Turun yliopisto
University of Turku

PREDICTION OF NEURODEVELOPMENT AND NEUROMOTOR TRAJECTORIES IN VERY PRETERM BORN CHILDREN UP TO 11 YEARS OF AGE

PIPARI Study

Sirkku Setänen

TURUN YLIOPISTON JULKAISUJA – ANNALES UNIVERSITATIS TURKUENSIS
Sarja - ser. D osa - tom. 1226 | Medica - Odontologica | Turku 2016

University of Turku

Faculty of Medicine
Department of Clinical Medicine
Pediatric Neurology
Pediatrics
Doctoral Programme of Clinical Investigation – CLIPD
Turku University Hospital
Turku, Finland

Supervised by

Professor Leena Haataja, MD, PhD
Pediatric Neurology
Children's Hospital
University of Helsinki
Helsinki University Hospital
Helsinki, Finland

Professor Liisa Lehtonen, MD, PhD
Department of Clinical Medicine
Pediatrics
University of Turku
Turku University Hospital
Turku, Finland

Reviewed by

Docent Kai Eriksson, MD, PhD
Department of Clinical Medicine
Pediatric Neurology
University of Tampere
Tampere University Hospital
Tampere, Finland

Professor Trond Markestad, MD, PhD
Department of Clinical Science
Pediatrics
University of Bergen
Haukeland University Hospital
Bergen, Norway

Opponent

Professor Lena Hellström-Westas, MD, PhD
Department of Women's and Children's Health
Pediatrics
Uppsala University
Uppsala University Hospital
Uppsala, Sweden

Cover photo: Sirkku Setänen (in memoriam of Lilly Dubowitz, the author of the Dubowitz neurologic examination and the original artwork, used here with courtesy of Leena Haataja)

The originality of this thesis has been checked in accordance with the University of Turku quality assurance system using the Turnitin OriginalityCheck service.

ISBN 978-951-29-6457-4 (PRINT)
ISBN 978-951-29-6458-1 (PDF)
ISSN 0355-9483 (Print)
ISSN 2343-3213 (Online)
Painosalama Oy - Turku, Finland 2016

To my children

ABSTRACT

Sirkku Setänen

Prediction of neurodevelopment and neuromotor trajectories in very preterm born children up to 11 years of age

PIPARI Study

University of Turku, Faculty of Medicine, Department of Clinical Medicine, Pediatric Neurology, Pediatrics, Doctoral Programme of Clinical Investigation – CLIPD, Turku University Hospital, Turku, Finland

Annales Universitatis Turkuensis, Medica-Odontologica, Turku, Finland 2016

Very preterm birth is a risk for brain injury and abnormal neurodevelopment. While the incidence of cerebral palsy has decreased due to advances in perinatal and neonatal care, the rate of less severe neuromotor problems continues to be high in very prematurely born children. Neonatal brain imaging can aid in identifying children for closer follow-up and in providing parents information on developmental risks.

This thesis aimed to study the predictive value of structural brain magnetic resonance imaging (MRI) at term age, serial neonatal cranial ultrasound (cUS), and structured neurological examinations during the longitudinal follow-up for the neurodevelopment of very preterm born children up to 11 years of age as a part of the PIPARI Study (The Development and Functioning of Very Low Birth Weight Infants from Infancy to School Age). A further aim was to describe the associations between regional brain volumes and long-term neuromotor profile.

The prospective follow-up comprised of the assessment of neurosensory development at 2 years of corrected age, cognitive development at 5 years of chronological age, and neuromotor development at 11 years of age. Neonatal brain imaging and structured neurological examinations predicted neurodevelopment at all age-points. The combination of neurological examination and brain MRI or cUS improved the predictive value of neonatal brain imaging alone. Decreased brain volumes associated with poorer neuromotor performance. At the age of 11 years, the majority of the very preterm born children had age-appropriate neuromotor development and after-school sporting activities. Long-term clinical follow-up is recommended at least for all very preterm infants with major brain pathologies.

Keywords: cerebral palsy, cognitive development, developmental coordination disorder, minor neurological dysfunction, motor development, neonatal brain imaging, neurodevelopmental impairment, neurosensory impairment, preterm infant, prospective follow-up

TIIVISTELMÄ

Sirkku Setänen

Pikkukeskosten neuromotorinen pitkäaikaiskehitys 11 vuoden ikään saakka ja sitä ennustavat tekijät

PIPARI-tutkimus

Turun Yliopisto, Lääketieteellinen tiedekunta, Kliininen laitos, Lastenneurologia, Lastentaudit, Turun yliopiston kliininen tohtoriohjelma (TKT), Turun yliopistollinen keskussairaala, Turku, Suomi

Annales Universitatis Turkuensis, Medica-Odontologica, Turku, Suomi 2016

Pikkukeskosuus on riski aivovauriolle ja poikkeavalle kehitykselle. Vaikka CP-vamman esiintyvyys on alkuvaiheen tehohoidon kehittymisen myötä vähentynyt, lievempiä neuromotorisia ongelmia esiintyy edelleen merkittävästi pikkukeskosina syntyneillä lapsilla. Varhaiset aivojen kuvantamistutkimukset voivat auttaa tunnistamaan pitkäaikaisseurantaa tarvitsevat lapset sekä antamaan vanhemmille tietoa kehitykseen liittyvistä riskeistä.

Tämän väitöskirjatyön tavoitteena oli selvittää lasketun ajan aivojen rakenteellisen magneettitutkimuksen, sarjoittaisen aivojen ultraäänitutkimuksen, ja pitkäaikaisseurannan aikana tehtyjen yksityiskohtaisten neurologisten tutkimusten ennustearvo pikkukeskosten kehitykselle 11 vuoden ikään asti osana PIPARI–tutkimusta (**Pi**eni**pa**inoisten **ri**skilasten käyttäytyminen ja toimintakyky imeväisiästä kouluikään). Tavoitteena oli myös kuvailla aivotilavuuksien yhteys neuromotoriseen pitkäaikaiskehitykseen.

Prospektiivinen seuranta sisälsi neurosensorisen kehityksen arvioinnin 2 vuoden korjatussa iässä, kognitiivisen kehityksen arvioinnin 5 vuoden kronologisessa iässä, sekä neuromotorisen kehityksen arvioinnin 11-vuotiaana. Varhaiset aivojen kuvantamistutkimukset sekä yksityiskohtaiset neurologiset tutkimukset ennustivat pikkukeskosten pitkäaikaiskehitystä kaikissa ikäpisteissä. Neurologisten tutkimustulosten yhdistäminen aivojen magneettitutkimuksen tai ultraäänitutkimusten löydöksiin paransi yksittäisen kuvantamistutkimuksen ennustearvoa. Pienemmät aivotilavuudet liittyivät heikompaan neuromotoriseen suoriutumiseen. Suurimmalla osalla pikkukeskosina syntyneistä lapsista oli ikätasoinen neuromotorinen kehitys ja liikuntaharrastus 11-vuotiaana. Pitkäaikaista kliinistä seurantaa suositellaan ainakin kaikille niille pikkukeskosille, joilla on todettu vaikea aivovaurio.

Avainsanat: CP-vamma, kehityksellinen koordinaatiohäiriö, kehityksellinen poikkeavuus, keskonen, kognitiivinen kehitys, lievä neurologinen poikkeavuus, motorinen kehitys, neurosensorinen poikkeavuus, prospektiivinen seuranta, varhainen aivojen kuvantaminen

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ABBREVIATIONS

BPD	bronchopulmonary dysplasia
CP	cerebral palsy
cMND	complex minor neurological dysfunction
cUS	cranial ultrasound
DCD	developmental coordination disorder
DCDQ	Developmental Coordination Disorder Questionnaire
ELBW	extremely low birth weight
FSIQ	Full Scale Intelligence Quotient
GMFCS	Gross Motor Function Classification System
GMs	general movements
GM	gray matter
HINE	Hammersmith Infant Neurologic Examination
IVH	intraventricular hemorrhage
MND	minor neurological dysfunction
Movement ABC	Movement Assessment Battery for Children
MRI	magnetic resonance imaging
NEC	necrotizing enterocolitis
NDI	neurodevelopmental impairment
NSI	neurosensory impairment
NPV	negative predictive value
PPV	positive predictive value
PVL	periventricular leukomalacia
ROP	retinopathy of prematurity
sMND	simple minor neurological dysfunction
SD	standard deviation
SGA	small for gestational age
VLBW	very low birth weight
V/B	ventricular/brain
WM	white matter
WPPSI	Wechsler Preschool and Primary Scale of Intelligence

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications, which are referred to in the text by the Roman numerals I–IV. Some previously unpublished data are also presented.

I Setänen S, Haataja L, Parkkola R, Lind A, Lehtonen L. Predictive value of neonatal brain MRI on the neurodevelopmental outcome of preterm infants by 5 years of age. *Acta Paediatr.* 2013 May; 102(5):492-497.

II Setänen S, Lahti K, Lehtonen L, Parkkola R, Maunu J, Saarinen K, Haataja L. Neurological examination combined with brain MRI or cranial US improves prediction of neurological outcome in preterm infants. *Early Hum Dev*. 2014 Dec; 90(12):851-856.

III Setänen S, Lehtonen L, Parkkola R, Aho K, Haataja L, on behalf of the PIPARI Study Group. Prediction of neuromotor outcome in preterm infants at 11 years of age using volumetric neonatal MRI and neurological examinations. *Dev Med Child Neurol.* 2016; DOI: 10.1111/dmcn.13030

IV Setänen S, Lehtonen L, Parkkola R, Matomäki J, Haataja L, on behalf of the PIPARI Study Group. The motor profile of preterm infants at 11 years of age. *Pediatr Res.* 2016; DOI:10.1038/pr.2016.90

1 INTRODUCTION

Advances in perinatal care and a more active approach to resuscitation during the past decades have led to a decrease in neonatal mortality and an increase in survival without neurodevelopmental impairment (NDI) in very preterm infants (Blencowe et al. 2013, Stoll et al. 2015). For example, survival without major morbidity has increased for infants born between 25 and 28 weeks from 43% in 1993 to 59% in 2012 (Stoll et al. 2015). Severe neurological impairments such as cerebral palsy (CP) have also decreased (Sellier et al. 2015), whereas the rate of milder forms of neuromotor dysfunction continues to be significantly high (Ferrari et al. 2012).

Predictive tools are needed to monitor the quality of neonatal care, to direct research to risk groups, to improve the identification of infants for closer follow-up, and to counsel parents about the developmental prognosis of their newborn (Latal 2009). Current practice in neonatal care most commonly only includes cranial ultrasound (cUS) imaging in detecting brain injuries in very preterm infants, even though brain magnetic resonance imaging (MRI) has potentially better prognostic value compared to cUS providing more information especially on white matter (WM), gray matter (GM), and cerebellum (Latal 2009). Moreover, regional brain volumes have been shown to associate with NDI in very preterm infants (Lind et al. 2011b).

There are no long-term data available on the associations between structural pathologies or volumetric alterations in the brain tissue at term age and neuromotor development in very preterm infants. Furthermore, it is not known whether structured neurological examinations in the neonatal period and throughout childhood can predict long-term outcome in very preterm infants, and thus provide more accurate information for parental guiding and introduction of early intervention programs (Latal 2009).

The focus of this thesis was on assessing long-term neuromotor trajectories and neurodevelopment in very preterm infants. Neonatal brain imaging has an important role in predicting long-term neurodevelopment. However, gaining a satisfactory level of positive predictive value (PPV) for long-term neurodevelopment has remained challenging. Therefore, the predictive value of a combination of neonatal neurological examination and concurrent neuroimaging was also evaluated.

2 REVIEW OF THE LITERATURE

2.1 Epidemiology of preterm birth

The World Health Organization defines preterm birth as any birth before 37 completed weeks of gestation. Preterm birth can be divided to extremely preterm birth (<28 weeks of gestation), very preterm birth (<32 weeks of gestation), and moderate to late preterm birth (32 to <37 weeks of gestation). Other commonly applied classifications for preterm infants are based on birth weight: extremely low birth weight (ELBW) (<1000 g), very low birth weight (VLBW) (<1500g), and low birth weight (<2500g). The most commonly used birth weight limits for small for gestational age (SGA) infants have been either <-2 standard deviations (SD) of the mean birth weight or <10th percentile for each gestational week.

Preterm birth can be spontaneous or induced labor due to complications during pregnancy (maternal or fetal). The etiologies and risk factors of preterm birth are known to be complex and multifactorial. The most common are spontaneous preterm labor with or without premature preterm rupture of membranes, multiple pregnancy, and pre-eclampsia (Goldenberg et al. 2008, Simmons et al. 2010).

An estimated worldwide rate of preterm births was 15 million (11.1%) in 2010, varying widely between countries (Blencowe et al. 2012). In Finland, preterm infants (n=3434) accounted for 5.9% of all live births (n=57639) in 2014 (National Institute for Health and Welfare 2015). A total of 473 (0.8%) infants were born <32 weeks of gestation or had a birth weight ≤1500g.

Despite improvements in survival rates (Stoll et al. 2015), complications of preterm birth have been shown to globally be the leading direct cause of child deaths after infectious causes in children younger than 5 years (Liu et al. 2012). Neonatal morbidities that have been shown to associate with an adverse outcome include bronchopulmonary dysplasia (BPD), intracranial hemorrhage, necrotizing enterocolitis (NEC), sepsis and retinopathy of prematurity (ROP) (Stoll et al. 2015). In addition to neonatal complications, preterm birth can have lifelong effects on neurodevelopmental functioning (Saigal, Doyle 2008, Simmons et al. 2010).

2.2 Neonatal brain imaging

2.2.1 Cranial ultrasound

In the late 1970s, serial cUS became a routine and widely used neuroimaging method for preterm infants. This most readily available, but operator-dependent, bedside technique for neonatal brain imaging uses high-frequency sound waves (5-10 MHz) without radiation exposure to detect differences in echodensity between tissues, which enables the detection of anatomic structures, hemorrhage, and fluid collections. Scannings are usually performed by neonatologists through the limited views offered by the acoustic windows of open fontanelles: most commonly used anterior fontanelle enables detection of cerebral hemorrhage, brainstem and posterior fossa are better seen through the mastoid fontanelle, while view through the posterior fontanelle allows better visualization of the trigone and occipital horn of the lateral ventricles improving detection of subtle intraventricular hemorrhage (IVH) (Hintz, O'Shea 2008). Even though cUS has been shown to detect some significant parenchymal lesions such as IVH, cystic changes (of which small lesions may collapse over time), and severe WM injuries (such as cystic periventricular leukomalacia, PVL, and ventriculomegaly due to periventricular WM loss), MRI has been shown to be more sensitive in identifying noncystic focal injuries or small lesions in the WM, diffuse WM injuries, cortical abnormalities, and posterior fossa lesions (Maalouf et al. 2001, Counsell et al. 2003, Rademaker et al. 2005, Ramenghi et al. 2007, Hintz, O'Shea 2008, Izbudak, Grant 2011, Jary et al. 2012, Smyser, Kidokoro & Inder 2012, Kwon et al. 2014). MRI is also more sensitive in finding cerebellar lesions which are rarely identified by cUS (de Vries et al. 2011, Hintz et al. 2015).

2.2.2 Magnetic resonance imaging

Since the 1980s, MRI has become a more routine neuroimaging approach also for preterm infants. This is due to many factors including optimized methods for detecting neonatal brain injury, greater availability of scanners, recognition of the safety profile without ionizing radiation, scanning without sedation (with simple feeding and swaddling, by using ear protection plugs and a hear protector, and by using polystyrene bead-filled “huggers”), compatible devices (monitoring, ventilators, warming equipment, integrated head coil), and motion artefact correction (Hintz, O'Shea 2008). Brain MRI is currently the only available imaging modality that enables accurate assessment of cortical folding and characterization of myelination, which are important developmental benchmarks (Smyser, Kidokoro & Inder 2012).

Total and regional brain volumes can be measured with three-dimensional MRI to quantitatively characterize alterations of brain development associated with prematurity

and brain injury (Kwon et al. 2014). Volumetric brain tissue segmentation technique in assessing preterm infants was first reported in the late 1990s showing a marked increase in cortical GM and in myelinated WM between weeks 29 and 41 of gestational age in preterm infants, emphasizing the vulnerability of the brain (Huppi et al. 1998).

Diffusion tensor imaging is based on water motion and enables assessment of microstructural development and maturation of the WM (Kwon et al. 2014). Previous findings from the PIPARI Study have shown a positive association between normal antenatal growth and WM maturation at term age in very preterm infants when using diffusion-weighted MRI (Lepomaki et al. 2012). Gestational age at birth was not found to have an effect on the results. Recent data has also shown the value of this advanced MRI technique in predicting CP in preterm infants with WM injury (Roze et al. 2015).

2.2.3 Findings in very preterm infants

Very preterm infants are susceptible to brain injury. This is due to many factors including rapid evolution of myelination and neuronal differentiation in this critical period of brain development in an extra-uterine environment in intensive care. Etiologies are not fully understood, but include infective, ischemic, and inflammatory insults (Counsell et al. 2003).

Early hemorrhages with subsequent ventricular dilatation are common findings in very preterm infants. A previous study with sequential MRIs has demonstrated that 43% of the extremely preterm infants had early hemorrhage, and half of the infants examined at term age had ventricular dilatation (axial diameter of >8mm at gestational age of ≤25 weeks, and >10mm at gestational age of >25 weeks) after IVH. On the other hand, more than half of the infants without previous hemorrhage had also ventricular dilatation (Dyet et al. 2006). Other typical findings in very preterm infants are 1) in cUS during neonatal hospital care: periventricular echodensities (65%), IVH (28%), and post-hemorrhagic ventricular dilatation (16%), cystic WM lesions (8%), and 2) in MRI around term age: diffuse and excessive high signal intensity within the WM (79%), multiple punctate WM lesions (17%), severe ventricular dilatation (11%), and decreased complexity of gyration (8%) (Leijser et al. 2009a, Leijser et al. 2009b). Diffuse WM injury is currently the most frequently observed form of WM changes, while cystic lesions in the WM have become rare (Counsell et al. 2003, Back 2015) (Figure 1). Preterm survivors have also been shown to display significant reductions in the growth of the cerebral cortex and subcortical GM structures that include the basal ganglia, thalamus, hippocampus, and cerebellum (Back 2015).

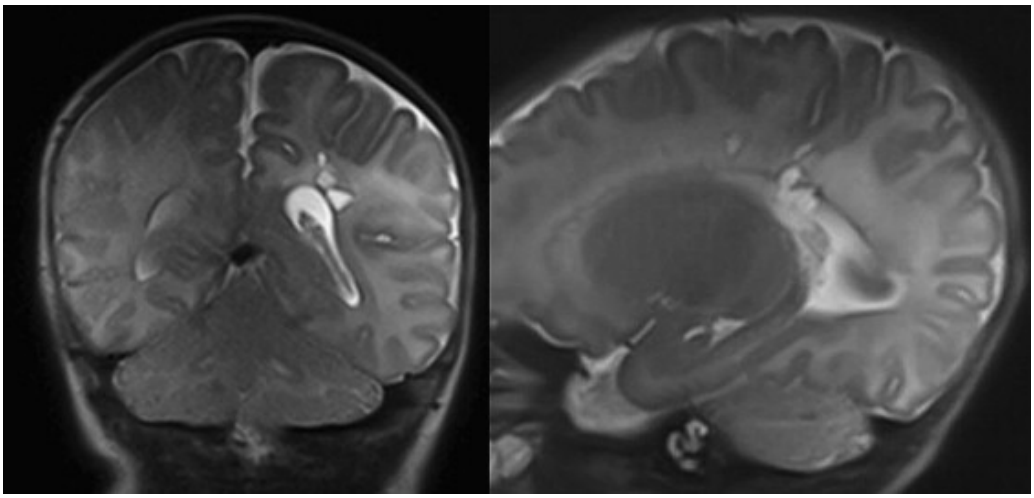


Figure 1. Coronal and sagittal T2-weighted images at term age of a preterm infant born at 34 weeks of gestation show small cysts in the left posterior periventricular white matter consistent with focal periventricular leukomalacia (Izbudak, Grant 2011).

