BioMag Laboratory
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NEUROMAGNETIC STUDIES ON SOMATOSENSORY FUNCTIONS IN HEALTHY SUBJECTS AND STROKE PATIENTS

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Academic Dissertation

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Contents

Abbreviations

BA	Brodmann's area
CS	Central sulcus
CNS	Central nervous system
EEG	Electroencephalography
ECD	Equivalent current dipole
EPSP	Excitatory postsynaptic potential
fMRI	Functional magnetic resonance imaging
IPSP	Inhibitory postsynaptic potential
ISI	Interstimulus interval
MCA	Middle cerebral artery
MEG	Magnetoencephalography
MRI	Magnetic resonance imaging
OC	Frontoparietal opercular cortex
PET	Positron emission tomography
PPC	Posterior parietal cortex
PSP	Postsynaptic potential
SD	Standard deviation
SEF	Somatosensory evoked field
SEP	Somatosensory evoked potential
SI	First somatosensory cortex
SII	Second somatosensory cortex
SQUID	Superconducting quantum interference device
TMS	Transcranial magnetic stimulation
VP	Ventroposterior nucleus of the thalamus
VPL	Ventroposterolateral nucleus of the thalamus
VPM	Ventroposteromedial nucleus of the thalamus

List of Publications

This Thesis is based on the following Publications:

I Wikström, H., Huttunen, J., Korvenoja, A., Virtanen, J., Salonen, O., Aronen, H.J. and Ilmoniemi, R.J. Effects of interstimulus interval on somatosensory evoked magnetic fields (SEFs): a hypothesis concerning SEF generation at the primary sensorimotor cortex. Electroenceph. clin. Neurophysiol. 1996, 100: 479–487.

II Wikström, H., Roine, R.O., Salonen, O., Aronen, H.J., Virtanen, J., Ilmoniemi, R.J. and Huttunen, J. Somatosensory evoked magnetic fields to median nerve stimulation: interhemispheric differences in a normal population. Electroenceph. clin. Neurophysiol. 1997, 104: 480–487.

III Huttunen, J., Wikström, H., Salonen, O. and Ilmoniemi, R.J. Human somatosensory cortical activation strengths: comparison between males and females and age-related changes. Brain Res. 1999, 818: 196–203.

IV Wikström, H., Roine, R.O., Salonen, O., Ilmoniemi, R.J., Aronen, H.J., Buch Lund, K., Salli, E. and Huttunen, J. Somatosensory evoked magnetic fields from the primary somatosensory cortex (SI) in acute stroke. Clin. Neurophysiol., 1999, 110: 916–923.

V Wikström, H., Roine, R.O., Aronen, H.J., Salonen, O., Sinkkonen, J., Ilmoniemi, R.J. and Huttunen, J. Specific changes in somatosensory evoked magnetic fields during recovery from sensorimotor stroke. Ann. Neurol., in press.

Introduction

The structure and functions of the brain have intrigued the human curiosity for thousands of years. The ancient investigators and the pioneers of modern neuroscience in the nineteenth and the early twentieth century based their theories of the functioning of the human brain on findings in behavioral and psychophysiological studies, on observations of incidental neurological patients, and on experiments conducted in non-human species. There were no means, available at that time, to investigate neuronal functions *in vivo* without injuring the experimental subject. In the 1920's a new technique, electroencephalography (EEG), was added to the methodological arsenal of neuroscientists. This breakthrough enabled scientists, for the first time, to noninvasively assess the electrical activity of the intact brain through the uncut scalp and the skull. Traditional EEG did not, however, allow for the accurate localization of brain functions.

During the present decade the rapid development of experimental techniques has made it possible to accurately locate functions of the intact, working human brain, and thereby investigate these functions without harming the experimental subject. The time-scale of neuronal signalling is in the order of milliseconds; of the available methods only magnetoencephalography (MEG) and electroencephalography (EEG) have that high temporal accuracy. The spatial resolution, on the other hand, is best in functional magnetic resonance imaging (fMRI), and better in MEG than in EEG, although the two latter methods look at essentially the same neuronal phenomena. However, MEG picks up mostly currents oriented tangentially with respect to the skull whereas EEG does not have such limitations.

Prior to this present study, a vast amount of information concerning human somatosensory cortical functions was already available. The response waveform that can be recorded over the contralateral scalp with either EEG or MEG after electrical stimulation of the median nerve at the wrist was well known from numerous publications. There was also a consensus concerning the area that gives rise to the initial cortical deflection peaking at about 20 ms after stimulation, the N20(m) response (m stands for magnetic). However, the events taking place in individual neurons and neuron populations that give rise to N20(m) and the subsequent deflections, are complex and have remained mostly unknown.

The first three Publications of this Thesis clarify some aspects of the processing of somatosensory information in the intact human cortex that have been left unanswered by previous studies. The effects of interstimulus interval (ISI) on somatosensory evoked magnetic fields (SEFs) in the primary somatosensory cortex (SI) are reported in Publication I, in which also a theory concerning SEF generation at SI is formulated. This theory is based on new evidence and on the observations of previous investigators both in animal models and in human subjects. As Publications IV-V deal with SEFs in stroke patients, it is essential to have a reference

group of healthy individuals; hence, SEFs to median nerve stimulation in a control group are described in Publication II. The effects of the subject's age and gender on the early SEFs are reported in Publication III.

Recently, several researchers have presented evidence pointing out the capacity of the developing and mature central nervous system in humans and other species to reorganize its functions in various physiological and pathophysiological conditions. It is likely that this phenomenon, referred to as neuronal plasticity, has a role in the recovery process that begins after ischemic damage to the brain. To explore this possibility and other aspects of post-stroke recovery, we studied patients with deficits in somatosensory and motor functions. Publication IV of this Thesis describes our observations on the relationship between functional deficits and SEF abnormalities in a relatively acute stage of cerebral infarct. Finally, in Publication V, we report studies on the mechanisms of recovery of somesthesis in the same patient group, also studied by means of clinical evaluation and SEFs.

Anatomical and functional organization of the cerebral cortex: basic principles

The neurons of the human cerebral cortex with their ample interconnections constitute the platform for the human mind. The surface area of the neocortex is 1000–1200 cm^2, its volume is about 300 cm^3 , and it contains roughly 5–10x10^{10} neurons (Creutzfeldt, 1995). Based on cytoarchitectonic differences, anatomists of the nineteenth and the early twentieth centuries formulated classifications according to which the cerebral cortex can be divided into distinct regions (*e.g.*, Exner, 1881). The map of Brodmann (1909) has prevailed over time; it is relatively simple and allows animal and human cortices to be compared.

The morphologically different cortical regions have proved to be dissimilar also functionally. More than century ago, Paul Broca (1865) demonstrated that a lesion in the middle part of the left frontal lobe produces expressive aphasia without manifest defects in other mental functions. Thereafter, investigators have sought to locate different mental functions in distinct anatomical subareas. During the first decades of the twentieth century this approach was challenged by a more holistic way of thinking that emphasized the co-operativeness of cortical regions. Both ways of thinking have turned out to be appropriate. Thus, the cerebral cortex contains areas that are clearly distinguishable from each other in terms of cytoarchitectonics, neuronal connections and responsiveness to sensory stimuli. Accordingly, circumscribed lesions can, as demonstrated by Broca, cause isolated psychophysiological defects. On the other hand, defects produced by small cortical lesions are not necessarily permanent; *e.g.*, sensory deficits caused by experimental lesions in the monkey somatosensory cortex disappear gradually within

months after the ablation (Peele, 1944). This kind of functional reorganization clearly speaks against rigid anatomical–functional coupling in the cerebral cortex.

Studies performed on experimental animals have shown that the functional organization of the cerebral cortex is extremely complex. Although certain cortical structures are dedicated predominantly to certain mental functions, *e.g.*, area 3b to the processing of somatosensory information, even in highly specialized parts of the cortex a subset of cells respond to complex stimuli consisting of features belonging to more than one sensory category. An example of such a cell is a neuron in the somatosensory post-central gyrus of the monkey which is activated when the animal obtains a food reward (Hyvärinen and Poranen, 1978). There are also areas containing groups of neurons responding to simple stimuli belonging to more than one sensory category, such as BA 7 of the monkey whixh can be activated both by somatic stimuli and by visual stimuli presented near the skin area where the somatic stimulation elicited discharges (Hyvärinen and Poranen, 1974).

The fact that all cortical areas are densely (inter)connected with other areas as well as with subcortical brain structures further complicates the study of the functional organization of the cerebral cortex. The significance of a certain cortical area to the entire brain is determined by the origin of its afferents and the targets of its efferents (Creutzfeldt 1995). The idea that the functional state of these connections might be capable of changing according to altered needs is not new (see, *e.g.*, Grünbaum and Sherrington, 1903). However, effective tools to explore this possibility in the working, intact human brain have not been available until quite recently. Over the last few years, numerous investigators have studied the capabilities of both mature and developing mammalian (including human) nervous system to change its functional strategies and resource allocation, *i.e.*, to undergo plastic changes. These studies have accumulated evidence showing that the responsiveness of cortical areas to peripheral stimuli can be modified according to behavioral needs. For example, it has been proposed that the visual cortex participates in the processing of somatosensory information in blind subjects (Cohen *et al.*, 1997). It remains to be clarified how the plastic properties of neuronal networks can be used in the rehabilitation of neurological patients and what are the factors that limit neuronal plasticity.

Functional organization of human somatosensory system

In addition to the individual studies cited, the following discussion is based on the textbooks by Kandel *et al.* (1991) and Creutzfeldt (1995).

Peripheral receptors

Somatosensory receptors are either specialized sense organs or bare nerve endings, depending on the sensory submodality they serve. Commonly, four submodalities are distinguished: the sense of touch, proprioception, the sense of temperature, and the sense of pain (see Fig. 1)

Ascending pathways

Somatosensory information is carried from the peripheral receptors to the central nervous system along the afferent fibres of the dorsal root ganglion cells (sensory information from the limbs and the trunk) and cranial nerves (sensory information from the head). Information related to touch and proprioception travels fast along thick myelinated fibres, whereas temperature and pain sensations are conducted more slowly along thin myelinated and unmyelinated axons. From the level of dorsal root ganglion cells, touch and proprioception are conveyed further by the dorsal column–medial lemniscal system. Axons of dorsal root neurons enter the dorsal column of the spinal cord and ascend toward the caudal medulla where they synapse with neurons of the dorsal column nuclei. Fibres leaving the dorsal column nuclei cross the midline and proceed contralaterally as the medial lemniscus towards the specific somatosensory relay of the thalamus, the ventroposterior nucleus (VP). Finally, tactile information reaches the cortex through the internal capsule. In contrast to tactile and proprioceptive information, fibres carrying information about pain and temperature either cross the midline already at the spinal level or do not cross at all, and enter the cortex chiefly through the spinothalamic system. A substantial portion of these axons do not terminate in the thalamus but elsewhere in the brain. Axons of this tract travel in the anterolateral part of the spinal cord. A small portion of tactile information is also carried in the spinothalamic system ensuring a minimal residual sensibility after damage to the medial lemniscal system.

Somatosensory thalamus

The largest and most important nucleus of the somatosensory thalamus is the ventroposterior nucleus (VP), which can be further divided into two subnuclei: ventroposterior lateral nucleus (VPL) and ventroposterior medial nucleus (VPM). Tactile and proprioceptive sensations from the face project to the VPM and from the rest of the body to the VPL. VPM and VPL, in turn, project to areas 3b, 2, and 1. Part of the VPL also project to the precentral motor cortex (4). Thalamic projections to area 3a arise mostly in the ventral intermedial nucleus (VIM). Besides VP, spinothalamic fibres are relayed to intralaminar, posterior, and nonspecific thalamic nuclei.

First somatosensory cortex

The first somatosensory cortex (SI) consists of four cytoarchitectonically and functionally distinct areas (Powell and Mountcastle, 1959a; Powell, 1977), all of which receive afferents from the ipsilateral thalamus (see Fig. 2).

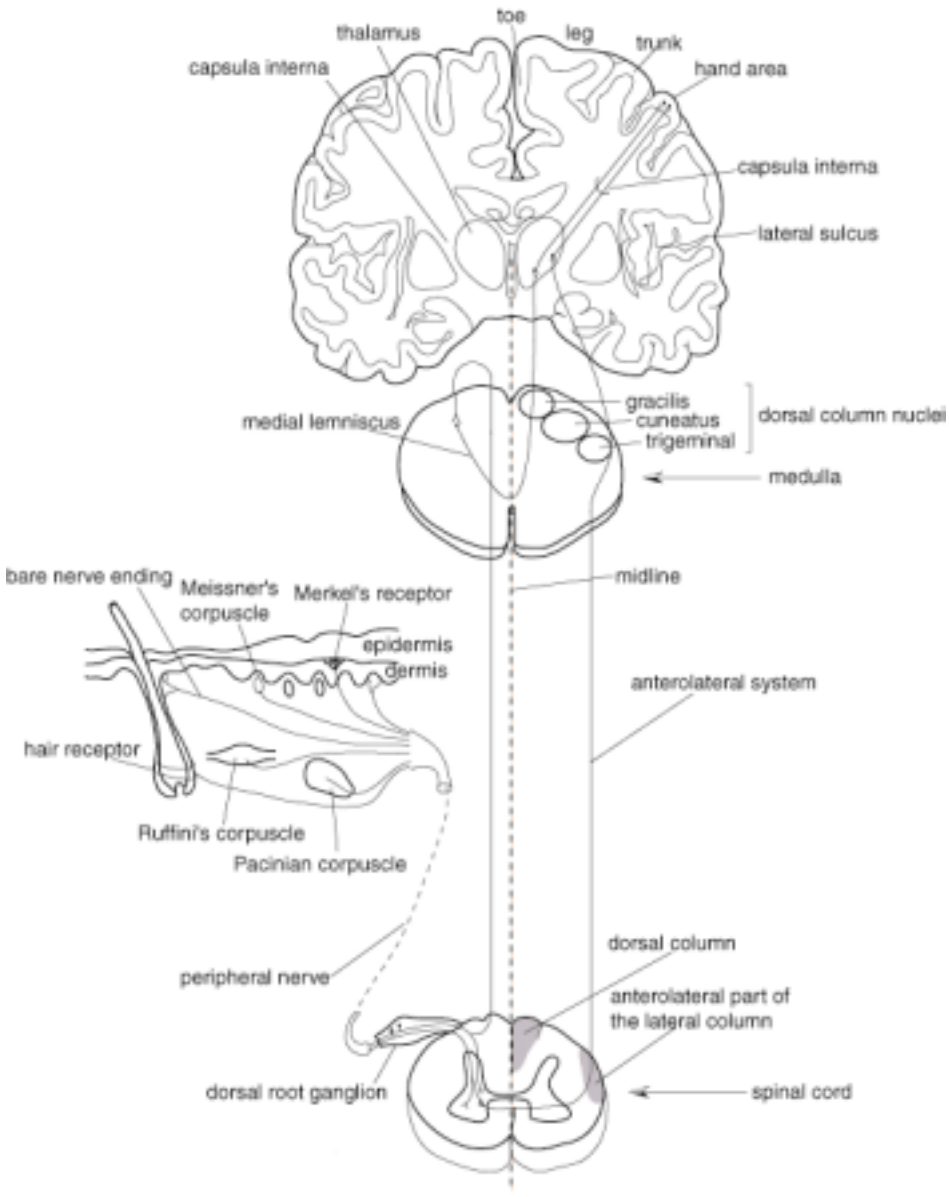

Fig. 1. Somatosensory pathways from the peripheral tissue to the primary sensory cortex. Information about proprioceptive, vibratory and touch sensations travel in the dorsal column–medial lemniscal system, and information about pain and temperature sensations in the anterolateral system. To the left, the mechanoreceptors of the skin are chematically presented. The superficial mechanoreceptor of hairy skin is the hair follicle receptor. In the hairless skin two types of superficial mechanoreceptors can be identified: the rapidly adapting Meissner's corpuscles and the slowly adapting Merkel's receptors. Corresponding receptors in subcutaneous tissue are the rapidly adapting Pacinian corpuscles and the slowly adapting Ruffini's corpuscles.

