et al. 1993, 1995). In addition, MEPs could also be evoked by stimulations of postcentral sulcus and the posterior parts of postcentral gyrus, which correspond functionally to S1. These MEPs had to be excluded because the estimated MT value (V/m) was exceeded in the posterior parts of precentral gyrus. Even if not conclusively proven in this present study, it is most probable that motoneuron populations are located also in postcentral gyrus as suggested also in earlier studies (Nii et al. 1996; Uematsu et al. 1992).

6.2 CHARACTERISTICS OF INTRACORTICAL INHIBITION AND FACILITATION IN M1 AND NPMA

The local balance of intracortical inhibition and excitation was rather similar in M1 and in NPMA in the upper limb muscle representations. In paired-pulse examinations, short ISIs decreased MEP amplitudes and induced SICI in both areas, whereas longer ISIs increased MEP amplitudes and induced ICF in both cortical locations. SICI was strongest at high (70-90% rMT) CS intensities in both areas.

SICI was stronger in M1 with 2 ms ISI and 80% CS intensity when compared to NPMA. This may be due to the more efficient activation of GABAergic synapses or reduced activation of facilitatory synapses responsible for short interval cortical facilitation (Peurala et al. 2008) in M1 occurring 2 ms after the stimulation. Earlier studies have shown that there are multiple intracortical neuronal circuits responsible for SICI, which have peak inhibitory effects at different latencies (Hanajima et al. 2003). Thus another possible explanation is the difference in intracortical neuronal circuits, which are active 2 ms after stimulation, in M1 and in NPMA.

Weaker SICI in NPMAs suggests that the afferent signals are less inhibited and the recruitment of motoneurons is facilitated when compared to M1. In other words, stronger SICI prevents the spread of neuronal activation more efficiently in M1, and this may be necessary when a focused motoneuron population needs to be activated.

SICI was induced in NPMAs with all CS intensities but in M1 only with higher CS intensities. With high CS intensities (70% and 90%) SICI was equally strong in both areas and there were no differences in inhibition with low CS intensities, nor between M1 and NPMA. Since the CS intensities were determined according to local rMT, absolute stimulation intensities were stronger in NPMAs. A threshold for SICI and ICF may not linearly follow MT in the different cortical areas (Chen et al. 1998), which means that stronger absolute CS intensities in NPMAs may activate GABAergic neurons more efficiently with low CS intensities described as 30% and 50% of local rMT when compared to the effect induced by low CS intensities in M1 .

6.3 MOTOR SKILL-SPECIFIC PLASTICITY IN MOTOR CORTICES

In motor skill specialists, cortical plasticity reflected as the size of actively used muscle representations differed depending on the demands of the trained skill. Figure skaters had larger leg muscle representations than controls in the dominant hemisphere, which most probably indicates the recruitment of additional motoneurons and/or weaker inhibition of motoneurons in the surroundings of optimal muscle representation. MT was not lower in

dominant hemisphere which means that neuronal membrane excitability was not affected by training. In the string instrument players, the representation area of the actively used hand muscle was smaller in the non-dominant hemisphere as compared to the dominant hemisphere and to the corresponding representation in the control subjects. String instrument players demonstrate also stronger SICI in representation of the actively used hand muscle in NPMA with 50% rMT CS intensity and 2 ms ISI than controls. In M1, SICI was reduced in the representation of the actively used hand muscle in the string instrument players with 3 ms ISI and 80% rMT CS intensity. The smaller representation area of actively used hand muscle in string instrument players emphasizes the importance of strictly controlled muscle movements induced probably by enhanced cortical inhibition in the surrounding region of optimal muscle representation. In this present study, the representations in NPMAs were more efficiently inhibited. The weaker SICI in optimal representation in M1 may be evidence of more effective recruitment of motoneurons locally as well as facilitation of incoming signals from neuronal networks connected with M1. MT differences were not observed between string instrument players and controls.

