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NEUROMAGNETIC STUDIES ON CORTICAL SOMATOSENSORY FUNCTIONS IN INFANTS AND CHILDREN – NORMAL DEVELOPMENT AND EFFECT OF EARLY BRAIN LESIONS

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ACADEMIC DISSERTATION

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ABBREVIATIONS

AH	Affected hemisphere
ANOVA	Analysis of variance
AS	Active sleep
CNS	Central nervous system
CP	Cerebral palsy
ECD	Equivalent current dipole
EEG	Electroencephalography
ELBW	Extremely low birth weight
EMG	Electromyography
EOG	Electro-oculography
FLAIR	Fluid-attenuated inversion recovery
fMRI	Functional magnetic resonance imaging
GABA	Gamma-aminobutyric acid
GW	Gestational week
ISI	Interstimulus interval
IVH	Intraventricular hemorrhage
MEG	Magnetoencephalography
MN	Median nerve
MRI	Magnetic resonance imaging
PPC	Posterior parietal cortex
PVL	Periventricular leukomalacia
QS	Quiet sleep
REM	Rapid eye movement
SD	Standard deviation
SEF	Somatosensory evoked magnetic field
SEP	Somatosensory evoked potential
SI	Primary somatosensory cortex
SIc	Contralateral primary somatosensory cortex
SIi	Ipsilateral primary somatosensory cortex
SII	Secondary somatosensory cortex
SIIc	Contralateral secondary somatosensory cortex
SIIi	Ipsilateral secondary somatosensory cortex
SQUID	Superconducting quantum interference device
SWS	Slow wave sleep
TMS	Transcranial magnetic stimulation
UH	Unaffected hemisphere
US	Ultrasound
WMD	White matter damage

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

I Lauronen L, Nevalainen P, Wikström H, Parkkonen L, Okada Y, Pihko E. Immaturity of somatosensory cortical processing in human newborns. NeuroImage 2006; 33: 195–203.

II Nevalainen P, Lauronen L, Sambeth A, Wikström H, Okada Y, Pihko E. Somatosensory evoked magnetic fields from the primary and secondary somatosensory cortices in healthy newborns. NeuroImage 2008; 40: 738–745.

III Nevalainen P, Pihko E, Metsäranta M, Andersson S, Autti T, Lauronen L. Does very premature birth affect the functioning of the somatosensory cortex? – A magnetoencephalography study. Int J Psychophysiol 2008; 68: 85–93.

IV Pihko E, Nevalainen P, Stephen J, Okada Y, Lauronen L. Maturation of somatosensory cortical processing from birth to adulthood revealed by magnetoencephalography. Clin neurophysiol 2009; 120: 1552–1561.

V Nevalainen P, Pihko E, Mäenpää H, Valanne L, Lauronen L. Bilateral abnormalities of somatosensory cortical processing in hemiplegic cerebral palsy. Submitted.

1. ABSTRACT

Background: Until recently, objective investigation of the functional development of the human brain *in vivo* was challenged by the lack of noninvasive research methods. Consequently, fairly little is known about cortical processing of sensory information even in healthy infants and children. Furthermore, mechanisms by which early brain insults affect brain development and later brain function are poorly understood. Deeper understanding of these phenomena is critical in order to provide the best possible care for infants and children with early brain lesions and those at risk for such insults and future neurological deficits.

Purpose and methods: In this thesis we used magnetoencephalography (MEG) to investigate the function of the somatosensory system of infants and children. The first studies on healthy individuals of different ages (newborns, infants, children, and adults) aimed at characterizing the normal developmental pattern of somatosensory evoked magnetic fields (SEFs) to stimulation of the hand area. We then applied this knowledge about normal neonatal SEFs and their development with age in two patient populations: very preterm infants at risk for neurological disorders and adolescents with hemiplegic cerebral palsy (CP).

Results: In newborns, stimulation of the hand activated both the contralateral primary (SIc) and secondary somatosensory cortices (SIIc). At both areas, the SEF characteristics differed from those of adults. While in adults the current orientation of the earliest SIc SEFs to median nerve (MN) stimulation quickly switches from anterior during the initial deflection to posterior during the second deflection, in newborns only an anteriorly pointing current source with a prolonged duration was detected at SIc. The same was present after tactile stimulation. Moreover, in newborns SIIc activity was enhanced during quiet sleep in contrast to the absence of SIIc responses during slow-wave-sleep in adults. After the newborn period, the early SIc SEF pattern systematically transformed with age, so that by age 2, the main early adult-like components were present.

In the very preterm infants, at term age the SIc and SIIc were activated at similar latencies as in the healthy fullterm newborns, but the SIc activity was weaker in the preterm group. In addition, the SIIc response was absent in four out of the six infants with brain lesions of the underlying hemisphere. In the CP adolescents, the types of underlying brain lesions included both subcortical as well as cortico-subcortical defects. In the patients with pure subcortical lesions, contrasting their unilateral clinical symptoms, the SIc SEFs of both hemispheres differed from those of controls. The distance between SIc representation areas for digits II and V was shorter and MN SEF morphology was altered, both bilaterally. In four of the five patients with cortico-subcortical brain lesions no normal early SEF components were evoked by stimulation of the palsied hand. The degree of alterations in MN SIc SEF, of all CP patients, correlated not only with lesion size and location on magnetic resonance images, but also with motor and tactile performance.

Conclusions: We showed in a relatively large number of newborn infants that somatosensory stimuli evoke activity at both the SIc and SIIc already a few days after fullterm birth. This demonstrates that the connections to and the neurons at these areas are developed enough to produce synchronous activation detectable extracranially. However, at this early age, the fundamental discrepancies between the cortical activation patterns in newborns and adults reflect the still developmental stage of the newborns' somatosensory system. Further maturation of the somatosensory system is manifested in the systematic change in the early SEFs during the first years of life. In the very preterm infants, the lack of the SIIc response, in particular, was associated with brain lesions. Determining the prognostic value of this finding remains a subject for future studies, however. In the patients with hemiplegic CP, the various uni- and bilateral SEF alterations reflect the complex nature of functional reorganization after an early brain insult. The wide spectrum of organization of sensorimotor functions underlying the common clinical symptoms, calls for investigation of more precisely designed rehabilitation strategies resting on knowledge about individual functional alterations in the sensorimotor networks.

2. INTRODUCTION

At the time of fullterm birth, development of the central nervous system (CNS) of a newborn infant is far from being complete. Transient fetal brain structures still exist (Kostovic and Rakic, 1990) and neurotransmitter systems are undergoing marked changes (Ben-Ari *et al.*, 2004; Herlenius and Lagercrantz, 2004; Dzhala *et al.*, 2005). Dendritic growth and synaptogenesis continue actively for months or even years after birth (Huttenlocher and Dabholkar, 1997; Gilbert, 2006), whereas myelination, axonal withdrawal, and synapse elimination can continue up to the second decade of life (Huttenlocher and Dabholkar, 1997; Gilbert, 2006). Due to the ongoing development of the CNS, early brain insults may result in different clinical outcomes than those in adulthood. The mechanisms underlying many developmental neurological deficits are, however, poorly understood because objective investigation of the functional development of the human brain *in vivo* has been difficult due to a lack of noninvasive investigation methods.

Most knowledge on the function of the somatosensory system in human infants and children comes from behavioral studies and recordings of somatosensory evoked potentials (SEPs) on the scalp with electroencephalography (EEG). Even in neonates, tactile object recognition has been explored with habituation paradigms (Streri *et al.*, 2000; Sann and Streri, 2008), whereas more precise techniques assessing different somatosensory modalities (*e.g.* pressure, proprioception, and thermal discrimination) separately are applicable in older children (Thibault *et al.*, 1994). The functional integrity of the somatosensory pathways has been studied with SEPs recorded from the scalp (Hrbek *et al.*, 1973; Desmedt *et al.*, 1976; Zhu *et al.*, 1987; Willis *et al.*, 1984; Laureau *et al.*, 1988; George and Taylor, 1991) and SEP abnormality has predicted future cerebral palsy (CP) (*e.g.* White and Cooke, 1994; Pike and Marlow, 2000). In recent decades, several new noninvasive brain research tools have revolutionized the field of neuroscience, but few studies have investigated infants or children. Magnetoencephalography (MEG) reflects, similar to EEG, cortical neuronal activation at a temporal resolution of millisecond scale. MEG, however, surpasses EEG in spatial domain as MEG is less sensitive to inhomogenities of the tissue between the active brain source and the extracranial measuring device, making source localization easier (Hämäläinen *et al.*, 1993). This is particularly advantageous in infants with open fontanels interfering with EEG source localization and age related skull thickness discrepancy complicating comparisons between age groups (Flemming *et al.*, 2005).

In this thesis we used MEG to explore somatosensory cortical function in newborns and infants. The aim was to characterize the typical features of newborn somatosensory evoked magnetic fields (SEFs) and their developmental course during the first years of life. This information was then utilized in further studies involving very preterm infants who are at risk for future neurological deficits and adolescents with hemiplegic cerebral palsy.

3. REVIEW OF LITERATURE

3.1. Magnetoencephalography (MEG)

3.1.1. Neural basis

Magnetoencephalography (MEG) signals are thought to mainly reflect synaptically induced intracellular currents flowing in the apical dendrites of cortical pyramidal neurons (Figure 1A). At chemical synapses, neurotransmitters mediate opening or closing of ion channels on the postsynaptic cell membrane resulting in current flux across the membrane (Kandel, 2000). At the site of an excitatory synapse, the net transmembrane current flow is directed into the cytoplasm locally depolarizing the originally negatively charged interior of the neuron. This site, where the positive current is directed inward, is called a *current sink*. From the current sink, the current flows along the dendrite to exit across the membrane at other sites, *current sources* (Figure 1B). At inhibitory synapses, neurotransmitter binding induces a current source at the site of the synapse resulting in local hyperpolarization of the postsynaptic neuron (Kandel, 2000). Cortical pyramidal cells receive excitatory input from, *e.g.*, subcortical structures and other pyramidal cells, whereas inhibitory input mostly comes from local interneurons. Excitatory synapses are usually axodendritic, while inhibitory synapses often lie on the cell body or at the base of an axon (DeFelipe *et al.*, 2002; Spruston, 2008).

From a distance the net intracellular currents seem like current dipoles oriented along the dendrites (Hämäläinen *et al.*, 1993). MEG signals are proportional to the magnitude of this net intracellular current, whereas the influence of the transmembrane current is negligible and that of the return passive-current very small. Traditionally, the dendrites were considered passive cable-like structures and consequently, the intracellular currents as passive products of the postsynaptic potentials. A recent series of studies, however, indicates that various active conductances (*i.e.* voltage- and calcium-dependent ion channels) on the dendrites and soma of cortical neurons also play a role in shaping neuronal activity and, hence, the temporal waveform of MEG signals (Okada *et al.*, 1997; Wu and Okada, 1998; 1999; 2000; Murakami *et al.*, 2002; 2003, Murakami and Okada, 2006).

In vivo MEG measurements reflect brain activity at the level of neuron populations. Activity of cortical pyramidal cells is effectively summated, because their apical dendrites are arranged in parallel with each other towards the pial surface (Figure 1B). On the contrary, non-pyramidal cells possessing more randomly oriented dendritic trees form electrically closed fields and contribute little to MEG signal. As the dipole moment for a single pyramidal cell is on the order of 0.2 pAm (Murakami and Okada, 2006), synchronous activity of tens of thousands of pyramidal neurons produces current dipoles with extracranially recordable moments on the order of 10 nAm (Hämäläinen *et al.*, 1993). The summation of postsynaptic potentials lasting tens of milliseconds is also temporally effective. On the contrary, although the voltage changes during action potentials are significantly greater than those associated with postsynaptic potentials, action potentials

contribute little to MEG signal, because of poor temporal summation due to their short duration of 1 ms. In addition, the magnetic field of a quadrupolar action potential more rapidly falls off with distance than that of a current dipole.

It should be noted that the net direction of the intracellular current flow (towards pia *vs.* towards the white matter) depends on the site of the initial current sink/source on the pyramidal cells. Even in the oversimplified "cable model", the orientation of an intracellular dipole formed by an active sink (excitation) at the distal end of an apical dendrite would equal that formed by an active source (inhibition) at the somatic end of the dendrite (Figure 1B). Furthermore, considering the active conductances on dendrites, it is evident, that the nature of the synaptic activity, excitatory *vs.* inhibitory, can not be determined solely based on extracranial signals.

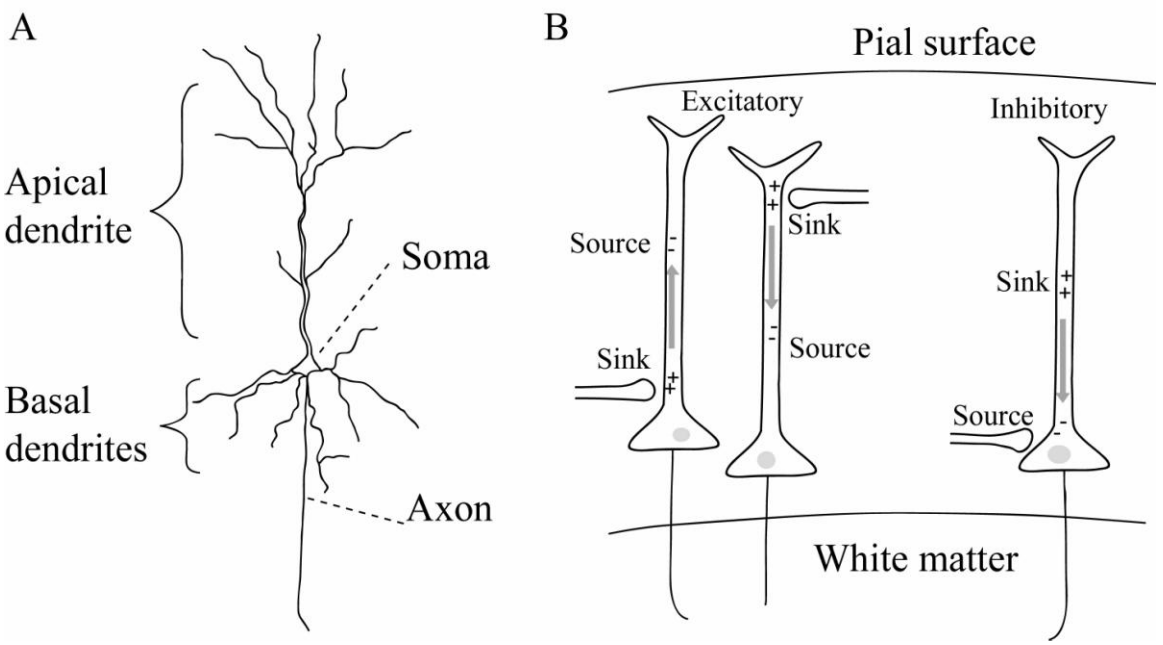

Figure 1. A) A schematic illustration of a pyramidal neuron. B) Direction of the intracellular current flow induced by excitatory synapses located at different portions of the apical dendrite and an inhibitory synapse located on the soma of pyramidal cells with "passive dendrites". The transmembrane currents and return-passive currents are not shown.

3.1.2. Theoretical background of modeling MEG signals

An electric current flowing inside a conductor produces a magnetic field detectable outside the conductor. In MEG, the activity dynamics of populations of cortical neurons are investigated by recording the magnetic fields outside the head. The distribution of the primary neuronal currents inside the head, however, cannot be uniquely determined from these extracranial magnetic fields. Therefore, some preconditions are necessary for

successful analysis of neuromagnetic data. All MEG source modeling approaches are based on a comparison of the measured data and that predicted by a model. In many situations, accurate estimates are obtainable by considering the brain as a spherical conductor, which simplifies further calculations. In a spherical conductor, currents oriented radially with respect to the sphere surface or located in the center of the sphere do not produce an external magnetic field. For MEG this means that neuronal currents oriented tangentially with respect to the skull, *i.e.*, fissural sources, have the greatest influence on the recorded signal (For a review, see Hämäläinen *et al.*, 1993).

The classical source model for MEG is the equivalent current dipole (ECD), which is useful in situations where the neuronal activation is restricted to a small area of the cortex. Such activity can be represented as a current dipole at the center of gravity of the active source. The magnitude, direction, and location of the ECD are estimated with the least squares search, which finds the set of parameter values that minimizes the difference between the measured magnetic fields and the fields predicted by the model. The ECD model performs well even when multiple sources are active simultaneously, as long as they are relatively far away from each other (Hämäläinen *et al.*, 1993).

3.1.3. Instrumentation

The weak extracranial magnetic signals are detected with sensors composed of a superconducting flux transformer connected to a SQUID (Superconducting QUantum Interference Device), which is a superconducting ring interrupted by two Josephson junctions. To maintain the superconductivity, the sensors are kept in liquid helium. In addition to the brain signal, the sensors pick up environmental noise, which can be several orders of magnitude higher than the brain signal. Therefore, the measurements are generally conducted in a magnetically shielded room. Additional noise cancellation can be obtained with certain flux transformer configurations. (Hämäläinen *et al.*, 1993)

The simplest flux transformer configuration is the magnetometer, which has a single pick-up coil (Hämäläinen *et al*., 1993). Magnetometers measure the magnetic field component perpendicular to the plane of the pick-up coil and, thus, give two response maxima with opposite field directions on opposite sides of a small dipolar source. In addition to nearby sources, magnetometers are also sensitive to sources further away. The sensitivity to such distant, often interfering, sources can be decreased with gradiometric configuration having an additional compensation coil used to cancel far-away interference sources manifesting themselves as homogeneous magnetic fields. The pick-up and compensation coils of a gradiometer can be arranged, *e.g.*, along the same radial axis with the former closer to head surface (axial gradiometer) or side by side in the same plane (planar gradiometer). Planar gradiometers measure the change of the field component along the plane and, consequently, show maximal responses just above source areas, whereas the axial gradiometers measure the change of the radial field component resulting in two opposite maxima in a similar manner to magnetometers (Hämäläinen *et al.*, 1993). The MEG recordings of this study were performed with a whole-head helmet-shaped sensor array consisting of 306 independent sensors: 204 planar gradiometers and

102 magnetometers (Elekta Neuromag®, Elekta Oy, Helsinki, Finland). Additionally, four of the infants of Study IV were measured with a pediatric MEG prototype 'babySQUID' (Okada *et al.,* 2006), which has 76 first-order axial gradiometers.

