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BRAIN PLASTICITY AND STROKE RECOVERY

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ACADEMIC DISSERTATION

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications, which will be referred to in the text by their Roman numerals.

I **Roiha K**, Kirveskari E, Kaste M, Mustanoja S, Mäkelä JP, Salonen O, Tatlisumak T, Forss N. Reorganization of the primary somatosensory cortex during stroke recovery. *Clin Neurophysiol.* 2011; 122(2):339-45

II Forss N, Mustanoja S, **Roiha K**, Kirveskari E, Mäkelä JP, Salonen O, Tatlisumak T, Kaste M. Activation in parietal operculum parallels motor recovery in stroke. *Hum Brain Mapp.* 2012; 33(3):534-41

III **Laaksonen K**, Kirveskari E, Mäkelä JP, Kaste M, Mustanoja S, Nummenmaa L, Tatlisumak T, Forss N. Effect of afferent input on motor cortex excitability during stroke recovery. *Clin Neurophysiol.* 2012; http://dx.doi.org/10.1016/j.clinph.2012.05.017

IV **Laaksonen K**, Helle L, Parkkonen L, Kirveskari E, Mäkelä JP, Mustanoja S, Tatlisumak T, Kaste, M., Forss N. Alterations in spontaneous brain oscillations during stroke recovery. *Submitted.*

Contributions of the author

All the publications included in this Thesis are results of teamwork. I performed the MEG recordings of the healthy control subjects and participated in the MEG recordings of the patients. In publications I, III, and IV, I performed the data analysis, interpreted the results and was the principal author of the manuscripts. In publication II, I participated in the data analysis, participated in the interpretation of the results, and in the preparation of the manuscript. In studies III and IV, I participated in the study design.

ABBREVIATIONS

AH	Affected hemisphere
AP	Action potential
ARAT	Action Research Arm Test
BEM	Boundary element model
BI	Barthel Index
BOLD	Blood oxygenation level dependent
CBF	Cerebral blood flow
DALY	Disability adjusted life years
ECD	Equivalent current dipole
EEG	Electroencephalography
FFT	Fast Fourier Transformation
fMRI	Functional magnetic resonance imaging
g	Goodness of fit
ICF	Intracortical facilitation
ICI	Intracortical inhibition
ISI	Interstimulus interval
LAI	Long-latency afferent inhibition
MEG	Magnetoencephalography
MI	Primary motor cortex
MRI	Magnetic resonance image
mRS	modified Rankin Scale
NIHSS	National Institutes of Stroke Scale
Peg	Nine-hole peg board test
PET	Positron emission tomography
PM	Premotor cortex
PPC	Posterior parietal cortex
PSP	Postsynaptic potential
PV	Parietal ventral area
SAI	Short-latency afferent inhibition
SEF	Somatosensory evoked field
SEP	Somatosensory evoked potential
SI	Primary somatosensory cortex

SII	Secondary somatosensory cortex
SMA	Supplementary motor area
SQUID	Superconducting quantum interference device
SSS	Signal space separation method
TBI	Traumatic brain injury
TMS	Transcranial magnetic stimulation
tSSS	Temporally extended signal space separation method
UH	Unaffected hemisphere
VPL	Ventral posterior lateral nucleus of the thalamus

ABSTRACT

Recovery from stroke is based on the capability of the brain to reorganize its structure and function after lesion. An acute stroke triggers a cascade of time-dependent metabolic and physiological reactions, which enable changes in the organization and function of widespread cortical regions. A wide range of studies, using various functional imaging methods, have thrown light on the reorganizational changes after stroke. However, less is known about the temporal evolution of these changes and their correlation to clinical recovery.

In this thesis, different aspects of neurophysiological changes related to sensorimotor recovery were studied in 18 patients with first-ever stroke in the middle cerebral artery territory, affecting upper limb motor function. Follow-up recordings of somatosensory evoked fields (SEF) and spontaneous rhythmic brain activity were performed with whole-head MEG within 1 week (T_0), 1 month (T_1), and 3 months (T_2) after stroke with concomitant evaluation of clinical outcome. MEG suits stroke studies especially well, as it is independent from hemodynamic alterations, and the signals are practically unaffected by morbid tissue.

The results indicated that the hand representation in the primary somatosensory cortex (SI) in the affected hemisphere (AH) was transiently enlarged at T_1 and returned to normal size concomitantly with clinical improvement of hand function (Study I). Study II showed that the activation in the contralateral secondary somatosensory cortex (cSII) was decreased in the AH at T_0 and increased during follow-up. The strength of cSII activation paralleled the recovery of hand function during the 3 months follow-up, suggesting that cSII may be an important region in mediating the somatosensory input to the motor cortex. The results in Study III indicated that afferent-input-modulated motor cortex excitability was increased in the AH in the acute phase after stroke and decreased during follow-up in association with recovery of hand function. Study IV showed that the ~10-Hz oscillations were enhanced in the AH at T_1 and T_2. Moreover, pathological perilesional low-frequency oscillations were detected in 7/16 patients at T_0, and the low-frequency oscillations persisted for at least 3 months in 4 patients. These 4 patients had a worse clinical outcome at T_2 than the rest of the patients.

The results indicate that even small lesions can cause widespread neurophysiological changes in the cortical network. Certain brain regions, such as SII, seem to be specifically important for the recovery of hand function. The results underline the importance of parallel recovery of the somatosensory and motor systems for fluent hand function. The most evident

neurophysiological changes were observed within 1 month after stroke in parallel with steepest improvement of clinical recovery, suggesting that the first 4 weeks are critical for functional recovery.

1 INTRODUCTION

Stroke is one of the leading causes of permanent disability in western countries. In recent years, therapeutic interventions such as thrombolysis have been developed to treat acute stroke. However, due to the short time window (within 4.5 hours from onset of symptoms) of this treatment, it still reaches the minority of stroke patients, and even then only half of the occluded vessels are re-canalized (Rha and Saver, 2007). Hence, for most patients intensive rehabilitation is the only way to minimize impairment and to regain lost function.

Rehabilitation is based on the capability of the central nervous system to reorganize and to adjust to environmental needs. Studies in animals have shown reorganization of the cerebral cortex both after peripheral deafferentation (Merzenich et al., 1984, Pons et al., 1991) and after central lesions (Frost et al., 2003, Nudo and Milliken, 1996, Xerri et al., 1998). In animals, cortical reorganization has been linked to changes in cortical inhibition (Jacobs and Donoghue, 1991).

Consistently, different aspects of cortical reorganization have also been observed in patients after stroke. Enlargement of cortical motor or somatosensory representation areas (Calautti et al., 2001, Rossini et al., 1998a, Rossini et al., 2001, Ward et al., 2003a, Ward et al., 2003b) and alterations in the cortical excitability (Butefisch et al., 2003, Liepert et al., 2000b, Manganotti et al., 2002, Ward and Cohen, 2004) have been detected in patients after stroke. However, the functional significance of these findings is not thoroughly understood.

Although plastic changes allow functional recovery, plasticity is not necessarily a solely positive phenomenon. For example, focal dystonia in musicians has been linked to an over activation of the primary sensorimotor cortex (Pujol et al., 2000), and prolonged pain in patients with complex regional pain syndrome (CRPS; Juottonen et al., 2002, Maihofner et al., 2003) and in patients suffering from phantom limb pain (Flor et al., 1995) has been linked to maladaptive plasticity.

The aim of this thesis was to study recovery of the somatosensory and motor cortices after acute stroke, and to correlate the observed neurophysiological changes with clinical recovery. To achieve this, we performed follow-up measurement of somatosensory evoked fields and spontaneous brain activity in 18 patients with first-ever stroke in the middle cerebral artery

territory. The motivation of this thesis was to better understand the mechanisms and temporal behavior of plastic changes after stroke, and to find objective parameters to monitor recovery after stroke.

2 REVIEW OF THE LITERATURE

2.1 Anatomy and physiology of the somatosensory system

2.1.1 Somatosensory pathways, touch

Somatosensory sensation comprises four major modalities: touch, proprioception, nociception, and temperature sense. These submodalities are mediated through two major pathways (dorsal column-medial lemniscus system and anterolateral system) to the brain (Kandel and Jessel, 1991). Discriminative touch is required to recognize the size, shape, weight, and texture of objects.

Touch is mediated via four types of mechanoreceptors which lie in the skin and underlying tissue. The rapidly adapting receptors (Meissner's corpuscles in the superficial skin and Pacinian corpuscles in the deeper tissue) detect changes in texture, whereas slowly adapting receptors (Merkel`s cells in the superficial skin and Ruffini's corpuscles in the deeper tissue) respond to sustained touch and pressure (Kandel and Jessel, 1991).

The information from these four receptor types is conveyed by axons of nerve cells in the dorsal root ganglia to the spinal cord. The majority of the central axons of the dorsal root ganglia neurons ascend in the ipsilateral dorsal column, which relays both tactile and proprioceptive information in a topographic arrangement, to the junction of the spinal cord and the medulla, where they synapse with second-order neurons in two dorsal column nuclei (nuclei cuneate and gracilis; Figure 1). The axons of the second-order neurons cross the midline in the medulla oblongata and ascend in the lemniscus medialis to the thalamus, where they synapse in the ventral posterior lateral nucleus (VPL) and to a lesser extent in the posterior nuclei with third-order neurons. Some tactile information is also relayed in the anterolateral system together with information about pain and temperature. Thus patients with dorsal column lesions retain some crude tactile sensibility (Kandel and Jessel, 1991).

The axons of third-order neurons relaying information from the cutaneous mechanoreceptors mainly terminate in Broadmann area 3b in the primary somatosensory cortex (SI), lying in the posterior wall of the central sulcus in the parietal lobe. From there, neurons project to Broadmann areas 1 and 2 in the primary somatosensory cortex, to the posterior parietal cortex

(PPC), and to the secondary somatosensory cortex (SII). Thalamic neurons also project directly to Broadmann areas 1 and 2 as well as to the PPC and SII.

The topographic arrangement of receptors in the skin is preserved throughout the whole somatosensory pathway, and the somatosensory cortex consists of several somatotopically organized maps of the body surface.

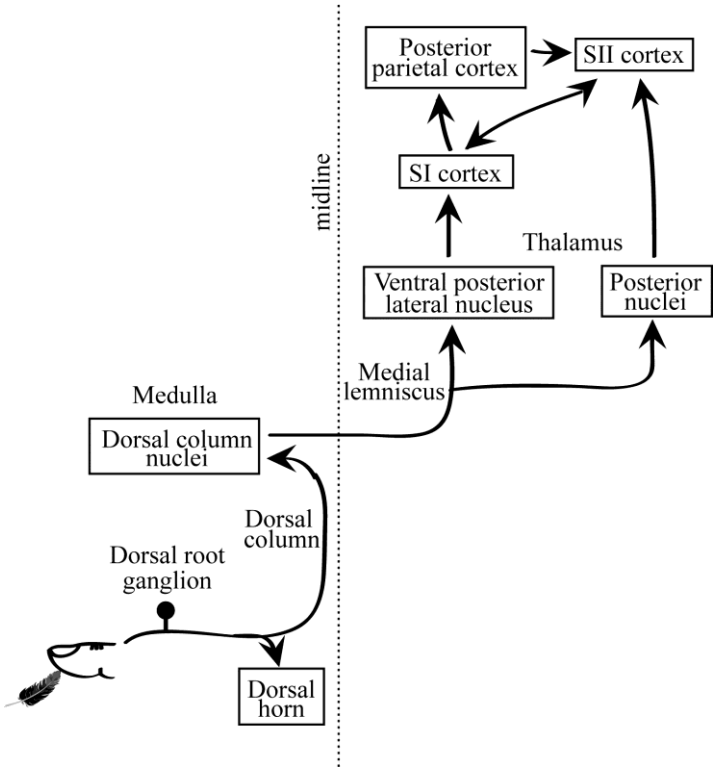

Fig.1. Diagram of the ascending somatosensory pathways. The dorsal column-medial lemniscus system relays tactile sensations and arm proprioception (modified from Martin and Jessel, 1991).

2.1.2 Primary somatosensory cortex (SI)

SI is located in the parietal lobe, in the posterior bank of the central sulcus and in the postcentral gyrus (Figure 2). It consists of Broadmann areas 3a, 3b, 1, and 2. Most thalamic fibers terminate in areas 3a and 3b. Areas 3b and 1 receive information from cutaneous mechanoreceptors, whereas areas 3a and 2 receive proprioceptive information from muscles and joints (Kandel and Jessel, 1991). All of these four areas are interconnected extensively. The information flows mainly in the anteroposterior direction from areas 3a and 3b to areas 1 and 2; at each stage of somatosensory processing, the size of the receptive field becomes larger and the feature-detecting properties become more complex (Hyvarinen and Poranen, 1978). Area 3b receives mainly information about simple stimulus-related properties, such as

intensity and site of stimulation, whereas areas 1 and 2 input are concerned with properties such as direction of movement on the skin and the three-dimensional perception of objects.

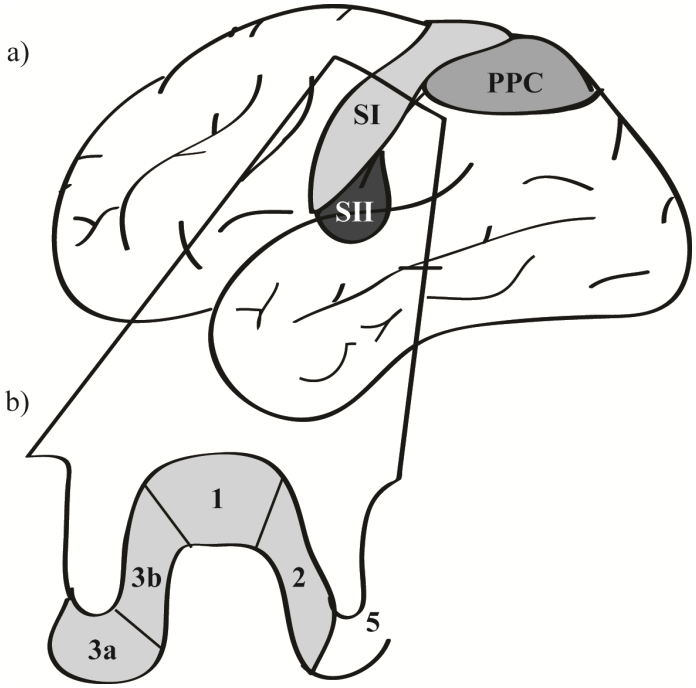

Fig.2 a) The anatomical locations of the three major divisions of the somatosensory cortices from a lateral perspective of the cortical surface. b) SI is subdivided into four cytoarchitectonic areas (Broadmann's areas 3a, 3b,1, and 2; modified from Gardner and Kandel, 2000).

The somatosensory projection from the body is somatotopically organized in SI. This means that each body part has its own representational area. Actually, each area in SI (Broadmann 3a, 3b, 2, and 1) has its own, completely independent body map, with the foot area lying most medially and the face area most laterally (Kaas et al., 1979). Each body part is represented according to its innervation density (Penfield and Jasper, 1954). Areas of the body that are densely innervated and important for tactile discrimination, such as the fingertips and lips, have a disproportionally large representation compared with areas with less extensive innervation, such as the trunk. This means that the receptive fields of cortical neurons innervating the fingertips are much smaller than the ones innervating the trunk. Although the general medial-to-lateral somatotopical organization is similar in all individuals, the sizes of representation area of different body parts are not fixed, but they vary between individuals and change by use (Clark et al., 1988, Jenkins et al., 1990). For instance, in monkeys who were trained to touch a rotating disk with their fingertips, the fingertip representations in

cutaneous area 3b were expanded after several weeks of touching the disk (Jenkins et al., 1990). In accordance, the representations of the left hand digits of string players have been shown to be larger than those in non-musicians (Elbert et al., 1995).

It is suggested that afferent connections to neurons in the somatosensory cortex are formed on the basis of correlated firing. In monkeys, increased correlation of afferent input, obtained by connecting surgically two adjacent fingers, fused the representation areas of these two fingers (Clark et al., 1988). In line with this study, in two patients who were studied before and after surgical separation of webbed fingers, the postsurgical hand representation was considerably larger than the presurgical hand representation, correlating with the new functional status of the separated fingers (Mogilner et al., 1993).

