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NEONATAL SOMATOSENSORY RESPONSES AND NEUROCOGNITION IN EXTREMELY LOW GESTATIONAL AGE CHILDREN

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ACADEMIC DISSERTATION

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To my family

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original articles, referred to in the text by their Roman numerals:

I Rahkonen P, Nevalainen P, Lauronen L, Pihko E, Lano A, Vanhatalo S, Pesonen A-K, Heinonen K, Räikkönen K, Valanne L, Autti T, Andersson S, Metsäranta M. Cortical somatosensory processing measured by magnetoencephalography predicts neurodevelopment in extremely low-gestational-age infants. Pediatr Res 2013 Jun;73(6):763-771.

II Nevalainen P, Rahkonen P, Pihko E, Lano A, Vanhatalo S, Andersson S, Autti T, Valanne L, Metsäranta M, Lauronen L. Evaluation of somatosensory cortical processing in extremely preterm infants at term with MEG and EEG. Clin Neurophysiol, in press.

III Rahkonen P, Heinonen K, Pesonen A-K, Lano A, Autti T, Puosi R, Huhtala E, Andersson S, Metsäranta M, Räikkönen K. Mother-child interaction is associated with neurocognitive outcome in extremely low gestational age children. Scand J Psychol 2014 Aug;55(4):311-318.

IV Rahkonen P, Lano A, Pesonen A-K, Heinonen K, Räikkönen K, Vanhatalo S, Autti T, Valanne L, Andersson S, Metsäranta M. Atypical sensory processing in extremely low gestational age children. Submitted

 In addition, some unpublished material has been presented.

ABBREVIATIONS

AD	Axial diffusion
ADC	Apparent diffusion coefficient
ADHD	Attention deficit hyperactivity disorder
AS	Active sleep
ASD	Autism spectrum disorder
BPD	Bronchopulmonary dysplasia
BSID-III	Bayley Scales of Infant and Toddler Development - Third Edition
CP	Cerebral palsy
DEHSI	Diffuse excessive high signal intensity
DQ	Developmental quotient
DTI	Diffusion tensor imaging
ECD	Equivalent current dipole
EEG	Electroencephalography
ELBW	Extremely low birth weight
ELGA	Extremely low gestational age
EMG	Electromyography
EOG	Electro-oculography
FA	Fractional anisotropy
GM	Gray matter
GMDS	Griffiths Mental Developmental Scales
GOF	Goodness of fit
GW	Gestational weeks
HNNE	Hammersmith Neonatal Neurological Assessment
IQ	Intelligence quotient
ITSP	Infant/Toddler Sensory Profile
IVH	Intraventricular hemorrhage
LBW	Low birth weight

LVCP	Left-sided vocal cord paralysis
MCI	Mother-child interaction
MEG	Magnetoencephalography
MND-1	Simple minor neurological dysfunction
MND-2	Complex minor neurological dysfunction
MRI	Magnetic resonance imaging
MRO	Mutually responsive orientation
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit
OR	Odds ratio
PDA	Patent ductus arteriosus
PLIC	Posterior limb of internal capsule
PVL	Periventricular leukomalasia
QS	Quiet sleep
RDS	Respiratory distress syndrome
ROP	Retinopathy of prematurity
SI	Primary somatosensory cortex
SII	Secondary somatosensory cortex
SEF	Somatosensory evoked magnetic field
SEP	Somatosensory evoked potential
SGA	Small for gestational age
SQ	Subscale quotient
SQUID	Superconducting quantum interference device
TEA	Term equivalent age
US	Ultrasonography
VD	Ventricular dilatation
VLBW	Very low birth weight
VLGA	Very low gestational age
WM	White matter

ABSTRACT

Despite advancements in neonatal intensive care and increased survival of extremely low gestational age (ELGA) infants, many ELGA infants still develop with motor, sensory, cognitive, and behavioral impairments. Predicting adverse neurodevelopmental outcome as early as possible is a challenge in neonatology. Structural neuroimaging methods partly fail to detect milder brain abnormalities that may interfere with later developmental outcome, and neurological assessment is more unreliable in the neonatal period than in childhood. Thus, additional methods are needed for earlier and more accurate recognition of ELGA infants with adverse neurodevelopmental outcome.

The first purpose of this study was to assess the value of measuring higher cortical function by neurophysiological methods in predicting outcome of ELGA infants. Second, we aimed to examine possible difficulties in behavioral somatosensory processing and in mother-child interaction and their associations with developmental outcome.

The lack of somatosensory evoked magnetic fields (SEFs) from the secondary somatosensory cortex (SII) in magnetoencephalography (MEG) at term equivalent age (TEA), reflecting abnormal higher cortical functioning during somatosensory processing, was associated with worse neuromotor outcome of ELGA infants at two years of corrected age, not foreseen with structural neuroimaging methods. Further, we showed that SII responses can also be detected by measuring somatosensory evoked potentials during electroencephalography (EEG-SEP).

The quality of mother-infant interaction in mother-ELGA child dyads did not differ from that in mother-term child dyads. However, among ELGA children worse child adjustment and lower quality of maternal and dyadic behavior were associated with lower neurocognitive outcomes. Half of the ELGA children presented atypical behavioral sensory processing at two years of corrected age. Sensation seeking was common in ELGA children with neonatal neuroanatomical lesions.

In conclusion, the functional neurophysiological methods MEG and EEG-SEP hold promise as valuable additional tools in predicting outcome of ELGA children. The quality of mother-infant interaction may play a significant role in optimizing cognitive outcome after extremely preterm birth. Atypical behavioral sensory processing in ELGA children is common, but the pathogenesis and developmental significance of this phenomenon call for more research in the future.

INTRODUCTION

Improved perinatal care, antenatal steroids, proactive approach at birth, surfactant therapy for treatment of respiratory distress syndrome (RDS), and technical improvements in neonatal intensive care are crucial factors commonly underlying the increased survival rates of ELGA infants during the last two decades (Aylward 2005, Vohr et al. 2005, Serenius et al. 2013). At the same time, the rate of adverse neurodevelopment in infants born extremely preterm has remained essentially unchanged or decreased only slightly (Saigal & Doyle 2008, Jonsdottir et al. 2012). These trends have led to an increasing total number of ELGA children susceptible to motor, sensory, cognitive, and behavioral impairments (Saigal & Doyle 2008).

Improved survival rates of ELGA infants have changed the focus in neonatal intensive care to the prevention of long-term neurodevelopmental impairments (Aylward 2005). Early recognition of ELGA infants at risk of later developmental problems is important for several reasons. First, investigation of structural and functional changes in ELGA infants' brain deepens the knowledge about the pathogenesis of preterm brain injury and can provide new ideas on preventing this. Second, the results of the studies predicting neurodevelopment could be used as inclusion criteria for rehabilitation trials. Third, feedback from the studies predicting later neurodevelopment may help neonatal intensive care units (NICUs) to develop their processes to prevent neonatal brain injury and to support favorable neurocognitive development. Fourth, it is important to produce more reliable assessments for parents about possible later developmental challenges of their ELGA children. And finally, limited financial resources could be directed to the intensified follow up of children at increased risk for developmental impairments.

The risk of neurosensory and cognitive impairment has been associated with grade III and IV intraventricular hemorrhage (IVH) and severe motor delay with periventricular leukomalasia (PVL) (Woodward et al. 2006). In several studies, moderate to severe white matter (WM) injury has been associated with adverse neurodevelopmental outcome (Miller et al. 2005, Dyet et al. 2006, Brown et al. 2009). However, neurodevelopmental problems have also been reported in preterm infants with normal brain magnetic resonance images (MRI) (Mirmiran et al. 2004, Skiold et al. 2012).

Functional clinical neurophysiological methods have been overshadowed by structural neuroimaging in studying preterm brain and predicting neurodevelopment of preterm infants (Vanhatalo & Lauronen 2006). Magnetoencephalography (MEG), a neurophysiological functional

method in newborn brain research, has enabled study of cortical somatosensory functions also beyond primary cortical areas (Nevalainen et al. 2008a), i.e., not only thalamo-cortical but also cortico-cortical connections.

Developmental outcome is not dependent only on preterm brain damage; many external factors, such as sociodemographic factors (Williams et al. 2013), and mother-infant interaction can mold the outcome (Wijnroks 1998, Feldman et al. 2002). In addition to neuromotor and cognitive impairments, ELGA children are at increased risk for sensory impairments, behavioral problems, such as inattention and hyperactivity (Bhutta et al. 2002, Saigal & Doyle 2008, Delobel-Ayoub et al. 2009), and symptoms of autism spectrum disorders (ASDs) (Johnson et al. 2010).

The first half of this thesis (Studies I and II) focuses on measuring higher cortical functions by MEG and assessing the potential clinical value of this method in predicting neurodevelopment of ELGA infants. Furthermore, we aimed at testing whether these cortico-cortical functions could be demonstrated in routine neonatal electroencephalogram (EEG) complemented with median nerve stimulation. The second half of the thesis (Studies III and IV) concentrates on descriptive research on the possible connections of mother-child interaction and sensory processing patterns of ELGA children with previous neonatal neuroanatomical lesions and short-term neurodevelopmental outcome.

REVIEW OF THE LITERATURE

1. Preterm infants

According to the World Health Organization's (WHO) International Classification of Diseases, an infant born before 37 gestational weeks is preterm, regardless of birth weight. Very low gestational age (VLGA) refers to infants born before 32 and extremely low gestational age (ELGA) to infants born before 28 weeks of gestation. In the literature, birth weight is another way to describe prematurity. Low birth weight (LBW) refers to a birth weight of less than 2500 g, and very low birth weight (VLBW) and extremely low birth weight (ELBW) to birth weights of under 1500 g and 1000 g, respectively. Gestational age has traditionally been calculated from the day of the last menstrual period (Steer 2005). However, Finland as well as many other developed countries use more accurate assessment of gestational age based on fetal crown-rump length in the first trimester ultrasonography (Goldstein & Wolfson 1994).

The incidence of prematurity has increased worldwide, also in many developed countries, during last two decades (Blencowe et al. 2012). For example, in the USA the incidence of prematurity has risen from about 9% in the 1990s to 12.2% in 2009 (Kochanek et al. 2012). However, in Finland the rate of prematurity has been very stable, between 5.1% and 5.4% from 1987 to 2005 (Jakobsson et al. 2008).

Of 61 371 births in 2010 in Finland, 3568 infants (5.8%) were born preterm, 363 (0.6%) were VLGA, and 197 (0.3%) were ELGA (National Institute for Health and Welfare 2010). ELGA birth is associated with increased perinatal mortality, as shown in Table 1. The total perinatal mortality (stillbirths and deaths during the first seven days of life) was 4.5 per 1000 live births in 2009-2010 in Finland (National Institute for Health and Welfare 2010).

Table 1. Perinatal mortality of ELGA newborns in Finland in 2009-2010.

Gestational age (weeks)	Stillbirths (n)	Live births (n)	Total (n)	Deaths 0-6 days (n)	Perinatal mortality (per 1000 births)
22	35	14	49	14	1000
23	21	32	53	15	679
24	21	44	65	8	446
25	19	55	74	9	378
26	17	70	87	16	379
27	17	91	108	6	213

2. Neurodevelopmental outcome of extremely low gestational age (ELGA) children

The survival rates of ELGA infants have increased dramatically worldwide during the last decades (Saigal, Doyle 2008). Decreasing rates of cerebral palsy (CP) (Platt et al. 2007, Robertson, Watt & Yasui 2007) and improving cognitive outcome at two years of corrected age have been reported (Wilson-Costello et al. 2007). However, major neonatal morbidity has remained unchanged from 1995 to 2006 (Costeloe et al. 2012). Thus, the growing group of ELGA survivors is still at risk of adverse developmental outcome, which may appear as motor, sensory, cognitive, or behavioral problems (Bhutta et al. 2002, Mikkola et al. 2005, Salt & Redshaw 2006, Saigal & Doyle 2008).

The rate of substantial neurosensory impairments, such as CP, severe visual impairment, deafness, epilepsy, and developmental quotient (DQ) <-2SD, or intelligence quotient (IQ) <-2SD among ELGA children varies between 25% and 35% in different studies, depending on the definition of impairments and their severity (Wood et al. 2000, Doyle & Victorian Infant Collaborative Study Group 2004, Mikkola et al. 2005). Furthermore, ELGA children, even without substantial neurosensory impairment or subnormal IQ, are at risk of developing minor neuromotor and coordination difficulties (Goyen, Lui & Woods 1998, Davis et al. 2007).

Cognitive problems can lead to academic underachievement and school difficulties, which have been reported in over 70% and 50% of adolescents with birth weight < 750 g and 750-1000 g, respectively. Among normal birthweight controls, school difficulties were present in 13% (Saigal et al. 2000). Especially, difficulties in mathematics, regardless of IQ scores, have been reported (Klebanov, Brooks-Gunn & McCormick 1994, Botting et al. 1998, Taylor, Espy & Anderson 2009), as have reduced language abilities (Barre et al. 2011, van Noort-van der Spek, Franken & Weisglas-Kuperus 2012) and executive dysfunction (Anderson, Doyle & Victorian Infant Collaborative Study Group 2004). Impaired learning ability has been shown to persist into adulthood in VLBW adults without neurosensory defects compared with term-born adults (Strang-Karlsson et al. 2010).

The risk of behavioral problems, particularly in social skills and attention, is increased in preterm infants (Anderson, Doyle & Victorian Infant Collaborative Study Group 2003, Reijneveld et al. 2006, Farooqi et al. 2007, Johnson & Wolke 2013). VLBW children have been reported to have 2.6 to 4 times increased risk for attention deficit hyperactivity disorder (ADHD) (Aylward 2005, Delobel-Ayoub et al. 2006, Reijneveld et al. 2006). Other behavioral problems associated with ELGA children include anxiety, depression, shyness, unassertiveness, withdrawn behavior, conduct disorders, and problems with social skills (Botting et al. 1997, Aarnoudse-Moens et al. 2009).

Although ELGA children are at higher risk for neurocognitive and behavioral problems, most of them adapt surprisingly well to the demands of adult life. They do better than expected on the basis of neurocognitive tests in academic achievements and executive functioning in everyday life (Strang-Karlsson et al. 2010, Pyhälä et al. 2011, Heinonen et al. 2013).

2.1. Brain injury

The ELGA infant's brain develops rapidly and is vulnerable to organizational disturbances and injuries due to ischemia, inflammation, excitotoxicity, free-radical attack, and other possible exogenous and endogenous insults during neonatal intensive care (Ferriero 2004, Volpe 2009). The total brain volume increases almost threefold, the cortical GM fourfold, and the myelinated WM fivefold from 29 gestational weeks to TEA (Huppi et al. 1998b). The brain development phases vulnerable to insults in ELGA infants are the migration phase, the organization phase, and the myelination phase (Aylward 2005). The migration phase of nerve cells, including radial migration from the ventricular zone to the cerebral cortex and deep nuclei, and tangential migration parallel to the cerebral cortex, occurs from three to five months of gestation, and glial cell migration can

continue even later. ELBW infants have been shown to possess a smaller and less complex cortical surface at 38 to 42 gestational weeks than term infants (Ajayi-Obe et al. 2000). The organization phase from six months of gestation to about three postnatal years includes establishment and differentiation of subplate neurons, alignment and layering of cortical plate neurons, dendritic and axonal ramification, synaptogenesis, and glial proliferation and differentiation. The myelination phase refers to myelin membrane formation around axons, which begins at the sixth month of pregnancy and continues to adulthood (Volpe 2008). The brain developmental phases are demonstrated in Figure 1.

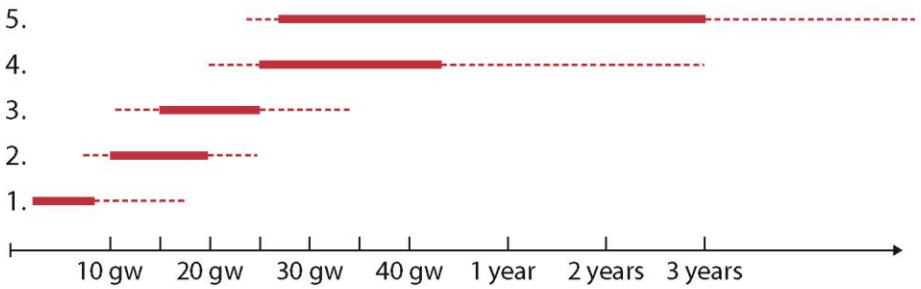

Figure 1. A schematic illustration of brain developmental phases. 1. Organogenesis, 2. Proliferation, 3. Migration, 4. Organization, 5. Myelination.

Disappearance of pre-myelinating oligodendrocytes, gliosis, and axonal damage are the typical findings in premature WM lesions (Marin-Padilla 1997, Haynes et al. 2003). The cortical subplate is a transient developmental layer in the human brain from 15 weeks of gestation to the age of 6 months and consists of oligodendrocytes, neurons migrating to the cortex, and transversing axons (Mrzljak et al. 1988, Kostovic et al. 2002, Kostovic & Jovanov-Milosevic 2006). The cortical subplate is vulnerable to direct injuries during the neonatal period in ELGA infants (Mrzljak et al. 1988, Kinney et al. 2012). Damage of the subplate neurons early in development can lead to failure in development of thalamo-cortical projections to cortical layer IV (Ghosh et al. 1990). Injury of subplate cells has been proposed as one possible mechanism for cortical deficits in ELGA infants because of the time correlation of peak period of subplate formation and vulnerability to brain

injury in ELGA infants and the crucial role of subplate neurons for the development of the cortex (McQuillen, Ferriero 2004).