3.1.4. The role of MEG within the field of current brain research

At present, a number of noninvasive brain research tools are available, but none is superior to the others both in time and space. Functional magnetic resonance imaging (fMRI) has an excellent spatial resolution, but does not allow accurate investigation of the fast temporal dynamics of the brain networks due to the slowness of the hemodynamic changes it reflects. MEG and EEG, which both reflect electrical currents in the brain, provide the best temporal accuracy. They have, however, important differences making them too complementary to each other. While MEG is insensitive to strictly radial currents, EEG reflects currents of all orientations. MEG is, however, well-suited for investigation of areas within walls of sulci, which are difficult to reach with other electrophysiological means, including invasive intracranial recordings (Hari *et al.,* 2010). Furthermore, inhomogenities between the active brain source and the measuring device smear the EEG distributions, while MEG is practically transparent to them (Hämäläinen *et al.,* 1993). This is particularly advantageous in infants with open fontanels (Okada *et al*., 1999; Flemming *et al.,* 2005). Nevertheless, to date MEG studies in infants are scarce, and development of devices particularly designed for infant studies has only advanced in recent years (*e.g.,* Okada *et al.,* 2006; Adachi *et al.,* 2010).

3.2. The somatosensory system

3.2.1. Functional anatomy in adults

The sense of touch is mediated from the skin mechanoreceptors via presynaptic dorsal root ganglion neurons, to target structures of the central nervous system (CNS). Some branches of these first order afferents terminate within the spinal grey matter to form local reflex circuits. Others carry the information cranially in the ipsilateral dorsal columns of the spinal cord to the gracile and cuneate nuclei of the medulla (Figure 2). Projections from these medullary nuclei cross to the contralateral side in the brain stem and continue via the contralateral medial lemniscal pathway to the ventroposterior complex of the thalamus. The thalamocortical axons then project through the internal capsule to the contralateral primary somatosensory cortex located in the postcentral gyrus of the anterior parietal lobe (Figure 2) (Kandel, 2000).

The primary somatosensory cortex (SI) consists of four distinct areas known as the Brodmann's areas 3a, 3b, 1, and 2 (Figure 2). Cutaneous information is mainly processed in areas 3b and 1, and proprioceptive information in area 3a. Area 2 is thought to integrate the two types of information (Hsiao, 2008). Each area of SI contains a complete representation of the body, a somatotopical map (Figure 2). The areas of the body with the highest density of mechanoreceptors (*e.g.* digits and lips) proportionally capture the

largest areas at SI (Kandel, 2000). Neurons at areas 3b and 1 have exclusively contralateral receptive fields, except for those representing areas in the body midline, such as the face and oral cavity. Part of the area 2 neurons may, however, have bilateral receptive fields even in the hand area. The most likely pathway for the ipsilateral cortical input is through the corpus callosum, whereas no evidence supports straight ipsilateral connections from the periphery to the primary somatosensory area. Again an exception is the trigeminal area, which may also be bilaterally represented at the level of the thalamus (Iwamura, 2000). In the vertical dimension, the neocortex, including the somatosensory area, is arranged into 6 layers (Kandel, 2000). Layer I, the most superficial layer, contains mostly dendrites of cells in the deeper layers as well as axons of cells located in other areas of the cortex. Layers II and IV are comprised of non-pyramidal granule cells, whereas layers III and V contain pyramidal cells. Layer VI is more heterogeneous (Kandel, 2000).

In addition to the four densely interconnected areas of SI, many higher order association areas participate in processing of somatosensory information. The secondary somatosensory cortex (SII) is located at the lateral end of the postcentral gyrus on the upper bank of the Sylvian fissure. SII neurons have large, bilateral receptive fields (Whitsel *et al.*, 1969) and it has been suggested to integrate information from the two body halves (Simoes and Hari, 1999; Simoes *et al.*, 2001). In addition, the SII has been linked with integration of somatosensory and motor information (Huttunen *et al.*, 1996; Forss and Jousimäki 1998), haptic size and shape perception (Hsiao, 2008), and tactile learning and memory (Ridley and Ettlinger, 1978). Moreover, SII is consistently activated by painful stimuli such as laser (for a review see Garcia-Larrea *et al.*, 2003).

Somatosensory information is also processed at the posterior parietal cortex (PPC), located posterior to the SI and including Brodmann's areas 5 and 7. PPC has connections to dozens of cortical regions and subcortical structures, and serves a variety of complex functions (Hyvärinen, 1982). In monkeys, area 5 neurons are activated by somatosensory stimuli as well as movements (Mountcastle *et al.*, 1975; Arezzo *et al.*, 1981) and area 7 neurons respond to somatosensory and visual stimuli (Hyvärinen, 1982). Thus, PPC is involved with gross-modal integration of somatosensory and visual information (Sack, 2009) and construction of a reference system of personal and extrapersonal space, to be used in guiding goal-directed movements (Hyvärinen, 1982). Accordingly, in humans lesions of these areas may cause, *e.g.*, misreaching for targets and a deficit called *sensory neglect*, in which information from the contralateral body half and visual space is disregarded despite intact somatic and visual senses.

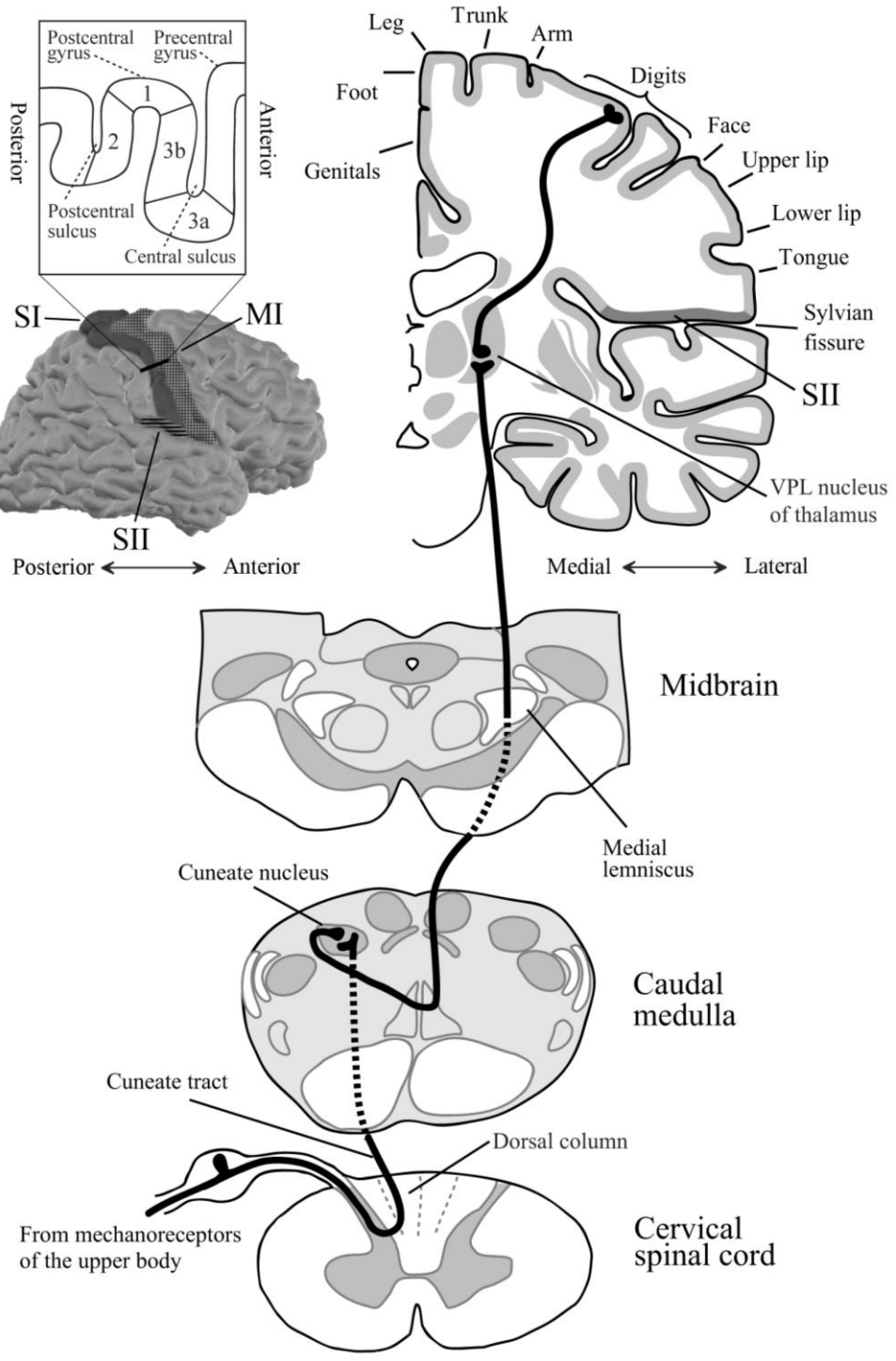

Figure 2: Below: the dorsal column-medial lemniscal pathway mediating the sense of touch. Information from the hand is mediated by the cuneate tract and nucleus. The somatotopical organization of the SI and the location of the SII on the upper lip of the Sylvian fissure are shown on the right. Up left: The primary somatosensory cortex (SI), primary motor cortex (MI), and secondary somatosensory cortex (SII) shown on a 3D reconstruction of the brain. In the insert: the four cytoarchitectonic areas of the SI. (SI = primary somatosensory cortex, SII = secondary somatosensory cortex, MI = primary motor cortex, VPL = ventral posterior lateral)

3.2.2. Development

3.2.2.1. The neocortex

The development of the central nervous system (CNS) begins in the process of neurulation when the neural plate transforms into the neural tube. Thereafter, the cranial part of the neural tube bulges to form the primary and secondary vesicles of the brain (Gilbert, 2006). The neural tube is originally composed of a one-cell-layer-thick germinal neuroepithelium, *i.e.*, the ventricular zone, the proliferative cell layer of the embryo (Bystron *et al.*, 2008). The cortical plate, which will eventually develop into the neocortex, is visible by the 12th gestational week (GW)[1] (Radoš *et al.*, 2006). During the next two to three weeks, two new layers become distinguishable below the cortical plate: a transient fetal structure called the subplate and the intermediate zone, which will form the cortical white matter (Bystron *et al.*, 2008). The subplate is suggested to serve as a "waiting compartment" for the thalamic and other nerve afferents and as a fetal circuitry compartment for potential interactions between these afferents and subplate neurons. Below the future SI, the subplate forms at around the 14th and 15th GW. Thereafter, it grows in thickness due to accumulation of afferent axons. It is the most prominent fetal layer during late second and early third trimester and at its thickest four times thicker than the cortical plate. Thereafter, it starts dissolving towards the end of the third trimester, being mostly resolved around the end of the first postnatal month below the SI (Kostović and Rakić, 1990).

Lamination of the cortical plate into the six distinct layers begins around the end of the second trimester in an inside out manner. The earliest born neurons form the deepest cortical layer (layer VI) and the last born ones the superficial layer II. The outermost layer I originates from the marginal zone (Bystron *et al.*, 2008). By fullterm age, most cortical neurons have attained their destinations at the different cortical layers (Kostović *et al.*, 1995). Laterally the cortex is organized into over 40 histologically and functionally distinct regions. The mechanisms regulating this area patterning include intrinsic genetic factors as well as extrinsic influences relayed to the cortex via thalamocortical afferents (O'Leary *et al.*, 2007). Folding of the cerebral sulci and gyri begins during the 3rd trimester. By the end of the 24th GW the basic sulcal pattern has been delineated and the central sulcus is visible (Holmes, 1986). Further folding of sulci and gyri, however, continues throughout the third trimester.

[1] GW, used in clinical practice, is traditionally calculated from the first day of the last menstruation, but presently determined by ultrasound scans during pregnancy. Gestational age is, thus, 2 weeks higher than the age calculated from conception.

3.2.2.2. Thalamocortical connections

By the 12th to 15th GW, three CNS fiber systems are recognizable in both histological and MRI sections: the corpus callosum, the fornix, and the cerebral stalk, a massive connection between the diencephalon and telencephalon containing all projection fibers of the internal capsule, including the thalamocortical afferents (Radoš *et al.,* 2006). In the primary somatosensory areas, the thalamic axons grow through the subplate between the 17th and 26th GW accumulating into its superficial parts at around the 23rd to 25th GW (Kostović and Rakić, 1990; Kostović *et al.*, 1995). During the early preterm period (26th–34th GW), these axons grow into the cortical plate forming the first thalamocortical connections, and thus constituting the anatomical pathway for sensory impulses from the periphery to the cortex before term. After the 35th GW, also the long corticocorticals (*e.g.* callosal fibers) grow into the cortical plate (Kostović and Jovanov-Milošević, 2006). Fairly little is known about further development of cortical connections in the neonatal period. Presumably, growth of the long afferents and long corticocortical connections ceases, but that of short corticocortical connections continues even several months postnatally (Kostović and Jovanov-Milošević, 2006). Initially, there is marked overproduction of axonal connections which will then be withdrawn during later development (Innocenti and Price, 2005).

3.2.2.3. Synaptogenesis

Dendritic growth begins during the 2nd trimester. It proceeds earlier for the cortical pyramidal neurons of layer V, followed by cells in the more superficial layers (Marin-Padilla, 1970; Mrzljak *et al.,* 1992). The first synaptic contacts appear above and below the developing cortical plate already by the 11th GW and thereafter the number of synapses increases progressively. Beginning at around the 25th GW synapses, including contacts from the thalamocortical afferents, are gradually transferred to different layers of the cortex (Molliver *et al.,* 1973). Several animal studies suggest that the first functional synapses on cortical pyramidal cells use gamma-aminobutyric acid (GABA) as their neurotransmitter (Ben-Ari *et al.,* 2004) and $GABA_A$ type receptors (Herlenius and Lagercrantz, 2004). In the adult CNS, GABA is a common inhibitory neurotransmitter. At early stages of development, however, $GABA_A$ receptor activation leads to depolarization of the postsynaptic neuron, due to a high intracellular Cl^- concentration. Thus, these earliest synapses are initially excitatory (Ben-Ari *et al.,* 2004). The early excitatory actions of GABA have been suggested to be a requirement for later excitatory glutamatergic synapse development (Wang and Kriegstein, 2008).

The period of active synaptogenesis exhibits different time courses at different cortical regions, continuing for several years postnatally in some areas (Huttenlocher and Dabholkar, 1997). It starts during the 2nd trimester from the primary sensory areas and proceeds towards higher order areas, following the course of myelination. Synaptogenesis seems to be originally intrinsically regulated and relatively random, whereas stabilization and elimination of synapses is activity dependent. Thus, marked overproduction of synapses occurs during development and, after a postnatal plateau period, the number of synapses decreases to only 60% of the maximum during the first two decades of life. The

synapses that are not included in neuronal circuits are gradually eliminated (Huttenlocher and Dabholkar, 1997).

3.2.2.4. The brain and somatosensory system of a newborn

In conclusion, at the time of fullterm birth, the anatomical substrate for somatosensory information to reach the cerebral cortex exists. In many ways, the development of the CNS, however, is incomplete at fullterm age. The subplate zone is dissolving but still exists, the neurotransmitter systems are undergoing marked changes, and the organization of cortical circuits is in progress. During the first postnatal months, synaptogenesis and establishment of short corticocortical connections are at their busiest. Developmental strengthening of appropriate cortical circuits, activity dependent elimination of synapses, and axonal withdrawal continue along with myelination for several years after birth.

3.3. Preterm infants

According to the World Health Organization (WHO) International Classification of Diseases, the term "preterm infant" refers to being born before completing the 37^{th} gestational week (GW) and "extremely immature" before completing the 28^{th} GW. Low birth weight refers to a birth weight between 1000 and 2499 g and "extremely low birth weight" (ELBW) to a birth weight of 999 g or less (WHO, 2007). According to the National Birth Register in Finland, 59 808 infants were born in 2008. Of these, 5.7% were born <37 GW, 1% <32 GW, and 0.4% <28 GW (Vuori and Gissler, 2009).

The increased survival of the extremely preterm infants is one of the greatest achievements of contemporary neonatal medicine (Vohr *et al.*, 2005). Many of these infants develop with neurological impairments, however. Preterm birth associates with increased morbidity in several areas. Pulmonary problems account for most deaths with respiratory distress syndrome being the leading cause (Wilson-Costello *et al.*, 2005). Later disabilities involve deficits in sensorimotor development, cognition, vision, and hearing (Marlow *et al.*, 2005; Mikkola *et al.*, 2005). Risk factors for adverse neurological outcome include periventricular leukomalacia (PVL), severe intraventricular hemorrhage (IVH), sepsis, bronchopulmonary dysplasia, and use of postnatal steroids (Vohr *et al.*, 2005; Mikkola *et al.*, 2005). In current clinical practice, cranial ultrasound scans are performed in the neonatal period to identify neonates at risk for neurodevelopmental deficits (Neil and Inder, 2004). An unfavorable prognosis is associated with IVH of grades III and IV and cystic PVL. On the other hand, many preterm infants with normal cranial ultrasound scans also have adverse outcomes (Laptook *et al.*, 2005). At term, moderate to severe white matter abnormalities in MRI predict cognitive and motor dysfunction (Woodward *et al.*, 2006).

The adverse neurological outcome in preterm infants is caused by a complex combination of primary destructive events and secondary maturational and trophic disturbances (Volpe, 2009a; 2009b). Approximately 90% of the neurological deficits in the preterm survivors

are now caused by white matter damage (WMD) (Khwaja and Volpe, 2008). It may include focal necrosis of the deep white matter (loss of all cellular elements) and a more diffuse injury in the central cerebral white matter (Figure 3). The focal necroses may be macroscopic forming cysts (cystic PVL) or microscopic (non-cystic PVL), the latter being significantly more common. A third form of WMD only encloses the diffuse component. The sites of focal necrosis are located at arterial border and end zones in the periventricular white matter. Low physiological blood flow to the white matter and its impaired autoregulation in preterm infants increase the risk of hypoxia and ischemia in these areas (Khwaja and Volpe, 2008). Moreover, WMD is accompanied by previously unrecognized neuronal and axonal loss in the cerebral white matter, thalamus, basal ganglia, cerebral cortex, brainstem, and cerebellum (Volpe, 2009a).