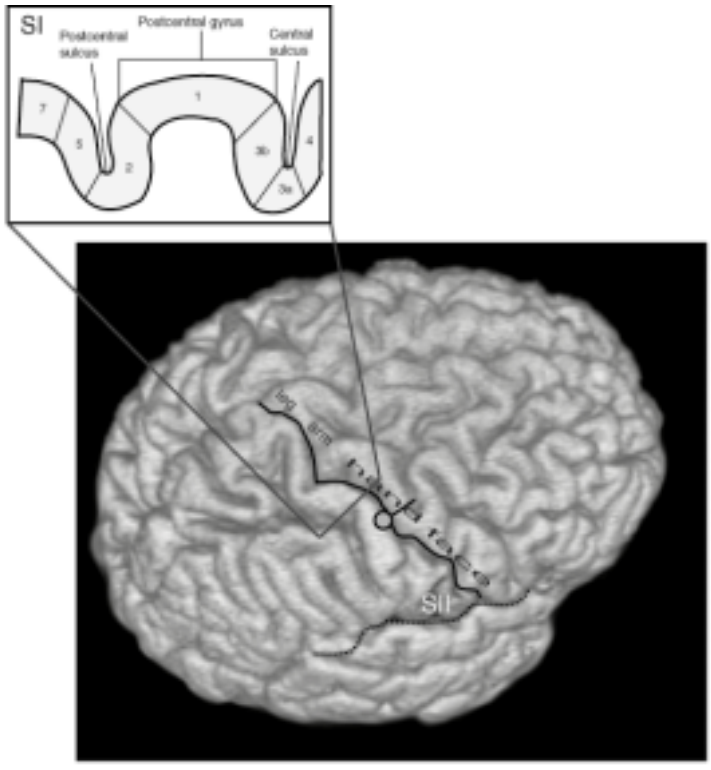

Fig. 2. A 3-dimensional surface-rendered magnetic resonance image (MRI) of the cerebral cortex viewed from the side and slightly posteriorly. Note the widened sulci due to normal ageing. The solid line depicts the central sulcus and the dashed line the lateral sulcus. The four cytoarchitectonic areas of SI: 3a, 3b, 1, and 2 and their neighbouring areas are shown in the enlargement. SII is located in the upper wall of the lateral sulcus. Central sulcus was distinguished by visual inspection of the MRI and by plotting the equivalent current dipole (ECD) of the N20m somatosensory evoked field (SEF) deflection on the MRI. The approximate locations and extents of the representations of some of the body parts along the central sulcus are also shown.

Areas 3a and 3b receive considerably denser thalamic innervation than areas 1 and 2 (Jones and Powell, 1970; Jones, 1975; Shanks and Powell, 1981). Within SI, areas 1, 2, and 3 are abundantly interconnected and project further to the precentral motor cortex (4), the posterior parietal association cortex (5), the frontoparietal operculum (OC), and the supplementary motor area (6; Jones and Powell, 1969; 1970; see Fig. 3). Fibres from SI also project to the contralateral SI and OC, with the exception of the most distal parts of the limbs. The interconnections of areas 3a, 3b, 2 and 1 are complex. For example, area 3b is connected with area 2 directly, and also indirectly via area 1. One characteristic attribute of the connections within the SI is that they join reciprocally the four cytoarchitectonic subdivisions of the SI that represent identical body parts (Werner and Whitsel, 1973).

On the other hand, areas 3b–2 can also be seen as successive steps in somatosensory information processing, where the receptive fields become larger and the relationship between stimulus and response more complex from rostral to caudal parts of the SI (Iwamura *et al.*, 1993; Kaas, 1993). Thus, the proportion of cells with receptive fields that combine different somatic sensory modalities and/or possess response characteristics that are not seen at the level of peripheral nerves (for example sensitivity to the direction of movement along the skin) increases toward the posterior parts of the SI (Hyvärinen and Poranen, 1978; Sur *et al.*, 1985). Further support for this view comes from lesion experiments with monkeys: area 3b damage can deactivate area 1 (Garraghty *et al.*, 1990). Besides excitatory receptive fields, SI neurons also possess inhibitory receptive fields. Hence, the response of a cortical cell to skin stimulation may be inhibited by simultaneous stimulation of a nearby and in some instances of a remote skin area (Mountcastle and Powell, 1959).

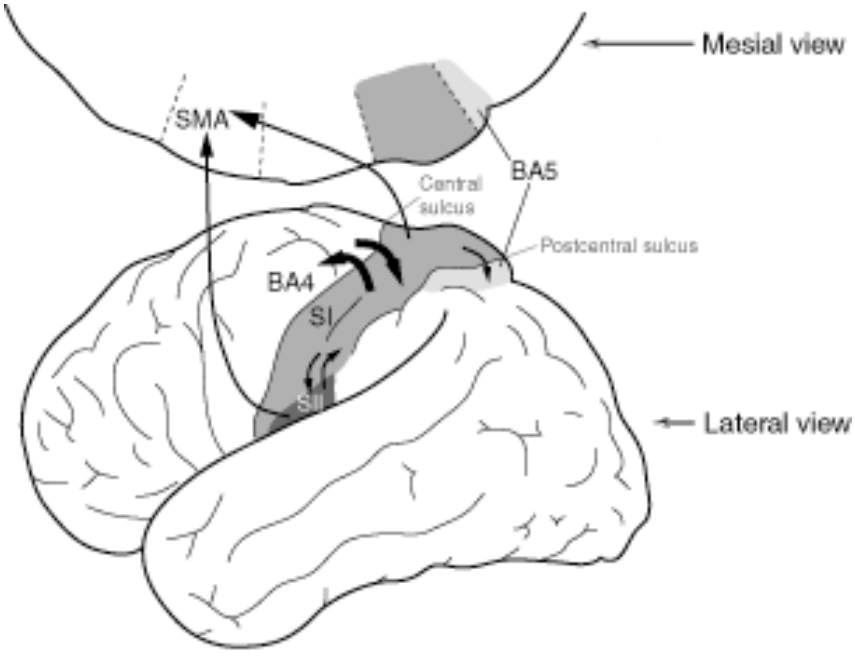

Fig. 3. Ipsilateral cortico-cortical connections of the somatosensory system.

Powell and Mountcastle (1959b) observed that the proportion of neurons responding to superficial cutaneous stimulation decreases toward the posterior parts of the SI. Several investigators have since confirmed that the four subregions of the SI have different response patterns to somatosensory stimuli. Area 3a receives thalamic input predominantly from muscle stretch receptors, while in area 3b and 1 cutaneous receptors dominate. Area 2 receives thalamic information mostly

from deep pressure receptors (*i.e.*, those in joint capsules, tendons, and muscles). However, there is a considerable overlap between the functional profiles of these areas.

Superimposed on this anteroposterior modality and receptive field size gradient is a mediolateral somatotopic organization of the SI. At least areas 3b, 1 and 2 contain an orderly representation of the body in which the lower body parts are represented medially and the upper parts laterally along the hemispheric convexity (Kaas *et al.*, 1979). The body surface is represented disproportionally on the cortex, with the fingertips and the mouth having the largest and the trunk and the thighs the smallest relative representations.

For obvious reasons, reports concerning the effects of direct stimulation of and intracortical recordings in the SI and reports on cortical ablations in humans are rare; all existing references are based on neurosurgical patients. Penfield and Jasper (1954) reported that stimulation of the postcentral gyrus is felt as numbness, tingling, and a feeling of electricity. Rarely, an illusion of a movement was noted. Penfield and Jasper also observed that the removal of the postcentral hand area results in astereognosis - an inability to manually recognize object shapes and their surface texture. In a more recent study, removal of the postcentral hand representation was reported to cause sensations of numbness and tingling, and decreased control of fine finger movements (Slimp *et al.*, 1986).

Frontoparietal opercular cortex

Most of the frontoparietal opercular cortex (OC) lies deep in the lateral sulcus. OC contains multiple distinct areas that each respond to different types of sensory stimuli (Burton and Robinson, 1981). The second somatosensory cortex (SII) is part of the OC. In humans, the SII is probably situated in the upper bank of the lateral sulcus just below the head representation of SI. In SII, the body is somatotopically represented in a somewhat cruder manner and in a mirror-symmetrical order with respect to SI, and with the axis of symmetry around the head region (Woolsey, 1958). The SII receives thalamic inputs from VPL (Jones and Powell, 1970), part of which are probably collaterals of afferents targeted to SI (Macchi *et al.*, 1959; Jones *et al.*, 1979). The SII is also reciprocally connected with BAs 3b, 2, and 1 in the same hemisphere (Jones and Powell, 1969; Pandya and Kuypers, 1969; Jones *et al.*, 1979), and projects to the perioral part of the contralateral SI and to the entire contralateral SII except for the distal segments of the limbs (Jones and Powell, 1969; 1973).

The functional significance of inputs from ipsilateral SI to SII are still being debated; some investigators consider them only modulatory (Zhang *et al.*, 1996), while others see them as the major input to SII, and favour the idea of serial rather than parallel processing of somatosensory information (Pons *et al.*, 1992). Most of the receptive fields of SII neurons are well-defined, less than 10 cm^2 and exclu-

sively contralateral (Robinson and Burton, 1980). The smallest receptive fields are those of the fingers. However, Burton and Robinson (1981) reported a 26% proportion of bilateral receptive fields in SII. SII neurons, unlike those in SI, do not maintain their response characteristics during repetitive stimulation; after a few seconds receptive fields shrink and excitatory thresholds are elevated (Whitsel *et al.*, 1969). The functional significance of SII remains poorly characterized. In their pioneering study, Penfield and Jasper observed a feeling of desire to move a limb and arrest of voluntary movement during stimulation of SII in some humans (Penfield and Jasper, 1954). On the basis of their observations, Penfield and Jasper suggested that "the function of this area (SII) is somehow related to voluntary somatic movement as well as to somatic sensation". Supporting this view, a recent MEG study attributed SII to sensorimotor integration (Huttunen *et al.*, 1996). It has also been suggested that the SII participates in tactile object recognition (Caselli, 1993). Ridley and Ettlinger (1976) proposed a role for SII in tactile learning and memory on the basis of their observations on disturbances in tactile object recognition of monkeys with bilateral SII ablations. The SII may also participate in the processing of the temporal features of somatosensory stimuli (Burton and Sinclair, 1991).

Besides SII there are several other areas in the frontoparietal operculum that respond to somatic stimulation. In the OC, cytoarchitectonic boundaries cannot be unambiguously determined and the nomenclature is, therefore, not consistent in the literature. According to Burton and Robinson (1981), area 7b is the posterior boundary of SII and one of opercular somatosensory areas in monkeys. According to Brodmann's nomenclature, this area would occupy part of area 40 in humans. The thalamic projections arise mainly in the pulvinar and posterior thalamic nuclei. The somatosensory receptive fields are usually bilateral, and the somatotopic organization is much less orderly than that of SII. Neurons responding to somatic stimulation can also be found in insular and retroinsular cortex as well as in the fundus of the lateral sulcus. The parietal ventral area (PV), situated immediately rostrally from the SII and adjacent to the face representation of SI, contains a body-surface representation that is mirror-symmetrical with respect to that of SII (Krubitzer *et al.*, 1995). In a recent study combining information acquired using both MEG and fMRI, separate foci in the parietal and frontal OC were shown to be activated by electrical stimulation of the median nerve (Korvenoja *et al.*, 1999).

Parietal association cortex

Posterior parietal association cortex (PPC) cannot be unambiguously defined; in principle all parietal areas excluding primary sensory areas, *i.e.*, visual and somatosensory areas, can be included. According to Creutzfeldt (1995), areas 5 and 7 are the most important ones. Area 5 is dedicated primarily to somatosensory processing, while area 7 also contains neurons that respond to visual stimulation. PPC does not receive major direct input from sensory organs; the afferents origi-

nate in primary sensory cortices and thalamic association nuclei. Although neurons in PPC can respond to simple sensory stimuli, this area is thought to be a higher level sensory processor than SI. For example, in area 5, 10 % of the neurons are activated when a monkey stretches out its hand to reach a target object. Parietal lesions in humans produce a variety of syndromes depending on the site of the lesion. Large lesions produce a striking deficit, *sensory neglect*, in which sensory stimuli on the contralateral side of the body, with respect to the lesion, are disregarded although no sensory deficit is present.

Other sensory areas

Stimulation of the mesial part of area 5 (supplementary sensory area according to Penfield and Jasper) elicits somatic sensations in humans (Penfield and Jasper, 1954; Woolsey *et al.*, 1979). This area, as well as area 6aβ in the mesial wall (supplementary motor area) of monkeys, receives afferents from SI and SII.

Magnetoencephalography

Theoretical background

Electric current flowing through a conductor produces a magnetic field that can be detected outside the conductor. Exceptions to this phenomenon are radially oriented current in a spherically symmetric conductor and the situation where opposing currents of same magnitude produce fields that cancel each other out. However, the distribution of an unknown current inside a given conductor cannot be uniquely retrieved from the externally measured magnetic field distribution, *i.e.*, the number of primary current distributions capable of producing a given externally measured magnetic field distribution is infinite (see, *e.g.*, Hämäläinen *et al.*, 1993). One must, therefore, set some preconditions to successfully interpret neuromagnetic data.

The current dipole is the most widely used source model in MEG research. This model is useful in situations where the neuronal activation under investigation is supposed to occur in a small cortical area, for example, in a portion of area 3b in the case of the somatosensory cortex. Fig. 4 depicts typical waveforms of MEG signals that occur in response to the stimulation, using rapid current pulses, of the right median nerve at the wrist. Also shown is a topographic magnetic field map calculated from the signals at 20 ms post-stimulus. A satisfactory solution to the inverse problem in this kind of situation is found by first assuming that the center of gravity of the activated brain area can be modeled by a point-like electric dipole and the brain itself by a sphere that best fits into the inner curvature of the skull as estimated from the subject's magnetic resonance images (MRIs). Then the least-squares search method is applied to estimate the magnitude (typically 10–50 nAm), direction, and position of an equivalent current dipole (ECD) that best

agrees with the data (Williamson and Kaufman, 1981). The resulting ECD lies midway between the two field extrema.

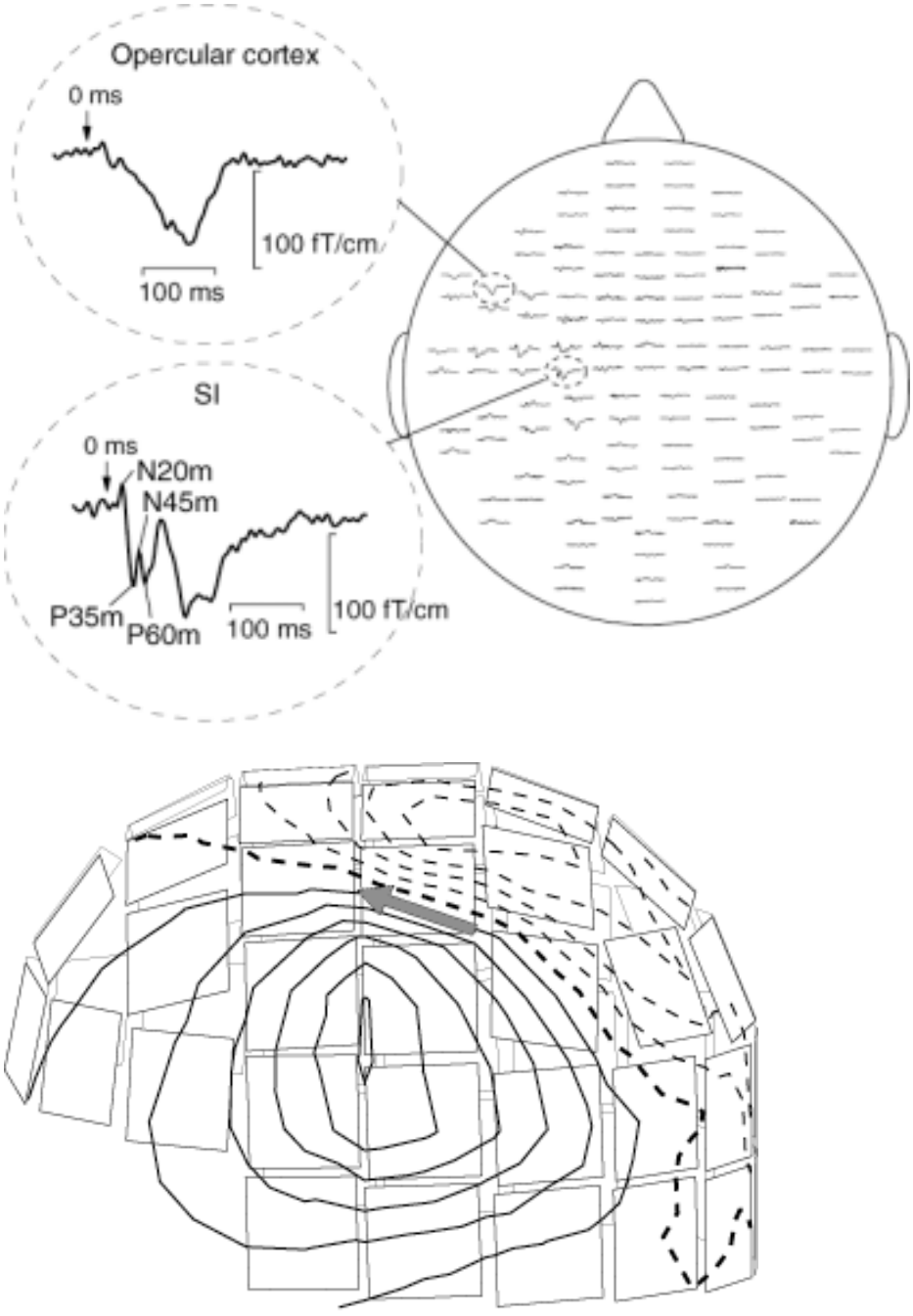

Fig. 4. Top: response waveforms evoked by right median nerve stimulationin the 122 recording channels of a helmet-shaped MEG device (Neuromag-122™). In the enlarge-

ments maximum-signal channels over the SI and opercular cortex are depicted. At SI, the four initial components of the response are pointed out.
Bottom: topographic magnetic field map and the corresponding equivalent current dipole (ECD) calculated from the signals during the peak of the N20m response. The contour step is 10 fT/cm and ECD strength is 10 nAm.