In addition to structural brain pathologies, preterm infants have been shown to have decreased brain volumes (Kwon et al. 2014). A systematic review has reported that brain tissue volume reductions in preterm infants have been demonstrated in cortical and subcortical GM, myelinated WM, and cerebellum, with a reciprocal increase in cerebrospinal fluid. Regional volume alterations have been described to include both decreased myelinated WM (in the brainstem, internal capsule and cerebellar peduncles), and unmyelinated WM (in central and orbitofrontal regions). Findings concerning subcortical and cortical GM volume alterations have been more inconsistent (Keunen et al. 2012). Moreover, WM injury and IVH in addition to perinatal risk factors and neonatal morbidities have been shown to associate with regional brain volume changes in very preterm infants (Keunen et al. 2012, Parikh et al. 2013).

2.2.4 Predictive value

Current practice in neonatal care most commonly only includes cUS imaging. The predictive capacity of cUS increases when performed frequently and by an experienced specialist, which is not always possible. Some have recommended brain MRI scanning at term age only for preterm infants with overt WM injury on cUS (de Vries, Cowan 2007), while others have highlighted the value of neonatal brain MRI of preterm infants as a routine component of neonatal intensive care (Latal 2009, Smyser, Kidokoro & Inder 2012, Plaisier et al. 2014). Furthermore, neuroimaging at term age has been emphasized as optimal in the prediction of long-term neurodevelopment in preterm infants (Bosanquet et al. 2013, Plaisier et al. 2014, Kwon et al. 2014, Hintz et al. 2015). Neonatal

brain imaging has been shown to provide varying values of prediction for major impairments, but high value in predicting normal neurodevelopment (Kwon et al. 2014).

The predictive value of brain MRI as a part of the assessment protocol of very preterm infants has been debated (Hintz, O'Shea 2008, Horsch et al. 2010, Janvier, Barrington 2012). Additionally, routine performance of MRI at term age without asking parental permission has been questioned as it may increase rather than decrease parents' concerns and confusion in some situations (Pearce, Baardsnes 2012). Therefore, knowledge of the predictive significance of different brain findings needs to be sufficient.

2.3 Neuromotor assessment methods

2.3.1 Neonatal assessment methods and their predictive value

The Neonatal Behavioral Assessment Scale is mainly used to evaluate the behavior of an infant (Brazelton 1973). It has also been administered in neurological examinations of preterm infants, although it has been standardized only for full-term infants. This assessment method is composed of 28 behavioral items (9-point-scale), 14 reflex items (4-point-scale), and supplementary items (9-point-scale) and includes following domains: habituation, social-interactive, motor system, state organization, state regulation, autonomic system, supplementary systems, reflexes and responses (Brazelton, Nugent 1995). It is time-consuming and therefore used mainly in research. The NICU Network Neurobehavioral Scale is developed based on the Neonatal Behavioral Assessment Scale to provide a standardized, valid and predictive biomarker of infants' behavior (Lester, Tronick 2004).

The Prechtl neurological test for full-term and preterm infants at 38-42 weeks of gestational age is wide including 42 items (Prechtl 1977). The domains are posture, motility, pathological movements, tremor, motor system, responses and reflexes (intensity and threshold), eye, state, and crying. The Prechtl neurological test at term age and neonatal serial cUS have been shown to provide high specificity and negative predictive value (NPV) (>90%) for normal neurological outcome and Bayley test results in preterm infants at 2 years of corrected age (Maas et al. 2000).

Neonatal motor assessment of preterm infants from the first days of life can be performed by the Dubowitz neurologic examination (Dubowitz, Dubowitz & Mercuri 1999) that is widely used both clinically and in research. The measurement subscales are tone and posture, tone patterns, reflexes, spontaneous movements, abnormal signs, and behavior. Importantly, preterm infants should be assessed according to normative data for different gestational age categories (Ricci et al. 2008), as the range of normal findings at term age has been found wider compared to term infants (Mercuri et al. 2003).

Deviant neurological signs in the Dubowitz neurologic examination have been shown to correlate with the presence of IVH recognized by cUS (Dubowitz et al. 1981). It has also been found to discriminate infants with significant MRI abnormalities with good NPV (92%), but low PPV (34%) (Woodward et al. 2004). Moreover, worse performance at term age has been shown to relate with increasing severity of concurrent WM abnormality regarding both total scores and subscales of spontaneous movements and behavior (Brown et al. 2009). Of the GM abnormalities, only delayed gyral maturation has been found to associate with the subscales of tone and spontaneous movements (Brown et al. 2009).

Amiel-Tison Neurologic Assessment is a qualitative instrument including assessment of cranial morphology, evaluation of neurosensory function and spontaneous motor activity, passive and active muscle tone, primitive reflexes, assessment of palate and tongue, adaptedness to manipulation, feeding autonomy, medical status, and unfavorable circumstances at the time of examination (Amiel-Tison 2002). It can be used in evaluating preterm infants from term age onwards. This assessment method has previously been shown to predict developmental performance including motor outcome at 2 years of corrected age (Simard et al. 2011, Leroux et al. 2013) and still at 6 years of age when performed at 9 months of corrected age (Harmon et al. 2015).

Prechtl's method for the assessment of general movements (GMs) is based on the observation of the quality of spontaneous movement patterns from videorecordings in two periods: writhing movements are present until 6 to 9 weeks of corrected age and change to fidgety movements that usually occur until 15 to 20 weeks of corrected age (Einspieler et al. 2007). This non-invasive although time-consuming method is also used in assessing preterm infants and has been shown to be highly predictive for CP (NPV and PPV up to 100%) (Darsaklis et al. 2011).

2.3.2 Toddler age assessment methods and their predictive value

Bayley Scales of Infant and Toddler Development (Bayley 1969) is a widely used method to assess cognitive and psychomotor development of preterm infants at 2 years of age. Its third version (Bayley 2005) includes motor scale of 72 gross motor and 66 fine motor items. The validity of this neuromotor assessment method in preterm infants has been shown to vary (sensitivity 59-82% and specificity 84-93%) depending on the age of the infant at assessment (Spittle, Doyle & Boyd 2008).

Neurological follow-up after the neonatal period can be performed by using the Hammersmith Infant Neurological Examination (HINE), an assessment method for infants between 2 and 24 months of age that is based on the same principles as the Dubowitz neurologic examination (Haataja et al. 1999). It includes assessment of cranial nerve function, posture, movements, tone and reflexes, description of motor

development, and description of behavioral state of the infant during examination. The test has been standardized for full-term infants between 12 and 18 months of age (Haataja et al. 1999), but there are no norms for preterm infants. However, it has been shown to reliably predict motor outcome (sensitivity 93-98%, specificity 85-100%) at 2 years of age in very preterm infants (Frisone et al. 2002, Romeo et al. 2009). Moreover, the HINE has been shown to provide additional information about the severity of CP (Romeo et al. 2008a). Even though normal findings or minor pathologies in cUS have been found to associate with optimal HINE scores and major pathologies with lower scores, no clear pattern between cUS findings and the HINE scores has been found (Frisone et al. 2002, Romeo et al. 2009). There are no previous data concerning the associations between neonatal brain MRI findings and HINE scores. In addition, the predictive value of the HINE for long-term neuromotor development in very preterm born children is not known.

The combination of the HINE and GMs at 3 months of age has been shown to be more effective than either of the assessments alone or serial cUS in predicting neurologic outcome at 2 years of age (Romeo et al. 2008b). However, it is noteworthy that prediction of later outcome becomes more reliable with time. Thus, there are no previous studies concerning the predictive value of Dubowitz neurologic examination performed as early as at term age for long-term neuromotor development. In addition, it has not been established whether combining the results of this examination to concurrent neuroimaging findings could improve the prediction of later neuromotor outcome.

The Hempel assessment is designed to evaluate minor neurological dysfunction (MND) such as mild dysfunction in muscle tone regulation, choreiform dyskinesia, or fine manipulative disability, as well as major neurological abnormalities at toddler age (1.5 to 4 years) with age-specific norms (Hempel 1993). The assessment focuses on the observation of motor functions in a standardized free field situation with following domains: prehension, sitting behavior, crawling behavior, standing behavior, walking behavior, head, and sensorimotor function (Hadders-Algra 2005). The manual was originally published as a thesis and therefore is not commercially available, but partial descriptions of the method have been reported in international publications.

2.3.3 Pre-school age and school age assessment methods

The modified Touwen examination is a standardized and age-specific neurological assessment to detect MND in children from 4 years onwards (Hadders-Algra 2010). It includes assessment of posture and muscle tone, reflexes, involuntary movements, coordination and balance, fine manipulation, associated movements, sensory function, and cranial nerve function (Hadders-Algra 2010). Simple MND (sMND) is defined as the presence of one or two dysfunctional domains and represents typical but non-optimal brain function, whereas complex MND (cMND) is defined as the presence of more than two dysfunctional domains and may be considered a borderline form of CP (Hadders-

Algra 2002). Applying the Touwen examination in research gives detailed and reliable (Peters et al. 2008) information about the association between neurological conditions and preterm birth, although it is primarily a tool for clinical practice (Hadders-Algra 2010).

The most commonly used and best validated norm-referenced test for detecting developmental coordination disorder (DCD) in children from 3 to 16 years, also in a high-risk population of very preterm infants (Dewey et al. 2011), is the Movement Assessment Battery for Children (Blank et al. 2012). The revised version (The Movement Assessment Battery for Children – Second Edition, The Movement ABC-2) (Henderson, Sugden & Barnett 2007) and its structural validity (Schulz et al. 2011) has previously been published. There are only a few studies using the latest version of the Movement ABC, which makes score comparisons difficult as higher scores indicated poorer performance in the previous version and better performance in the revised version. The age bands are also different, although both versions include parts of manual dexterity, aiming and catching, and balance (Blank et al. 2012). Another tool to assist in the identification of DCD is the Developmental Coordination Disorder Questionnaire 2007 (DCDQ'07), a recently revised parent report where parents are asked to compare their child's motor performance to that of his/her peers concerning the interference of motor difficulties in everyday functional activities. It has been shown to have a sensitivity and specificity of 89% and 76%, respectively, in the age group of 10 to 15 years (Wilson et al. 2009).

2.4 Neurodevelopment and its prediction

Very preterm infants are at risk for adverse neurodevelopmental outcomes, even though most of them have been shown to survive without major impairment (Blencowe et al. 2013, Rysavy et al. 2015). While severe deficits can be detected by the age of 2 years, long-term follow-up is needed because less severe problems are often not detected until school age (Latal 2009).

2.4.1 Neuromotor development

Very preterm infants are at a higher risk for impairments in motor development than term infants (Evensen et al. 2004, de Kieviet et al. 2009, Edwards et al. 2011, Zwicker et al. 2012, Synnes et al. 2015). The rate of neuromotor difficulties has been reported to be significantly high, from 20-50%, in children born very prematurely (Latal 2009, Ferrari et al. 2012) potentially affecting peer interactions and socialization. Motor problems have been shown to continue even when entering adulthood as 20% of the children born with VLBW had severe motor impairment both at the age of 14 and 23 years (Husby et al. 2013).

2.4.1.1 Cerebral palsy

Very preterm birth is a major risk factor for CP, which is a collective term for non-progressive disorders of the development of movement and posture and the most common cause of significant motor impairment in children. Due to advances in perinatal and neonatal care during the past decades, the prevalence of CP has significantly decreased both in all live-born infants (to 0.2%) and in high-risk populations (to 3.6% in VLBW children) apart from the most immature infants (4.6% in ELBW children) (Platt et al. 2007, Sellier et al. 2015). Also the functional limitations of children with CP have become less severe when referred to Gross Motor Function Classification System (GMFCS) (van Haastert et al. 2011).

Up to 90% of children with CP have been shown to have abnormal findings in MRI (Krageloh-Mann, Cans 2009). However, the prevalence of cystic PVL has been shown to be significantly decreased, along with the prevalence of CP, in a large cohort of preterm infants born between 1990 and 2005 (van Haastert et al. 2011). In a prior review, periventricular WM lesions (PVL or consequences of IVH or both) have been shown to be the most common findings in very preterm born children with CP (Krageloh-Mann, Cans 2009). Abnormal imaging patterns in the posterior limb of the internal capsule have also been shown to associate with CP, as the internal capsule is known to consist of WM fibres that pass through the basal ganglia, and carry the major motor and sensory tracts to and from the cortex and spinal cord (Cowan, de Vries 2005). Injury to the corticospinal tract has recently been shown to precede reduced volume of the thalami at term age in preterm infants with cystic PVL, the majority of whom later developed CP (Kersbergen et al. 2015).

A systematic review has recently evaluated the accuracy of tests to predict CP in high-risk populations showing that GMs is the most reliable single method in predicting CP (summary estimates of sensitivity and specificity 98% and 91%), followed by brain MRI at term age (86-100% and 89-97%), neurological examination (88% and 87%), and cUS (74% and 92%) (Bosanquet et al. 2013). A combination of GMs and neurobehavioral assessment of preterm infants or either of these combined with MRI have all been shown to increase sensitivity and specificity for CP compared to a single test (Constantinou et al. 2007). Moderate and severe WM abnormalities in neonatal brain MRI have been shown to associate significantly with CP in extremely preterm infants (Skiold et al. 2012). Combining GMs with brain MRI findings at term age has been shown to increase the prediction up to 100% (Skiold et al. 2013).

2.4.1.2 Minor neurological dysfunction

A high proportion of children born very preterm have been shown to have MND at pre-school age (44%) (Arnaud et al. 2007). There are two different forms of MND: sMND

has been suggested to represent typical but non-optimal brain function with limited clinical significance, whereas cMND has been considered as a distinct form of CP associated with structural brain pathology (Hadders-Algra 2002). Male sex has been shown to be a risk factor for MND, while MND itself has been shown to increase risk for other developmental challenges such as lower cognitive skills, learning difficulties, behavioral problems, and poorer academic achievement (Hadders-Algra 2002, Arnaud et al. 2007, Ferrari et al. 2012). Even though the predictive value of GMs for MND at school age has been demonstrated, further studies are needed to evaluate whether neurological examinations at different age-points can identify children with MND (Ferrari et al. 2012). Major pathologies in early cUS have been shown to increase risk for cMND at the age of 5 years (Arnaud et al. 2007). However, there are no studies concerning the predictive value of neonatal brain imaging including also MRI for MND at school age.

2.4.1.3 Developmental coordination disorder

DCD is defined as a motor impairment in the absence of any obvious neurological and structural abnormality or cognitive impairment that interferes with activities of daily living or academic performance (Blank et al. 2012). The prevalence of DCD in children born with VLBW or very preterm has been reported to vary from 9.5% to 51% compared to 5-6% in all school aged children, the prevalence being higher in boys (Zwicker et al. 2012, Blank et al. 2012, Ferrari et al. 2012, Zwicker et al. 2013, Kirby, Sugden & Purcell 2014). Largely varying prevalence rates have been shown to derive from differences in definition and assessment tools (Kirby, Sugden & Purcell 2014). There is growing evidence regarding the co-occurence of DCD and other developmental disorders such as social, emotional, and attentional problems, and learning difficulties (Blank et al. 2012, Rigoli, Piek & Kane 2012, Zwicker et al. 2012, Kirby, Sugden & Purcell 2014). Additionally, more than half of the children with DCD in mainstream or special education have been shown to have cMND (Peters, Maathuis & Hadders-Algra 2011). The percentage of overlapping of DCD and MND in very preterm born children is not known. Neuroimaging studies of children with DCD are scarce and include mostly functional MRI or diffusion tensor imaging (Zwicker et al. 2012, Peters, Maathuis & Hadders-Algra 2013). A recent systematic review has summarized studies on relations between DCD and neuroimaging in very preterm infants indicating that WM pathologies and major brain MRI pathologies are related to motor impairment (Peters, Maathuis & Hadders-Algra 2013). However, only a few studies have assessed association between neonatal imaging and DCD at school age and the sample sizes have been small. There are no long-term data available on the associations between structural pathologies or volumetric alterations in the brain tissue at term age and neuromotor development in very preterm infants.

Prior functional MRI studies have demonstrated different activation of multiple brain regions (particularly in parts of the frontal, temporal, and parietal lobes, and cerebellum) during visuomotor and attention or inhibition tasks in children with DCD compared to typically developing children at 10 to 11 years of age. Based on the current knowledge concerning the etiology of DCD, it has been suggested that WM lesions in the periventricular region and the internal capsule are the neural substrates of severe motor impairment varying from DCD to CP, but more neuroimaging studies are required to better understand these correlates (Peters, Maathuis & Hadders-Algra 2013).

2.4.2 Neurosensory development

Preterm birth is a risk for hearing impairment, the prevalence ranging between 1 to 7 % depending on definitions (Fawke 2007, Saigal, Doyle 2008). The rate of severe hearing impairment was recently reported to be 2% in a large cohort of extremely preterm infants (Hintz et al. 2015). It has been suggested that the coexistence of risk factors for sensorineural hearing loss, including abnormal cUS, may be more important than the individual factors themselves among very preterm infants (Marlow, Hunt & Marlow 2000). Smaller volume of brain stem at term age has been shown to associate with neurosensory disability (CP or hearing loss) in preterm infants (Valkama et al. 2001).

The prevalence of blindness or severe visual impairment has been reported to vary between 1 to 8% (Fawke 2007, Saigal, Doyle 2008). Recently, the rate of severe visual impairment was shown to be 1 % in a large cohort of extremely preterm infants (Hintz et al. 2015). Very preterm infants are known to be at risk of developing visual and visual-perceptual impairment not only because of ROP (Fawke 2007, Saigal, Doyle 2008), but also secondary to brain lesions, such as severely abnormal optic radiations, and the involvement of the thalami (Ramenghi et al. 2010). The ability of visual fixation has been suggested to correlate with widespread WM networks and relate with neurocognitive development up to 5 years of age in preterm infants (Stjerna et al. 2015).

2.4.3 Cognitive development

Very preterm born children have increased risk for cognitive impairment (Anderson 2014). The prevalence of cognitive impairment in very preterm born children has been shown to vary from 7% (Munck et al. 2012) to 21% (Marlow et al. 2005) at pre-school age with mean Full Scale Intelligence Score (FSIQ) score 12 points below that of their term born peers (Kerr-Wilson et al. 2012). However, the cognitive outcome of the children from the PIPARI Study cohort has been shown to be better than previously described both at the age of 2 years of corrected age (Munck et al. 2010) and at 5 years of chronological age (Lind et al. 2011a) corresponding to the normative mean of the

FSIQ. Furthermore, the stability of cognitive outcome has been found good between these ages (Munck et al. 2012).

Numerous studies have described associations between major cUS abnormalities and cognitive impairment in very preterm infants. However, the predictive validity of major cUS findings has been shown to be poorer for cognitive than motor outcome (Hintz, O'Shea 2008). The PIPARI Study has shown that major MRI pathologies at term age predicted NDI with a PPV of 33.3%, while normal brain MRI had a NPV of 98.1% on NDI including cognitive impairment at 2 years of corrected age (Munck et al. 2010). These findings are similar to previous results showing that MRI abnormalities at term age may predict an adverse neurodevelopmental outcome at 2 years of age (Woodward et al. 2006). Increasing severity of WM abnormalities and significant cerebellar lesions have also been shown to associate independently with adverse neurodevelopmental outcomes at 18 to 22 months' corrected age (Hintz et al. 2015). Similarly, a common neonatal image phenotype including diffuse WM injury has been found to associate with adverse neurodevelopmental outcome at 2 years of chronological age (Boardman et al. 2010). Irrespective of the presence of overt brain injury, infants with NDI have demonstrated significantly smaller total and regional brain volumes and significantly larger ventricles (Plaisier et al. 2014). Similarly, decreased regional brain volumes at term age have been shown to associate with poorer neurodevelopment at 2 years of corrected age (Lind et al. 2011b).