Enlarged muscle representations and widely overlapped proximal and distal muscle representations have been reported previously in motor skill specialists mastering a skill, which demands repeatedly simultaneous activation of multiple muscles in order to achieve correct movements (Pearce et al. 2000; Tyc et al. 2005). The figure skaters showed a similar enlargement of the cortical representation of actively used leg muscle. The degree of overlapping in proximal and distal leg muscle representations could not be determined in this study because the stimulations evoked infrequently a few responses in proximal leg muscles and the distribution of MEP amplitudes could not be analyzed. In figure skating, co-activation of proximal and distal leg muscles is needed in all skating elements, especially in the jumps, and in maintaining the correct skating position (Fassi et al. 1980; Taylor and Psycharakis 2009). According to this finding and previous studies, one could postulate that motor skills demanding co-activation of multiple muscles benefit from cortical plasticity directed to recruit additional motoneuron capacity leading to more efficient innervation of the actively used muscles and seamless co-activation of adjacent muscles as a consequence of greater overlap of representations.

Smaller non-dominant ADM muscle representation in string instrument players shows that a motor skill demanding single muscle movements may direct cortical plasticity towards a more focal recruitment of motoneurons. Non-dominant, left, ADM muscle is one of the most extensively trained muscles in string instrument players and is believed to have a more independent role in string instrument playing than in the adjacent hand muscles (Mozart 1948; Rosenkranz et al. 2005). The left OP muscle, which is less used in string instrument playing, showed a similar trend towards a smaller representation area in string instrument players as compared to controls but the difference was not statistically significant. Previous TMS studies have shown enlarged actively used muscle representations in fine motor skill specialists including string instrument players (Pascual-Leone et al. 1993; Schwenkreis et al. 2007). In the study of Schweinkreis et al. (2007), the target muscle in string instrument players was the first dorsal interosseus (FDI). The differences in reorganization of muscle representations in fine motor skill specialists may be explained by use-dependent demands of single muscles. Co-activation level of adjacent muscles may determine whether the plasticity is directed on focusing or enlarging muscle representations. In fMRI studies, professional musicians have shown more focused cortical activation patterns than amateurs or non-musicians (Hund-Georgiadis and von Cramon 1999; Jancke et al. 2000; Krings et al. 2000; Lotze et al. 2003). Both diminished and an increased grey matter density have been observed in sensorimotor cortices in musicians when compared to less adept and to non-trained controls (Bangert and Schlaug 2006; James et al. 2013).

Cortical areas receiving sensory information focus and sharpen the afferent information by suppressing the activation of adjacent neurons outside the primary receptive field. The presence of this kind of surround inhibition is well-established, at least in sensory and in visual cortices (Blakemore et al. 1970; Mountcastle and Powell 1959). Surround inhibition has an important role also in the motor system. The muscle representations in M1 are surrounded by an inhibitory zone (Wilson et al. 1993). Cortical representations of actively used muscles are facilitated, while adjacent muscle representations are inhibited (Sohn and Hallett 2004). In addition, surround inhibition regulates the execution of movements at the subcortical level (Mink 1996). In M1, surround inhibition is thought to sharpen motor output via GABA(A) mediated horizontal neurons (Beck et al. 2008) and has been demonstrated to be important in the performance of complex non-powerful motor sequences (Beck et al. 2009; Beck and Hallett 2010). Smaller left ADM muscle representation in string instrument players reflects most probably stronger surround inhibition, which sharpens motor output and allows the independent use of a muscle. In paired-pulse examinations, distinct motoneurons or muscle representations in NPMAs were more effectively inhibited in the string instrument players than in the controls reflecting the more focused cortical control of the actively used muscle towards the optimal target in M1.