The ECD model can be used in situations where multiple, temporally overlapping sources are activated, provided that they are located relatively far away from each other. When two identically oriented, side-by-side located sources in the brain are simultaneously active, the use of the single-dipole model results in an ECD that is deeper and stronger than the actual ones (Okada, 1985). The ECD location estimate is most reliable in the direction perpendicular to the dipole orientation vector and less reliable in the direction of depth and along the ECD vector (Cohen and Cuffin, 1983). In the spherical model, only current sources oriented tangentially to the skull are believed to generate magnetic fields that can be detected outside the head. Since real heads deviate from the model sphere, radial source currents may actually have some impact on the extracranially measured magnetic fields.

Instrumentation

The relative weakness of neuromagnetic signals compared to environmental magnetic noise makes the recording of these signals problematic. Neuromagnetic signals are typically in the order of 50–500 fT, which is one part in 10^9 or 10^8 of the earth's magnetic field. The only means of detecting these tiny biomagnetic signals is to use a SQUID (Superconducting QUantum Interference Device), which is a superconducting ring interrupted by one or two Josephson junctions. To maintain the superconducting state of this device the temperature must be kept near absolute zero. For this reason the measurement array, consisting of several individual SQUIDs, needs special container where the SQUIDs are bathed in liquid helium that keeps them at a temperature of 4 K (see Fig. 5). Being an extremely sensitive device, a SQUID easily picks up environmental noise which masks the small neuronal signals so that they become indistinguishable. This problem has been partially solved by building magnetically shielded rooms that exclude much of the outside magnetic field fluctuations. In addition, instead of using simple magnetometers, the effects of magnetic field disturbances can be reduced using gradiometric detector configurations that detect magnetic field gradients instead of homogeneous fields. These are useful, since even inside a shielded room magnetic field fluctuations caused by nearby noise sources, such as the heart of the subject, are present. In the Neuromag-122 system (Ahonen *et al.*, 1993) used in the present study, the 122 sensors of the helmet-shaped detector array are figure-of-eight-shaped planar gradiometers that are highly sensitive to magnetic fields produced by nearby sources and insensitive to distant sources. A gradiometer like this detects the maximum signal just above a current source. The 122 gradiometers are arranged in 61 pairs, which measure two orthogonal derivatives of the magnetic field. With this system, the signals arising from the whole convexial cortex excluding the lowermost temporal areas can be simultaneously measured. The am-

plitude of the measured signal diminishes rapidly as the distance between the detectors and the source increases; signals arising in deep brain structures are, therefore, not easily discerned in individual sensors. However, the detection of deep-brain activation using MEG has recently been reported (Tesche, 1996).

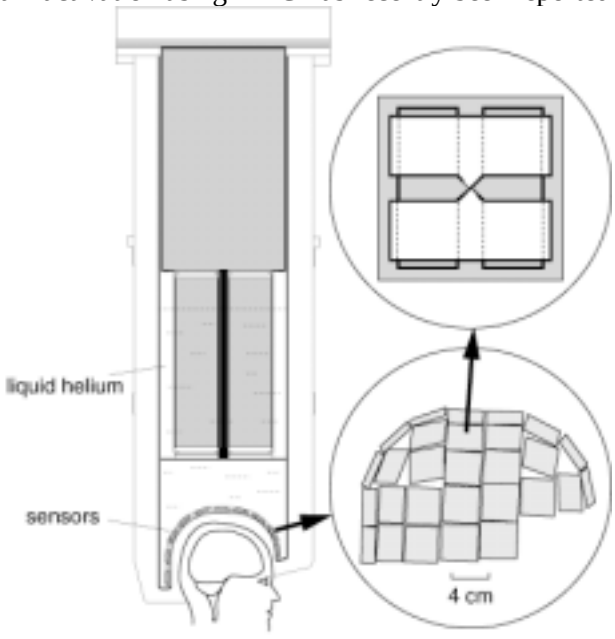

Fig. 5. Schematic illustration of the Neuromag-122™-device. The 122 sensors are figure-of-eight -shaped gradiometers, arranged in 61 pairs which measure two orthogonal derivatives of the radial component of the magnetic field. Each pair detects the maximal signal right above a dipolar source. Adapted from Hämä-läinen *et al.* (1993).

The neural basis of MEG

A typical neuron has three morphologically distinct regions: the soma, the dendrites, and the axon. Neurons are of many different shapes; pyramidal-shaped cells constitute two-thirds of the neurons of cerebral cortex (Creutzfeldt, 1995). The soma is the metabolic center of the cell. The dendrites, which are the major input channels of the cell, emerge from the soma. The apical dendrite projects toward the cortical surface and arborizes after leaving the soma. The basal dendrites emerge at the opposite poles of the soma and project laterally. The axon, the output channel of the neuron, leaves the soma at the axon hillock and on its way to subcortical white matter sends collaterals backwards to the parent cell and also to the neighbouring neurons. The pyramidal cells are the most likely candidates for the production of extracranially detectable electromagnetic signals, since the long apical dendrites run parallel to neighbouring dendrites in sensory cortices. Thus, external magnetic fields generated by temporally overlapping activity do not cancel out as may be the case for interneurons, in which the dendrites are oriented in a less orderly manner.

Although much evidence of the location of different types of synapses in the neuron is derived from studies done using animal preparations, it can be assumed that thalamocortical afferents in the human cerebral cortex are excitatory and terminate mainly on small dendritic protrusions, the dendritic spines, of the

apical and basal dendrites relatively close to the soma (Creutzfeldt and Houchin, 1974; Creutzfeldt, 1995). Inhibitory synapses, which are abundant near the soma and the axon hillock, are contacted mainly by inhibitory interneurons. These, in turn, are innervated by thalamocortical afferents or corticocortical fibres, such as recurrent collaterals from neighbouring axons.

When excitatory transmitter substance molecules (typically glutamate) are released from the presynaptic side of an excitatory synapse, an excitatory postsynaptic potential (EPSP) emerges in the postsynaptic cell. EPSPs are mostly due to the opening of ionic channels permeable to Na^+ and K^+ ions. The Na^+ ions enter the cell and lead to relative depolarization of the cell membrane, *i.e.*, the normally negatively charged interior becomes less negative with respect to the extracellular side of the membrane. EPSPs are conducted mostly passively in the neuron, spreading both in the direction of the more distant parts of the dendritic tree and the soma. The strength of the current diminishes with the distance from the synapse. The length constant of this decay depends on the intracellular resistance and on the membrane conductance in such a way that the greater the intracellular resistance and the more permeable the cell membrane, the shorter the spread of the EPSP along the dendrite (see, *e.g.*, Kandel *et al.*, 1991). If a sufficient number of EPSPs overlap in time, without too much simultaneous inhibition, the threshold of active depolarization at the axon hillock is reached and the cell fires.

Inhibitory postsynaptic potentials (IPSPs) are mainly initiated by the binding of gamma-aminobutyric acid (GABA) in post-synaptic receptors. This leads to the opening of Cl^- channels, which, in turn, leads to an increase in the negative potential of the cell interior. As a result, firing (*e.g.*, stimulus-locked activity in the somatosensory cortex), is suppressed. In each neuron, the effects of EPSPs and IPSPs are summated, and the question of whether a particular neuron fires an action potential at a certain time point or not, depends on the net effect of these opposing driving forces (see, *e.g.*, Creutzfeldt and Houchin, 1974). Furthermore, those synapses that are located near the axon hillock are more effective in producing action potentials than those located in other parts of the neuron.

From a distance, the intracellular currents produced by summated EPSPs and IPSPs look like current dipoles oriented along the dendrites (Hämäläinen *et al.*, 1993). As the intracellular current flows in two opposing directions when, for example, an EPSP is launched from a dendritic spine at a distance from the soma, the net dipole strength and orientation in the neuron depend not only on the relative proportions of inhibition and excitation in the cell but also on the loci of the activated synapses (Creutzfeldt and Houchin, 1974). This means that if a PSP is initiated at the very end of an apical dendrite the dipole orientation is opposite to that in a situation where a similar PSP arrives at the near-soma dendritic membrane.

Using extracranial measurement devices, it is not possible to detect currents flowing in individual neurons. Rather, the simultaneous activity of neuron populations is needed to produce a recordable signal. The dipole moment produced by a single PSP is about 20 fAm (Hämäläinen *et al.*, 1993). As the dipole moments measured outside the head are in the order of 10 nAm, roughly a million simultaneous, similar PSPs (either IPSPs or EPSPs) are needed to produce a typical evoked response. Taking into account the estimated neuron density of the human somatosensory cortex (Rockel *et al.* 1980), and the fact that about 2/3 of the cortical neurons are pyramidal cells (Creutzfeldt, 1995), it can be estimated that simultaneous, single EPSPs or IPSPs in all pyramidal cells in a cortical cylinder with a base of 10 mm^2 can produce an evoked response of 10 nAm. Alternatively, the estimation of the activated cortical area can be done on the basis of typical cortical current densities (about 0.1 $\mu A / mm^2$). This approach results in a cubic region of 100 mm^3 to be needed to produce an ECD of 10 nAm (Williamson and Kaufman, 1981). In reality, it is not possible to accurately estimate the size of the cortical area generating a given ECD (Hari, 1999). All neurons receive thousands of inputs, and PSPs overlap in time in single neurons. Moreover, simultaneous IPSPs and EPSPs tend to cancel out and not all pyramidal cells in a given cortical area can necessarily be assumed to be concurrently activated in response to a single afferent volley. The level of synchrony in the firing of the neuronal ensemble that produces a given response also has an impact on the dipole moments.

The duration of individual EPSPs in a neuron is 10-30 ms, whereas IPSPs last typically 70-100 ms; action potentials last about 1 ms (Creutzfeldt, 1995). PSPs are, therefore, more effectively temporally summated than action potentials. However, the effectiveness of temporal summation depends also on synchrony. In a situation where a number of neurons fire simultaneously action potentials may be effectively summatted. Magnetic fields produced by PSPs are often dipolar. Dipolar fields decrease more slowly than quadrupolar fields that are produced by most action potentials. Consequently, although magnetic fields produced by action potentials have been detected in peripheral tissue (Wikswo *et al.*, 1980), PSPs probably contribute more to the generation of cerebral magnetic fields than action potentials. However, Curio *et al.* (1994) have suggested that the high-frequency low-amplitude spike bursts that can be detected in wideband EEG and MEG recordings over the SI might reflect presynaptic, highly synchronous action potentials in area 3b.

Differences between EEG and MEG

Electroencephalography (EEG) detects electric potential differences on the scalp. EEG and MEG are closely related; in both methods, the measured signals

are generated by synchronized neuronal activity, and they both allow this activity to be traced with the millisecond precision necessary for studying the sequence of activation of different cortical areas reacting to a given stimulus. There are, however, important differences between the two techniques. Whereas MEG is insensitive to currents flowing perpendicularly to the skull, these currents are readily sensed by EEG (Grynszpan and Geselowitz, 1973). Furthermore, electric potentials are greatly affected by concentric inhomogeneities in tissue conductivities, *i.e.*, those of the skull and the scalp, whereas magnetic fields are not (Grynszpan and Geselowitz, 1973; Williamson and Kaufman, 1981; Ilmoniemi, 1995). These inhomogeneities smear electric field patterns resulting in less restricted field maps with EEG than with MEG recordings. Consequently, source localization, especially differentiation between two simultaneously active cortical areas, is more accurate with MEG. With MEG, the spherically symmetric conductor model of the head, the sphere fitted to the inner curvature of the skull near the cortical area of interest, is sufficient (Hämäläinen and Sarvas, 1987), whereas a detailed multicompartment model is needed for the analysis of EEG data (Rush and Driscoll, 1969). MEG recordings performed using gradiometric detector arrays are not as sensitive as EEG to relatively near-by electromagnetic noise sources, such as neck-muscle activity. This advantage, however, also produces lowered sensitivity to activity in deep brain structures and in large cortical areas. Thus, special analysis tools are needed to extract deep brain activity from the hybrid response waveforms dominated by more superficial cortical activity (see, *e.g.*, Tesche and Karhu, 1997).

The aforementioned differences between EEG and MEG make the interpretation of magnetic fields less complicated than that of electric potentials. EEG measurements, on the other hand, can provide information about radial sources that cannot be obtained using MEG.

Other non-invasive means to study the working human brain

Functional magnetic resonance imaging (fMRI) is the most widely used technique in the study of the functions of the intact human brain. FMRI takes advantage of the physiological phenomenon that variations in neuronal activity produce changes in local oxygen concentration, *i.e.*, in the blood oxyhemoglobin content (Kwong, 1995). FMRI is a truly noninvasive technique; the magnetic fields used in the typical clinical devices (up to 3 T) are not harmful. Using the latest experimental designs it is possible to achieve a spatial resolution to within a millimeter and a temporal resolution within a few seconds (Rosen *et al.*, 1998).

In transcranial magnetic stimulation (TMS), a strong, brief current pulse (peak value 2–15 kA) is delivered to a coil placed over the part of the cortex one wishes to stimulate (Barker and Jalinous, 1985; Ilmoniemi *et al.*, in press). This current pulse creates a magnetic field pulse that, in turn, induces an electric field in the underlying cortex. TMS has been used clinically to measure excitability thresholds and conduction times in patients with motor deficits and in basic neuroscience to temporarily block activity of certain brain areas. Magnetic stimulation is safe when used cautiously (Pascual-Leone *et al.*, 1993).

In positron emission tomography (PET), the detection of two photons emitted from the annihilation of a positron and an electron is used to reconstruct the distribution of a positron emitting isotope within an object (Leenders *et al.*, 1984). With PET it is possible to quantitatively measure the distribution of various radionuclides attached to physiologically active substances that are distributed in the human body according to function. Owing to the use of radionuclides, PET is actually an invasive technique. With PET scans, data gathered during several minutes is compressed on to one image. It is not possible to determine the timing of neuronal activation with high temporal resolution using this technique.

Somatosensory evoked responses

The measurement of neuronal activity evoked by the stimulation of peripheral nerves has been used to evaluate both physiological and pathophysiological functions of the human somatosensory system for decades. Somatosensory evoked potentials (SEPs) are routinely measured for diagnostic purposes in many neurological patient groups, whereas somatosensory evoked magnetic fields (SEFs) are used mainly in research.

Stimulation

Different types of stimuli are used to activate somatosensory cortical areas, although electrical stimulation of peripheral nerves, such as tibial and median nerves, is the most widely used. Although vibratory or tactile stimulation (*e.g.*, air-puff stimulation) is more natural than electrical stimulation of a nerve trunk, electric stimulation produces large signals and is easy to carry out.

The median nerve is a mixed nerve containing muscle, joint, tendon, and cutaneous afferent fibres. Cutaneous afferents, however, outnumber other fibre types (Sunderland and Bedbrook, 1949). Halonen *et al.* (1988) found cortical responses to stimulation of purely motor nerves to be ill-defined and of small amplitude whereas stimulation of pure sensory fascicles yielded clear responses. Gandevia and Burke (1990) have also reported that N20 and P25 deflections

after electric stimulation of purely motor thenar fascicles are of small amplitude. Furthermore, cutaneous stimulation of the hand applied with simultaneous electrical stimulation of the median nerve has been shown to affect cortical SEP amplitudes (Jones and Power, 1984). Thus, from previous reports it can be concluded that cortical responses to electrical stimulation of the median nerve trunk at the wrist are mainly mediated by cutaneous afferent fibres, although muscle afferents also contribute to a lesser extent.

The initial cortical median nerve SEP deflections grow with increasing stimulation intensities until the motor threshold is reached, whereas deflections peaking later than 30 ms show minor changes even after that level has been reached until the stimulus intensity is 2x the motor threshold (Huttunen, 1995). In a recent MEG study, P35m, PPC, and bilateral OC responses were saturated at the motor threshold, whereas N20m became stronger above that level (Jousmäki and Forss, 1998). Since stimulus intensities that are several times the motor threshold are painful, the strength is adjusted to be slightly over the motor threshold of the abductor pollicis brevis muscle which is acceptable although maximal responses for all deflections are not reached (Lüders *et al.*, 1985).

Time-locked stimulus-evoked cortical activity is of relatively small amplitude compared with cortical background activity. Therefore, many individual responses (100–1000, depending on the purpose) must be averaged to yield an adequate signal-to-noise ratio. In order to make measurement times reasonable, short ISIs are preferable to long ones. The ISI itself, however, significantly affects cortical responses. Many short-latency SEP and SEF deflections that peak over SI (at 20–60 ms post-stimulus) have been shown to attenuate when the ISIs shorten (Teszner *et al.*, 1982; Tiihonen *et al.*, 1989). However, some components have been reported to grow when the ISIs shorten (Narici *et al.*, 1987; Huttunen and Hömberg, 1991). For SI SEPs, Pratt *et al.* (1979) suggested that an ISI of approximately 0.13 s is sufficient to reliably record the early (up to 30 ms) components. The longer latency SEFs, peaking around and over 100 ms, arising near the SII (Hari *et al.*, 1993) and in parietal cortical areas (Forss *et al.*, 1994) are more vulnerable to short ISIs than SI SEFs. The posterior parietal response reported by Forss *et al.* was, for example, undetectable with an ISI of 0.3 s in any of their subjects.