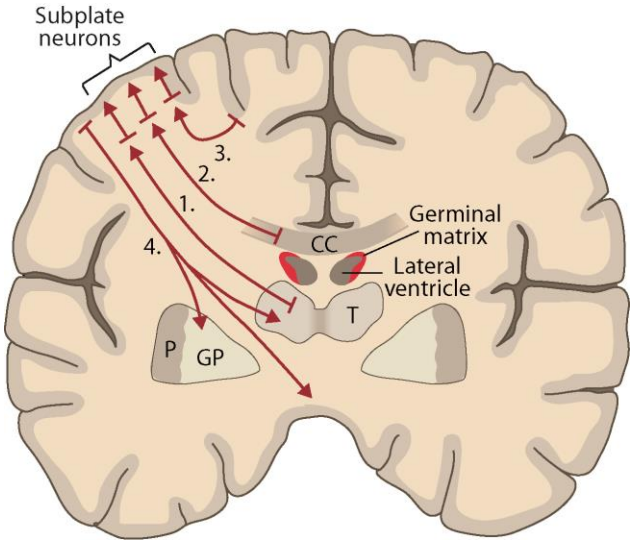

Figure 2. Critical stages in cortical development of ELGA infants. Axons from the thalamus (1), corpus callosum (2), and cortex (3) synapse on subplate neurons. Subplate neurons send axons to the cortex, enabling cortical development before the thalamo-cortical and cortico-cortical fibers reach the cortex (4). The descending axons from the cortex to the thalamus, basal ganglia, and corticospinal tracts are shown. Abbreviations: CC, corpus callosum; GP, globus pallidus; P, putamen; T, thalamus.

The germinal matrix, a collection of neuronal-glial precursor cells in the developing brain, is located between the caudate nucleus and the thalamus (Ballabh 2010). It is highly vascularized and susceptible to hemorrhage for many reasons (e.g. hypocarbia, arterial hypotension, high cerebral venous pressure, patent ductus arteriosus, and restlessness, all leading to fluctuating cerebral blood flow) (Van Bel et al. 1987, Mullaart et al. 1994, Coughtrey, Rennie & Evans 1997, Erickson et al. 2002). Advancements in neonatal intensive care have not resulted in a markedly reduced incidence

of intraventricular hemorrhage (IVH), which remains one of the major complications in ELGA infants. The incidence of IVH is 15-25% and 30-40% among infants born at 28-31and 25-27 gestational weeks, respectively (Larroque et al. 2003, Dyet et al. 2006). However, the incidence of severe grade III-IV IVH is much lower, 6.3% in a recent cohort study (Bolisetty et al. 2014). Risk factors of IVH include asphyxia, spontaneous vaginal preterm delivery, and lower gestational age (Vohr & Ment 1996, Larroque et al. 2003). Traditionally, IVH is classified into four grades. Grade I represents subependymal bleeding, grade II intraventricular bleeding without ventricular enlargement, grade III intraventricular bleeding with ventricular enlargement, and grade IV intraventricular bleeding with parenchymal affision (Papile et al. 1978). This classification has been criticized for being based on anatomical findings and disregarding pathogenesis. IVH grade IV has later been demonstrated to represent periventricular hemorrhagic infarction rather than periventricular expansion of IVH (Volpe 2008). The majority of IVHs appear in the first 48 hours of life and are asymptomatic, and the diagnosis is based on cranial ultrasonography (US) (Ballabh 2010). IVH is associated with later decreased cerebellar and cortical volume (Vasileiadis et al. 2004, Srinivasan et al. 2006, Tam et al. 2009). Long-term outcome among preterm IVH survivors depends on the severity of IVH. The incidence of CP, mental retardation, or both is estimated to be about 15%, 25%, 50%, and 75% after grade I, grade II, grade III, and grade IV IVH, respectively (Volpe 2008). In a recent study by Bolisetty et al. (2014), among 1472 ELGA survivors the incidence of CP was 30% after grade III-IV IVH, 10.4% after grade I-II IVH, and 6.5% without IVH. However, the associated WM injury is the most important factor modifying the outcome of IVH (Volpe 2008).

Periventricular hemorrhagic infarction has been reported in 10% of infants with birth weight < 750 g and in 2% of those with birth weight between 750 g and 1500 g (Bassan et al. 2006). A complication of IVH, resulting often in poor outcome, is post-hemorrhagic ventricular dilatation (VD). The incidence of VD varies from 5-15 % in grade II IVH to 65-85% in grade III-IV IVH. Disturbance in reabsorption of cerebrospinal fluid and obliterate arachnoiditis in the posterior fossa are supposed to be the underlying pathogenetic mechanisms of post-hemorrhagic VD (Volpe 2008). Especially, hydrocephalus requiring operative treatment (shunt) is associated with adverse neurodevelopmental outcome (de Vries et al. 2002, Brouwer et al. 2008).

Periventricular leukomalasia (PVL) can be either a focal or diffuse injury of the cerebral WM. In focal PVL, localized necrosis in periventricular WM can be either macroscopic, i.e., detectable by US (cystic PVL), or microscopic (non-cystic PVL) (Volpe 2009). The latter is much more common

in modern NICUs, where cystic PVL occurs in < 5% of VLBW infants (Larroque et al. 2003, Woodward et al. 2006). Impaired cortical development (Inder & Volpe 2000) and deep GM injury (Rees & Inder 2005) have been associated with focal PVL. In very preterm infants with cystic PVL, the prevalence of CP at five years of age has been reported to be about 60% (Beaino et al. 2010).

In diffuse PVL, premyelinating oligodendrocytes are reduced and increased oligodendroglial progenitors do not seem to be able to differentiate into mature myelin-producing cells. As a result, hypomyelination, ventriculomegaly, and diffuse signal abnormalities in MRI as well as abnormal diffusion parameters in diffusion tensor imaging (DTI) are seen (Volpe 2009). Pathogenesis of periventricular white matter injury (WMI) is not fully understood, but ischemia and inflammation are assumed to play a central role. Ischemia is particularly injurious to preterm WM because of immature cerebral blood flow autoregulation and vulnerability of vascular end zones and border zones. On the other hand, inflammation is known to activate microglial cells to produce cytokines, which are damaging to WM. Other mechanisms presented in the pathogenesis of periventricular WMI include excitotoxicity and free radicals (Back 2006, Volpe 2008). Diffuse periventricular WMI at TEA, reported in over 50% of VLBW infants in imaging studies, has been associated with adverse neurocognitive outcome at two years of corrected age (Volpe 2009).

Advances in neuroradiology have increased the recognition of preterm cerebellar injury (Bodensteiner & Johnsen 2005, Limperopoulos et al. 2005), which seems to include a prominent hemorrhagic component. Two studies reported an incidence of cerebellar hemorrhagic infarction of almost 20% in infants with birth weight < 750 g (Limperopoulos et al. 2005) and 9% in infants born before 30 weeks of gestation (Biran et al. 2011). Primary hemorrhage into the germinal matrix of the cerebellum and vaso-occlusive hemorrhagic infarction have been suggested as underlying mechanisms of cerebellar hemorrhagic infarction (Johnsen, Bodensteiner & Lotze 2005).

The contribution of cerebellar injury to neurodevelopmental outcome in preterm infants remains unclear. In some studies, isolated hemorrhagic cerebellar injury has been associated with motor and cognitive deficits as well as with delayed language skills (Limperopoulos et al. 2007), whereas others have found no association with neurodevelopmental outcome (Steggerda et al. 2013).

2.2. Parent-child interaction and socioeconomic factors

Developmental outcome of ELGA infants is supposed to be affected by numerous factors in addition to the course and complications of neonatal intensive care. Early mother-child interaction is one factor that has been studied as a predictor of neurodevelopmental outcome (Wijnroks 1998, Feldman et al. 2002).

The literature regarding mother-preterm child interaction is controversial. Some of the studies have reported worse mother-preterm infant interaction than in mother-infant dyads with term children (Gerner 1999), and the mothers of preterm children have been described as more controlling and less sensitive in the interaction with their children (Muller-Nix et al. 2004, Forcada-Guex et al. 2006). Others have found no differences in mother-infant interaction between preterm and term infant-mother dyads (Korja et al. 2008, Montirosso et al. 2010). Neurological impairments of ELGA infants have been proposed as confounding factors in assessing parent-child interaction, because they might challenge the development of sensitive parenting and appropriate mutual interaction. However, high-quality early mother-infant interaction has been suggested to mitigate the influence of prematurity on cognitive development (Wijnroks 1998, Forcada-Guex et al. 2006).

Important environmental factors affecting ELGA infants' neurodevelopmental outcomes include socioeconomic status of the preterm child's family, the mother's educational level, and maternal physical and mental health (Aylward 2005). In a recent retrospective study assessing the effect of gestational age at birth and maternal characteristics on school skills, the strongest predictor of reduced school skills was mother's educational level. Socioeconomic factors seemed to be more emphasized among extremely preterm infants than among late preterm infants (Williams et al. 2013).

2.3. Atypical sensory processing

Behavioral sensory processing can be defined as the capability to register, adapt, interpret, and organize sensory stimuli in a flexible manner (Miller et al. 2007). Although in routine follow-up ELGA children seem to often present atypical sensory responses to everyday sensory stimuli, the literature on sensory processing in preterm infants is scarce (Wickremasinghe et al. 2013). In a few studies with varying gestational ages of preterm children and varying ages at sensory processing

assessments, increased Sensation Seeking (Case-Smith, Butcher & Reed 1998), increased oral and auditory sensory processing dysfunction (Bart et al. 2011), and atypical sensory profile in terms of under-responsiveness (Low Registration), over-responsiveness (Sensation Avoiding and/or Sensory Sensitivity), Sensation Seeking, and auditory, tactile and vestibular processing have been reported (Wickremasinghe et al. 2013).

Atypical sensory behaviors are common in autism spectrum disorders (ASDs) and attention deficit hyperactivity disorder (ADHD), where the main findings are under-responsivity and Sensation Seeking, respectively (Baranek et al. 2006, Schoen et al. 2009, Ghanizadeh 2011). Interestingly, positive screening rates (e.g. on the Modified Checklist for Autism in Toddlers) for ASD in preterm children are as high as 16-40% (3-5% in term children), while the incidence of ASD with diagnostic tests (e.g. Autism Diagnostic Interview-Revised) in preterm children is about 5% (about 1% in the general population) (Limperopoulos et al. 2008, Johnson et al. 2010, Pinto-Martin et al. 2011). This has raised the question of whether false-positive autism screening test scores in preterm children are more due to atypical sensory processing than true autistic features (Luyster et al. 2011).

Neonatal brain injury, neurodevelopmental impairments, early exposure to repeated painful interventions, noise, bright light, and other sensory stimulation have been suggested as possible factors affecting development of abnormalities in sensory processing in ELGA infants (Walker et al. 2009, Marco et al. 2011).

3. Prediction of neurocognitive development by structural neuroimaging and clinical neurophysiological methods

3.1. Structural neuroimaging

3.1.1. Ultrasonography (US)

Cranial US is an excellent method for screening of IVH and ventricular dilatation, for diagnosing ischemic lesions, and for recognizing congenital abnormalities in NICUs (Wezel-Meijler & de Vries 2014). It is easy to use bedside, relatively inexpensive, non-invasive, and repeatable. Through

the anterior fontanel, US gives good information about the ventricles and the periventricular areas (Vohr et al. 1999, Maalouf et al. 2001, Inder et al. 2003).

Most of the IVHs can be found in early US examinations during the first two weeks of life, while late US follow-up can reveal PVL, VD, or late IVHs (Ment et al. 2002). The classification of IVHs is presented in Section 2.1.

PVL can be classified into three categories based on US. Grade 1 represents increased echogenicity in the periventricular regions, grade 2 includes increased echogenicity with small fronto-parietal cysts, and grade 3 periventricular echogenicity with extensive cystic lesions (de Vries et al. 1993). However, in an autopsy study the sensitivity of US in diagnosing PVL has been reported to be only 50% (Carson et al. 1990).

Despite many advantages, US has poor sensitivity in detecting WM injury in preterm infants, (Kuban et al. 1999, Debillon et al. 2003) and visibility to posterior fossa structures and peripheral brain parenchymal regions is restricted (Carson et al. 1990, Steggerda et al. 2009). Using the posterior fontanel as a supplemental acoustic window improves visualization of the cerebellum, the tentorium, the occipital parenchyma, and the occipital horns of lateral ventricles (Wezel-Meijler & de Vries 2014). The limited ability of US to detect slight WM or GM abnormalities is supported by the observation that adverse neurodevelopment has been reported also in VLBW infants with normal findings in neonatal US examinations (Isaacs et al. 2000, Volpe 2003).

US has been in clinical use for more than 30 years for evaluating the preterm brain, and the associations between US findings and neurodevelopmental outcomes have been widely investigated (Neil & Inder 2004). In most of these studies, 30-60% of infants who later develop CP have presented abnormalities in neonatal brain US studies (O'Shea, Klinepeter & Dillard 1998, Valkama et al. 2000, Nelson et al. 2003), but de Vries et al. (2004) reported much higher sensitivity (95%) for US to predict CP in a very preterm population. One explanation for the higher sensitivity in their study could be the higher frequency (every week) of US examinations and longer follow-up (up to TEA) with US than in most US studies.

3.1.2. Magnetic resonance imaging (MRI)

Conventional MRI is a structural neuroimaging method providing detailed information about parenchymal WM and GM abnormalities, the cerebellum and other structures of the posterior fossa,

and the quality of myelinization and gyral maturation in the brain of the ELGA infant (Inder et al. 2003, Woodward et al. 2006, Steggerda et al. 2009). Further, MRI can reveal lesions of hypoxic-ischemic insults and developmental abnormalities in the brain structure (Huppi & Barnes 1997). Although MRI overshadows US in detecting WM injuries (Felderhoff-Mueser et al. 1999, Inder et al. 2003), preterm infants with normal MRI at TEA may still present adverse neurodevelopmental outcome (Mirmiran et al. 2004).

Several scoring methods have been used to classify WM lesions on the basis of , for example, periventricular WM volume loss, WM signal abnormality, ventricular dilatation, thinning of the corpus callosum, and myelination deficits (Woodward et al. 2006, Back, Riddle & McClure 2007, Leijser et al. 2010). Since moderate to severe abnormalities on MRI at TEA are associated with adverse neurodevelopmental outcome, and abnormal MRI findings predict CP with higher sensitivity than serial cranial US, MRI around TEA has been recommended for routine use in predicting neurodevelopment of ELGA infants (Mirmiran et al. 2004, Woodward et al. 2006).

In a recent study of 106 very preterm (<32 gestational weeks) infants Woodward et al. (2012) reported no obvious impairments in intelligence, language, or executive functioning at the age of four and six years in very preterm infants with normal WM in MRI at TEA, compared with term infants (n=109). However, even mild WM abnormalities were associated with lower IQ scores and executive functioning delays, and with moderate-to-severe WM abnormality the adjusted (child sex, neonatal medical risk, and family social risk) odds ratio (OR) for intellectual delay rose 8-fold, for language delay 4.5-fold, and for executive functioning delay 5-fold in very preterm children compared with term children at six years of age (Woodward et al. 2012). Ventriculomegaly at TEA (Woodward et al. 2006, de Bruine et al. 2011, Maunu et al. 2011), which is supposed to reflect diffuse WM injury, and punctate WM lesions (de Bruine et al. 2011) have been associated with adverse neurodevelopmental outcome.

MRI enables the assessment of total and regional brain volumes, which can be measured with different semi-automatic brain segmentation methods. Decreased total brain, cerebellar, and regional brain volumes have been reported in preterm infants (Nosarti et al. 2002, Tolsa et al. 2004), as have diminished WM and GM volumes (Nosarti et al. 2008). At present, clinical use of these semi-automatic systems is still rare (Prastawa et al. 2005, Anbeek et al. 2008). In a study of 164 VLBW infants, manually measured decreased volumes of total brain tissue, cerebrum, frontal lobes,

basal ganglia, thalami, and cerebellum were associated with adverse neurodevelopmental outcome (Lind et al. 2011).

Diffuse excessive high signal intensity (DEHSI), first reported in 1999 in very preterm infants at TEA (Maalouf et al. 1999), refers to high signal intensity in the WM, approaching the signal intensity of cerebrospinal fluid on MRI, and it is often present in the periventricular frontal and parieto-occipital areas (de Bruine et al. 2011). Recent studies have not found associations between DEHSI and adverse neurodevelopmental outcome at two years of age (de Bruine et al. 2011, Kidokoro et al. 2011). De Bruine et al. (2011) concluded that DEHSI can be considered a "prematurity-related developmental phenomenon" on the basis of high incidence (89% in infants <32 GW) of DEHSI around TEA, but total disappearance after 50 gestational weeks, and the lack of an association of DEHSI with neurodevelopmental outcome.