2.1.3 Secondary somatosensory cortex (SII)

SII, located in the parietal operculum along the superior bank of the lateral sulcus, was first described by Adrian in electrophysiological studies in cats (Adrian, 1941). Since then, it has been described in many other animals including primates (Woolsey, 1946). In humans, the SII region was first described by Penfield and Jasper (1954) by means of electrical stimulations of the lateral sulcus during neurosurgery. The first noninvasive observations of activation in the SII region were described in magnetoencephalographic recordings (Hari et al., 1984). The definition of the boundaries and connections of SII has been challenging; the smaller size and the location of SII render it much more difficult to study than SI (Burton, 1986). Moreover, a variety of different adjacent regions to SII with responsiveness to somatosensory stimuli have been found in different species, but the boundaries of these regions have been difficult to determine (Burton, 1986). Microelectrode recordings in monkeys (Krubitzer et al., 1995) and fMRI in humans (Disbrow et al., 2000) have revealed at least two somatotopically organized areas in the parietal operculum: the SII cortex, and rostral to it, the parietal ventral area (PV), which have mirror symmetric maps of the body surface and share common boundaries at the representations of the face, hands and feet. The activation patterns within SII and PV have been shown to be highly variable across subjects (Disbrow et al., 2000), which has further hampered the exact determination of the boundaries of SII.

SII shows somatotopical organization, with cranial parts of the body located anterolaterally and caudal parts posteriomedially. In general, the receptive fields of neurons in SII are larger

and more overlapping than in SI (Burton, 1986, Mazzola et al., 2006). It appears that the spatial differentiation of the body map in SII is sufficiently developed to provide a resolution capable of identifying the body part that has been touched, but the spatial discrimination is not as good as in SI (Burton, 1986).

In contrast to SI, SII is bilaterally activated to unilateral stimulation and neurons in SII have been shown to have bilateral receptive fields (Whitsel et al., 1969, Robinson and Burton, 1980, Mazzola et al., 2006). In accordance with the relatively large, overlapping, and bilateral receptive fields of SII, the functional role of SII in primates has been suggested to be critical for coordinating sensorimotor tasks involving multiple body parts, such as the digits of the hand or the two hands (Simoes and Hari, 1999, Disbrow et al., 2000).

In rhesus monkeys, ablation of the SII region led to impairment of discrimination of the shape and texture of objects (Murray and Mishkin, 1984). Accordingly, in humans, lesions of SII have been suggested to be associated with tactile agnosia (Caselli, 1993). However, this view was challenged by a subsequent study showing consistently abnormal somatosensory evoked potentials (SEPs) in SI in patients with tactile agnosia (Mauguiere and Isnard, 1995). In agreement with the latter findings, impaired SII activation was always associated with abnormal SI responses in the damaged hemisphere of chronic stroke patients (Forss et al., 1999).

2.1.4 Other somatosensory cortices

The posterior parietal cortex (PPC) is located posterior to area 2 in SI. In humans, the PPC stretches over Broadmann areas 5 and 7. However, the borders of PPC are not strictly delineated. In addition to dense connections with ipsi- and contralateral SI and SII, PPC is connected with the visual, auditory, and motor cortices. Thus, PPC is not a pure somatosensory association area; rather, it combines somatosensory information from personal body parts with extrapersonal spatial information and serves higher-level cognitive functions related to movement (Andersen and Buneo, 2002, Hyvarinen, 1982). Thus, lesions of PPC cause complex defects such as disturbances in spatial perception, visuomotor integration, and selective attention. Probably the most well-known consequence of a lesion in the right PPC is neglect syndrome, a deficit in the visuospatial perception of the left side of the body as well as the environment on the left side.

Parts of the mesial cortex are also activated during somatosensory processing (Caselli, 1993, Forss et al., 1996, Penfield and Jasper, 1954). This area is known as the supplementary sensory area, and it probably stretches over the mesial area 5 and anterior portion of mesial area 7 (Caselli, 1993). Extensive lesions of this area caused disruption of somesthetic processing and apraxia (Caselli, 1993). Activation in the mesial cortex in response to somatosensory stimuli has been shown to be attention dependent (Forss et al., 1996).

2.1.5 Cortical connections of somatosensory areas

Studies in monkeys have shown dense, topographically specific, reciprocal connections from all four areas in SI (3a, 3b, 1, and 2) to SII (Jones et al., 1978). Input from the different areas appear to converge within SII in the representation of a given body part (Friedman et al., 1980). SI also has efferent projections to areas 5 and 7 in the ipsilateral PPC. In addition to intrahemispheric connections, SI has transcallosal connections to homotopical areas in the SI of the opposite hemisphere. These connections are sparse between areas 3b and relatively dense between areas 2 (Killackey et al., 1983). Moreover, transcallosal connections between hand and foot representations within each field are much less dense than those between face and trunk representations; in area 3b they are practically non-existent (Killackey et al., 1983). SI also has transcallosal connections to somatotopically-related areas in the contralateral SII (Burton, 1986). However, the functional significance of these connections is not well known. In stroke patients, an SII response ipsilateral to the stimulated impaired hand was found in all patients regardless of the responsiveness of the contralateral SI and/or SII, suggesting that ipsilateral SII may be activated mainly directly through thalamocortical connections (Forss et al., 1999).

Area SII has shown to have connections to the insular cortex and to area 7 in the PPC (Burton, 1986). Moreover, SII is connected in a topographical fashion to contralateral SII via transcallosal connections (Burton, 1986).

2.2 Motor function and sensorimotor integration

Voluntary movements require a complex interaction of cortical motor areas and an integration of sensory input with motor programs. The motor cortices, divided into the primary motor

cortex (MI) and the premotor areas, are located anterior to the central sulcus, occupying approximately the posterior third of the frontal lobes. MI is located in the precentral gyrus and in the anterior wall of the central sulcus (Broadmann area 4). The somatototopical organization of MI resembles the organization of SI: the foot area is located most medially and the face area most laterally. Body parts such as the face, hands, and fingers that are used in motor tasks requiring precision and fine control have disproportionally large representations.

The premotor areas, comprising Broadmann's area 6 anterior to MI consist of two major areas: medially, the supplementary motor area (SMA) and laterally, the premotor cortex (PM). The premotor areas project to MI and to subcortical structures (striatum and thalamic nuclei) as well as directly to the spinal cord. Stimulation of the premotor areas often evoke complex movements involving multiple joints and bilateral body parts (Krakauer and Ghez, 2000).

2.2.1 Cortical connections between somatosensory and motor cortices

Discriminative touch and proprioception are essential for the execution of fine, skilled movements. Although some direct thalamocortical afferent connections to MI exist (Asanuma et al., 1979), the modulatory afferent input to the motor cortex is mediated mainly via cortico-cortical connections from SI and SII (Chen et al., 1999, Disbrow et al., 2000, Hinkley et al., 2007). Studies in monkeys have shown direct connections from areas 1 and 2 in SI to area 4 in ipsilateral MI, whereas direct connections between the main cutaneous area 3b and MI have shown to be sparse or even non-existent (Jones et al., 1978). In contrast, area SII has been shown to have strong anatomical connections to area 4 in ipsilateral MI and to SMA (Jones and Wise, 1977).

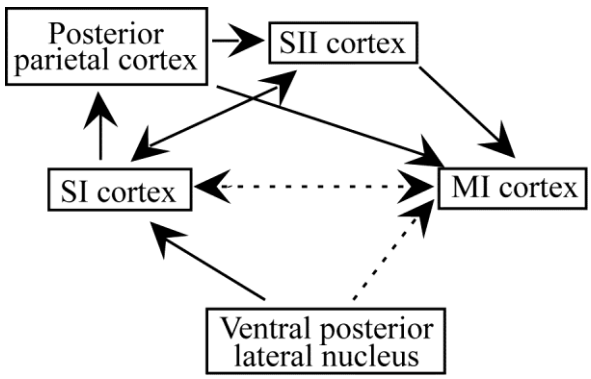

Fig.4 Ipsilateral connections between somatosensory cortices and the primary motor cortex.

2.2.2 Sensorimotor integration

Fluent motor performance requires an integration of afferent somatosensory input with motor programs to adjust the strength, speed, and range of movements. For example, in monkeys, a combined removal of the dorsal column and SI led to permanent severe deficits of hand dexterity (Asanuma and Arissian, 1984). Accordingly, a patient with severe peripheral sensory neuropathy and intact motor circuits was relatively unable to use his hands in daily life, as he could not automatically correct or maintain movements without visual feedback (Rothwell et al., 1982).

In addition to anatomical connections between SII and MI (Jones and Wise, 1977), functional imaging studies have shown a close interaction between SII activation and motor functions. Navigated transcranial magnetic stimulation (nTMS) of the SII region has been shown to facilitate motor performance in healthy subjects (Raij et al., 2008). Deficient activation of SII has been observed in patients with impaired hand dexterity due to Unverricht-Lundborg type epilepsy or focal dystonia (Butterworth et al., 2003, Forss et al., 2001). Taken together, SII seems to play an essential role in sensorimotor integration, especially in tasks involving multiple, functionally-related body parts (Disbrow et al., 2000, Hinkley et al., 2007).

It has been proposed that afferent somatosensory input mediates its effect on motor functions by modulating the excitability of motor cortex neurons before and during movement (Asanuma and Arissian, 1984, Favorov et al., 1988). Accordingly, reduced afferent input due to transient ischemic block of cutaneous afferents or transient immobilization of a limb has been shown to cause motor cortex disinhibition (Brasil-Neto et al., 1992, Todd et al., 2006). In line with these findings, in a TMS study, decreased inhibition of the ipsilesional motor cortex was observed in stroke patients with defective somatosensory input due to lesions in SI or VPL (Liepert et al., 2004).

Taken together, the integration of afferent somatosensory input from multiple body parts, such as the two hands or the fingers of a hand, with motor functions, may be mainly mediated via SII. The integration of afferent somatosensory input with motor programs may function by changing the excitability of motor cortex neurons. Thus, defective sensorimotor functioning may result from insufficient somatosensory feedback due to somatosensory system

dysfunction or from defective sensorimotor integration due to altered afferent modulation of motor cortex neuron activity.

2.3 Spontaneous brain oscillations

Neurons of the cerebral cortex exhibit intrinsic oscillations (Llinas, 1988). The synchronous oscillations of neuronal populations form the basis of cerebral cortical rhythms. Various cortical brain regions in the healthy human brain exhibit their own intrinsic, frequency-specific rhythms with modality-specific reactivity. The best known cortical rhythms of the human brain are the alpha rhythm, detected over the posterior parts of the brain, and the mu-rhythm, detected over the rolandic regions. These rhythms and their modulation are well detectable with electroencephalographic (EEG) and MEG recordings (Salmelin and Hari, 1994a, Steriade et al., 1990). The thalamus has been suggested to play an essential role in driving cortical rhythmic activity (Hughes and Crunelli, 2005, Steriade and Llinas, 1988), and thalamic lesions have been shown to attenuate cortical rhythmic activity (Makela et al., 1998).

Over the last few years, cortical rhythms have attracted new widespread interest. For decades, cortical rhythms were interpreted to reflect an idling state of the neurons (Pfurtscheller et al., 1996), but the differences in spatial and temporal occurrence, as well as in modality-specific reactivity of these rhythms, suggest that these rhythms have higher functional significance (Salmelin et al., 1995). However, the exact functional role of cortical rhythms is still under debate. Cortical rhythms have been suggested to have an important role in cognitive processing (Llinas and Ribary, 1993, Jensen et al., 2002, Haegens et al., 2010, Palva et al., 2005) and in perceptual binding of distributed neural activity (Fries, 2005, von der Malsburg, 1995). Moreover, changes in the amplitude or frequency of brain rhythms may reveal pathological phenomena of the brain (Lewine et al., 1999, Pfurtscheller et al., 1981, Tecchio et al., 2007, Van Huffelen et al., 1984).

2.3.1 Posterior alpha rhythm

The posterior alpha rhythm, first described by Hans Berger in 1929 (for a review see Niedermeyer, 1999), is the best known cortical rhythm. It occurs during wakefulness in the frequency range of 8−13 Hz over the posterior region of the brain. This rhythm is blocked by eye opening and re-appears with eye closure. Alpha rhythms with the same peak frequency

have been recorded from both the visual thalamus (lateral geniculate and pulvinar nuclei) and from the visual cortex (Lopes Da Silva and Storm Van Leeuwen, 1977). Although simultaneously-recorded alpha rhythms from the thalamus and from the cortex have been shown to be partly coherent, the coherence between alpha rhythms recorded between closely spaced electrodes in the cortex has been shown to be much stronger than thalamocortical coherence (Lopes Da Silva and Storm Van Leeuwen, 1977). The genesis of the alpha rhythm is still not thoroughly understood. It has been assumed that there are several generator areas of alpha rhythms in the cerebral cortex and that the rhythm spreads from these areas in different directions (Lopes Da Silva and Storm Van Leeuwen, 1977, Steriade et al., 1990). However, so far there has been no evidence of a synchronizing mechanism for the alpha rhythm at the cortical level (Steriade et al., 1990), whereas the thalamic reticular nucleus has been suggested to play an essential role in the synchronization of thalamic oscillations (Steriade and Deschenes, 1984). Thus, it is assumed that there are both thalamocortical and cortico-cortical systems which interact in the generation of these rhythms (Steriade et al., 1990).

Alpha oscillations have been suggested to play an important functional role in cognitive processing (Jensen et al., 2002, Palva et al., 2005) and in orienting attention (Foxe et al., 1998, Handel et al., 2011). Occipital alpha is supposed to reflect inhibition of task-irrelevant areas, thus directing the sensory inflow to task-relevant areas (Jensen and Mazaheri, 2010).

2.3.2 Rolandic mu rhythm

The features of the cortical rhythm detected over the rolandic regions were first described in detail by Gastaut et al. in 1952 (for a review see Niedermeyer, 1999). The rhythm consists of a slower alphoid (~10 Hz) and a faster beta (~20 Hz) component. Relatively independent mu rhythm generating systems exist in both hemispheres (Storm van Leeuwen et al., 1976). The alphoid component of the rolandic mu rhythm has been suggested to be generated mainly in the postcentral gyrus in the primary somatosensory cortex (Salmelin et al., 1995, Salmelin and Hari, 1994b), whereas the beta component has been shown to have its main generator areas in the primary motor cortex (Pfurtscheller et al., 1996, Salmelin and Hari, 1994b). The beta rhythm has been shown to be coherent with the simultaneously recorded EMG signal from an isometrically contracted limb muscle (Conway et al., 1995, Salenius et al., 1997a), which further supports the association of the beta rhythm with motor functions.

The reactivity of the rolandic mu rhythm indicates that it is closely related to sensorimotor functions. The mu rhythm is suppressed by movement execution, observation or even motor imagery (Hari et al., 1998, Neuper and Pfurtscheller, 1996, Salenius et al., 1997b, Salmelin and Hari, 1994b). The rhythm is suppressed already 1-2 s before movement and subsequently increased (rebound) 0.5-2.5 s after movement termination (Pfurtscheller, 1992, Salmelin and Hari, 1994b). In addition to motor activation, afferent somatosensory input, such as peripheral tactile or electric stimulation, also elicits an initial suppression followed by a rebound of the mu rhythm (Salenius et al., 1997b, Salmelin and Hari, 1994b). The reactivity of the rhythm is bilateral to unilateral movement or somatosensory stimulation, but the reactivity in the contralateral hemisphere to the site of the movement/somatosensory stimulation is more pronounced (Salenius et al., 1997b, Salmelin and Hari, 1994b). Both alphoid and beta components of the mu rhythm display movement-related reactivity, but the reactivity, especially the rebound, is faster and stronger for the beta component than for the alphoid component (Pfurtscheller, 1992, Salenius et al., 1997b, Salmelin and Hari, 1994b).