IVH originates from the ventricular zone (*i.e.* germinal matrix), which is still functionally active extrauterinally in preterm infants. Because of the impaired regulation of the cerebral blood flow and mechanical fragility, this highly vascularized area, located subependymally and beside the lateral ventricles, is prone to hemorrhage. The hemorrhage and associated periventricular hemorrhagic infarctions may then lead to destruction of the white matter and significant tissue loss, interruption of thalamocortical fibers, and impaired development of the overlying cortex (Volpe, 2009a).

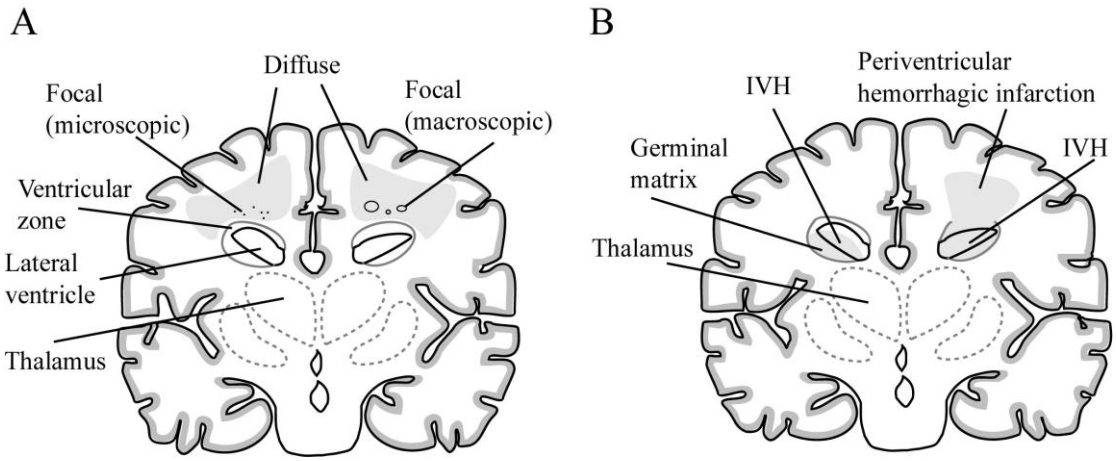

Figure 3. Schematic images displaying the typical brain areas injured in preterm infants. A) White matter damage (WMD): macroscopic (cystic PVL) and microscopic (non-cystic PVL) focal components as well as areas of diffuse injury. B) Intraventricular hemorrhage (IVH) originating from the germinal matrix with and without periventricular hemorrhagic infarction.

3.4. Cerebral palsy (CP)

3.4.1. Overview

Cerebral palsy (CP) is a persistent disorder of movement and posture caused by a non-progressive lesion of the developing brain. It is a symptom complex with a multifactorial etiology rather than a specific disease. In Europe, the incidence of CP was 2 to 3 per 1000 live-born infants in the year 2000 (Cans *et al.,* 2000). The incidence of CP depends on birth weight and gestational age (Pharoah *et al.,* 1998; Vohr *et al.,* 2005) and presently preterm infants constitute a considerable proportion of the children diagnosed with CP annually. In a recent study, 11% of infants born before 32nd GW and 18% of the ones born before 27th GW developed CP (Vohr *et al.,* 2005). A recent Finnish study reported rates of 14% in ELBW infants in total and 19% in ELBW infants born <27th GW (Mikkola *et al.,* 2005).

In most CP patients, several risk factors as well as prenatal, perinatal, and postnatal events account for the disability. In preterm infants, PVL or IVH are the most common types of brain pathology underlying CP (Vohr *et al.,* 2005). Corticospinal and thalamocortical tracts pass close to the affected areas and are prone to injury (Figure 3). In fullterm infants, the etiological causes include malformations, infections, vascular episodes, and head injury (Cans *et al.,* 2004). CP can be classified into spastic, dystonic, ataxic, dyskinetic, and choreoathetotic forms based on the predominant movement constraint. These are further grouped according to the affected extremities (mono-, di-, hemi-, and quadriplegia) (Cans *et al.,* 2000). The diagnosis of CP is often delayed. Clinical symptoms may not be detectable until 6 months to 2 years of age in infants who develop hemiplegia. In some, even deterioration and loss of pre-existing skills occurs (Bouza *et al.,* 1994).

3.4.2. Organization of the sensorimotor system in hemiplegic CP

During normal development in humans, the corticospinal axons reach the lower cervical spine by the 26th GW and extensive innervation of spinal neurons, including monosynaptic innervation of motoneurons, occurs before fullterm birth (Eyre *et al.,* 2000). It seems that this corticospinal motor innervation is originally bilateral, and in normally developing children, the ipsilateral connections are mostly withdrawn during the first two years of life (Eyre *et al.,* 2001). After an early unilateral brain insult, the motor representation may organize either in the normal location at the contralateral hemisphere, *i.e.,* ipsilesionally, or at the ipsilateral hemisphere, *i.e.,* contralesionally, depending on the timing, location, and extent of the lesion (Staudt *et al.,* 2002; 2004; 2006; Eyre, 2007). The mechanism for preservation of the ipsilateral corticospinal projections may involve activity-dependent competition for spinal synaptic space (Eyre, 2007). In several infants who had suffered a unilateral perinatal stroke (either arterial or venous infarction), motor evoked potentials (MEPs) elicited in the muscles of the contralateral arm by transcranial magnetic stimulation (TMS) of the affected hemisphere were reduced systematically with age. Eventually, the contralateral MEPs that were present right after the insult gradually disappeared during the first 2 years of life whereas the ipsilaterally (*i.e.* from the

unaffected hemisphere) evoked MEPs persisted in the palsied hand (Eyre *et al.,* 2007). This gradual withdrawal of normal contralateral connections and preservation of ipsilateral connections to the palsied hand may also account for the delayed manifestation of signs of hemiplegia and loss of acquired motor skills in some children (Eyre *et al.,* 2007). The type of reorganization (normal contralateral *vs.* preserved ipsilateral) is strongly associated with neurological outcome. Normal hand motor control is only attained when the normal contralateral connections persist, whereas ipsilateral motor representation is associated with more severe motor impairment and mirror movements of the paretic hand (Staudt *et al.,* 2002; Eyre *et al.,* 2007).

On the contrary, primary somatosensory representation has generally remained in the ipsilesional hemisphere, even in patients with contralesionally organized motor representation (Staudt *et al.,* 2004; 2006; Guzzetta *et al.,* 2007). In such patients, the somatosensory thalamocortical tracts are indeed able to bypass the white matter lesions as demonstrated with magnetic resonance diffusion tractography (Staudt *et al.,* 2006). The fiber count in the thalamocortical somatosensory tract in hemiplegic CP patients, however, may be reduced (Thomas *et al.,* 2005). The differences between reorganization patterns of motor and somatosensory systems are suggested to arise from distinct developmental time courses of thalamocortical and corticospinal connections (Kostović and Judaš, 2002; Staudt *et al.,* 2006).

3.5. Somatosensory evoked responses

The term "evoked response" signifies a temporary change in the electrical activity of the brain induced by an external stimulus. This change can be detected extracranially with MEG which records evoked magnetic fields.

3.5.1. Somatosensory evoked magnetic fields (SEFs) to stimulation of the hand area in adults

In adults, the earliest cortical activation after somatosensory stimulation is detected at the contralateral primary somatosensory cortex (SIc). Depending on the site of peripheral stimulation, the location of the activated source varies according to the somatotopical organization of SI. The first ever SEF study already reported the source to thumb stimulation to be approximately 2 cm more lateral than that of little finger stimulation (Brenner *et al.,* 1978). Thereafter, SI somatotopy has been repeatedly demonstrated with MEG (Baumgartner *et al.,* 1991; Hari *et al.,* 1993; Yang *et al.,* 1993; Nakamura *et al.,* 1998). The hand representation area is located posterior to the omega-shaped curvature of the central sulcus with the fingers occupying a 15–20 mm strip in the postcentral gyrus (Okada *et al.,* 1984; Baumgartner *et al.,* 1991; Hari *et al.,* 1993; Hari and Forss, 1999). The somatotopical map shows remarkable plasticity after changes in peripheral input. MEG has been able to detect its remodeling after, *e.g.,* amputations (Flor *et al.,* 1995) and surgical separation of originally fused fingers in patients with syndactyly (Mogilner *et al.,* 1993).

After median nerve (MN) stimulation, the SIc SEF response consists of several components: N20m, P35m (sometimes referred to as P30m), and P60m (Figure 4). All these components have dipolar field patterns: the N20m equivalent current dipole (ECD) points anteriorly, whereas the P35m and P60m ECDs point posteriorly. The N20m is considered the analogue of the N20 SEP, the earliest cortical SEP component thought to reflect the initial excitatory thalamic input to Broadman's area 3b of SI, and more specifically, the depolarization of layer III pyramidal cell bodies and their proximal apical dendrites (Allison *et al.,* 1989; Allison *et al.,* 1991b). A recent current source-density analysis conducted in anesthetized piglets, however, revealed two dipolar generators underlying the peak of N20/N20m, both directed towards the cortical surface. After the arrival of the initial thalamocortical volley in layer IV, the current sink of the first generator shifted towards more superficial layers (II–III) and the sink of the second generator to layer V (Ikeda *et al.,* 2005). Thus, the generation mechanism of the human N20m may also still need to be further detailed.

The cell level generation mechanisms of the P35m and P60m are not well understood. According to one theory (Huttunen and Hömberg, 1991; Wikström *et al.,* 1996; Restuccia *et al.,* 2002; Huttunen *et al.,* 2008), inhibitory postsynaptic potentials play a critical role in the generation of the P35m. This suggestion is based on similar recovery times of excitatory and inhibitory synapses and the N20m and P35m SEFs, respectively (Wikström *et al.,* 1996), as well as pharmacological manipulations (Huttunen *et al.,* 2001; 2008). Interestingly, patients with Angelman syndrome, caused by a deletion in the gene coding one of the $GABA_A$ receptor subunits, lack the P35m response (Egawa *et al.,* 2008). Another theory proposes excitation of distal portions of the apical dendrites as the generation mechanism of the P30 SEP, the analog of P35m SEF (Allison *et al.,* 1989; 1991b). Furthermore, the more anterior location of the P35m, than N20m ECD, has led to a suggestion of contribution from the primary motor area (MI) (Kawamura *et al.,* 1996; Porcaro *et al.,* 2008). Excision of MI does not, however, affect N20-P30 SEPs (Allison *et al.,* 1991a), whereas they are completely abolished by SI excision (Allison *et al.,* 1991a) or lesion (Sonoo *et al.,* 1991). Furthermore, since ECDs estimate the center of gravity of the activation, an extended activated area along the omega-shaped hand section of the central sulcus may explain the more anterior location of P35m ECD, (Huttunen, 1997).

The generation mechanisms underlying the P60m are probably even more complex and many closely located areas are likely to contribute (Huttunen *et al.,* 2006). Contribution from area 2 in the postcentral sulcus was suggested due to a slightly more posterior location of P60m ECD compared to N20m ECD (Huttunen *et al.,* 2006). Furthermore, the two responses, P35m and P60m, clearly react differently to some situations, despite their similarities in current orientation, interstimulus interval (ISI) dependence (Wikström *et al.,* 1996), and response to certain pharmaceuticals (Huttunen *et al.,* 2001; 2008). In a paired pulse paradigm, P60m completely recovered with a 100-ms ISI, whereas the P35m was strongly attenuated (Huttunen *et al.,* 2008). In addition, patients with pediatric degenerative CLN5 disease (a Finnish variant of late infantile neuronal ceroid lipofuscinoses) have giant N20m and P35m SEFs, whereas the P60m is nonexistent (Lauronen *et al.,* 2002).

Compared with MN SEFs from the SIc, electrical stimulation of fingertips elicits SEFs at SIc with similar morphology (N20m-P35m-P60m), but with approximately 4 ms longer latency due to the more distal stimulation site (Kaukoranta *et al.,* 1986). Also after airpuff or tactile stimulation of the fingers, the initial response at around 30 ms (referred to as M30 in this thesis) is generated by an anteriorly pointing dipolar source (Forss *et al.,* 1994b; Lauronen *et al.,* 2006; Pihko *et al.,* 2009), which in some subjects is too weak for ECD modeling (Biermann *et al.,* 1998; Mertens and Lütkenhöner, 2000; Simões *et al.,* 2001). M30 is likely to correspond to the MN N20m, and thus represent the earliest thalamic input to SI. The most prominent tactile SEF response is, however, the deflection following the M30 at around 45 to 50 ms with an underlying ECD pointing posteriorly (Biermann *et al.,* 1998; Mertens and Lütkenhöner, 2000; Simoes *et al.,* 2001; Nevalainen *et al.,* 2006). We will refer to this deflection as M50 according to its approximate latency in our studies. Though M50 can not be considered the exact analog of the MN P35m, similar mechanisms are likely to underlie the two responses as the ECD properties are very similar (Mertens and Lütkenhöner, 2000). The weaker amplitude of the tactile SEFs from the SIc, compared to MN SEFs, is explained by the smaller amount of activated afferents, though stimulation jitter may also play a role (Mertens and Lütkenhöner, 2000). The commonly found latency delay of tactile *vs.* electrically elicited SEFs and SEPs (after accounting for the more distant stimulus site, when comparing to MN at the wrist) may arise from the mechanoreceptor transduction time and slower conduction velocity of cutaneous afferents (*e.g.* Nakanishi *et al.,* 1973; Hashimoto, 1987) or a longer stimulus rise time as suggested by Hashimoto (1988).

In healthy adults, stimulation of the hand area does not generally evoke SEFs at the ipsilateral SI (SIi) (*e.g.* Hari and Forss, 1999), though exceptions exist (MN stimulation: Korvenoja *et al.,* 1995; Kanno *et al.,* 2003; tactile stimulation: Zhu *et al.,* 2007; Pihko *et al.,* 2010). Furthermore, the early SIc MN responses are not affected by preceding stimulation to the MN of the other hand (with 20−120 ms ISI), indicative of little to no interaction of the responses from the two hands at SI. On the contrary, such conditioning stimulus to the median or ulnar nerve of the same hand causes attenuation of most SIc responses (Huttunen *et al.,* 1992). Finally, contamination from the contralateral hand could also explain the occasional detection of SIi SEFs (Hari and Imada, 1999). In certain patient populations, however, SIi SEFs are frequent and may reflect increased interhemispheric spread of cortical excitation. In fact, presence of SIi SEFs correlated with the tendency for generalized seizures in patients with the Unverricht-Lundborg type of progressive myoclonus epilepsy (Forss *et al.,* 2001). Also, intracranial SEP recordings in epilepsy patients evaluated for surgery have revealed weak activity at the SIi, but not necessarily area 3b, in a minority of patients (Noachtar *et al.,* 1997).

In contrast to the SI, as most SII neurons have bilateral receptive fields, SEFs are commonly recorded from both hemispheres after unilateral stimulation (Hari *et al.,* 1983; 1984; Hari and Forss, 1999). SII activity peaks at 60 to 80 ms after MN stimulation, often slightly earlier in the contralateral SII (SIIc) (Hari and Forss, 1999). SII responses are more variable and, in general, more dependent on the experimental set-up and vigilance state of the subject than SI responses. For example, changes in stimulation frequency more

easily affect SII than SI responses (Hari *et al.*, 1990; 1993; Wikström *et al.*, 1996; Hamada *et al.*, 2003). Moreover, inputs from the two hands strongly interact at the SII (Simões and Hari, 1999) as demonstrated by attenuation of SII responses after simultaneous (Shimojo *et al.*, 1996) or alternating stimulation (ISI 1.5 s) of the bilateral MNs (Wegner *et al.*, 2000). Furthermore, attending to the stimulus enhances the SII SEFs, whereas they diminish during sleep stages S1 and S2 (Kitamura *et al.*, 1996; Kakigi *et al.*, 2003) and become undetectable during slow wave sleep (SWS) (our own unpublished observation in 8 healthy adults).

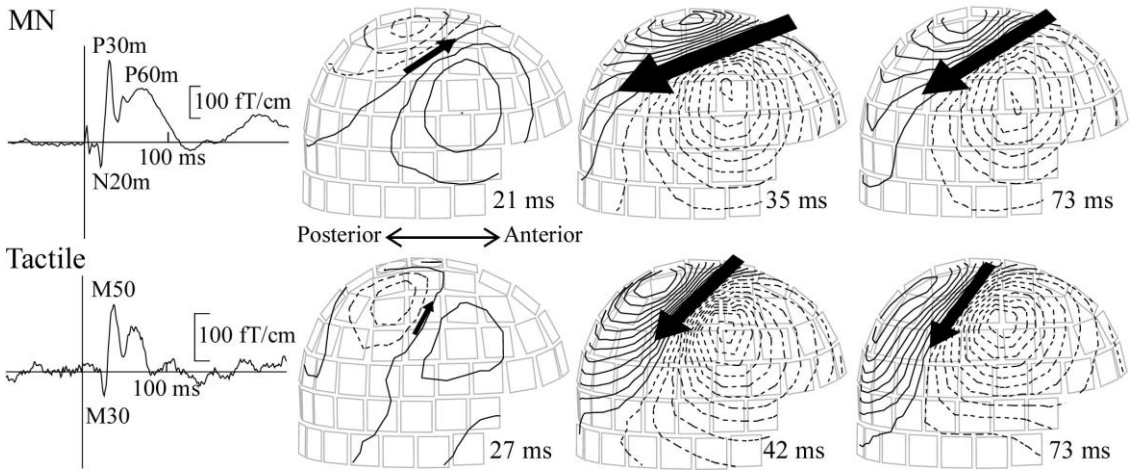

Figure 4: SIc SEF responses to electrical stimulation of the left median nerve (MN, top part of the figure) and tactile stimulation of the left index finger (bottom) in a healthy adult subject. The waveform is displayed from one planar gradiometer channel over the source. Note that the amplitude scale is different for MN and tactile stimulation. The contour maps show the magnetic field distribution reflected on the helmet surface at the time of the main peaks: N20m, P35m, and P60m for MN stimulation as well as M30, M50, and a later peak at 73 ms for tactile stimulation. The solid lines indicate magnetic flux entering and the dashed lines magnetic flux exiting the head. Note that the contour step is 80 fT/cm for the MN responses and 20 fT/cm for tactile responses.