3.1.3. Diffusion tensor imaging (DTI)

DTI is based on the diffusion of water in different tissues, and it is used to evaluate brain structures at a microstructural level (Basser & Pierpaoli 2011). DTI is based on MRI technology, and Brownian motion of water molecules is used to create image contrast (Le Bihan et al. 1986). In neonates, both WM injury and WM development can be evaluated by DTI (Huppi & Dubois 2006). Isotropy refers to the unrestricted diffusion of water, i.e., diffusion is equal in all directions, whereas anisotropy refers to the directionally restricted diffusion of water molecules. Water diffusion in WM is dependent on several microstructural elements such as the degree of myelination and the density of axonal fibers (Le Bihan et al. 1986). In WM fibers, water diffusion is mainly parallel to fibers, and perpendicular diffusion is restricted, which can be used in defining the direction and location of WM tracts and the degree of myelinization (Moseley et al. 1990).

Furthermore, DTI provides specific variables, such as fractional anisotropy (FA), axial diffusion (AD), radial diffusion (RD), and apparent diffusion coefficient (ADC), which can be used in assessing WM microstructural characteristics. FA indicates the degree of water diffusion anisotropy regardless of the overall water diffusion coefficient. It can vary from zero (isotropic diffusion) to one with increasing anisotropy (Huppi & Dubois 2006).

Studies in adults have shown the viability of DTI as an early indicator of stroke because DTI can demonstrate abnormalities on water diffusion maps much before any abnormalities can be seen in

conventional MRI (Warach et al. 1992). In ELGA infants, the early detection of brain injury could enable trials with well-timed neuroprotective therapies for infants (Huppi & Dubois 2006).

FA increases with increasing age in preterm infants without WM insults (Huppi et al. 1998a, Miller et al. 2002). In contrast, FA is reduced and ADC increased in preterm infants with WM injury (Dyet et al. 2006). DTI studies in preterm infants have reported associations of decreased FA and increased ADC in the posterior limb of the internal capsule (PLIC) and corpus callosum with adverse neurodevelopment (Krishnan et al. 2007, Mathur, Neil & Inder 2010). Further, Rose et al. (2009) reported lower FA and higher ADC values in the splenium of corpus callosum of VLBW males relative to VLBW females, and reduced splenium of corpus callosum and right PLIC FA were associated with adverse neurodevelopmental outcome.

3.2. Functional neurophysiological methods

3.2.1. Somatosensory evoked potentials (SEPs)

Somatosensory evoked potentials (SEPs) have provided the possibility to assess the integrity and function of somatosensory tracts (peripheral pathways and cortical responses) in newborns over the last few decades (Pihko & Lauronen 2004). SEP studies in preterm infants have been inspired by the idea of perceiving possible dysfunction in the somatosensory system of these high-risk infants, thus enabling early rehabilitation as well as obtaining new information about the early development of the somatosensory system (Pike & Marlow 2000, Pihko & Lauronen 2004).

SEPs with median nerve stimulation have been recorded in infants as early as 25 gestational weeks (Hrbek, Karlberg & Olsson 1973). After median nerve stimulation, N1 response peaking about 30 ms after stimulation at term age is the first contralateral parietal response in newborn SEP (Gibson, Brezinova & Levene 1992, Karniski 1992). The latency of this N1 response continues to decrease up to three years of age because of progress in myelination and maturation of the somatosensory network (Garcia et al. 2000).

The earliest SEP components have been the main focus in the majority of SEP studies in newborns and infants (Laureau & Marlot 1990, George & Taylor 1991, Gibson, Brezinova & Levene 1992).

Filter settings and the time windows used in these studies have prevented the detection and analysis of later SEP components with longer latencies (Pihko & Lauronen 2004).

Three later responses, in addition to the early N1 response, have been found in studies focusing on long latency responses: deflections around 100 ms, 150 ms, and 230 ms after median nerve stimulation (Hrbek, Karlberg & Olsson 1973, Karniski 1992). A positive deflection at 230 ms is best presented in quiet sleep, whereas active sleep diminishes the amplitude of this deflection (Desmedt & Manil 1970). Thus, sleep stages are essential to take into account in SEP studies in preterm and term newborn infants (Pihko & Lauronen 2004).

In several studies in preterm infants, functioning of the somatosensory system has been assessed by measuring SEPs from median (Hrbek, Karlberg & Olsson 1973, Karniski 1992, Pierrat, Eken & de Vries 1997, Smit et al. 2000) and tibial nerves (White & Cooke 1994, Pierrat, Eken & de Vries 1997, Pike & Marlow 2000). Abnormalities in both median (Willis et al. 1989, de Vries et al. 1992, Pierrat, Eken & de Vries 1997) and tibial (White & Cooke 1994, Pierrat, Eken & de Vries 1997, Pike & Marlow 2000) nerve SEPs have been associated with later CP, but with varying sensitivity and specificity. Possible explanations for this variability are differences in SEP methods and patient profiles as well as difficulties in technical reliability of SEP measurements in ELGA infants (Smit et al. 2000). Suboptimal SEP recording setups, adapted mostly from adult studies, may play a central role in difficulties of SEP measurements in preterm infants (Vanhatalo & Lauronen 2006). Probably due to these technical challenges, SEP measurements in ELGA infants have only played a minor role in evaluating the preterm brain, despite the fact that EEG and SEP assess brain function, unlike US and MRI, which visualize brain structures (Vanhatalo & Lauronen 2006).

3.2.2 Magnetoencephalography (MEG)

Magnetoencephalography (MEG) is a noninvasive method of studying brain function. It detects very weak extracranial magnetic fields produced by currents generated in the cerebral cortex (Nevalainen et al. 2008a, Nevalainen et al. 2008b, Pihko et al. 2011). Because the magnetic fields produced by the cerebral cortex can be several magnitudes smaller than environmental noise, MEG measurements are performed in a magnetically shielded room. MEG measures brain activity at the level of neuron populations by detecting magnetic fields outside the head with sensors (magnetometers and gradiometers) composed of a superconducting flux transformer connected to a

Superconducting Quantum Interference Device (SQUID). The sensors are surrounded by liquid helium in order to maintain the superconductivity (Hämäläinen et al. 1993).

The successful modeling of the neuromagnetic data has some preconditions because the distributions of the currents inside the brain are not possible to determine unambiguously merely from measured extracranial magnetic fields. The MEG source modeling can be done by using a sphere as a model of the brain for calculations. Equivalent current dipole (ECD) is a typical MEG source model that is useful when the measured cortical activation originates in a small area of the cortex. The magnitude, direction, and location of the ECD can be estimated and presented (Hämäläinen et al. 1993).

With MEG, it is possible, also in newborn term infants and ELGA infants at TEA, to detect somatosensory evoked magnetic fields (SEF) from both primary (SI) and secondary (SII) somatosensory cortices (Nevalainen et al. 2008a, Nevalainen et al. 2008b, Pihko et al. 2011). The locations of SI and SII are shown in Figures 3 and 4.

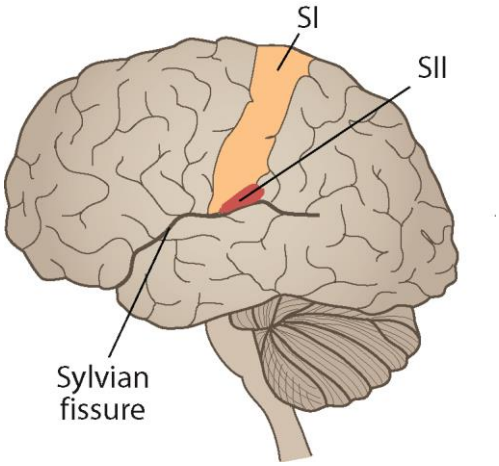

Figure 3. Lateral view of the adult brain showing the location of the primary somatosensory cortex (SI) and the secondary somatosensory cortex (SII).

In a first MEG study analyzing both SI and SII responses in ELGA infants, Nevalainen et al. (2008) reported normal SI response in all 16 ELGA infants and 16 term controls, suggesting normal

development of somatosensory tracts from periphery to SI at term also in ELGA infants. In contrast, ELGA children with absent SII response were often noted to have anatomical lesions in the affected hemisphere in structural neuroimaging (Nevalainen et al. 2008b).

MEG has as accurate a temporal resolution as EEG; they both detect cortical neuronal activation to one millisecond accuracy. In spatial accuracy, MEG is superior to EEG, being less sensitive to extracortical factors, such as open fontanels and different skull thickness, in differently aged children (Flemming et al. 2005). Compared with functional MRI, which assesses neural activity indirectly based on changes in blood flow, MEG has better temporal resolution (milliseconds in MEG vs. seconds in fMRI), is quiet, and requires no magnetic field exposure. However, functional MRI has an excellent spatial resolution (millimeters) that clearly overshadows MEG (centimeters) (Dale et al. 2000).

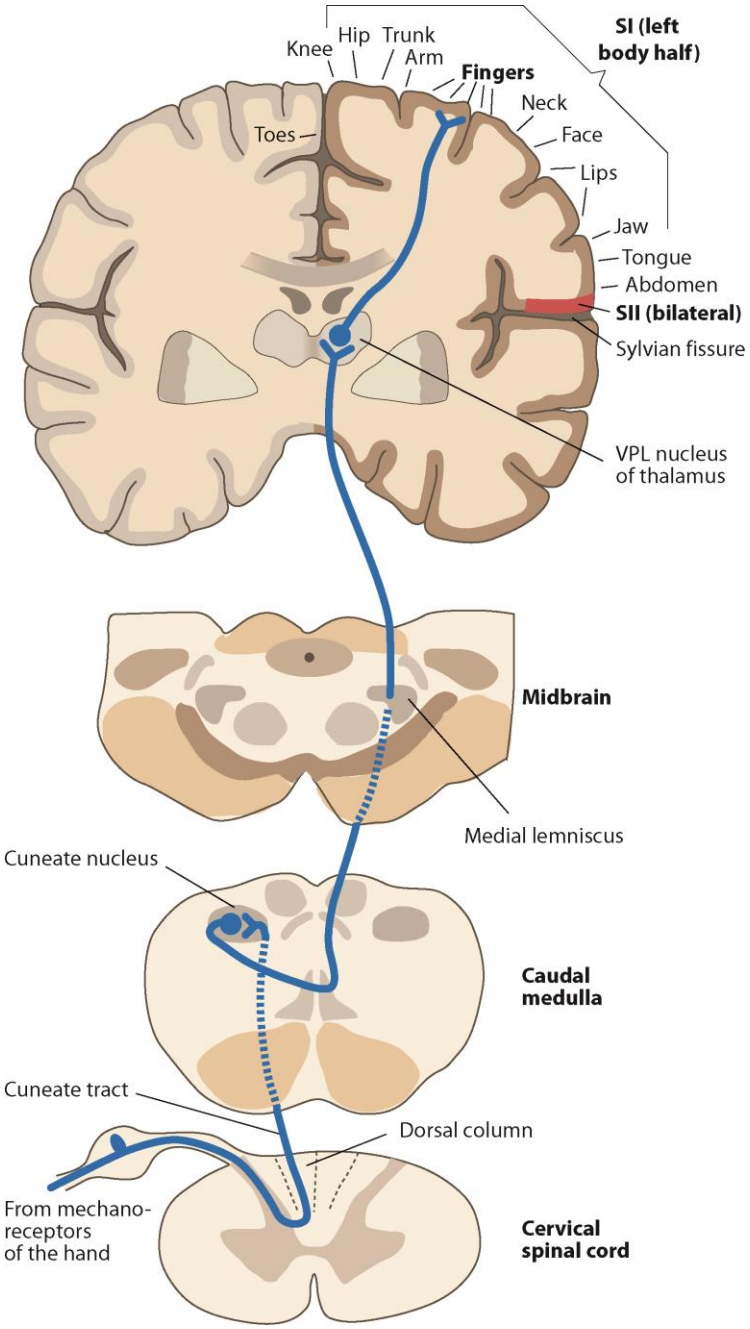

Figure 4. Upper: Posterior view (coronal section) of the adult brain showing the location of the primary somatosensory cortex (SI) and the secondary somatosensory cortex (SII). Lower: Cross-sections of cervical spinal cord, caudal medulla, and midbrain showing the dorsal column-medial lemniscus pathway of somatosensory tracts. Modified with permission from Nevalainen (2010).

AIMS OF THE STUDY

The present thesis aimed at evaluating ELGA children with neurophysiological functional methods and neuroimaging during the neonatal period and relating these findings to neurodevelopmental outcome at two years of corrected age using validated age-specific neurological and neuropsychological methods.

Specific aims in Studies I-IV were as follows:

I to determine whether abnormal SEFs in MEG at TEA in ELGA infants are associated with adverse neurodevelopmental outcome at two years of corrected age.

II to test whether SII responses can be detected in ELGA infants in routine neonatal EEG complemented with median nerve stimulation and whether measurement of SII responses provides additional value to neonatal neurological evaluation and neuroimaging in predicting later neurodevelopmental outcome.

III to assess the role of maternal interaction in relation to the neurocognitive outcomes of ELGA children, with a special emphasis on effects of early neurological disabilities and neonatal risk factors on mother-child interaction.

IV to describe the patterns of behavioral sensory processing in ELGA children at two years of corrected age and to investigate whether neonatal risk factors, neonatal complications, or current neurocognitive function are associated with atypical sensory processing.

SUBJECTS AND METHODS

1. Subjects

The study protocol was approved by the Ethics Committee of the Hospital District of Helsinki and Uusimaa (Dnro HUS 277/E7/2005) on 28.2.2006, and the appendix for the study protocol was approved on 16.10.2008.

Altogether, 85 ELGA infants (born before 28 gestational weeks) from the neonatal intensive care unit (NICU) of Helsinki University Central Hospital and 22 healthy infants (14 males and 8 females) born at term from the maternity ward of the Department of Obstetrics, Helsinki University Central Hospital were recruited for the multimethodological study between May 2006 and September 2008. Six ELGA infants died during neonatal intensive care and one ELGA infant's parents refused to participate in the follow-up examinations. Consequently, the final study population included 78 ELGA infants (49 males and 29 females). Figure 5 describes ELGA children and Figure 6 term children in different examinations at TEA and at two years of corrected age.

Study I focused on cortical somatosensory processing measured by MEG in predicting neurodevelopment. Because of the technical demands of MEG measurements, exclusion criteria for Study I were need for respiratory support or constant monitoring at TEA. Thirty-nine ELGA infants were eligible to undergo MEG measurement at 37+6 to 44+4 weeks of gestational age (mean 41.1 weeks). Of these, 30 ELGA infants underwent the Griffiths Mental Developmental Scales (GMDS) (Brandt I 2001) and Hempel neurological examination (Hempel 1993) at two years of corrected age. Two uncooperative ELGA children were excluded from the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) (Bayley 2005) Cognition Scale and one ELGA child because the examination was not possible in her native language. In addition, two inattentive children failed to complete the Receptive Language Scale and one child the Expressive Language Scale. Of controls, 11 healthy term infants underwent MEG recording 1 to 23 days after birth at the gestational age of 38+0 to 43+1 weeks (mean 41.0 weeks). All term children were assessed at two years of age with GMDS (Brandt I 2001) and Hempel neurological examination (Hempel 1993) and nine of them also with BSID-III (Bayley 2005).

Study II focused on somatosensory evoked magnetic fields (SEF) measured by MEG and somatosensory evoked potentials (SEP) measured by electroencephalography (EEG). The study

population consisted of the same 39 ELGA infants (19 females and 20 males) as in Study I, who underwent successful MEG examination at a gestational age between 38+0 and 44+4 weeks. Of these, MRI was performed for 37 and neonatal neurological examination for 32 ELGA infants at TEA. Of infants with normal secondary somatosensory cortex (SII) responses in MEG, successful EEG-SEP recording was available for four ELGA infants to stimulation of the right median nerve and for six infants to stimulation of the left median nerve. Controls for MEG recordings were 46 healthy full-term newborns reported in a previous study (Nevalainen et al. 2012).

Study III focused on mother-child interaction and its associations with neurodevelopmental outcome. At two years of corrected age, 78 ELGA children and 22 term children were invited to neurodevelopmental assessment comprising two clinical visits a few days apart. Mother-child dyads were videotaped during a 15-minute structured play session in conjunction with the clinical visit. Sixty ELGA and 18 term children completed the first and 48 ELGA and 16 term children completed also the second visit. Of the 78 ELGA children, nine had a native language other than Finnish, six lived in another hospital district, and 16 dropped out for unknown reasons.

Study IV focused on sensory processing in ELGA children. The study population consisted of 44 ELGA and 9 term children whose parents completed the Infant/Toddler Sensory Profile questionnaire at two years of corrected age (Dunn 2002). Of these, 43 ELGA children and 9 term children were assessed with GMDS (Brandt I 2001) and Hempel neurological examination (Hempel 1993), and 39 ELGA children and 8 term children also with BSID-III (Bayley 2005).