2.4.4 Longitudinal follow-up studies

Long-term follow-up studies evaluating both neurosensory and cognitive outcomes with neonatal brain MRI are required to enable more accurate differentiation between findings that are associated with major developmental disabilities and those without clinical relevance (Hintz, O'Shea 2008). There are some prospective studies following up the long-term neurodevelopment including neuromotor outcome of preterm infants.

The Victorian Infant Collaborative Study Group has followed extremely preterm and/or ELBW infants born in Australia in 1979-1980, 1985-1987, 1991-1992, 1997, and 2005 at 2, 5, 7-8, and 14-18 years of age (Doyle, Casalaz & Victorian Infant Collaborative Study Group 2001, Roberts et al. 2009, Kelly et al. 2015). Neurosensory disabilities in these cohorts have been widely studied with stable rates over decades with the latest rate of severe disability (8%) at the age of 8 years in 1997 (Roberts et al. 2009). In this same cohort of 1997, the prevalence of DCD was shown to be 16% at the age of 8 years (Roberts et al. 2011). The relationship between neonatal cUS and neurodevelopmental dysfunction at this same age-point has been studied in the cohort of 1991-1992 showing significant association only with most severe IVH (Sherlock et al. 2005). The Victorian Infant Brain Study of children born very preterm between 2001 and 2003 includes also brain imaging by MRI at term age (Spittle et al. 2011). Even though neurodevelopment

up to late school age in these cohorts have been widely studied, the data is mostly based on cognitive outcomes and no structured neurological examinations at different age-points have been performed. Data on neurodevelopmental outcome of the latest cohort has not been published.

The EPICure studies are population-based studies of survival and later health status in extremely preterm infants born <26 weeks of gestational age in United Kingdom and The Republic of Ireland in 1995 and in England in 2006 (Moore et al. 2012). The original EPICure study included assessments of the surviving children at 2.5, 6, and 11 years of age, while the EPICure 2 study has evaluated neurodevelopmental disabilities at the age of 2 and 3 years of age to enable comparisons of survival and outcomes between these cohorts. These studies have shown an unchanged rate of 20% of severe disability at the age of 3 years (Moore et al. 2012), being consistent still at the age of 6 years (Marlow et al. 2005). Even though the motor functioning at 6 years of age in the original cohort has been described (Marlow et al. 2007), no structured neurological examinations have been performed during the longitudinal follow-up.

The Finnish ELBW Cohort Study Group (FinELBW) has focused on follow-up of a national cohort of children born in 1996-1997 (Mikkola et al. 2005). The prevalence of severe disability was 20% at the age of 5 years. According to a standardized neurological examination, 21% had sMND, and 7% had cMND. The data concerning neuromotor performance at school age has not been published.

A population-based EPIPAGE (Etude Epidémiologique sur les Petits Ages Gestationnels) cohort study includes very and moderately preterm infants born in France in 1997 (Marret et al. 2013). The study protocol included neonatal cUS examinations and follow-up assessments at 2, 5, and 8 years of age. The rate of severe disability in very preterm infants at 5 years of age was 5% (Larroque et al. 2008), and 14% were shown to have motor deficiency and 11% at least one severe neurodisability at the age of 8 years (Marret et al. 2013). However, a standardized neurological examination was only performed at the age of 5 years as previously described (Arnaud et al. 2007, Larroque et al. 2008, Marret et al. 2013).

The Norwegian Extreme Prematurity Study Group has observed extremely preterm or ELBW infants who were born in Norway between 1999 and 2000 (Markestad et al. 2005). At 2 years of corrected age, 8% had major neurosensory disability, and major cUS pathology was the dominating predictor (Leversen et al. 2010). At 5 years of chronological age, 6% had severe disability, 23% had FSIQ<85, and 15% had DCD (Leversen et al. 2011, Leversen et al. 2012).

The EXPRESS Study has evaluated the short- and long-term outcomes of extremely preterm infants born in Sweden during 2004-2007 (EXPRESS Group et al. 2009). Neurodevelopmental outcome has been studied at the age of 2.5 years with rate of 11%

of severe disability (Serenius et al. 2013). Studies of the sub-cohorts of the EXPRESS Study have also evaluated neonatal brain imaging (Horsch et al. 2010) and its predictive value (sensitivity 50-100%, specificity 92-100%) for later neurodevelopment as described previously (Skiold et al. 2012, Skiold et al. 2013). So far there is no published data concerning long-term neurodevelopment including neuromotor examinations.

Another French group, the LIFT (Loire Infant Follow-up Team), has followed a large cohort of moderately preterm infants born between 2003 and 2008 (Leroux et al. 2013). Neurodevelopmental outcome has been studied at the age of 2 years of corrected age with a rate of 24% of non-optimal development (Perivier et al. 2015). In addition, the predictive value of structured neurological examinations at term age for neuromotor development at 2 years of corrected age has been published including also information about neonatal brain imaging findings for the majority of the infants (Leroux et al. 2013). There is no published data concerning structured neurological examinations after term age.

Even though there are many longitudinal follow-up studies including a wide range of outcomes at different age-points, there are no previous studies evaluating the neuromotor trajectory of a single child. Moreover, it is not known how sequential structured neurological examinations predict long-term neuromotor development in very preterm infants. The longitudinal use of motor classification systems and volumetric MRI needs to be explored to better understand developmental processes in preterm infants (Fawke 2007).

3 AIMS OF THE STUDY

The objective of this thesis was to study the predictive factors of neurodevelopment and neuromotor trajectories in very preterm born children up to 11 years of age. The specific aims were:

1. To study the predictive value of neonatal brain imaging for long-term neurodevelopment in very preterm infants (I-IV) and to study the additional predictive value of neonatal neurological examination for neurosensory development in very preterm infants at 2 years of corrected age, when combined with concurrent brain imaging findings (II).

2. To determine the associations between brain volume measurements at term age and long-term neuromotor development in very preterm infants (III and IV).

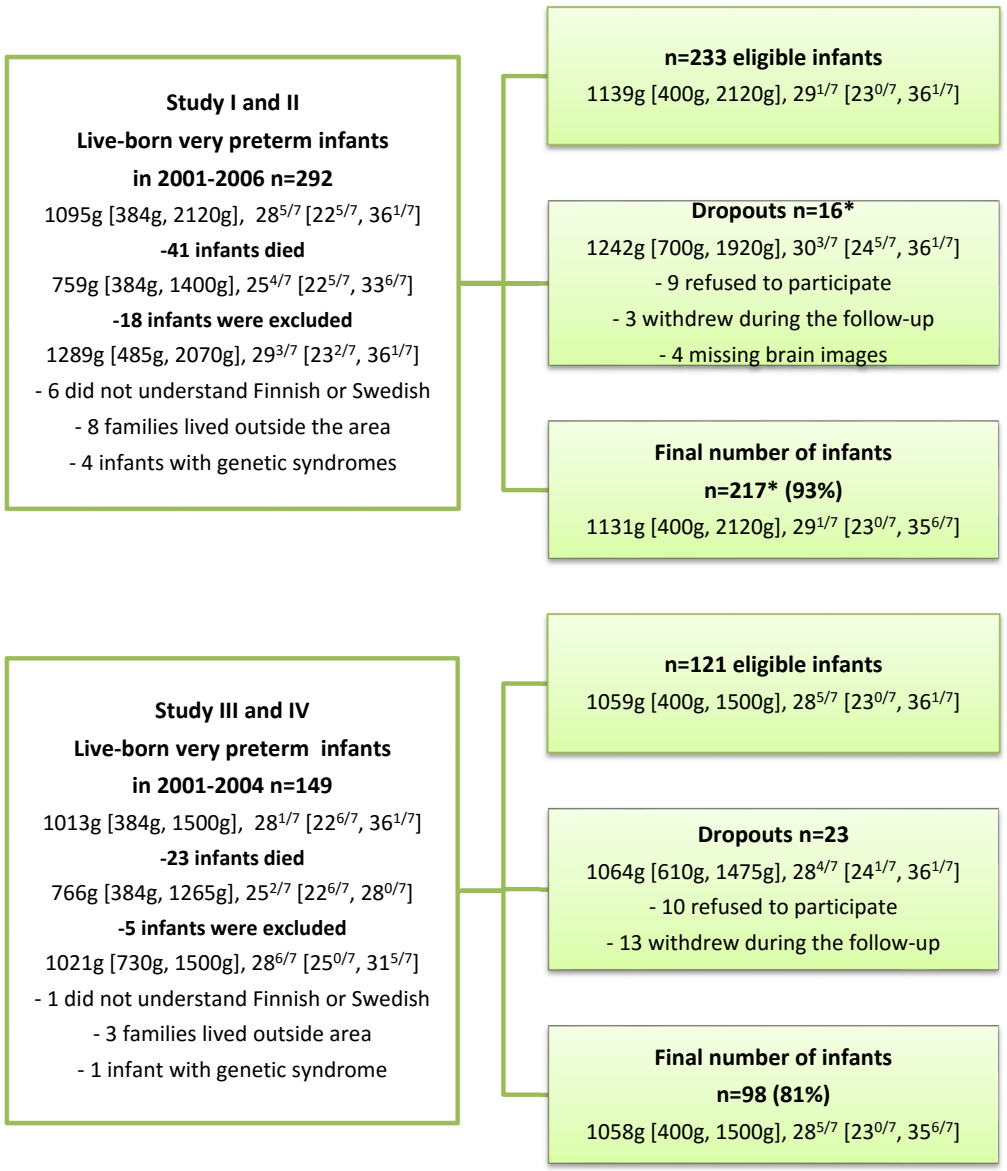
3. To study the predictive value of sequential structured neurological examinations during the longitudinal follow-up for long-term neuromotor development of very preterm born children (III and IV).

4. To describe the neuromotor trajectories and the neuromotor profile of very preterm born children up to 11 years of age (I-IV).

4 MATERIALS AND METHODS

4.1 Participants

This study is part of the multidisciplinary PIPARI Study (**Pi**eni**pa**inoisten **ri**skilasten käyttäytyminen ja toimintakyky imeväisiästä kouluikään, The Development and Functioning of Very Low Birth Weight Infants from Infancy to School Age), a prospective follow-up study of very preterm infants born to Finnish- or Swedish-speaking families during a six-year period (2001 to 2006), at Turku University Hospital, Finland. From 2001 to the end of 2003, the inclusion criteria was a birth weight ≤1500 grams in preterm infants born <37 gestational weeks. From the beginning of 2004, the inclusion criteria were broadened to include all infants born below the gestational age of 32 weeks, regardless of birth weight. All the study infants were included in Studies I and II, as the shorter follow-up time of up to 5 years of chronological age meant that all the required data was already available. Only the infants born between January 2001 and April 2004 were included in Studies III and IV due to the longer follow-up time of 11 years. This cut-off was chosen because the MRI equipment was upgraded thereafter. The flow charts of the participants are shown in Figure 2.



*There was one infant missing neurological examination at term age and therefore not included in Study II.

Figure 2. The flow chart of the participants, mean [minimum, maximum] birth weights and gestational ages in weeks (modified from Studies I-IV).

4.2 Methods

The study design is shown in Figure 3. The age of the very preterm infants was corrected for prematurity until the age of 2 years, after which the chronological age was used.

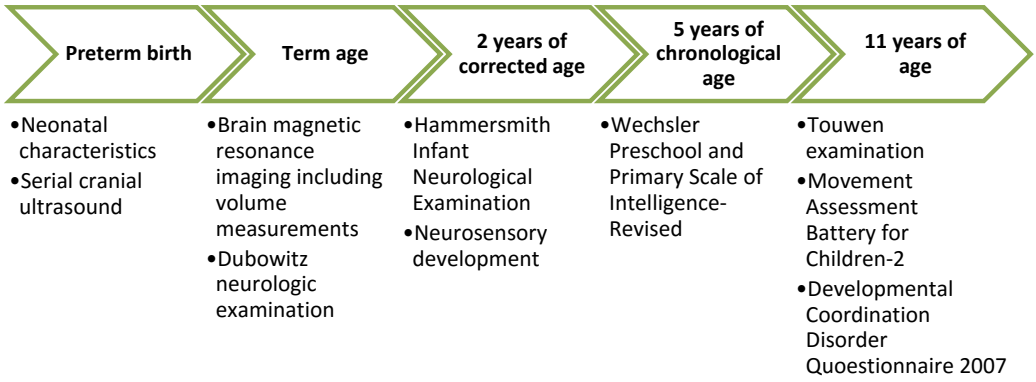


Figure 3. The study design.

4.2.1 Background data

Neonatal background data were obtained from the medical records using the Vermont-Oxford Network criteria to enable comparisons between international research centers. Neonatal characteristics used in this study were birth weight, gestational age, sex, cesarean section, SGA status (<-2SD), BPD (supplemental oxygen required at 36 post-menstrual age), sepsis, NEC (surgical), and ROP (treated).

4.2.2 Neonatal brain imaging

cUS examinations were performed at 3 to 5 days, at 7 to 10 days, and at 1 month of age by the attending neonatologist in neonatal intensive care unit (Reiman et al. 2008). Thereafter they were performed monthly until discharge from the hospital and at term age. The cUS examinations were performed with a 7-MHz vector transducer (Sonos 5500 Hewlett-Packard, Andover, Mass). IVH was classified from grade I to IV (Papile et al. 1978). The cUS examination at term age was performed with a 7.5-MHz vector transducer (Aloka SSD 2000, Aloka Co, Ltd, Tokyo, Japan) from January 2001 to August 2002 and an 8-MHz vector transducer (General Electric Logic 9 [General Electric, Waukesha, WI]) from September 2002 to March 2007. The cUS examination at term age

was performed by a pediatric radiologist unaware of both the clinical information and the result of the brain MRI examination of the infant. The infants were categorized into three groups according to the most pathologic findings on cUS examinations: 1) Normal findings: no abnormalities, germinal layer/plexus cysts, subependymal pseudocysts, or calcifications, 2) minor pathologies: IVH grade I/II, germinal layer necrosis, or ventricular dilatation, and 3) major pathologies: IVH grade III/IV, cystic PVL II/III, thalamic lesion, focal infarction, convexity hemorrhage, or ventricular dilatation following a hemorrhage with need for therapeutic intervention (Rademaker et al. 2005).

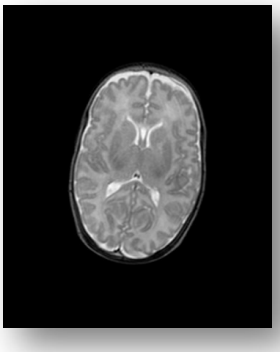
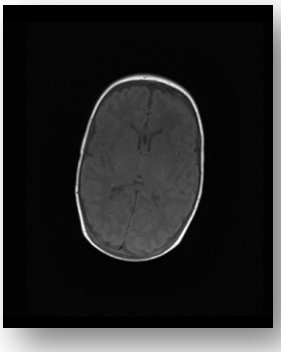
Brain MRI was performed at term age (Maunu et al. 2009). The images were analyzed and volume measurements were manually performed by one neuroradiologist who was unaware of both the clinical information and the results of the cUS examinations of the infant. The imaging took place during postprandial sleep without any pharmacological sedation or anesthesia. The infants were swaddled to calm them and to reduce movement artifacts in the imaging. A pulse oximeter was routinely used during MRI examinations. Ears were also protected (3M Disposable Ear Plugs 1100; 3M, Brazil and Wurth Hearing protector, Art.-Nr. 899 300 232, Wurth, Austria). For infants born between 2001 and April 2004, the MRI equipment was an open 0.23-T Outlook GP (Philips Medical, INC, Vantaa, Finland) equipped with a multipurpose flexible coil fitting the head of the infant, until it was upgraded to the 1.5-T Philips Intera (Philips Medical Systems, Best Netherlands) for the remainder of the study infants born thereafter.

Axial T2-weighted images, coronal three-dimensional T1-weighted images and coronal T2-weighted images of the entire brain were obtained when using the 0.23-T equipment. With the 1.5-T equipment, axial T2-weighted, axial T1-weighted, and sagittal T2-weighted images were obtained. All of the sequences were optimized for the imaging of a term infant brain. The total imaging time was about 25 minutes. The extracerebral space was measured manually from the MRIs. A cut-off value of 4 mm was used according to a previous study (McArdle et al. 1987). The width of the extracerebral space was measured in front of the frontal lobe, where the extracerebral fluid space is widest. The group of infants with an extracerebral space of 5 mm was analyzed separately, because accuracy of the measurement was 1 mm. Ventricular/brain (V/B) ratio was obtained from the width of the frontal horns of the lateral ventricles divided by the width of the brain tissue at the same plane of cerebral image. The infants were categorized into three groups according the structural MRI findings (normal findings, minor pathologies, and major pathologies) (Table 1) to evaluate the relationship between the brain pathology and the developmental outcome.

Table 1. The classification of the structural brain magnetic resonance imaging findings (modified from Study I).

Normal findings:

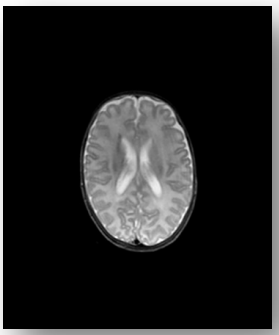
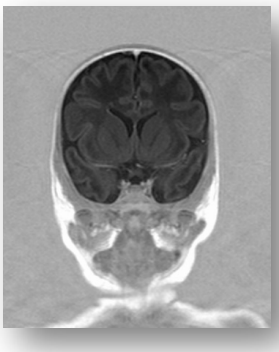
- normal brain anatomy (cortex, basal ganglia and thalami, posterior limb of internal capsule, white matter, germinal matrix, corpus callosum and posterior fossa structures)
- width of extracerebral space <5 mm
- ventricular/brain (V/B) ratio <0.35

Axial T2-weighted slice and axial T1-weighted slice are examples of normal brain findings.

Minor pathologies:

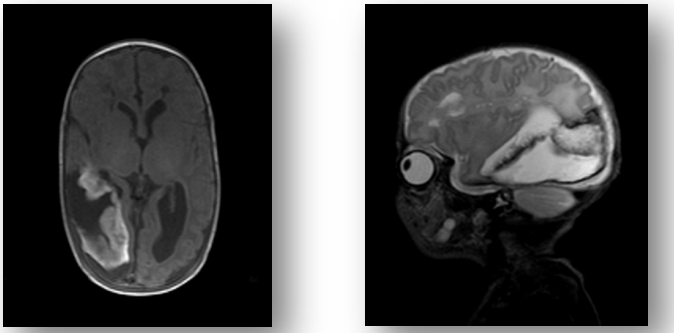
- consequences of intraventricular hemorrhages (IVH) grade I/II
- caudothalamic cysts
- width of the extracerebral space of 5 mm
- V/B ratio of 0.35

Axial T2-weighted slice and coronal T1-weighted slice show consequences of caudothalamic hemorrhages grade II on the right side of the brain.

Major pathologies:

- consequences of IVH grade III/IV
- injury in cortex, basal ganglia, thalamus or internal capsule, with injury of corpus callosum, cerebellar injury, white matter injury
- increased width of extracerebral space >5 mm
- V/B ratio >0.35
- ventriculitis
- other major brain pathology (infarcts)



T1-weighted axial slice and sagittal T2-weighted slice show large post-hemorrhagic lesion on right temporo-occipital region of the infant.