6.4 ROLE OF MUSCLE REPRESENTATIONS IN M1 AND NPMA IN CORTICAL PLASTICITY

These studies suggest that use-dependent cortical plasticity may be manifested in motor cortices as expansion or suppression of the representations of actively used muscles. In motor skill specialists, all stimulation points evoking MEPs in target muscles were accepted for analysis when the size of optimal muscle representations were determined i.e. stimulations evoking MEPs from NPMAs were not separated and the recruitment of motoneurons purely from NPMAs in motor-skill specialists and controls were not analysed. Nevertheless, one could speculate that motor-skills or motor sequences demanding co-activation of proximal and distal muscles may benefit from the recruitment of additional motoneurons also from NPMAs. Instead, skills demanding highly focused activation of single muscles may benefit from suppressed representations and the role of motoneurons in NPMAs will be less important when maintaining that skill. In the learning phase of a new fine motor skill, the muscle representations enlarge (Karni et al. 1995; Kim et al. 2004; Pascual-Leone, Nguyet et al. 1995). Although not examined in this study, muscle representations in NPMAs may have been recruited during the learning phase of a skill also for more independently used muscles, even if they had suppressed after years of practice and consolidation of a skill.

Increased activation in NPMAs has been detected during paretic limb movements in stroke patients suffering pyramidal tract damage (Ward et al. 2003; Ward et al. 2006). The best recovery is correlated to decreased activation in NPMAs and increased activation of primary motor cortices (Carey et al. 2006; Ward et al. 2003; Ward et al. 2006). This explains why the increased activation and possible recruitment of motoneurons in NPMAs is interpreted as being less successful in reducing motor impairment than recruitment of motoneurons from M1. Nevertheless, the poor-recovery patients with severe pyramidal tract damage may benefit from reorganization and recruitment of motoneurons from NPMAs even if the motor output from these areas is less efficient than that originating from M1 (Fridman et al. 2004; Ward 2011). DTI and TMS studies have shown positive correlations in the efficiency of pyramidal tract connections from PMd and the extent of stroke recovery (Fridman et al. 2004; Schulz et al. 2012). Poor-recovery patients perform multijoint movements such as synergestic flexion when attempting isolated hand movements. This may be associated with the recruitment of reticulospinal tracts from the surviving cortical areas (Baker 2011). According to the present findings, multijoint

movements could be produced also after recruitment of motoneurons from NPMAs via monosynaptic connections to the lower motoneurons.

6.5 FUTURE CONSIDERATIONS

Functional muscle representations in NPMAs may have a crucial role in the recovery after brain damage such as ischemic stroke especially in patients suffering a severe lesion in corticospinal tract originating in M1. If corticospinal tract fibers originating in PMA and SMA are intact, the patient probably has some motor recovery capacity. Previous TMS studies have shown that the appearance of MEPs in a paretic hand in a short time-window after stroke predicts a better recovery (Stinear 2010). The recruitment of additional motoneuron capacity from NPMAs as well as the effect of rehabilitative therapy for recruitment of motoneurons from NPMAs should be studied in patients with a lesion affecting M1 or the pyramidal tract originating from M1. These studies are needed before intact corticospinal tracts from NPMAs may be considered as a positive sign when predicting recovery capacity after ischemic stroke. However, the stimulation of PMA and SMA should be included in nTMS examinations of ischemic stroke patients and other patients suffering motor cortex lesions when diagnosing the degree and extent of corticospinal tract damage. In addition, the rehabilitative effect of rTMS should be studied in muscle representations in NPMAs. The rehabilitation effect of rTMS has been demonstrated in stroke patients when targeted to the M1. rTMS pulses delivered to contra- or ipsilesional M1 may release plasticity in the affected hemisphere and increase efficiency in ipsilesional motoneurons (Khedr et al. 2005; Murase et al. 2004; Sung et al. 2013). By rTMS, the recruitment of motoneurons from NPMAs might be facilitated.