It has been suggested that there are at least two distinct beta rhythms with different frequencies and different functional roles (Hall et al., 2011, Jurkiewicz et al., 2006, Pfurtscheller et al., 1997, Szurhaj et al., 2003). These different beta components have been reported to behave differently in their reactivity to movement, with the lower beta (~15 Hz) component contributing more to the movement-related rebound and the higher beta (~20 Hz) component displaying quite a similar pattern of reactivity than the alphoid component (Pfurtscheller et al., 1997). In line with these findings, the suppression and rebound of the beta rhythm have been suggested to have different generator areas: the rebound has its main sources in MI in the precentral gyrus (Jurkiewicz et al., 2006, Salmelin et al., 1995), whereas the sources of suppression have been more variable (Feige et al., 1996, Jurkiewicz et al., 2006).

The rebound of the beta rhythm is dampened by motor cortex activation due to movement execution, observation or motor imagery (Hari et al., 1998, Salenius et al., 1997a, Schnitzler et al., 1997), and it has been suggested to reflect deactivation, removal of excitation (Pfurtscheller, 1992, Salmelin et al., 1995), or active inhibition of the motor cortex (Chen and Hallett, 1999, Franzkowiak et al., 2010). Accordingly, decreased motor cortex excitability has been detected with TMS from 200 ms to 1000 ms after digit or median nerve stimulation, a time course comparable to the beta rebound (Abbruzzese et al., 2001, Chen et al., 1999). A

combined MEG and magnetic resonance spectroscopy study showed a linear relation between the beta rebound strength and the inhibitory neurotransmitter γ-Aminobutyric acid (GABA; Gaetz et al., 2011), further strengthening the inhibitory role of the beta rebound. Consistently, the beta rebound has been shown to be attenuated in disorders with suspected motor cortex hyperexcitability or disinhibition such as Unverricht-Lundborg type epilepsy or complex regional pain syndrome (Juottonen et al., 2002, Silen et al., 2000, Visani et al., 2006, Kirveskari et al., 2010).

2.3.3 Other cortical rhythms

In addition to the well known occipital alpha and rolandic mu rhythms, a less well known tau rhythm in the the 8–10 Hz range has been observed in the temporal-lobe (Tiihonen et al., 1991). This rhythm is not dampened by opening the eyes, but it is transiently suppressed by auditory stimuli (Lehtela et al., 1997). The sources of this rhythm cluster to the supratemporal cortex, close to the generator sites of auditory evoked fields (Lehtela et al., 1997). In addition, a sigma rhythm in the 7–9 Hz range has been observed in the parietal operculum, most likely in the SII (Narici et al., 2001). The sources of this rhythm were observed clearly lateral to the sources of the sensorimotor mu rhythm and superior to the sources of the tau rhythm. The sigma rhythm has been shown to react bilaterally to median nerve stimulation with an initial suppression and a subsequent rebound of the rhythm (Della Penna et al., 2004).

2.3.4 Pathological low-frequency oscillations

Injured neuronal tissues generate abnormal cortical low-frequency oscillations in the frequency range below 4 Hz. These oscillations were first classified as “delta-waves” in 1936 by Grey Walter, who localized cerebral tumors due to pathologic low-frequency oscillations (for a review see Amzica and Lopes da Silva, 2011). However, nowadays the delta term is also related to physiological cortical activities during sleep and anesthesia, and it is defined as oscillations in a frequency band between 0–4 Hz (IFSECN, 1974), thus the delta term does not reveal the mechanism underlying these oscillations.

Studies in animals have suggested that partial cortical deafferentation may play a pivotal role in the generation of pathological low-frequency oscillations. These low-frequency oscillations

have been suggested to have a role in guiding axonal sprouting after brain lesions (Carmichael and Chesselet, 2002), thus promoting recovery.

In humans, pathological low-frequency oscillations have also been detected after traumatic brain injury (TBI) and stroke (Butz et al., 2004, Huang et al., 2009, Lewine et al., 1999, Vieth, 1990). In a study combining MEG and diffusor tensor imaging (DTI), pathological low-frequency oscillations were found in co-occurrence with axonal injury in patients with TBI (Huang et al., 2009). A combined MEG and proton magnetic resonance spectroscopic imaging study suggested an association between pathological low-frequency oscillations and abnormal metabolic activity in preserved but dysfunctioning cortical neurons adjacent to an ischemic lesion (Kamada et al., 1997). In TBI patients, low-frequency activity has been linked to certain cognitive symptoms (Huang et al., 2012), whereas no correlations with clinical parameters and low-frequency oscillations have been found in stroke patients (Butz et al., 2004).

2.4 Stroke

According to the World Health Organization, stroke is defined as " rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24 h or leading to death with no apparent cause other than that of vascular origin" (Hatano, 1976). The definition does not distinguish between the causes of stroke, but includes intracerebral and subarachnoid hemorrhage, and ischemic cerebral infarction. Around 75 % of all strokes are ischemic (Thrift et al., 2001). The sudden interruption of the blood supply to the brain results in neurological deficits such as sensorimotor impairment, inability to produce or to understand speech, or defects in the visual field.

2.4.1 Epidemiology

Stroke causes approximately 10 % of all deaths worldwide and is the second most common cause of death after ischemic heart disease (WHO, 2008, Lopez et al., 2006). Globally, the incidence of stroke was estimated at approximately 9 million in the year 2004 (WHO, 2008), and in Finland there were approximately 10500 incident hospital-treated stroke patients each year from 1999 to 2007 (Meretoja et al., 2011). In high-income countries, stroke is the

second leading cause of disability, as measured by disability adjusted life years (DALY), after ischemic heart disease (Lopez et al., 2006). Only around one third of patients recover fully from stroke (WHO, 2002), the remaining surviving patients suffer from permanent disability. Stroke causes a significant burden on the society in developed countries. As a diagnostic entity, stroke is ranked 6th place, consuming around 3 % of total health care costs (Evers et al., 2004). It has been suggested that stroke mortality is decreasing more rapidly than stroke incidence, which will place increased demands on the health-care system (Donnan et al., 2008).

2.4.2 Risk factors

The most important risk factor for stroke is advanced age. Other non-modifiable risk factors are male sex, black race, and family history of stroke. The most important modifiable risk factor is hypertension. Other modifiable risk factors are dyslipidemia, smoking, diabetes, obesity, physical inactivity, and atrial fibrillation (Goldstein et al., 2011) .

2.4.3 Treatment of stroke

Stroke is an emergency situation in which rapid re-supplement of the cerebral blood flow can minimize damage of brain tissue and thus prevent severe neurological deficits. In the last few years, considerable progress in the treatment of acute stroke has been made (Donnan et al., 2008). Thrombolysis therapy with the recombinant tissue plasminogen activator alteplase, when used within 4.5 hours, enhances the chance of favorable outcome. However, the benefit of the treatment decreases the longer the treatment is delayed from stroke onset (Lees et al., 2010). Efforts have been made to develop additional interventions to treat acute stroke, among others the enhancement of thrombolysis with low-frequency ultrasound or mechanical thrombectomy with special devices (Donnan et al., 2008).

Despite the progress in acute treatment, stroke is still the most common cause of permanent disability among elderly people (Donnan et al., 2008). Thus, for most patients, intensive rehabilitation is the most efficient way to regain lost function. Clinical experience has shown that early systematic treatment by an interdisciplinary team improves the prospects of successful rehabilitation. However, the effectiveness of rehabilitation varies among patients

and it declines with time. No clear evidence of the benefit of rehabilitation continued after one year post stroke exists (Aziz et al., 2008). In the last few years, efforts have been made to better understand the mechanisms underlying recovery of function, with the target to develop new effective therapeutic strategies (Ward and Cohen, 2004).

2.5 Plasticity and functional reorganization after stroke

2.5.1 Neuroplasticity

According to the Oxford English dictionary, plasticity refers to the quality of being easily shaped or moulded. The term plasticity was first introduced to neuroscience in 1890 by William James in reference to the tendency of human behavior to be modifiable (for a review see Pascual-Leone et al., 2005). Plasticity is not an occasional occurrence in the central nervous system; rather, it is ongoing, allowing the central nervous system to reorganize and to adjust to environmental needs throughout an individual's life (Pascual-Leone et al., 2005).

At the functional and structural level, plasticity comprises, e.g., the reorganization of representational maps in the cerebral cortex. Such reorganization occurs, e.g., after changes in afferent input, motor learning or after loss of function due to lesions in the central nervous system (Merzenich et al., 1984, Nudo and Milliken, 1996, Nudo et al., 1996a). On one hand, plasticity is a mechanism for development and learning. For instance, the cortical representation of the reading finger in Braille readers has been shown to be enlarged as a result of intensive training (Pascual-Leone and Torres, 1993). On the other hand, plasticity can also be maladaptive and a cause of pathology. Thus, in amputees, the reorganization of the cerebral representation area of the amputated limb has shown to be associated with phantom limb pain (Flor et al., 1995).

At the cellular level, neuroplasticity comprises, e.g., the unmasking of previously existing silent connections (Jacobs and Donoghue, 1991) which lead to a rapid modulation of cortical representational maps that can occur within minutes (Braun et al., 2001). Changes over longer periods of time involve additional mechanisms such as axonal and dendritic sprouting, and formation of new and strengthening of pre-existing synapses (Carmichael et al., 2001, Stroemer et al., 1995). All these plastic changes are driven by both behavioral changes and mediated by local molecular changes.

2.5.2 Reorganization of representational maps after stroke

A study in monkeys showed that after photothrombotically induced small lesions to distal forelimb representation areas in MI, the remaining forelimb representation areas adjacent to the stroke also shrank without training, and the monkeys did not regain lost function (Nudo and Milliken, 1996). In contrast, in monkeys who received training, these areas were spared or they even enlarged concomitantly with recovery of function (Nudo et al., 1996b). In humans, in addition to enlarged motor- and somatosensory representation areas within the primary sensorimotor cortices (Rossini et al., 2001, Rossini et al., 1998b, Weiller et al., 1993, Ward et al., 2003b), more large-scale changes have also been observed after stroke. Motor tasks have been shown to activate secondary motor areas such as the SMA, PM, and even contralesional primary and secondary motor areas after stroke (Weiller et al., 1993, Ward et al., 2003b). Both enlarged representation areas in the primary sensorimotor cortices (Rossini et al., 2001, Rossini et al., 1998b) and recruitment of secondary association areas (Rossini et al., 2001, Rossini et al., 1998b, Ward et al., 2003b) have been associated with poor clinical outcome.

Longitudinal studies have shown that, in patients with good recovery, the neuronal activation pattern may initially be enlarged and include non-primary motor regions, but re-focuses towards more normal contralateral activation patterns in parallel with recovery, while in patients with residual impairment the recruitment of secondary motor areas remains (Calautti et al., 2001, Ward et al., 2003a). A study with patients who received constraint-induced movement therapy demonstrated that during therapy the cortical representation of the affected hand in MI in the affected hemisphere (AH) enlarged in parallel with recovery of hand function. In follow-up examinations up to 6 months after treatment, the motor performance of the affected hand had remained good, although the cortical representation in the AH had returned to normal (Liepert et al., 2000a). Studies in monkeys have suggested that reorganization of cortical representations is learning-dependent and not simply use-dependent. Enlargement of cortical maps was observed in monkeys in parallel with new motor skill acquisition, whereas corresponding changes were not observed in monkeys who simply repeated a task that they performed optimally from the initial exposure of the task (Nudo et al., 1996a, Plautz et al., 2000). Taken together, reorganization of cortical representation maps occurs after stroke, and this reorganization may be related to re-learning of motor skills.

2.5.3 Changes in excitation/inhibition balance after stroke

Several studies in humans and animals have indicated hyperexcitability both in the affected and unaffected hemispheres after stroke (Buchkremer-Ratzmann and Witte, 1997, Butefisch et al., 2003, Domann et al., 1993, Liepert et al., 2000b, Manganotti et al., 2002). Changes in cortical excitability have been linked to unmasking of silent connections and thus to reorganization of cortical representations (Jacobs and Donoghue, 1991). On the other hand, a normalization of cortical excitability has been associated with good recovery of stroke patients (Calautti et al., 2001, Swayne et al., 2008). In line with these findings, hyperexcitability of the motor cortex has been linked to impaired motor performance in several other neurological disorders such as Unverricht-Lundborg Type Epilepsy or focal dystonia (Abbruzzese et al., 2001, Silen et al., 2000).

Motor cortex activity depends on the balance between the influences of several different excitatory and inhibitory systems. These influences range from effects of local corticocortical inhibitory circuits to effects of interhemispheric and afferent connections. TMS allows a segregation of several different types of excitatory and inhibitory circuits. However, the different excitatory and inhibitory influences are complex even in healthy subjects, and the interaction of these is not well known (Chen, 2004). Most TMS studies on stroke patients have applied intracortical inhibition (ICI) and intracortical facilitation (ICF) paradigms (Liepert et al., 2005, Liepert et al., 2000b, Manganotti et al., 2002). The effect of afferent input on motor cortex excitability after stroke is less studied. A previous TMS study evaluated changes in both ICI and afferent inhibition after stroke (Di Lazzaro et al., 2012). They found that changes in afferent inhibition correlated well with long-term recovery, but no correlations with recovery and ICI were found. This study further corroborates earlier findings that cortical excitability modulated by afferent input is driven by different circuits than those mediating ICI or ICF (Sailer et al., 2002).

2.6 FUNCTIONAL BRAIN IMAGING IN STROKE

2.6.1 Magnetoencephalography (MEG)

MEG is a totally noninvasive method which measures, from outside the skull, the magnetic fields produced by neuronal currents. MEG has an excellent temporal resolution on the

millisecond scale and the locations of underlying neuronal activity can be estimated from the measured signals under suitable conditions with a spatial accuracy of a few millimeters. MEG is especially suitable for stroke studies, as it is independent from hemodynamic alterations and as the presence of morbid tissue does not significantly affect the distribution of the neuronal signals (Huang et al., 1990).

The first MEG signals were measured in 1968 by David Cohen using induction coils as the detector (for a review see Hari and Kaukoranta, 1985). The subsequent development of SQUID (superconducting quantum interference device) sensors by James Zimmermann led to the rapid development of MEG instrumentation (for a review see Hämäläinen et al., 1993).

Present-day MEG devices are designed with a helmet-shaped sensor array that covers the whole head and allows the recording of neuronal activation over the whole brain. Thus it enables investigations of simultaneous activation of multiple cortical sites forming a neuronal network.

2.6.1.1 Neural basis of MEG signals

When neurons are activated they produce time-varying electrical currents. We can distinguish between two main types of currents, the fast action potential (AP) and the more protracted postsynaptic potential (PSP). An AP lasts only for ~1 millisecond and it produces two oppositely-directed dipoles. The quadrupolar field produced by these dipoles diminishes rapidly with distance. In contrast, a PSP forms one single current dipole whose magnetic field decays much more slowly as a function of distance than that of a quadrupole. Moreover, a PSP lasts tens of milliseconds, allowing the summations of several simultaneous PSPs (Hämäläinen et al., 1993). MEG measures mainly the magnetic fields produced by PSPs in the apical dendrites of pyramidal cells in the cerebral cortex. The apical dendrites lie perpendicular to the cortex and in parallel with each other, which allows the summation of magnetic fields of tens of thousands of neurons, hence producing a signal strong enough to be measured from outside the skull.

2.6.1.2 Instrumentation

The magnetic field generated by neuronal currents is typically around 50−500 fT outside the head, which is 10^9 times weaker than the earth's steady magnetic field (Hämäläinen et al., 1993). Therefore, MEG measurements are, in general, performed in a magnetically shielded room to avoid contamination of the cerebral signals with artifacts caused by external magnetic noise.