In addition to the SI and SII, hand area stimulation evokes SEFs also at the posterior parietal cortex (PPC) usually peaking at around 70 to110 ms. Areas on both the anterior (area 2 of SI) and posterior (areas 5 and 7) walls of the postcentral sulcus, may contribute in generating this activity (Forss *et al.*, 1994a). While MN stimulation activates the contralateral PPC, airpuff stimuli consistently activated the right PPC regardless of the side of stimulation, suggesting predominance of the right PPC in processing of natural stimuli (Forss *et al.*, 1994b). Finally, activation of an area located on the mesial wall close to the end of the central sulcus can be detected with MEG at approximately 110 to 140 ms, particularly when the subject is attending to the stimulus (Forss *et al.*, 1996). As the side of this mesial source, contralateral *vs.* ipsilateral, varied between subjects, the authors

concluded bilateral activation to be most likely. The exact area generating this activity was located clearly anterior to the supplementary sensory area and may, thus, involve the mesial part of area 4 as well as the supplementary motor area. Regarding the role of these areas in motor planning and the attention dependence of the mesial SEFs, this source may reflect motor preparation in case a stimulus related movement would be needed (Forss *et al.,* 1996).

3.5.2. SEFs and SEPs in newborns and infants

The earliest newborn SEF studies showed that the early response to MN stimulation consisted of two peaks at approximately 30 (referred to as n-M30 in this thesis to discriminate it from the tactile M30 response in adults) and 60 ms (M60), whereas after tactile stimulation of the index finger the 30-ms component was usually not distinguishable from the broad 60 ms deflection (M60) (Pihko *et al.,* 2005). In addition, the response amplitudes of the tactile M60 and a later M200 were shown to depend on sleep stage, both were higher in quiet (QS) than active sleep (AS) (Pihko *et al.,* 2004). In comparisons involving six newborns, the source locations of the MN components n-M30 and M60 did not significantly differ from each other, but a distinct generator area was suggested for a later M200 (Pihko *et al.,* 2005). One study investigated tactile SEFs in infants at palmar (6–8 months) and pincers (11–21 months) grasp stages (Gondo *et al.,* 2001). In the latter group, the latency of the first cortical response was shorter, whereas the amplitude of a later response peaking at around 100 ms was higher for the thumb, but not the ring finger stimulation.

In contrast to the rare infant SEF studies, the developmental SEP literature is vast. The N1 peaking at around 30 ms at term age is the first prominent contralateral parietal response to MN stimulation in infants (Desmedt and Manil, 1970; Hrbek *et al.,* 1973; Laget *et al.,* 1976; Zhu *et al.,* 1987; Laureau *et al.,* 1988; Laureau and Marlot 1990; George and Taylor, 1991; Karniski, 1992; Gibson *et al.,* 1992). It develops to the adult N20 over several years (*e.g.* Laget *et al.,* 1976). Until approximately age 3, the N1 latency decreases (Bartel *et al.,* 1987; Zhu *et al.,* 1987; Taylor and Fagan, 1988) due to the increase in conduction velocity (García *et al.,* 2000) following myelination and maturation of the pathways. Thereafter, the latency starts to prolong as the effect of physical growth of the body and limbs overpowers that of maturation. Despite the prolonging of absolute latencies, the conduction velocities continue to increase for several years, particularly in the central portion of the afferent pathways (Boor and Goebel, 2000; Müller *et al.,* 1994).

Most SEP studies in newborns and infants concentrated on the earliest SEP components (Zhu *et al.,* 1987; Laureau *et al.,* 1988; Laureau and Marlot 1990; George and Taylor, 1991; Gibson *et al.,* 1992) and used filter settings not even allowing detection of components with longer latencies (see Pihko and Lauronen, 2004). The ones also considering the longer-latency components (Desmedt and Manil, 1970; Hrbek *et al.,* 1973; Laget *et al.,* 1976; Karniski, 1992) consistently found, in term newborns, three deflections following the early N1 response at the central contralateral area: a positive deflection at approximately 100 ms, a negativity at around 150 ms, and a second positive peak at a

latency around 230 ms (Desmedt and Manil, 1970; Hrbek *et al.,* 1973; Laget *et al.,* 1976; Karniski, 1992). Of these the later positive peak was more prominent in SWS (*i.e.* quiet sleep) but attenuated in rapid eye movement sleep (REMS *i.e.* active sleep) (Desmedt and Manil, 1970). Laget *et al.* (1976) further investigated development of the SEP morphology in infants of different ages. Already at 2 to 6 weeks of chronological age, the wide neonatal N1 was interrupted by a deflection of opposite polarity, which by the age of 7 to 16 weeks crossed the baseline. Whereas this initial "adult-like" N1-P1 sequence appeared at such an early age, some adult-like features were only attained by the age of 3 to 4 years (Laget *et al.,* 1976).

Median (Hrbek *et al.,* 1973; Willis *et al.,* 1984; Klimach and Cooke, 1988a, b; Majnemer *et al.,* 1990; Karniski, 1992; Karniski *et al.,* 1992; Pierrat *et al.,* 1996, 1997; Taylor *et al.,* 1996; Smit *et al.,* 2000) and tibial nerve SEPs (White and Cooke, 1994; Pierrat *et al.,* 1997; Pike and Marlow, 2000) have been used to assess the functional integrity of the somatosensory pathways also in preterm infants. MN stimulation elicits SEPs recordable on the scalp as early as the 25th GW (Hrbek *et al.,* 1973) and in well designed measurement settings they can be detected within the first week of life in all neurologically normal preterm infants born between the 26th and 32nd GWs (Taylor *et al.,* 1996). In the youngest preterm infants the most striking feature of the scalp SEP is a large negative wave with a mean duration of 1500 ms in infants younger than 30 GW (Hrbek *et al.,* 1973). The amplitude of this wave gradually decreases with age and an earlier N1 component appears after the 29th GW (Hrbek *et al.,* 1973). Its latency then decreases rapidly towards term (Hrbek *et al.,* 1973; Klimach and Cooke, 1988a; Karniski *et al.,* 1992; Taylor *et al.,* 1996; Smit *et al.,* 2000). Based on a longer latency of the N1 at term in preterm infants compared with latencies reported from fullterm infants, Smit and colleagues (2000) suggested delayed maturation of sensory pathways in the preterm infants. This finding was, however, not corroborated by others (Klimach and Cooke, 1988a; 1988b).

In preterm infants, both abnormal MN (Klimach and Cooke, 1988b; Willis *et al.,* 1989; Majnemer *et al.,* 1990; de Vries *et al.,* 1992; Pierrat *et al.,* 1997) and posterior tibial nerve SEPs predict future cerebral palsy (CP) (White and Cooke, 1994; Pierrat *et al.,* 1997; Pike and Marlow, 2000). The specificity, sensitivity, and positive and negative predictive values have, however, varied considerably between studies. This variation is probably explained by differences in patient inclusion criteria, methods of SEP assessment, and outcome measure as well as technical difficulties in reliably recording the responses, particularly in the youngest infants (Smit *et al.,* 2000). Moreover, with the accumulating knowledge on brain development, it has become evident that the generally applied SEP recording setups (adapted from adult studies) are in many ways suboptimal for studies of preterm infants (see Vanhatalo and Lauronen, 2006).

4. AIMS

Our general aim was improving the knowledge on functional development of the somatosensory system in early childhood, particularly the neonatal period, using MEG. The information gained on normal development was then applied in studies of two patient populations: very preterm infants, at risk for brain lesions and adverse neurological outcome, and adolescents with hemiplegic cerebral palsy (CP). The specific aims of the Studies I–V were as follows:

I To determine the possible differences between SEFs of newborns and adults, and the nature of these differences.

II To identify the cortical generators underlying the newborn SEFs. Additional aims were determination of the stimulus rate and sleep stage effects on neonatal SEFs originating from different cortical areas.

III To determine the possible differences in SEFs at term equivalent age between fullterm and preterm infants. The additional aim was to reveal any correlations between individual deviations from the normal cortical activation pattern in the preterm infants and anatomical lesions of the underlying hemisphere.

IV To demonstrate the pattern of SEF development from the newborn form to the adult form. In addition, we aimed to confirm that the previously observed differences between newborns and adults were not caused by vigilance state, but were true developmental differences.

V To reveal effects of early brain lesions underlying hemiplegic CP on function of the cortical somatosensory areas and somatotopy of the contralateral primary somatosensory cortex (SIc). Furthermore, we searched for correlations between abnormalities in SIc activity pattern in individual patients and the severity of their motor and sensory symptoms as well as neuroimaging findings.

5. METHODS

5.1. Study design

Altogether 113 subjects participated in the 119 MEG measurements constituting this thesis (Table 1). These included 84 healthy subjects of different ages as well as 29 patients: 16 very preterm infants and 13 adolescents with hemiplegic CP.

Table 1. The number of measurements for the studies of the thesis according to age, vigilance state, and stimulation type. Note that some subjects were measured both asleep and awake, and in some both median nerve and tactile stimulation were applied. #Altogether 40 newborns underwent an MEG measurement. The data of some newborns were included in several of the Studies I–IV. *Two infants were measured at 6 and 12 months and one at the ages of 6, 12, and 18 months and 2 and 3 years. Thus, altogether 19 infants/children participated in the 25 measurements between ages 6 months and 6 years. (n = number, MN = Median nerve, mo = months, y = years, CP = cerebral palsy)

	Healthy subjects						**Patients**	
	Newborns	**6 mo**	**12–18 mo**	**1.6–6 y**	**12–18 y**	**Adults**	**Preterm**	**CP**
Study	I–IV	IV	IV	IV	V	I, IV	III	V
Total n	40#	9*	8*	8*	13	12	16	13
Awake	1	-	-	8	13	12	-	13
Asleep	40	9	8	4	-	9	16	-
MN	12	-	-	-	13	1	-	13
Tactile	34	9	8	8	13	12	16	13

5.2. Subjects

5.2.1. Newborns

In total 40 healthy fullterm newborns participated in the studies (17 females, 23 males). Study I included 26, Study II 21, Study III 16, and Study IV 20 healthy newborns. Some of the newborns were included in several studies. All newborns were recruited from the maternity ward of the Helsinki University Central Hospital during years 2003–2007. Their gestational age ranged between 37 and 42 weeks. MEG in all newborns was recorded 1 to 6 days after birth, except for three newborns of Study IV who were recorded approximately 3 weeks after birth (postnatal days 17, 20, and 23). The 1 min Apgar scores ranged between 5 and 10 with the 5 min follow-up scores all exceeding 8. The birth weight ranged between 2622 and 4460 g, the head circumference between 33 and 37.5 cm, and body length between 46 and 54 cm.

5.2.2. Infants and children

The older infants and children (altogether 25 measurements of 19 infants) of Studies I and IV were children of the laboratory personnel or of their friends and relatives. They were divided into three age groups: 6-month-olds (n = 9; 3 females, 6 males), 12–18-month-olds (n = 8; 3 females, 5 males), and 1.6−6-year-olds (n = 8; 2 females, 6 males). Two of the subjects were measured twice at 6 and 12 months and one 5 times at the ages of 6, 12, and 18 months as well as at 2 and 3 years.

5.2.3. Very preterm infants

Study IV included 16 infants (10 females, 6 males) born before the 28th GW (gestational age range: 24 weeks and 1 day to 27 weeks and 6 days). Their birth weight ranged between 660 and 1110 g, body length between 30.5 and 36.5 cm, and head circumference between 20.7 and 25.5 cm. They were all patients in the neonatal intensive care unit (NICU) of the Helsinki University Central Hospital (HUCH) and recruited by a neonatologist. At the time of the MEG measurement, the post menstrual age ranged from 37 weeks 6 days to 43 weeks 2 days, weight between 2350 and 3615 g, body length between 42.5 and 51 cm, and head circumference between 32 and 38.5 cm, and the infants no longer needed extra oxygen, monitoring, or constant measuring of oxygen saturation. For more details of the infants' clinical background, please see Table 1 of Study III.

5.2.4. Adolescents with CP

A child neurologist recruited 13 patients (aged 11 to 17 years, 8 females and 5 males) with congenital, spastic, hemiplegic CP to participate in Study V. The hemiplegia was left-sided in three and right-sided in ten patients. The underlying brain lesion extended to the sensorimotor cortex in five patients, whereas eight had purely subcortical lesions. Six patients had epilepsy and five were on antiepileptic medication when MEG was recorded. One patient had undergone anterior callosotomy in 2003 (three years before the MEG measurement) for treatment of her epilepsy (continuos spikes and waves during sleep). Five of the CP patients had been born preterm. For details of the patients' clinical background, please refer to Table 1 of Study V.

5.2.5. Healthy adolescents

For each CP patient of Study V, we selected an age and sex matched healthy control (13 adolescents; 12 to 18 years) to undergo the same MEG experiment. Each control was also assigned to have "an affected" hemisphere according to the patient's lesion side. (Note: The statistical analyses performed on patient subgroups only included those controls that were originally selected for the patients in that particular subgroup.)

5.2.6. Adults

Altogether 12 healthy adult volunteers (8 females, 4 males) participated in MEG recordings in awake and sleep states. Three of them were, however, not able to fall asleep during the measurement and consequently, only awake data was obtained from these subjects. Adult sleep measurements were conducted during the night, except for two subjects who were sleep deprived and measured during the day. All adult subjects were members of the laboratory personnel or friends of the researchers. Data from the awake measurements of 10 adults were included in Study I, whereas both sleep and awake recordings were analyzed for Study IV.

5.3. MEG studies

5.3.1. Stimulation

The tactile stimuli, used in all studies, were delivered to the finger tips with diaphragms driven by an air pressure pulse (Somatosensory Stimulus Generator, 4-D NeuroImaging Inc., San Diego, USA). In Studies I−IV the stimulus was given to the tip of the left index finger with an interstimulus interval (ISI) of 2 s. In Study II, 11 newborns underwent additional sessions with ISIs of 0.5 and 4 s, and in the remaining 10 the right index finger was stimulated in an additional session. In Study V, tactile stimulation was given sequentially to the tips of digits II and V of both hands with an ISI of 1 s between the different digits. Consequently, the ISI between two stimuli to the same digit was 4 s. Electrical median nerve (MN) stimulation at the wrist was used in Study I (left MN) and Study V (left and right MNs in separate sessions). In both studies the ISI was 2 s and the stimulation intensity was set just above the motor threshold.

5.3.2. Recordings

The MEG recordings were performed in the BioMag Laboratory of the Helsinki University Central Hospital (HUCH). These measurements were conducted in a magnetically shielded room (Euroshield Ltd., Finland) with a whole-head helmet-shaped MEG sensor array consisting of 306 independent channels: 204 planar gradiometers and 102 magnetometers (Elekta Neuromag®, Elekta Oy, Helsinki, Finland). EEG was recorded for sleep stage monitoring with one to three silver-silver-chloride disposable electrodes placed at F4, P4, Cz, or P3. Electro-oculogram (EOG) was recorded from two electrodes, one above the left and the other below the right eye canthi. The reference electrode was on the left mastoid and the ground electrode on the forehead. In the sleep measurements of older infants and adults the submental electromyography (EMG) was also recorded. EEG and MEG were bandpass filtered at 0.03–257 Hz and, depending on the study, the sampling rate was between 987 and 1002 Hz. Additionally, four subjects of Study IV, aged 12–30 months, were studied at The Mind Research Network and BRaIN Imaging Center in Albuquerque (ABQ), New Mexico, USA. These subjects were measured with a pediatric MEG prototype ‘babySQUID’ with 76 axial gradiometers

(Okada *et al.,* 2006), also located in a magnetically shielded room. No EEG, EOG, or EMG was recorded from these subjects.

5.3.3. Procedure

In the beginning of each measurement, the EEG and EOG electrodes were attached on the scalp (only EOG was used in awake subjects). Four position indicator coils were attached on a cloth cap in infants and children, and on the skin in the 6-year-olds, adolescents, and adults. The coil positions, relative to anatomical landmarks, were determined with a three-dimensional digitizer (Polhemus) to construct an individual Cartesian coordinate system. In this coordinate system the preauricular points determined the *x*-axis, which pointed to the right. The *y*-axis was perpendicular to the *x*-axis pointing towards the nasion, and the *z*-axis, perpendicular to the *x*-*y*-plane, pointed upwards. In the beginning of each recording set, the head position inside the sensor array was determined by feeding the position indicator coils with excitation currents to find their positions by modeling them as magnetic dipoles.

When necessary, the infant was fed before placing him/her on a bed next to the MEG measuring helmet (Figure 5). In Studies I–IV, the MEG device was in a supine position. Newborns and 6-month-olds lay with the right hemisphere downwards over the occipital part of the helmet. Older children and adults lay on their back. One or two researchers were in the measurement room with the infants and children in order to hold the stimulator on the index finger and observe the subject's behavior. The researcher(s) coded the infant's behavior (whether the eyes were open or closed and the presumed sleep stage) onto trigger channels linked to the raw data file. This behavioral coding, together with EEG and EOG, served for off-line sleep stage determination. The complete session with each infant lasted approximately two hours. The stimulation and recording started when the infant was asleep and lying still. No sedation was used in any measurement. In the measurements of adults, electrophysiological data alone determined the sleep stage. In Study V, the MEG device was in an upright position and the subject was sitting comfortably watching a self chosen film without audio. Each complete session in Study V lasted approximately one and a half hours.