Volume measurements were manually performed on a GE workstation (GE AW1.0, GE Medical Systems, Milwaukee, USA) by the same neuroradiologist by separating visually the cerebrospinal fluid from the brain tissue image by image (Maunu et al. 2009). The anatomical differentiation of the brain was based on both anatomical landmarks and signal intensity differences of the brain structures. The volumes of the total brain tissue (total brain volume minus ventricle volumes), the cerebrum, the cerebellum, the frontal lobes, the brain stem (medulla oblongata together with pons), the basal ganglia together with the thalami, and ventricles (lateral ventricles, third and fourth ventricles) were measured. A T1-weighted field echo sequence with a time of repetition of 30 ms, a time of echo of 10 ms, a flip angle of 45°, a slice thickness of 5 mm, a field of view of 220x220 mm^2, and a matrix of 256x256 in the coronal plane were obtained. The reproducibility of these measurements was assessed by a repeated volume measurement of 20 children, performed by another neuroradiologist, who was blinded to the results of the first measurement (Lind et al. 2011b).

4.2.3 Dubowitz neurologic examination

Neurological examination at term age was performed by an experienced physician and physiotherapists, using a standardized proforma of the Dubowitz neurologic examination (Dubowitz, Dubowitz & Mercuri 1999). It included 34 items with measurement subscales of tone and posture (10 items), tone patterns (5 items), reflexes (6 items), spontaneous movements (3 items), abnormal signs (3 items), and behavior (7 items). The assessment proforma (Appendix 1) consisted of five alternative findings for each of the items, and the examiner circled the one that corresponded most closely to the infant's performance. The number of items outside the normal range was defined according to gestational age specific norms (Ricci et al. 2008). The infants born <25 weeks of gestational age were assessed according to the same criteria that the infants born between $25^{0/7}$ and $27^{6/7}$ weeks of gestational age as there are no norms for this subgroup. Similarly, the infants born between $33^{0/7}$ and $34^{6/7}$ weeks of gestational age were assessed according to the criteria for infants born ≥35 weeks of gestational age. The cut-off value for a result outside of the normal range in the neurological examination was set at ≥1 because even a single deviation from the term age norm reference (Ricci et al. 2008) in the neurological examination indicated an increased risk for later impairment.

4.2.4 Hammersmith Infant Neurological Examination

Neurological development was reassessed at 2 years of corrected age by an experienced physician and physiotherapists, using the HINE (Haataja et al. 1999). It consisted of 37 items that were further divided into three sections: 1) cranial nerve function, posture, movements, tone and reflexes (26 items), 2) description of motor development (8 items), and 3) description of behavioral state of the infant during examination (3 items). All the item scores in the first section were summed up yielding a maximum score of 78. The optimal total scores for full-term infants at 12 and 18 months of age (≥73 and ≥74, respectively) (Haataja et al. 1999) were not used. Instead, as there are no norms for either very preterm or full-term born children at 2 years of age, a cut-off score of >70 was used for this preterm population. It was derived from a cut-off of the 90th percentile of the healthy preterm infants (normal findings or minor pathologies in brain MRI and no neurosensory impairment, NSI). The whole proforma of the HINE is shown in Appendix 2.

4.2.5 Neurosensory impairment

NSI was defined at 2 years of corrected age and included at least one of the following findings: CP, severe hearing impairment or severe visual impairment. The diagnosis of CP, including the grading of functional severity by GMFCS (Palisano et al. 1997), was

ascertained by a child neurologist at 2 years of corrected age after a systematic clinical follow-up. Severe hearing impairment was categorized as a hearing impairment with a cut-off of 40 dB or hearing loss requiring amplification in at least one ear, and severe visual impairment was determined as a visual acuity <0.3, or blindness (Maunu et al. 2009).

4.2.6 Neurodevelopmental impairment

The children's cognitive level at 5 years of chronological age (+0-2 months) was evaluated by a psychologist using a short form of Wechsler Preschool and Primary Scale of Intelligence - Revised (WPPSI-R), Finnish translation (Wechsler 1995) with subtests of information, sentences, arithmetic, block design, geometric design and picture completion (Lind et al. 2011a). FSIQ (normal mean=100, SD 15) was calculated based on the scores of the subtests and a quotient of ≥85 (>-1 SD) was considered normal intelligence, a quotient of 70-84 (-2 SD to -1 SD) slightly below normal and a quotient of ≤69 (<-2 SD) significantly below normal. The cut-off of 85 for FSIQ was used, because it was close to a -2 SD level in the control group of the regional cohort of full-term Finnish children (mean 112, SD 15) (Lind et al. 2011a). At 5 years of chronological age, the definition of NDI included FSIQ<85 and/or at least one of the components of NSI determined at 2 years of corrected age.

4.2.7 Touwen examination

Neurological examination at 11 years of age was performed by the author (Setänen) using the latest version of the Touwen examination (Hadders-Algra 2010). This examination included eight domains: posture and muscle tone, reflexes, involuntary movements (athetotiform movements, choreiform movements and tremor), coordination and balance, fine manipulation, associated movements, sensory function, and cranial nerve function. Hand preference, head circumference, weight, and length were recorded. The domains were classified as dysfunctional according to the criteria of the manual using a computerized scoring system (Hadders-Algra 2010). sMND was defined as the presence of one or two dysfunctional domains, and cMND as the presence of more than two dysfunctional domains. The presence of an isolated dysfunctional domain in reflexes did not qualify for the classification of sMND. All the examinations were video-recorded and reviewed together with an experienced child neurologist to ensure a consensus regarding the details of the assessments. The examiner was unaware of the children's brain imaging findings or neonatal histories at the time of the examination. The whole proforma of the Touwen examination is shown in Appendix 3.

4.2.8 Movement Assessment Battery for Children-2

The motor assessment was completed at 11 years of age by using the Movement ABC-2 (Henderson, Sugden & Barnett 2007) to identify children with movement difficulties. Most of the clinical examinations were performed by the author (Setänen). The Movement ABC-2 included three domains: manual dexterity (3 items), aiming and catching (2 items), and balance (3 items). All the items were scored based on the best of two attempts as raw scores that were then further calculated to standard scores equating to percentiles of each domain and total test score, accordingly. A total test score ≤56 (≤5th percentile) denoted a significant movement difficulty. A total test score of 57-67 (>5th to 15th percentile) suggested a risk of having a movement difficulty (monitoring required). Any total test score >67 (>15th percentile) indicated no movement difficulty. The age band 3 (11 to 16 years) was used and the test was scored according to 11-year-old children's norms, as the use of identical test tasks and references for all children was found preferable even though some children had not yet turned 11 years at the time of the examination. The free Finnish translation of the proforma of the Movement ABC-2 is shown in Appendix 4.

4.2.9 Developmental Coordination Disorder Questionnaire 2007

The DCDQ'07 was completed by interview (mostly author Setänen) based on an unofficial Finnish translation (Appendix 5) of the original version of the questionnaire (Wilson et al. 2009). It consisted of 15 items grouped into three distinct factors: 1) control during movement, 2) fine motor and handwriting, and 3) general coordination. All the items were scored using a 5-point Likert scale. Total scores (15-75) were calculated by summing up items. A total score ≤57 indicated DCD.

4.3 Ethics

All parents gave informed consent for the whole follow-up study (I–IV). In addition, all children provided their informed consent for Studies III and IV. The PIPARI Study protocol was approved by the Ethics Review Committee of the Hospital District of Southwest Finland in December 2000 and in January 2012.

4.4 Statistical analysis

NPV was defined as the probability that infants with normal findings truly had a normal developmental outcome. The PPV was defined as the probability that infants with abnormal findings truly had an abnormal developmental outcome. Generalized score

statistic was used to compare paired NPV and PPV values (Leisenring, Alonzo & Pepe 2000).

Univariate associations between either brain MRI or cUS and continuous response variables were studied using a linear model. This linear model was also used to study the association between the Dubowitz neurologic examination at term age and the HINE at 2 years of corrected age. The associations were further studied using either MRI or cUS and the Dubowitz neurologic examination as predictor variables of the HINE. The associations between the Dubowitz neurologic examination at term age and NSI at 2 years of corrected age were studied using logistic regression analysis. The association was further studied controlling for either brain MRI or cUS. All statistical models were fitted using the scores of the Dubowitz neurologic examination and the HINE as continuous variables, but descriptive statistics are also shown for dichotomized values of the two variables. Univariate associations between the subscales of the Dubowitz neurologic examination and response variables were studied using Pearson correlation for the HINE and point biserial correlation for NSI.

Multinomial logistic regression models were used to study the associations between brain volumes and the results of Touwen examinations controlling for brain pathology. As the data distribution of the ventricular volume was right skewed, the variable was log transformed before further analysis. Because the results of the neurological examinations were not normally distributed, the following bivariate analyses were performed using non-parametric methods. Associations between continuous (the Dubowitz neurologic examination and the HINE) and ordinal variables (the Touwen examination) were studied using Spearman's correlation coefficient. Continuous variables were compared between study infants and drop-outs using Mann-Whitney U-test and comparisons between two categorical variables were done using the chi-square test or Fisher’s exact test, as appropriate.

Pearson's correlation was used to study the univariate associations between two continuous variables (the Movement ABC-2 and the DCDQ’07). Univariate associations between continuous Movement ABC-2 percentile and categorical predictor variables were studied using regression analysis. Associations between brain volumes and continuous Movement ABC-2 percentile were studied using regression analysis controlling for brain pathology, gender, SGA status and gestational age.

All continuous variables are presented with mean (SD) [min, max]. Statistical analyses were completed using SAS (Version 9.3 for Windows; SAS Institute Inc., Cary, NC, USA), and p-values <0.05 were considered as statistically significant.

5 RESULTS

5.1 Background characteristics

All the infants were born ≤1500g or <32 weeks of gestational age. Therefore, there were more SGA infants in the group of infants born ≥32 weeks of gestational age (96% in Studies I and II, and 100% in Studies III and IV) than in those born <32 weeks of gestational age (27% in Studies I and II, and 30% in Studies III and IV). A total of 19 (9%) infants had birth weight >1500g. The neonatal characteristics of the very preterm infants are shown in Table 2.

Table 2. Neonatal characteristics of the very preterm infants (modified from Studies I-IV).

Characteristics	Study I and II (n=217)*	Study III and IV (n=98)
Birth weight, mean (SD) [minimum, maximum], g	1131 (330) [400, 2120]	1058 (277) [400, 1500]
Gestational age at birth, mean (SD) [minimum, maximum], wk	$29^{0/7}$ ($2^{5/7}$) [$23^{0/7}$, $35^{6/7}$]	$28^{5/7}$ ($2^{5/7}$) [$23^{0/7}$, $35^{6/7}$]
Males, n (%)	122 (56), and 121 (56)*	47 (48)
Females, n (%)	95 (44)	51 (52)
Cesarean section, n (%)	134 (62)	57 (58)
Small for gestational age, n (%)	81 (37)	37 (38)
Bronchopulmonary dysplasia, n (%)	29 (13)	15 (15)
Sepsis, n (%)	35 (16)	23 (23)
Necrotizing enterocolitis, surgical, n (%)	10 (5)	4 (4)
Retinopathy of prematurity, laser treated, n (%)	8 (4)	2 (2)

*There was one infant missing neurological examination at term age and therefore not included in Study II.

5.2 Neonatal brain imaging

All the infants were examined by serial cUS and brain MRI. Regional brain volume measurements were obtained from 198 (91%) infants. The mean age at the time of MRI examination was $40^{0/7}$ (SD 2.6 days, [$39^{1/7}$, $41^{3/7}$]).

One hundred and thirteen (52%) of the infants had normal findings in cUS, 86 (40%) had minor pathologies, and 18 (8%) had major pathologies.

One hundred and twenty (55%) of the infants (n=217) had normal MRI, 39 (18%) had one or more minor, 23 (11%) one major, 9 (4%) several major and 27 (12%) both minor and major findings in the MRI at term age. In all very preterm infants with major pathologies (n=59, 27%), the most common findings were WM injury (n=29, 13%), capsula interna injury (n=21, 10%), ventriculitis (n=21, 10%) and V/B ratio >0.35 (n=21, 10%). There were seven different single major pathologies (n=33, 15.2%) (capsula interna injury, WM injury, ventriculitis, corpus callosum injury, haemorrhage in posterior fossa structures, V/B ratio >0.35, extracerebral space >5 mm). The minor pathologies were consequences of IVH grade I (n=49, 22.6%), an extracerebral space of 5 mm (n=15, 6.9%) and a V/B ratio of 0.35 (n=9, 4.1%).

The mean values of regional volumes (ml) were as follows: total brain tissue 399.7 (SD 49.2, [254.0, 514.9]), ventricles 368.9 (SD 20.3, [2.3, 222.9]), cerebrum 368.9 (SD 46.6, [233.0, 479.8]), frontal lobes 126.7 (SD 23.7, [67.0, 194.1]), basal ganglia and thalami 25.4 (SD 4.7, [13.0, 42.8]), cerebellum 24.5 (SD 4.8, [8.2, 37.8]), and brain stem 6.4 (SD 2.6, [2.5, 14.9]).

Percentages of neurodevelopmental outcomes in each category of neonatal brain imaging findings (MRI and cUS) are shown in Table 3. Associations between neonatal brain volumes and neuromotor outcome at 11 years of age are shown in Table 9.

Table 3. Brain imaging findings and neurodevelopmental outcomes.

	MRI, n (%)			cUS, n (%)		
	Normal findings	Minor pathologies	Major pathologies	Normal findings	Minor pathologies	Major pathologies
Dubowitz neurologic examination at term age (number of items outside the normal range)						
<1 n=53 (25%)	32/120 (27)	9/38 (24)	12/58 (21)	35/113 (31)	14/85 (16)	4/18 (22)
≥1 n=163 (75%)	88/120 (73)	29/38 (76)	46/58 (79)	78/113 (69)	71/85 (84)	14/18 (78)
Hammersmith Infant Neurological examination at 2 years of corrected age (total score)						
≤70 n=32 (15%)	8/116 (7)	7/38 (18)	17/54 (31)	12/109 (11)	13/84 (15)	7/15 (47)
>70 n=176 (85%)	108/116 (93)	31/38 (82)	37/54 (69)	97/109 (89)	71/84 (85)	8/15 (53)
Neurosensory impairment at 2 years of corrected age						
NSI n=17 (8%)	1/120 (1)	0/38 (0)	16/58 (28)	0/113 (0)	6/85 (7)	11/18 (61)
CP n=14 (6%)	1/120 (1)	0/39 (0)	13/58 (22)	0/113 (0)	5/86 (6)	9/18 (50)
Severe hearing impairment n=4 (2%)	0/120 (0)	0/39 (0)	4/58 (7)	0/113 (0)	2/86 (2)	2/18 (11)
Neurodevelopmental impairment at 5 years of chronological age						
NDI n=41 (22%)	9/100 (9)	5/35 (14)	27/51 (53)	15/97 (15)	13/74 (18)	13/15 (87)
FSIQ <85 n=31(17%)	8/100 (8)	5/35 (14)	18/47 (38)	15/98 (15)	10/73 (14)	6/11 (55)
Touwen examination at 11 years of age						
Normal n=38 (39%)	25/55 (45)	10/20 (50)	1/13 (8)	26/48 (54)	11/37 (30)	1/5 (20)
sMND n=41 (42%)	25/55 (45)	7/20 (35)	9/13 (69)	17/48 (35)	20/37 (54)	4/5 (80)
cMND n=11 (11%)	5/55 (9)	3/20 (15)	3/13 (23)	5/48 (10)	6/37 (16)	0/5 (0)
Movement ABC-2 at 11 years of age (in children without CP)						
>5th n=82 (91%)	52/55 (95)	18/20 (90)	10/13 (77)	44/48 (92)	33/37 (89)	5/5 (100)
≤5th n=8 (9%)	3/55 (5)	2/20 (10)	3/13 (23)	4/48 (8)	4/37 (11)	0/5 (0)

MRI=magnetic resonance imaging, cUS=cranial ultrasound, NSI=neurosensory impairment, CP=cerebral palsy, NDI=neurodevelopmental impairment, FSIQ=Full Scale Intelligence Quotient, sMND=simple minor neurological dysfunction, cMND=complex minor neurological dysfunction, Movement ABC-2=Movement Assessment Battery for Children-2

5.3 Dubowitz neurologic examination

All the infants (n=216) included in Study II were examined with the Dubowitz neurologic examination at term age. The mean postmenstrual age of the infants at the time of examination was 40 weeks (SD 2.5 days, [$38^{5/7}$, $42^{1/7}$]). The mean number of items outside the normal range in the Dubowitz neurologic examination was 2.0 (SD 2.1, [0.0, 13.0]). Fifty-three (24.5%) of the infants had no items outside the normal range. Neonatal brain imaging findings in these infants are shown in Table 3. Gestational age subgroups are shown in Table 4. The number of items outside the normal range according to brain MRI and cUS categories are shown in Table 5.

Table 4. The gestational age subgroups in the Dubowitz neurologic examination at term age and the number of items outside the normal range; mean (SD, [minimum, maximum]).

<25 weeks	n=15 (7%)	2.2 (SD 3.2, [0.0, 13.0])
$25^{0/7}$-$27^{6/7}$ weeks	n=55 (25%)	2.2 (SD 2.2, [0.0, 10.0])
$28^{0/7}$-$29^{6/7}$ weeks	n=61 (28%)	2.0 (SD 2.0, [0.0, 9.0])
$30^{0/7}$-$31^{6/7}$ weeks	n=56 (26%)	1.5 (SD 1.5, [0.0, 7.0])
$32^{0/7}$-$34^{6/7}$ weeks	n=26 (12%)	2.2 (SD 1.7, [0.0, 5.0])
≥35 weeks	n=3 (1%)	5.3 (SD 2.1, [3.0, 7.0])

Table 5. The number of items outside the normal range in the Dubowitz neurologic examination at term age according to brain magnetic resonance imaging (MRI) and serial cranial ultrasound (cUS) categories; mean (SD, [min, max]).

	MRI	cUS
Normal findings	1.8 (SD 1.8, [0.0, 9.0])	1.7 (SD 1.7, [0.0, 9.0])
Minor pathologies	1.8 (SD 2.0, [0.0, 10.0])	2.4 (SD 2.4, [0.0, 13.0])
Major pathologies	2.5 (SD 2.6, [0.0, 13.0])	2.3 (SD 2.0, [0.0, 6.0])

All infants with CP had at least one item outside the normal range in the Dubowitz neurologic examination (Table 6). There were 4.1 (SD 3.1, [1.0, 13.0]) and 1.9 (SD 1.9, [0.0, 10.0]) deviant items in infants with and without CP, respectively. Items that were more frequently outside the normative range in the children with CP (n=14) were posture (opisthotonus or arms flexed and legs extended) (n=6, 43%, p=0.002), eye appearance (does not open eyes, persistent nystagmus, strabismus, roving eye movements or

downward deviation (n=2, 14%, p=0.01), visual orientation (does not follow or focus on stimuli, stills, focuses, follows briefly to the side but loses stimuli) (n=5, 36%, p=0.004), flexor tone (compare arm and leg traction: arm flexion >leg flexion, difference >1 column) (n=4, 29%, p=0.01), and head control (sitting: neck extension >neck flexion, difference >1 column).

Table 6. Number of items outside the normal range in the Dubowitz neurologic examination at term age in children with cerebral palsy (CP) (n=14), in children with neurosensory impairment (NSI) (n=17), and in children without NSI (n=199) at 2 years of corrected age.

Number of items outside the normal range	CP, n (%)	NSI, n (%)	No NSI, n (%)
0	0 (0)	0 (0)	53 (27)
1	3 (21)	5 (29)	52 (26)
2	1 (7)	2 (12)	38 (19)
3	3 (21)	3 (18)	24 (12)
4	2 (14)	2 (12)	11 (6)
5	1 (7)	1 (6)	13 (7)
6	3 (21)	3 (18)	1 (1)
7	0 (0)	0 (0)	4 (2)
8	0 (0)	0 (0)	1 (1)
9	0 (0)	0 (0)	1 (1)
10	0 (0)	0 (0)	1 (1)
11-12	0 (0)	0 (0)	0 (0)
13	1 (7)	1 (6)	0 (0)

The Dubowitz neurologic examination was significantly related to the HINE total scores at 2 years of corrected age (R2=0.04, b=-0.6, p=0.003). The NPV of no items outside the normal range in the Dubowitz neurologic examination for HINE total score >70 was 88.5%, and the PPV of one or more items outside the normal range for total score ≤70 was 16.7%.