The magnetic fields are measured with SQUID sensors which are embedded in liquid helium (-269 º C) to maintain superconductivity. The magnetic fields are coupled to the SQUIDS with pickup coils, which convert the magnetic signals into electric currents. The present device (Elekta Neuromag®, Helsinki, Finland), used both in the Brain Research Unit, Aalto University and in the BioMag Laboratory, HUCH, consists of 102 triple sensor elements, each comprising two orthogonal planar gradiometers and one magnetometer. The design of the pickup coils is important for the sensitivity of the SQUID to different source currents and artifacts. A gradiometer is figure-eight shaped and it consists of two coils which are wound in opposite directions. With this design, signals originating from the background noise produce practically homogeneous fields in the coils and are thus canceled out. In contrast, signals coming from nearby sources in the brain produce a net change in the output of the coils. Because the field gradient of a dipolar source is steepest just above the source, planar gradiometers give strongest signals just above the cortical sources. A magnetometer consists of only one single pick-up loop; it is sensitive to magnetic signals from the brain but also much more sensitive to environmental noise than a gradiometer (Hämäläinen et al., 1993, Hari, 2011).

2.6.1.3 Source analysis

MEG measures non-invasively magnetic fields produced by neuronal currents. In principle, several current distributions can produce identical magnetic field patterns outside the head. Thus, there is no unique solution for the reconstruction of the sources underlying the measured signals. This is called the inverse problem. However, with accurate prior knowledge of the anatomy and physiology of the brain, the MEG signals can be constrained to meaningful solutions (Hämäläinen et al., 1993) .

In MEG analysis, the head is typically modeled as a spherical homogeneous conductor. This model approximates the head geometry around the sensorimotor cortex, the area of main interest in our studies, reasonably well (Hämäläinen et al., 1993). In a spherical conductor model, radially orientated currents do not produce measurable magnetic fields outside the conductor, because the intracellular currents and the simultaneously produced opposing volume currents cancel each other out. Thus, MEG measures mainly activity from neurons in the fissures of the cortex, which produce currents tangential to the head surface (Hämäläinen et al., 1993). Luckily, the main cortical areas of the sensorimotor system are located within the fissures and are thus easily detected with MEG.

2.6.1.4 Comparison of MEG and EEG

MEG and EEG are closely related to each other, as the primary currents causing the signals are the same. The main advantage of MEG over EEG is that the skull and other tissues surrounding the brain practically do not affect the magnetic fields, whereas they substantially distort the electric potentials measured by EEG. Thus, the spatial resolution of MEG is much better than that of EEG. In contrast to EEG, MEG is reference-free, which makes the interpretation of source locations of magnetic signals more straightforward (Hari, 2011). The advantage of EEG is the much cheaper and more flexible instrumentation, which enables telemetric, long-term, and bed-side recordings.

MEG is mainly sensitive to tangential currents, whereas EEG also detects radial currents. Moreover, EEG is more sensitive to very deep sources. Simultaneous MEG and EEG recordings may be advantageous because the acquired information can complement each other (Hari, 2011).

2.6.2 Other functional imaging methods

Over the past few years, there has been growing interest in the study of functional reorganization of the cerebral cortex after stroke. Considerable efforts have been made to better understand the underlying mechanisms promoting or prohibiting stroke recovery. In addition to MEG and EEG, functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and transcranial magnetic stimulation (TMS) have been widely used for functional brain imaging after stroke.

PET and fMRI rely on the assumption that changes in neuronal activity are closely coupled to changes in cerebral blood flow (CBF) due to an increase in metabolism. PET is a nuclear imaging technique, in which the distribution of a radioactive tracer is measured to make assessments of CBF, oxygen consumption, and glucose metabolism in the brain tissue (Eliassen et al., 2008). Most fMRI studies use blood oxygenation level dependent (BOLD) imaging techniques. The BOLD signal is based on the different magnetic properties of oxygenated and deoxygenated hemoglobin. In regions with increased CBF, the concentration of oxygenated and deoxygenated hemoglobin changes, which can be detected as changes in the BOLD signal (Ward, 2007).

TMS is a tool which allows the noninvasive stimulation of the cerebral cortex using a rapidly changing magnetic field. Among other things, it can be used to investigate or manipulate the physiology of the motor system. The response of motor cortices to stimulation is determined by measuring the size, latency, and required stimulus intensity of motor-evoked responses in a target muscle. These measures have been widely used in stroke recovery studies to probe the motor system physiology and to detect changes in intracortical and interhemispheric excitation/inhibition balance.

All these imaging techniques have certain limitations. Given the complexity of the mechanisms underlying recovery from stroke, the best understanding of the functionality of the cerebral cortex after stroke could potentially be achieved by combining these methods (Eliassen et al., 2008).

2.7 SOMATOSENSORY EVOKED RESPONSES

Somatosensory evoked potentials (SEPs) and somatosensory evoked fields (SEFs) can be used to investigate the physiology and functional organization of the somatosensory system. In clinical use, alterations in strength, latency, generator areas and morphology of somatosensory evoked responses can reveal pathological phenomena.

Single cortical responses to external stimuli are difficult to distinguish from background noise. Thus, SEPs and SEFs are typically studied by averaging responses time-locked to the stimulus to improve the signal-to-noise ratio. Electric stimuli to peripheral nerves have been

widely used to study the somatosensory system since they are easy to apply and produce clear and strong responses. However, electric stimulation activates a large variety of fibers innervating both muscle and skin (Burke et al., 1981). In contrast, tactile stimulation, used in our studies, is a more natural stimulus and it selectively activates rapidly adapting cutaneous mechanoreceptors and elicits clear responses in cytoarchitectonic area 3b, the main cutaneous area of SI (Forss et al., 1994b).

SEPs can be recorded directly from the cortex during surgery or with implanted intracranial electrodes, or noninvasively from the scalp. Scalp SEPs are widely used since they are easy to measure. However, the skull and other extracerebral tissues differ in their electric conductivities, thus they smear the electric potentials and weaken the spatial resolution of EEG.

The earliest cortical SEP responses to electric median nerve stimulation are observed as a surface negative deflection (N20) over the contralateral parietal cortex at about 20 ms after the stimulus, followed by a surface positive deflection (P30) at about 30 ms. A waveform with similar latencies but opposite polarity (P20, N30) is recorded from the frontal scalp, and an intermediate waveform (P25,N35) is recorded near the central sulcus (Allison et al., 1991). Several scalp and intracecebral SEP studies in healthy subjects as well as lesion studies in humans and monkeys have suggested that these potentials are generated by one tangential source in area 3b and one radial source in area 1 in contralateral SI (Allison et al., 1991). However, some studies have suggested that the radial source may be generated in the precentral cortex (Desmedt and Cheron, 1981, Mauguiere et al., 1983).

2.7.1 Somatosensory evoked fields (SEFs)

SEFs were first described by Brenner et al. who studied the somatotopical organization of generator areas of the magnetic signals to thumb and little finger stimulation in SI (Brenner et al., 1978). Since then, many others have reported similar findings for SEFs (Hari et al., 1984, Okada et al., 1984). Compared with SEPs, SEFs have the advantage of a much better spatial resolution. By measuring SEFs in response to somatosensory stimuli applied to different parts of the body, it is possible to reproduce quantitatively the entire somatosensory homunculus in the primary somatosensory cortex (Nakamura et al., 1998). One of the most interesting applications in the study of somatotopically-organized SEFs is the reorganization of

representation areas in SI, as discussed in sections 2.1.2 and 2.4. In addition to functional mapping of cortical representation areas, SEFs can be used to study the functional organization of the whole cortical somatosensory network (Forss et al., 1994a, Hari et al., 1983). Thus, alterations at different levels of the cortical sensory processing stream can be investigated totally noninvasively.

The earliest response to electric median nerve stimulation (N20m) peaks at about 20 ms, and the corresponding equivalent current dipole (ECD) points anteriorly in the contralateral SI. The next deflection (P35m) peaks at 30−35 ms, and the corresponding ECD is also located in the contralateral SI but has approximately opposite polarity (Tiihonen et al., 1989). The earliest response to tactile somatosensory stimulation of the digits using balloon diaphragms driven by compressed air is elicited over the contralateral SI at 50−60 ms; the corresponding ECD is oriented posteriorly, corresponding to the P35m response (Mertens and Lutkenhoner, 2000). The differences in latencies can be explained by differences in the rise time of the stimuli, the different stimulation sites, and the transduction from mechanical stimulation to a neural response. The longer rise time of the tactile stimulus results in a temporally-smeared input to the somatosensory cortex, which produces an insufficient early synchronization of the SI neural population (Mertens and Lutkenhoner, 2000). This insufficient early synchronization together with the smaller number of stimulated afferent fibers probably explains the lack of a correlate of the N20m response after tactile stimulation.

Later responses to somatosensory stimulation are detected at around 100 ms in bilateral parietal opercula at locations corresponding to the SII region (Hari et al., 1983, Hari et al., 1984). In general, the SII response contralateral to the stimulated hand peaks slightly earlier and more strongly than the SII response ipsilateral to the stimulated hand (Hari et al., 1983, Hari et al., 1984). In addition, activation has been observed at 70−110 ms in the contralateral PPC (Forss et al., 1994a) and in the mesial cortex (Forss et al., 1996). Latencies in the later responses do not significantly differ between tactile and electrical stimulation (Forss et al., 1994b).

Averaged SEF amplitudes depend on the interstimulus interval (ISI; Forss et al., 1994a, Hari et al., 1993, Tiihonen et al., 1989, Wikstrom et al., 1996). Long-latency responses, generated outside of SI, may be conveyed through polysynaptic pathways and typically have a longer recovery cycle than short-latency responses (Forss et al., 1994a, Hari et al., 1990). Such long-

latency responses are best detected at ISIs greater than 1 s and require ISIs around 3 s to be optimally recorded. An ISI of 1 s, however, is sufficient to record optimal short-latency responses (Wikstrom et al., 1996, Hari et al., 1983, Huttunen et al., 1992, Mertens and Lutkenhoner, 2000).

The amplitudes of SI responses, generated mainly in area 3b, to median nerve stimulation, have been shown to increase almost linearly with increasing stimulus intensity up to 3 times sensory perception threshold (Jousmaki and Forss, 1998, Lin et al., 2003), emphasizing the crucial role of SI in encoding the somatosensory stimulus intensity. The PPC and SII responses have been shown to saturate at a stimulus intensity 2 times sensory perception threshold (Lin et al., 2003) corresponding to stimulation intensity slightly above motor threshold (Jousmaki and Forss, 1998). These later responses have been shown to be strongly modulated by selective attention (Mima et al., 1998, Mauguiere et al., 1997, Hamada et al., 2003). The modulation by attention together with the strong convergence of afferent somatosensory input and connections to other association cortices suggest that SII and PPC are involved in higher-order processing of somatosensory signals (Jousmaki and Forss, 1998, Lin et al., 2003).

3 AIMS OF THE STUDY

The aim of this thesis was to study noninvasively alterations in the sensorimotor network in the acute phase after stroke and during recovery, and to correlate these changes with recovery of hand function. The specific aims were the following:

1. To correlate the reorganization of the SI hand representation area with recovery of hand function to find out if representational changes are associated with functional recovery after stroke (Study I).

2. To evaluate how changes in the activation of the somatosensory cortical network are associated with motor recovery after stroke (Study II).

3. To study how afferent somatosensory input modulates motor cortex excitability after stroke and how it is associated with recovery of hand function (Study III).

4. To investigate how alterations in spontaneous brain activity and presence of pathological low-frequency oscillations correlate with functional recovery after stroke (Study IV).

4 MATERIALS AND METHODS

4.1 Subjects

4.1.1 Stroke patients

Twenty-three patients with first-ever stroke in the middle cerebral artery territory were initially recruited within 3 days from stroke onset from the Department of Neurology, Helsinki University Central Hospital (HUCH). Exclusion criteria were earlier neurological diseases, neurosurgical operations or head traumas, severe psychiatric disorder, unstable cardiovascular condition and poor general condition. Four patients were excluded from the study after the first measurement, three because MRI revealed prior silent strokes and one because of a re-infarction after the first measurement. One patient's MEG data could not be reliably analyzed due to large artifacts, and was thus excluded from further analysis. Thus, the follow-up data of 18 patients (9 females; age 44−84 years, mean 66 ± 2 years; all right handed) were used for further analysis (Table I). One patient refused to participate in the third measurement because of claustrophobia; the rest successfully underwent all three measurements. Five of the patients received thrombolysis therapy in the acute phase. Nine patients were rehabilitated individually at a rehabilitation hospital and six at an outpatient clinic. No specific rehabilitation was needed for five patients. All patients gave written informed consent.

Table 1 Clinical data of the patients

Patient	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Sex	M	F	M	F	F	M	F	M	M	M	M	F	F	F	M	F	F	M
Age	60	72	74	84	55	68	72	44	62	57	67	67	68	74	78	72	48	61
AH	R	L	L	R	R	L	R	L	L	R	R	L	L	R	L	L	L	R
Site	C	C	C	C	CS	CS	CS	CS	CS	CS	S	S	S	S	S	S	S	S
Size	0.1	0.3	0.4	1	70	48	24	34	5	106	7	1	3	5	10	3	1	4

AH, affected hemisphere. C, cortical. CS, cortico-subcortical. S, subcortical. Size, lesion volume in cm^3.

4.1.2 Control subjects

For Studies I, III, and IV, ten healthy control subjects (5 females, mean age 61 ± 2 years, all right-handed) were recruited for the study. In Study II, the data of 18 control subjects (11 females, mean age 55 ± 2 years) were used for analysis. All control subjects gave written informed consent.

4.2 CLINICAL TESTING

The patients underwent clinical examination within 1 week (T_0), at 1 month (T_1), and at 3 months (T_2) after stroke. A neurologist from the research team performed National Institutes of Stroke Scale (NIHSS) scoring to evaluate stroke-related deficits, and Barthel Index (BI) and modified Rankin scale (mRs) scoring to evaluate the patients' ability to cope in daily life. Tactile sensitivity (light and sharp touch) was categorized into two groups: normal or decreased (as compared with the healthy hand). To evaluate hand motor function and fine motor skills, a physio- or ergotherapist performed the Action Research Arm Test (ARAT; Koh et al., 2006) and the 9-hole peg board test (Peg; Heller et al., 1987). In ARAT, gripping, pinching, arm lifting, and picking objects is tested in four subtests. The performance is evaluated from 0 to 57 points, with 57 being the best score. In Peg, nine pegs have to be removed and replaced one at a time into nine holes as quickly as possible. The time needed to finish the task is measured. In our studies, 120 s was set as the maximum time, and this value was given if the task could not be performed faster.

4.3 STIMULATION

Balloon diaphragms driven by compressed air (Mertens and Lutkenhoner, 2000) were used to deliver tactile stimuli (duration 141 ms, peak 50 ms) to the fingertips. The stimulus intensity was kept constant for all patients and control subjects to allow exact comparisons of the results during recovery. All subjects were able to detect the stimulus as light touch. The patients wore ear plugs to avoid perception of any stimulus-related sound. The thumb and little finger of both hands were stimulated alternately with an ISI of 1005 ms to define the extent of the hand representation area in the SI cortex (Study I). To evaluate changes in the activation of the somatosensory network (Study II) and the effect of afferent input on motor cortex excitability (Study III), both index fingers were stimulated alternately with an ISI of 3005 ms.

4.4 MAGNETOENCEPHALOGRAPHIC RECORDINGS

The MEG recordings were performed with a 306-channel helmet-shaped neuromagnetometer (Elekta Neuromag®, Helsinki, Finland) and carried out in the BioMag laboratory, HUCH, in a magnetically-shielded room. Before the measurements, four indicator coils were placed on the scalp. Magnetic signals produced by tiny currents fed into the coils were detected in the

beginning of each measurement to align the exact head position with respect to the sensor array. During the recordings, the subjects were either in a sitting or supine position with the head supported against the helmet-shaped sensor array. Raw-data and evoked responses (~120 responses to thumb and little finger stimulation of both hands in the first session and ~60 responses to stimulation of both index fingers in the second session) were recorded. In a third session, spontaneous brain activity with eyes open and eyes closed was recorded for three minutes each. Eye movements were monitored with a vertical electro-oculogram, and MEG epochs that coincided with eye movements were automatically rejected from the data. The patients were instructed to relax, to keep their head and fingers in constant position, and not to pay any attention to the stimuli. A nurse inside the magnetically shielded room observed the patients for their general condition and for any possible movements. The signals were band-pass filtered between 0.03−308 Hz and digitized at 941 Hz.