SEF waveforms

Brenner *et al.* (1978) reported the detection of magnetic field fluctuations with a single-channel axial gradiometer following electric stimulation of the subject's finger. Since then, SEFs have been studied by many groups (Teszner *et al.*, 1982; Hari *et al.*, 1984; Okada *et al.*, 1984; Wood *et al.*, 1985; Huttunen *et al.*, 1987; Tiihonen *et al.*, 1989; Hari *et al.*, 1993; Kakigi, 1994; Vanni *et al.*, 1996). A typical SEF waveform, over the contralateral SI, in response to electrical stimulation of the median nerve trunk at the wrist is presented in Fig 6.

Approximately 20 ms after stimulation, the initial acitivation of the SI cortex can be seen as a brief peak in the response waveform. This peak is referred to as N20m. The ECD corresponding to N20m can be found in the SI contralaterally with respect to the stimulated side. Subsequently, a peak of opposite polarity, P35m, can be detected at 30–40 ms. N45m, pointing approximately in the same direction as N20, is the third deflection seen when short ISIs are used, and is followed by P60m. The waveform after N20m shows interindividual variability. The orientations of N20m and P35m ECDs agree well with a generator model where two tangential sources with opposite polarities are sequentially activated in area 3b. This view is supported by intracortical (Broughton *et al.*, 1967; Allison *et al.*, 1989) as well as combined MEG and EEG recordings (Wood *et al.*, 1985). The generator areas, however, are not completely overlapping; the P35m source is located somewhat antero-medially with respect to the source of N20m (Tiihonen *et al.*, 1989). When cutaneous branches of the median nerve are stimulated, the ECDs are located more superficially than those resulting from mixed nerve stimulation (Kaukoranta *et al.*, 1986). This might indicate that area 3a also contributes to a SEF waveform evoked by mixed nerve stimulation. Since tangential sources predominate MEG recordings, the cytoarchitectonic areas underlying SEFs should vary according to the anatomical location of the representation of the stimulated body part. Accordingly, since the foot area lies in the mesial cortex between the hemispheres, all four cytoarchitectonic areas should produce currents that are located tangentially with respect to the skull (Hari *et al.*, 1996). SI responses have been shown to be arranged somatotopically (Brenner *et al.*, 1978; Hari *et al.*, 1984; Okada *et al.*, 1984), as should be expected on the basis of the knowledge concerning cortical organization.

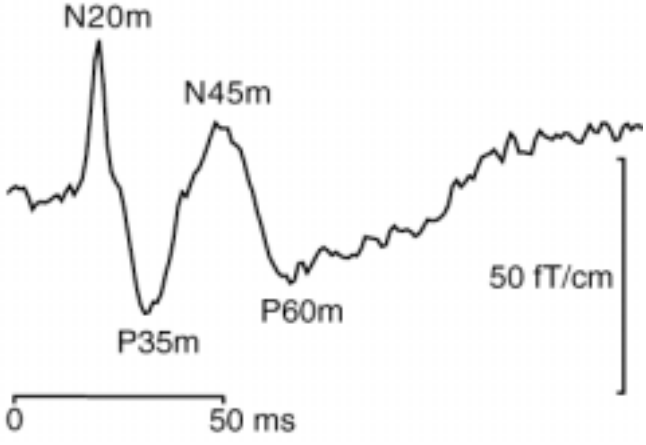

Fig. 6. Waveform of the maximum-signal channel over SI after stimulation of the median nerve at the wrist using an ISI of 1 s.

The estimation of cortical sources of long-latency SEFs is more complicated than those of early responses: field distributions are often complex at long latencies and multiple, temporally overlapping sources are often seen. Subject- and stimulus-related variables, for example, the attentional state and the ISI, also have more impact on long- than short-latency activity. The generator areas of deflections following N20m and P35m are thus somewhat ambiguous, although most of the SEF waveform before 100 ms can be explained with sources located near the contralateral SI (Huttunen *et al.*, 1987). Responses arising in the OC have been observed bilaterally at latencies of about and above 80 ms (Hari *et al.*, 1983; 1993), and recently also in the latency range of 20 ms using special data analysis methods (Korvenoja *et al.* 1999; Karhu and Tesche, 1999). The OC contains several areas that respond to somatic stimulation. However, Hari *et al.* like Karhu and Tesche attributed these responses specifically to the SII. The long-latency SII responses show remarkable interindividual variability. Like SI activity, SII responses seem to be somatotopically organized. Besides SII, long-latency SEFs have also been attributed to contralateral parietal association areas posteriorly from the SI (Forss *et al.*, 1994), to the mesial cortex (Forss *et al.*, 1996), and to the ipsilateral SI (Korvenoja *et al.*, 1995).

Comparison between SEFs and somatosensory potentials (SEPs)

Although the median nerve SEP waveform over parietal areas is largely similar to the corresponding SEF waveform, there are some differences probably owing to the fact that mostly fissural activity is seen in median nerve SEFs. The P20-N30 SEP deflection recorded over the frontal scalp and approximately at same latency peaking N20-P30 deflection over parietal areas reflect the activity of neurons in area 3b that can be seen in the SEF waveform as the N20m and P35m deflections (Wood *et al.*, 1985; Allison *et al.*, 1989; Allison *et al.*, 1991). The peak latency of N20m is slightly longer than that of N20 (Nagamine *et al.*, 1998), which may reflect the contribution of radial generator(s) to N20 deflection. Additionally, a P25-N35 SEP deflection is recorded at the central scalp electrodes and probably reflects the activity of BA 1 neurons, which is not visible in SEF recordings.

A P45-N80 complex over the frontal scalp and its parietal counterpart N45-P80 are apparently also generated in area 3b (Allison *et al.*, 1989). In the same latency range, activity in BA 1 is also seen. Because the SEP waveform after the first tens of milliseconds is complex, it is difficult to find clear-cut magnetic counterparts for the later responses. The P100 and N100 deflections obtained in scalp-recorded and intracranial recordings near the lateral sulcus show a field distribution that suggests tangentially oriented generator in the upper wall of the lateral sulcus. This source most likely corresponds to the OC (or SII) activity that is seen in SEF recordings around 100 ms. The origin of the late SEP deflections remains, however, a question in dispute. *E.g.*, Nagamine *et al.* (1998) did not observe a clear peak in the simultaneous EEG recording during the

magnetic SII deflection. Peaking over regions close to the lateral sulcus, SEP deflections, probably generated by radial sources, are also seen (Allison *et al.*, 1989).

Effects of subject properties on SEPs and SEFs

Age

Evidence from several lines of research indicates that aging increases cortical excitability. In the monkey, the number of binding sites for glutamate has been observed to increase with aging (Dykes *et al.*, 1984). In old rats, excitatory receptive field sizes grow (Reinke and Dinse, 1996), and in elderly humans tactile spatial acuity decreases (Sathian *et al.*, 1997). The latter would be expected if receptive fields in somatosensory cortical areas grow with aging. Age-related changes are also apparent in scalp-recorded SEPs. In particular, the amplitudes of the components following the initial cortical N20 deflection tend to increase with aging (Shagass and Schwartz, 1965; Lüders, 1970; Desmedt and Cheron, 1981; Kakigi and Shibasaki, 1991). It is, however, difficult to interpret the results of these SEP studies, since possible age-related changes in the volume conductor, the head, rather than the neurons themselves cannot be ruled out. This issue is discussed in Publication III.

Gender

Several research reports have confirmed the effects of gonadal steroid hormones on the development and function of the cerebral cortex (*e.g.*, McEven *et al.*, 1997). In humans, the balance between excitatory and inhibitory neurotransmission has been observed to fluctuate during the estrous cycle (Al-Dahan *et al.*, 1994; Al-Dahan and Thalmann, 1996). Furthermore, SEP amplitudes are generally higher in females than in males (Ikuta and Furuta, 1982). This may be due to differences between the sexes in signal processing in somatosensory cortical areas or the volume conductor's properties. This issue was scrutinized in Publication III.

Attention

Attention effects on SEPs have been demonstrated especially for the late (>100 ms) components of the evoked response (Desmedt and Robertson, 1977). Since the origin of these responses is obscure, the specific neural phenomena underlying these observations have remained unsolved. However, in a recent SEF study, active attention in a somatosensory discrimination task appeared to increase the bilateral SII responses whereas SI activity was not affected (Mima *et al.*, 1998). In another MEG study, attention of somatosensory stimuli appeared to strengthen a late SEF response originating in the mesial cortex near the central sulcus (Forss *et al.*, 1996).

Recovery after ischemic cerebral infarction

Mechanisms of ischemic neuronal injury

Ischemic stroke is caused by thrombosis or embolism in a cerebral artery. A small number are due to other types of hemodynamic disturbances, such as orthostatic hypotension, that produces a critical fall in the perfusion of a brain area nourished by a previously stenosed artery (see, *e.g.*, Strandgaard and Paulson, 1990).

Ischemic brain damage is mediated by three major mechanisms: increases in calcium concentration in the ischemic tissue, acidosis, and the production of free radicals (Siesjö, 1992). The pathological calcium influx in the neurons is thought to be mediated by agonist-operated calcium channels, in particular those gated by glutamate. This mechanism is commonly referred to as excitotoxic cell death. The exact cellular mechanisms mediating this phenomenon are not known. According to one view, irregularly occurring waves of depolarization, accompanied by calcium transients, would lead to the activation of lipases, proteases and endonucleases, which would damage the energy-depleted cells (Siesjö, 1992; Nagahiro *et al.*, 1998). Electrophysiological studies in experimental animals have revealed hyperexcitability in the cortex adjacent to a lesion during the first week after lesion induction (Hagemann *et al.*, 1998).

During the first hours after the initiation of symptoms, the ischemic brain area contains zones with different degrees of pathology ranging from a kernel of necrotic tissue to damaged, but still viable cells. The ischemic penumbra, *i.e.*, the area of viable tissue surrounding the necrotic center, is the major focus of research aiming at reducing infarct size. The time that the neurons in the penumbra can survive depends on the gravity of the perfusion defect and on the brain area in question. On the basis of results of animal and patient studies, it can, though, be generalized that reperfusion should be achieved within two or three hours from the ictus to be able to reduce the infarct size (Caplan, 1997; Nagahiro *et al.*, 1998)

Diaschisis

The term diaschisis was first used by von Monakov in 1914 to distinguish remote, local effects of a brain lesion from widespread systemic alterations such as unconsciousness. Although von Monakov originally postulated that a hemispheric lesion leads to loss of excitation in remote areas that are connected to the lesioned area *e.g.*, through the *corpus callosum*, it now seems more likely that the effects are rather disinhibitory (see Andrews, 1991, for a recent review).

The time course of clinical recovery

In monkeys, the severe motor paresis that is produced by ablating the precentral hand area disappears within a few weeks of the ablation (Grünbaum and Sher-

rington, 1903). Also, after the excision of one or more of BAs 1–3, somatosensory functions are restored gradually during the first nine post-operative months (Peele, 1944). The amelioration of human stroke patients' subjective symptoms that cause disability in everyday life is most rapid during the first few post-stroke months (Carroll, 1962; Skilbeck *et al.*, 1983; Kotila *et al.*, 1984; Dombovy and Bach-y-Rita, 1988). In most patients, virtually no further progress is seen after 1–2 years from the ictus. However, in some individuals the recovery process may continue for years (Aguilar, 1969; Dombovy and Bach-y-Rita, 1988).

Possible recovery mechanisms

During the first week after the ictus, paresis and other deficits are partially caused by brain edema, which accumulates in the acute phase due to an increase of osmotically active particles in the infarcted tissue. Edema increases intracranial pressure and thereby causes malfunction in the "healthy" brain areas. Consequently, part of the early recovery is related to edema absorption. Besides this, adaptive changes in the structure and functions of neuron populations, *i.e.*, reorganization, have been proposed as having a major role in the recovery process. Several theories on how reorganization would be mediated have been formulated, although direct evidence favouring any one of these has not yet been presented.

One plausible recovery mechanism is the unmasking of latent pathways. According to this theory, existing but normally nonfunctioning synapses would become active when they are released from the inhibitory control of the damaged area (Wall, 1980; Dombovy and Bach-y-Rita, 1988; Lee and van Donkelaar, 1995; Seil, 1997). Thus, diaschisis (see above) may actually aid recovery. Evidence for the existence of dormant neuronal connections comes from animal studies: in monkeys, reorganization of somatosensory cortical maps after digit amputation takes place immediately after the operation (Calford and Tweedale, 1991), as does the reorganization of motor maps after peripheral nerve transsection in adult rats (Jacobs and Donoghue, 1991). These rapid changes imply the pre-existence of pathways that become functional after the experimental lesions.

Compensation for lost functions by a functionally related brain area is another option. When large cortical areas are destroyed, there may not be sufficient surviving tissue near the infarcted area to allow local functionally relevant reorganization to take place. In such a situation, representations might shift to functionally closely related but more distant brain regions (Lee and van Donkelaar, 1995). There is evidence that the supplementary motor area in monkeys can take over new functions following damage to the primary motor cortex (Aizawa *et al.*, 1991).

Synaptic sprouting and the formation of new synapses may contribute to post-stroke recovery (Dombovy and Bach-y-Rita, 1988; Seil, 1997). Raisman and Field (1973) demonstrated that when one of two major inputs to a rat's septal nucleus cell is destroyed, the remaining input spreads to occupy the synapses formerly occupied by the damaged input. In elderly humans, the dendritic trees of neurons are more extensive than in the young (Buell and Coleman, 1979); this phenomenon probably reflects the formation of new synapses. However, there is no proof that sprouting or synaptogenesis is correlated with beneficial behavioral changes or that it takes place after a stroke.

The restoration of lateral inhibitory connections, which apparently are crucial for the functioning of cortical networks (Hicks and Dykes, 1983; Dykes *et al.*, 1984), has also been suggested to underlie post-stroke recovery (Dombovy and Bach-y-Rita, 1988).

Several studies have shown that changes in the functional organization of cortical networks take place in various physiological and pathophysiological situations both in human subjects and experimental animals. These changes may be accomplished by several mechanisms including sprouting, synaptogenesis, and the unmasking of latent connections. In the monkey, small lesions in 3b have been shown to cause rearrangements in the scale of hundreds of micrometers in the locations of the neuron populations that can be activated by the stimulation of a given skin area (Jenkins and Merzenich, 1987).

In SEF studies in humans, the functions of primary sensory areas have been shown to differ between musicians and non-musicians implying behaviour-related plasticity in the intact brain (Elbert *et al.*, 1995; Pantev *et al.*, 1998). Also revealed by MEG studies, arm amputation has been observed to cause functional reorganization in cortical networks of human patients (Ramachandran, 1993; Flor *et al.*, 1995).

Uncrossed fibres in the corticospinal tract may also contribute to functional recovery. Evidence supporting this possibility comes from observations in individual patients. *E.g.*, Lee and van Donkelaar (1995) reported a patient who suffered from a cerebral hemorrhage resulting in severe right hemiplegia. The patient improved gradually, but three years later the patient had a second hemorrhage in an almost identical location in the right hemisphere. This resulted in a mild sensorimotor deficit in the left arm, but also produced a marked worsening of the right hemiparesis. Using TMS, Netz *et al.* (1997) presented evidence for the unmasking of latent corticospinal projections in stroke patients, although this phenomenon was seen in patients with poor recovery which thus casts doubt on its functional relevance.

A recent animal study suggests that further deterioration of neuronal networks, adjacent to a cortical lesion, takes place if retraining of the lost skills is not started. Thus, a small lesion confined to a portion of the hand representation at the SI results in a further loss of hand territory in the adjacent, undamaged cortex of a monkey. Retraining of hand use after such a lesion prevents this loss (Nudo *et al.*, 1996). The specific neuronal mechanisms underlying the beneficial effect of training remain unknown.

Electrophysiological and functional imaging studies in stroke

Many investigators have studied the electrophysiology of ischemic stroke by means of SEPs (*e.g.*, Miyoshi *et al.*, 1971; Tsumoto *et al.*, 1973; La Joie *et al.*, 1982; Mauguière *et al.*, 1983; Reisecker *et al.*, 1986; Chester and McLaren, 1989; Zeman and Yiannikas, 1989; Macdonell *et al.*, 1991; Yokota *et al.*, 1991; Kovala *et al.*, 1993). Their findings, however, have been partially conflicting. Some researchers have reported that SEP deficits are correlated with defects in both superficial touch sensation and input from deep receptors (*i.e.*, those activated by joint movements and vibration; Miyoshi *et al.*, 1971; Yokota *et al.*, 1991). Tsumoto *et al.* (1973), on the other hand, claimed that abnormal short-latency SEPs in brain infarct are solely due to joint-position and vibration sense defects. The usefulness of SEPs in the prediction of the final functional outcome after stroke has also been the subject of many studies (*e.g.*, La Joie *et al.*, 1982; Chester and McLaren, 1989; Zeman and Yiannikas, 1989; Kovala, 1991). It can be concluded that reduced SEP amplitudes in the acute phase are more often associated with poor than good functional outcome, but SEPs can not substitute for clinical evaluation in the prediction of the outcome. When the present work was started, there was only one published study on SEFs in stroke patients. In that preliminary report, deficient graphestesia (*i.e.*, ability to identify figures drawn on the skin) was associated with small N20m amplitude (Maclin *et al.*, 1994). Forss *et al.* (1999) observed a correlation between the N20m ECD strength and the severity of the sensory loss in the six patients with right-hemisphere stroke that they examined. Mäkelä *et al.* (1991) reported on auditory evoked magnetic fields in patients who had suffered a stroke in the temporal cortex; the auditory N100m deflection was missing in some of these patients.