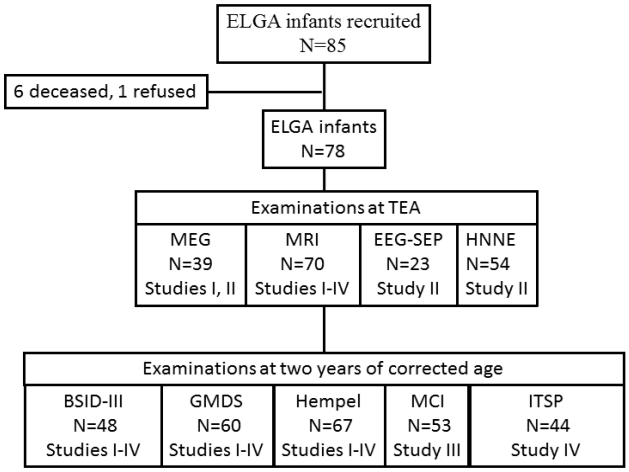

Figure 5. Examinations of ELGA infants at TEA and at two years of corrected age. **Abbreviations: MEG, magnetoencephalography; MRI, magnetic resonance imaging; EEG-SEP, electro-encephalography and somatosensory evoked potentials; HNNE, Hammersmith Neonatal Neurological Assessment; BSID-III, Bayley Scales of Infant and Toddler Development – Third Edition; GMDS, Griffiths mental developmental scales; Hempel, Hempel's structured neurological examination; MCI, mother-child interaction, i.e., Erickson's Scales, Mutually Responsive Orientation, and Quality of Relationship; ITSP, Infant/Toddler Sensory Profile.**

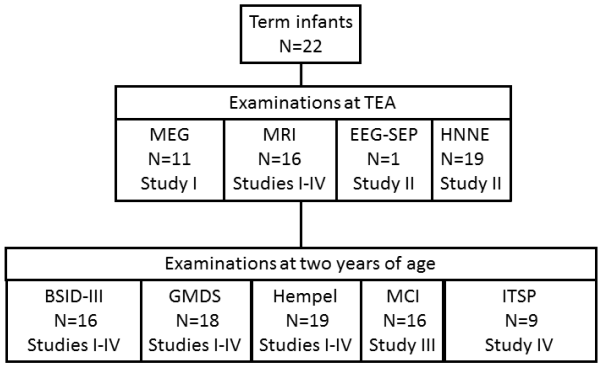

Figure 6. Examinations of term infants at TEA and at two years of age.

See Figure 5 for abbreviations.

2. Methods

2.1. Collection of clinical data (Studies I, II, III, and IV)

Obstetric and postnatal data of neonatal clinical course and complications were collected from hospital records. Gestational age was based on the first trimester ultrasonography. Birth weight z-scores for gestational age and sex were based on the Finnish growth reference data (Pihkala et al. 1989).

Cesarean section included both elective and emergency sections. Chorionamnionitis was defined by standard clinical and laboratory criteria, including maternal fever > 38°C, tenderness of the uterus and purulent discharge, elevated C-reactive protein concentration, leukocyte counts, and placental histology.

Prophylactic surfactant was given to every ELGA infant after birth at the delivery unit. Respiratory distress syndrome (RDS) was diagnosed as an oxygen requirement in combination with typical RDS findings in chest X-ray by the age of 72 hours. Bronchopulmonary dysplasia (BPD) was defined as a need for additional oxygen at 36+0 weeks of gestational age. Dexamethasone treatment for severe pulmonary disease was recorded.

Septicemia included episodes with both clinical symptoms and positive bacterial culture. Necrotizing enterocolitis (NEC) was diagnosed according to clinical criteria (presence of bloody stool with abdominal distension and abnormal gastrointestinal radiology, or macroscopic findings supporting NEC in laparotomy). PDA was defined as hemodynamically significant when it was treated either medically with indomethacin or ibuprofen, operatively, or both.

At two years of corrected age, the socioeconomic status of the parents was evaluated with a questionnaire including family structure and education, occupation, and incomes of both parents. Mothers who failed to complete the questionnaire were called for a telephone interview, but a language barrier prevented some of these interviews. Mother's education was used in analyses in Studies I, III, and IV. Missing data of mother's education were imputed with a series mean for 10 of 42 mothers in Study I, for 8 of 64 mothers in Study III, and for 6 of 53 mothers in Study IV.

2.2. Brain US and MRI (Studies I, II, III, and IV)

Serial brain US was performed by radiologists for ELGA infants at the age of one day, three days, one week, two weeks, and four weeks, at TEA, and at three months of corrected age. Intraventricular hemorrhages were classified as grade I-IV (Papile et al. 1978). Grade I represents subependymal bleeding, grade II intraventricular bleeding without ventricular enlargement, grade III intraventricular bleeding with ventricular enlargement, and grade IV periventricular parenchymal hemorrhagic infarction. The highest grade of IVH in serial cranial US was recorded.

Brain MRI (1.5T) including T2-weighted axial and T1-weighted 3D sagittal images was performed near term equivalent age on 29 of 30 ELGA infants and on 10 of 11 term controls in Study I, on 38 of 39 ELGA infants in Study II, on 46 of 48 ELGA infants and on 12 of 16 term controls in Study III, and on 42 of 44 ELGA infants and on 6 of 9 term controls in Study IV.

Two experienced neuroradiologists classified the MRI images according to Woodward et al. (2006). WM was classified as normal, mildly abnormal, moderately abnormal, or severely abnormal on the basis of five variables: WM signal abnormality, periventricular WM volume loss, cystic abnormalities, ventricular dilatation, and thinning of the corpus callosum. Contrary to Woodward et al. (2006), who used the following three grades for thinning of the corpus callosum: normal, focal thinning, and global thinning, we used only two grades: normal or global thinning. Our neurologists found focal thinning of the corpus callosum too unreliable to define. This modification had, however, no effect on our results because only six ELGA infants had noticeable corpus callosum thinning and none of them would have been classified into a more severe group of overall WM abnormality even if thinning of the corpus callosum would have been graded as 3 instead of 2. WM classification is presented in Table 2.

Table 2. Classification of WM in MRI (modified from Woodward et al. 2006).

WM grading in MRI	Description
WM signal abnormality	
Grade 1	Normal T1- and T2-weighted signals throughout WM
Grade 2	Focal regions of high T1- or T2-weighted signals
Grade 3	Multiple regions of high T1- or T2-weighted signals (more than two regions per hemisphere).
Periventricular WM loss	
Grade 1	Normal periventricular WM volume with small ventricles
Grade 2	Mild reduction in periventricular WM volume with mild to moderate increased ventricles
Grade 3	Marked reduction in WM volume with marked increased ventricles
Cystic abnormalities	
Grade 1	Normal with no cystic abnormalities
Grade 2	A single focal cyst with diameter less than 2 mm
Grade 3	Multiple cysts or a singlecyst larger than 2 mm
Ventricular dilatation	
Grade 1	Normal with no evidence of dilatation
Grade 2	Moderate enlargement
Grade 3	More global enlargement
Thinning of the the corpus callosum	
Grade 1	Normal with thick corpus callosum
Grade 2	Thinning of the corpus callosum
Overall WM abnormality	
No abnormality	Total score 5 to 6
Mild abnormality	Total score 7 to 9
Moderate abnormality	Total score 10 to 12
Severe abnormality	Total score 13 to 14

Gray matter (GM) was classified on the basis of three variables: GM signal abnormality, quality of gyral maturation, and size of the subarachnoid space (Woodward et al. 2006). In the original classification by Woodward et al., quality of gyral maturation was assessed with a three-grade scale: grade 1 represented normal for 40 weeks, grade 2 two to four weeks delay in gyral development (i.e. consistent with 36 to 40 weeks of gestation), and grade 3 more than four weeks delay in gyral development. Because our neuroradiologists found grade 2 too unreliable to distinguish from grade

1, we modified the classification into two grades (Table 3). GM classification is presented in Table 3.

Table 3. Classification of GM in MRI (modified from Woodward et al. 2006).

GM grading in MRI	Description
GM cortical signal abnormality	
Grade 1	Normal
Grade 2	High signal intensity in the cortex on axial T1- and/or loss of cortical ribbon signal on axial T2-weighted MRI
Quality of gyral maturation	
Grade 1	Normal for 40 weeks of gestation
Grade 2	more than 4 weeks delay
Size of subarachnoid space	
Grade 1	Small subarachnoid space
Grade 2	Mildly enlarged CSF space with visible enlargement of the space between the major sulci and the interhemispheric space in addition to the extracerebral space
Grade 3	More substantially enlarged global subarachnoid space with visible cerebrospinal fluid between many gyri as well as interhemispheric and extracerebral space

2.3. Magnetoencephalography (MEG) (Studies I and II)

MEG was recorded in a magnetic shielded room (ETS; Lingren Euroshield Oy, Eura, Finland) with a whole-head adult-sized helmet-shaped sensor array consisting of 306 independent channels: 204 gradiometers and 102 magnetometers (Vector-view, Elekta Neuromag Oy, Helsinki, Finland). EEG from one to three electrodes and electro-oculography (EOG) from two electrodes, one above the left and the other below the right eye, were recorded for sleep stage monitoring. The reference electrode was on the left mastoid and the ground electrode on the forehead.

Before the measurement, the EEG and EOG electrodes were attached and a cloth cap was applied over them. Four position indicator coils were attached on the cap and their positions were digitized with respect to anatomical land-marks with a 3-D digitizer. The MEG helmet was in supine position and the infant lay with one hemisphere downwards over the occipital part of the helmet. One or two researchers were in the recording room with the healthy control infants. ELGA infants were accompanied by an experienced nurse from the NICU.

The tactile stimulus was given to the tip of the index finger by a thin elastic membrane expanded by an air pressure pulse delivered through a plastic tube (Somatosensory Stimulus Generator, 4-D NeuroImaging Inc., San Diego, CA, USA). The interstimulus interval was 2 s. The researcher/nurse held the stimulus on the infant´s index finger, observed the infants behavior, and coded his/her alertness (eyes open/closed) and the behaviorally presumed sleep stage onto special trigger channels linked to the raw data file.

The complete session with each infant lasted from two to four hours. The stimulation and the recordings were started when the infant naturally fell asleep. The infants were not sedated, but they were fed before being placed on a bed next to the MEG measuring helmet.

All MEG data were analyzed by a single MEG researcher who was blinded to infants' neurodevelopmental outcome. MEG data were first preprocessed with a Spatiotemporal Signal Space Separation (tSSS) method of the MaxFilter software (Elekta Neuromag, Helsinki, Finland) to remove possible magnetic artifacts (Taulu & Simola 2006, Medvedovsky et al. 2009). Periods with movement artifacts were manually discarded from the data before averaging it according to the sleep stage. The sleep stages were characterized as quiet (QS), intermediate, or active (AS) (Prechtl 1974) using EEG, MEG, EOG, and behavioral coding (Pihko et al. 2004). Averaged QS data were used for further analyses.

The contralateral SI (M60) and contra- and ipsilateral SII (M200) sources (Nevalainen et al. 2008a) were modeled with equivalent current dipoles (ECDs) using a spherical conductor model which was individually constructed based on each infant's anatomical MRIs. When MRI was not available, the average sphere origin calculated from the other infants' MRIs was used. Single dipoles, from an individually selected subset of MEG channels underlying the measured hemisphere, were then modeled with 1-ms intervals around the visually determined peaks. When there was no clear peak, no dipolar field pattern, and/or the ECD could not be modeled with required goodness of fit (GOF >70%), the response was considered to be absent.

2.4. Somatosensory evoked potentials during EEG (EEG-SEP) (Study II)

We modified our routine EEG protocol to stimulate the median nerve during routine EEG and to average the SEP data afterwards. We named this method EEG-SEP. For EEG-SEP, the EEG was recorded in a separate session with silver-silver chloride electrodes implemented in a whole-head EEG cap according to the international 10-20 system (Figure 7) and referenced to Cz. The sampling rate for EEG was 1000 Hz. Additional channels were recorded with disposable silver-silver chloride electrodes: EOG separately from lateral left and right eye canthi referenced to linked mastoids, ECG, and EMG. Respiration (movement of the chest wall) was detected with the strain gauge. SEPs were elicited by electrical stimulation of the right and left median nerves (in separate runs) at the wrist with 0.2 ms constant-current pulses. The intensity was set just above the motor threshold, and interstimulus interval was 1 s.

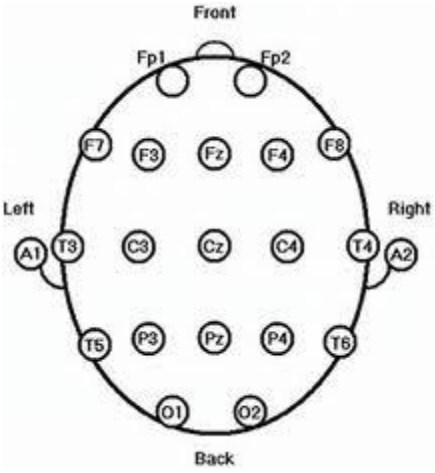

Figure 7. The ten-twenty EEG electrode system of the International Federation.

The sleep states were scored offline using EEG, ECG, respiration, EOG, and EMG. Movement artifacts were manually discarded. The data segments scored as QS were exported to BESA®, epoched (-100 to 800 ms), and averaged. Data containing a minimum of 100 averages in QS were further evaluated visually by three investigators using bipolar montage and electrical field maps. The SI and SII responses were searched from predefined time frames based on SEF responses in MEG. The SI response was considered to be present when there was a unilateral response in the centroparietal electrodes in the time frame of 15-100 ms and the electrical field pattern was

compatible with an anteriorly pointing dipolar source at the primary somatosensory cortex, i.e., there was a frontal positivity and parieto-occipital negativity. The contra- and ipsilateral SII responses were (independently) considered to be present when there was a detectable response in the montage with lower temporoparietal electrodes (T3 and/or T5 or T4 and/or T6) referenced to Fz between 180 and 300 ms and the electrical field pattern was compatible with a superiorly pointing dipolar source at the secondary somatosensory cortex, i.e., there was positivity at the vertex and negativity contra- or ipsilaterally in the mastoid area.

2.5. Neonatal neurological examination (Study II)

Hammersmith Neonatal Neurological Assessment (HNNE) was performed by an experienced pediatric neurologist for 32 ELGA infants at TEA in Study II. HNNE includes 34 items in six categories: tone, tone patterns, reflexes, movements, abnormal signs, and orientation and behavior. The normative data presented (Ricci et al. 2008) were used to classify the performance in each category as normal or deviant. The deviant category was defined as abnormal posture, tone and tone patterns (combined), abnormal spontaneous movement quantity and/or quality, deviant visual or missing auditory orientation or at least two deviant items in the categories of reflexes, abnormal signs, orientation, and behavior. The neurological abnormality was defined as mild with one deviant category, moderate with two to three deviant categories, and severe with more than three deviant categories. HNNE was defined as normal when no deviant categories were observed.

2.6. Neurocognitive outcome at two years of corrected age (Studies I, II, III, and IV)

Neurocognitive outcome was assessed with three different methods at two years of corrected age. The Griffiths Mental Developmental Scales (GMDS) (Brandt I 2001) and a structured toddler-age specific Hempel neurological examination (Hempel 1993) were performed by an experienced child neurologist during the first clinical visit and Bayley Scales of Infant and Toddler Development - Third Edition (BSID-III) (Bayley 2005) were administered and scored by certified examiners during the second clinical visit.

The GMDS contain five subscales: Locomotor, Personal and Social, Hearing and Language, Eye-Hand Coordination, and Performance. The overall developmental quotient (DQ) is calculated on the basis of the scores from subscales and the child's exact (corrected) age. In the GMDS,

developmental impairment was classified as mild, moderate, or severe on the basis of the English normative sample (mean DQ = 100.5, SD =11.8) (Huntley 1996), which has been used in studies assessing neurodevelopmental outcome (Vohr et al. 2000, Wood et al. 2000, Marlow et al. 2005, Sansavini et al. 2011). Total DQ from 76.9 to 88.6 (-1SD to -2SD) was defined as mild impairment, from 65.1 to 76.8 (-2SD to -3SD) as moderate impairment and ≤ 65 (<-3SD) as severe impairment.

A structured Hempel neurological examination (Hempel 1993) comprises five categories assessing neurological dysfunction: dysfunctional muscle tone regulation, reflex abnormalities, gross motor dysfunction, fine motor dysfunction, and rarely occurring miscellaneous disorders, e.g. mild cranial nerve palsy or consistent tremor. One dysfunctional category leads to simple minor neurological dysfunction (MND-1), and two or more dysfunctional categories to complex minor neurological dysfunction (MND-2). CP was defined using the Gross Motor Function Classification System (GMFCS) for Cerebral Palsy (Rosenbaum et al. 2002).

Cognition, receptive language and expressive language were assessed in BSID-III. We omitted the categories gross motor and fine motor functions from the assessments in BSID-III because they were already assessed in GMDS. In BSID-III, a category was scored as untestable if there were too many unscorable items or judgement was unreliable according to the certified examiner.

2.7. Mother-child interaction (Study III)

Mother-child interaction was used in analyses in Study III. A structured play session was videotaped during the clinical visit at two years of corrected age. Mothers were asked to guide their child to open a present and build a jigsaw puzzle (5 min), to play freely with new attractive toys (5 min), and to encourage the child to clean up the toys at the end of the session (5 min). Mothers were instructed to interact with their children in their normal manner. Mother-infant interaction was assessed and coded from videotapes by a research assistant (Master's level student in psychology), who was unaware of the child's neurocognitive status, gestational age, and size at birth. Five pilot tapes were coded by the research assistant and two senior researchers (neuropsychologists) independently to assess the research assistant's coder reliability. Inter-coder reliabilities were calculated.