Figure 5. MEG measurement of a newborn

5.3.4. Sleep stage analyses

The sleep stage analyses were based on the electrophysiological data and the behavioral coding in infants, whereas in adults only electrophysiological data was used. In newborns the sleep stage was characterized as quiet sleep (QS) when the observing experimenter had coded the eyes to be closed and the respiration pattern to be regular, EEG showed *tracé alternant* (Figure 6A) or high-voltage low-frequency activity, and EOG showed no saccadic eye movements. The sleep stage was characterized as active sleep (AS) when the eyes were closed, respiration pattern was irregular, occasional facial twitches occurred, and EEG showed low-voltage high-frequency activity together with saccadic eye movements in the EOG (Figure 6B) (Prechtl, 1974).

For older infants, children, and adults the sleep stages were classified according to the guidelines from the classical EEG criteria (Rechtshaffen and Kales, 1968). In the awake state, the activity had low-amplitude mixed-frequency or rhythmic alpha in the parieto-occipital channels. Disappearance of alpha activity and appearance of slow eye movements characterized 'S1'. Appearance of sleep spindles or K-complexes signified the 'S2' stage. In slow wave sleep (SWS), slow-frequency high-amplitude activity comprised over 20% of the 30-s analysis window. During rapid eye movement (REM) sleep, EEG showed low-voltage mixed-frequency activity together with episodic rapid eye movements and low-amplitude submental EMG. Periods when the sleep stage could not be unambiguously specified were excluded from further analyses. In Study IV, the data from awake state, REM-sleep, and non-REM stages S2 and SWS were further analyzed.

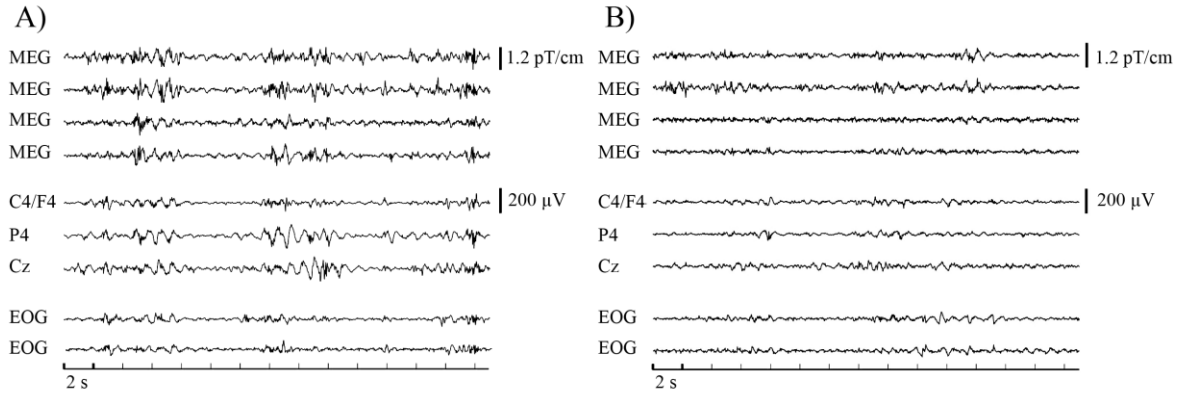

Figure 6: Period of raw MEG and EEG data from a healthy newborn A) in QS and B) in AS.

5.3.5. Data analyses

The data of Study I were preprocessed with a Signal Space Separation (SSS) method (Taulu *et al.*, 2004), and data of Studies II−V measured in Helsinki with a Spatiotemporal Signal Space Separation (tSSS) method (Taulu and Simola, 2006) of the MaxFilter™ software (Elekta Neuromag, Helsinki, Finland) to improve the signal to noise ratio by removing possible magnetic artifacts caused by, *e.g.*, dental braces and the heart. tSSS was performed in a 4-s time window, thereby suppressing all frequencies below 0.25 Hz. We used the default correlation limit of 0.98 except for one patient (P5) of Study V, in whom the correlation limit was lowered to 0.9 (Medvedovsky *et al.*, 2009) to appropriately remove artifacts caused by residual magnetic particles from prior brain surgery. After tSSS, the result file was carefully examined before averaging. In the sleeping subjects, the data were averaged according to the sleep stages and periods with movement artifacts were manually discarded from the averages. No less than 92 epochs were averaged for each condition in each subject. Refer to Studies I−V for exact numbers of averages.

The location, strength, and orientation of the neural sources were estimated by calculating equivalent current dipoles (ECDs) in a spherical conductor model. The subset of MEG channels included in the modeling process was individually selected for each subject and response. The 100-ms period before stimulus was used as a baseline. The averaged signals from tactile stimulation trials of all studies and MN stimulation trials of Study I (after removing the stimulus artifact) were digitally lowpass filtered at 90 Hz prior to analysis. In addition, in Studies I and IV, the signals were highpass filtered at 1 Hz. No further off-line filtering was applied to the MN data of Study V. The peak of each deflection was determined by modeling single dipoles with 1-ms intervals around the visually determined peaks. The ECD with the greatest dipole moment and a dipolar field pattern was selected for further analysis. The goodness of fit values of the chosen dipoles exceeded 65% in Studies I, II, and III, 70% in Study IV, and 75% in Study V. A time-varying multidipole model was calculated in order to study the overall explanation by the modeled ECDs for data from all sensors.

5.4. Magnetic resonance imaging (MRI)

For Study III the MRI was performed on all patients using a 1.5-Tesla scanner (Philips Medical Systems Achieva). The MRI findings were classified according to Woodward *et al.* (2006). For Study V, the MRI studies were performed with a 3-Tesla unit (Philips Intera Achieva). An experienced neuroradiologist (author LV of Study V) performed the structural analyses from T2-weighted axial and coronal images and axial FLAIR (fluid-attenuated inversion recovery) images. The location and extent of the lesion was scored, as well as the possible extension along the white matter tracts of the internal capsule and brain stem. Lesion type was also noted (destructive or developmental). T1-weighted images were used for MEG-MRI integration and figures.

5.5. Behavioral tests

In Study V, an occupational therapist examined the somatosensory ability with Semmes-Weinstein monofilaments of the affected hand. She used a five-piece filament kit (Bell-Krotoski and Tomancik, 1987), where the filament size was marked with log forces[2] representing threshold values for touch. The therapist also measured the dynamic and static 2 point discrimination (2-PD) ability at the tip of digits II and V (Moberg, 1990). In the dynamic test, the ability to discriminate 2 to 3 mm separation was considered normal, whereas that of 4 to 6 mm moderate, and 7 to 9 mm poor. In the static 2-PD test the distances were 2 to 6 mm (normal), 7 to 10 mm (moderate) 11 to 15 mm (poor), and over 16 mm (untestable). For statistical analyses, the results of the static and dynamic tests were combined so that score 1 indicates normal ability in both tests, score 2 moderate ability in one and normal in the other test, and score 3 moderate to poor ability in both tests.

The therapist further evaluated the motor performance of the CP patients with Manual Ability Classification System (MACS) (Eliasson *et al.*, 2006). MACS reflects the bimanual ability in everyday life ranked into 5 levels. Level 1 indicates minor difficulties in handling objects that require fine motor control or efficient coordination between hands. Patients at Level 3 can not handle all objects and their degree of independence is related to the adjustments made to the environment. Level 5 indicates severe impairment, meaning participation in daily activities consists of, at best, simple movements in specific situations (Eliasson *et al.*, 2006).

[2] Log forces: 2.83 = normal touch (score 6); 3.61 = diminished light touch (score 5); 4.31 = diminished protective touch (score 4); 4.56 = loss of protective sensation (score 3); 6.65 = only deep touch (score 2); more than 6.65 = untestable (score 1).

5.6. Statistical analyses

Statistical comparison of sleep stages, ISIs, or distinct SEF components within a single group were performed with either repeated measures analysis of variance (ANOVA) or paired, two-tailed t-tests. One-way ANOVA was used for comparisons between age groups in Study IV. Preterm infants were compared with the fullterm controls by using Student's two-tailed t-tests. For comparisons between the CP patients and their controls we applied a two-factor repeated measures ANOVA, in which the group was set as the independent factor and hemisphere (affected or unaffected) as the dependent factor. In case of tactile stimulation, the digit (II or V) was added as another dependent factor. For the comparisons of source strengths, the strength was considered to be 0 nAm when a response could not be modeled with an ECD. For the angular data (directions of the ECDs), circular statistics were used. In addition, in Study V we applied non-parametric tests (Weighted Kappa or The Phi Coefficient) to correlate the level of SEF changes with clinical and imaging findings and X^2 test when comparing the categorical frequencies between patients and controls, *e.g.*, existence of certain SEF components. Furthermore, when the expected count for any cell in the analysis was less than 5 we applied the Fisher's exact test instead of the X^2 test. The level of statistical significance was set at $P<0.05$.

5.7. Ethical considerations

The Ethics Committee for Pediatrics, Adolescent medicine, and Psychiatry, Hospital District of Helsinki and Uusimaa, approved the study protocol. All adult subjects gave their informed consent. For the newborns, infants, and children (6 years and younger), the informed consent was obtained from the parents. (The children 3 years and older also themselves gave informed consent.) The adolescents gave their informed consent together with their parents. None of the examinations is considered harmful or caused pain to the subjects. All MEG sleep measurements were performed during natural sleep and no subjects were sedated. The infants were placed on the measurement bed after falling asleep usually in the arms of their parents or one of the researchers. The stimuli did not wake up the subjects. All subjects were informed that they were free to discontinue their participation at any time without any particular reason. The measurements of infants, too young to express themselves in words, were discontinued if the infant was restless.

Inclusion of subjects that were children of friends or colleagues of the researchers greatly facilitated MEG studies in the age group of 6 months to 6 years. In this age group, no measurements could have been accomplished without active participation of a parent. We considered it highly beneficially for the parent to be familiar with the measurement environment and the researchers in order to make the infant/child feel comfortable during the preparations and measurement. None of the parents were subordinates of or in any other way obliged for the researchers.

6. RESULTS

6.1. SEFs in newborns

The normal SEF pattern in the newborn period was characterized in Studies I and II. The results were further corroborated in Studies III and IV.

6.1.1. Differences between newborn and adult responses (Study I)

The early contralateral SEFs to stimulation of the hand area in newborns, compared to adults, differed both in latency and orientation of the underlying current flow (Figure 7). Electrical MN stimulation at the wrist elicited the first cortical response in the contralateral hemisphere at around 30 ms in newborns (n-M30; mean latency of the 11 subjects in AS 30 ± 1.6 ms). The magnetic field pattern of this response was dipolar with the equivalent current dipole (ECD) pointing anteriorly similar to the well known adult N20m (Figure 7). After this initial activity, the ECD in the newborns continued to point anteriorly during the second deflection peaking at around 60 ms (M60) [mean latency 51 ± 7.1 ms in AS (n = 11) and 56 ± 17.1 ms in QS (n = 12)] (Figure 7). On the contrary, in adults the N20m is followed by the P35m deflection with an ECD oriented posteriorly. In newborns, such a P35m-like response with posteriorly oriented ECD was completely absent. The ECD locations of both neonatal responses (n-M30 and M60) were consistent with the activity being generated at the contralateral primary somatosensory cortex (SIc).

After tactile stimulation of the index finger, the first prominent response in newborns peaked at around 60 ms (M60), whereas a separate 30-ms component was usually not distinguishable from the broad deflection. The ECD underlying the tactile M60 pointed anteriorly and had a location consistent with the activity arising from the SIc. In adults, the most prominent early cortical response, peaking at around 50 ms (M50), had a posterior ECD orientation similar to the P35m. In two adults, a weaker earlier cortical response peaked at around 30 ms with an anterior ECD direction corresponding to the MN N20m.

6.1.2. Origins of the contralateral SEFs: effect of sleep stage and interstimulus interval (ISI) (Study II)

In Study II, 19 healthy newborns were recorded in QS and 11 in AS with a 2-s ISI. In general, tactile stimulation of the index finger (ISI 2 s) elicited two main responses in the contralateral hemisphere, the M60 and another prominent deflection peaking at around 200 ms (M200) (Figure 8). Both responses had dipolar magnetic field patterns. M60 could be modeled with an ECD in 19/19 newborns in QS and 10/11 in AS, and M200 in 18/19 newborns in QS and 5/11 in AS. As noted above, the ECD underlying the M60 pointed anteriorly and its location was consistent with the SIc (Figures 8 and 9). The ECD of the later deflection, M200, was localized significantly more inferiorly {mean difference 16 mm in QS [Student's t-test: $P < 0.0001$ (n = 18)]} and laterally {mean difference 7 mm [$P = 0.001$ (n = 18)]} than the M60 ECD (Figure 9). Furthermore, the M200 ECD pointed superiorly (Figure 8).

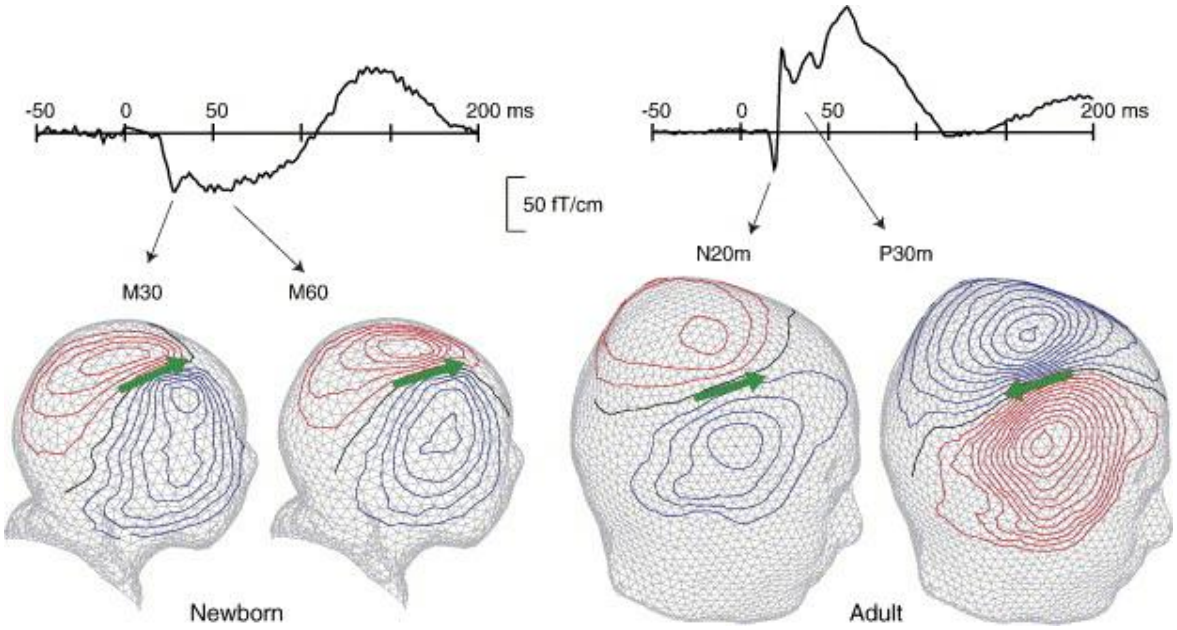

Figure 7. Early SEFs to median nerve stimulation in a newborn and an adult. In the upper row the waveforms from one gradiometer channel showing the maximal response. Below are the contour maps reflected on the skull surface. The red lines indicate magnetic field exiting the head and blue lines field entering the head. The first responses (n-M30 and N20m) have similar ECD directions, but for the following responses (M60 and P35m) the ECD directions are opposite. (Reprinted from NeuroImage, Vol 33, Lauronen L, Nevalainen P, Wikström H, Parkkonen L, Okada Y, Pihko E, Immaturity of somatosensory cortical processing in human newborns, page no. 197, Copyright (2006), with permission from Elsevier.)

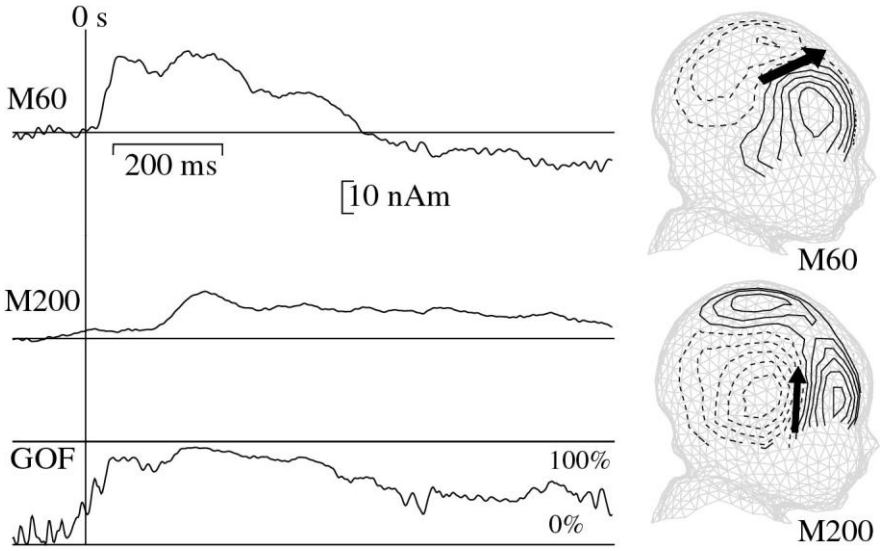

Figure 8. M60 and M200 responses of one healthy newborn. Left: source waveforms and goodness of fit when M60 and M200 ECDs are included in the multidipole model. Right: contour maps at the M60 and M200 peaks reflected on a spherical surface. The solid lines indicate magnetic field entering the head and the dashed lines field coming out of the head.