PET and fMRI studies on recovery after motor paresis have revealed changes in movement-related cortical functions (Weiller *et al.*, 1992; Cao *et al.*, 1998). Enhanced activation of several cortical areas including the contralateral cerebellum and ipsilateral premotor cortex has been seen during movements of the recovered hand.

Aims of the study

The main interest was to study, by means of magnetoencephalography, the neuronal recovery mechanisms of sensory functions in patients who had ischemic stroke. With the aim of finding a good stimulation paradigm, the effects of ISI on somatosensory evoked magnetic fields (SEFs) were investigated first. In order to distinguish stroke-induced changes in patients' SEFs from normal individual variation, we also studied the effects of age and gender on SEFs, as well as the interhemispheric differences of SEF parameters in healthy subjects. The specific aims were:

I To establish the effects of ISI on median nerve SEFs.

II To determine normal limits for SEF parameters and for their interhemispheric variation.

III To establish the effects of age and gender on SEFs.

IV To characterize the effects of acute middle cerebral artery (MCA) stroke on median nerve SEFs.

V To clarify the mechanisms of post-stroke recovery of somatosensory functions.

Subjects and Methods

Subjects

Altogether 43 healthy subjects (21 males, 22 females; aged 20 to 73 years) participated in Studies I-III (see Table 1).

		Controls		Patients	
		females	males	females	males
Study	I	4	5		
	II	13	10		
	III	22	21		
	IV			3	12
	V			2	12

Table 1. Patients and control subjects in each study.

The group investigated in Study II was used as the healthy reference group for the stroke patients, and was thus age-matched to the patient groups of Studies IV and V. SEFs from nine of the healthy subjects were recorded in two separate sessions to assess their reproducibility in serial recordings.

Fifteen in-patients of the Helsinki University Central Hospital's stroke unit participated in Study IV and 14 in Study V. All patients except two with pontine lesions had middle cerebral artery (MCA) territory strokes. One patient of Study IV did not participate in Study V, which included thus two patients not included in Study IV. Three of the altogether 17 patients of Studies IV and V were left-handed; three were females; the ages were in the range of 25 to 77 years. Originally, 32 patients were recruited. Eventually, 15 were excluded due to poor cooperation, magnetic artifacts in the recordings, or old lesions in the MRIs. Two patients had previous infarcts as revealed by MRIs. These patients were included only in Study V. None of the patients had other manifest neurological diseases.

Clinical evaluation

Prior to each SEF recording, I performed a clinical examination to the patient. Two-point discrimination ability, somatosensory extinction, pain, vibration, and joint-position senses, as well as muscle strength, were assessed. Widely used clinical indices describing the patient's overall functional status (Barthel, SSS, and Rankin scores) were routinely determined in the ward. The patients' symptoms had first appeared 1–18 days before the first MEG recording.

Anatomical imaging

Thirty-three healthy subjects (including all aged over 40 years and all participating in Studies I and II) underwent magnetic resonance imaging to exclude

those with subclinical brain lesions. MRIs were also obtained from each patient 0–3 days after the first MEG recording.

Subject preparation

Before each MEG recording session, three position indicator coils were attached to the subject's head. The positions of these coils and those of the nasion and the two preauricular points, were determined using a digitizer. This was necessary to be able to align the head and the magnetometer coordinate systems and to locate the measured cortical activity using the MRIs.

Recording

The recordings were performed using a device consisting of 122 planar gradiometers in a helmet-shaped detector array (Neuromag Ltd., Helsinki, Finland; Ahonen *et al.*, 1993). During a recording, the patient sat inside a magnetically shielded room watching a video film (Euroshield Ltd., Eura, Finland).

Before each MEG recording, when the subject was seated under the magnetometer dewar, current was passed through the position indicator coils and the resulting magnetic field was measured with the magnetometer. The coil locations were determined from these signals and a transformation between the head and magnetometer coordinate systems was obtained.

In SEF recordings the right (studies I and III) or both (studies II, IV, and V) median nerves were alternately stimulated at the wrist. The stimulus intensity was just above the motor threshold of the abductor pollicis brevis muscle, determined by visual inspection; the interstimulus interval (ISI) was 3 s per nerve, with the exception of Study I, in which five different ISIs (0.15, 0.3, 1, 3, and 5 s) were used.

The signals were band-pass filtered at 0.03–310 Hz and sampled at 940 Hz. The analysis time was 400 ms including a 50-ms prestimulus baseline. Two separate averaged responses containing 100–200 sweeps each were obtained. The electro-oculogram was monitored to detect and automatically reject sweeps with signals exceeding 150 μV. For MEG artifacts, the rejection limit was set at 3000 fT/cm.

Source modelling for SEFs

In each patient and control subject, the brain was modeled with a sphere best fitting the inner surface of the skull in the vicinity of the central sulcus. Equivalent current dipoles (ECDs) were used when estimating the locations and activation strengths of the neural generators of the SEF deflections. The locations, strengths and orientations of the ECDs were calculated with the least-squares method using data from 14–40 channels so that the maximum signal channel of a given deflection was located in the middle of the channel-set used. For those

patients who participated in both Studies IV and V, the ECDs were fitted two times independently. For SI responses, the typical goodness-of-fit (*g*) value exceeded 90% (Hämäläinen *et al.*, 1993). The limit for acceptance was 80 % in studies I, IV, and V, and 90 % in studies II and III. For opercular responses, however, three ECDs with *g*-values of 77% were accepted.

In Publications I–IV SEF deflections arising at the SI were referred to as N20m, P35m, N45m and P60m, according to their typical peak latencies and corresponding evoked potential polarities over the SI. In Publication V, N20m was named N1m and the following deflection peaking at the opposite direction P1m (usually P35m; in two patients P35m was bilaterally missing and P60m was thus designated P1m). In this Thesis, however, SI deflections are referred to as N20m, P35m and P60m consistently. For the responses at the contralateral opercular cortex (referred to as OCc in this Thesis and Publications IV and V and as SIIc in Publications I–III), the first recognizable peak (typically around 80–100 ms) was analyzed. When needed, signal-space projection (Uusitalo and Ilmoniemi, 1997) was used to remove SI activity coinciding with the OC response. Responses at the ipsilateral OC (referred to as OCi) as well as those at the posterior parietal cortex (PPC) showed marked variation between the two separate recording sessions as well as between individuals and were only analyzed in Study I.

Data Analysis

The limits for the normality of the ECD variables in patients were based on recordings in the healthy subjects. In patients, the amplitude, location or latency of an ECD was considered abnormal if it differed from the control-group mean by more than 2.5 standard deviations (SD). Since the amplitude of N20m is age-dependent, a regression line was calculated using the least-squares method to establish normal limits (mean ± 2.5 SD) for its dipole moment for patients of different ages. The ECD amplitudes, latencies, and coordinate values in the control group were compatible with the normal distribution (Kolmogorov-Smirnov test).

Differences in ECD locations, latencies, and strengths between two recording sessions were assessed. The relative ECD strength difference was calculated by dividing the absolute value of the difference in dipole moments (nAm) by the larger dipole moment. A change in amplitude, latency or location of a given ECD in a patient was considered abnormal if it exceeded the mean +2.5 *SD* of the control group.

With an ISI of three seconds, which was used in the patient recordings, the OCc response cannot be discerned in some healthy subjects. However, in all nine control subjects tested during two separate sessions, the OCc deflection from a given hemisphere was either present or absent in both recordings. In patients,

the appearance of an initially undetectable OCc response was therefore considered to reflect a recovered OC function. A deflection was considered absent in a given time-range if the inspected field-pattern was non-dipolar and the deflection's amplitude in the SEF waveform in the level of the baseline noise.

The ECD parameters at different ISIs (Study I) were compared using an analysis of variance for repeated measures. Individual differences between means were evaluated with post-hoc comparisons according to the Newman-Keuls method. In Study II, the significances of the interhemispheric differences were analyzed using *t*-tests for paired measurements. In Study III, a multiple linear regression model was used. In the statistical analysis of the patients' ECD parameters (Study V), the sign test and the *V*-square test were used.

Results and discussion

Study I: ISI effects on SEFs

Results

The SI response consisted of four separate deflections, N20m, P35m, N45m, and P60m in all subjects. In Fig. 7, the typical waveform near the left SI with three different ISIs is depicted. The ECDs of N20 and N45 pointed anteriorly with respect to the head, and those of P35m and P60m posteriorly. The P35m ECDs were on the average slightly more medially located than the N20m ECDs, as demonstrated also in earlier studies (Huttunen *et al.*, 1987; Tiihonen *et al.*, 1989).

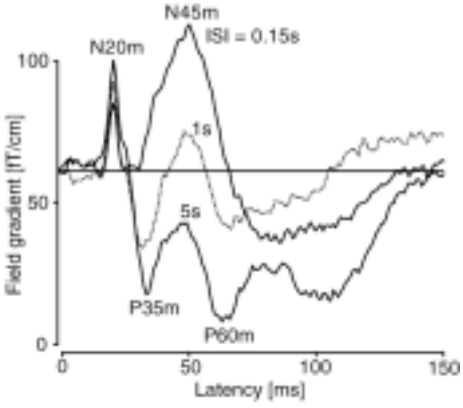

Fig. 7. The longitudinal SEF gradient over the left SI at 3 different ISIs in a healthy subject. The small variation in the N20m waveform may be due to small changes in the head position in different runs; such changes do not affect the ECD strengths since the head position is taken into account in the dipole fitting procedure.

The ECD orientations, locations, and latencies were not significantly affected by the ISI, whereas the ECD strengths were ISI dependent. Fig. 8 shows the average ECD strengths of all analyzed SEF components at the five different ISIs.

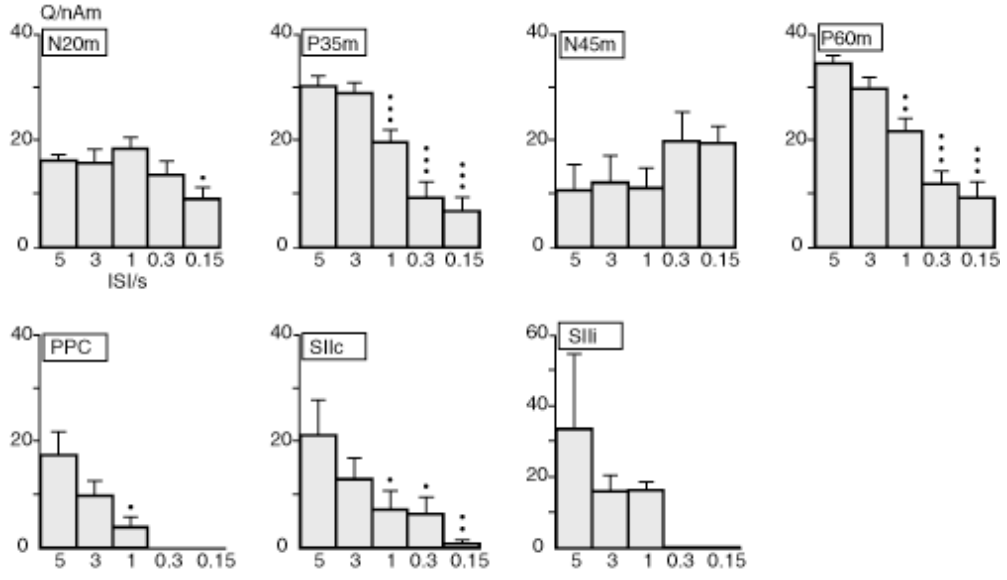

Fig. 8. The average ECD strengths of SEFs at five different ISIs. The dots denote different significance levels in the Newman-Keuls test where the ECD strengths at the different ISIs were compared with the ECD strength at the 5 s ISI (*p<0.05, **p<0.005, ***p<0. 0005). The bars denote standard error of means.

N20m was the most stable deflection. However, post-hoc comparisons revealed slight difference between the ISIs of 0.15 and 5 s. P35m and P60m were both gradually attenuated with shortening ISIs over the entire ISI range. In most subjects, P35m and P60m were completely absent at 0.15-s ISI. N45m was often indiscernible at long ISIs and dominated the whole SI response at the 0.15-s ISI. PPC responses, *i.e.*, responses with ECD locations posterior with respect to N20m, P35m, and P60m, were discerned in 7/9 subjects, and declined rapidly with shorter ISIs. OCc responses were seen in all subjects, whereas clear OCi responses were observed only in seven subjects. The OC responses peaked typically at 80–130 ms; the OCi peak was usually somewhat later than the corresponding OCc peak in the same subject. The OCc responses showed clear ISI dependence, whereas this effect did not reach the significance threshold (p<0.05) for OCi responses.

Discussion

Our findings are in agreement with the previous information concerning the ISI dependence of median nerve SEFs. However, only part of the features described in the present study were observed in each of the earlier studies. Thus, Teszner *et al.* (1982) noted a decrease of P60m when the ISI was shortened from 8 to 1 s; Tiihonen *et al.* (1989) reported an attenuation of P27m with a slight reduction of N20m when the ISI was reduced from 0.5 to 0.2 s; Karhu *et al.* (1994) observed a diminution of P35m between ISIs of 2 and 0.4 s; Narici *et al.* (1987) found that N45m grew towards the shortening ISIs and dominated the steady-state response.

From previous SEP studies it can be concluded that the ISI dependence and waveforms of SI SEFs closely resemble those of parietally recorded SEPs (*e.g.*, Tomberg *et al.*, 1989; Huttunen and Hömberg, 1991), with the exception that the peak latencies of SEPs are slightly shorter than those of SEFs (Nagamine *et al.*, 1998). It is likely that this discrepancy reflects the effects of radially oriented sources on SEP waveforms.

The cortical generation of SEF (and SEP) patterns has remained obscure. Evidence from different types of studies has led to the consensus view that short-latency SEPs, in the range of 20–40 ms, are generated in postcentral BAs 1 and 3, and are mainly mediated by cutaneous afferent fibres (*e.g.*, Allison *et al.*, 1991). The precise neuronal phenomena underlying the W-shaped SEF waveform separable into N20m, P35m, N45m, and P60m deflections are not known. Direct information linking cell-level electric events to extracranially recordable magnetic field fluctuations is not available. However, intracellular recordings from various brain areas have revealed similarities in the ISI behavior of PSPs and SI SEFs. Thus, in cats' motor cortex secondary EPSPs, evoked by stimulation of the ventrolateral nucleus of thalamus, grew with shortening ISIs, whereas the primary IPSPs disappeared at stimulation frequencies above 5–8 Hz (Nacimiento *et al.*, 1964). Hellweg *et al.* observed the disappearance of the primary IPSPs from cortical cells during stimulation of the infraorbital nerve of a cat with shortening ISIs (Hellweg *et al.*, 1977). In the guinea-pig neocortical slice preparation Deisz and Prince noted attenuation of both the primary and secondary IPSPs when the ISI was gradually shortened beginning from 10 s (Deisz and Prince, 1989). In contrast to IPSPs, the primary EPSPs only diminish at ISIs less than 0.2 s (Nacimiento *et al.*, 1964). Thalamic stimulation using ISIs of 0.1-0.2 s leads to an enhancement of a secondary EPSP, which follows the primary EPSP at about the same latency as the N45m deflection follows N20m (Purpura *et al.*, 1964; Klee, 1966; Creutzfeldt and Houchin, 1974)

Vertical current densities during the initial surface positive-negative deflection after somatosensory stimulus at the SI of cats closely resemble those derived from a computational model where this primary response is modelled by an

EPSP-IPSP sequence (Towe, 1966). The response waveforms of human electrocorticographic (Allison *et al.*, 1989), SEP (Desmedt *et al.*, 1987) and SEF recordings together with the above discussed similarity of the ISI behavior of SEF components and PSPs suggest that short-latency SEF deflections might reflect sequential PSPs in area 3b of the SI. Thus, N20m would represent the initial EPSP, P35m the initial IPSP, N45m the secondary EPSP, and P60m the secondary IPSP in pyramidal neurons. This interpretation requires, however, a closer examination.