The Erickson scales (Egeland et al. 1990) were used to assess maternal parenting and child's behavior during the two teaching tasks (a jigsaw puzzle and a cleaning-up task). The Erickson scales include six sections (*Supportive Presence, Hostility, Intrusiveness, Clarity of Instruction,*

Sensitivity in Timing in Instruction, Confidence) assessing maternal parenting and seven sections (*Persistence, Enthusiasm, Negativity, Compliance, Experience of the Session, Affection Toward Mother, Avoidance*) assessing the child's behavior in interaction, each coded on a seven-point scale. Descriptions of the scales are presented in Table 4. Inter-coder reliabilities were >0.84 for maternal parenting and >0.79 for the child's behavior. The average of the two separate tasks was used. In addition, a summary score of maternal *Sensitive-responsiveness* was constructed by adding up *Sensitivity and Timing in Instruction, Supportive Presence, Clarity of Instruction*, and *Confidence* and then subtracting *Intrusiveness* and *Hostility*.

Mother-child relationship in mother-child dyads was assessed with Mutually responsive orientation (MRO) (Aksan, Kochanska & Ortmann 2006) and Quality of Relationship (Egeland et al. 1990). MRO assesses coordinated routines, harmonious communication, mutual cooperation, and emotional ambience in the mother-child dyad on a five-point scale (1=very untrue of dyad, poor relationship, 5=very true of dyad, excellent relationship). The average score of the three play situations was used in the analyses. Inter-coder reliabilities were >0.81. Quality of Relationship (Egeland et al. 1990) assesses the sense of relatedness, mutual engagement, and affective and/or verbal sharing between the mother and child on a seven-point scale. The two teaching tasks were coded and the average score was used in analyses. Inter-coder reliabilities were >0.78.

Table 4. The Erickson scales.

Mother-child interaction scale	Description
Child's behavior	
Persistence	A measure of the extent to which the child actually is problem-oriented in the session
Enthusiasm	Child's confidence and eagerness to do the tasks. His/her active interest and investment in activities
Negativity	The degree to which child shows anger, dislike, or hostility toward the mother
Compliance	Child's willingness to listen to mother's suggestions in the setting and to comply with her requests in a reasonable manner
Experience of the Session	Describes child's experience of feelings of success and competence in the tasks and confidence in having a good relationship with his/her mother
Affection Toward Mother	Child's positive regard and sharing of happy feelings with the mother and the degree of an overall positive orientation towards mother
Avoidance	Child's tendencies or clear attempts in the session to avoid interacting with the mother
Maternal parenting	
Supportive Presence	Mother's expression of emotional support and positive regard by encouraging, giving support and confidence, reassuring and acknowledging the child's accomplishments on the tasks
Hostility	Mother's expression of anger, discounting, or rejecting of the child
Intrusiveness	Mother's lack of respect of the child's autonomy by interfering with the child's needs, desires, interests, or behaviors
Clarity of Instruction	Mother's ability to give her child instructions and feedback in a usable form, to structure the situation so that the child knows what the nature and goals of the task are, without solving the task herself
Sensitivity and Timing in Instruction	The timing and coordination of hints in response to the child's efforts and actions
Confidence	Reflects mother's belief that she can work successfully with the child in the situation and that the child will behave appropriately

2.8. Sensory profiles (Study IV)

Data on sensory processing at two years of corrected age were collected with the Infant/Toddler Sensory Profile (ITSP) (Dunn 2002), translated into Finnish, which is a 48-item questionnaire for parents to report the frequency of their child's responses to various sensory experiences on a five-point scale (almost always, frequently, occasionally, seldom, and almost never). The items are divided into five sections of sensory systems: Auditory, Visual, Tactile, Vestibular, and Oral Sensory Processing. Examples of the questions are shown in Table 5. Furthermore, four quadrant scores are calculated: Low Registration, Sensation Seeking, Sensory Sensitivity, and Sensation Avoiding. Low Registration refers to the child's unawareness of available sensations; children are described as disregarding or being unaware of their surroundings. Sensation Seeking refers to the child's interest in and pleasure with all types of sensation; children with increased Sensation Seeking are described as hyperactive and disruptively behaving and having an excessive desire for sensory stimuli. Sensory Sensitivity is a measure of the child's ability to notice sensations, and Sensation Avoiding refers to the child's desire to avoid sensations.

Lower scores indicate higher frequency of atypical sensory response. Scores between -1 SD and +1 SD from the mean represent typical performance. Definite Difference corresponds to scores outside ±2 SD and Probable Difference to scores between ±1 SD and ±2 SD (Dunn 2002). Scores below -1 SD represent atypical responses "more than others" (ITSP gives the lowest points for almost always) and scores above +1 SD atypical responses "less than others" (ITSP gives the highest points for "almost never"). The focus of this study was on the lower end of the scoring continuum, and we classified child's sensory processing ability as probably atypical if she/he scored between -1 SD and -2 SD, and definitely atypical if she/he scored under -2 SD in order to display a more coherent group of children with similar sensory behaviors, i.e., "more than others" on the scale in question.

Forty-four parents of ELGA infants completed the Infant/Toddler Sensory Profile questionnaire. Missing data were imputed with a mean of nearby points in 23 items of all 2548 items analyzed. Nine parents of term children completed the Infant/Toddler Sensory Profile, but because of the small number of these control children they were not included in statistical analyses.

Table 5. General structure of ITSP questionnaire and some examples of the questions.

Section	Number of questions and an example. The parents answer on a 5-point scale: almost always, frequently, occasionally, seldom, or almost never.
General Processing	3 questions. E.g. My child withdraws from situations.
Auditory Processing	10 questions. E.g. I have to touch my child to gain attention.
Visual Processing	7 questions. E.g. My child enjoys looking at shiny objects.
Tactile Processing	15 questions. E.g. My child becomes very upset if own clothing, hands, and/or face are messy.
Vestibular Processing	6 questions. E.g. My child resists having head tipped back during bath.
Oral Sensory Processing	7 questions. E.g. My child is unaware of food or liquid left on lips.

2.9. Statistical analyses

Data were analyzed by using Microsoft PASW Statistics 18.0 for Windows (SPSS Inc., Chicago, IL, USA). For continuous variables, unpaired comparisons were done with a non-parametric Mann-Whitney-U test when data did not follow normal distribution (e.g. GMDS quotients) and with t-test when data followed normal distribution (e.g. BSID-III results). Categorical variables were compared by χ^2- test or Fisher's exact test. Bonferroni corrections for multiple comparisons were applied in Study II. In Study III, we used logistic regression to assess the association of WM abnormalities in MRI at TEA with neurodevelopmental outcome measures. Non-parametric Spearman's correlation was performed to assess mother-child interaction and neurocognitive outcome as a continuous variable. Mother-child interaction variables were regressed on mother's education, and adjusted p-values were computed using the residual as a dependent variable. In addition, Cohen's d-values were calculated to assess the effect sizes of the associations between mother-child interaction and neurocognitive outcome. $0.20<d\leq0.50$ represents a small effect, $0.50<d\leq0.80$ a moderate effect, and $d>0.80$ a large effect (Cohen & Jacob, 1977). In Study IV, the linear regression model was adjusted in order to examine the extent to which PDA operation was independently associated with sensory profile quadrants and sections. Birth weight, gestational age at birth, and mother's education were included in the model. A p-value <0.05 was considered statistically significant.

RESULTS

1. Clinical characteristics of study populations

Table 6. Characteristics of ELGA infants in Studies I-IV.

	Study I (n=30)		Study II (n=39)		Study III (n=48)		Study IV (n=44)	
Gestational age at birth (weeks)	26.5	(1.2)	26.5	(1.2)	26.3	(1.2)	26.3	(1.2)
Birth weight (grams)	884	(181)	884	(181)	876	(194)	850	(190)
Male	15	(50.0)	20	(51.3)	31	(64.6)	25	(56.8)
Mother´s age (years)	32.5	(4.6)	32.0	(4.7)	31.6	(4.5)	31.6	(5.3)
Mother´s educational attainment								
Low	1	(3.8)	1	(3.0)	1	(2.1)	2	(4.5)
Middle	15	(57.7)	20	(60.6)	32	(66.7)	29	(65.9)
High	10	(38.5)	12	(36.4)	15	(31.3)	13	(29.5)
SGA	10	(33.3)	10	(25.6)	10	(20.8)	12	(27.3)
Twins	7	(23.3)	9	(23.1)	14	(29.2)	8	(18.2)
Cesarean section	16	(53.3)	21	(53.8)	28	(58.3)	24	(54.5)
IVH grade III-IV	3	(10.0)	6	(15.4)	7	(14.6)	5	(11.4)
WM abnormalities in MRI at TEA[1]	6	(20.7)	9	(23.7)	17	(37.0)	12	(28.6)
GM abnormalities in MRI at TEA[1]	8	(27.6)	10	(26.3)	10	(21.7)	8	(19.0)
RDS	19	(63.3)	25	(64.1)	36	(75.0)	31	(70.5)
Sepsis	10	(33.3)	13	(33.3)	20	(41.7)	17	(38.6)
NEC	1	(3.3)	2	(5.1)	4	(8.3)	2	(4.5)
ROP	6	(20.0)	8	(20.5)	12	(25.0)	12	(27.3)
BPD at 36+0 GW	12	(40.0)	15	(38.5)	24	(50.0)	22	(50.0)
PDA medically and/or operatively treated	20	(66.7)	28	(71.8)	39	(81.3)	34	(77.3)
PDA operatively treated	10	(33.3)	13	(33.3)	21	(43.8)	17	(38.6)

Data are shown as mean (SD) or n (%)

[1] One MRI was missing in Studies I and II, and two MRIs in Studies III and IV.

Patients in Studies I and II are the same. Overlapping of patients in Studies I, II, III, and IV exists.

Because of the large number of drop-outs in Studies III and IV, a comparison between ELGA study populations and drop-outs in terms of essential neonatal risk factors is presented in Table 7. Significant differences between these groups were not observed.

Table 7. Comparison between ELGA study populations and drop-outs in Studies III and IV.

	Study III ELGA (n=48)		Study III drop-outs (n=30)		Study IV ELGA (n=44)		Study IV drop-outs (n=34)	
Gestational age at birth (weeks)	26.3	(1.2)	26.3	(1.1)	26.3	(1.2)	26.4	(1.2)
Birth weight (grams)	877	(194)	854	(152)	850	(190)	890	(162)
Male	31	(64.6)	18	(60.0)	25	(56.8)	24	(70.6)
IVH grade III-IV	7	(14.6)	5	(16.7)	5	(11.4)	7	(20.6)
WM abnormalities in MRI at TEA[1]	17	(37.0)	9	(37.5)	12	(28.6)	14	(50.0)*
RDS	36	(75.0)	19	(63.3)	31	(70.5)	24	(70.6)
ROP	12	(25.0)	12	(41.3)	12	(27.3)	12	(35.3)
BPD 36+0 GW[2]	24	(50.0)	10	(38.5)	22	(50.0)	12	(40.0)
PDA operatively treated	21	(43.8)	14	(46.7)	17	(38.6)	18	(52.9)

Data are shown as mean (SD) or n (%)
[1] Six MRIs of drop-outs are missing in Studies III and IV.
[2] Data of four drop-outs are missing.
*Fisher's exact test, p=0.08.
Overlapping in patients and drop-outs exists between Studies III and IV.

Table 8. Characteristics of term controls in Studies I and III.

	Study I (n=11)		Study III (n=16)	
Gestational age at birth (weeks)	40.3	(0.9)	40.2	(0.9)
Birth weight (grams)	3605	(482)	3613	(354)
Male	9	(81.8)	11	(68.8)
Mother´s age (years)	32.6	(4.1)	32.2	(4.5)
Mother´s educational attainment				
Low	0	(0)	0	(0)
Middle	4	(44.4)	5	(31.3)
High	5	(55.6)	11	(68.8)
SGA	0	(0)	0	(0)
Twins	0	(0)	0	(0)
Cesarean section	2	(16.7)	1	(6.3)

Data are shown as mean (SD) or n (%)
Overlapping in term controls exists between Studies I and III.

2. Neurocognitive outcome of ELGA children

The neurocognitive outcome of children in Study III is shown in Table 9.

Table 9. Results of GMDS, BSID-III, and Hempel neurological examination at two years of (corrected) age in Study III.

	ELGA (n=48)		Term (n=16)		p
GMDS DQ Score	90.0	(7.4)	91.4	(3.6)	0.88
GMDS locomotor SQ	87.8	(9.1)	90.9	(2.7)	0.22
GMDS personal and social SQ	89.9	(7.1)	90.7	(4.2)	0.95
GMDS hearing and language SQ	89.0	(12.6)	90.9	(7.5)	0.38
GMDS eye-hand coordination	90.7	(8.8)	91.9	(5.1)	0.87
GMDS performance SQ	92.5	(6.7)	92.3	(4.8)	0.35
BSID-III cognition	10.1	(2.3)	12.1	(3.0)	0.02
BSID-III language receptive	11.8	(3.1)	13.1	(3.2)	0.20
BSID-III language expressive	9.5	(3.6)	11.0	(3.5)	0.19
Hempel neurological examination normal	23	(48)	15	(94)	0.001
Hempel MND-1	8	(17)	0	(0)	0.08
Hempel MND-2	12	(25)	1	(6)	0.10
Hempel CP	5	(10)	0	(0)	0.18

Data are shown as mean (SD), except for the results of the Hempel neurological examination, which are shown as n (%).

In Study III, which represents the largest number of infants among these four studies, the mean cognition score in BSID-III was significantly higher ($p<0.05$) in term children [12.1 (SD 3.0)] than in ELGA children [10.1 (SD 2.3)]. No statistical difference was observed in mean receptive language scores [13.1 (SD 3.2) in term and 11.8 (SD 3.1) in ELGA children, $p=0.20$] or mean expressive language scores [11.1 (SD 3.5) in term and 9.5 (SD 3.6) in ELGA children $p=0.19$]. The results of the Hempel neurological examination were normal in 48%, MND-1 in 17%, MND-2 in 25%, and CP was diagnosed in 10% of ELGA children. In GMDS, DQ was normal in 30 ELGA children (70%), while mild impairment was observed in 11 (26%), moderate impairment in 1 (2%), and severe impairment in 1 (2%), according to the English normative sample (Huntley 1996). The results of GMDS were missing in 5 ELGA children in Study III.

3. Brain US and neurodevelopmental outcome

In Study I, 8 (26.7%) of 30 ELGA infants had IVH; grade I-II IVH in (16.7%) and grade III-IV IVH in 3 (10%). In Studies III and IV, grade I-II IVH was present in 17 (35.4%) of 48 and in 11 (25%) of 44 ELGA infants, respectively; the corresponding figures for grade III-IV IVH were 7 (14.6%) and 5 (11.4%). In Study III, half (51%) of the ELGA infants without grade III-IV IVH performed normally in the Hempel neurological examination at two years of corrected age. However, two (5%) of the infants without IVH had CP at two years. Outcome was unfavorable (MND-2 or CP) in five (71%) of seven ELGA infants with grade III-IV IVH compared with 12 (29%) of 41 ELGA infants without grade III-IV IVH (Fisher's exact $p=0.08$). The results of neonatal US examinations in Study III and the neurodevelopmental outcome of ELGA infants at two years of corrected age are shown in Table 10.

Table 10. IVH in neonatal brain US and neurodevelopmental outcome at two years of corrected age in Study III.

	No IVH (n=31)		IVH grade I-IV (n=17)		IVH grade III-IV (n=7)	
GMDS DQ Score	90.1	(5.5)	89.8	(10.2)	87.4	(17.2)
GMDS locomotor SQ	88.2	(7.7)	86.9	(12.2)	82.7	(19.2)
GMDS personal and social SQ	89.8	(6.5)	90.0	(8.6)	90.8	(12.4)
GMDS hearing and language SQ	87.7	(12.9)	92.0	(12.0)	89.2	(19.6)
GMDS eye-hand coordination	91.2	(5.3)	89.5	(14.3)	83.5	(21.7)
GMDS performance SQ	93.3	(3.6)	90.7	(10.9)	90.8	(14.0)
BSID-III cognition	10.8	(2.0)	9.5	(2.7)	9.1	(3.8)
BSID-III language receptive	11.8	(2.2)	11.7	(4.3)	11.7	(5.0)
BSID-III language expressive	9.1	(3.4)	10.0	(4.0)	8.3	(4.6)
Hempel neurological examination normal	15	(48)	8	(47)	2	(29)
Hempel MND-1	6	(19)	2	(12)	0	(0)
Hempel MND-2	8	(26)	4	(24)	2	(29)
Hempel CP	2	(6)	3	(18)	3	(43)

Data are shown as mean (SD), except for the results of the Hempel neurological examination, which are shown as n (%).

4. Brain MRI and neurodevelopmental outcome

In Study I, 23 (79%) of 29 ELGA infants had normal WM in brain MRI at TEA. WM was defined as mildly abnormal in six ELGA infants (21%), and no moderate or severe WM abnormalities were present. Mild WM abnormalities were not associated with neurodevelopmental outcome measured with any of the three methods used (GMDS, BSID-III, Hempel). Mild GM abnormalities were

observed in eight ELGA infants (27%), without any association with their neurodevelopmental outcome at two years of corrected age.

In Study III, mild or moderate WM abnormalities in MRI were found in 17 ELGA infants (37%), and in the remaining infants WM was normal. GM was defined as mildly abnormal in 10 ELGA infants (22%). WM or GM abnormalities in MRI at TEA were associated with neither mother-child interaction at two years of corrected age nor findings in GMDS, BSID-III, or Hempel neurological examination. One of the term controls presented also with mild WM abnormalities, but her Hempel neurological examination was normal at two years of age. The WM findings in MRI at TEA in Study III and the neurodevelopmental outcome of ELGA infants at two years of corrected age are shown in Table 11.