4.5 DATA ANALYSIS

4.5.1 Preprocessing of the data

To suppress artificial signals caused by interfering sources, the signal space separation method (SSS; Taulu et al., 2004) or its temporal extension (tSSS; Taulu and Simola, 2006) implemented in the MaxFilter^{TM} software was applied. The SSS method efficiently suppresses external magnetic artifacts from the measured data. The method relies on Maxwell equations and divides the signals into components arising from inside the sensor array and from the environment surrounding the sensor array (Taulu et al., 2004). SSS is a purely spatial method and the interference rejection factor grows with increasing distance from the interference source. The SSS method is not able to efficiently extract artifacts caused by sources lying very close to the sensor array (e.g. dental work or other magnetic components in the body). tSSS, however, also suppresses artifacts caused by nearby sources, in addition to distant interference, by utilizing the temporal behavior of the signals (Taulu and Simola, 2006). Similar temporal patterns in both internal and external SSS subspaces suggest that a nearby artifact source has generated the field, and those signals are removed from the data. Earlier studies have successfully applied both SSS and tSSS methods to clinical MEG data (Nevalainen et al., 2008, Park et al., 2009, Tanaka et al., 2009). In Studies I and II, either the SSS or tSSS method was applied, depending on the data quality, to preprocess the data of the

patients and the control subjects. In Studies III and IV, all data were preprocessed with the tSSS method.

In Study IV, a signal space projection (Uusitalo and Ilmoniemi, 1997) was applied to remove the cardiac artifacts from the data. The signal space characteristic of cardiac artifacts was estimated by averaging the MEG signals with respect to the magnetocardiographic signal, applying principal component analysis to the average, and selecting the two components associated with the highest singular values. These components were projected out from the tSSS-processed continuous data.

4.5.2 Dipole modeling

To identify the sources of SEFs, equivalent current dipoles (ECDs) best describing the local source currents were calculated with a least-squares method (Studies I and II). Deflections exceeding the noise level in averaged signals were visually detected to divide the data into time periods of interest. In each time period, the ECD best describing the most dominant source was chosen using a subset of channels (10−18) over the response area. The calculations resulted in single dipoles, located three-dimensionally (x, y, z) in a spherical conductor model. The goodness of fit (g) was calculated to determine in percentage how much of the measured field variance the dipole accounted for. Only ECDs with a $g > 85$ % at the selected time period were accepted. Single dipole fitting sufficiently explained the activation in SI (Study I), and the source strengths of the responses were measured at the peak amplitude of the single ECDs. In Study II, the number of ECDs found varied from 0 to 6. After identifying single dipoles, the analysis period was extended to the entire time period of the signals, and all channels were taken into account in computing a time-varying multidipole model. The validity of the multidipole model was evaluated by comparing the measured signals with responses predicted by the model. If signals of any brain region were left inadequately explained by the model, the data were re-evaluated to find a more accurate estimation for the generator areas. In Study II, the source strengths of the responses were determined from the peak amplitudes of the ECDs in the multidipole model.

The Euclidean distance between the sources of the earliest responses to thumb and little finger stimulation were calculated to determine the size of the hand representation area in the SI cortex (Study I).

4.5.3 Temporal-spectral-evolution method (TSE)

The temporal-spectral-evolution (TSE) method (Salmelin and Hari, 1994b) gives a reliable measure of the amount of event-related rhythmic activity with respect to time. The TSE method was applied to evaluate stimulus-related changes in rhythmic beta activity (Study III). Before TSE calculations, the dominant beta peaks were defined from amplitude spectra calculated from spontaneous brain activity (eyes open), and the frequency range of strongest modulation of beta activity was determined from time-frequency representations (TFRs; Tallon-Baudry et al., 1997) in each subject. Thereafter, the averaged SEFs were subtracted from the raw data, which were then band-pass filtered through an individually-chosen frequency range. The frequency ranges were 10 Hz in width and between 12 and 26 Hz. Next, the filtered signals were rectified and time-locked averaged to the stimulus. The analysis period was 3.5 s with a pre-stimulus baseline of 300 ms. Event-related modulation (suppression and rebound) of rhythmic beta activity was quantified using 2–4 MEG channels (1–2 channels over each hemisphere) showing the strongest modulation. The absolute suppression/rebound values, determined from the peak amplitude of deflection, were converted into relative values by calculating the increase/decrease of the rhythm with respect to the pre-stimulus baseline.

4.5.4 Analysis of spontaneous brain activity

4.5.4.1 Spectral analysis

To determine the amount of rhythmic brain activity in different frequency ranges, amplitude spectra were calculated (separately for eyes open and eyes closed) by applying Fast Fourier Transformations (FFTs) with a sliding window and 50 % overlap (Studies III and IV). Windowing minimizes the spectral leakage. To evaluate the amplitudes of rhythmic brain activity in the 5–90 Hz range, a flat-top window of 2048 samples giving a frequency resolution of ~0.5 Hz was used, and spectral peaks were quantified from the channels showing strongest deflections. A flat-top window was chosen as it gives accurate amplitude estimation, given that amplitude strengths were of particular interest. To search for potential pathological low-frequency oscillations in the <4 Hz range (Study I), a Hanning window of 8192 samples yielding a frequency resolution of ~0.1 Hz was applied. A Hanning window

gives a better frequency separation than the flat-top window, which is especially important in identifying low-frequency oscillations.

4.5.4.2 Minimum current estimate in the frequency domain (fdMCE)

The sources of spontaneous oscillatory activity were localized using L1-norm based frequency domain minimum current estimation (fdMCE; Jensen and Vanni, 2002). As in spectral estimation, in fdMCE, the data are windowed into subsections of time and Fourier transforms are calculated for each window. To identify sources of ~10-Hz oscillations, an individual frequency range around the ~10-Hz peak, detected in the spectra, was defined for each subject and Hanning-windowed, half-overlapping FFTs with a 0.46 Hz frequency resolution were computed across the recording. To identify sources of pathological low-frequency activity, the same procedure was applied with a 0.23 Hz frequency resolution for a <4 Hz range. Thereafter, source localizations were estimated using L1 minimum norm estimation for the transformed data. A boundary element model (BEM) of a standard brain was used to restrict the search volume to the brain and a spherical conductor model was used for forward computations. The source locations were projected to the BEM surface and the strength of oscillatory activity was defined over each hemisphere over a standard (~10-Hz oscillations) and an individually-selected (low-frequency oscillations) region of interest (ROI).

4.5.5 Statistical analysis

Repeated measures ANOVAs with within subjects factors time (T_0, T_1, T_2) and hemisphere (affected, unaffected) were used to analyze the differences in the MEG parameters and in the hand function tests. When a significant main effect or an interaction between time and hemisphere was detected, pair-wise comparisons with paired t-tests were performed between different time points or between hemispheres. Bonferroni correction was used to control for multiple comparisons. Parameters between patients and control subjects were compared with independent samples t-tests. Correlations were evaluated with Spearman's correlation coefficient.

5 EXPERIMENTS

5.1 SI REORGANIZATION AFTER STROKE (STUDY I)

Studies in humans and animals have shown that movement or somatosensory stimulation related activation areas in the cerebral cortex are enlarged after stroke (Nudo et al., 1996b, Rossini et al., 2001, Rossini et al., 1998b, Ward et al., 2003a, Ward et al., 2003b). In this study, we investigated the temporal evolution of plastic reorganization in the SI cortex in 15 first-ever acute stroke patients (3 patients were excluded because of technical problems in the MEG measurements, preventing reliable analysis of the data) and correlated the changes with recovery of hand function. Follow-up measurements were performed within 1 week (T_0), 1 month (T_1), and 3 months (T_2) after stroke and the MEG findings were compared with findings of the healthy control subjects.

5.1.1 Results

The patients recovered well: the affected hand function in the 9-hole peg board test (Peg) and in the ARAT was significantly improved at T_1 and T_2 as compared with T_0 (57 ± 10 s and 45 ± 9 s *vs.* 79 ± 10 s, $p < 0.05$ for Peg; and 49 ± 4 and 50 ± 5 *vs.* 37 ± 5, $p < 0.005$ for ARAT). At T_2, the affected hand function did not significantly differ from the healthy hand function (45 ± 9 s *vs.* 26 ± 2, $p = 0.08$ for Peg; and 50 ± 5 *vs.* 57 ± 0, $p = 0.15$ for ARAT). At T_1, the size of the hand representation area in the SI cortex in the affected hemisphere (AH) was enlarged as compared with T_0 or T_2 (12.6 ± 0.8 mm *vs.* 9.6 ± 0.8 mm and 10.2 ± 0.8 mm, respectively, $p < 0.05$; Figure 5.1.1). Moreover, the SI hand representation size in the AH at T_1 was significantly larger than in the unaffected hemisphere (UH) and in the control subjects (12.6 ± 0.8 mm *vs.* 10.8 ± 0.8 mm and 9.5 ± 0.6 mm, respectively, $p < 0.005$).

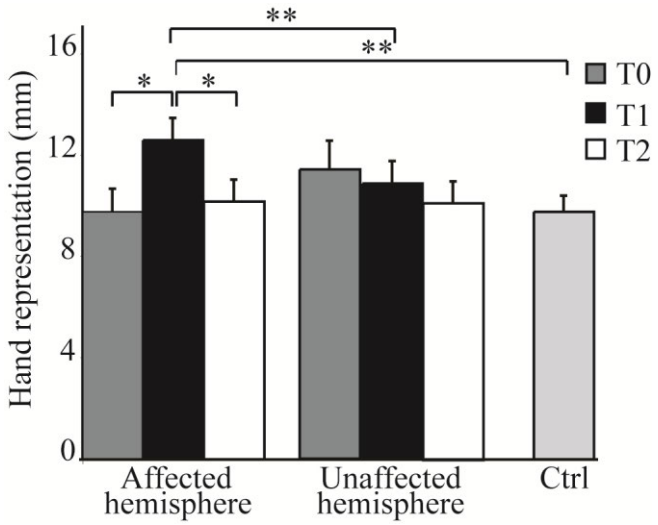

Fig. 5.1.1 Mean (+SEM) size of the hand representation in the SI cortex in all three measurements of the patients (n = 15 for T_0 and T_1, and n = 14 for T_2) and in the control subjects (n = 10; right and left hand pooled; $^{*}p < 0.05$, $^{**}p < 0.005$).

At whole group level, no correlation between the enlargement of the SI hand representation and hand function was found. However, in patients with subcortical infarction (n = 8) the increase in the SI hand representation during the first month after stroke correlated strongly with impairment of hand function ($r_s = 0.8$, $p < 0.01$; Figure 5.1.2).

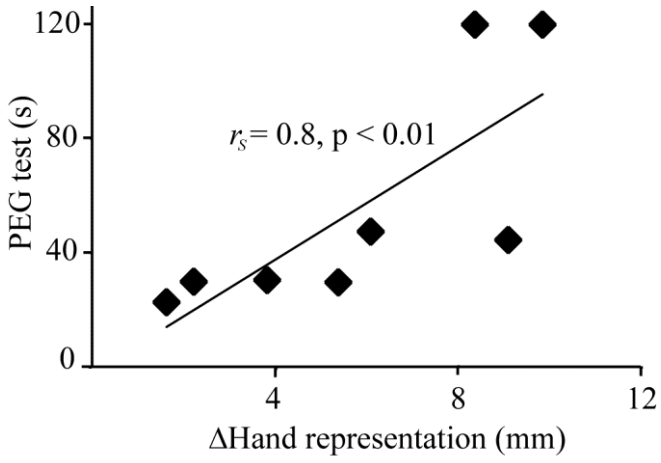

Fig. 5.1.2 Correlation between the increase in the size of the SI hand representation during the first month after stroke (Δ hand representation = size of the hand representation at T_1 – size of the representation at T_0) and the results of the Peg test at T_1 in subcortical stroke patients. The Peg test is evaluated in seconds needed for the task; the shorter the time, the better the hand function. Regression line is shown in black.

5.1.2 Discussion

In the patients, the SI hand representation in the AH was transiently enlarged 1 month after stroke and returned to normal size at 3 months, concomitantly with recovery of hand

dexterity. Earlier MEG studies have indicated a tendency towards a larger hand representation in the AH than in the UH at 9 weeks to 6 months after stroke, in association with incomplete recovery of hand function (Rossini et al., 2001, Rossini et al., 1998b). In the present study, an initial enlargement of the hand representation was also observed in patients who recovered well later on. The size of the hand representation returned to normal size in parallel with recovery of hand function.

Studies in animals have indicated that cortical plasticity is learning-dependent and not simply use-dependent. In monkeys who were trained for a new task, cortical map changes in motor representations were observed in parallel with improvement of performance (Nudo et al., 1996a). In contrast, no such changes were observed in monkeys who just repeated a simple task that they performed optimally from the beginning (Plautz et al., 2000). In line with these findings, enlarged cortical representation of the affected hand in MI was observed in chronic stroke patients during constraint-induced movement therapy in parallel with clinical improvement of hand function. After this treatment, the cortical representation of the hand returned to normal, whereas the motor performance remained good (Liepert et al., 2000a). We suggest that the transient enlargement of the SI hand representation in our stroke patients may reflect the re-learning of motor skills, whereas the normalization of the representation size may reflect the maintenance of re-learned function.

5.2 SII ACTIVATION AFTER STROKE

Fluent motor function requires continuous inflow of somatosensory input to the motor system. In this study, we recorded SEFs to tactile index finger stimulation within 1 week (T_0), 1 month (T_1), and 3 months (T_2) after stroke with concomitant evaluation of clinical recovery (NIHSS, BI, mRS, ARAT, Peg) to study the effect of altered activation in the somatosensory cortical network on motor recovery after stroke. Eighteen first-ever stroke patients and 18 healthy control subjects were enrolled in the study.

5.2.1 Results

The patients recovered well, and all clinical parameters improved significantly from T_0 to T_1 and T_2 ($p < 0.005$; Table 5.2.1; Figure 5.2.1).

Table 5.2.1 Clinical scores of the patients (Peg, ARAT, mean ± SEM; NIHSS, BI, mRs, median ± SEM)

	Peg (ah)	Peg (uh)	ARAT(ah)	ARAT(uh)	NIHSS	BI	mRS
T_0	84 ± 9	36 ± 4	35 ± 5	56 ± 0	4 ± 1	60 ± 7	3 ± 0
T_1	59 ± 10	28 ± 1	46 ± 5	57 ± 0	2 ± 0	90 ± 4	2 ± 0
T_2	51 ± 9	26 ± 1	48 ± 4	57 ± 0	1 ± 0	100 ± 3	2 ± 0

T_0, within 1-7 days; T_1, 1month; T_2, 3 months from stroke onset. ah, affected hand. uh, unaffected hand. Peg, 9-hole peg board test, time (s). ARAT, Action Research Arm Test (0–57). NIHSS, National Institutes of Health Stroke Scale (0–42). BI, Barthel Index (0–100). mRS, modified Rankin Scale (0-6).