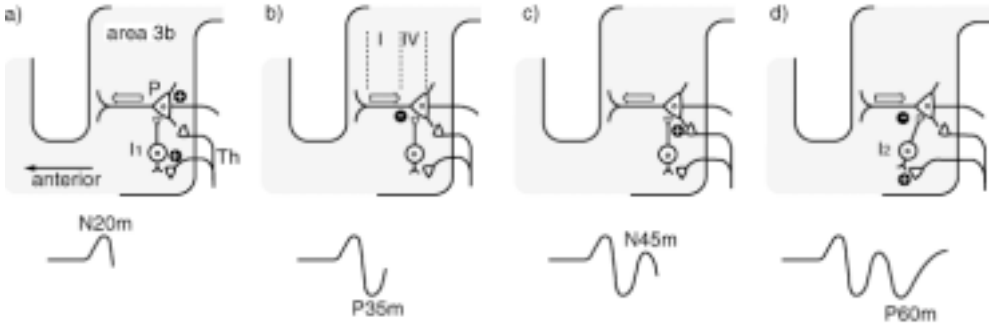

Fig. 9. Schematic illustration of a model for SEF generation at SI in a parasagittal section of area 3b. N20m is generated by summated EPSPs resulting from excitation at the basal and apical dendrites of the pyramidal neurons (P) close to the cell soma by specific thalamo-cortical axons (Th). Passive currents spreading to the distal parts of the apical dendrites form a net current dipole pointing in anterior direction, which is consistent with the N20m ECD orientation (a). P35m arises from population IPSPs in the soma or near-soma membranes of the apical dendrites of pyramidal neurons. Because of this, the dipole orientation is opposite to N20m (b). The IPSPs are due to thalamocortical excitation of the inhibitory interneurons (I1). N45m represents the secondary EPSPs (c) in the pyramidal cells and P60m the secondary IPSPs (d) mediated by another class of inhibitory interneurons (I2).

In Fig. 9, a schematic illustration of the hypothetical model for SEF generation at the SI is presented. In this model, both inhibitory and excitatory synaptic contacts are thought to be located in the soma, or the near-soma membrane (Creutzfeldt and Houchin, 1974; Creutzfeldt, 1995). There is, however, no conclusive evidence that the bulk of, say, excitatory synapses are not situated on more distal parts of the dendritic trees of pyramidal neurons.

One might argue that the significantly different locations of the generators of N20m, P35m, and P60m (Huttunen *et al.*, 1987; Tiihonen *et al.*, 1989; Kawamura *et al.*, 1996) would demonstarate against our model. However, inhibitory and excitatory receptive fields do not completely overlap (Mountcastle and Powell, 1959). Hence the centers-of-gravity of the summated IPSPs and EPSPs,

which, when modeled with ECDs correspond to the dipole locations, might not exactly coincide.

The ISI behavior of the PPC and the OC responses observed in the present study agree with the scarce information available (Hari *et al.*, 1993; Forss *et al.*, 1994). The neural events underlying these responses remain to be clarified in future studies. A recent study showed that OC responses are influenced by the attentional state of the subject (Mima *et al.*, 1998). One might speculate that opercular areas possibly have a role in the linking of environmental input coming to lower-level somatosensory areas with the subjective inner world experienced by the conscious human mind.

Study II: Interhemispheric SEF differences

Results

Twenty-three healthy subjects, age-matched with the infarct-patient group, participated in Study II. The SI waveform consisted of N20m, P35m, and P60m deflections. N20m could be discerned bilaterally from the SEFs in all 23 subjects, whereas P35m was unilaterally missing in one, and P60m bilaterally in another subject. Responses arising in OCc were seen in 17/23 subjects, and in OCi in 10/23 subjects. The OCc response was elicited in 13 subjects by left-sided and in 15 subjects by right-sided stimulation. The OCi responses often had amplitudes close to the noise-level, and, therefore, were not included in the analysis. PPC responses were unclear and inseparable from concomitant SI activity in most of the subjects, and were omitted from the analysis. Table 2 gives the mean peak latencies and ECD coordinates and strengths in each hemisphere together with the corresponding variances for the analyzed deflections.

		Latency [ms]		*x* [mm]		*y* [mm]		*z* [mm]		*Q* [nAm]	
N20m	L	22.5	(1.6)	–39.6	(5.1)	12.5	(7.9)	93.8	(4.9)	20.9	(6.8)
	R	22.4	(1.5)	44.5	(6.3)	15.1	(9.8)	93.0	(5.3)	19.8	(7.5)
P35m	L	36.0	(5.5)	–35.2 ***	(4.9)	10.0 *	(8.7)	97.4 ***	(4.6)	32.0	(15.9)
	R	36.0	(5.7)	37.9 ***	(5.1)	12.3 **	(7.3)	96.0 **	(5.8)	34.5	(17.1)
P60m	L	59.1	(12.1)	–38.5	(6.1)	10.2 *	(7.4)	96.6 ***	(4.9)	30.0	(12.7)
	R	58.2	(11.3)	41.1 ***	(5.8)	12.9	(8.6)	95.6 ***	(5.1)	28.7	(10.2)
SIIc	L	103.8	(17.6)	–47.5	(7.0)	19.7	(9.9)	66.4	(8.4)	17.3	(10.0)
	R	99.9	(22.1)	48.9	(8.5)	23.8	(9.0)	60.3	(9.1)	18.2	(12.7)

Table 2. Mean peak latencies, ECD coordinates and strengths (*Q*) of the 4 main deflections in left (L) and right (R) hemispheres. Standard deviations are given in parentheses. None of the distributions differed significantly from a normal distribution (Kolmogorov–Smirnov test). ***, ** and * denote significance levels of $p < 0.001$, <

0.01 and < 0.05, respectively, in *t*-tests when the coordinates of P35m and P60m were compared with those of N20m in the same hemisphere.

Altogether 39 N20m ECDs exceeded the limiting *g*-value of 90 %. When these were superimposed on the individual MRIs 26 dipoles fell in the central sulcus (CS), 10 in the postcentral sulcus, one in the postcentral gyrus, one in the precenral sulcus, and one in the precenral gyrus. For two dipoles this information was not available. The ECDs that did not fall in the CS, fell within 2.8–16.0 (mean 8.1; *SD* 3.2) mm of it.

Table 3 gives the mean interhemispheric asymmetries for the ECD coordinates and strengths, and limits for normal values as estimated as being within 2.5 SD from the means. In the head coordinate system based on external landmarks, the ECDs of the SI deflections were located more laterally and those of N20m and P60m also more anteriorly in the right hemisphere than in the left. In individual subjects, interhemispheric location differences were usually larger for N20m than for the other SI deflections. The largest differences were seen in the direction of *x*-coordinate, exceeding 10 mm in five subjects for N20m, and in three subjects for both P35m and P60m.

	Δ*x* [mm]		Δ*y* [mm]		Δ*z* [mm]		Δ*Q* [%]	
	Range	Mean ± 2.5SD	Range	Mean ± 2.5SD	Range	Mean ± 2.5SD	Range	Mean ± 2.5SD
N20m	–7.5...27.3	(5.1 ± 22) #	–6.2...14.8	(3.1 ± 14) #	–10.7...4.8	(–0.4 ± 10)	0.5...61.2	(17.1 ± 42)
P35m	–5.7...17.1	(3.2 ± 15) ∗	–7.0...9.1	(0.9 ± 13)	–9.6...6.0	(–1.3 ± 11)	2.8...47.7	(17.2 ± 31)
P60m	–10.7...17.4	(2.7 ± 15) ∗	–8.3...14.9	(2.7 ± 15) ∗	–6.1...6.7	(–1.3 ± 9)	0.7...54.4	(19.7 ± 39)
SIIc	–8.9...11.7	(2.4 ± 21)	–6.3...20.7	(4.1 ± 22)	–27.0...8.5	(–5.0 ± 21)	6.7...68.6	(46.2 ± 52)

Table 3. Interhemispheric asymmetries in the ECD coordinates and strengths of the 4 major SEF deflections. ∗ denotes $p<0.05$ and # <0.02. *A* positive difference indicates greater absolute value in the right hemisphere. None of the distributions differed significantly from a normal distribution (Kolmogorov–Smirnov test).

Superimposing the OCc ECDs on the MRIs showed that 14 of them were located in the precentral gyrus, two in the postcentral gyrus, six in the insular cortex, and six in the superior temporal gyrus. There were no systematic interhemispheric differences in the coordinates or source strengths of the SIIc responses. The interhemispheric variability was on average greater in SIIc than in the SI.

Discussion

Only one previous study assessing interhemispheric SEF asymmetries has been published (Rossini *et al.*, 1994). Rossini *et al.* did not find asymmetries for the SI ECD locations that at the group level would be biased in any direction. However, they reported that SI sources were on average slightly stronger in the left hemisphere than in the right. These observations are in variance with ours. The maximal interhemispheric coordinate asymmetries and the mean interhemispheric N20m source strength asymmetry in our study, on the other hand, agree with those reported by Rossini *et al.* Different coordinate systems and possibly differences in the subject groups are likely to underlie the observed discrepancies between the two studies.

The fact that in our study the ECD source locations were estimated with respect to external landmarks adds a possible source of error to the interpretation of the interhemispheric location asymmetries. One might claim that the observed asymmetries do not reflect true cerebral asymmetries. Indeed, previous reports on the anatomic interhemispheric comparisons of the human brain have not revealed notable asymmetries in the locations and orientations of the central sulci (Habib, 1989; Galaburda *et al.*, 1990; Glicksohn and Myslobodsky, 1993).

The localizing accuracy of MEG is highest in the direction perpendicular to the current flow (see, *e.g.*, Yamamoto *et al.*, 1988). For the SI ECDs, the *x*-axis is almost perpendicular to the dipole orientations. Therefore, the fact that in some subjects the interhemispheric difference in the absolute values of the *x*-coordinates of the ECDs was roughly zero, whereas in other subjects it was over 1 cm more likely reflects true individual differences in the asymmetry of the location of the hand area than the interhemispheric differences along either the *z* or *y*-axis.

Twelve of the thirty-nine of N20m ECDs did not fall on the central sulcus when plotted on the individual MRIs. With a model head, the localization accuracy of MEG is less than 5 mm (Yamamoto *et al.*, 1988). In a study involving 22 healthy volunteers and 70 neurological patients, the deviation of the N20m ECD location from the posterior wall of the CS was on the average 5 mm with a SD of 3.5 mm (Kawamura *et al.*, 1996), corresponding well with ours.

When the OCc response could be detected bilaterally, the interhemispheric asymmetry of the ECD locations was in the same order of magnitude as those for the SI responses. However, in agreement with previous observations (Hari *et al.*, 1993), these responses were frequently difficult to identify or completely undetectable in one or both hemispheres. The *g*- values of the OC responses were often poor, which suggests that a single-dipole is an inadequate model of neuronal activation in the OC. Indeed, somatosensory stimulation activates several adjacent areas in the OC (Burton *et al.*, 1993). This is evident also in fMRI

studies using electric median nerve stimulation (Korvenoja *et al.*, 1999). Another possible source of error when modeling the neuronal generators of OC responses is the inadequacy of the spherical head model especially in the anterior temporal regions (Hämäläinen and Sarvas, 1987). As a conclusion, the OCc source locations can only be considered as suggestive.

Study III: Age and gender effects on SI SEFs

Results

SI SEFs (N20m, P35m, and P60m deflections) to right median nerve stimulation were studied in 43 healthy volunteers, age range 20–73 years (21 males). Table 4 presents the mean latencies and ECD coordinates in both sexes. The sources tended to be more medial in females than in males.

	N20m	N20m	P35m	P35m	P60m	P60m
Latency (ms)	22.2 (1.9)	23.5 (1.9)*	35.6 (4.8)	39.1 (4.1)*	62.7 (17.3)	69.3 (11.4)
x (mm)	-38.9 (5.1)	-40.3 (3.4)*	-33.6 (5.6)	-36.6 (5.0)	-36.2 (5.7)	-38.6 (5.9)
y (mm)	10.1 (9.3)	11.6 (8.9)	11.5 (9.5)	11.4 (7.5)	9.9 (9.5)	10.6 (7.9)
z (mm)	91.9 (7.9)	97.4 (7.0)*	94.8 (5.5)	99.7 (9.8)	94.7 (6.7)	98.5 (5.8)

Table 4. Mean latencies and ECD coordinates in females (the left-side column of each pair) and in males. The latencies of N20m and P35m were longer, the N20m *x*-coordinate lower and the *z*-coordinate higher for males than for females ($p < 0.05$; marked with an asterisk), while none of the other values differed significantly between the groups.

The latencies of N20m and P35m were shorter in females than in males. The N20m latency was positively correlated with age ($p<0.02$), which was mainly due to a positive correlation in males ($r=0.50$, $p<0.02$) rather than in females ($r=0.21$, $p<0.1$).

In most subjects, the source strength of N20m ranged from 10 to 25 nAm. However, in three subjects aged over 50 years the ECD strength was about 30 nAm. The source strength never exceeded 25 nAm in subjects younger than 30 years.

Furthermore, the source strength was below 10 nAm in 36% of the subjects younger than 30 years but in none older than 60 years. In Fig. 10 the SI SEF waveform and the topographic magnetic field maps of N20m in a 20-year-old and a 65-year-old male are shown. The N20m is weaker in the young subject. In

multiple regression analysis, N20m amplitude was positively associated with age (p<0.02), whereas the amplitudes of P35m and P60m were not.

The source strengths were not found to be correlated with either of our two estimates of cortical atrophy: the width of the central sulcus at the SI hand area and an overall cortical atrophy index, evaluated visually from the MRIs, on a scale from 0 to 3. Interestingly, however, both indices were higher in males than in females and in older than in younger subjects.

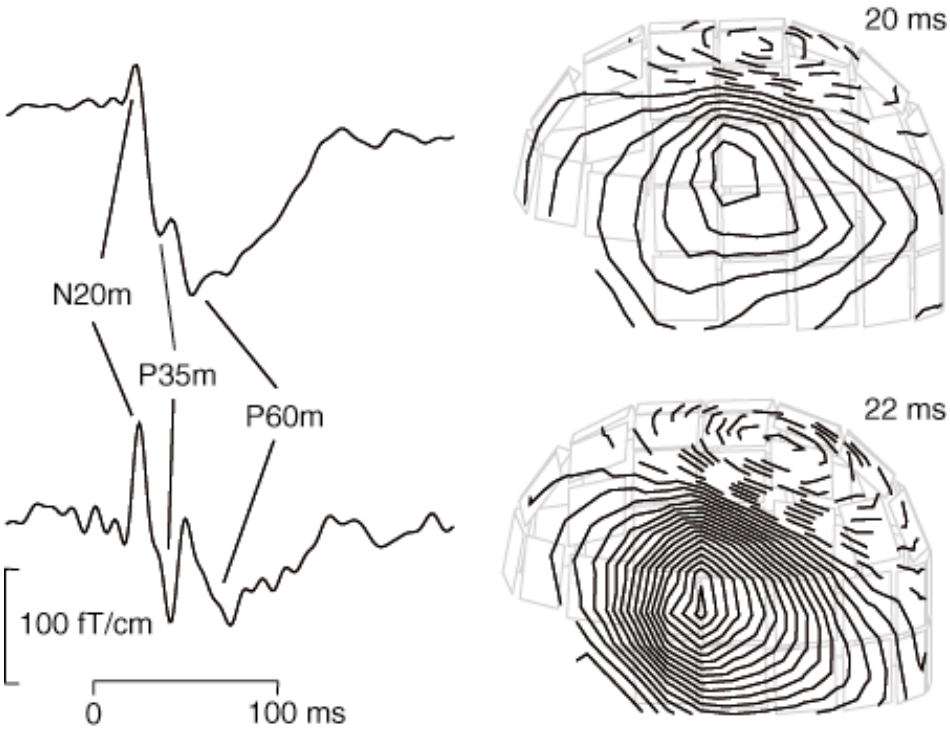

Fig. 10. The SEF waveform over the left SI and the topographic magnetic field map of the N20m deflection in a young and an elderly male. The N20m is clearly weaker in the young subject (upper half of the image).

Discussion

The sex differences that we observed in the peak latencies and source locations can be explained by the different dimensions of both the conducting pathways and the cranium in females and males. Our observation that the amplitudes of the SEF deflections did not differ between the sexes, indicates that the previously reported lower SEP amplitudes in males (Ikuta and Furuta, 1982) are probably due to gender differences in the properties of the volume conductor (*i.e.*, the skull and the adjacent tissues).

In SEF latencies, the only significant age-related change was the prolongation of N20m peak latency. This change was largely confined to males, which is in agreement with previous finding in SEPs in which the slope of the age related latency increase in N20 was steeper in males (Allison, 1987). This might be due to the more rapid structural aging in males than in females (McMurphy *et al.*, 1996).

The age-related amplitude changes observed in SEPs are clearly at variance with our present findings. Whereas we observed enhancement of the N20m deflection only, SEP literature reports enhancements in other early cortical deflections as well (Desmedt and Cheron, 1981; Kakigi and Shibasaki, 1991). In the SEP studies the strengths of the deflections were peak-to-peak amplitudes measured from the channels with the strongest signals; in our study the strengths were the ECDs' dipole moments. Furthermore, the possible age-related changes in the volume conductor's properties are not reflected in SEFs as much as they are reflected in SEPs. The radial sources that affect the SEP patterns are invisible to MEG. All these differences between the methods of the present study and those of previous SEP studies may have contributed to the dissimilarities in the results.