Table 11. WM abnormalities in brain MRI and neurodevelopmental outcome of ELGA infants at two years of corrected age in Study III.

	WM normal (n=29)		WM abnormality mild (n=15) or moderate (n=2) (n=17)		p
GMDS DQ Score	90.0	(7.9)	90.9	(6.4)	0.85
GMDS locomotor SQ	88.4	(8.8)	89.1	(6.5)	0.89
GMDS personal and social SQ	90.0	(6.7)	89.8	(8.2)	0.96
GMDS hearing and language SQ	88.5	(13.1)	91.1	(11.2)	0.82
GMDS eye-hand coordination	90.5	(10.2)	91.5	(6.3)	0.90
GMDS performance SQ	92.6	(6.0)	92.9	(8.0)	0.27
BSID-III cognition	10.2	(2.6)	9.9	(1.8)	0.44
BSID-III language receptive	12.0	(3.2)	11.6	(2.9)	0.49
BSID-III language expressive	9.4	(3.5)	9.9	(3.7)	0.80
Hempel neurological examination normal	15	(52.0)	8	(47.1)	0.76
Hempel MND-1	4	(13.8)	3	(17.6)	0.73
Hempel MND-2	9	(31.0)	3	(17.6)	0.32
Hempel CP	1	(3.5)	3	(17.6)	0.10

Data are shown as mean (SD), except for the results of the Hempel neurological examination, which are shown as n (%).

5. MEG and neurodevelopmental outcome at two years of corrected age

In Study I, we could detect the first SEF response from contralateral SI, which has been the main focus of earlier SEP studies, in all ELGA infants and controls. The SII response, peaking at about 200 ms after tactile stimulation, was defined as abnormal when it was absent both contra- and ipsilaterally in either hemisphere (right or left). The contralateral SII response was absent in nine ELGA infants in the right hemisphere and in eight ELGA infants in the left hemisphere, but ipsilateral stimulation showed the SII response in the right hemisphere in three of the nine infants and in the left hemisphere in three of the eight infants whose response was missing to contralateral stimulation. Thus, the SII response was defined as abnormal in nine of 30 ELGA infants and in one term infant.

The abnormality of SII response in ELGA infants was associated with lower total DQ and locomotor SQ in GMDS ($p<0.01$), as shown in Figure 8. A trend of worse eye-hand coordination was noted, but it did not reach significance ($p=0.07$).

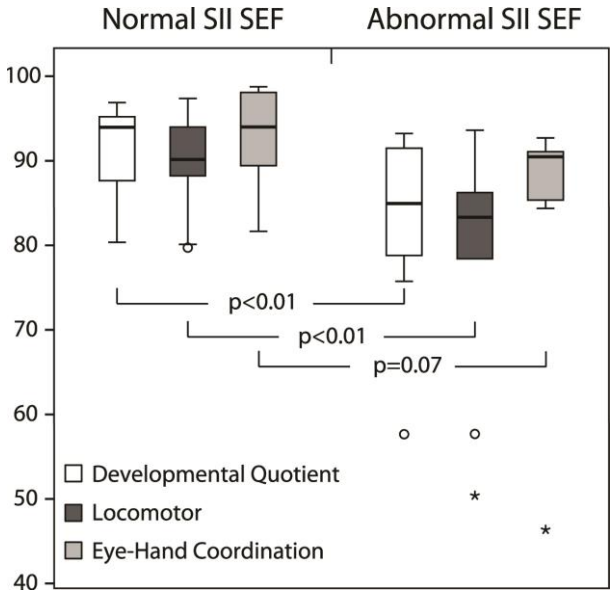

Figure 8. Griffiths Mental Developmental Scales (GMDS) quotients in ELGA children with normal and abnormal secondary somatosensory cortex (SII) response in magnetoencephalography (MEG). ° and * show outliers.

In contrast, scores in BSID-III (cognition, language receptive, language expressive) did not differ between ELGA infants with normal or abnormal SII response. No difference was observed in clinical characteristics and previous medical history of ELGA infants with normal or abnormal SII response. Normal SII response preceded normal result in Hempel neurological examination more often than abnormal SII response (62% vs. 22%, $p<0.05$). SII responses in MEG at TEA in Study I and neurodevelopmental outcome of ELGA infants at two years of corrected age are shown in Table 12.

Table 12. Neurodevelopmental outcome (two years) of ELGA infants with normal and abnormal SII responses in MEG at TEA, and term infants.

	ELGA				Term	
	Normal SII-response (n=21)		Abnormal SII-response (n=9)	p	(n=11)	
GMDS DQ Score	91.8	(4.6)	82.8 (11.2)	<0.01	91.1	(3.7)
GMDS locomotor SQ	90.0	(4.8)	78.7 (14.8)	<0.01	90.0	(2.6)
GMDS personal and social SQ	91.3	(6.5)	84.2 (9.9)	0.08	90.8	(5.1)
GMDS hearing and language SQ	91.5	(8.0)	78.4 (18.9)	0.09	88.4	(9.2)
GMDS eye-hand coordination SQ	92.3	(6.0)	84.6 (14.6)	0.07	92.2	(4.5)
GMDS performance SQ	93.8	(4.2)	88.3 (9.9)	0.09	94.2	(2.3)
BSID-III cognition[a]	10.8	(1.7)	9.4 (3.9)	0.25	13.3	(3.2)
BSID-III language receptive[b]	12.6	(2.2)	10.4 (4.9)	0.15	14.3	(3.1)
BSID-III language expressive[c]	11.3	(2.7)	8.5 (5.2)	0.11	10.4	(4.5)
Hempel neurological examination normal	13	(61.9)	2 (22.2)	<0.05	10	(83.3)
Hempel neurological examination MND-1	3	(14.3)	2 (22.2)	0.59	1	(9.1)
Hempel neurological examination MND-2	4	(19.0)	4 (44.4)	0.15	0	(0)
Hempel neurological examination CP	1	(4.8)	1 (11.1)	0.52	0	(0)

Data are shown as mean (SD) or n (%)

[a] 6 ELGA missing/ 2 term missing

[b] 7 ELGA missing/ 2 term missing

[c] 8 ELGA missing/ 2 term missing

Among three ELGA infants with grade III-IV IVH, two had normal SII response and one abnormal SII response in MEG. Of these, the two with normal SII response performed well in neurodevelopmental examinations at two years of corrected age (DQ 96.9 and 94.5, locomotor SQ 94.0 and 88.0, and Hempel neurological examination normal and MND-2, respectively), whereas the one with abnormal SII had worse neurodevelopmental outcome (DQ 57.7, locomotor SQ 50.4, and Hempel neurological examination MND-2). The one ELGA infant with delayed M60 (SI response) peak latency performed normally in GMDS, BSID-III, and Hempel neurological examination at two years of corrected age. In contrast, one term infant with abnormal SII response presented also focal regions of high T1- or T2-weighted signals in MRI, and his performance at two years on neurodevelopmental tests was worse than term children on average (e.g. DQ in GMDS 86.4 vs. 91.8 on average), although his Hempel neurological examination was normal.

Correspondingly, the one ELGA infant with abnormal SII response and mild WM abnormalities in MRI performed worse in neurodevelopmental examinations at two years of corrected age than five ELGA children with mild WM abnormalities but normal SII response (Table 13).

Table 13. MEG and US at TEA, and neurological outcome at two years of corrected age in five ELGA infants with WM abnormalities in MRI.

Gestational age (weeks)	SII in MEG	US (IVH)	Neurological examination[b]	DQ in GMDS	Locomotor SQ in GMDS
25+4	Abnormal	Normal	MND-2	91.5	85.0
27+3	Normal	Normal	MND-1	94.1	97.4
27+2	Normal	Normal	Normal	96.5	94.0
27+2	Normal	Grade III sin Grade II dx	Normal	96.9	94.0
23+6	Normal	Normal	Normal	87.3	90.2
27+6	Normal	Normal	MND-1	94.0	88.2

6. EEG-SEP

The quality of data in EEG-SEP recordings was adequate (i.e., the required number of averages during QS was met) in six ELGA infants to stimulation of the left median nerve and in four infants to stimulation of the right median nerve for retrospective analysis in infants with SII response present in MEG. In EEG-SEP, the SI response was detectable in every infant, as it was also in

MEG. To stimulation of the right median nerve, the contralateral SII response was detectable in all four infants in EEG-SEP, and to stimulation of the left median nerve in four of six infants. In the only term infant with both MEG and EEG-SEP recording available, contralateral SI and SII responses to stimulation of both hands were detected with both MEG and EEG-SEP. Ipsilateral responses in EEG-SEP were detected in two of three infants and in neither of two infants who presented ipsilateral SII response in MEG to stimulation of the right and the left hand, respectively. Figure 9 shows the time course and electrical field patterns of SEPs from SI and SII in one newborn.

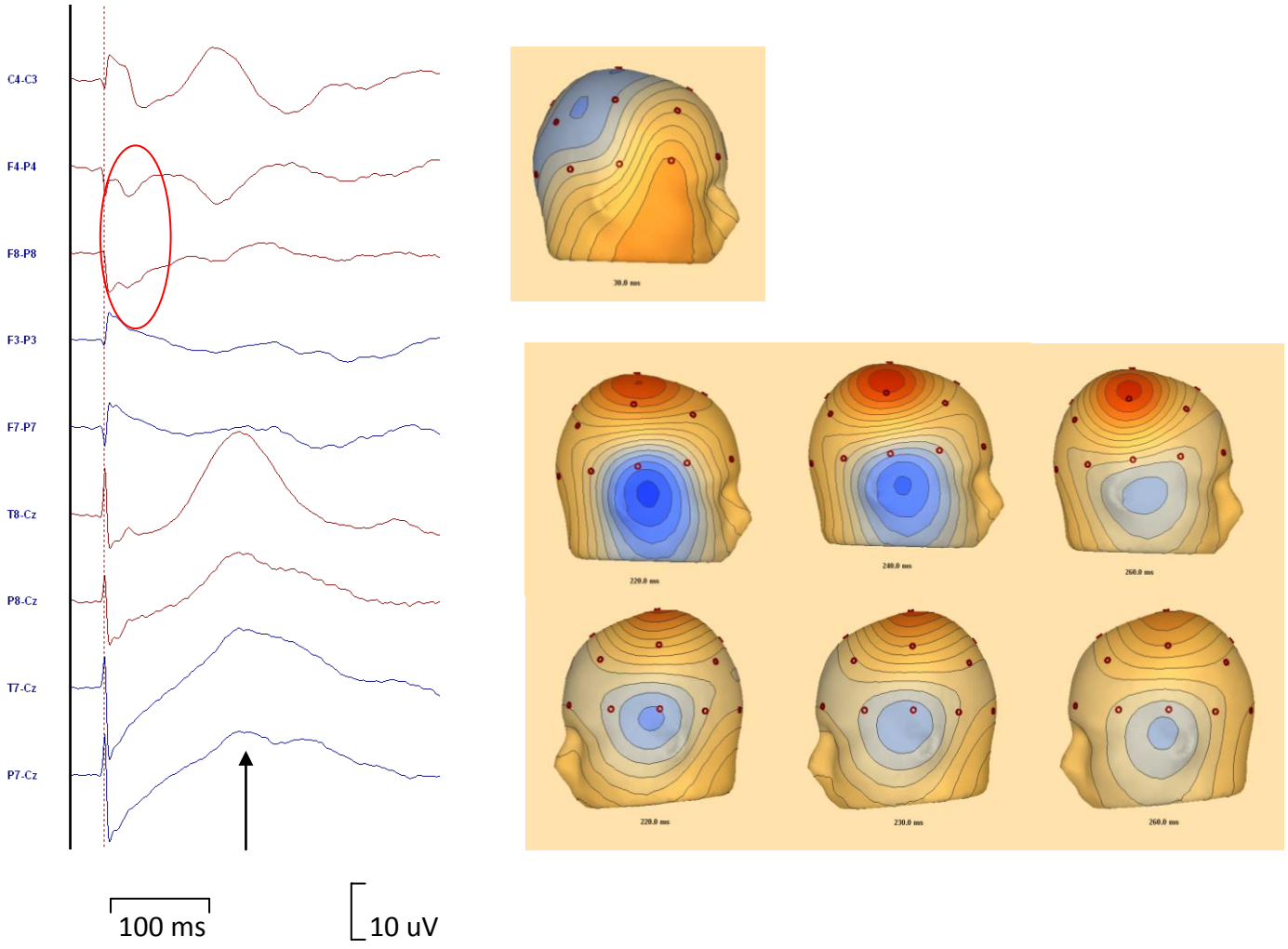

Figure 9. Time course and electrical field patterns of SEPs from SI and SII. **The left panel shows the SEP responses to left median nerve stimulation in one newborn. The earliest SI responses are detected in**

frontoparietal derivations and are indicated with a red circle. The black arrow denotes the time point of the SII responses, which are detected in the bipolar derivations T8/P8 and T7/P7 referenced to Cz. The dotted line indicates timing of the stimulus. On the right are the electric field patterns showing the SI (at 30 ms, upper line) and contralateral (SIIc at 220, 240, and 260 ms, middle line) and ipsilateral (SIIi at 220, 240, and 260ms, lower line) SII potential maps for left median nerve stimulation. The SII response field patterns are consistent with a superiorly pointing dipolar source at the secondary somatosensory cortex, i.e., positivity at the vertex and negativity contra- or ipsilaterally in the mastoid area.

7. Mother-child interaction and neurocognitive outcome

The quality of interaction of ELGA children and their mothers was equal to that of term children and their mothers in all aspects; child's, mother's, and dyadic behavior. For instance, mean maternal *Sensitivity and timing in instruction* was 5.6 (SD 1.2) and 5.6 (SD 0.9), p=0.61, and *Sensitive-responsiveness* 20.5 (SD 5.1) and 20.0 (SD 3.8), p=0.29, in preterm and term dyads, respectively.

However, among ELGA children, DQ <-1SD in GMDS was associated with lower mother-child interaction scores in Child's *Persistence*, *Enthusiasm*, *Compliance*, *Experience of the session,* and *Avoidance*, Maternal *Supportive presence* and *Sensitive-responsiveness,* and *Quality of relationship.* Accordingly, Child's *Enthusiasm*, *Experience of the session,* and *Avoidance*, maternal *Supportive presence* and *Sensitivity and timing in instructions,* and *Quality of relationship* were associated with cognition <-1SD in BSID-III (Table 14), and all of these associations represented large effects (Cohen's d > 0.80). All mother-infant interaction scores were adjusted for mother's education in statistical analysis because mothers of term infants had higher educational status than mothers of ELGA infants. All of these associations remained significant also when cognition in BSID-III and DQ in GMDS were used as continuous variables (Spearman's rs > 0.31, p-values < 0.04).

Neuroimaging findings reflecting neonatal brain injury at TEA (WM or GM abnormalities in MRI or grade III-IV IVH in US) were not associated with poorer scores in mother-ELGA infant dyads. Further, neurological impairments at two years of corrected age were not associated with any other mother-child interaction scale except child's *Experience of the session* (p<0.05).

Table 14. Mother-child interaction scores in ELGA children with DQ<-1SD or DQ≥-1SD in GMDS and cognition <-1SD or ≥1-SD in BSID-III.

Mother-child interaction scale	DQ <-1SD		DQ ≥1-SD			Cognition <-1SD		Cognition ≥1-SD		
	(n=13)		(n=30)		p[a]	(n=5)		(n=43)		p[a]
Child's scale										
Persistence	4.6	(1.7)	5.9	(1.1)	0.02	3.9	(1.9)	5.7	(1.3)	0.05
Enthusiasm	4.5	(1.2)	5.8	(1.0)	<0.01	3.9	(1.4)	5.5	(1.1)	0.02
Negativity	1.4	(0.4)	1.3	(0.8)	0.24	1.3	(0.7)	1.4	(0.8)	0.43
Compliance	4.6	(1.4)	5.8	(1.2)	0.03	4.3	(1.5)	5.4	(1.4)	0.19
Experience of the Session	5.2	(1.1)	6.3	(1.0)	<0.01	4.4	(1.1)	6.1	(1.1)	<0.01
Affection Toward Mother	4.2	(1.1)	5.0	(1.1)	0.09	3.9	(1.8)	4.8	(1.1)	0.27
Avoidance	2.7	(1.8)	1.4	(0.6)	0.02	4.0	(2.0)	1.6	(1.0)	0.03
Maternal scale										
Supportive Presence	5.5	(1.1)	6.5	(0.7)	<0.01	5.0	(1.2)	6.4	(0.8)	0.01
Hostility	1.0	(0.1)	1.1	(0.2)	0.22	1.0	(0.0)	1.0	(0.1)	0.09
Intrusiveness	2.4	(1.2)	1.7	(0.7)	0.11	2.0	(1.3)	1.8	(0.9)	0.70
Clarity of Instruction	5.0	(1.7)	6.0	(1.1)	0.16	4.4	(1.9)	5.9	(1.2)	0.20
Sensitivity and Timing in Instruction	4.9	(1.6)	5.9	(0.9)	0.12	4.1	(1.7)	5.8	(1.0)	0.04
Confidence	5.5	(1.5)	6.3	(1.0)	0.28	4.7	(1.8)	6.3	(1.0)	0.08
Sensitive-responsiveness	17.1	(5.8)	21.9	(3.9)	0.02	14.3	(6.4)	21.3	(4.6)	0.05
Mother-child relationship										
Mutually Responsive Orientation	3.7	(1.1)	4.4	(0.7)	0.09	3.1	(1.5)	4.3	(0.8)	0.08
Quality of Relationship	4.7	(1.3)	5.9	(0.9)	<0.01	4.0	(1.7)	5.7	(1.0)	0.03

Data are shown as mean (SD). [a] Adjusted for mother's education

8. Sensory profiles

The Sensory profiles of ELGA children in the ITSP quadrants were probably or definitely atypical (< -1 SD representing responses "more than others") in terms of Low Registration (23%), Sensory Avoiding (18%), Sensation Seeking (14%), and Sensory Sensitivity (7%). Almost half (48%) of the ELGA children presented typical performance in all ITSP quadrants. In the small control group (n=9), an atypical ITSP quadrant (Low Registration) was observed in only one child. In Sensory Profile sections, Vestibular Processing and Oral Sensory Processing were probably or definitely atypical (<-1SD) in 18%, Visual Processing in 16%, Tactile Processing in 9%, and Auditory Processing in 7% of ELGA children. No significant differences between the ELGA study population and drop-outs were observed in terms of gestational age, birth weight, sex, BPD, RDS, ROP, grade III-IV IVH in US, and WM and/or GM abnormalities in MRI (p-values>0.05).