The role of muscle representations in NPMAs in use-dependent plasticity will require also future examinations. The recruitment of motoneurons from NPMAs in skills demanding co-activation of several muscles seems probable but larger studies will be needed to verify this finding. The small sample size in studies III and IV make the results of motor skill learning –related plasticity more indicative than conclusive. Thus it remains also an open question whether this kind of use-dependent cortical plasticity and skill acquisition can be facilitated by rTMS. Excessive use-dependent cortical plasticity may be manifested as writer's cramp or musician's dystonia, in which cortical inhibition is reduced (Beck et al. 2008; Hallett 2006). The observations of altered balance in local cortical inhibitory and excitatory interneurons in M1 and in NPMA in healthy fine motor skill specialists may be used when pathogenesis of task-specific dystonias is studied. rTMS has been used to increase and normalize cortical inhibition in these patients and to reduce the pathological co-activation of muscles (Borich et al. 2009; Siebner et al. 1999). These present studies indicate that suppression of actively used muscle representations have an important role in control of fine motor skills. The more focused cortical activation is most probably produced by the enhanced surround inhibition. The "restrictive" plasticity in inhibitory networks in fine motor skill specialists needs to be studied to clarify how to increase the inhibition and reduce the co-activation of muscles by rTMS in musicians suffering from dystonia.

7 Summary and Conclusions

This thesis presents the distribution of pyramidal tract motoneurons in cerebral cortex, characterizing the function of inhibitory and excitatory interneurons in muscle representations in M1 and in NPMA and reveals the dynamic nature of use-dependent cortical plasticity required for different motor skills.

The most important novel finding in this study was that hand muscle representations reside in contralateral NPMA in addition to M1. The other finding with great novelty value was the diminished functional representation of actively used hand muscle in fine motor skill specialists indicating the importance of highly focused cortical control of intended movements in fine motor skills.

The major findings in brief:

I Pyramidal tract motoneurons reside in NPMAs, mainly in PMd and in SMA, in addition to M1.

II The use-dependent cortical plasticity differs in the motor cortices depending on the demands of the trained motor skill and may be manifested as diminished or enlarged muscle representations.

III Pyramidal tract motoneurons originating in NPMAs may produce efficient muscle movements in several muscles. Differences in optimal direction of stimulating current and in muscle activation pattern between M1 and NPMAs indicate that muscle representations in NPMAs are most probably distinct from the representations located in M1.

IV The local intracortical inhibition-excitation balance is shifted slightly towards reduced inhibition in muscle representations in NPMAs. The slightly decreased inhibition may facilitate the recruitment of motoneurons from NPMAs when additional motoneuron capacity is needed.

V Cortical plasticity inducing reorganization towards smaller or more efficiently suppressed muscle representation may be beneficial in those skills demanding single muscle movements, while plasticity towards expanded representations is more likely related to skills demanding co-activation of proximal and distal muscles.

VI Plasticity in intracortical inhibitory neurons may be essential in restricting the spread of cortical activation in skills demanding strictly controlled single muscle movements.

In conclusion, the results of this thesis show that pyramidal tract motoneurons are widely distributed to M1 and NPMA and the muscle representations in NPMAs may produce efficient muscle movements in multiple muscles. Motoneurons originating in NPMAs may be especially crucial when pyramidal tract fibers originating in M1 are damaged due to ischemic stroke or other brain lesion. The next step is to verify the

recruitment of muscle representations in the NPMAs in stroke patients and to evaluate the correlation in efficiency of connections from the NPMAs and motor recovery. Muscle representations in NPMAs may also have an important role in use-dependent plasticity when additional motoneuron capacity is needed. This type of plasticity is related to motor skills demanding co-activation of multiple muscles. In addition to the recruitment of motoneurons, plasticity directed towards more focused cortical activation and diminished muscle representations may be beneficial in skills demanding highly controlled movements of single joints.

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Selja Vaalto

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Functional muscle representations in human cortex were mapped with navigated transcranial magnetic stimulation (nTMS). As a novel finding, hand muscles' representations reside in non-primary motor areas in addition to primary motor cortex. It is also shown that long-term motor skill –specific plasticity in the motor cortices may lead to either focused or enlarged muscle representations depending on the nature of the trained skill.

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