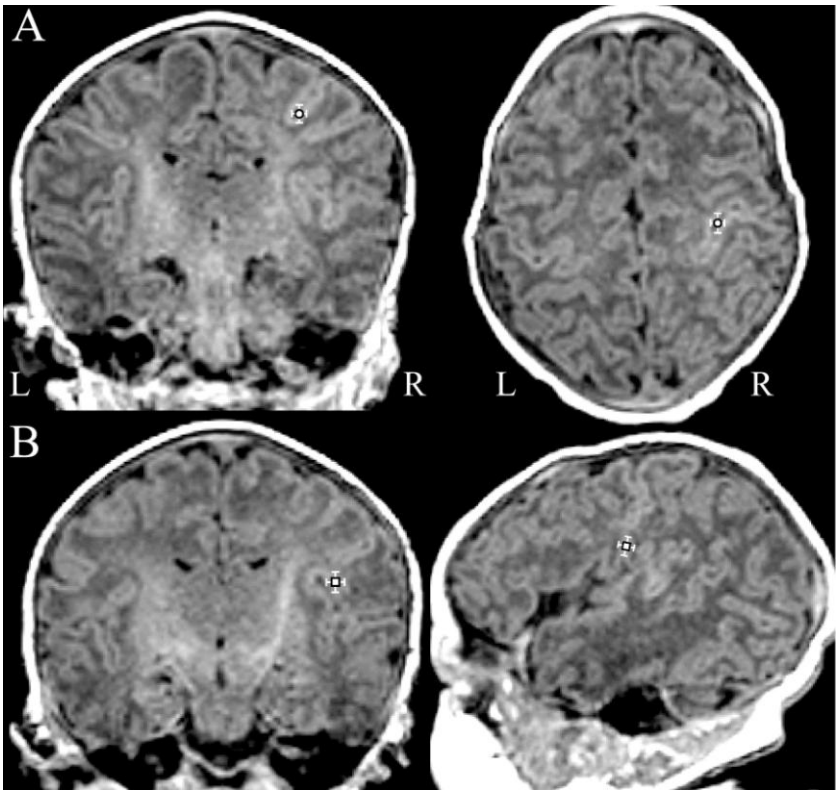

Figure 9. A schematic image visualizing the average ECD locations (mean of 18 newborns) of M60 (A) and M200 (B) in quiet sleep (ISI 2 s) relative to brain anatomy at fullterm age (MRI of one healthy newborn). Note that the locations of M60 and M200 coincide with the SI (on the posterior bank of the central sulcus) and SII (on the superior lip of the Sylvian fissure) on the MRI. The white bars denote the standard error of mean.

The ECD strengths of M60 and M200 (ISI = 2 s) were compared for AS and QS in 10 newborns with data available from both sleep stages. The M200 ECD was significantly weaker in AS than QS, whereas the M60 strength did not significantly differ (Figure 10A) [ANOVA (n = 10) main effect: sleep stage $F(1,9) = 11.09$; $P = 0.009$; *Post hoc* M60 $P = 0.26$, M200 $P = 0.04$]. Furthermore, the effect of the interstimulus interval (ISI) (0.5, 2, or 4 s) was evaluated in the 8 newborns in whom recordings with all three ISIs were successfully accomplished in QS. The ECD strength of the M200 significantly attenuated with the 0.5-s ISI compared to longer ISIs (2 and 4 s), whereas the M60 was not significantly affected (Figure 10B) [ANOVA (n = 8) 2-way interaction ISI x response M60/M200: $F(2,14) = 6.94$; $P = 0.008$; *Post hoc* for M200: 0.5-s *vs.* 2-s ISI $P = 0.03$; 0.5-s *vs.*4-s ISI $P < 0.001$].

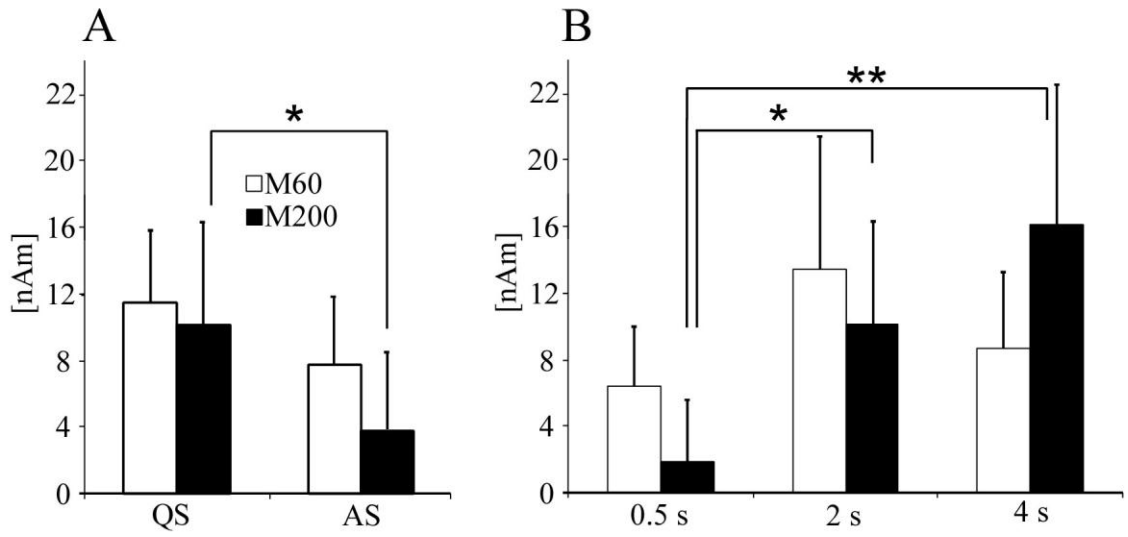

Figure 10. Average source strengths (nAm) with the bars denoting the standard deviations: M60 (white) and M200 (black) A) in quiet (QS) and active sleep (AS) (n = 10); B) with the three ISIs in QS (n = 8). The M200 ECD was significantly weaker in AS than QS as well as with the 0.5-s ISI compared to the longer ISIs. *P < 0.05, ** P < 0.001 (9B reprinted from NeuroImage, Vol 40, Nevalainen P, Lauronen L, Sambeth A, Wikström H, Okada Y, Pihko E. Somatosensory evoked magnetic fields from the primary and secondary somatosensory cortices in healthy newborns, page no. 742, Copyright (2008), with permission from Elsevier.)

6.1.3. Ipsilateral responses (Study II)

The ipsilateral (right) hand was stimulated in ten newborns, while recording from the right hemisphere. Eight newborns were measured in QS and six in AS. In QS, a response with latency, ECD orientation, and location similar to those of the M200 (elicited by stimulation of the contralateral, left hand) was detected in four newborns. In two (including one with the M200-like response), a response with ECD source location similar to that of the M60 was detectable. In AS, a 120-ms peak was visible in the waveforms of 5/6 newborns, but the response could only be modeled with an ECD in one and was therefore, left out of further analysis.

6.2. Developmental changes in SEFs (Studies I, IV)

In Studies I and IV, we also recorded SEFs from infants and children at different ages between 6 months and 6 years. The data from the four infants measured in Albuquerque was only evaluated visually and the waveforms corresponded to those obtained from measurements conducted in Helsinki. In the following, only data from the Helsinki measurements are presented.

At 6 months of age, the tactile SEF still resembled that of newborns with anteriorly pointing ECDs underlying the earliest responses. Instead of a single M60 peak, however, the earliest response consisted of two peaks (M30-M60) separated by a notch (Figure 11). In Study IV, we found that with age the notch continued to increase in amplitude, crossing the baseline in several 12- and 18-month-olds. By age 2, it was strong enough to be modeled with a posteriorly oriented ECD similar to the typical adult M50 response (Figure 11). The M50 was also the main early SI response in children (3–6 y) (Study IV) and adolescents (12–18 y) (Study V). This developmental change in SEF was independent of the vigilance state. It should be noted that although the M50 was the most prominent tactile SEF response in older subjects, the earlier peak at around 30 ms was still detectable in most adults and could be modeled with an anteriorly pointing ECD in 71% of them in Study IV.

The ECD orientations of M30 (newborn M60) responses did not differ between the age groups. The M50 ECD orientation, which was practically opposite to that of the M30 ECD, was also concordant across all age groups in which it could be modeled (12–18 mo, 1.6–6 y, and adults). ECD locations of both responses, the M30/M60 and M50, were in accordance with the activity being generated at the SIc and correlated with subject age in a way that in older subjects the ECDs were located more superiorly (correlation of age and *z*-coordinate $r = 0.53$; $P < 0.0001$) and laterally (correlation of age and *x*-coordinate $r = 0.58$; $P < 0.0001$).

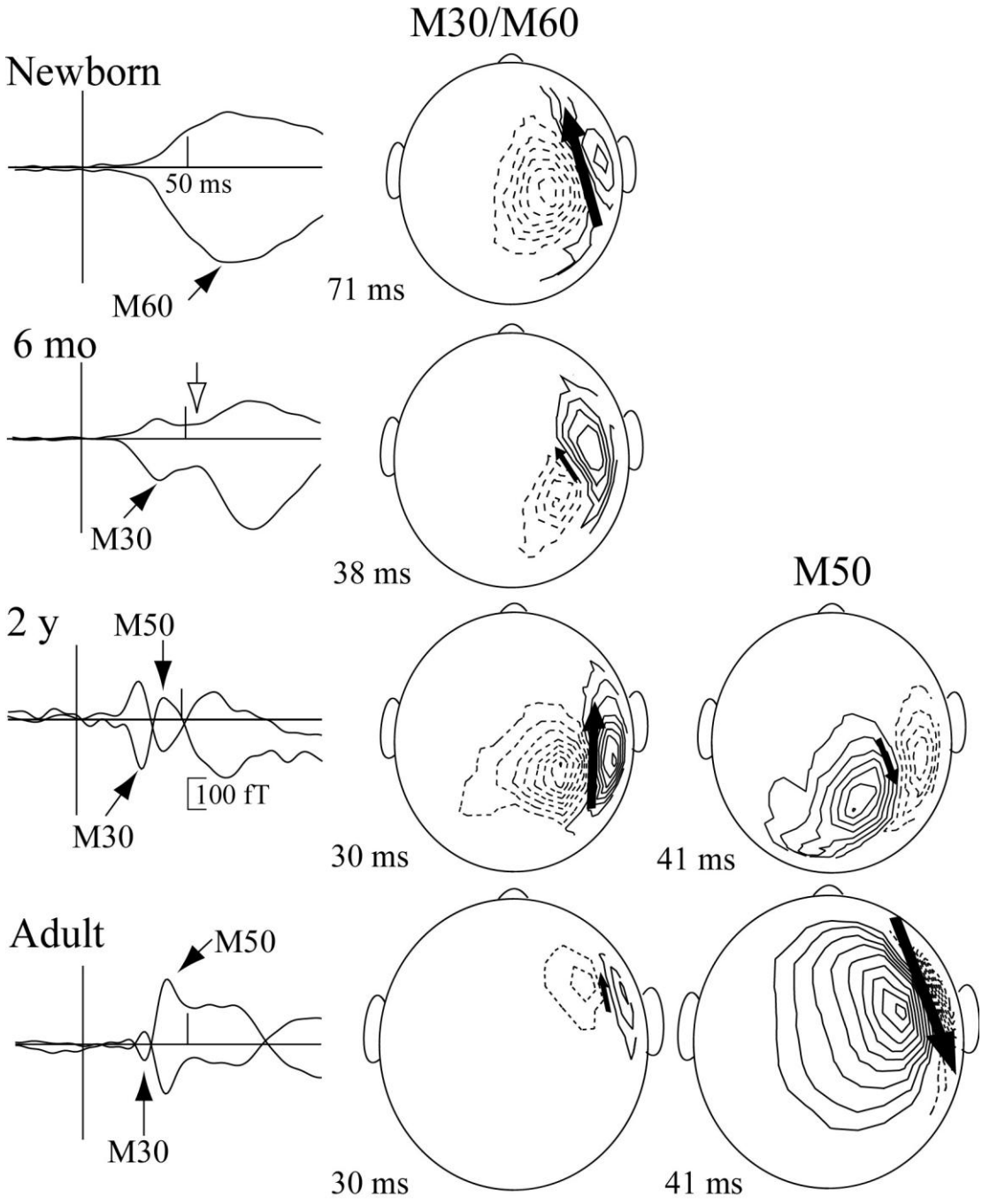

Figure 11. Developmental changes in SEFs. The early SEFs from a newborn (QS), a 6-month-old infant (SWS), a 2-year-old child (S2), and an adult (S2). SEF waveforms from two magnetometer channels are shown on the left. The main responses are indicated by the black arrows and the emerging M50 notch by the white arrow in the 6-month-old infant. A proper M50 is only present in the 2-year-old child and the adult. On the right, the contour maps during the main deflections are reflected on spherical heads and viewed from above. Dashed lines indicate magnetic field coming out of the head and continuous lines field entering the head. The equivalent current dipole (ECD), shown by an arrow, is directed anteriorly during M30/M60 and posteriorly during the M50. The midpoint of the ECD corresponds to the locations of the active brain source. Note that the ECD arrow size and the magnetic field contour step are set individually and are not comparable across subjects.

6.3. SEFs in very preterm infants (Study III)

The general morphology of the contralateral SEFs in QS, M60 followed by M200, or their latencies did not differ at term age between the preterm infants and their healthy fullterm control subjects (Figure 12). The ECD strength of the M60 response was weaker in the preterm group, however [preterm infants 7.9 (3.2) nAm; controls 11.9 (5.9) nAm; Student's two-tailed t-test: P = 0.02]. No group level differences existed for M200. At the individual level, M200 was absent in four preterm infants all of whom had lesions of the underlying hemisphere depicted by MRI and/or ultrasound (US). All infants with normal US and MRI findings correspondingly had a normal M200. Two preterm infants with a brain lesion, however, had a normal M200, but the M200 was missing from one control (Table 2).

Table 2. Details of the lesions in those preterm infants with abnormal neuroimaging findings of the right hemisphere together with the presence/absence of M200. In addition to the infants presented in this Table, nine infants had no abnormalities in the right hemisphere in US or MRI and one infant had normal US, but the MRI could not be evaluated due to movement artifact. All these ten infants had a normal M200 response. (# refers to subject number in Study III, gr = grade, IVH = intraventricular hemorrhage, MRI = magnetic resonance imaging, PVL = periventricular leukomalacia, US = ultrasound)

#	Imaging findings	M200
1	Right sided IVH gr. I	-
2	Moderate PVL	-
6	Calcifications (more on the left)	-
10	Right sided IVH gr. IV with enlarged right ventricle	-
7	Right sided IVH gr. IV	+
14	Moderate PVL; signs of old right sided hemorrhage in MRI (No hemorrhage detected in US)	+

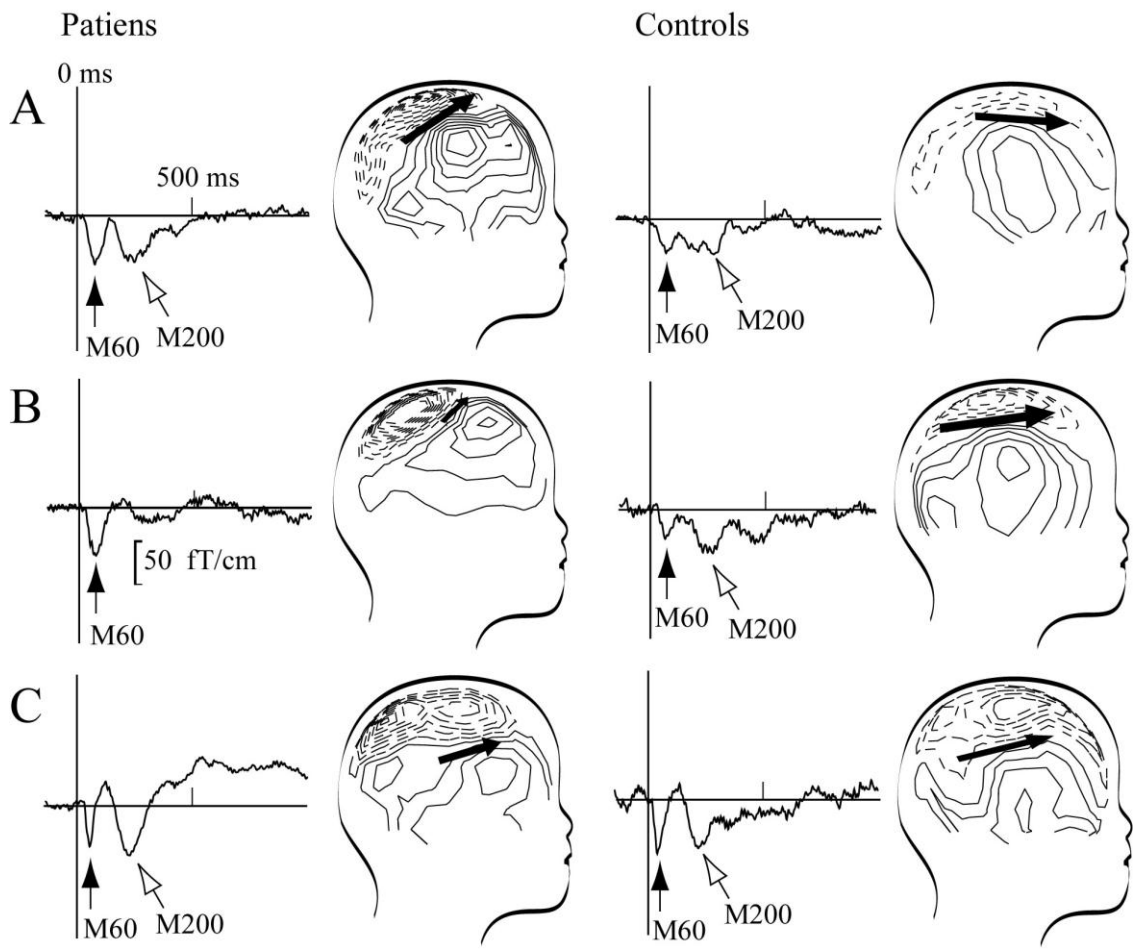

Figure 12. The SEF waveform from one gradiometer channel in three patients (left) and three controls (right). A) a patient with normal imaging findings and SEFs, B) a patient with moderate periventricular leucomalacia (PVL) and absent M200 (Patient 2 in Table 2), C) a patient with moderate PVL but normal M200 (Patient 14 in Table 2). In general, the morphology of the waveforms is similar, M60 (black arrows) followed by M200 (white arrows) in patients and controls (except for Patient B). The contour maps correspond to the M60 response, showing similar contour patterns in patients and controls. The contour step is 60 fT/cm, the dotted lines indicate magnetic flux exiting the head and the solid lines magnetic flux entering the head.