There was no single test item that alone correlated statistically significantly with the HINE total scores or NSI at 2 years of corrected age. The subscales of the Dubowitz neurologic examination that correlated with the HINE total scores were tone patterns (r=-0.25, p<0.001), posture and tone (r=-0.18, p=0.01) and behavior (r=-0.13, p=0.07). The same subscales correlated with NSI: tone patterns (r=-0.18, p=0.01), posture and tone (r=-0.13, p=0.06) and behavior (r=-0.19, p=0.01).

The number of items outside the normal range in the Dubowitz neurologic examination at term age correlated with the results of the Touwen examination at 11 years of age

(r=0.22, p=0.03). The domain of orientation and behavior (eye appearances, auditory orientation, visual orientation, alertness, irritability, consolability, and cry) correlated with the Touwen examination in the group of all very preterm children (r=0.32, p=0.001) and in very preterm children without CP (r=0.39, p<0.001).

5.4 Hammersmith Infant Neurological Examination

Two hundred and eight (96%) children were examined using the HINE. Mean age at examination time was 2 years of corrected age (SD 9 days, [-71 days, +60 days]). The mean total score of the examinations was 72.9 (SD 5.6, [38.0, 78.0]). One hundred and seventy-six (85%) of the children had HINE scores >70. Of the 32 (15%) children scoring ≤70, 17 (53%) had major pathologies in brain MRI and 7 (22%) in cUS (Table 3). The mean total score in the HINE was 54.3 (SD 10.34, [38.0, 74.0]) and 73.9 (SD 2.6, [67.0, 78.0]) in infants with and without CP, respectively (Table 8).

Brain MRI explained 11.9% of the variation in the HINE total scores (p<0.001). Major brain pathologies on MRI reduced the HINE total scores compared to normal findings (b=-0.7 for minor pathologies and b=-4.5 for major pathologies, respectively). cUS explained 13.2% of the variation in the HINE total scores (p<0.001). Major brain pathologies on cUS reduced the HINE total scores compared to normal findings (b=-1.4 for minor pathologies and b=-7.9 for major pathologies, respectively).

The NPV of normal findings or minor brain pathologies for the HINE scores >70 were 90.3% (MRI) and 87.1% (cUS). The difference between NPV of MRI and cUS was statistically significant (p=0.04). The PPV of major brain pathologies for total score ≤70 were 31.5% (MRI) and 46.7% (cUS). The difference between PPV of MRI and cUS was not statistically significant (p=0.17). The Dubowitz neurological examination and brain MRI at term age together explained 14.9% of the variation in the HINE at 2 years of corrected age. The Dubowitz neurological examination and cUS together explained 17.2% of the variation in the HINE at 2 years of corrected age. Thus the Dubowitz neurologic examination at term age improved the predictive value of MRI (R_2 change=0.03, p=0.01) and cUS (R_2change=0.04, p=0.002). The PPV improved from 31.5% to 35.7% (MRI) (p=0.17) and from 46.7% to 63.6% (cUS) (p=0.04), and the NPV of 90.3% (MRI) (p=0.54) and 87.1% (cUS) (p=0.06) remained the same.

The total score of the HINE at 2 years of corrected age correlated with the results of the Touwen examination at 11 years of age (r=-0.39, p<0.001). The probability of having cMND increased as the total test score of the HINE decreased. The NPV of a HINE total score >70 for neurological outcome without cMND was 88.9%, and the PPV of a total score ≤70 for cMND was 22.2%. The domains of posture (r=-0.46, p<.001), movements (r=-0.42, p<.001), tone (r=-0.25, p=0.01), and reflexes and reactions (r=-0.25, p=0.01) correlated with the Touwen examination in the group of all very preterm born children.

In children without CP, the domain of posture correlated with the Touwen examination (r=-0.3, p=0.004). The neuromotor trajectories of the very preterm infants without CP from 2 years of corrected age to 11 years of age are shown in Table 7.

Table 7. Total score of the Hammersmith Infant Neurological Examination (HINE) in very preterm born children at 2 years of corrected age compared with the results of the Touwen examination and the Movement Assessment Battery for Children-2 (Movement ABC-2) at 11 years of age.

HINE	Touwen examination, n (%)			Movement ABC-2, n (%)	
	Normal	*sMND*	*cMND*	*Normal*	*DCD*
≤70, n=9 (10%)	2 (22)	5 (56)	2 (22)	8 (89)	1 (11)
>70, n=81 (90%)	36 (44)	36 (44)	9 (11)	74 (91)	7 (9)

5.5 Neurosensory impairment

Of all the infants, 14 (6%) had CP and 4 (2%) had severe hearing impairment at 2 years of corrected age. There were no children with severe visual impairment. A total of 17 (8%) children had NSI. Sixteen (94%) of them had major pathologies in brain MRI and 11 (65%) in cUS (Table 3). The characteristics of the children with CP are shown in Table 8 (modified from Study II). The NPV of normal findings or minor brain pathologies for developmental outcome without CP were 99.4% (MRI) and 97.5% (cUS) (p=0.06). The PPV of major brain pathologies for CP were 6.1% (one major pathology in MRI), 44.0% (several major pathologies in MRI), 22.4% (one or more major pathologies in MRI), and 50.0% (cUS) (p=0.06).

A higher number of items outside the normal range in the Dubowitz neurologic examination increased the risk for CP (OR=1.4, CI 95% 1.2–1.8, p<0.001), and for NSI (OR=1.4, CI 95% 1.1–1.6, p=0.002). The associations remained when controlling for either brain MRI or cUS findings.

The NPV of no items outside the normal range in the Dubowitz neurologic examination for development without NSI was 100%, and the PPV of one or more items outside the normal range for NSI was 10.4%. Neurological examination improved the PPV of major brain pathologies for NSI from 27.6% to 34.8% (MRI), and from 61.1% to 78.6% (cUS) (p<0.001).The NPV of no items outside the normal range in the Dubowitz neurologic examination combinated with normal findings or minor brain pathologies remained the same, 99.4% (MRI), and 97.0% (cUS) (p=0.03).

Table 8. The characteristics of the children with cerebral palsy (CP) (n=14).

Characteristics	Data
Neonatal characteristics	
Birth weight, mean (SD) [minimum, maximum], g	976 (296) [560, 1500]
Gestational age at birth (SD) [minimum, maximum]	$27^{5/7}$ ($3^{2/7}$) [$23^{3/7}$, $35^{1/7}$]
Males, n (%)	8 (57)
Females, n (%)	6 (43)
Cesarean section, n (%)	8 (57)
Small for gestational age, n (%)	5 (36)
Bronchopulmonary dysplasia, n (%)	4 (29)
Sepsis, n (%)	5 (36)
Necrotizing enterocolitis, surgical, n (%)	3 (21)
Retinopathy of prematurity, laser treated, n (%)	0 (0)
CP type, n (%)	
Spastic diplegia	7 (50)
Spastic hemiplegia	4 (29)
Spastic triplegia	2 (14)
Dystonic	1 (7)
Gross Motor Function Classification System (GMFCS), n (%)[a]	
I (walks without restrictions)	2 (15)
II (walks without assistive device)	6 (46)
III (walks with assistive mobility devices)	3 (23)
IV (self-mobility with limitations)	2 (15)
V (self-mobility severely limited)	0 (0)
The number of deviant items in the Dubowitz neurologic examination at equivalent age, mean (SD) [minimum, maximum]	4.1 (3.1) [1.0, 13.0]
Total score of the Hammersmith Infant Neurological Examination at 2 years of corrected age, mean (SD) [minimum, maximum]	54.3 (10.3) [38.0, 74.0]
The Full Scale Intelligence Quotient at 5 years of chronological age, mean (SD [minimum, maximum][b]	82.7 (32.7) [39.0, 120.0]
Percentile for the total test score of the Movement Assessment Battery for Children-2, mean (SD)[minimum, maximum[c]	6 (14) [0,37]

[a]Data missing for 1 (7%) infant.
[b]Data missing for 8 (57%) children.
[c]Data missing for 6 (43%) children.

5.6 Neurodevelopmental impairment

One hundred and seventy-eight of 217 (82%) WPPSI-R assessments were completed at 5 years of chronological age. There were 4 (2%) children who were too severely handicapped to be assessed. They were included in the analysis as having a significant cognitive impairment (FSIQ<70). Of all the infants, 31 (17%) had FSIQ<85. The mean values of FSIQ according to structural brain MRI categories were as follows: 104.2 (SD 15.0, [63.0, 140.0]) in children with normal findings (n=100, 56%), 102.4 (SD 15.6, [70.0, 128.0]) in children with one or more minor pathologies (n=35, 20%), 94.6 (SD 18.8, [42.0, 133.0]) in children with one major pathology (n=29, 16%), and 86.8 (SD 23.4, [39.0, 120.0]) in children with several major pathologies (n=14, 8%). The NPV for normal cognitive outcome (FSIQ≥85) were 92.0% (normal findings in MRI), 85.7% (minor brain pathologies in MRI), 90.4% (normal findings or minor brain pathologies in MRI) and 85.4% (cUS) (p=0.008). The PPV of major brain pathologies for cognitive impairment (FSIQ<85) were 35.5% (one major pathology in MRI), 43.8% (several major pathologies in MRI), 38.3% (one or more major pathologies in MRI) and 54.5% (cUS) (p=0.23).

A total of 41 (22%) children had NDI including NSI at 2 years of corrected age and/or cognitive impairment at 5 years of age. Twenty-seven (66%) of them had major pathologies in brain MRI and 13 (32%) in cUS (Table 3). The NPV for developmental outcome without NDI were 91.0% (normal findings in MRI), 85.7% (minor brain pathologies in MRI), 89.6% (normal findings or minor brain pathologies in MRI) and 83.6% (cUS) (p=0.003).The PPV of major brain pathologies for NDI were 38.7% (one major pathology in MRI), 75.0% (several major pathologies in MRI), 52.9% (one or more major pathologies in MRI), and 86.7% (cUS) (p=0.001).

5.7 Touwen examination

The neonatal characteristics of the 98 preterm infants examined at the age of 11 years are shown in Table 2. A total of 97 (99%) children were examined by the Touwen examination. One child with CP was not examined at the age of 11 years. Of all infants, 96 (98%) were examined by brain MRI at term age. All the background characteristics (Table 2) and structural brain MRI findings of the study infants and drop-outs (n=23) were compared. The only statistically significant difference was that the children lost to follow-up were born by cesarean section more often compared to the study infants (p=0.01).

The mean age at the time of examination was 11 years and 2 months (SD 4 months, [10 years and 6 months, 11 years and 9 months]). Of all children, 41 (42%) had sMND, 11 (11%) had cMND, and eight (8%) had CP. Three of the 11 (27%) children with cMND

had major pathologies in brain MRI and none in cUS (Table 3). The NPV of normal findings or minor brain pathologies for developmental outcome without cMND were 89.6% (MRI) and 87.1% (cUS) (p=0.17). The PPV of major brain pathologies for cMND were 23.1% (MRI) and 0.0% (cUS) (p=0.07).

Decreased volume of cerebellum increased the risk for sMND as shown in Table 9. Decreased volumes of total brain tissue, frontal lobes, basal ganglia and thalami, and cerebellum increased the risk for cMND or CP.

Table 9. The associations between brain volumetric findings at term age, simple minor neurological dysfunction (sMND), complex minor neurological dysfunction (cMND) or cerebral palsy (CP), and the Movement Assessment Battery for Children-2 (Movement ABC-2) total scores in very preterm born children at 11 years of age (modified from Studies III and IV).

	sMND OR (95% CI)	p	**cMND or CP** OR (95% CI)	p	**Movement ABC-2** b (95% CI)	p
Total brain tissue	0.99 (0.98-1.00)	0.18	0.99 (0.97-1.00)	0.04	0.20 (0.10-0.30)	<0.001
Ventricles	0.50 (0.23-1.06)	0.08	0.59 (0.23-1.50)	0.27	-0.23 (-6.80-6.33)	0.94
Cerebrum	0.99 (0.98-1.01)	0.28	0.99 (0.97-1.00)	0.07	0.20 (0.10-0.30)	<0.001
Frontal lobes	0.98 (0.96-1.00)	0.10	0.96 (0.93-0.99)	0.01	0.32 (0.12-0.51)	0.002
Basal ganglia and thalami	0.93 (0.84-1.02)	0.12	0.87 (0.76-0.98)	0.03	1.65 (0.85-2.45)	<0.001
Cerebellum	0.89 (0.79-0.99)	0.04	0.83 (0.71-0.96)	0.02	1.16 (0.21-2.11)	0.02
Brain stem	0.89 (0.75-1.05)	0.17	0.82 (0.64-1.03)	0.10	2.13 (0.53-3.73)	0.01

Considering sMND and cMND or CP, the analyses were adjusted for structural brain magnetic resonance imaging (MRI) categories. Considering the total scores of the Movement ABC-2, the analysis was adjusted for gestational age, small for gestational age status, gender, and MRI categories.

The very preterm born children had findings outside the normal range in different domains in the Touwen examination as follows: posture and muscle tone (n=16, 17%), reflexes (n=28, 29%), involuntary movements (n=1, 1%), coordination and balance (n= 93, 96%), fine manipulation (n=73, 75%), associated movements (n=86, 89%), sensory function (n=6, 6%), and cranial nerve function (n=10, 10%). The proportions of dysfunctional domains were: posture and muscle tone (n=7, 7%), reflexes (n=24, 25%),

involuntary movements (n=1, 1%), coordination and balance (n= 34, 35%), fine manipulation (n=23, 24%), associated movements (n=34, 35%), sensory function (n=0, 0%), and cranial nerve function (n=10, 10%).

The mean head circumference (cm), weight (kg) and length (cm) of the children were 53.3 (SD 1.8, [48.9, 59.1]), 36.3 (SD 8.1, [22.4, 73.9]), and 144.4 (SD 7.6, [125.5, 164.1]), respectively. The hand preference was right in 86 (88%) children, left in eight (8%) children, and ambidextrous in three (3%) children. Girls performed marginally better in the Touwen examination than boys (p=0.04). There was no statistically significant univariate association between gestational age or SGA status and the results of the Touwen examination.

5.8 Movement Assessment Battery for Children-2

All the children without CP (n=90) were examined using the Movement ABC-2 at 11 years of age. Seven (88%) of the eight children with CP could be examined. The Movement ABC-2 was performed during the same follow-up visit as the Touwen examination. The mean percentile for the total test score was 36 (SD 23, [0, 84]). The mean percentiles for domains of manual dexterity, aiming and catching, and balance were 36 (SD 23, [0, 91]), 32 (SD 26, [1, 95]), and 52 (SD 32, [0, 91]), respectively. The distribution of the three domains and the total test scores is shown in Figure 4.

There were 82 (84%) children with normal motor outcome, 79 (96%) of which had a total test score >67 (>15th percentile), and 3 (4%) had a total test score of 57-67 (>5th-15th percentile) in the Movement ABC-2. In these children, the mean percentile for the total test score was 42 (SD 20, [9, 84]). The mean percentiles for domains of manual dexterity, aiming and catching, and balance were 41 (SD 22, [2, 91], 37 (SD26, [1, 95]), and 59 (SD 27, [9, 91]). Fifty-two (63%) of the children with normal motor outcome participated regularly in after-school sporting activities. Thirty-eight (46%) of the children with normal motor outcome had no MND, while 36 (44%) had sMND and 8 (10%) had cMND according to the concurrent Touwen examination.

There were 8 (8%) children having scores ≤56 (≤5th percentile) in the Movement ABC-2 who were determined to have DCD. The mean percentile for the total test score in these children was 4 (SD 2, [1,5]). The mean percentiles for domains of manual dexterity, aiming and catching, and balance were 11 (SD 16, [1,50]), 10 (SD 10, [1,25]), and 11 (SD 12, [1,37]). Two (25%) of the children with DCD participated regularly in after-school sporting activities. All the children with DCD had at least sMND according to the concurrent Touwen examination: five (63%) had sMND and three (38%) had cMND. Seven of the eight (88%) children with DCD were born extremely preterm and/or with ELBW, representing 16% of all (n=45) extremely preterm and/or ELBW children without CP examined by the Movement ABC-2 at the age of 11 years.

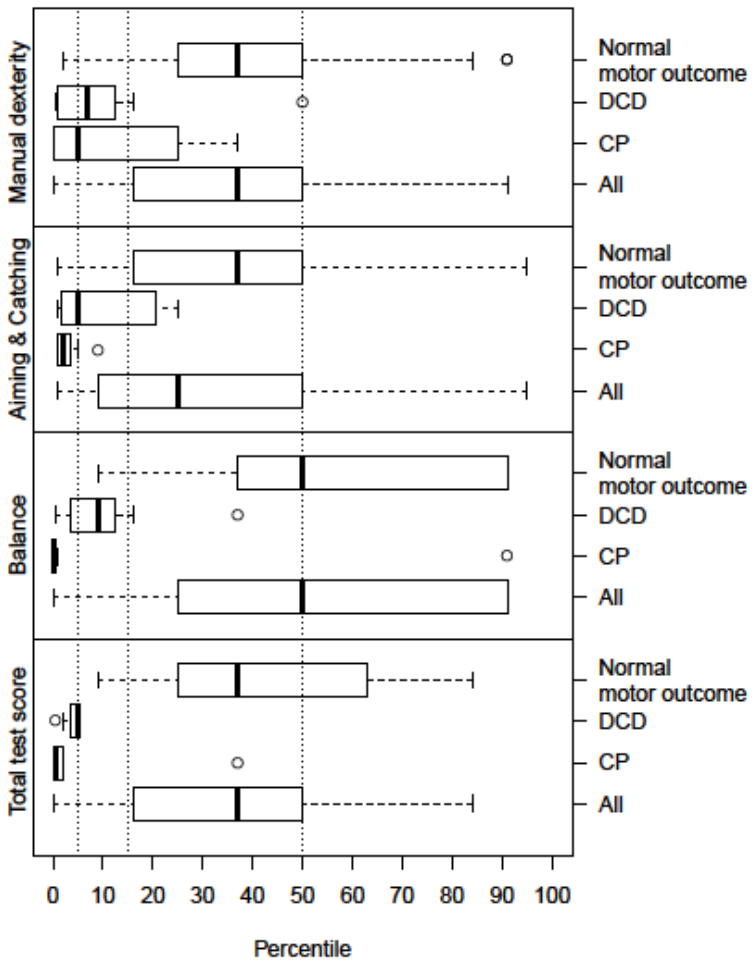


Figure 4. The boxplot of the percentiles for the three domains and total test scores of the Movement Assessment Battery for Children-2 examinations in very preterm born children with normal motor outcome (n=82), developmental coordination disorder (DCD) (n=8), cerebral palsy (CP) (n=8), and in all children (n=98). Vertical dashed lines of the percentiles 5, 15, and 50 show the cut-offs of significant movement difficulty, risk of having a movement difficulty, and the mean of the norm population, respectively.

There were 8 (8%) children with CP. The mean percentile for the total test score in these children was 6 (SD 14, [0,37]). The mean percentiles for domains of manual dexterity, aiming and catching, and balance were 13 (SD 15, [0,37]), 3 (SD 3, [1,9]), and 13 (SD 34, [0,91]), respectively. One (14%) of the children with CP participated regularly in after-school sporting activities.