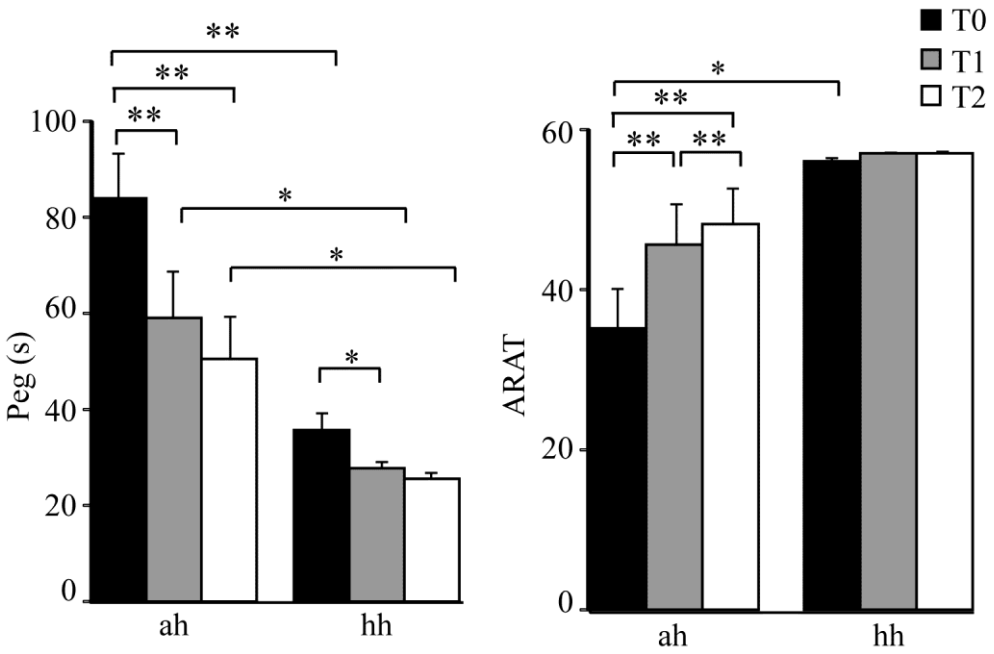

Fig.5.2.1 Mean (+ SEM) Peg times and ARAT scores of the patients (n = 18 for T_0 and T_1, and n = 17 for T_2) at T_0, T_1, and T_2. ah, affected hand. hh, healthy hand. (*p < 0.05, **p < 0.005).

In the control subjects, tactile stimulation elicited responses in contralateral SI at 58 ± 1 ms and in bilateral SII regions at 109 ± 6 ms and 118 ± 4 ms (contra- and ipsilateral SII, respectively). At T_0, SI responses were found in 15 patients and contralateral SII (cSII) responses in 9 patients. Latencies of the responses were comparable with latencies of the control subjects. At T_1 and T_2, SI responses were detected in all patients and cSII responses in 17 patients. When an SII response was detected, it was always preceded by an SI response. In the patients, the SI responses were significantly stronger in the UH than in the AH at T_0 and T_1. No time effect was observed for the SI responses. In contrast, the cSII response in the AH

was significantly weaker at T_0 than at T_1 or T_2 (14 ± 4 nAm *vs.*25 ± 5 nAm and 26 ± 4 nAm, respectively, $p < 0.05$; Figure 5.2.2). Moreover, the cSII response in the AH at T_0 tended to be weaker than in the UH (14 ± 4 nAm *vs.* 25 ± 6 nAm, $p = 0.06$) and was significantly weaker than in the control subjects (14 ± 4 nAm *vs.* 29 ± 2 nAm, $p < 0.01$). No significant differences between the hemispheres were observed in the ipsilateral SII responses.

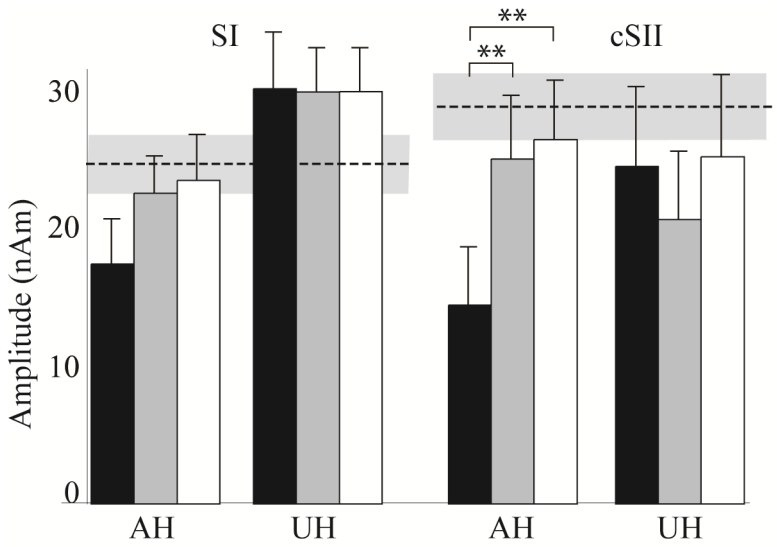

Fig 5.2.2 Mean (+SEM) amplitudes (nAm) of SI and cSII responses in the patients (n = 18 for T_0 and T_1, and n = 17 for T_2) in the affected hemisphere (AH) and unaffected hemisphere (UH) to contralateral tactile finger stimulation. The mean (+SEM) amplitudes of the control subjects (n = 18; right and left hand pooled) are shown with dashed and grey horizontal lines (**p < 0.005).

The amplitudes of the SII responses correlated with results of the Peg test at all time points ($r_s = -0.6$, $p < 0.01$ for T_0; $r_s = -0.5$, $p < 0.05$ for T_1, and $r_s = -0.6$, $p < 0.05$ for T_2; Figure 5.2.3). In contrast, SI responses did not correlate with results of the Peg test at any time point.

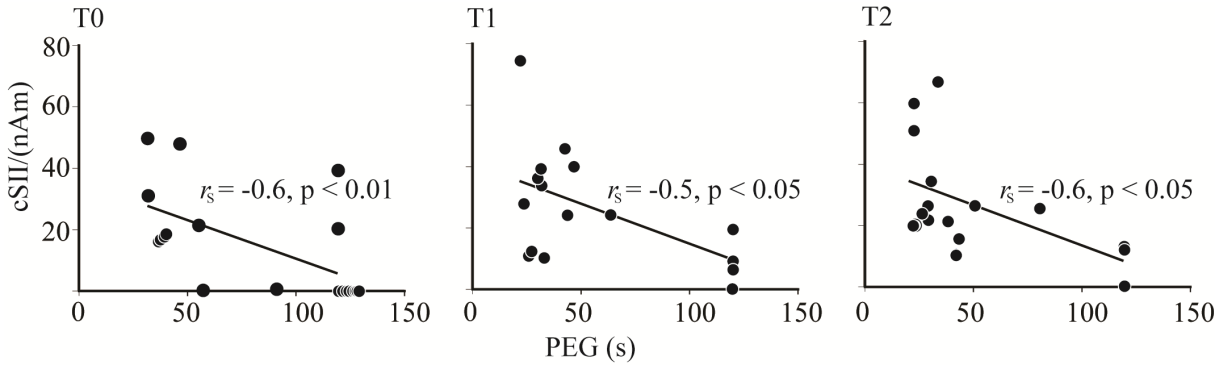

Fig. 5.2.3 Correlation between the strength of SII activation and Peg time (s) of the affected hand at 1 week (T_0), 1month (T_1), and 3 months (T_2) from stroke. Regression line is in black.

5.2.2 Discussion

In the patients, the strength of SII activation was decreased in the AH compared with the UH and the control subjects in the acute phase and increased during follow-up. The strength of SI activation was also decreased in the AH compared with UH, but no significant increase of SI activation was observed during follow-up. The strength of SII activation, but not SI activation, in the AH correlated with results of hand function tests both in the acute phase and during recovery, indicating that the SII region is important in hand sensorimotor functions.

Earlier studies on somatosensory activation after stroke have shown varying correlations between the strength of SI activation and clinical outcome (Oliviero et al., 2004, Rossini et al., 2001, Wikstrom et al., 2000). In healthy subjects, the SI amplitude has been shown to reflect tactile sensitivity and stimulus properties like intensity (Hari et al., 1993, Huttunen et al., 1987, Tiihonen et al., 1989). In line with these findings, a follow-up study in stroke patients showed improved 2-point discrimination in patients with increase of SI responses during follow-up (Wikstrom et al., 2000). Alterations in activation of the SII region, suggested to be involved in higher-order somatosensory processing (Jousmaki and Forss, 1998, Lin et al., 2003, Simoes and Hari, 1999, Disbrow et al., 2000), have so far not been studied with whole-head MEG.

Somatosensory input is crucial for fluent motor functions. Continuous inflow of somatosensory input to the motor system is needed to adjust the speed, range, and strength of movements. Despite some direct afferent thalamic connections to MI (Asanuma et al., 1979), somatosensory input to the motor cortex is suggested to be mediated mainly via cortico-cortical connections (Chen et al., 1999, Disbrow et al., 2000, Hinkley et al., 2007). Anatomical studies have shown strong connections from SII to MI (Jones and Wise, 1977, Mori et al., 1989), whereas connections from the main cutaneous area 3b in SI to MI have been shown to be sparse (Jones et al., 1978). A close interaction between SII activation and motor functions have also been shown in functional imaging studies in humans. Navigated TMS of the SII region facilitates motor performance in healthy subjects (Raij et al., 2008). In addition, clinical studies have shown an association between SII activation and motor functions. For instance, Unverricht-Lundborg type progressive myoclonus epilepsy patients with absent SII activation had more severe motor symptoms than the patients in whom SII activation was observed (Forss et al., 2001).

We suggest that the deficient SII activation in our acute stroke patients reflects insufficient flow of somatosensory input to the motor cortex, which results in impaired sensorimotor integration. During follow-up, activation in SII paralleled motor recovery of hand function, supporting the view that the SII region is an important node in sensorimotor integration.

5.3 MOTOR CORTEX EXCITABILITY AFTER STROKE

Motor cortex excitability has been shown to be altered after stroke (Butefisch et al., 2003, Liepert et al., 2000b, Manganotti et al., 2002). In addition to cortical excitatory and inhibitory circuits, afferent input has also been suggested to modulate motor cortex excitability (Asanuma and Arissian, 1984, Favorov et al., 1988). The effect of afferent input on motor cortex excitability can be studied by monitoring the reactivity of the motor cortex beta rhythm to somatosensory stimulation, which elicits an initial suppression followed by a subsequent rebound of the rhythm. The rebound of the rhythm is suggested to reflect decreased motor cortex excitability (Chen et al., 1999, Franzkowiak et al., 2010, Gaetz et al., 2011, Salmelin et al., 1995). In this study, we monitored the reactivity of the beta rhythm to tactile index finger stimulation in 18 patients after acute stroke (T_0) and during recovery (T_1 and T_2), as well as in 10 healthy control subjects. The rebound of the beta rhythm was correlated with hand function as evaluated with the Peg test. Moreover, the rebound was correlated with the strength of the SEFs (adapted from Study II) to determine how alterations in motor cortex rhythms are modulated by changes in afferent input.

5.3.1 Results

In the control subjects, the beta rhythm started to decrease at 120 ± 15 ms after stimulus and reached its peak at 250 ± 15 ms in both hemispheres. The subsequent rebound started at 550 ± 35 ms after stimulus and peaked at 900 ± 85 ms. Comparable latencies of suppression and rebound were found in both hemispheres in the patients.

In the patients, the beta rebound was weaker at T_0 than at T_1 or T_2 in both the AH and UH ($p < 0.01$ for the AH, $p < 0.05$ for the UH; Table 5.3.1.; Figures 5.3.1 and 5.3.2). Moreover, the beta rebound in the AH at T_0 was significantly weaker than that in the control subjects ($p <$

0.05). Within patients, the beta rebound in the AH was significantly weaker than in the UH at all time points ($p < 0.005$ for T_0; $p < 0.001$ for T_1; $p < 0.05$ for T_2).

Table 5.3.1 SEF amplitudes (mean ± SEM) to index finger tactile stimulation of the affected hand (adapted from Study II), and beta rebound (increase of the rhythm with respect to the reference baseline; mean ± SEM) in patients and in control subjects

	SI ampl, AH (nAm)	SII ampl, AH(nAm)	Rebound, AH (%)	Rebound, UH (%)
T_0	17 ± 3	14 ± 4	22 ± 7	43 ± 7
T_1	22 ± 3	25 ± 5	43 ± 11	68 ± 9
T_2	23 ± 3	26 ± 4	37 ± 9	57 ± 7
Ctrl.	25 ± 3	31 ± 3	61 ± 11	61 ± 11

T_0, 1-7 days; T_1, 1 month; T_2, 3 months after stroke. Ctrl.; control subjects (left and right hands pooled). SI, primary somatosensory cortex. SII, secondary somatosensory cortex. AH, affected hemisphere. UH, unaffected hemisphere.

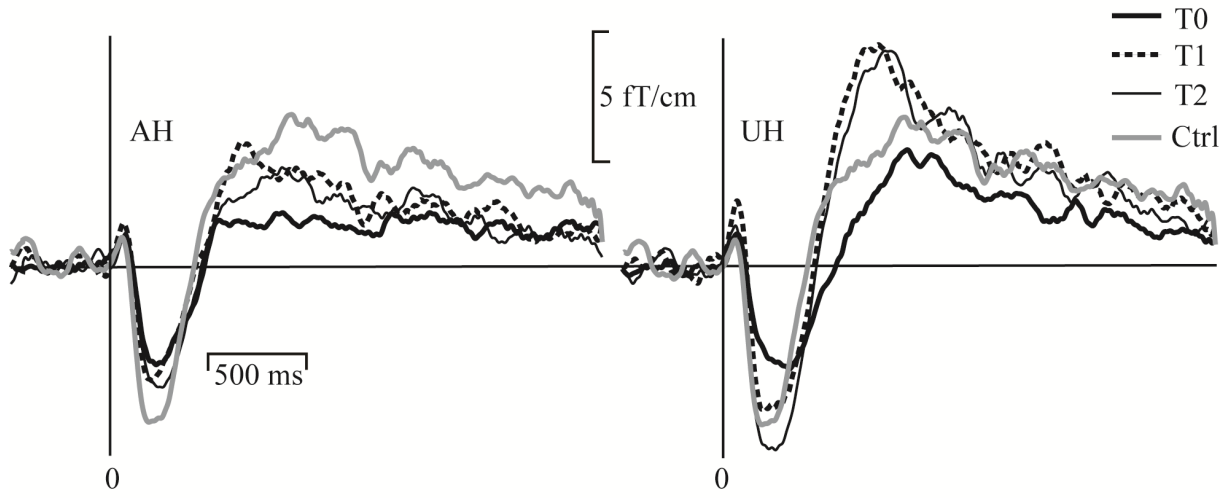

Fig. 5.3.1 Average strength of the beta rhythm (15–25 Hz) over the sensorimotor region in the affected (AH) and unaffected (UH) hemispheres to contralateral tactile index finger stimulation within 1 week (T_0), 1month (T_1), and 3 months (T_2) after stroke and in the control subjects (right and left hemispheres pooled). 0 indicates the onset of the tactile stimulus.

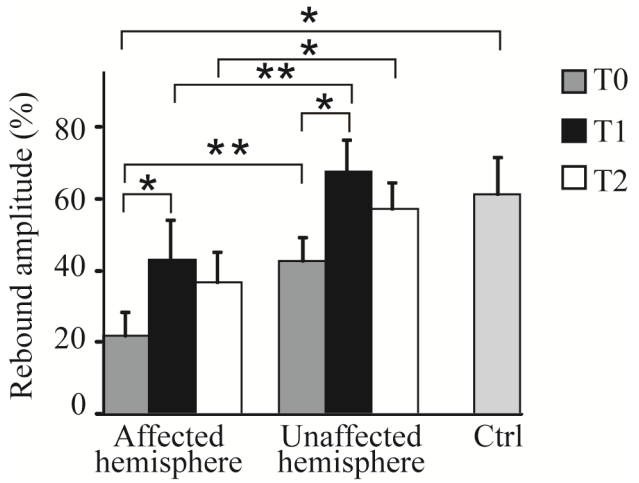

Fig.5.3.2 Mean (+SEM) strength of the beta rebound over the sensorimotor region in the affected and unaffected hemispheres to contralateral tactile index finger stimulation at 1 week (T_0), 1month (T_1), and 3 months (T_2) from stroke and in the control subjects (right and left hemispheres pooled; *p< 0.05, **p < 0.005).

No association between absent/diminished rebound and decreased tactile sensitivity was observed. The strength of the beta rebound in the AH correlated with Peg results of the affected hand in all three measurements (nonlinear regression $r_s = -0.8$, $p < 0.001$ for T_0; $r_s = -0.5$, $p < 0.05$ for T_1; and $r_s = -0.6$, $p < 0.05$ for T_2; Figure 5.3.3).