Of 42 ELGA infants, 11 (26%) presented with a mild and one (2%) with a moderate WM abnormality, and 8 (19%) showed a mild GM abnormality in MRI at TEA. WM and/or GM abnormalities were observed in 16 ELGA infants (38%). All ELGA children with atypical Sensation Seeking had WM and/or GM abnormalities in MRI at TEA (Table 15).

Table 15. Brain MRI at TEA and Sensory Profile quadrants at two years of corrected age.

	MRI (n=42)		
	Normal WM and GM (n=26)	**Abnormal WM and/or GM (n=16)**	**p**
Atypical Low Registration	6 (23)	3 (19)	1.00
Atypical Sensation Seeking	0 (0)	6 (38)	0.002
Atypical Sensory Sensitivity	2 (8)	1 (6)	1.00
Atypical Sensation Avoiding	5 (19)	2 (13)	0.69

Data are shown as n (%).

Five ELGA infants (11%) had grade III-IV IVH during neonatal intensive care. Of the six ELGA children with an atypical Sensation Seeking profile at two years of corrected age, grade III-IV IVH in neonatal US was observed in three, WM abnormality in MRI at TEA in four, and GM abnormality in five. All of these abnormal early neuroimaging findings were associated with later atypical Sensation Seeking ($p<0.05$). Other quadrants or sections in ITSP were not associated with brain injury-related neuroimaging findings.

MEG was performed on 27 of 44 ELGA infants, and SII response was abnormal in 10. Abnormal SII responses were not associated with atypical scores in ITSP ($p>0.05$).

Of neonatal risk factors, operatively treated patent ductus arteriosus (PDA) was associated with atypical Sensation Seeking ($p=0.04$, adjusted p for gestational age, birth weight, and mother's education< 0.01) and Oral Sensory Processing ($p=0.02$, adjusted $p<0.01$). Eight ELGA children had atypical (<-1SD from the mean for children without disabilities) Oral Sensory Processing, and five of them had undergone operative treatment of PDA. All of these children's parents reported feeding problems, and a gastrostomy tube was inserted into one child at 1.5 years of corrected age.

BPD, RDS, NEC, ROP, sepsis, or birth as SGA were not associated with scores in ITSP ($p>0.05$). Atypical scores in the Sensory Profile questionnaire were not more prevalent did not exist more in children with adverse neurodevelopmental outcome at two years of corrected age assessed with BSID III, GMDS, or Hempel neurological examination ($p>0.05$).

9. Prediction of neurological outcome by combining neonatal neurological examination with neuroimaging and neurophysiological methods

In Study II, the SI response in MEG (right hemisphere: 39 infants, mean latency 63 ± SD 12 ms; left hemisphere: 33 infants, 62 ± 11 ms) was detectable in all infants, and the contralateral SII response in 26 of 39 ELGA infants in the right (mean latency 229 ± 46 ms) and in 22 of 33 ELGA infants in the left hemisphere (241 ± 36 ms). Compared with the term controls used in Study II, (Nevalainen et al. 2012) of the 38 of 42 infants who presented a contralateral SII response in the right hemisphere, and in all 11 infants who presented the response in the left hemisphere, SII response was present significantly ($p=0.01$ and 0.04 in right and left hemispheres, respectively) more often in term infants than in ELGA infants. No significant difference was observed in peak latencies or source strengths of SI and SII responses between ELGA and term infants.

Of ELGA infants, 29 underwent HNNE, MRI and MEG at TEA, and Hempel neurological examination at two years of corrected age. Favorable (normal or MND-1, n=19) or unfavorable (MND-2 or CP, n=10) outcome could not be predicted satisfactorily with any of these three examinations at TEA (see Table 16). Table 17 shows sensitivity, specificity, and predictive values of moderately or severely abnormal HNNE, unilaterally abnormal SII in MEG at TEA, abnormal WM in MRI at TEA, and grade III-IV IVH in neonatal serial US, as well as combinations of these examinations for predicting outcome at two years of corrected age.

Both ELGA infants with severely abnormal HNNE presented with CP at two years of corrected age. Of infants with moderately abnormal HNNE, three of nine (33%) showed an unfavorable outcome (MND-2 in all), as did five of 18 (28%) of those with mildly abnormal or normal neurology at TEA. Among these infants, four of the six (66%) with unilaterally abnormal MEG developed MND-2 or CP, whereas among infants with normal MEG only four of 18 (22%) developed MND-2. Interestingly, all three infants with bilaterally absent SII SEFs in MEG presented normal neurological outcome at two years of corrected age. Mild WM abnormalities in MRI at TEA were not associated with unfavorable neurological outcome. CP was observed at two years of corrected age in the only infant with moderately abnormal WM at TEA. IVH grade III-IV predicted unfavorable outcome in five of the six infants. However, also five infants with normal US had an unfavorable outcome.

Table 16. Results of HNNE of ELGA infants, highest grade of IVH detected in serial cranial US, WM in term-age MRI, SII responses in MEG at term age, and result of Hempel neurological examination at two years of corrected age.

HNNE	US	WM in MRI	SII response in MEG	Outcome (Hempel)
Normal	Normal	Normal	Normal	Normal
Normal	Normal	Normal	Normal	Normal
Normal	IVH grade I dx	Normal	Normal	Normal
Normal	Normal	Normal	Normal	MND1
Normal	Normal	Normal	Unilaterally abnormal	MND2
Normal	IVH grade IV dx	Normal	Unilaterally abnormal	MND2
Mild	Normal	Normal	Normal	Normal
Mild	Normal	Mildly abnormal	Normal	Normal
Mild	Normal	Mildly abnormal	Normal	Normal
Mild	IVH grade II dx	Normal	Normal	Normal
Mild	Normal	Normal	Bilaterally abnormal	Normal
Mild	Normal	Normal	Bilaterally abnormal	Normal
Mild	Normal	Normal	Bilaterally abnormal	MND1
Mild	IVH grade I sin	Mildly abnormal	Normal	MND1
Mild	IVH grade I dx	Normal	Unilaterally abnormal	MND1
Mild	Normal	Normal	Normal	MND2
Mild	IVH grade IV sin, grade II dx	Mildly abnormal	Normal	MND2
Mild	IVH grade III sin, grade III dx	Mildly abnormal	Unilaterally abnormal	CP
Moderate	Normal	Normal	Normal	Normal
Moderate	Normal	Normal	Normal	Normal
Moderate	IVH grade III sin, grade II dx	Mildly abnormal	Normal	Normal

Moderate	Normal	Normal	Unilaterally abnormal	Normal
Moderate	Normal	Normal	Normal	MND1
Moderate	Normal	Mildly abnormal	Normal	MND1
Moderate	Normal	Normal	Normal	MND2
Moderate	IVH grade IV dx	Normal	Normal	MND2
Moderate	Normal	Normal	Unilaterally abnormal	MND2
Severe	IVH grade III sin, grade III dx	Moderately abnormal	Normal	CP
Severe	Normal	Mildly abnormal	Unilaterally abnormal	CP

The dark gray highlights adverse outcome (MND-2 or CP) and IVH grade III-IV in US, moderately abnormal WM in MRI, and unilaterally absent SII response in MEG. The light gray highlights milder abnormalities in US, MRI, and bilaterally abnormal SII in MEG that were not associated with unfavorable outcome.

Table 17. Sensitivity, specificity, and predictive values of moderately or severely abnormal HNNE, unilaterally abnormal SII in MEG at TEA, abnormal WM in MRI at TEA, and grade III-IV IVH in neonatal serial US for predicting outcome at two years of corrected age.

	Sensitivity	Specificity	PPV	NPV
HNNE	50	68	45	72
MEG	50	74	50	74
MRI	40	74	44	70
US	50	95	83	78
HNNE or MEG	80	47	44	82
MEG or neuroimaging (MRI, US)	80	47	44	82
Any of three modalities (HNNE, MEG, neuroimaging)	90	32	41	86

Data are shown as %

DISCUSSION

This thesis assessed the value of measuring secondary somatosensory cortex responses at TEA in predicting neurodevelopmental outcome of ELGA children. Further, we investigated the role of maternal interaction in relation to the neurocognitive outcomes of ELGA children and the sensory processing abilities of these children at two years of corrected age. The results are discussed in the following categories:

1. Somatosensory evoked magnetic fields (SEFs) recorded by MEG in predicting neurodevelopment of ELGA children (Studies I and II)

This is the first study investigating SII responses recorded by MEG as a predictor of neurodevelopmental outcome in ELGA children. Previous functional somatosensory studies assessing neurodevelopmental outcome of children born preterm have been SEP studies and have focused on the first cortical response, which represents intactness of somatosensory tracts from the periphery to the SI (Pike & Marlow 2000, Vanhatalo & Lauronen 2006). Karniski et al. (1992) proposed that SEP responses with longer latencies can also be detected reliably and the 200 ms response could be used in evaluating the somatosensory system of preterm infants (Karniski 1992, Karniski et al. 1992). In the MEG study of ELGA infants by Nevalainen et al. (2008), absent SII responses at TEA were often noted in ELGA infants and supported by neuroanatomical findings in MRI or US in the underlying hemisphere. On the other hand, SI response was detectable in all ELGA and term infants suggesting intact somatosensory pathways from the periphery to SI (Nevalainen et al. 2008b).

The theoretical basis of interest in studying SII responses in preterm infants derives from previous observations on the role of SII neurons in processing of somatosensory information. SII neurons have bilateral receptive fields (Whitsel, Petrucelli & Werner 1969), and they have been suggested to integrate somatosensory information from the two body halves (Simoes & Hari 1999) and to integrate somatosensory and motor information (Huttunen et al. 1996). Thus, SII responses are supposed to represent higher cortico-cortical processing of somatosensory information, and the absence of SII responses may represent not only damage in the somatosensory networks, but also overall reduced cortico-cortical connectivity.

Study I showed the association between absent SII responses at TEA and adverse neuromotor outcome, i.e., decreased DQ and locomotor SQ in GMDS in ELGA children with relatively mild neuroanatomical lesions in MRI at TEA. About one-quarter of ELGA infants had mild WM abnormalities in MRI, and moderate to severe WM lesions did not exist in this study group, thus, we examined ELGA infants with only minor signs of brain abnormalities in neuroimaging. Woodward et al. (2011) presented a much higher incidence for WM lesions in infants born before 32 gestational weeks at TEA (58%, 15%, and 3% for mild, moderate, and severe WM lesions, respectively). The fact that in Study I we evaluated infants with fewer complications than is typical in ELGA infants can be confirmed by comparing the incidence of WM abnormalities between Study I and Study III (21 % vs. 37%, p=0.08). At least two explanations for this difference can be offered. First, MEG is a time consuming and delicate method; in infants, one recording can take two to four hours, and measurements are easily disturbed by external artifacts. Consequently, MEG recordings can be done only for ELGA infants not requiring respiratory assistance or constant monitoring at TEA. Second, a stressful period in NICU with their infant with neonatal brain complications in structural neuroimaging studies might lower parents' motivation to expose their child to extra examinations. On the other hand, our study population is representative of infants who leave NICU without any visible neuroanatomical lesions, but are nevertheless at risk for adverse neurodevelopmental outcome. Specifically this group of ELGA infants requires additional methods for recognizing increased risk as early as possible. In Study I, MEG was superior to structural neuroimaging in prediction of neuromotor outcome, but this result calls for a larger study to assess the value of SII assessment in ELGA infants with more severe neuroanatomical lesions.

At the individual level in Study I, two patients with severe IVH but normal SII response in MEG presented better neurodevelopmental outcome than one patient with severe IVH and abnormal SII response in MEG. Furthermore, five infants with abnormal WM but normal SII response at TEA had better neurodevelopmental outcome than one infant with WM abnormalities in MRI combined with abnormal SII response in MEG. These observations support the complementary value of SII assessments in predicting neuromotor development in ELGA infants and led to the investigation of combinations of clinical assessments, structural neuroimaging, and functional neurophysiological methods in Study II.

In Study II, both infants with a severely abnormal neonatal neurological examination had CP at two years, but milder abnormalities in neonatal examination did not always lead to unfavorable outcome. Further, normal neonatal examination alone did not guarantee favorable outcome. This is

not unexpected since assessment of cortical functions with neurological examinations is markedly more difficult in neonates than in older children and adults. For example normal variation in tone from hypotonia in the preterm phase to hypertonia at TEA may complicate assessment of neonatal neurological abnormalities, possibly leading to adverse outcome, particularly in cases with absent signs of asymmetry (Cioni et al. 1997).

Networks of the central nervous system are under rapid development in early infancy, and signs of abnormal neurological function may sometimes only be revealed in childhood, when more complex neuromotor functions are supposed to develop. The brain damage of prematurity leading to adverse neuromotor outcome or cognitive defects has been suggested as a complex combination of primary destructive events and secondary maturational and nutritional disturbances (Volpe 2009). The underlying neuropathology is variable and not yet fully understood, but the most common lesion seems to be diffuse PVL with accompanying neuronal and axonal damage, which has been displayed in cerebral WM, thalamus, basal ganglia, cerebral cortex, brain stem, and cerebellum (Volpe 2009). Less common but still important mechanisms of preterm brain damage are cystic PVL and severe IVH with periventricular hemorrhagic infarction (Volpe 2009). The difficulties in predicting neurodevelopment of ELGA infants with a single method may be related to this complex underlying pathophysiology affecting the function of large nervous networks in the brain.

Unilaterally absent SII responses in MEG revealed two ELGA infants with normal or mildly abnormal neonatal neurological examination and normal MRI at TEA, but unfavorable (MND-2) neurological outcome at two years of corrected age. Measurement of SII responses in MEG can reveal disturbed cortico-cortical connectivity without any behavioral correlate in the neonatal neurological examination, which may nevertheless result in later adverse neurodevelopmental outcome. Unexpectedly, all three infants with bilaterally absent SII responses performed normally in the Hempel neurological examination at two years of corrected age. The number of these infants is too small to draw any conclusions, but, interestingly, bilaterally absent SII responses were reported in a previous study in four of 42 healthy term newborns, whereas unilaterally absent SII responses, i.e., differences between hemispheres, were not observed (Nevalainen et al. 2012).

Neurophysiology can provide additional objective methods to assess the function of the central nervous system. Although new clinically available neurophysiological methods have not been produced recently, advancements in data analysis methods have improved the potential of these

methods to assess preterm brain function and to shed light on the underlying pathological phenomena.

The data of Study II suggest that measuring SEFs, especially SII response by MEG, complements neonatal neurological examination and structural neuroradiology in predicting neuromotor outcome of ELGA infants. None of these methods was better in predicting neurological outcome alone than in combination. SII response assessment can produce complementary information as part of the developmental risk assessment of ELGA infants.

2. Detection of SII responses in EEG-SEP (Study II)

MEG recordings in neonates are time-consuming and technically demanding, and the availability of MEG devices is restricted; in Finland, for example, MEG measurements are available only in Helsinki (Bio Mag Laboratory, Helsinki University Central Hospital), Espoo (Brain Research Unit, O.V. Lounasmaa Laboratory, Aalto University), and soon also Jyväskylä. Thus, Study II aimed at retrospectively investigating, whether SII responses could be detected with a clinically widely used neurophysiological method, EEG, in combination with median nerve stimulation.

In human adults, SII responses were first recognized some 30 years ago with MEG because it is easier to differentiate SI and SII sources from the magnetic field than from the electric potential distribution (Hari et al. 1983). Accordingly, SII responses in neonates were first observed in MEG measurements (Nevalainen et al. 2008a), although some earlier SEP studies had paid attention to responses with longer latencies after the first N1 reflection. In all of these studies, the pattern of somatosensory EEG response at the central contralateral area past the first N1 reflection consisted of three components: a positive deflection at approximately 100 ms, a negative deflection at around 150 ms, and a second positive deflection at around 230 ms (Desmedt & Manil 1970, Hrbek, Karlberg & Olsson 1973, Karniski 1992, Karniski et al. 1992). This second positive deflection also has other similarities besides the temporal latency with the M200 (SII response) in MEG; they both are more prominent in QS and attenuated in AS, and their strongest positivity is located at the vertex (Desmedt & Manil 1970, Pihko & Lauronen 2004).