Although the dendritic tree of pyramidal neurons is more extensive in old than young humans (Coleman, 1987), it is unlikely that a change like this is responsible for the selective growth of N20m during aging as observed in the present study. Since all the early SEF deflections are likely to be generated by similar pyramidal cells, a change in the physical properties of these cells should be reflected in the rest of the deflections as well. We propose that the growth of N20m in elderly humans reflects an age-related increase in cortical excitability.

Study IV: correlation of SEFs in acute sensorimotor stroke with clinical impairments

Results

Fifteen patients were studied using bilateral median nerve stimulation. Table 5 shows clinical data and ECD strengths in the affected and unaffected hemisphere. Table 6 shows the lesion locations and volumes in each patient.

Patient	Age	Sex	Side	Duration	Sensory deficits						Motor paresis	Q_{N20m}		Q_{P35m}		Q_{P60m}	
					2p	Pain	Temperature	Vibration	Position	Extinction		H	D	H	D	H	D
Motor stroke																	
1	56	m	L	15	–	–	–	–	–	–	mild	16	20	23	16	14	36*
2	49	m	L	1	–	–	–	–	–	–	severe	17	10	26	17	15	17
3	59	m	R	8	–	–	–	–	–	–	severe	17	31	34	23	43	50
4	48	f	L	2	–	–	–	–	–	–	mild	3	3	33	28	31	28
Sensory stroke																	
5	65	m	L	4	++	+	–	+	na	+	none	55#	35	37	25	76#	49
6	51	m	R	3	++	+	–	–	–	–	none	28	0*	31	0*	29	0*
7	59	f	L	5	+	+	–	+	+	–	none	19	15	44	30	22	21
8	48	m	L	2	++	+	+	+	+	+	none	17	25	19	23	19	15
Sensorimotor stroke																	
9	64	m	L	11	++	+	+	+	+	na	severe	17	0*	71	13*	0	0
10	26	f	L	13	–	+	–	–	+	–	severe	21	15	22	18	26	29
11	48	m	L	2	++	+	na	na	+	+	severe	11	0*	30	0*	32	0*
12	64	m	R	3	+	+	+	–	–	+	mild	16	18	47	24*	55	0*
13	56	m	R	6	++	+	+	+	+	na	severe	22	0*	0	0*	36	13*
14	61	m	R	4	–	+	+	+	–	–	severe	8	7	15	0*	28	6*
15	52	m	L	2	–	–	+	+	–	–	mild	10	10	11	15	27	30

Table 5. Clinical and experimental data. Side denotes infarcted hemisphere; L, left; R, right, Duration indicates days between onset of the symptoms and SEF recording. 2p denotes 2-point discrimination ability: – (non-affected), + (affected) and ++ (absent). Pain, temperature, vibration, and position senses and contralateral somatosensory extinction are characterized as – (non-affected), or + (affected). Na denotes non-available data. Q_{N20m}, Q_{P35m} and Q_{P60m} indicate the dipole moments corresponding to the ECDs of N20m, P35m and P60m, respectively. Values marked with * are abnormally low compared with those of the normal population or show abnormally large interhemispheric difference. Values marked with # are abnormally high compared with those of the normals. H denotes healthy and D diseased hemisphere.

Patient	Lesion Side	Volume (cm^3)	Thalamus	Capsula Interna	Parietal Lobe	Frontal Lobe	Parietal Operculum	Frontal Operculum	Basal Ganglia	Other
Motor stroke										
1	L	9				x		x	x	
2	L	3		x		x			x	
3	R	<1								Pons
4	L	3		x					x	
Sensory stroke										
5	L	7			x	x	x	x		
6	R	<1	x							
7	L	2			x		x	x	x#	
8	L	59		x	x	x	x			
Sensorimotor stroke										
9	L	76		x	x *	x	x	x		Cerebellum
10	L	14	x	x					x	
11	L	50		x	x *	x	x			
12	R	100			x *	x	x	x		
13	R	31		x	x	x		x		
14	R	13	x	x		x			x	
15	L	<1								Pons

Table 6. The volumes and locations of the infarcts. Parietal and Frontal lobe denote hemispheric areas outside the parietal and frontal opercular cortices, respectively. * denotes the involvement of the SI hand area. # indicates lesion in the right hemisphere.

Four patients had only a mild motor stroke. In them, the SEFs were normal on the affected side. In five of the eleven patients with sensory or sensorimotor stroke a coincidence of attenuated SI SEFs and reduced 2-point discrimination was observed. This was particularly striking for the N20m deflection: it was undetectable, *i.e.*, the field pattern during the latency range of 15-25 ms was non-dipolar on inspection, in all patients with absent 2-point discrimination ability. Only one patient with reduced SI SEFs (P35m and P60m deflections) had normal 2-point discrimination ability. Conversely, SI SEFs were symmetric in two out of three patients who only had other types of sensory symptoms (see Table 7). Three patients with lesions in the OC had deficient 2-point discrimination ability even though the SI SEFs were symmetric.

ECD strength abnormalities were scarce in the unaffected hemisphere; only one patient had enhanced responses on the non-affected side. Latency abnormalities on either side were seen in three patients. ECD location abnormalities that could be considered to be a result of plastic changes in neuronal networks rather than tissue displacements due to edema formation were not observed. All ECDs were located close to the Ω-shaped cortical convolution that characterizes the hand area.

	SI SEFs normal	SI SEFs reduced
2-p normal	6	1
2-p reduced	3	5

Table 7. The 15 patients categorized according to 2-point discrimination ability and SEF amplitudes over the diseased hemisphere.

Dicussion

There are earlier reports trying to link SEP abnormalities to distinct abnormalities in somatosensory functions, but the observations have been partially conflicting (*e.g.*, Miyoshi *et al.*, 1971; Tsumoto *et al.*, 1973; Mauguière *et al.*, 1983; Yokota *et al.*, 1991). The inconsistencies of the different SEP studies make it difficult to conclude whether short latency SEPs reflect afferent input to the SI from deep receptors (those activated by joint movements and vibration, possibly also muscle afferents) or from superficial cutaneous receptors subserving discriminative touch, or from both.

The present results suggest that the SI SEFs are more related to 2-point discrimination than to the other somatosensory submodalities. The absence of the N20m deflection in particular was always associated with the loss of 2-point discrimination ability. Previous findings of Maclin *et al.* (1994) from five patients with sensorimotor stroke showing that the strength of N20m correlated

with graphestesia scores (the ability to identify numbers or letters drawn on the skin) are in agreement with our findings. Forss *et al.* (1999) did not separately assess 2-point discrimination ability, but linked attenuated N20m with lowered tactile sensibility. The N20 SEP and N20m SEF deflections are generated in area 3b pyramidal neurons (Wood *et al.*, 1985; Allison *et al.*, 1989), which have small receptive fields (Hyvärinen and Poranen, 1978) and receive input mainly from cutaneous afferent fibres (see *e.g.*, Kaas, 1993). Discriminative functions, such as 2-point discrimination and graphestesia, are very likely to be mediated by neurons possessing these properties.

Three patients with purely sensory symptoms had lesions in the left opercular cortex with some spreading to the adjacent tissue as shown by the MRIs. However, the MRIs revealed no lesions in the SI, and intact afferent connectivity of the SI was confirmed by normal SEFs. Previous findings indicate that ventrolateral opercular lesions, probably encompassing SII, impair tactile object recognition but leave basic somatosensory functions such as 2-point discrimination intact (Caselli, 1993). The present results pose a challenge to this view, and suggest that lesions in the OC can interfere with the perception of simple somatic sensations. Taken together, our findings suggest that in the relatively acute phase of stroke both an intact SI and a properly functioning OC are required for even simple somatosensory perceptions to reach the consciousness.

We did not observe shifts in the ECD source locations that we assumed to be related to functional reorganization of cortical networks. Since tissue edema often distorts cortical structures in the acute phase, it is extremely difficult to dissociate a true reorganizatory ECD source shift from a tissue swelling effect.

Study V: SEF changes during recovery from sensorimotor stroke

Results

Fourteen patients participated in Study V. In those without a noticeable sensory deficit, SI SEFs remained unchanged at the end of the follow-up period (see Tables 8 and 9).

	SI SEFs no change	SI SEFs increase
2-p no change	7	1
2-p recovery	1	5

Table 8. The 14 patients categorized according to the recovery of 2-point discrimination ability and the growth of SEF amplitudes over the diseased hemisphere during the follow-up period.

Table 9 a. Clinical and experimental findings in patients in whom 2-point discrimination recovered. Data in the acute-phase is presented on the first and data at follow-up on the second line. Days indicate time interval from the first symptoms to the initial examination. Vol. indicates the infarct volume; affected areas are marked with x. * denotes lesion in the SI hand area, # old lesion in the left hemisphere. *2-p* indicates 2-point discrimination ability: affected/non-affected side; ∞ signifies complete inability to distinguish between two points. Pain/temperature (P/T), vibration (Vibr), and position (Pos) senses as well as motor paresis are characterized as - (not affected), or + (affected). Na denotes non-available data. Q_{N20m} and Q_{P35m} indicate the ECD strengths of N20m and P35m, respectively, in the healthy (H) and diseased (D) hemisphere. Values in bold characters indicate abnormal change in ECD strength between acute phase and follow-up.

N:o		Age	Sex	Side	Days	Barthel	SSS	Rankin	*Vol.* (cm^3)	Thalamus	Internal Capsule	Parietal Lobe	Frontal Lobe	Other	Q_{N20m} H	Q_{N20m} D	Q_{P35m} H	Q_{P35m} D	*2-p* (mm)	Sensory symptoms P/T	Sensory symptoms Vibr	Sensory symptoms Pos	Motor paresis
1	acute	51	m	R	3	100	58	2	<1	x					30	0	29	0	∞/24	+	–	–	–
	follow-up					100	58	2							20	0	22	**25**	35/20	+	–	–	–
2	acute	64	m	L	11	55	16	4	76		x	x*	x	Cerebellum	18	0	36	0	∞/9	+	+	+	+
	follow-up					75	34	4							26	**11**	33	**17**	35/10	+	+	+	+
3	acute	64	m	R	3	65	27	3	100			x*	x		17	23	44	26	50/15	+	–	–	+
	follow-up					100	56	1							18	15	47	**59**	13/13	–	–	–	+
4	acute	77	m	L	4	70	40	3	9	x#			x		23	12	33	15	50/10	+	–	–	+
	follow-up					na	50	3							18	18	23	**40**	12/20	+	–	–	+
5	acute	63	m	R	5	90	54	3	71	x#		x	x	Basal ganglia#	12	9	18	15	40/13	+	–	–	+
	follow-up					100	58	2							19	18	34	**45**	10/15	–	–	–	+
6	acute	48	m	L	2	30	na	4	59		x	x	x		17	25	19	23	∞/20	+	+	+	–
	follow-up					100	na	2							32	15	**59**	19	15/15	+	+	–	–

Table 9 b. Clinical and experimental findings in patients in whom 2-point discrimination did not recover. Data in the acute-phase is presented on the first and data at follow-up on the second line. Days indicate time interval from the first symptoms to the initial examination. Vol. indicates the infarct volume; affected areas are marked with x. * denotes lesion in the SI hand area. *2-p* indicates 2-point discrimination ability: affected/non-affected side; ∞ signifies complete inability to distinguish between two points. Pain/temperature (P/T), vibration (Vibr), and position (Pos) senses as well as motor paresis are characterized as - (not affected), or + (affected). Na denotes non-available data. Q_{N20m} and Q_{P35m} indicate the ECD strengths of N20m and P35m, respectively, in the healthy (H) and diseased (D) hemisphere. In patient 9 P35m is actually P60m. Values in bold characters indicate an abnormal change in the ECD strength.

N:o		Age	Sex	Side	Days	Barthel	SSS	Rankin	*Vol.* (cm^3)	Thalamus	Internal Capsule	Parietal Lobe	Frontal Lobe	Other	Q_{N20m} H	Q_{N20m} D	Q_{P35m} H	Q_{P35m} D	*2-p* (mm)	Sensory symptoms P/T	Sensory symptoms Vibr	Sensory symptoms Pos	Motor paresis
7	acute	65	m	L	4	100	54	2	7			x	x		57	36	38	25	∞/20	+	+	na	–
	follow-up					100	54	1							45	41	22	34	∞/8	+	–	–	–
8	acute	48	m	L	2	na	na	4	50		x	x*	x		15	0	27	0	∞/∞	+	+	+	+
	follow-up					90	48	3							32	0	**76**	0	∞/11	+	+	+	+
9	acute	56	m	R	6	25	18	4	31		x	x	x		23	0	37	13	∞/∞	+	+	+	+
	follow-up					85	49	3							26	0	37	**29**	∞/20	+	+	+	+

Table 9 c. Clinical and experimental findings in patients in whom 2-point discrimination was not affected. Data in the acute-phase is presented on the first and data at follow-up on the second line. Days indicate time interval from the first symptoms to the initial examination. Vol. indicates the infarct volume; affected areas are marked with x. *2-p* indicates 2-point discrimination ability: affected/non-affected side; ∞ signifies complete inability to distinguish between two points. Pain/temperature (P/T), vibration (Vibr), and position (Pos) senses as well as motor paresis are characterized as - (not affected), or + (affected). Na denotes non-available data. Q_{N20m} and Q_{P35m} indicate the ECD strengths of N20m and P35m, respectively, in the healthy (H) and diseased (D) hemisphere. In patient 14 P35m was actually P60m. There were no significant changes in the ECD strengths in any of these patients.

N:o		Age	Sex	Side	Days	Barthel	SSS	Rankin	*Vol.* (cm^3)	Thalamus	Internal Capsule	Parietal Lobe	Frontal Lobe	Other	Q_{N20m} H	Q_{N20m} D	Q_{P35m} H	Q_{P35m} D	*2-p* (mm)	Sensory symptoms P/T	Sensory symptoms Vibr	Sensory symptoms Pos	Motor paresis
10	acute	56	m	L	15	70	47	2	9				x	Basal	16	21	22	16	5/12	–	–	–	+
	follow-up					100	52	2						ganglia	17	17	19	18	10/16	–	–	–	+
11	acute	48	f	L	2	100	58	1	3		x			Basal	3	na	30	26	12/16	–	–	–	+
	follow-up					100	58	1						ganglia	na	11	40	34	na/na	–	–	–	+
12	acute	61	m	R	4	65	50	3	13	x	x		x	Basal	9	11	12	0	20/20	+	+	–	+
	follow-up					100	56	2						ganglia	11	10	15	0	15/20	+	+	–	+
13	acute	52	m	L	2	100	58	1	<1					Pons	8	10	11	16	25/20	+	+	–	+
	follow-up					100	58	0							8	4	21	19	15/12	–	–	–	+
14	acute	26	f	L	13	70	42	4	14	x	x			Basal	22	16	26	27	15/10	+	–	+	+
	follow-up					100	49	2						ganglia	21	15	37	39	15/14	–	–	–	+

Figure legends:

1. Response waveforms to left median nerve stimulation in patient 1, who suffered from a small right-sided posterior thalamic lesion resulting in non-detectable SEFs in the first recording (thin lines). In the second recording (thick lines), P1m had recovered, while a clear-cut N1m could not be discerned. The 61 magnetometer channel pairs are viewed from the top of the head with the nose pointing upwards. The two channels of each pair measure orthogonal derivatives of the magnetic field gradient. In the enlargement, the maximum SEF signal overlying the right SI is depicted.

2. The dipole moments of the ECDs corresponding to N1m and P1m in the acute and follow-up recordings. P1m grew significantly during follow-up ($p < 0.009$, sign test), whereas N1m did not ($p < 0.8$). Two-point discrimination recovered in patients 1-6 (thick lines) during the follow-up period.

3. Response waveforms on the affected side in all patients (1-14). The channel with the strongest signal over SI in the first recording (thin line) and in the second recording (thick line) is shown. Cases are numbered according to Tables 1-3. Asterisks denote improved 2-point discrimination ability during follow-up. Note that a difference in signal waveform does not necessarily mean a significant difference in the ECD strengths; differences paralleled by significant ECD strength changes are shaded.

4. Isofield contour maps and MRIs showing the ECD locations corresponding to P1m in the first (dot) and in the follow-up recording (square) in patient 5, in whom the right parietal cortex and white matter immediately caudal to the central sulcus were damaged. Dashed lines represent magnetic flux entering and solid lines exiting the head. The contour line separation is 20 fT/cm. In the field map, the arrow illustrates the location and orientation of the ECD. In the MRI slices, the infarct area is marked with arrows.

Fig. 11 depicts response waveform from a patient with a posterior thalamic infarct and pure sensory paresis. The enhancement of P35m (or P60m) deflection during the follow-up period is clearly visible. In 6/12 patients with sensory or sensorimotor paresis, P35m or P60m increased significantly during the follow-up period.