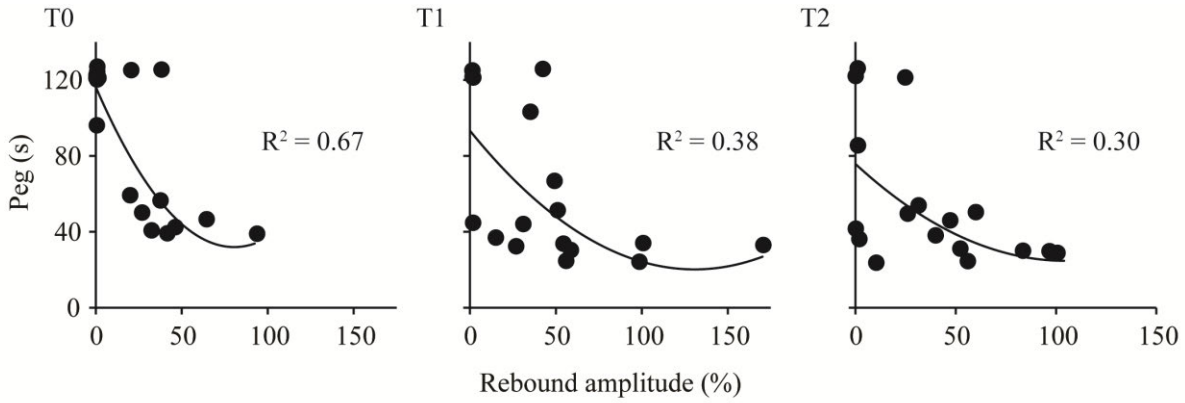

Fig. 5.3.3 Association between the strength of beta rebound in the affected hemisphere and the Peg time (s) of the affected hand at 1 week (T_0), 1month (T_1), and 3 months (T_2) from stroke. Nonlinear (x^2) regression curve is shown in black.

At T_0, the strength of SII activation correlated with the strength of the beta rebound ($r_s = 0.5$, $p < 0.05$), whereas no correlation between SI activation and beta rebound was found.

5.3.2 Discussion

In the patients, the beta rebound was decreased in the AH at the acute phase after stroke, suggesting increased motor cortex excitability after acute stroke. The beta rebound increased during follow-up, suggesting decreasing motor cortex excitability during stroke recovery. These findings are in line with a recent TMS study suggesting reduced short-latency afferent inhibition in the AH after acute stroke (Di Lazzaro et al., 2012). The strength of beta rebound correlated with hand function test results at the acute phase and during recovery, suggesting that increased excitability is associated with poor control of hand function, and that a return towards normal excitability is associated with good recovery of hand function. These findings are in line with earlier studies, showing increased motor cortex excitability in association with impaired fine motor skills in patients suffering from Unverricht-Lundborg Type Myoclonus epilepsy or complex regional pain syndrome (Canafoglia et al., 2004, Juottonen et al., 2002, Schwenkreis et al., 2003, Silen et al., 2000). Accordingly, several studies in stroke patients, applying different measures of motor cortex excitability, have shown that motor cortex excitability is increased in the acute phase, but returns to normal if the patients recover well (Calautti et al., 2001, Swayne et al., 2008, Ward et al., 2003a).

As discussed in Study II, anatomical studies in animals (Jones and Wise, 1977, Mori et al., 1989) and functional studies in humans (Disbrow et al., 2000, Hinkley et al., 2007) have suggested that the SII region may be important in integrating somatosensory information with motor functions. In our study, the strength of the beta rebound correlated with the strength of SII but not with SI activation in the acute phase after stroke. This finding supports the earlier suggestions that the modulatory afferent input to motor cortex excitability may be mediated via SII.

In principle, all observed changes of motor cortex excitability could be solely due to recovery of somatosensory afferents. However, in the light of our results, this possibility is not likely. SI amplitudes increase almost linearly with increasing stimulus intensity (Jousmaki and Forss, 1998, Torquati et al., 2002). In our patients, the stimulus intensity was kept constant across all measurements; hence enhanced afferent input due to recovery of somatosensory afferents would elicit increased SI amplitudes. However, no significant changes in SI amplitudes in our stroke patients were observed (Study II). Neither was there a clear relationship between absent/diminished rebound and decreased tactile sensitivity. We suggest that the changes in the beta rebound result from recovery of both the somatosensory and the motor systems. The

parallel recovery of the sensory and motor systems allows a fluent sensorimotor integration, which is a prerequisite for normal hand dexterity.

5.4 SPONTANEOUS BRAIN OSCILLATIONS AFTER STROKE

Alterations in the frequency and amplitude of spontaneous rhythmic brain activity have been associated with pathological phenomena in the brain (Lewine et al., 1999, Pfurtscheller et al., 1981, Van Huffelen et al., 1984) and have even been suggested to predict recovery from stroke (Tecchio et al., 2007). In this study, we recorded spontaneous brain activity in 16 first-ever stroke patients within 1 week (T_0), 1 month (T_1), and 3 months (T_2) after stroke and in ten healthy control subjects, to find out how alterations in spontaneous brain oscillations are associated with functional recovery after stroke.

5.4.1 Results

The main sources of the ~10-Hz oscillations in the eyes-open condition were detected in the temporo-parietal region, clearly distinct from occipital alpha sources (Fig. 5.4.1), but slightly lateral to the typical location of rolandic ~10-Hz oscillations.

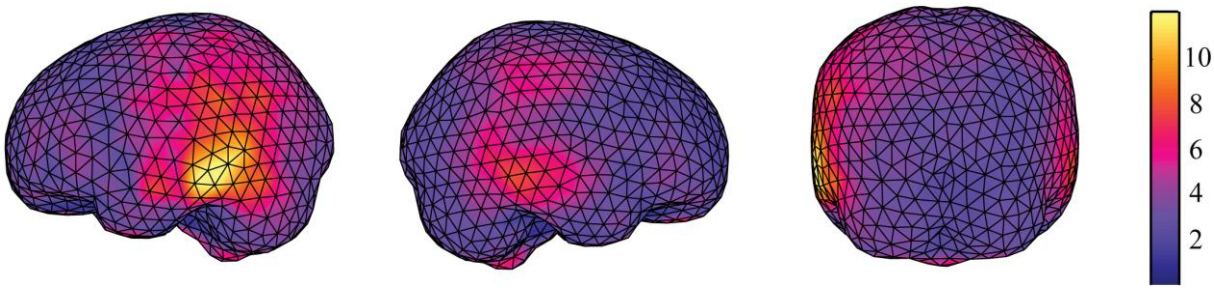

Fig 5.4.1 Averages of sources of ~10-Hz oscillations (eyes open) in the patients with lefthemispheric stroke (arbitrary scale). The sources are clearly stronger in the affected hemisphere.

In the patients, the source strength of ~10-Hz oscillations (eyes open) in the AH was significantly stronger than in the UH at T_1 and at T_2 (2.6 ± 0.3 nAm *vs.* 1.6 ± nAm, $p < 0.05$ and 2.5 ± 0.3 nAm *vs.* 1.7 ± 0.2 nAm, $p < 0.05$, respectively; Figure 5.4.2). The strength of ~10-Hz oscillations in the AH at T_1 and T_2 had a tendency to be stronger than in the control subjects (2.6 ± 0.3 nAm *vs.* 1.9 ± 0.2 nAm, $p = 0.08$ and 2.5 ± 0.3 nAm *vs.* 1.9 ±0.2 nAm, $p = 0.10$, respectively). In contrast, no differences in the strength of the ~10-Hz oscillations for

the eyes-closed conditions or the rolandic beta rhythm were detected between the hemispheres or between patients and control subjects. The amplitude of the ~10-Hz sources seemed to increase in bursts, showing strong variation in source strength from window to window used in FFT estimation. As fdMCE calculates the mean strength of all the FFT-windows, the absolute values for the ~10-Hz sources are rather small.

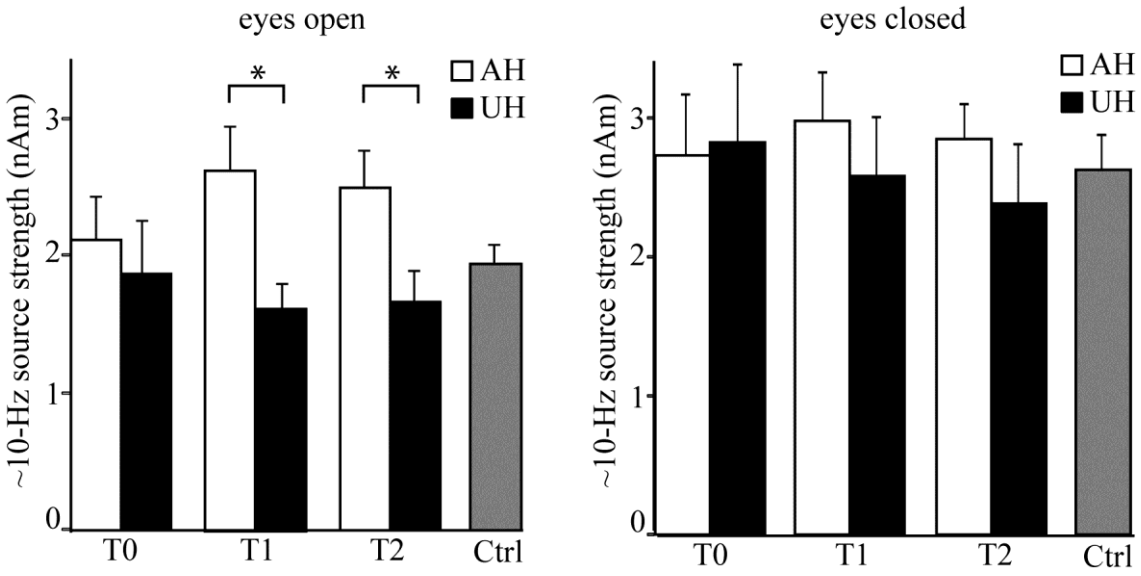

Fig. 5.4.2 Mean (+SEM) source strength of ~10-Hz oscillations (eyes open) over the affected hemisphere (AH) and unaffected hemisphere (UH) of the patients and in the control subjects (right and left hemispheres pooled, *p < 0.05). T_0, within 1 week; T_1, 1month, and T_2, 3 months after stroke.

Pathological low-frequency oscillations at <4 Hz with strongest amplitudes on average at 1 ± 0.1 Hz were detected in 7/16 patients at T_0, in 6 patients at T_1, and in 4 patients at T_2. In patients with cortical involvement of the stroke, the sources of low-frequency oscillations were detected in the surrounding of the cortical lesion (Figure 5.4.3). The patients with low-frequency activity had a significantly larger lesion than the rest of the patients (35 ± 15 *vs.* 2 ± 1 cm^3, $p < 0.05$). The 4 patients showing persistence of low-frequency activity at T_2 had a worse clinical outcome than the rest of the patients (88 ± 21 *vs.* 33 ± 3, $p < 0.001$ for Peg; 3 ± 1 *vs.*1 ± 0, $p < 0.05$ for NIHSS).

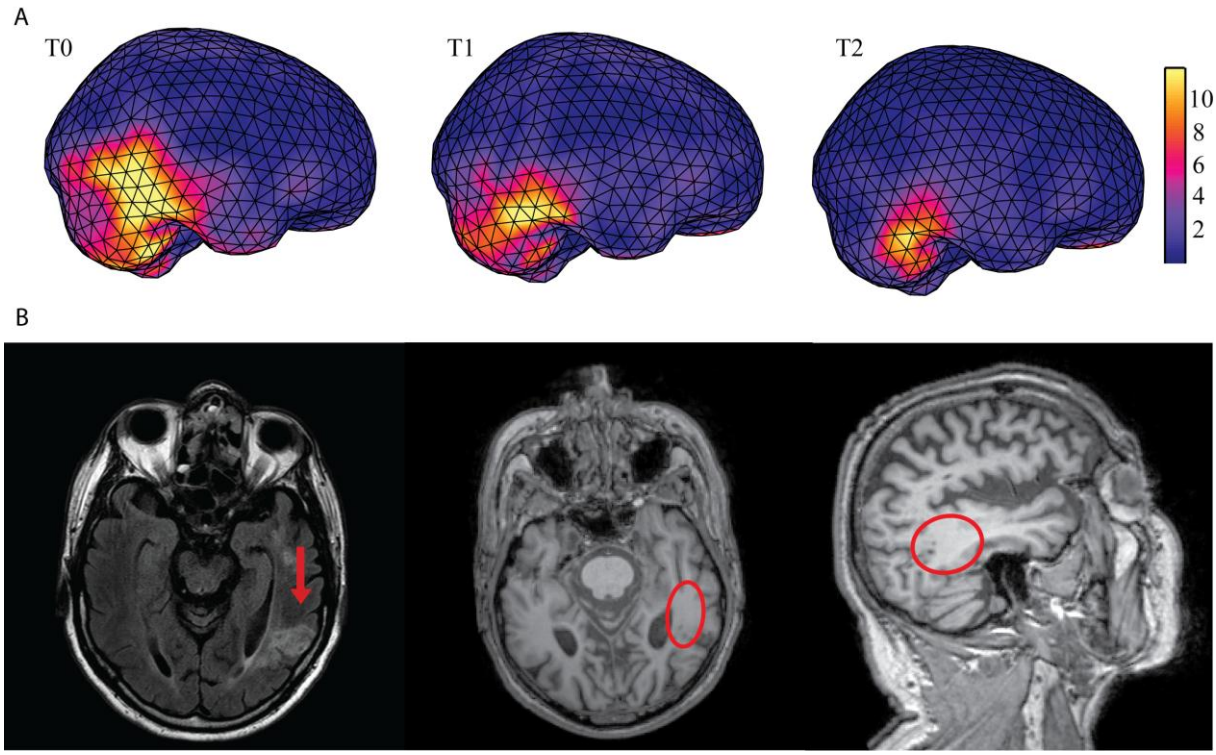

Fig. 5.4.3 A) Source location of pathological low-frequency activity within 1 week (T_0), 1month (T_1), and 3 months (T_2) after stroke (arbitrary scale). B) MRIs from the same patient; the arrow points to the cortical lesion; the ellipsoids illustrate the generator area of pathological low-frequency oscillations.

5.4.2 Discussion

In the patients, the strength of ~10-Hz oscillations was increased for the eyes-open condition in the AH at T_1 and T_2 as compared with the UH. In contrast, no differences between the hemispheres were observed for the eyes-closed condition. The source locations were distinct from those of occipital alpha sources, but slightly lateral to the typical location of rolandic ~10-Hz sources. In addition to occipital and rolandic ~10-Hz oscillations, sources of rhythmic activity in 7–10 Hz range have been detected in the temporal-lobe (tau rhythm; Tiihonen et al., 1991) and in the parietal operculum (sigma rhythm; Narici et al., 2001). The source location of the prominent ~10-Hz oscillations detected in our patients could agree with the location of the sigma rhythm, found in the SII region. However, a contribution of rolandic ~10-Hz oscillations to these sources cannot be excluded. Although the exact generator areas for the ~10-Hz oscillations cannot be determined, the differences between the eyes-open and eyes-closed conditions indicate that the occipital alpha rhythm does not contribute to this rhythm. Rather we suggest that the enhanced ~10-Hz oscillations detected in the AH of our stroke patients reflects a somatosensory rhythm, with possible contribution of both the rolandic and the SII regions.

The sigma rhythm has not been extensively studied, and to our knowledge no earlier reports of alterations of this rhythm in stroke patients exist. Earlier observations of alterations in the strength of rolandic ~10-Hz oscillations in stroke patients have been controversial, as both increases and decreases of the oscillatory amplitudes have been observed (Pfurtscheller et al., 1981, Tecchio et al., 2006, Tecchio et al., 2005, Van Huffelen et al., 1984). One previous study found that in patients with mild or moderate deficits, rolandic ~10-Hz oscillations increased in the acute phase after stroke. In patients with severe neurological deficits, this increment was observed months later in association with slow clinical recovery (Pfurtscheller et al., 1981). In the present study, no clear association between the strength of ~10-Hz oscillations and clinical outcome was observed. However, the steepest improvement in clinical function was observed from T_0 to T_1, and the ipsilesional increase in ~10-Hz oscillation amplitudes was observed at T_1.