Brain MRI explained 17.8% of the variation in the Movement ABC-2 total scores ($p<0.001$) in all children and 7.8% in children without CP ($p=0.03$). Major brain pathologies on MRI reduced the Movement ABC-2 total scores compared to normal

findings (b=-3.5 for minor pathologies and b=-25.2 for major pathologies in all children, and b=-3.6 for minor pathologies and b=-17.9 for major pathologies in children without CP, respectively). Three (38%) of the eight children with DCD had major pathologies in brain MRI and none in cUS (Table 3). The NPV of normal findings or minor brain pathologies for normal motor outcome were 93.5% (MRI) and 90.6% (cUS) (p=0.13). The PPV of major brain pathologies for DCD were 23.1% (MRI) and 0.0% (cUS) (p=0.07).

Decreased volumes in all brain regions associated with lower Movement ABC-2 total scores as shown in Table 9. The associations remained statistically significant when excluding the children with CP. Of the other background characteristics shown in Table 2, gestational age (r=0.26, p=0.01), birth weight (r=0.25, p=0.01), and BPD (R^2=0.07, p=0.009) were significantly associated with poorer Movement ABC-2 total scores.

The mean percentile for the total test score in the concurrent Movement ABC-2 examination was 47 (SD 19, [16, 84]) in children without MND, 35 (SD 21, [2, 75]) in children with sMND, and 24 (SD 26, [1, 84]) in children with cMND. A statistically significant correlation was found between the results of the Touwen examination and the Movement ABC-2 (r=-0.37, p<0.001).

The ROC-curve of the predictive value of the Movement ABC-2 for the results of the concurrent Touwen examination was done (Figure 5), suggesting that the cut-off of 16 percentile would be the most accurate to include both high sensitivity (0.73) and specificity (0.82).

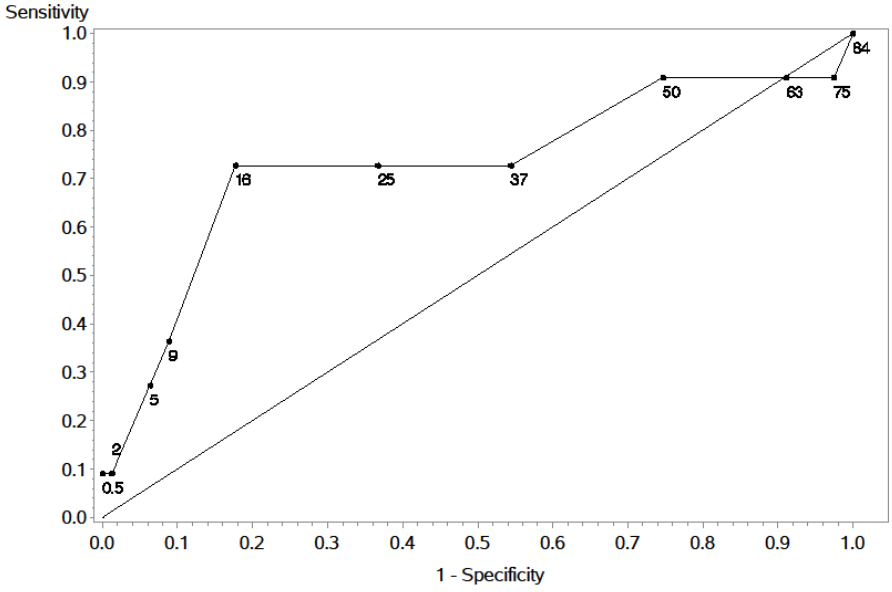


Figure 5. The ROC-curve of the predictive value of the Movement Assessment Battery for Children-2 for the results of the concurrent Touwen examination of very preterm born children at the age of 11 years.

5.9 Developmental Coordination Disorder Questionnaire 2007

All parents were interviewed according to the DCDQ'07 when the children (n=98) were 11 years old. In children with normal motor outcome, the mean total score of the parental questionnaire DCDQ'07 was 67 (SD 7, [46, 75]), and 7 (9%) children had a total score ≤57 indicating DCD. In children with DCD, the mean total score of the DCDQ'07 was 52 (SD 14, [35, 74]), and 4 (50%) had a total score ≤57. In the children with CP, the mean total score of the DCDQ'07 was 49 (SD 10, [37, 68]), and 6 (86%) had a total score ≤57. The DCDQ'07 correlated with the Movement ABC-2 total scores ($r=0.43$, $p<0.001$).

6 DISCUSSION

This thesis describes for the first time the neuromotor trajectory and the long-term neurodevelopment of very preterm infants up to 11 years of age with the predictive value of neonatal brain imaging and structured neurological examinations during the prospective follow-up. This information was derived from a regional population of very preterm infants with a high coverage of both neonatal brain imaging and examinations during the follow-up.

6.1 The clinical value of neonatal brain imaging in predicting long-term neurodevelopment in very preterm infants

6.1.1 Magnetic resonance imaging and cranial ultrasound

This thesis is unique in describing the neonatal brain imaging findings of very preterm infants including both MRI and cUS with regard to all the follow-up examinations performed from term to 11 years of age. Up-to-date literature suggests that MRI at term age is superior to cUS being currently the best imaging tool available in predicting long-term neurodevelopment (Kwon et al. 2014, Plaisier et al. 2014). According to the results of the present thesis, brain MRI at term age had the highest NPVs for all outcome measures (the difference was statistically significant for all but 11-year outcome), whereas serial neonatal cUS had better PPV regarding outcomes at 2 and 5 years of age (the difference was statistically significant only considering NSI at 2 years of corrected age). The fact that MRI is more sensitive than cUS in detecting even small brain lesions (Kwon et al. 2014, Back 2015) was also shown in this thesis, as significantly more major pathologies were found by brain MRI (27%) compared to cUS (8%). This may explain the lower PPV of brain MRI found in comparison with cUS at early ages when less severe neuromotor impairments have not manifested yet.

Brain MRI was shown to be better than cUS in predicting abnormal neuromotor outcome at 11 years of age, even though the difference was not statistically significant. This finding suggests that cUS may not be able to predict long-term neuromotor outcome in children who escape CP, but have impaired neuromotor development. On the other hand, diffuse WM injuries can be visualized by MRI (Kwon et al. 2014, Back 2015), which explains its better PPV in predicting non-optimal long-term motor development. These results should be interpreted with caution due to the small number of children with neuromotor impairment. A Norwegian cohort study of extremely preterm children did not, either, find major cUS pathologies predictive for the Movement ABC scores at the age of 5 years (Leversen et al. 2011). The findings from an Australian cohort of very

preterm born children are consistent with the present results showing an association between WM abnormalities in MRI and motor impairment at 5 years of age (Spittle et al. 2011). There are no previous studies reporting the predictive value of neonatal brain imaging findings for neuromotor development at 11 years of age. In addition to shorter follow-up times, previous research findings are difficult to compare because of inconsistency in brain imaging methods and classifications of imaging findings, in selection of populations and inclusion criteria, and in assessment methods used to determine motor outcome.

The highest PPVs for both imaging modalities (MRI 53% and cUS 87%) were attained for NDI at 5 years of chronological age, which is understandable as it includes, in addition to cognitive impairment, also all the major NSIs. The highest NPVs (MRI 99% and cUS 97%) were attained for CP, whereas ruling out less severe neuromotor impairments was found to be more difficult. The main difference between brain MRI and cUS was found in the prediction of normal cognitive outcome at 5 years of age: there were statistically significantly more false negative findings according to cUS than brain MRI. According to previous knowledge, the predictive validity of cUS findings has been thought to be better considering CP than cognitive development (Hintz, O'Shea 2008). However, the variation within reported predictive values of MRI and cUS for CP is large due to different classifications of brain imaging findings (Kwon et al. 2014, de Vries et al. 2011). A recent systematic review has pointed out that major MRI pathologies have been shown to be associated with worse cognitive performance until 9 years of age (Plaisier et al. 2014).

Current practice in neonatal care in Turku University Hospital includes both brain MRI at term age and serial cUS. The results of the present thesis showing the different strengths and weaknesses of both imaging modalities confirm that brain MRI and cUS complement each other (de Vries, Cowan 2007, de Vries et al. 2011) supporting also the routine use of brain MRI at term age (Latal 2009, Smyser, Kidokoro & Inder 2012, Plaisier et al. 2014). However, it should be emphasized that brain imaging findings never equal brain function. Therefore, even though the brain MRI and cUS aid clinicians in identifying infants with increased risk for later developmental problems, good functional outcome can be achieved despite major lesions. Structured neurological examinations up to 2 years of corrected age are needed at least in the follow-up of the very preterm infants with major brain pathologies, because of the increased risk for NSI.

6.1.2 The predictive value of the Dubowitz neurologic examination at term age combined with concurrent brain imaging

Both brain MRI at term age and serial neonatal cUS were excellent in predicting normal neurosensory development at 2 years of corrected age, cognitive development at 5 years of chronological age, and neuromotor development at 11 years of age. The high NPV of

these examinations is in line with previous studies (Kwon et al. 2014) and this information is likely to be relieving for families and clinicians even though this thesis did not evaluate this important point of view any further. Nevertheless, due to the unique plasticity of the neonatal brain, it remains a challenge to get a high PPV, because many neurological deviations normalize during the development in early infancy. Moreover, as neurodevelopment has multifactorial background, environmental factors become more important over time considering cognitive development. It is likely that this holds true also considering neuromotor outcome, because it is difficult to isolate cognitive outcomes from neuromotor impairment and NSI (Linsell et al. 2015).

The present thesis is the first one to study the combined predictive value of a structured neurological examination and concurrent brain MRI or cUS in very preterm infants. The Dubowitz neurologic examination statistically significantly improved the prediction of NSI at 2 years of corrected age: the PPV of MRI improved from 28% to 35%, and the PPV of cUS from 61% to 79%, respectively. Similarly, the integrated use of GMs and brain MRI has been shown to improve the predictive specificity for CP from 98% to 100% (Skiold et al. 2013). In conclusion, a combination of clinical assessment and brain imaging methods provide most accurate predictive value for abnormal outcome.

The prediction of abnormal outcome can also be improved by more accurate classification of brain imaging findings. When predicting later outcome by using one or several major pathologies in brain MRI as separate categories, the PPV was shown to improve for CP, cognitive impairment, and NDI from 6% to 44%, from 36% to 44%, and from 39% to 75%, respectively. Different classification systems have been proposed and used to interpret MRI data. The PIPARI Study has systematically used the composite classification system presented in this thesis providing a classification system that can be employed in different clinical settings.

6.1.3 Regional brain volumes

Current literature concerning associations between neonatal brain volumes and long-term neurodevelopment in preterm infants is scarce. Decreased regional brain volumes have previously been shown to associate with worse neurodevelopment in preterm infants at 2 and 5 years of age in the PIPARI Study cohort (Lind et al. 2010, Lind et al. 2011b). The present thesis showed that decreased brain volumes of total brain tissue, frontal lobes, basal ganglia and thalami, and cerebellum increased the risk for cMND or CP, and decreased volumes of all regional brain volumes associated with poorer motor outcome still at 11 years of age even when excluding children with CP. In contrast, a recent study with a similar sample size did not find correlations between automatically segmented brain volumes at term age and the Movement ABC-2 scores at age 5.5 years (Keunen et al. 2016). The difference might be explained by the fact that the present thesis included more children with major brain pathologies and also more children with CP. The follow-

up rate was also higher in this thesis. It is possible that motor problems manifest more clearly with increasing age. In addition, the brain volumes were measured manually in the present thesis, because there was no standardized volumetric measuring method for term infant brain in the beginning of the study period. Considering cMND, this thesis is the first one to show the associations between reduced volumes of total brain tissue, frontal lobes, basal ganglia and thalami, and cerebellum and poor outcome according to the Touwen examination at the age of 11 years.

The lack of normative data for different regional brain volumes at term age limits the clinical use of brain volume measurements in predicting long-term neuromotor outcome in very preterm infants. Therefore, validation of cut-off values for brain volumes in large normative samples is required to implement this knowledge into clinical practice. In addition, the limitation of automatic brain volumetric measurements is the possible presence of major brain pathologies like hemorrhages, which can cause inaccuracy in the results. The automatic measurements are based on signal intensity differences of for example gray and white matter. Brain pathologies can cause signal intensity changes, which are difficult for the automatic method to classify.

In conclusion, neither brain MRI nor cUS was shown to be an accurate predictor of long-term neurodevelopmental outcome, but combined with structured neurological examinations they provide the best available tools to aid clinicians in predicting the neurodevelopment of very preterm infants.

6.2 The role of sequential and structured neurological examinations in the follow-up of very preterm infants

6.2.1 Dubowitz neurologic examination at term age

Only a quarter of the very preterm infants had no items outside the normal preterm range in the Dubowitz neurologic examination at term age, which strengthens previous knowledge of a wide range of findings in very preterm infants (Mercuri et al. 2003) and supports the use of preterm norms (Ricci et al. 2008). The Dubowitz neurologic examination at term age has previously been shown to relate to concurrent cerebral abnormalities in MRI without using the preterm norms of the Dubowitz neurologic examination (Brown et al. 2009). In contrast, neither MRI nor cUS could differentiate the infants according to the results of the Dubowitz neurologic examination in the present thesis. However, the preterm norms (Ricci et al. 2008) used were shown to be valid as all the children with CP or NSI at 2 years of corrected age had at least one item outside the normal range in the term age examination. There was no single item that was found to associate with abnormal outcome alone; instead, a correlation between deviations in subscales of tone patterns, posture and tone, and behavior and major impairment was

found. This knowledge can be relevant in the clinical follow-up in identifying the very preterm infants with increased risk for later major impairments.

The predictive values of the Dubowitz neurologic examination at term age for the HINE, and neurosensory development at 2 years of corrected age were NPV of 89% and 100%, and PPV of 17% and 10%, respectively. Moreover, the results of the Dubowitz neurologic examination were associated with neurological performance at 2 and still at 11 years of age, which may be helpful in clinical follow-up as well. Of all the domains of the Dubowitz neurologic examination, the domain of orientation and behavior associated with the neurological performance at 11 years of age. A systematic review has previously described the clinimetric properties of nine different neuromotor assessment tools for preterm infants during the first year of life (Spittle, Doyle & Boyd 2008). In the first months of life, the predictive validity was shown to be greatest for GMs considering CP at 2 years of age. However, this systematic review did not include the Dubowitz neurologic examination or the Amiel-Tison Neurologic Assessment, which at term age has previously shown to predict a lower risk of suboptimal neuromotor status at 2 years of corrected age (Leroux et al. 2013). These results showing a good ability of a structured neurological examination to predict normal outcome are in line with the findings of the present thesis, which is the first to show the predictive value of the Dubowitz neurologic examination at term age for neuromotor development in very preterm born children at 2 years of age. Moreover, the term age findings were found to associate with neuromotor outcome still at 11 years of age.

6.2.2 Hammersmith Infant Neurological Examination at 2 years of corrected age

A wide range of neurological findings was found in very preterm born children still at 2 years of corrected age assessed by the HINE. Compared to term age examination, the proportion of abnormal findings was smaller, yet there are no preterm norms for the HINE to enable comparison of these results. At term age, neurological performance is more variable as it is affected by behavioral state. At 2 years of age, the variation of the neurological performance has become narrower enabling more accurate classification of neurological findings.

A significant correlation was found between the results of the HINE at 2 years of corrected age and the Touwen examination at 11 years of age. The NPV and PPV of the HINE for cMND were 89% and 22%. There are no previous studies reporting the predictive value of a structured neurological examination such as the HINE at 2 years of corrected age for later neuromotor outcome. Previous results from the Norwegian cohort have shown that a motor assessement at 2 years of corrected age in children without major impairments predicted DCD at the age of 5 years with NPV of 84%, and PPV of 36% (Leversen et al. 2012). However, motor delay at 2 years of corrected age was based on a pediatric assessment by addressing eight milestone abilities, and no structured

neurological examination was performed at either age-point making comparison to these results difficult. This thesis is first to provide information about the neuromotor trajectories of individual very preterm born children. Despite the correlation between the results of the HINE and the Touwen examination, there was no stability of neuromotor outcome between 2 and 11 years of age considering individual children, as only one of the eight children with DCD and two of the eleven children with cMND had poor performance according to the HINE already at 2 years of corrected age.

Of all the domains of the HINE, the domains of posture, movements, tone, and reflexes and reactions associated with the long-term neuromotor development in the group of all children, while the domain of posture associated with the long-term neuromotor development in children without CP. The HINE has been shown to give additional information about neuromotor development in children with CP (Romeo et al. 2008a). The results of this thesis showed the associations between the results of the HINE and long-term neuromotor development also in children without CP. This new information may be of clinical significance helping to identify children without CP with higher risk for later neuromotor difficulties.

In conclusion, the clinical role of sequential use of the Dubowitz neurologic examination and the HINE is to provide a structured neurological follow-up method for very preterm infants, which is easy to administer, to score, and to repeat in order to see which of the abnormal findings normalize, remain stable or worsen. The results of this thesis provide new information about the predictive value of these structured neurological examinations. Normal results from structured neurological examinations both at term age and at 2 years of corrected age were shown to strongly predict normal neuromotor development up to 11 years of age. The NPV of structured neurological examinations was shown to be as good as that of neonatal brain imaging considering neuromotor outcome. Better PPV, however, was achieved with neonatal brain imaging findings, but even the PPV improved statistically significantly when the findings were combined with structured neurological examination at term. The significant proportion of normally developing children with either major MRI or cUS pathologies also supports the sequential use of functional measures like the Dubowitz neurologic examination and the HINE during the longitudinal follow-up of very preterm infants. Furthermore, it should be noted that all units do not have the resources for routine neonatal brain imaging including MRI. This emphasizes the role of sequential structured neurological examinations in the clinical follow-up of very preterm infants.

6.3 Long-term neuromotor development of very preterm born children

Literature concerning long-term neuromotor outcome in very preterm born children often refers only to CP. However, less severe neuromotor difficulties such as cMND and DCD are important to take into account as motor impairments affecting everyday functioning.

6.3.1 Minor neurological dysfunction at 11 years of age

This thesis showed a high proportion of sMND (39%) at the age of 11 years, which is in line with the prevalence of sMND (41%) in the French cohort at the age of 5 years (Arnaud et al. 2007). In contrast, a significantly higher prevalence of cMND (11%) was found in the present thesis using the complete protocol of the modified Touwen examination compared to 3% in the EPIPAGE cohort using the short version of the neurological examination. This disagreement can partly be explained by the use of different versions of the Touwen examination, as its modified short form is not validated and may unaccurately indicate sMND and cMND (Hadders-Algra 2010). The children lost to follow-up are unlikely to have contributed to this difference as the only statistically significant difference compared to the study population was the mode of delivery. Another study has reported a significantly higher prevalence of cMND when using a full protocol of the Touwen examination at school age (39%) and still at early adulthood (33%) in very preterm infants born in 1977 and 1978 in the Netherlands (Schothorst, Swaab-Barneveld & van Engeland 2007). This difference can be explained by less advanced perinatal and neonatal care practices at that time. A more recent study of preterm infants born between 1992 and 1997 also in the Netherlands has shown a twofold prevalence of cMND (22%) at the age of 7 to 11 years (Bruggink et al. 2008) compared to the present findings.

It is possible that neurological assessments performed by one examiner (author Setänen) could have resulted in systematically biased results. However, re-evaluation of all unclear ratings from the video-recordings was performed together with an experienced child neurologist in order to ensure the reliability of the ratings, which reduced the risk of this kind of bias. The test-retest, inter-assessor or intra-assessor reliabilities were not studied, but have been previously reported to be good for the modified Touwen examination when applied in a relatively healthy population (Peters et al. 2008). Another possible explanation for the good neuromotor outcome of the very preterm infants described here is the intensive follow-up of the families participating with low attrition in the PIPARI Study, which itself provides a positive intervention and makes parents aware of the developmental risks of their children. Therefore, the parents may be more active in supporting the neuromotor development of their children, as is suggested by the fact that the majority of the very preterm born children had an after-school sporting activity.