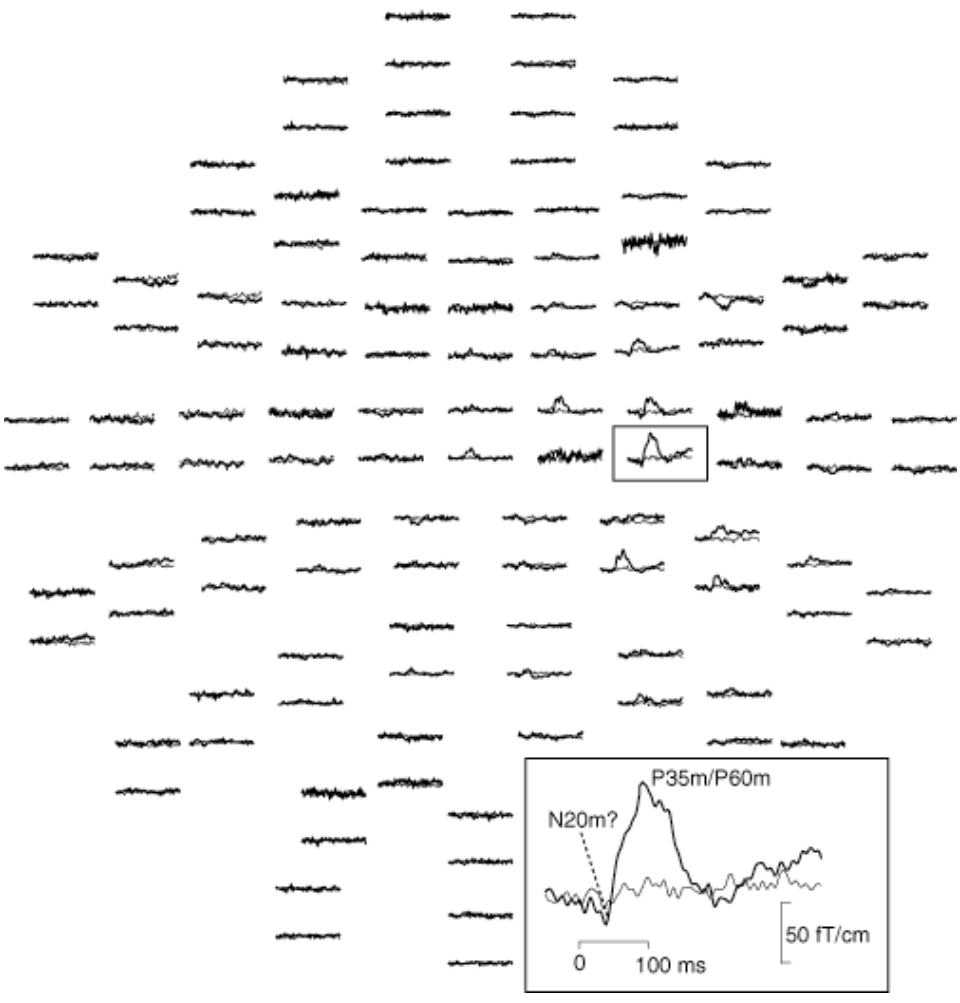

Fig. 11. Response waveforms to left median nerve stimulation in patient 1, who suffered from a small right-sided posterior thalamic lesion resulting in non-detectable SEFs in the first recording (thin lines). In the second recording (thick lines), P35m had recovered, while a clear-cut N20m could not be discerned. The 122 magnetometer channels are viewed from the top of the head with the nose pointing upwards. In the enlargement, the maximum SEF signal overlying the right SI is depicted.

In Fig. 12, this phenomenon is demonstrated at group level as well. N20m, on the other hand, was relatively stable between the two recordings. Significant enhancement was seen in one patient only (see Table 7 and Fig. 12). In five of the six patients with recovered P35m/P60m, the enhancement was paralleled by the recovery of 2-point discrimination ability, while in one patient tactile discrimination did not improve despite an increase in P60m. Conversely, 2-point discrimination improved in only one of those patients with no change in P35m/P60m, whereas tactile discrimination and P35m/P60m (as well as N20m)

were unchanged in the remaining seven patients. All patients with intact 2-point discrimination (*i.e.*, <35 mm) in the second examination also had a normal N20m deflection at that time.

The lateralization of the SEF components did not change during the follow-up period. ECD location shifts exceeding the normal limits were seen in three affected hemispheres.

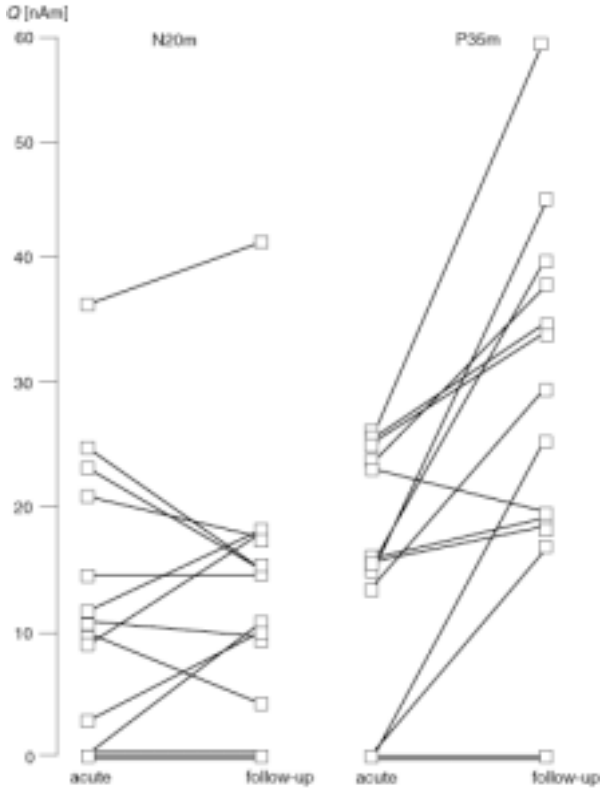

Fig. 12. The dipole moments of the ECDs corresponding to the peaks of N20m and P35m in the acute and follow-up recordings. P35m grew significantly during follow-up (p = 0.009, sign test), whereas N20m did not. Bold lines indicate the recovery of 2-point discrimination during the follow-up period.

Discussion

Although the studied cohort was heterogeneous with respect to lesion location and size, we were able to show a correlation between an objective neurophysiological measure and the recovery of a basic sensory function. Namely, the recovery of discriminative touch was associated with an increase of the second cortical deflection after median nerve stimulation (either P35m or P60m). No previous follow-up studies on SEFs in stroke patients have been published; the few existing ones on SEPs have mainly focused on the correlation between the initial SEP impairment and the final overall functional outcome, while the relationship between the recovery of different SEP components and different somatic sensory submodalities has remained unclarified. Macdonell *et al.* (1991), however,

linked the recovery of P45 SEP deflection, which probably corresponds to our second cortical deflection, to the recovery of pain/temperature and joint position senses. They did not assess discriminative touch.

Several lines of evidence have pointed out that even the mature central nervous system of the monkey and humans is capable of plastic changes. Thus, experimentally induced small lesions in area 3b of a monkey bring forth rearrangements at a scale of hundreds of micrometers in the locations of neuron populations that can be activated by stimulating a given skin area (Jenkins and Merzenich, 1987). So far, no reports have been published on the possible reorganization of cortical maps after subcortical lesions producing cortical deafferentation. In human stroke patients, recovery-related changes in the activation patterns of various cortical regions has been reported in motor paresis (Weiller *et al.*, 1992; Cramer *et al.*, 1997; Cao *et al.*, 1998). Although we did not observe changes in the locations of the neural generators underlying the SI SEF deflections that could be interpreted as having resulted from plastic changes, we did observe amplitude growths of these deflections. Inherently for the ECD model, a growth of the cortical source area of a given magnetic deflection is seen as the growth of the ECD's dipole moment, *i.e.*, the deflection's amplitude (Okada, 1985). Therefore, it is possible that in some patients with enhanced P35m/P60m responses, the cortical areas generating it had, in fact, been enlarged. Another plausible explanation for the amplitude growths is an increase in the coherence of activity in the surviving neurons (Ahissar and Ahissar, 1994). This mechanism should, however, also narrow the SEF deflections, which was not observed in the present study.

The SI cortex was directly involved in the ischemic lesion in 3 patients, and partially deafferented in 10 patients by lesions affecting the subcortical white matter, the thalamus or the pons. Both deafferentation (Wall and Egger, 1971; Dykes and Lamour, 1988; Ziemann *et al.*, 1998) and ischemia (Krnjevic *et al.*, 1991; Luhmann *et al.*, 1993; Sober *et al.*, 1997) can lead to impaired inhibition in the affected cortical region. Hyperexcitability is also typical of cerebral cortex adjacent to a lesion during the first week after lesion induction.(Büchkremer-Ratzmann and Witte, 1997; Hagemann *et al.*, 1998) Pathologic reflexes and mass movements, which are often seen after a stroke, as well as epileptic convulsions, can be seen as manifestations of defective inhibition. Discriminative touch, on the other hand, is likely to depend on small excitatory receptive fields in the cortical neurons responsible for this function. In the SI, the average receptive field size is smallest in area 3b, which is thus a good candidate to mediate discriminative touch (Kaas, 1993). Furthermore, the maintenance of small receptive fields relies on properly functioning lateral inhibitory connections (Dykes *et al.*, 1984). In the present study, the recovery of P35m in patients with improved discriminative touch could reflect the re-establishment of inhibitory functions in the SI.

Recent functional imaging studies have emphasized the possibility that some lateralized functions are overtaken by the undamaged hemisphere (Weiller *et al.*, 1992; Cramer *et al.*, 1997; Cao *et al.*, 1998). In the present study, however, no abnormal SEFs from the ipsilateral SI when the affected hand was stimulated were observed. Even so, our finding that P35m grew significantly in the undamaged hemisphere of two patients (when the unaffected hand was stimulated) implies that changes in excitability may also occur on the 'healthy' side. Previously, occasional remarks of enhanced SEPs in the unaffected hemisphere of stroke patients have been published (Nakashima *et al.*, 1985).

Methodological remarks

The dipole model used in the present study is supposed to relatively accurately capture the main features of neuronal activation in brain areas where stimulus-locked activity is concentrated on small, well-defined neuronal ensembles. This is the case in the SI during the first tens of milliseconds following median nerve stimulation. The spherical head model used in the present study has also been shown to be suitable for parietal areas (Hämäläinen and Sarvas, 1987). However, in the lower temporal areas where the OC responses arise the spherical model is less accurate. Another source of error when estimating the source locations and strengths of OC activity is the presence of multiple, nearby, temporally overlapping sources (Korvenoja *et al.*, 1999). Therefore, the activation patterns and source locations obtained for the OC sources in the present study must be considered only tentative. Realistically shaped conductor models and the use of data obtained with other functional imaging methods, such as fMRI, as constraints for ECD location estimation, will probably effectively reduce at least some of these errors in future studies.

The control group of the present study was relatively small and the interindividual variation of ECD parameters was considerable. Therefore, we chose to use relatively loose limits for normality (mean ± 2.5 SD). This is likely to diminish our sensitivity for detecting abnormalities. Also the variation of ECD parameters between two separate recording sessions using the same subject was quite large, and a number of N20m ECDs did not fall exactly on the central sulcus. These observations reflect the inaccuracy of our source localization procedures. In an experiment where an artificial dipole was placed in a model skull filled with saline the localization accuracy using a 7 channel gradiometer array was 3 mm (Yamamoto *et al.*, 1988). There are several factors that may have decreased our localization accuracy. First, it was not possible to absolutely stabilize the subject's head inside the magnetometer helmet. Also small inaccuracies in the localization of the cardinal points with the digitizer, as well as the use

of the spherical head model can add noise to the results. Sometimes the signal-to-noise ratio was also relatively poor. However, we considered that prolonging the recording session in acutely ill patients would increase the risk for head movements and thus be more harmful than the relatively small number of averages in our SEFs. Using a reclining position and on-line head-position measuring would probably greatly increase the accuracy of ECD source localization in studies performed on patients with major disease and therefore poor cooperation.

Overview

The present study was started with the aim of characterizing the basic electrophysiology of the somatosensory system in patients with unilateral ischemic stroke that causes disturbances in somatosensory and motor functions. In order to do this, it was essential to build up a normative database consisting of healthy subjects that would match with the patient group. The three first Studies of this Dissertation clarified some aspects of information processing in the somatosensory cortical areas of normal subjects and were based on recordings in the control group. In the following two Studies the relationship between somatosensory deficits and SEF abnormalities in stroke patients was investigated.

Our results confirmed and extended the previous investigators' findings on the ISI dependence of SI SEFs. Thus, P35m and P60m were strongly ISI dependent and attenuated significantly when the ISI was shortened from 5 to 1 s. Significant reduction in the N20m amplitude was seen only at an ISI of 0.15 s. N45 deflection tended to increase with shortening ISIs, however, this effect was not statistically significant. OCc and PPC responses deminished rapidly when the ISI was shortened.

The neuronal mechanisms underlying SEPs and SEFs have been poorly understood. However, it is generally agreed that N20 SEP and N20m SEF deflections are generated in area 3b pyramidal neurons. The comparison of our present findings with the previous results of several studies done using neocortical slice preparations or anesthetized experimental animals revealed a close resemblance between the ISI dependence of median nerve evoked responses and PSPs. More precisely, P35m and P60m attenuated toward shortening ISIs as did the primary and secondary cortical IPSPs. The relative stability of N20m regardless of the ISI resembled that of primary cortical EPSPs; N45m behaves much like the secondary cortical EPSP being enhanced toward shortening ISIs. Based on these considerations we presented a tentative model for SI SEF generation in which N20m reflects the summation of initial EPSPs in the pyramidal neurons of area 3b, P35m the subsequent IPSPs, N45m the secondary EPSPs, and P60m the secondary IPSPs. This model is, of course, hypothetical and overlooks the complexity of intracortical connections and the differences between experimental

animal preparations and intact human subjects, simplifies the termination patterns of thalamocortical afferents on pyramidal cells, and we can not offer direct evidence to support our view. Nevertheless, we consider that it would be worthwhile testing our model's validity, *e.g.*, by means of pharmacological interventions.

No sex-related differences in the source strengths of the SI SEFs were observed. Thus, we conclude that the kind of differences revealed by previous SEP studies are probably due to gender differences in the volume conductor's properties. The N20m deflection was stronger in older individuals than in younger. The growth of N20 probably reflects increased cortical excitability in older subjects.

Using data from 23 healthy subjects we built up a normative database from which we derived the limits for normality for the ECD parameters (*i.e.*, latency, coordinate values, and strength) in stroke patients. Although the normal interindividual and interhemispheric variation of the SEF parameters was considerable, we were able to distinguish clearly abnormal response patterns in several patients on the basis of our normal values.

Stroke causing dysfunction of discriminative touch was manifested as diminished SI SEFs in five of the eight patients who had reduced 2-point discrimination ability. The three remaining patients had lesions in the opercular cortex. In particular, the absence of N20m deflection was always associated with a lack of 2-point discrimination ability. Although a detectable N20m deflection was mandatory, it alone was not sufficient to ensure fully functional 2-point discrimination. Input from deep receptors or noci- and thermoceptors seemed to have a lesser impact on SI SEFs. As a combination of normal SI SEFs and absent 2-point discrimination was observed in three patients with opercular lesions, it appears likely that at least during the first few post-stroke days a relatively low-level somatosensory function such as 2-point discrimination may be dependent on the functionality of opercular somatosensory areas.

During a follow-up period of 2–3 months, the initially severely impaired 2-point discrimination ability recovered in 6/14 patients. This recovery was paralleled by the growth of P35m in five patients; in one of these patients N20m also grew. At group level, the amplitude of P35m grew significantly during the follow-up period, whereas that of N20m did not. We propose that the growth of P35m, reflects the re-establishment of inhibitory circuitry in the SI. Since in the ECD model enlargement of a cortical area that gives rise to a given SEF deflection is seen as an increase in the corresponding ECD strength, it is possible that the cortical area generating P35m had enlarged in those patients with enhanced P35m at follow-up.

Conclusion

The present study showed that magnetoencephalography can be used to bring forth new aspects of the functions of both normal and severed human brains that are not likely to be detected by other currently available functional imaging methods. We demonstrated that it is possible to find objective neurophysiological correlates to basic conscious perceptions such as 2-point discrimination ability. Our results indicate that defects in discriminative touch are reflected at a low level of somatosensory information processing, namely in the second cortical deflection of the median nerve SEF approximately 30 ms after the stimulation. Based on our and other investigators' findings with healthy subjects and animal models, we postulate that P35m reflects the initial inhibitory postsynaptic potentials in area 3b of the primary somatosensory cortex.

My sincere hope is that this study will be a step forward in the understanding of the functions and recovery mechanisms of the mature human brain and that our findings will prove beneficial to patients.

Acknowledgments

Now that I look back upon the 5 years during which I have worked in BioMag Laboratory of the Helsinki University Central Hospital, I find these years rewarding in many aspects. Science has been hard work, but above all, interesting and fun. My son was also born during this period. The laboratory started only one year before I begun working here. In the very beginning we were not a scientific community but merely a group of individuals working each on their own projects. Since then, the group has grown, and a warm and open atmosphere has developed.

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