In healthy subjects, both rolandic and occipital ~10-Hz oscillations have been associated with cognitive processing (Llinas and Ribary, 1993, Jensen et al., 2002, Haegens et al., 2010, Palva et al., 2005), and particularly in directing the flow of information to optimize performance (Haegens et al., 2012, Jensen and Mazaheri, 2010). In light of these findings, it may be that the enhancement of ~10-Hz activity in the AH observed in our stroke patients could possibly be engaged in allocating resources for recovery mechanisms. However, this remains hypothetical, and future studies are needed to understand the functional significance of enhanced ~10-Hz oscillations in the AH after stroke.

Perilesional low-frequency oscillations have been detected in earlier stroke studies (Butz et al., 2004, Fernandez-Bouzas et al., 2000, Vieth, 1990), but the functional significance has remained unclear. In the present study, low-frequency oscillations could be detected in 7 patients in the acute phase, and in 4 patients, low-frequency activity still persisted 3 months after stroke. In a rat study, pathological low-frequency oscillations after thermal ischemic lesions were strongly correlated with axonal sprouting, suggesting that low-frequency oscillations may have a role in plastic reorganization after brain lesion (Carmichael and Chesselet, 2002). On the other hand, a study combining MEG and proton magnetic resonance spectroscopic imaging, suggested that pathological low-frequency oscillations are associated with abnormal metabolic activity in malfunctioning perilesional neurons (Kamada et al., 1997). In the present study, the patients with low-frequency activity had larger lesions and the

patients with persistent low-frequency activity had a worse clinical outcome at T_2 than the rest of the patients. However, as the number of patients with persistent low-frequency activity was small, and the follow-up period was only 3 months, no definitive conclusions about the clinical significance of low-frequency oscillations can be drawn.

An earlier MEG study suggested that alterations in spontaneous brain oscillations may be used to predict the outcome from stroke; particularly delta (2–3.5 Hz) power in the UH and gamma (33.5–44 Hz) power in the AH were found to predict long-term outcome after stroke (Tecchio et al., 2007). We did not find clear UH delta or AH gamma peaks in our patients. Pathological low-frequency oscillations were detected in less than half of our patients and the presence of low-frequency oscillations significantly correlated with lesion size, thus this parameter is not likely to provide any additional information in predicting outcome after stroke. In contrast, ~10-Hz activity is a very robust signal, which is detected practically in every subject; and enhancement of AH ~10-Hz activity was detected at some time point in 13/16 of our well-recovering patients. Thus enhanced ~10-Hz activity may have functional significance in recovery from stroke. Future studies should aim at investigating if enhanced ~10-Hz activity could be used to predict the outcome from stroke.

6 GENERAL DISCUSSION

In this thesis, different levels of adaptive alterations in the sensorimotor system after acute stroke were studied in a longitudinal design. The aim was to elucidate the temporal evolution of plastic changes after acute stroke and their correlation to clinical recovery in order to better understand the recovery mechanisms of the injured human brain.

6.1 Temporal evolution of plastic changes after stroke

Although the brain alters its structure and function throughout life, injury to the central nervous system seems to be a special trigger that elicits plastic mechanisms (Nudo, 2006). Focal brain injury results in a variety of time-dependent metabolic and pathophysiological reactions which enable widespread cortical regions to change structure and function. Although there is a wide range of studies investigating plastic changes such as changes in cortical somatosensory and motor representations (Calautti et al., 2001, Rossini et al., 1998a, Rossini et al., 2001, Ward et al., 2003a, Ward et al., 2003b) or excitability (Butefisch et al., 2003, Liepert et al., 2000b, Manganotti et al., 2002, Ward and Cohen, 2004) after stroke, longitudinal data recording the evolution of these changes are rare. A study in monkeys indicated that, if motor rehabilitation was delayed over 1 month after stroke, the spared hand representation areas within the peri-infarct area of the motor cortex were not maintained, although the monkeys achieved recovery of hand function after delayed training (Barbay et al., 2006). In contrast, if monkeys obtained early post-infarct rehabilitation the hand representation areas in the peri-infarct zone were maintained or even enlarged (Nudo et al., 1996b). These results suggest that, during early rehabilitative training, the cerebral cortex may be more capable of reorganizing, whereas in chronic stages other compensatory mechanisms may emerge.

In line with the animal studies, in our Studies I, II, and III, all significant changes in brain activation were observed within the first month after stroke: the size of the hand representation in the SI cortex in the AH (Study I), the strength of cSII activation in response to affected hand stimulation (Study II), and the strength of the beta rebound in the AH (Study III) all increased significantly from T_0 to T_1. Also the increase in ~10-Hz oscillations was observed at T_1. The steepest improvement in clinical function was observed in parallel with the detected functional changes.

We did not control our patients for any specific rehabilitative treatment. All patients were treated in the Department of Neurology, Helsinki University Central Hospital in the acute phase, usually for 1 to 2 weeks, and afterwards the patients received specific treatment according to their individual needs. Thus, we cannot distinguish between the effects of rehabilitative training and spontaneous recovery on neurophysiological changes and clinical improvement. Clinical experience has shown that further recovery still occurs after 1 month from stroke, but changes are more subtle. In line with these findings, clinical improvement was still observed from T_1 to T_2 in our studies, although no significant changes in the measured neurophysiological parameters were observed in that time period. It may be that within the first month after stroke, the cerebral cortex is particularly responsive to plastic changes, and after that time window, other compensatory mechanisms take over to yield functional recovery. This finding would encourage clinicians to force the initiation of effective rehabilitative training as early as possible. However, it is also possible that we did not observe further significant changes in neurophysiological parameters after 1 month because most of our patients had already recovered well. Future follow-up studies with more severe stroke patients should aim at investigating whether there is a time window for plastic changes after stroke, and whether it would be beneficial to extend this time window to improve clinical outcome.

6.2 Motor cortex excitability after stroke

Animal studies have indicated increased excitability after central ischemic lesions in cortical areas both in the AH and UH. These changes have been observed both after photothrombotically-induced lesions (Buchkremer-Ratzmann and Witte, 1997, Domann et al., 1993) and after middle cerebral artery occlusion (Reinecke et al., 1999), suggesting that changes in excitability are independent of the lesion mechanism.

In humans, most of the earlier studies on motor cortex excitability after stroke have been performed with TMS and intracortical inhibition (ICI) and intracortical facilitation (ICF) paradigms (Liepert et al., 2005, Liepert et al., 2000b, Manganotti et al., 2002, Swayne et al., 2008). There are only a few studies using TMS after conditioning somatosensory stimulation to detect changes in motor cortex excitability after stroke (Di Lazzaro et al., 2012, Oliviero et al., 2005). Changes in motor cortex excitability due to alterations in afferent input are most

likely mediated by different circuits than those mediating ICI or ICF (Sailer et al., 2002). A recent TMS study evaluated both short-latency ICI (SICI) and short-latency afferent inhibition (SAI) in stroke patients and found a correlation between SAI and clinical recovery, but not between SICI and recovery. TMS recordings after somatosensory stimulation have shown, in addition to SAI, long-latency inhibition at approximately 200 ms, called as "long-latency afferent inhibition" (LAI; Chen et al., 1999, Sailer et al., 2002). LAI occurs bilaterally after unilateral somatosensory stimulation and has been suggested to be predominantly mediated via polysynaptic cortico-cortical projections (Abbruzzese et al., 2001, Chen et al., 1999, Sailer et al., 2003). Both paradigms, LAI in TMS and beta rebound in MEG, use peripheral afferent input to study changes in cortical excitability. In both methods, unilateral afferent stimulation induces bilateral changes in cortical excitability at comparable long latencies. It is not known if LAI and beta rebound share any common mechanisms, but such comparison would be an interesting target for future investigations.

6.3 Cortical excitability and reorganization of the cerebral cortex

Earlier studies have suggested that altered cortical excitability is a prerequisite for cortical reorganization after stroke. Jacobs and Donoghue (1991) suggested that expansions of motor cortical representations are dependent on adjustments in local inhibition, and proposed that inhibitory circuits are critically placed to unmask latent intracortical connections and to readjust cortical motor presentations. However, representational changes are not restricted to the motor cortex. Direct intracortical measurements in rats demonstrated an enlargement of representational areas of the vibrissae in the somatosensory cortex in the neighbourhood of an ischemic cortical lesion (Schiene et al., 1999). This enlargement was linked to decreased intracortical inihibition (ICI), due to a reduction of $GABA_A$ receptors, which may lead to an unmasking of pre-existing silent connections (Schiene et al., 1996). In line with these findings, we found a transient expansion of the hand representation area in the SI cortex one month after stroke (Study I).

In our patients, the strength of the beta rebound (measured in Study III) and the enlargement of the SI hand representation (Study I) did not correlate. However, it has to be noted that the beta rebound reflects the afferent modulation of motor cortex excitability. Changes in afferent-input-modulated inhibition can occur independent of changes in local inhibitory circuits, as was shown in an earlier TMS study combining afferent inhibition and ICI (Di

Lazzaro et al., 2012). In fact, it is not well known how different excitatory and inhibitory systems interact together (Chen, 2004). An earlier TMS study investigating ICI after short-latency (1−10 ms) median nerve stimulation conditioning suggested that short-latency afferent inhibition may reduce ICI (Ridding and Rothwell, 1999). However, the interaction between long-latency afferent inhibition, which probably would resemble the beta rebound we studied, and ICI is not well known. Clarifying the interaction of afferent and intracortical inhibitory circuits would further help to understand the complex interplay between plastic reorganization and different inhibitory and excitatory mechanisms.

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6.4 Sensorimotor integration

Prior studies in monkeys and in humans have indicated that the SII cortex participates in sensorimotor integration, especially in tasks involving multiple functionally-related body parts like both hands or the digits of one hand (Disbrow et al., 2000, Forss et al., 2001, Hinkley et al., 2007, Jones et al., 1978, Raij et al., 2008). However, the exact functional role of SII in sensorimotor integration remains uncertain. In our Studies II and III, we suggest that modulatory afferent input reaches the motor cortex via SII. Furthermore, we suggest that the somatosensory input is integrated with motor functions by modulating the excitability of the motor cortex.

Both, changes in motor cortex excitability and deficient SII activation, have been reported in several disorders with motor impairment, such as Unverricht-Lundborg Type Epilepsy, focal dystonia, and Parkinson disease (Abbruzzese et al., 2001, Boecker et al., 1999, Butterworth et al., 2003, Forss et al., 2001, Sailer et al., 2003, Silen et al., 2000). However, the association between motor cortex excitability and SII activation has not yet been directly studied. To our knowledge, we are the first to suggest that the SII region may mediate motor functions by modulating the motor cortex excitability.

SII activation and strength of beta rebound correlated at T_0, but not at T_1, or T_2. The strength of SII activation in the AH was normalized already at T_1, whereas the beta rebound in the AH was still weaker than in the UH still at T_1 and T_2. Changes in the strength of the beta rebound are not likely to result solely from the integrity of the somatosensory inflow to the motor cortex. In addition, the functional integrity of the motor cortex including local cortical excitability influences is likely to affect the strength of the beta rebound. A faster recovery of

the afferent somatosensory system than the motor system may explain the discrepancy in the correlation between SII activation and beta rebound in the acute phase but not during follow-up.

6.5 Future perspectives in monitoring recovery after stroke

Monitoring stroke recovery is complex, since the definition of successful outcome varies and many physical and psychosocial aspects may affect neurological functions (Duncan et al., 2000). Still, a precise definition of recovery is lacking, and so far, evaluation of the efficacy of rehabilitation has mainly been based on a variety of clinical parameters. Although it is known that early rehabilitation is a powerful tool to modulate recovery after stroke, early extensive training may sometimes be maladaptive. A forced overuse of the affected forelimb in rats after brain injury led to exaggeration of the neuronal injury (Kozlowski et al., 1996). Hence, it is important to find parameters for objective monitoring of recovery from stroke and to define optimal parameters for successful rehabilitation. Searching for such parameters was one motivation of this thesis.

In light of our findings, one suitable parameter for monitoring recovery from stroke appears to be the enlargement of the hand representation in the SI cortex. Animal studies have shown that increased motor repetition alone is not sufficient to drive changes in cortical representation maps, rather, it demands acquisition of new skills (Nudo et al., 1996a, Plautz et al., 2000, Remple et al., 2001). In line with these findings, in a study with stroke patients receiving constraint-induced movement therapy, a significant increase in the cortical representation of the affected hand was observed in parallel with significant improvement of motor functions. In follow-up measurements up to 6 months after treatment, the motor performance had remained good, but the cortical representation had decreased and normalized (Liepert et al., 2000a). Hence, the transient enlargement of cortical representations, also observed in our study, may reflect the acquisition of new skills, and may thus provide an objective parameter to monitor the sufficiency of rehabilitative training.

Our results clearly extend the earlier knowledge of sensorimotor recovery after stroke. However, many issues still remain unresolved. Earlier studies have indicated that post-stroke recovery mechanisms in cortical versus subcortical strokes may differ (Ameli et al., 2009, Liepert et al., 2005). The correlation between the enlargement of SI hand representation and hand motor function in patients with subcortical stroke but not in patients with cortical lesions

(Study I) was in accordance with this idea. However, as the number of patients with pure cortical strokes was small, no definitive conclusions about the differences in the recovery mechanisms between different stroke sites can be drawn from our data. Future studies should aim at comparing neurophysiological changes after cortical and subcortical strokes.

All the changes in neurophysiological parameters studied in this thesis were observed within the first month after stroke, indicating that the brain's maximum responsiveness to plastic changes may be restricted to a relatively short time window. However, all our patients recovered relatively well, thus it may also be that no further changes were observed because of the relatively good clinical outcome 1 month after stroke. Another possibility is that the steepest changes in neurophysiological parameters occur within 1 month and that the evolution of changes decelerates from then on. Hence, 1 month and 3 months would be too close in time to observe any significant changes. Future studies should aim at including more severe stroke patients in follow-up measurements, and follow-up measurements should be performed at least over 6 months or even a year to obtain better understanding of the brain's capability for plastic changes beyond the subacute phase.

We observed changes in various cortical neurophysiological parameters that were associated with clinical recovery after stroke. It may be meaningful to study the effect of therapeutic interventions such as repetitive TMS or pharmacological treatment on these parameters to evaluate whether the time window for these alterations can be extended, and whether it has a positive influence on recovery. Such knowledge may further help to define the optimal parameters for successful rehabilitation and to allow better targeting of therapeutic interventions.

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7 SUMMARY & CONCLUSIONS

In this thesis, plastic changes related to hand sensorimotor functions were studied in 18 acute stroke patients in a longitudinal design. The main results shed light on alterations in the central sensorimotor mechanisms important for fluent hand function. The observed transient enlargement and subsequent normalization of the SI hand representation in our stroke patients (Study I) strengthens the earlier observations of differences in learning-dependent and use-dependent plasticity. This finding underlines the importance of sufficient challenge during rehabilitation in order to provoke plastic reorganization in the brain.

The observation that patients with persisting perilesional low-frequency oscillations have a worse clinical outcome than the other patients (Study IV) may indicate that this phenomenon is an indicator of more severe brain lesions. On the other hand it may also be a signal of ongoing plastic reorganization and thus longer follow-up times would be needed to elucidate the clinical significance of perilesional low-frequency oscillations.

Our observations in Studies II and III add important knowledge to the role of afferent input in motor functions. The observed changes in cSII but not in SI activation in parallel with recovery of hand dexterity strongly indicate that cSII is an important node in mediating the modulatory somatosensory input to the motor cortex. This finding is further supported by the correlation of the beta rebound, suggested to reflect the effect of afferent input on motor cortex excitability, with cSII activation (Study III). Furthermore, the increase in beta rebound in association with hand motor recovery underlines the importance of parallel recovery of the sensory and motor systems to allow fluent sensorimotor integration, which is a prerequisite for normal hand function.

MEG provides a suitable tool to study cortical neurophysiological alterations after stroke. We observed a variety of alterations which seem to be significantly related to clinical recovery. In the future, studies with more severe stroke patients and longer follow-up times as well as interventional studies may lead to an improvement of individually designed and well-targeted rehabilitation to maximize the recovery potential after stroke.

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Kristina Laaksonen

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