The present thesis provided new information about the co-occurrence of neuromotor impairments in very preterm born children. Ninety percent of the children with normal motor outcome without DCD had normal neurological development or sMND. Less than 40% of children with DCD had cMND at the age of 11 years. This overlapping of DCD and cMND is less than in a previous study of children in mainstream or special education reporting that more than half of the children with DCD had also cMND at the age of 8 to 9 years (Peters, Maathuis & Hadders-Algra 2011). The real difference may be even greater as their study did not include very preterm born children.

6.3.2 Developmental coordination disorder at 11 years of age

The majority of very preterm born children performed within normal variation considering motor outcome at 11 years of age. The prevalence of DCD (9%) in this cohort of very preterm infants was significantly lower compared to previous studies (Roberts et al. 2011, Leversen et al. 2011, Blank et al. 2012, Ferrari et al. 2012, Zwicker et al. 2013, Husby et al. 2013). This difference may be due to differences in patient populations and variations in the age-point at the time of examination. When including only the extremely preterm or ELBW infants of the PIPARI cohort, the prevalence of DCD (16%) was similar to that in the comparable cohorts from Norway (Leversen et al. 2012) and Australia (Roberts et al. 2011).

A possible explanation for the good neuromotor outcome in very preterm born children described here is that more than half of the children with normal motor development participated regularly in organized sporting activities outside school, which potentially reinforces normal motor development. On the other hand, having regular after-school sporting activities may in itself indicate sufficient motor functioning for peer-group physical activities and potentially supports also social abilities. Sporting activities have been shown to associate with better quality of life (Gopinath et al. 2012). Only a quarter of the children with DCD had after-school sporting activities. This is in agreement with a previous study showing that fewer very preterm born children with motor impairment participated in organized after-school sports compared to those without motor impairment (Wocadlo, Rieger 2008).

Previous studies (Leversen et al. 2011, Blank et al. 2012, Zwicker et al. 2012, Zwicker et al. 2013) have found an association between gender and SGA status and motor outcome, which is in contrast with findings from this thesis. Nevertheless, also previous results of the PIPARI Study have demonstrated that SGA infants have similar developmental outcomes compared to other very preterm infants in this cohort (Maunu et al. 2011, Lind et al. 2011b, Leppanen et al. 2014). In addition to SGA status and gender, also gestational age and major brain pathology were included in regression analyses, as previous findings from PIPARI Study and current literature have suggested that these variables are

significant and prevalent risk factors for later neurodevelopmental problems (Munck et al. 2010, Linsell et al. 2015).

Parental ratings of the children's motor difficulties according to DCDQ'07 were found to detect half of the children with DCD, suggesting that parents have difficulties in estimating their children's motor abilities. These findings are in line with previous results of a moderate correlation found between the DCDQ and the Movement ABC in children receiving mainstream or special education at school age (Peters, Maathuis & Hadders-Algra 2011). The results of this thesis are also similar to findings from an Australian cohort of ELBW born children at the age of 8 years using a different questionnaire (Roberts et al. 2011), which highlights the use of parental questionnaires as an assistive tool beside clinical examination in detecting DCD (Blank et al. 2012).

Reliable statistical analysis considering predictive factors to differentiate the children with DCD and CP was not possible due to the small number of children having these impairments. However, children with DCD seemed to be born with lower gestational age and with lower birth weight than children with CP. Considering neonatal brain imaging findings, the majority of children with CP had major pathologies in the structural brain MRI, whereas of the children with DCD, fewer had major pathologies compared to children with CP. Furthermore, none of the children with CP had normal findings in the neonatal cUS, whereas none of the children with DCD had major pathologies. According to volumetric findings, children with CP had significantly larger ventricles than children with DCD. More research based on larger groups is still needed in order to differentiate the mechanisms for neuromotor impairments more clearly (Spittle, Orton 2014).

6.4 Strengths and limitations

The strengths of this thesis include the use of a prospective design, examinations being carried out at several age-points with a diverse range of outcomes and without knowledge of neonatal brain imaging findings, and a low attrition during the remarkably long follow-up period from birth to 11 years of age. Furthermore, there was very little variation in the age of the participants at the time of any of the examinations. The high follow-up rates of 93% at 2 years of corrected age, 84% at 5 years of chronological age and 81% still at the age of 11 years were greater than usual in studies with such a long follow-up time. Moreover, the drop-outs were not found to significantly differ from the study infants.

In addition to the strengths, certain limitations should also be noted. A weakness of this thesis is the lack of a control group, which would have required considerably more resources. A possible limitation is also that the cut-off scores for the HINE at 2 years of corrected age were defined according to this cohort, because there are no norms for preterm children. On the other hand, these data could be used in the future as a reference for very preterm infants. Another possible technical limitation is the MRI equipment

(0.23-T) used in the beginning of this study and its upgrading (1.5-T) during the follow-up. However, the incidence of brain lesions did not increase after the MRI equipment upgrading, which supports comparability in the study population. The lack of normative data for different regional brain volumes at term age makes comparisons to other studies and clinical implementations challenging. In addition, T2-weighted images were obtained, but they were not used for the volume measurements, as there was a gap in the T2-weighted images between slices. Consequently, the continuous T1-weighted images were used instead. It might be noted that the slice thickness on the T1-weighted images was rather thick (5mm). This, however, allowed sufficient signal to noise ratio for interpretation. It is possible that partial volume effect may have caused some error on the volume measurements; however, the error would be similar in all infants. The reliability of the volume measurements was ensured by repeated volume measurements by another neuroradiologist.

The reliability of the neurological examinations at term age and at 2 years of corrected age was ensured by experienced specialists, who trained and supervised the use of the Dubowitz neurologic examination and the HINE. A final major strength of this thesis is that all the examinations of the children at the age of 11 years were performed using the latest and complete protocols of the assessment methods (the Touwen examination, the Movement ABC-2 and the DCDQ'07) by the author (Setänen). Moreover, the results of the DCDQ'07 were only used to support the results of the MABC-2 as the DCDQ'07 is not designed to be used alone to identify DCD. Instead, the diagnosis also requires valid clinical measures (Wilson et al. 2009). All the examinations when the children were 11 years old were video-recorded and re-evaluated together with an experienced child neurologist to ensure the reliability of the ratings.

6.5 Future perspective and clinical implications

The Dubowitz neurologic examination has already been implemented in the follow-up protocol of very preterm infants in Turku University Hospital. The HINE is performed at 2 years of corrected age. The sequential use of these structured neurological examinations improves the quality of clinical follow-up. In general, there is no routine follow-up of very preterm born children after this age-point. Based on the results of this thesis, structured neurological examinations are recommended up to 2 years of corrected age at least in the follow-up of the very preterm infants with major brain pathologies, because of the increased risk for NSI. However, due to many other developmental risks associated with very preterm birth, a long-term follow-up up to early adolescence is recommended for all very preterm infants irrespective of brain imaging findings. However, this may be difficult to implicate due to the limited resources of health care systems. In Finland the follow-up occurs in child welfare clinics. Importantly, sporting activities are recommended to all very preterm born children in order to support neuromotor

development. The teachers of these children should also be informed of the neuromotor difficulties due to very preterm birth, thus enabling them to encourage the children to participate and attain their individually set goals.

This thesis indicated that the Movement ABC-2, which is easy to administer and score, is a good clinical tool for identification and follow-up of children with motor problems. Although the Touwen examination, which is primarily a tool for clinical practice, provides detailed information about the association between neurological conditions and preterm birth (Hadders-Algra 2010), its implementation to the follow-up protocol of very preterm infants is challenging. It is time-consuming when appropriately administered: the whole examination takes approximately 30 minutes, video-recording is recommended because of the many details of the examination, and the findings need to be entered to a computerized scoring system to obtain the final result of the child's neurological performance.

cUS often detects major brain pathologies, which may increase parents' anxiety. The combination of brain MRI and cUS, on the other hand, provides better definition of the nature of the brain lesion, which may be relieving for the parents. There are no studies of the effects of neonatal brain imaging on parental anxiety. However, false positives based on brain MRI can possibly cause additional stress (Doria, Arichi & Edwards 2014). Parental stress, in turn, has been shown to associate with children's developmental problems at 5 years of age in the PIPARI Study cohort (Huhtala et al. 2014). The highly important parental point of view of neonatal brain imaging needs to be evaluated. Even so, more research is needed also on interventions to optimize development in children with major brain lesions.

The development of new MRI techniques, such as diffusion tensor imaging, may further improve the prediction of abnormal neurodevelopment, helping to counsel parents and allocate early interventions (Schneider et al. 2014). For example, WM apparent diffusion coefficients have been shown to be associated with a worse developmental performance at 2 years of age, suggesting that it would be of prognostic value for neurodevelopmental outcome in preterm infants with no abnormalities on conventional brain MRI (Krishnan et al. 2007). Additionally, neonatal diffusion tensor imaging has been shown to predict CP in preterm infants with periventricular hemorrhagic infarctation (Roze et al. 2015). However, long-term follow-up data of these methods are still needed.

7 SUMMARY AND CONCLUSIONS

The following results considering the prediction of long-term neurodevelopment and neuromotor trajectories in very preterm born children up to 11 years of age were obtained in this thesis:

- Neonatal brain imaging (MRI or cUS) findings predicted neuromotor development up to 11 years of age.
- The Dubowitz neurologic examination at term age improved the predictive value of both neonatal MRI and cUS for 2-year neurosensory outcome.
- Decreased brain volumes at term age associated with poorer neuromotor performance at 11 years of age.
- Normal neurological performance at term age or at 2 years of corrected age, as well as lack of major brain pathology, predicted normal neurosensory and neuromotor performance (NPV from 87% to 100%) up to 11 years of age.
- Neuromotor development was within normal variation in the majority of the children at 11 years of age.

In conclusion, structural brain MRI at term age, serial neonatal cUS, and structured neurological examinations predicted long-term neurodevelopment in very preterm infants. Regional brain volumes provided a potential tool for identifying risk groups for later neuromotor impairment. Structured neurological examinations up to 2 years of corrected age are recommended at least in the follow-up of very preterm infants with major brain pathologies, because of the increased risk for NSI. However, due to many other developmental risks associated with very preterm birth, a long-term follow-up up to early adolescence is recommended for all very preterm infants irrespective of brain imaging findings. Although very preterm born children had an overall good neuromotor profile up to early adolescence, many of them continue to have more difficulties in neuromotor performance compared to their full-term born peers. Moreover, most of the very preterm born children had after-school sporting activities that may explain better performance; therefore, sporting activities could be recommended to all very preterm born children.

ACKNOWLEDGEMENTS

This thesis was a part of the PIPARI Study investigating long-term neurodevelopment and its prediction in very preterm infants. The work for this thesis began in 2011 and was carried out at the Department of Pediatric Neurology and Pediatrics, the University of Turku and Turku University Hospital. I sincerely thank everyone who has contributed and encouraged me to finish this thesis.

I owe my deepest gratitude to my supervisors Professor Leena Haataja, MD, and Professor Liisa Lehtonen, MD, for your endless time and support during these years. Leena, I admire your warm and calm approach to anything you do. I appreciate your wise advices that you have given for me in difficult situations in life. Liisa, your enthusiastic, tireless and hard-working attitude to research and clinical work is admirable. You have always been demanding and critical, but never forgetting compliments when the work is finished. I am grateful for having you as a research godmother for my children as well.

I am grateful to Docent Kai Eriksson, MD, and Professor Trond Markestad, MD, for reviewing this thesis with diligence and constructive comments. I also want to express my warm gratitude to Docent Aulikki Lano, MD, for your positive comments and help to improve the quality of this thesis. I am honored and grateful to Professor Lena Hellström-Westas, MD, for agreeing to be the opponent of this thesis. Tuuli Laaksonen, thank you for carefully checking the English of this thesis.

It has been a privilege to be a part of this wonderful multidisciplinary PIPARI Study group. I want to thank professor emeritus Matti Sillanpää for introducing me to the fascinating world of pediatric neurology and research by supervising my advanced studies. I also want to thank all my co-authors and co-researchers. Professor Riitta Parkkola, MD, thank you for your guidance and encouragement with difficult issues concerning neonatal brain imaging. Professor Päivi Rautava, MD, and Docent Helena Lapinleimu, MD, I am grateful that I have been able to share thoughts with you. My deepest gratitude is directed to Jaakko Matomäki. You have been invaluable not only as a statistician but also by offering your time whenever needed to solve almost any problem during this project. Mira Huhtala, I want to thank you for all your guidance, peer support and cheerful moments during these years.

I would like to warmly thank all the PIPARI families for your great commitment to this research project. You made this work possible. I also want to thank Satu Ekblad for your contribution in organizing all the appointments for clinical examinations of the very preterm born children. I thank also Päivi Tuomikoski-Koiranen for all your help especially with the stadiometer. Aija Lindholm, thank you for lending all the equipment for the motor examinations. Timo Tuovinen, thank you for your help in all the practical

things. I want to thank the Follow-up clinic of preterm infants, the Department of Otorhinolaryngology, and the Department of Gynecology and Obstetrics for the examination room in Turku University Hospital. I thank Annika, Karoliina, Katri, and Sanna, for your help in video-recording all the examinations, and Jere, for your amazing work for the educational video of the Touwen examination. Supervising your advanced studies has also taught me a lot. Thank you, Sanni Huhtala, for the fantastic performance in the educational video. Tuomo Lehtonen, MD, thank you for the smooth collaboration in performing all the ophthalmological examinations of these children. Finally, I am sincerely grateful for Anna Nyman, who carried out all the neuropsychological examinations. I admire your expertise as well as your support for me during these years. It has been such a pleasure to share everyday life in research work and all the clinical challenges with you.

The research project has provided many unforgettable visits: with Anna N. and Liisa to Stockholm, with Katri and Leena to Groningen, and with Anna A., Liisa, Mikael, Mira, Samuli, and Simo to San Diego.

I would like to express my special thanks to my mentor, Professor Olli Ruuskanen, MD, the head of the Research unit "Tutkari", the excellent working office for young researches provided by the Turku University Hospital Foundation. It has been a privilege to have your support, encouragement and inspiring conversations with our common sense of humor. I also wish to thank all my friends and colleagues in "Tutkari" for sharing all ups and downs during this project: Andreina, Anna E., Anna N., Anna P., Heidi, Jaakko, Johanna O., Johanna U., Katja, Kirsi, Kjell, Lauri, Liisa J., Marika, Miia, Mikael, Milla, Mira, Nora, Olli, Paula, Ulla, Sari, and Sergey. I can't imagine better way of doing research than in this great group of young and ambitious colleagues supporting and encouraging each other, not forgetting our joyful parties.

I wish to thank all my collegues and co-workers in Korpo hälsovårdcentral, Åbolands sjukhus, Turun Rokotetutkimusklinikka, and Department of Pediatric Neurology and Pediatrics in Turku University Hospital for your flexibility and understanding to this research project. Especially my tutor, Harri Arikka, MD, I want to express my warmest thanks for your endless support and guidance in clinical work.

The following foundations and institutions are acknowledged for their important financial support during this study: The Foundation for Paediatric Research, Arvo and Lea Ylppö Foundation and The Foundation of Märtha Donner, The Finnish Cultural Foundation, the Finnish Medical Society Duodecim, Turunmaa Duodecim Society, The Turku University Hospital Foundation, the EVO funding of the South-West Finland and Pirkanmaa Hospital Districts, and the Turku University Doctoral Programme of Clinical Investigation. I would also like to thank The National Graduate School of Clinical Investigation for offering excellent support both financially and in teaching.

I want to warmly thank my parents, Pia and Hannu, and my parents-in-law, Mirjami and Olli, for helping so much with our children enabling me to finish this thesis with irregular working hours. I am especially grateful for my grandmother, Pirkko, for always being such interested in my research work.

I would also like to thank my friends from choir, orchestra, football and organizational activities. These “after-school sporting activities” have always been very important for me giving new energy for work and everyday life with small children as well. I am thankful for my dear friends outside research life, especially Aakki, Afos, Anu, Helena, Inkku, Jenny, Juha, Katri K., Karo, and Lallu.

Dear Kerttu and Pirkka, there is nothing more important in my life than you. Your endless joy in everyday life would never let me forget that. Dear Johannes, I am deeply grateful for your support and encouragement during this challenging project. You have always believed in me and been such a wonderful dad and husband. I would not be here without you.

Turku, April 2016

REFERENCES

Amiel-Tison, C. 2002, "Update of the Amiel-Tison neurologic assessment for the term neonate or at 40 weeks corrected age", *Pediatric neurology,* vol. 27, no. 3, pp. 196-212.

Anderson, P.J. 2014, "Neuropsychological outcomes of children born very preterm", *Seminars in fetal & neonatal medicine,* vol. 19, no. 2, pp. 90-96.

Arnaud, C., Daubisse-Marliac, L., White-Koning, M., Pierrat, V., Larroque, B., Grandjean, H., Alberge, C., Marret, S., Burguet, A., Ancel, P.Y., Supernant, K. & Kaminski, M. 2007, "Prevalence and associated factors of minor neuromotor dysfunctions at age 5 years in prematurely born children: the EPIPAGE Study", *Archives of Pediatrics & Adolescent Medicine,* vol. 161, no. 11, pp. 1053-1061.

Back, S.A. 2015, "Brain Injury in the Preterm Infant: New Horizons for Pathogenesis and Prevention", *Pediatric neurology,* vol. 53, no. 3, pp. 185-192.

Bayley, N. 2005, *Bayley Scales of Infant and Toddler Development,* 3rd edition edn, Harcourt Assessment, San Antonio.

Bayley, N. 1969, *Bayley Scales of Infant Development Manual,* The Psychological Corporation, New York.

Blank, R., Smits-Engelsman, B., Polatajko, H., Wilson, P. & European Academy for Childhood Disability 2012, "European Academy for Childhood Disability (EACD): recommendations on the definition, diagnosis and intervention of developmental coordination disorder (long version)", *Developmental medicine and child neurology,* vol. 54, no. 1, pp. 54-93.

Blencowe, H., Cousens, S., Oestergaard, M.Z., Chou, D., Moller, A.B., Narwal, R., Adler, A., Vera Garcia, C., Rohde, S., Say, L. & Lawn, J.E. 2012, "National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications", *Lancet (London, England),* vol. 379, no. 9832, pp. 2162-2172.

Blencowe, H., Lee, A.C., Cousens, S., Bahalim, A., Narwal, R., Zhong, N., Chou, D., Say, L., Modi, N., Katz, J., Vos, T., Marlow, N. & Lawn, J.E. 2013, "Preterm birth-associated neurodevelopmental impairment estimates at regional and global levels for 2010", *Pediatric research,* vol. 74 Suppl 1, pp. 17-34.

Boardman, J.P., Craven, C., Valappil, S., Counsell, S.J., Dyet, L.E., Rueckert, D., Aljabar, P., Rutherford, M.A., Chew, A.T., Allsop, J.M., Cowan, F. & Edwards, A.D. 2010, "A common neonatal image phenotype predicts adverse neurodevelopmental outcome in children born preterm", *NeuroImage,* vol. 52, no. 2, pp. 409-414.

Bosanquet, M., Copeland, L., Ware, R. & Boyd, R. 2013, "A systematic review of tests to predict cerebral palsy in young children", *Developmental medicine and child neurology,* vol. 55, no. 5, pp. 418-426.

Brazelton, T.B. 1973, *Neonatal Behavioral Assessment Scale,* Lippincott, Philadelphia.

Brazelton, T.B. & Nugent, J.K. 1995, *Neonatal Behavioral Assessment Scale,* Cambridge, University Press, Cambridge.

Brown, N.C., Inder, T.E., Bear, M.J., Hunt, R.W., Anderson, P.J. & Doyle, L.W. 2009, "Neurobehavior at term and white and gray matter abnormalities in very preterm infants", *The Journal of pediatrics,* vol. 155, no. 1, pp. 32-8, 38.e1.