6.4. SEFs in adolescents with CP (Study V)

6.4.1. Tactile stimulation

After tactile stimulation of digits II and V of both hands, the M50 was the most prominent early deflection in all 13 healthy control adolescents (mean latency for all fingers 44 ± 3.8 ms, n = 13) and in all eight patients with pure subcortical lesions (45 ± 4.3 ms, n = 8). Of the patients with cortico-subcortical lesions, stimulation of the normal hand elicited the M50 in all the five (mean latency for normal hand 54.1 ± 8.1 ms, n = 5), but that of the palsied hand in only one (P5 in Table 3). The M50 ECDs were located at the SIc, in somatotopical order so that, when superimposed on individual MRIs of the patients, digit V area was medial to digit II area along the central sulcus.

The Euclidian distance between M50 ECD locations for the two stimulated digits was shorter in the patients with subcortical lesions (n = 8) than their controls (n = 8) in both hemispheres [Affected hemisphere (AH): 5.3 ± 2.8 mm (patients) *vs.* 10.6 ± 5.8 mm (controls); Unaffected hemisphere (UH): 7.1 ± 3.2 mm (patients) *vs.* 10.5 ± 4.4 mm (controls); ANOVA main effect: group $F(1,14) = 5.58$; $P = 0.03$; *Post hoc* UH: $P = 0.04$, AH: $P = 0.01$] (Figure 13). In the five patients with cortico-subcortical lesions, this Euclidean distance in the UH was 10.9 ± 2.9 mm.

After tactile stimulation, the ipsilateral primary somatosensory cortex (SIi) was activated more frequently in the patients with subcortical lesions (n = 7/8, altogether 11 digits) than their controls (n = 1/8, 3 digits) (Fisher's exact test: $P = 0.005$). The peak latencies of the SIi responses were generally a few milliseconds longer than those of the SIc responses. Notably, 64% of the SIi responses of these patients were evoked by stimulation of the normal hand. Of the five patients with cortico-subcortical lesions, stimulation of the normal hand elicited activity in the ipsilateral (*i.e.* affected) hemisphere near SI in two. SIi activity to stimulation of the palsied hand was evoked in none of these five patients.

6.4.2. Median nerve stimulation

In all controls, stimulation of both MNs elicited the three main early responses from the SIc: N20m, P35m, and P60m. These three peaks were also present in all the eight patients with subcortical lesions for the UH. On the affected side, N20m was absent in three and P60m in two (Figure 14). An additional P25m peak (with posterior ECD orientation) was more often present in these patients (6/8 UHs and 8/8 AHs) than their controls (1/8 UH and 2/8 AHs) (X^2 $P < 0.001$). Furthermore, the P35m peaked on average 4.5 ms later in both hemispheres of these patients than their controls (38.3 ± 4.7 ms *vs.* 33.8 ± 2.8 ms, n = 8 in both groups) [ANOVA main effect: group $F(1,14) = 7.11$; $P = 0.02$; *Post hoc* UH $P = 0.04$; AH $P = 0.002$].

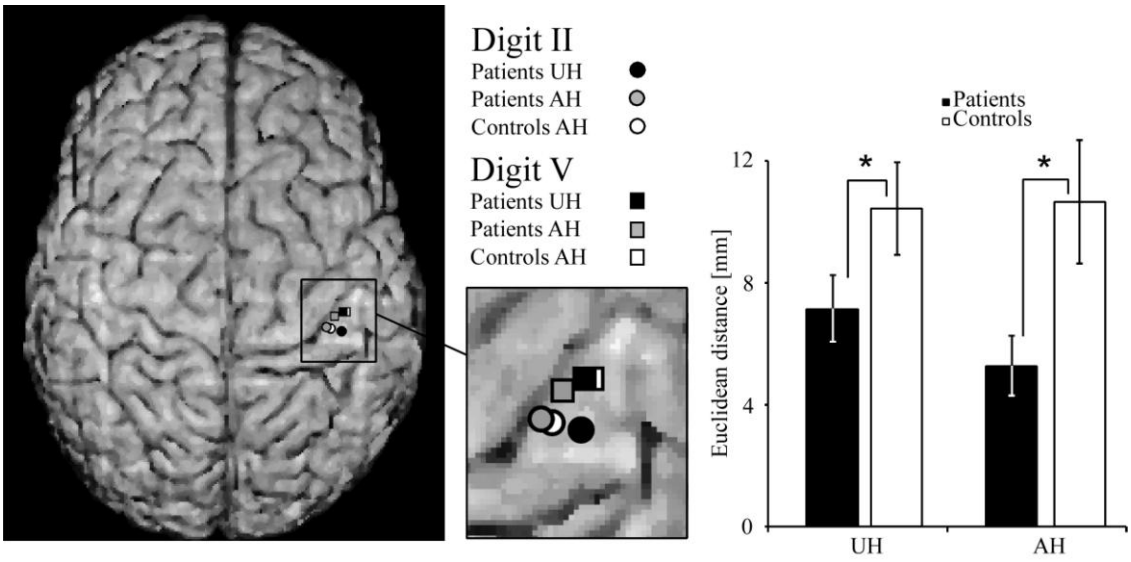

Figure 13. A schematic illustration visualizing the Euclidean distances separating digit II and V representation areas on an average brain. The group average (from eight patients with subcortical lesions and eight controls) locations of M50 ECDs of patients' AH and UH and one hemisphere of controls are all superimposed on the same hemisphere for comparison. Note the smaller distance between the ECD locations of the two fingers in the patients, particularly in the AH. The graph on the right shows the average Euclidean distances with the narrow bars indicating standard errors of mean. * $P < 0.05$. (AH = Affected hemisphere, UH = Unaffected hemisphere)

In all five patients with cortico-subcortical lesions, MN stimulation of the normal hand elicited the N20m-P35m-P60m sequence, whereas on the palsied side, none of these components were detectable in four patients, the same patients in whom the M50 was absent after tactile stimulation. In the fifth patient (P5 in Table 3) N20m was absent, but P35m and P60m were present. Despite the absent early MN SEF components in AH, the most prominent activation within the first 200 ms occurred in the vicinity of the contralateral sensorimotor area in all these five patients (Figure 14).

The secondary somatosensory cortices, contralateral (SIIc) and ipsilateral (SIIi), were frequently activated in controls and patients with subcortical lesions. On the contrary, in patients with cortico-subcortical lesions SII activity was rare. Most notably, stimulation of the palsied hand evoked SIIc activity in none and SIIi activity in only one (P3 of Table 3) of the five patients. Due to a great variability of latencies and source strengths, we did not further compare the ECD properties of the SII responses. SIi activity within 100 ms after MN stimulation was not detected in any control or patient. Posterior parietal cortex (PPC) and mesial cortex activation was inconsistent in both patients and control subjects and was, therefore, not analyzed further. It is, however, noteworthy that neither area was activated in any of the patients with cortico-subcortical lesions.

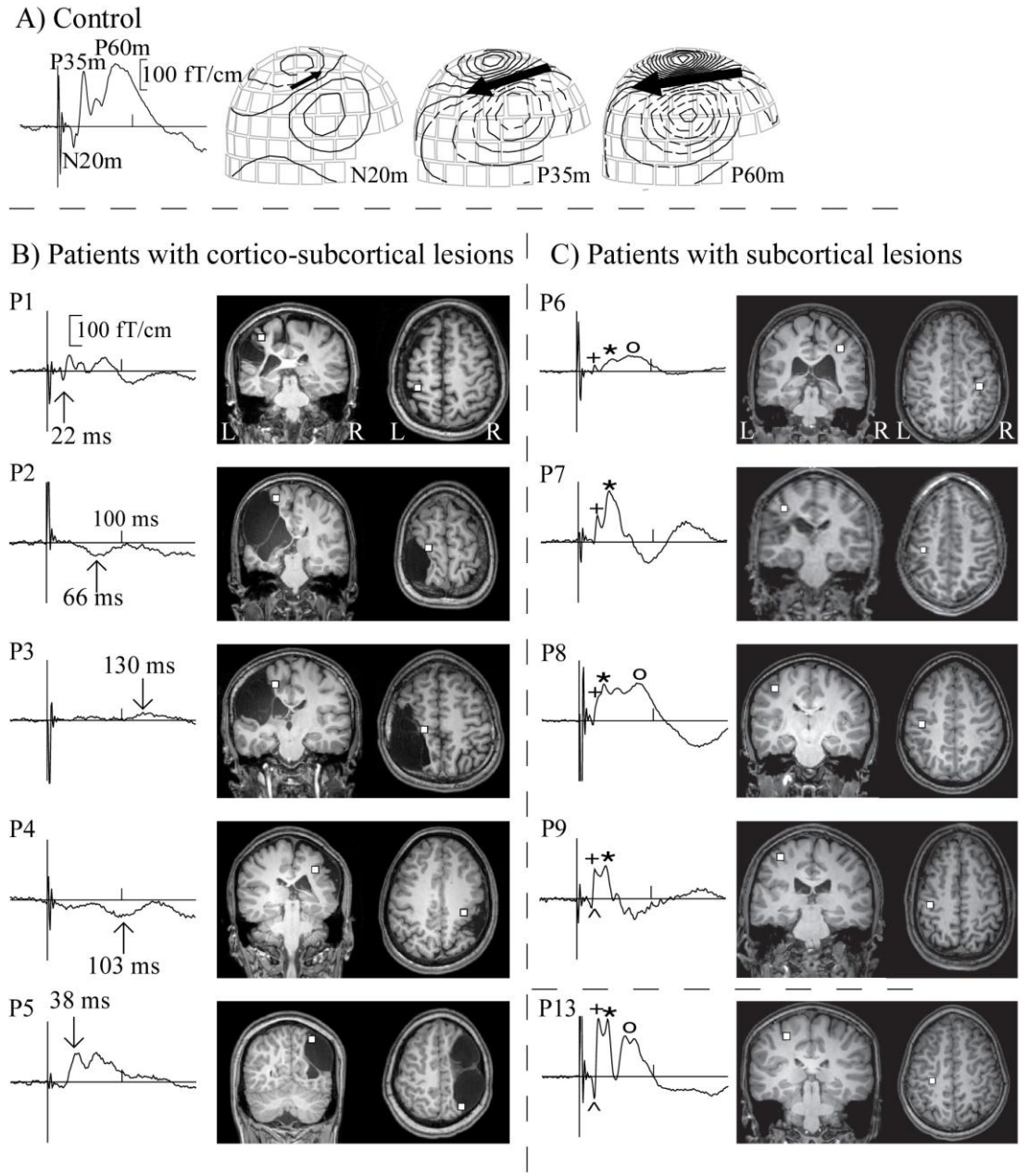

Figure 14. A) A typical control subject. On the left the SEF waveform from one gradiometer channel above the right SI showing maximal response after stimulation of the left MN. On the right the isofield contour maps during the main deflections (N20m, P35m, P60m) reflected on the helmet surface. Dashed lines indicate field coming out of the head and continuous lines field entering the head. B) Patients with cortico-subcortical lesions (P1–5). C) Patients with pure subcortical lesions (P6–9 with one or two MN SEF components absent, P13 representing the four patients with N20m, P35m, and P60m MN responses present). Left column for both patient groups shows the maximal response waveforms from one gradiometer channel after stimulation of the MN of the palsied hand. For P1–5 the arrow points to the earliest contralateral response, superimposed on the MRIs. For P6–9 and P13, the N20m is marked with ^, P25m with +, P35m with *, and P60m with o. The P35m (P6–9,13) which was present in all of these patients is superimposed on individual MRIs. Note that SEFs of P1–4 have no normal components and the P25m is present in all patients of column C.

6.4.3. Comparison of results from MEG, MRI, and behavioral tests

To correlate the MEG results with clinical data and imaging findings we divided the patients into three categories according to the number of absent SIc MN SEF components (N20m, P35m, P60m) (Table 3); Group A: none of the three components present at AH, Group B: one or two MN component absent at AH, Group C: all three components present. These categories correlated with lesion type (Phi $P = 0.01$; most patients with cortico-subcortical lesions had no normal MN SEF components) and lesion size in the MRI (Weighted Kappa: $P = 0.004$; large lesions in the MRI were associated with more components absent). The results of the behavioral tests also correlated with SEF categories [Weighted Kappa: Manual ability Classification System (MACS) $P = 0.01$; 2 point discrimination (2-PD) for digit II $P < 0.001$].

Table 3. Classification of the CP patients according to SEFs from the affected hemisphere together with MRI findings and results from clinical examinations of the palsied hand. Lesion size 3: an infarction of the whole middle cerebral artery (MCA) area or a corresponding size of some other type of lesion; 1: a spot type lesion. MACS scores (Eliasson *et al.*, 2006) describe bimanual ability of CP patients in everyday life. They are generally given from I to V, where I signifies, at most, minor disability in fine hand motor function. In our patients the worst score was III, indicating difficulties in performing everyday activities and dependency on environmental adjustments. The 2-PD test score 1 indicates that both static and dynamic 2-PD abilities were normal, 2 indicates moderate ability in one and normal in the other test, and 3 moderate to poor ability in both tests (for normality levels in each test, please refer to the methods section). (Gr = Group, GA = Gestational age, MN SEF = median nerve somatosensory evoked magnetic field, CS = Cortico-subcortical, S = Subcortical, MACS = manual ability classification system, 2-PD = 2 point discrimination, DII = Digit II, np = not performed, nf = not feasible)

Gr	#	GA if preterm	MN SEF	Lesion location	Lesion type	Lesion size	MACS	2-PD DII
A	**P1**	40+3	Major abn.	CS	Infarction	3	nf	np
	P2	32+5	Major abn.	CS	Infarction	3	III	np
	P3	40+2	Major abn.	CS	Infarction	3	III	3
	P4	40+2	Major abn.	CS	Polymicrogyria	3	II	3
B	**P5**	40+1	Minor abn.	CS	Infarction	3	III	2
	P6	31+1	Minor abn.	S	PVL	3	III	2
	P7	42+6	Minor abn.	S	Infarction	2	II	np
	P8	40+1	Minor abn.	S	Infarction	2	I	2
	P9	28+5	Minor abn.	S	Porencephaly	1	II	np
C	**P10**	34+5	Normal	S	Infarction	2	I	1
	P11	32+2	Normal	S	Infarction	1	I	1
	P12	42+1	Normal	S	Infarction	1	I	1
	P13	41+6	Normal	S	Infarction	1	I	1

6.4.4. Effect of gestational age

Of all the CP patients, five had been born preterm (Table 3). The lesion was cortico-subcortical in one of these five patients (Patient 2). In the other four, the defect was in the periventricular white matter, additionally involving the thalamus in one (Patient 6) and the internal capsule in two patients (10 and 11). No obvious differences existed in SEFs between the CP patients born preterm and those born fullterm, though no proper statistical comparison between these groups could be made because of the insufficient number of subjects in each group.

7. DISCUSSION

In this thesis we were able to demonstrate that somatosensory MEG measurements can be reliably conducted in newborns and young infants. We showed previously unknown, major differences in the early cortical responses from the primary somatosensory area between newborns and adults. We further demonstrated how the cortical activity pattern of newborns develops to the adult form over the first years of life. Finally, we applied the acquired knowledge about normal neonatal SEFs and their development with age in two patient populations: preterm infants and adolescents with hemiplegic cerebral palsy.

7.1. Methodological considerations

One of our greatest challenges was establishing a reliable method for somatosensory infant MEG measurements and data analysis, which I have described in detail in the methods section An MEG measurement session involving infants requires a lot of time and patience. All our recordings were performed when the infants were in natural sleep. Most of the failures in infant measurements resulted from the infant not falling asleep within two hours after which the session was generally interrupted. Altogether four newborns, not included in the number of subjects of the thesis, who arrived at the laboratory to participate in these studies, did not fall asleep within the time limit. When the infant did fall asleep, our success rate in the recordings was very high. Data of only one newborn were completely excluded because of problems with the measurement of head position during the recording. In several infants, the head position measurement had to be repeated to get a reliable estimation, however. The challenges in head position measurement are most likely due to the disproportion between the size of the sensor helmet, designed for adults, and that of a newborn's head. This results in longer distance from some of the position indicator coils to the MEG sensors and, consequently, worse signal-to-noise ratio for the head position measurement than in adults. SEFs could be identified and modeled with ECDs in all infants in whom the measurement was successfully carried through, though some SEF components were missing in a few infants. Our experience is that the head of a newborn needs to be right on the surface of the measuring helmet for reliable SEF recordings. Therefore, it was not possible to record from both hemispheres simultaneously. This sets certain limits on the experimental setups by, *e.g.*, doubling the measurement time when both ipsilateral and contralateral activity is of interest.

Possible head movements during the measurement constitute another important issue in infant MEG studies. We compensated for this by conducting the recordings when the infants were asleep and lying still. When occasional twitches occurred and the head moved, the MEG recording was interrupted and the head position measurement was repeated. We did not use continuous head position measurement because upon project initiation this was not yet available in our laboratory. In the future, continuously measuring the head position may facilitate the infant measurements as at least part of the head movements can be compensated without interrupting the measurement.

Based on the experience from the Study I, we found tactile stimulation to be easier to apply in small infants than electric MN stimulation. In addition, artifacts in MEG produced by the electrical MN stimulation are greater in newborns, due to the proximity of the stimulus to the sensors. Furthermore, the parents were often more compliant with the tactile than the electrical stimulus. We decided to use tactile stimulation in the other studies involving infants, since the tactile stimulation produced a response in the contralateral somatosensory cortex as reliably as MN stimulation.

7.2. SEFs to median nerve stimulation

7.2.1. Healthy newborns

In newborns, the first cortical magnetic response after MN stimulation at the wrist reached its maximum at about 30 ms (n-M30). This signifies that the somatosensory pathway from the periphery to the cortex is developed enough to produce early synchronous activation of cortical neurons. The latency delay compared with the adult N20m agrees with the previous infant SEP studies (Hrbek *et al.,* 1973; Willis *et al.*, 1984; Laureau and Marlot, 1990; George and Taylor, 1991) and is most likely due to incomplete myelination of the pathway, even though the distance from the hand to the cortex is shorter than in adults. The similar generation area and orientation of the n-M30 and N20m current sources also suggest that similar cortical mechanisms may underlie the two responses.