In the present study, the SII SEP responses were detectable in most infants with normal SII responses in MEG. The information from MEG facilitated detection of SII responses from EEG-SEP. Several preconditions were required to confirm the presence of SII responses in EEG-SEP.

First, the latency had to be distinctly separable from SI response and occur around 200 ms as in MEG. Second, the electric field pattern had to situate inferiorly to the SI source, and the generator current had to point upwards so that location would match with SII location in the parietal operculum in MEG. These precautions were inevitable because electrode positions were not digitized, and thus, accurate source localization was not possible directly from EEG-SEP data.

As EEG-SEP measurements were analyzed retrospectively, the stimulation set-up was not optimal for detection of SII responses since a routine set-up used for evaluation of e.g. asphyxiated neonates was used. This resulted in some limitations; for instance the interstimulus interval in all but one infant was 1s, not 2 s as in MEG recordings. In previous studies, shortening of the interstimulus interval from 2 s to 0.5 s led to smaller SII responses in MEG (Nevalainen et al. 2008a). Further, stimulation methods were different: tactile stimulation of the index finger in MEG and electrical stimulation of the median nerve in EEG-SEP. In addition, recordings were performed in separate sessions. Consequently, it would be unrealistic to expect the results of these recordings to be exactly the same. In order to compare the MEG and EEG adequately for assessment of neonatal SII responses, these measurements should be performed simultaneously using the same stimulation method. Although electrical median nerve stimulation has been mainly used in assessing somatosensory responses in SEP studies, tactile stimuli could be implemented also in EEG-SEP recordings in the NICU since they have been shown to evoke detectable prominent activity even in the raw EEG signal without averaging in preterm infants before TEA (Vanhatalo et al. 2009).

In addition, MEG and EEG are two different neurophysiological methods with different sensitivities. EEG is sensitive to the electrical activity of the whole brain, including radial and deep sources of activity, whereas magnetic fields detected with MEG originate mostly from activity of tangential and superficial sources. MEG is usually sensitive to the activity in the SI and SII because these responses can often be modeled with current dipoles tangential to the surface of the head. In addition, MEG is less sensitive to changes in the conductivity of intervening tissue between the source and measurement device (Flemming et al. 2005).

Despite these limitations and the fact that the EEG-SEP settings were not optimal for detection of SII responses, they were nevertheless detectable in most infants who presented normal SII response in MEG. These results suggest that evaluation of SII responses, which can be used as a complementary method in predicting neurodevelopment of ELGA infants at TEA as shown in Studies I and II, could be performed even bedside in NICU with EEG-SEP. This would offer a

clinically feasible method to evaluate cortical function beyond the primary sensory areas. However, these results call for a larger study in preterm and term infants comparing assessments of somatosensory responses in EEG-SEP and MEG, and evaluating the role of absent SII responses in EEG-SEP in predicting neurodevelopment of ELGA infants.

3. Mother-child interaction, sensory processing abilities, and neurocognitive outcome of ELGA children at two years of corrected age (Studies III and IV)

At two years of corrected age, the quality of interaction did not differ between mother-ELGA child dyads and term dyads. This observation is in line with many previous studies (Greenberg & Crnic 1988, Korja et al. 2008, Montirosso et al. 2010), although more passive and compliance-compulsive behavior in interaction at 18 months of age in preterm infants has been reported (Muller-Nix et al. 2004). In a systematic review, Korja et al. (2011) concluded that differences in maternal interaction behavior between mothers of preterm and full-term infants seem to be most evident during the first six months of life, with differences diminishing by six and 12 months of corrected age. Preterm infants and their mothers do not seem to be at greater risk for insecure attachment than term infants and their mothers at 12 months of corrected age (Korja, Latva & Lehtonen 2011). Thus, equal quality of interaction of ELGA and term dyads at two years of corrected age in the present study supports earlier observations.

However, within the group of ELGA children, those with lower results (<-1SD) in neurocognitive tests were less persistent and enthusiastic and more avoidant in the interaction situation than ELGA children with normal results in neurocognitive assessments. Correspondingly, mother's scores in *Supportive presence* and *Sensitivity in timing of instructions* and *Sensitive-Responsiveness* were lower in mothers of ELGA infants with lower (<-1SD) results in neurocognitive tests. Because of the small number of the children with neurocognitive impairment, the statistical analysis was also conducted by using DQ in GMDS and Cognition in BSID-III as continuous variables. All associations described above remained significant, suggesting that our findings describe the association between mother-child interaction and neurocognitive development in the whole ELGA population in our study, not only those with adverse neurocognitive development. Importantly, ELGA child's neuroanatomical findings at TEA suggesting brain injury (i.e., WM or GM abnormalities in MRI or grade III-IV IVH in US) or adverse neurological outcome at two years of corrected age were not associated with difficulties in mother-child interaction.

Since both mother-child interaction and neurocognitive outcome were assessed at the same age in our study, conclusions about the direction of the effects cannot be drawn. It is possible that a child with adverse neurocognitive outcome can behave less persistently, compliantly and enthusiastically and be more avoidant in interaction in early childhood, resulting in the mother's poorer sensitivity and responsiveness in interaction with her child. However, previous studies in preterm children have also suggested that better maternal responsiveness predicts better cognition and language and social skills later (Beckwith & Rodning 1996, Milgrom, Westley & Gemmill 2004). Further, better quality of mother-child interaction in term mother-child dyads has been associated with better neurocognitive development (Crnic et al. 1983, Goldsmith & Davidson 2004). In addition, several intervention studies suggest that improvement in mother-child interaction can be achieved with interventions (Meijssen et al. 2010, Ravn et al. 2011), leading to better developmental outcome of the child (Brisch et al. 2003, Newnham, Milgrom & Skouteris 2009).

The results of this study support the importance of the quality of mother-child interaction in the neurocognitive development of ELGA children. Consequently, special attention should be paid to parent-child interaction in outpatient clinics during follow-up of ELGA children to identify the families that might benefit from support in more sensitive parenting.

In Study IV, half of the ELGA infants displayed probable atypical sensory processing (<-1SD) at least in one of the quadrants or scales in ITSP. Because our aim was to investigate associations between atypical sensory processing and neuroanatomical findings and neurodevelopment, we defined probable atypical sensory processing as scores <-1SD in ITSP quadrants and sections. Thus, we avoided grouping together both ends of the spectrum, i.e., "more than others" and "less than others", unlike previous ITSP studies in ELGA infants (Wickremasinghe et al. 2013). Our reported incidence of atypical sensory processing is therefore not directly comparable with previous studies in preterm infants. Low Registration was the most common difference in our study, which is compatible with an earlier report (Wickremasinghe et al. 2013). ITSP is a screening test, not a diagnostic test, and thus, the aim should be to find both exceptionally high and low scores to identify children with possible problems in behavioral responses to everyday sensory stimuli. However, our aim here was to discriminate between the different ends of the spectrum to make more coherent groups of children in order to illustrate possible underlying associations of atypical sensory processing with neonatal risk factors.

Although occupational therapists, physiotherapists, child neurologists, pediatricians, and parents have often made observations about atypical behavioral responses to everyday sensory input in ELGA children, very few studies exist on sensory processing in preterm infants. Sensory processing disorder (SPD) is not universally acknowledged as an independent diagnosis, but more as a characteristic difficulty in processing sensory information in different developmental behavioral disorders, such as ASD and ADHD (Section on Complementary and Integrative Medicine 2012). This lack of uniform diagnostic criteria as well as the uncertain etiology of this phenomenon may hinder publishing of empirical research about differences in sensory processing.

Interestingly, in screening tests for symptoms of ASD, positive rates for ELGA children have been as high as 20-40% (Johnson et al. 2010, Moore et al. 2012), while positive screening rates for children born at term remains between 3% and 5% (Yama et al. 2012). The actual incidence of ASD using diagnostic techniques is about 1% in the general population and about 5% in children born preterm (Pinto-Martin et al. 2011). Associated neurodevelopmental impairments have been suggested as one possible explanation for these high positive screening rates in ELGA infants (Moore et al. 2012, Stephens et al. 2012). The typical sensory behavior pattern for children with ASD is under-responsiveness to sensory stimuli, which has been reported to distinguish the children with autism from those with developmental delays or typical development (Baranek et al. 2006). Low Registration, which was the most common finding in ELGA infants in the present study, represents sensory under-responsiveness, i.e., children are described to disregard or be unaware of their surroundings (Miller et al. 2007). This kind of response pattern to sensory stimuli may explain partly the high screening rates of ASD in ELGA children, and may complicate diagnosing ASD in young children born premature.

Notably, the ITSP results were not associated with neurodevelopmental outcome at two years of corrected age, which is in line with previous reports (Case-Smith, Butcher & Reed 1998, Wickremasinghe et al. 2013). In contrast, neuroanatomical findings at TEA, i.e., grade III-IV IVH in US and WM or GM abnormalities in MRI, were associated with an atypical Sensation Seeking profile.

Children with increased Sensation Seeking are described as hyperactive and disruptively behaving and as having an excessive desire for sensory stimuli, all symptoms and behavior patterns that are characteristic of ADHD (Miller et al. 2007). A novel finding in our study was that Sensation Seeking in ELGA children is more common in those with neonatal neuroanatomical findings related

to brain insults. The brain injury of prematurity appears to involve both cerebral WM and neuronal-axonal structures in the thalamus, basal ganglia, cerebral cortex, and cerebellum (Volpe 2009). Sensation Seeking behavior, among other differences in sensory processing, has been presented to manifest anomalously in functioning neural networks between the neocortex, basal ganglia and cerebellum (Koziol, Budding & Chidekel 2011). Further, in children with sensory processing disorders DTI studies have revealed microstructural changes in WM, particularly involving the posterior cerebral tracts (Owen et al. 2013). On the basis of these observations, preterm brain injury could serve as an etiology for atypical Sensation Seeking.

Sensation Seeking is commonly seen in children with ADHD. In MRI studies of children with ADHD, researchers have reported reduced volumes in the total cerebral volume, the basal ganglia, the corpus callosum, the cerebellum, and the total gray matter volume as well as the mean cortical volume (Emond, Joyal & Poissant 2009). In this context, the increased Sensation Seeking in ELGA children with WM and GM abnormalities is an intriguing finding since the risk of ADHD is known to be higher in preterm than in the general population (Lindstrom, Lindblad & Hjern 2011).

ELGA infants are exposed to repeated stronger sensory stimulation in NICU compared with term infants in uterus at the same gestational age, which has been suggested as a potential factor underlying impaired sensory processing in ELGA infants (Walker et al. 2009, Marco et al. 2011). This suggestion is supported by recent evidence about learning-induced neural plasticity in newborn infants exposed to certain auditory stimulation from 29 weeks of gestation to birth (Partanen et al. 2013).

Almost every fifth ELGA infant showed atypical Oral Sensory Processing; this finding has been reported in late preterm infants previously (Bart et al. 2011). Surgical closure of PDA may damage the left laryngeal nerve by the clip or ligature, or the nerve may even disrupt during the operation, resulting in left-sided vocal cord paralysis (LVCP) (Zbar et al. 1996). In recent reports, the incidence of LVCP (studied by direct laryngoscopy) after surgical closure of PDA has been as high as 40-67% in VLBW children (Benjamin et al. 2010). Persistent feeding problems and increased requirements of tube feeding, respiratory support, and prolongation of hospital stay have been described in children with LVCP (Als et al. 2004). However, because of the small sample size and multiple correlations, there is a risk of type I error in the association between atypical Oral Sensory Processing and surgical closure of PDA.

4. Strengths and limitations of the study

The homogeneous study population is an important strength of this study. The outcome of preterm children is known to be associated with gestational weeks (Sansavini et al. 2011), which emphasizes the value of examining only children born extremely preterm, especially when neurodevelopmental and brain functional measures are the main focus. Our study population represents well the results of treatment in modern NICU; grade III-IV IVH in 10-15% of infants, no cystic PVL, and at TEA 20-37% of infants presented WM abnormalities in MRI, most of them mild. Further, we were able to perform MRI at TEA on almost every ELGA infant: 29 of 30 in Study I, all 39 in Study II, 47 of 48 in Study III, and 43 of 44 in Study IV. In addition, neurodevelopmental outcome at two years of corrected age was assessed with three different methods: GMDS, Hempel neurological examination, and BSID-III. For example, in Study III the associations of mother-child interaction with neurocognitive outcome were significant with both GMDS and BSID-III, which reinforces the value of the results. In Study IV, the assessment of both sensory processing ability and neurodevelopmental outcome at two years of corrected age was valuable in excluding the role of age in our results since the incidence of sensory processing dysfunction increases from early childhood up to preschool-early school age (Ben-Sasson et al. 2009).

Serving as a limitation in Study III is the assessment of mother-child interaction only at the age of two years. Several assessments, e.g. at three or six months of corrected age, would have enabled the evaluation of possible changes in interaction and directions of the effects between interaction and developmental outcome. In addition, the small number of infants with cognitive delay in BSID-III (n=5) is a limitation in Study III, but the association between mother-child interaction and cognition remained significant also when neurocognitive measures were used as continuous variables, verifying that the observed association was not limited only to children with cognitional problems.

Overall, the number of term controls was quite small (n=22), and, unfortunately, we were unable to keep their families motivated to participate in every assessment during the two-year follow-up. Because of their low number (n=9), we were unable to use term controls in statistical analyses in Study IV. A possible selection bias exists in recruitment of term controls because most of their parents had a high education, leading to a difference in sociodemographic background between ELGA and term children. Further, the large number of ELGA drop-outs in Studies III (30 of 78 surviving ELGA children) and IV (34 of 78 surviving ELGA children) is a noteworthy limitation.

Use of GMDS scales for children aged up to two years created a ceiling effect on our GMDS results. Thus, ELGA infants without developmental impairments and term infants could have probably scored higher in GMDS if we had used also scales for infants over two years, but the GMDS results for ELGA infants with developmental impairments would have probably remained unchanged. Thus, without this ceiling effect in Study I, the difference between ELGA infants with abnormal and normal SII responses would have been larger. In Study III, this ceiling effect is not likely to have affected the number of ELGA infants with DQ<-1SD. In Studies II and IV, the GMDS results were not in a central role.

The limitations in detecting SII from EEG-SEP (Study II) discussed more thoroughly earlier included retrospective study set-up, shorter interstimulus interval in EEG-SEP than in MEG recordings, different stimulation methods in EEG-SEP and MEG, and temporal distance of these two recordings in separate sessions.

In Study IV, the number of ELGA children with atypical behavioral responses in different quadrants in ITSP remained quite small, and the results should be tested later in a larger preterm sample. We defined atypical behavioral response as the lower continuum of the spectrum, i.e., "more than others". This can be seen both as a limitation and strength of this study, since previous studies in preterm children have combined both "more than others" and "less than others" as atypical performance, rendering comparison of our results with others more difficult. This kind of approach can be reasonable in screening of children with possible problems in behavioral sensory processing, but our aim was to investigate the background of possible factors leading to atypical sensory processing in ELGA children, and in this context combining two opposing ends of the behavioral spectrum is not reasonable. ITSP is a validated questionnaire for parents that gives a good overall picture about possible problems in behavioral sensory processing that may challenge a child's ability to manage everyday life. However, in future studies, combining this method with direct observation by, for example, an occupational therapist in the examination setting would reinforce the results.

Finally, the assessment of neurodevelopmental outcome of ELGA infants at two years of corrected age is not as reliable as assessment at pre-school or school age. Although the majority of neuromotor disabilities can be detected by the age of two years, milder cognitive impairments, such as learning problems and behavioral problems, can be difficult or impossible to discover before

school age (Saigal & Doyle 2008). Thus, extending this study to assessments and measurements at pre-school age is warranted.

CONCLUSIONS

Absent SII responses to tactile stimulation in MEG in ELGA infants were associated with impaired neurodevelopment, especially worse neuromotor functions, at two years of corrected age. Further, measuring SII responses surpassed structural neuroimaging (brain MRI and US) in predicting adverse neuromotor development.

The combination of measuring SII responses by MEG, neonatal neurological examination, and structural neuroimaging was superior in predicting neurological outcome of ELGA infants compared with any of these three methods alone. Unilaterally absent SII responses helped to identify some ELGA infants with normal structural neuroimaging and normal neonatal neurological examination but unfavorable neurological outcome.

In addition to MEG, SII responses can be detected by recording SEPs during a clinical EEG measurement (EEG-SEP), which enables bedside SII assessments with this widely available neurophysiological method.

Lower quality of mother-child interaction was associated with lower neurocognitive outcome among ELGA infants, although no differences in interaction were observed between term and preterm mother-child dyads. Abnormalities in neuroimaging at TEA or neurological impairments at two years of corrected age in ELGA children were not associated with impaired mother-child interaction.

Atypical behavioral sensory processing among ELGA children was common, and all children with Sensation Seeking had neuroanatomical lesions in MRI at TEA. Atypical sensory symptoms may overlap with symptoms of ASD and may partially account for the high positive screening rates of ASD among ELGA children.

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