After the initial N20m/n-M30, the SIc activity in adults and newborns, however, differed dramatically. In the newborns, the anterior orientation of the M60 source current was similar to that of the n-M30, whereas in adults the well known P35m with posterior current orientation follows the N20m (*e.g.* Wood *et al.*, 1985; Hari and Forss, 1999). Some previous neonatal SEP studies seemingly disagree with this result by reporting an "adult-like" N1-P1 sequence with only slightly prolonged latencies (Willis *et al.,* 1984; Laureau *et al.,* 1988; George and Taylor, 1991). This is, however, likely to be an artificial effect of the highpass filter setting applied in these studies (see Pihko and Lauronen, 2004) as others (using a lower highpass cutoff value), showed clearly distinct morphology of early SEPs in newborns compared with adults (Desmedt and Manil, 1970; Hrbek *et al.,* 1973; Laget *et al.*, 1976; Karniski, 1992; Karniski *et al.*, 1992). Furthermore, the SEP over the central contralateral area represents activity at both areas 3b and 1, the latter of which is considered to be mostly invisible to MEG. Whereas the N1 is probably generated at area 3b and detected both by EEG and MEG, the P1 SEP may reflect activity of area 1 (Karniski *et al.,* 1992).

At present, no consensus concerning the generation mechanism of the adult P35m exists (see Review of literature section). Both excitation of the distal portions of the apical dendrites (Allison *et al.*, 1989; Allison *et al.*, 1991b) and inhibition of the proximal parts may contribute (Huttunen and Hömberg, 1991; Wikström *et al.*, 1996; Valeriani *et al.*, 1998; Restuccia *et al.*, 2002). In newborns, the wide initial deflection (nM30-M60) may reflect prolonged excitation in the proximal parts of apical dendrites, for which there are several possible underlying causes, *e.g.*, slow kinetics of intrinsic membrane conductances and immature neurotransmitter receptors.

In cortical neurons of rat pups, the excitatory postsynaptic potentials last several hundreds of milliseconds and inhibitory responses are completely absent (Kim *et al.*, 1995). The prolonged excitation may be due to slow deactivation kinetics of the glutamate receptors at this developmental stage (Moody and Bosma, 2005). Furthermore, though GABAergic synapses are formed even before the glutamatergic ones, during early development, $GABA_A$ receptor activation excites neurons due to a high intracellular Cl^- concentration (Moody and Bosma, 2005; Represa and Ben-Ari, 2005; Dzhala *et al.*, 2005). In rodents, the upregulation of the K^+-Cl^- cotransporter KCC2 expression and the following decrease in the intracellular Cl^- changes the effect of GABA from excitatory to inhibitory postnatally (Rivera *et al.*, 1999; Ben-Ari *et al.*, 2004; Herlenius and Lagercrantz, 2004; Represa and Ben-Ari, 2005). In human neonates, upregulation of KCC2 expression parallels changes in the slow-frequency EEG activity from preterm to term age (Vanhatalo *et al.*, 2005). At full term, however, KCC2 expression is still lower than in adult cortex (Dzhala *et al.*, 2005). In our newborns, the SEF waveform is surprisingly similar to that seen in patients with Angelman syndrome, caused by a deletion in the $GABA_A$ receptor subunit gene (a wide initial deflection with an anteriorly pointing ECD and absent P35m) (Egawa *et al.*, 2008).

Also, the course of synaptogenesis beginning from the deep cortical layers and progressing towards more superficial layers has been suggested to account for the changing properties of SEP responses during early development (Kostović *et al.*, 1995; Kostović and Judaš, 2002). According to current knowledge, a significant portion of short cortico-cortical connections are established postnatally (Kostović and Jovanov-Milošević, 2006) with active synaptogenesis continuing for several months or even years after birth (Huttenlocher and Dabholkar, 1997). Thus, the lack of P35m-like response could also simply reflect a lack of functional short cortico-cortical connections necessary for mediating the response.

7.2.2. CP patients

In the CP patients, the most prominent cortical response to MN stimulation was always found at the contralateral primary somatosensory cortex (SIc) or in nearby areas. Thus, our findings support the notion (*e.g.* Guzzetta *et al.,* 2007) that the organization of the somatosensory system does not follow that of the motor system, which may shift to the ipsilateral hemisphere by preservation of the normally withdrawn ipsilateral corticospinal tracts (Eyre, 2007). Accordingly, our experience from the somatosensory newborn studies is that early SEFs are predominantly detected at the SIc at fullterm age, in contrast to bilateral MEPs elicited by TMS (Eyre, 2007).

Interestingly, however, in both hemispheres of the CP patients with subcortical lesions an additional peak, P25m, preceded the P35m, in contrast to a single P35m peak of most controls. The P25m, or P22m in some studies, generally appears as a small notch in the ascending phase of P35m. It may, however, be enhanced in patients with various subtypes of cortical myoclonus (Mima *et al.*, 1998; Forss *et al.*, 2001) as well as some adult stroke patients (Forss *et al.*, 1999). Our own unpublished observation is that P25m becomes more pronounced in healthy adults with higher stimulation frequencies (ISI 300 ms). Thus the prominent P25m, together with the delayed P35m, may reflect dysfunction in the information processing sequence at SI. Whether these differences are directly caused by the lesion or secondary to the reduction of movement and sensory experience needs further investigation.

In four of the five CP patients with cortico-subcortical lesions, SIc responses to stimulation of the palsied hand were markedly abnormal, but behaviorally tactile function was only moderately impaired. In infant macaques, the SIIc is able to compensate, at least partly, for the functions of an ablated SI area (Burton *et al.*, 1990), which is not the case in adult macaques (Pons *et al.,* 1988). In adult stroke patients with abnormal SIc SEFs, SIIc responses were absent, but SIIi response was always present (Forss *et al.,* 1999). Of our five patients, SIIi activity was detected in one and that of the SIIc in none. PPC, mesial cortex, or SIi were neither activated in any of the five patients. Previously, in CP patients with cortical defects, normal latency SEPs were evoked in the affected hemisphere by stimulation of the palsied hand (Guzzetta *et al.,* 2007). Our findings, thus, partly agree (location) and partly disagree (latency) with this previous study.

7.3. SEFs to tactile stimulation

7.3.1. Healthy newborns

After tactile stimulation, the current sources underlying the main early SEFs of newborns (M60) and adults (M50) had opposite orientations, in accordance with the MN results. The source location and anterior current orientation of the newborn M60 were consistent with activation of the SIc. On the contrary, the generation area of the M200 was located significantly more inferior and lateral to that of M60. The relative location of the M200

source compared to the M60 source and the vertical orientation of the M200 source current are typical for responses originating from the secondary somatosensory cortex (SII) on the upper bank of the Sylvian fissure (Hari *et al.,* 1983; Karhu *et al.,* 1991; Hari *et al.,* 1993). We therefore suggest that the M200 represents activity of the SII indicating that both the connections to and the neurons at the SII are sufficiently developed to produce a detectable SEF response at fullterm age. In addition, in four out of eight newborns, stimulation of the ipsilateral hand during quiet sleep evoked SEFs with source location and orientation coinciding with those of the M200 evoked by stimulation of the contralateral hand. Bilateral SII activation after unilateral hand area stimulation is also commonly detected in adult MEG studies (Hari *et al.,* 1983; Hari and Forss, 1999).

In newborns, the M200 source strength was significantly affected by the change in ISI, unlike that of the M60. The SII SEFs in adults are also more easily affected by ISI than the SEFs from SI (Hari *et al.,* 1990; Hari *et al.,* 1993; Forss *et al.,* 1994a; Wikström *et al.,* 1996). In practical terms, for a reliable recording of evoked potentials a longer ISI is required in young infants than in older subjects (Desmedt and Manil, 1970; George and Taylor 1991). Reduction of the measurement time, however, favors the use of shorter ISIs in MEG of newborns and infants, since the recording cannot be easily extended beyond awakening. Since we found no significant group level difference in either response (M60 or M200) between the 2 and 4 s ISIs, we conclude that 2 s is the most suitable ISI (of the three ISIs that were tested) to study these particular responses. When only the M60 is of interest, even an ISI as short as 0.5 s may suffice.

Sleep stage did not significantly affect the M60 strength, which is in accordance with the SI responses in the adults of Study IV, as well as previous reports of adults (Kitamura *et al.,* 1996; Kakigi *et al.,* 2003). In a previous newborn MEG study, the M60 amplitudes calculated from vectorsums attenuated in AS compared with QS (Pihko *et al.,* 2004). Thus, a weak tendency towards enhanced M60 in QS in neonates may exist, but this effect did not reach the significance level in our Study II investigating the activation magnitude at the source rather than sensor level. In adults, the SII responses are generally diminished in sleep (Kitamura *et al.,* 1996, Kakigi *et al.,* 2003) and completely absent in slow-wave sleep (our own unpublished observation). On the contrary, in newborns, M200 was stronger in QS (characterized by slow-wave activity) than AS (characterized by rapid eye movements like REM sleep of adults). Thus, even though the sleep stages of newborns and adults are not fully comparable, their effect on SII activity is markedly different. The mechanisms and possible physiological significance of this phenomenon remain yet unknown.

7.3.2. Development

The early SEFs systematically transformed over the first years of life so that in children 2 years and older, sources underlying the early responses to tactile stimulation were similar to those of adults in terms of orientations (M30 with anteriorly pointing ECD followed by M50 with posterior ECD orientation). As the age effect was independent of vigilance state, we conclude that it reflects development of the functional somatosensory

network. In adults, M50 is likely to represent similar events as the P35m after MN stimulation. As P35m has been linked to 2 point discrimination (2-PD) ability (Wikström *et al.,* 1996), in behavioral terms its lack, or the lack of M50, in newborns could reflect yet deficient lateral inhibition, corresponding to poorly developed tactile discrimination capability. Based on the present knowledge, however, it is not possible to say whether the SEF transformation parallels development of 2-PD ability, because its behavioral testing is not feasible in children until the age 4–6, when 2-PD is already well developed (Thibault *et al.,* 1994; Hermann *et al.,* 1996; Menier *et al.,* 1996) as is the SEF pattern.

7.3.3. Very preterm infants

The M60 was present after tactile stimulation in all the very preterm infants at term age, reflecting functional somatosensory pathways from the periphery to the SIc. In line with a previous SEP study, we found no difference in M60 latency (Klimach and Cooke, 1988a). In our study, however, the patients were on average 2.6 cm shorter than the control infants. The difference in body length hampers direct comparison of the response latencies and may mask a small but true difference in the conduction velocity. The source strength of M60 was, however, weaker in the patients than controls suggesting lower firing synchrony and/or a smaller number of active neurons in the SIc. In animal models, hypoxia or ischemia may lower the amplitudes of SEPs (Coyer *et al.,* 1986; McPherson *et al.,* 1986). MRI studies in human preterm infants have revealed increased cerebrospinal fluid volumes compared to term infants (*e.g.* Inder *et al.,* 2005). Although we did not perform volumetric analyses of the MRIs, differences in cerebrospinal fluid volumes should not have significantly influenced our results as MEG is practically insensitive to conductivity differences between the neural source and the device (Hämäläinen *et al.,* 1993) and our analysis was conducted on source rather than sensor level.

7.3.4. CP patients

One of the main new findings from Study V was that within the SI the cortical sources underlying the M50 responses, after tactile stimulation of contralateral digits II and V, were located significantly closer to each other in the CP patients with subcortical lesions than in controls. Importantly, the effect was seen in both hemispheres. These changes in SIc hand representation may be either a direct result of the lesion and/or result from inappropriate sensory experience due to the movement disability during development. The SI somatotopical map is known to be capable of undergoing significant remodeling according to sensory experience. In adult owl monkeys, surgical fusion of adjacent digits results in a fusion of the SI receptive fields (Allard *et al.,* 1991) as does solely training consisting of synchronous tactile stimulation to adjacent fingers (Wang *et al.,* 1995). In humans, altered peripheral input after amputations (Flor *et al.,* 1995), or surgical repair of syndactyly, induce SIc map plasticity (Mogilner *et al.,* 1993). The same applies for carpal tunnel syndrome (Tecchio *et al.,* 2002) and chronic pain (Juottonen *et al.,* 2002; Vartiainen *et al.,* 2008; 2009). In our patients the shorter distance could reflect fusion of cortical finger representation areas due to difficulties in fine hand motor control and, consequently, inappropriate sensory experience.

Interestingly, in these patients with subcortical lesions we consistently found changes not only to stimulation of the palsied hand but also the normal hand. Previously, bilateral changes in the cortical representation areas were seen in patients with unilateral focal hand dystonia (loss of control of individual finger movements) (Elbert *et al.*, 1998) and an animal model of the same condition (Byl *et al.*, 1997). The underlying mechanisms remain unknown, however. Transient cortical changes on the unaffected side have been reported after finger amputation in flying foxes (Calford and Tweedale, 1988) and unilateral SI lesions in flying foxes and monkeys (Clarey *et al.*, 1996). In human adults with unilateral stroke, decreased callosal inhibition was suggested to lead to enhanced excitability in the unaffected hemisphere (Forss *et al.*, 1999). Further studies in CP patients are necessary to confirm the present findings and to determine the underlying mechanisms and their significance.

7.4. SEFs from the ipsilateral primary somatosensory cortex (SIi)

In two of the eight healthy newborns, stimulation of the ipsilateral (right) hand evoked activity in the right hemisphere with source location very close to that of M60 evoked by stimulation of the contralateral (left) hand. In these two newborns the ipsilateral source was most likely at or near the SI. In an fMRI study of newborns, SIi responses were as strong and frequent as those from the SIc (Erberich *et al.*, 2006). In our study, the SIi responses were clearly less consistent than the SIc responses in accordance with another fMRI report (Arichi *et al.*, 2010). Even in the two infants showing SIi SEFs in our study, the latencies were longer than those of the M60 responses for the contralateral hand. Anatomically, a greater amount of callosal fibers in newborns compared to adults could account for the neonatal SIi responses. For example in newborn monkeys, the number of callosal axons is three times greater than in adult monkeys, and in human neonates too the cross sectional area of the corpus callosum decreases towards the end of gestation and still during the first two postnatal months (Innocenti and Price, 2005). On the contrary, to our knowledge, no anatomical evidence favors existence of direct ipsilateral projections (transient or permanent) from the hand area to the primary somatosensory cortex.

In Study V, SIi responses to tactile stimulation were more frequent in the patients with subcortical lesions than their controls. Most of these responses were evoked from the normal hand and recorded in the affected hemisphere. These findings should not therefore be taken as support for contralesional reorganization of the somatosensory representation. In healthy adults, stimulation of the hand area rarely evokes SEFs from the SIi (Hari and Forss, 1999; Kanno *et al.*, 2003), though exceptions exist (MN stimulation: Korvenoja *et al.*, 1995; Kanno *et al.*, 2003; tactile stimulation: Zhu *et al.*, 2007; Pihko *et al.*, 2010). Frequent SIi activity in certain patient populations may reflect brain pathology and increased excitability (Mima *et al.*, 1998; Forss *et al.*, 2001). Thus, the ipsilateral responses provide further evidence on changes in organization and/or function of the affected hemisphere and interplay between the SI areas. Since tactile stimulation also activated the SIi in three controls, SIi activation in the patients can not be considered abnormal *per se*. Interestingly, MN stimulation evoked no SIi activity within the first 100 ms in any patient or control.

7.5. Correlation of SEFs with behavioral and MRI data in the very preterm infants and CP patients

Our data from the very preterm infants highlight the importance of also analyzing the long-latency responses from areas other than the primary somatosensory cortex as the M200 was absent in four infants with anatomical lesions in the right hemisphere. Two infants with a comparable lesion had, however, a normal M200. Furthermore, in one control infant, the M200 deflection, though detectable in the waveforms, did not have a dipolar field pattern and its source could not be modeled. Thus, the prognostic significance of the absence/presence of M200 remains to be seen. It is noteworthy, that in Study V the SII activity was frequent in the control adolescents and the CP patients with purely subcortical lesions, but SIIc responses were not present in any of the CP patients with cortico-subcortical lesions and also the most severe clinical symptoms.

Furthermore, in Study V, absence of one or more of the early SIc MN SEF components correlated with location and size of the anatomical lesions as well as with motor and somatosensory skills. Previously, large defects and the late timing of the insult during development were associated with worse motor outcome in hemiplegic patients (Staudt *et al.*, 2002; 2004). Motor skills do not necessarily correlate with somatosensory abilities, however (Cooper *et al.*, 1995). SEPs, on the other hand, have closely correlated with motor function in hemiplegic children and 2 point discrimination ability of the palsied hand (Cooper *et al.*, 1995). The correlation found in our study demonstrates that the SEF findings are also clinically relevant. Further understanding of the individual functional changes underlying the common clinical symptoms may aid in developing more precise rehabilitation and treatment methods.

8. CONCLUSIONS

We have shown, in a relatively large number of newborns, that somatosensory stimulation evokes activity at both the SI and SII already a few days after birth. At this early age, the opposite current orientation underlying the main response from the contralateral primary somatosensory cortex in newborns, M60, compared with that of adults, P35m/M50, reflects the still developmental stage of a newborn's somatosensory system. Similarly, the enhancement of the newborn SII response (M200) during quiet sleep is in contrast with the lack of SII responses during slow-wave sleep in adults. The systematic change of SEFs during the first years of life reflects development of the cortical somatosensory circuits.

Study III showed that novel information about deficits in the cortical processing of the somatosensory information in preterm infants can be obtained with MEG. The normal latency and morphology of SEFs in the preterm infants recorded at term age suggest functional somatosensory pathways. The weaker strength of M60 may, however, reflect less synchronous firing and/or fewer activated neurons at SI. The association between absence of the M200 response and anatomical lesions in four preterm infants demonstrates that activity patterns at areas outside SI may also reveal clinically interesting information on the somatosensory system of infants. Determining the prognostic significance of this finding, however, remains a challenge for future studies.

Study V revealed differences of somatosensory processing within the SI in both hemispheres of hemiplegic CP patients with subcortical brain lesions as compared to their controls. Furthermore, no normal early SIc SEFs were detectable in the affected hemisphere of most patients with cortico-subcortical lesions. These results highlight the complex nature of functional reorganization after an early brain insult. Deeper understanding of the various changes in the functional sensorimotor networks underlying the common clinical symptoms of CP patients may ultimately enable more precise tailoring of rehabilitation and treatment strategies.

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