Bruggink, J.L., Einspieler, C., Butcher, P.R., Van Braeckel, K.N., Prechtl, H.F. & Bos, A.F. 2008, "The quality of the early motor repertoire in preterm infants predicts minor neurologic dysfunction at school age", *The Journal of pediatrics,* vol. 153, no. 1, pp. 32-39.

Constantinou, J.C., Adamson-Macedo, E.N., Mirmiran, M. & Fleisher, B.E. 2007, "Movement, imaging and neurobehavioral assessment as predictors of cerebral palsy in preterm infants", *Journal of perinatology : official journal of the California Perinatal Association,* vol. 27, no. 4, pp. 225-229.

Counsell, S.J., Rutherford, M.A., Cowan, F.M. & Edwards, A.D. 2003, "Magnetic resonance imaging of preterm brain injury", *Archives of disease in childhood.Fetal and neonatal edition,* vol. 88, no. 4, pp. F269-74.

Cowan, F.M. & de Vries, L.S. 2005, "The internal capsule in neonatal imaging", *Seminars in fetal & neonatal medicine,* vol. 10, no. 5, pp. 461-474.

Darsaklis, V., Snider, L.M., Majnemer, A. & Mazer, B. 2011, "Predictive validity of Prechtl's Method on the Qualitative Assessment of General Movements: a systematic review of the evidence", *Developmental medicine and child neurology,* vol. 53, no. 10, pp. 896-906.

de Kieviet, J.F., Piek, J.P., Aarnoudse-Moens, C.S. & Oosterlaan, J. 2009, "Motor development in very preterm and very low-birth-weight children from birth to adolescence: a meta-analysis", *JAMA : the*

journal of the American Medical Association, vol. 302, no. 20, pp. 2235-2242.

de Vries, L.S. & Cowan, F.M. 2007, "Should cranial MRI screening of preterm infants become routine?", *Nature clinical practice.Neurology,* vol. 3, no. 10, pp. 532-533.

de Vries, L.S., van Haastert, I.C., Benders, M.J. & Groenendaal, F. 2011, "Myth: cerebral palsy cannot be predicted by neonatal brain imaging", *Seminars in fetal & neonatal medicine,* vol. 16, no. 5, pp. 279-287.

Dewey, D., Creighton, D.E., Heath, J.A., Wilson, B.N., Anseeuw-Deeks, D., Crawford, S.G. & Sauve, R. 2011, "Assessment of developmental coordination disorder in children born with extremely low birth weights", *Developmental neuropsychology,* vol. 36, no. 1, pp. 42-56.

Doria, V., Arichi, T. & Edwards, D.A. 2014, "Magnetic resonance imaging of the preterm infant brain", *Current pediatric reviews,* vol. 10, no. 1, pp. 48-55.

Doyle, L.W., Casalaz, D. & Victorian Infant Collaborative Study Group 2001, "Outcome at 14 years of extremely low birthweight infants: a regional study", *Archives of disease in childhood.Fetal and neonatal edition,* vol. 85, no. 3, pp. F159-64.

Dubowitz, L.M., Levene, M.I., Morante, A., Palmer, P. & Dubowitz, V. 1981, "Neurologic signs in neonatal intraventricular hemorrhage: a correlation with real-time ultrasound", *The Journal of pediatrics,* vol. 99, no. 1, pp. 127-133.

Dubowitz, L.M.S., Dubowitz, V. & Mercuri, E. 1999, *The Neurological Assessment of the Preterm and Full-Term Newborn Infant,* 2nd edn, Mc Keith Press, London.

Dyet, L.E., Kennea, N., Counsell, S.J., Maalouf, E.F., Ajayi-Obe, M., Duggan, P.J., Harrison, M., Allsop, J.M., Hajnal, J., Herlihy, A.H., Edwards, B., Laroche, S., Cowan, F.M., Rutherford, M.A. & Edwards, A.D. 2006, "Natural history of brain lesions in extremely preterm infants studied with serial magnetic resonance imaging from birth and neurodevelopmental assessment", *Pediatrics,* vol. 118, no. 2, pp. 536-548.

Edwards, J., Berube, M., Erlandson, K., Haug, S., Johnstone, H., Meagher, M., Sarkodee-Adoo, S. & Zwicker, J.G. 2011, "Developmental coordination disorder in school-aged children born very preterm and/or at very low birth weight: a systematic review", *Journal of developmental and behavioral pediatrics : JDBP,* vol. 32, no. 9, pp. 678-687.

Einspieler, C., Marschik, P.B., Milioti, S., Nakajima, Y., Bos, A.F. & Prechtl, H.F. 2007, "Are abnormal fidgety movements an early marker for complex minor neurological dysfunction at puberty?", *Early human development,* vol. 83, no. 8, pp. 521-525.

Evensen, K.A., Vik, T., Helbostad, J., Indredavik, M.S., Kulseng, S. & Brubakk, A.M. 2004, "Motor skills in adolescents with low birth weight", *Archives of disease in childhood.Fetal and neonatal edition,* vol. 89, no. 5, pp. F451-5.

EXPRESS Group, Fellman, V., Hellstrom-Westas, L., Norman, M., Westgren, M., Kallen, K., Lagercrantz, H., Marsal, K., Serenius, F. & Wennergren, M. 2009, "One-year survival of extremely preterm infants after active perinatal care in Sweden", *Jama,* vol. 301, no. 21, pp. 2225-2233.

Fawke, J. 2007, "Neurological outcomes following preterm birth", *Seminars in fetal & neonatal medicine,* vol. 12, no. 5, pp. 374-382.

Ferrari, F., Gallo, C., Pugliese, M., Guidotti, I., Gavioli, S., Coccolini, E., Zagni, P., Della Casa, E., Rossi, C., Lugli, L., Todeschini, A., Ori, L. & Bertoncelli, N. 2012, "Preterm birth and developmental problems in the preschool age. Part I: minor motor problems", *The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians,* .

Frisone, M.F., Mercuri, E., Laroche, S., Foglia, C., Maalouf, E.F., Haataja, L., Cowan, F. & Dubowitz, L. 2002, "Prognostic value of the neurologic optimality score at 9 and 18 months in preterm infants born before 31 weeks' gestation", *The Journal of pediatrics,* vol. 140, no. 1, pp. 57-60.

Goldenberg, R.L., Culhane, J.F., Iams, J.D. & Romero, R. 2008, "Epidemiology and causes of preterm birth", *Lancet (London, England),* vol. 371, no. 9606, pp. 75-84.

Gopinath, B., Hardy, L.L., Baur, L.A., Burlutsky, G. & Mitchell, P. 2012, "Physical activity and sedentary behaviors and health-related quality of life in adolescents", *Pediatrics,* vol. 130, no. 1, pp. e167-74.

Haataja, L., Mercuri, E., Regev, R., Cowan, F., Rutherford, M., Dubowitz, V. & Dubowitz, L. 1999, "Optimality score for the neurologic examination of the infant at 12 and 18 months of age", *The Journal of pediatrics,* vol. 135, no. 2 Pt 1, pp. 153-161.

Hadders-Algra, M. 2010, Neurological Examination of the Child with Minor Neurological Dysfunction, Mac Keith Press, London.

Hadders-Algra, M. 2005, "The neuromotor examination of the preschool child and its prognostic significance", *Mental retardation and*

developmental disabilities research reviews, vol. 11, no. 3, pp. 180-188.

Hadders-Algra, M. 2002, "Two distinct forms of minor neurological dysfunction: perspectives emerging from a review of data of the Groningen Perinatal Project", *Developmental medicine and child neurology,* vol. 44, no. 8, pp. 561-571.

Harmon, H.M., Taylor, H.G., Minich, N., Wilson-Costello, D. & Hack, M. 2015, "Early school outcomes for extremely preterm infants with transient neurological abnormalities", *Developmental medicine and child neurology,* vol. 57, no. 9, pp. 865-871.

Hempel, M.S. 1993, "Neurological development during toddling age in normal children and children at risk of developmental disorders", *Early human development,* vol. 34, no. 1-2, pp. 47-57.

Henderson, S.E., Sugden, D.A. & Barnett, A.L. 2007, *Movement assessment battery for children (examiner's manual),* 2nd edn, Pearson Assessment, London.

Hintz, S.R., Barnes, P.D., Bulas, D., Slovis, T.L., Finer, N.N., Wrage, L.A., Das, A., Tyson, J.E., Stevenson, D.K., Carlo, W.A., Walsh, M.C., Laptook, A.R., Yoder, B.A., Van Meurs, K.P., Faix, R.G., Rich, W., Newman, N.S., Cheng, H., Heyne, R.J., Vohr, B.R., Acarregui, M.J., Vaucher, Y.E., Pappas, A., Peralta-Carcelen, M., Wilson-Costello, D.E., Evans, P.W., Goldstein, R.F., Myers, G.J., Poindexter, B.B., McGowan, E.C., Adams-Chapman, I., Fuller, J., Higgins, R.D. & SUPPORT Study Group of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network 2015, "Neuroimaging and neurodevelopmental outcome in extremely preterm infants", *Pediatrics,* vol. 135, no. 1, pp. e32-42.

Hintz, S.R. & O'Shea, M. 2008, "Neuroimaging and neurodevelopmental outcomes in preterm infants", *Seminars in perinatology,* vol. 32, no. 1, pp. 11-19.

Horsch, S., Skiold, B., Hallberg, B., Nordell, B., Nordell, A., Mosskin, M., Lagercrantz, H., Aden, U. & Blennow, M. 2010, "Cranial ultrasound and MRI at term age in extremely preterm infants", *Archives of disease in childhood.Fetal and neonatal edition,* vol. 95, no. 5, pp. F310-4.

Huhtala, M., Korja, R., Lehtonen, L., Haataja, L., Lapinleimu, H., Rautava, P. & PIPARI Study Group 2014, "Associations between parental psychological well-being and socio-emotional development in 5-year-old preterm children", *Early human development,* vol. 90, no. 3, pp. 119-124.

Huppi, P.S., Warfield, S., Kikinis, R., Barnes, P.D., Zientara, G.P., Jolesz, F.A., Tsuji, M.K. & Volpe, J.J. 1998, "Quantitative magnetic resonance imaging of brain development in premature and mature newborns", *Annals of Neurology,* vol. 43, no. 2, pp. 224-235.

Husby, I.M., Skranes, J., Olsen, A., Brubakk, A.M. & Evensen, K.A. 2013, "Motor skills at 23 years of age in young adults born preterm with very low birth weight", *Early human development,* vol. 89, no. 9, pp. 747-754.

Izbudak, I. & Grant, P.E. 2011, "MR imaging of the term and preterm neonate with diffuse brain injury", *Magnetic resonance imaging clinics of North America,* vol. 19, no. 4, pp. 709-31; vii.

Janvier, A. & Barrington, K. 2012, "Trying to predict the future of ex-preterm infants: who benefits from a brain MRI at term?", *Acta Paediatrica (Oslo, Norway : 1992),* vol. 101, no. 10, pp. 1016-1017.

Jary, S., Kmita, G., Wroblewska, J. & Whitelaw, A. 2012, "Quantitative cranial ultrasound prediction of severity of disability in premature infants with post-haemorrhagic ventricular dilatation", *Archives of Disease in Childhood,* vol. 97, no. 11, pp. 955-959.

Kelly, C.E., Chan, L., Burnett, A.C., Lee, K.J., Connelly, A., Anderson, P.J., Doyle, L.W., Cheong, J.L., Thompson, D.K. & Victorian Infant Collaborative Study Group 2015, "Brain structural and microstructural alterations associated with cerebral palsy and motor impairments in adolescents born extremely preterm and/or extremely low birthweight", *Developmental medicine and child neurology,* .

Kerr-Wilson, C.O., Mackay, D.F., Smith, G.C. & Pell, J.P. 2012, "Meta-analysis of the association between preterm delivery and intelligence", *Journal of public health (Oxford, England),* vol. 34, no. 2, pp. 209-216.

Kersbergen, K.J., de Vries, L.S., Groenendaal, F., van Haastert, I.C., Chew, A.T., Makropoulos, A., Dawson, S.L., Cowan, F.M., Benders, M.J. & Counsell, S.J. 2015, "Corticospinal Tract Injury Precedes Thalamic Volume Reduction in Preterm Infants with Cystic Periventricular Leukomalacia", *The Journal of pediatrics,* vol. 167, no. 2, pp. 260-8.e3.

Keunen, K., Isgum, I., van Kooij, B.J., Anbeek, P., van Haastert, I.C., Koopman-Esseboom, C., Fieret-van Stam, P.C., Nievelstein, R.A., Viergever, M.A., de Vries, L.S., Groenendaal, F. & Benders, M.J. 2016, "Brain Volumes at Term-Equivalent Age in Preterm Infants: Imaging Biomarkers for Neurodevelopmental Outcome through Early School Age", *The Journal of pediatrics,* .

Keunen, K., Kersbergen, K.J., Groenendaal, F., Isgum, I., de Vries, L.S. & Benders, M.J. 2012, "Brain tissue volumes in preterm infants: prematurity, perinatal risk factors and neurodevelopmental outcome: a systematic review", *The journal of maternal-fetal & neonatal medicine : the official*

journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians, vol. 25 Suppl 1, pp. 89-100.

Kirby, A., Sugden, D. & Purcell, C. 2014, "Diagnosing developmental coordination disorders", *Archives of Disease in Childhood,* vol. 99, no. 3, pp. 292-296.

Krageloh-Mann, I. & Cans, C. 2009, "Cerebral palsy update", *Brain & development,* vol. 31, no. 7, pp. 537-544.

Krishnan, M.L., Dyet, L.E., Boardman, J.P., Kapellou, O., Allsop, J.M., Cowan, F., Edwards, A.D., Rutherford, M.A. & Counsell, S.J. 2007, "Relationship between white matter apparent diffusion coefficients in preterm infants at term-equivalent age and developmental outcome at 2 years", *Pediatrics,* vol. 120, no. 3, pp. e604-9.

Kwon, S.H., Vasung, L., Ment, L.R. & Huppi, P.S. 2014, "The role of neuroimaging in predicting neurodevelopmental outcomes of preterm neonates", *Clinics in perinatology,* vol. 41, no. 1, pp. 257-283.

Larroque, B., Ancel, P.Y., Marret, S., Marchand, L., Andre, M., Arnaud, C., Pierrat, V., Roze, J.C., Messer, J., Thiriez, G., Burguet, A., Picaud, J.C., Breart, G., Kaminski, M. & EPIPAGE Study group 2008, "Neurodevelopmental disabilities and special care of 5-year-old children born before 33 weeks of gestation (the EPIPAGE study): a longitudinal cohort study", *Lancet (London, England),* vol. 371, no. 9615, pp. 813-820.

Latal, B. 2009, "Prediction of neurodevelopmental outcome after preterm birth", *Pediatric neurology,* vol. 40, no. 6, pp. 413-419.

Leijser, L.M., de Bruine, F.T., Steggerda, S.J., van der Grond, J., Walther, F.J. & van Wezel-Meijler, G. 2009a, "Brain imaging findings in very preterm infants throughout the neonatal period: part I. Incidences and evolution of lesions, comparison between ultrasound and MRI", *Early human development,* vol. 85, no. 2, pp. 101-109.

Leijser, L.M., Steggerda, S.J., de Bruine, F.T., van der Grond, J., Walther, F.J. & van Wezel-Meijler, G. 2009b, "Brain imaging findings in very preterm infants throughout the neonatal period: part II. Relation with perinatal clinical data", *Early human development,* vol. 85, no. 2, pp. 111-115.

Leisenring, W., Alonzo, T. & Pepe, M.S. 2000, "Comparisons of predictive values of binary medical diagnostic tests for paired designs", *Biometrics,* vol. 56, no. 2, pp. 345-351.

Lepomaki, V., Paavilainen, T., Matomaki, J., Hurme, S., Haataja, L., Lapinleimu, H., Liisa Lehtonen, L., Komu, M., Parkkola, R. & PIPARI Study Group 2012, "Effect of antenatal growth and prematurity on brain white matter: diffusion tensor study", *Pediatric radiology,* vol. 42, no. 6, pp. 692-698.

Leppanen, M., Lapinleimu, H., Lind, A., Matomaki, J., Lehtonen, L., Haataja, L., Rautava, P. & PIPARI Study Group 2014, "Antenatal and postnatal growth and 5-year cognitive outcome in very preterm infants", *Pediatrics,* vol. 133, no. 1, pp. 63-70.

Leroux, B.G., N'guyen The Tich, S., Branger, B., Gascoin, G., Rouger, V., Berlie, I., Montcho, Y., Ancel, P.Y., Roze, J.C. & Flamant, C. 2013, "Neurological assessment of preterm infants for predicting neuromotor status at 2 years: results from the LIFT cohort", *BMJ open,* vol. 3, no. 2, pp. 10.1136/bmjopen-2012-002431. Print 2013.

Lester, B.M. & Tronick, E.Z. 2004, "History and description of the Neonatal Intensive Care Unit Network Neurobehavioral Scale", *Pediatrics,* vol. 113, no. 3 Pt 2, pp. 634-640.

Leversen, K.T., Sommerfelt, K., Elgen, I.B., Eide, G.E., Irgens, L.M., Juliusson, P.B. & Markestad, T. 2012, "Prediction of outcome at 5 years from assessments at 2 years among extremely preterm children: a Norwegian national cohort study", *Acta Paediatrica (Oslo, Norway : 1992),* vol. 101, no. 3, pp. 264-270.

Leversen, K.T., Sommerfelt, K., Ronnestad, A., Kaaresen, P.I., Farstad, T., Skranes, J., Stoen, R., Bircow Elgen, I., Rettedal, S., Egil Eide, G., Irgens, L.M. & Markestad, T. 2011, "Prediction of neurodevelopmental and sensory outcome at 5 years in Norwegian children born extremely preterm", *Pediatrics,* vol. 127, no. 3, pp. e630-8.

Leversen, K.T., Sommerfelt, K., Ronnestad, A., Kaaresen, P.I., Farstad, T., Skranes, J., Stoen, R., Elgen, I.B., Rettedal, S., Eide, G.E., Irgens, L.M. & Markestad, T. 2010, "Predicting neurosensory disabilities at two years of age in a national cohort of extremely premature infants", *Early human development,* vol. 86, no. 9, pp. 581-586.

Lind, A., Haataja, L., Rautava, L., Valiaho, A., Lehtonen, L., Lapinleimu, H., Parkkola, R., Korkman, M. & PIPARI Study Group 2010, "Relations between brain volumes, neuropsychological assessment and parental questionnaire in prematurely born children", *European child & adolescent psychiatry,* vol. 19, no. 5, pp. 407-417.

Lind, A., Korkman, M., Lehtonen, L., Lapinleimu, H., Parkkola, R., Matomaki, J., Haataja, L. & PIPARI Study Group 2011a, "Cognitive and neuropsychological outcomes at 5 years of age in preterm children born in the 2000s", *Developmental medicine and child neurology,* vol. 53, no. 3, pp. 256-262.

Lind, A., Parkkola, R., Lehtonen, L., Munck, P., Maunu, J., Lapinleimu, H., Haataja, L. & PIPARI Study Group 2011b, "Associations between regional brain volumes at term-equivalent age and development at 2 years of age in preterm children", *Pediatric radiology,* vol. 41, no. 8, pp. 953-961.

Linsell, L., Malouf, R., Morris, J., Kurinczuk, J.J. & Marlow, N. 2015, "Prognostic Factors for Poor Cognitive Development in Children Born Very Preterm or With Very Low Birth Weight: A Systematic Review", *JAMA pediatrics,* , pp. 1-11.

Liu, L., Johnson, H.L., Cousens, S., Perin, J., Scott, S., Lawn, J.E., Rudan, I., Campbell, H., Cibulskis, R., Li, M., Mathers, C., Black, R.E. & Child Health Epidemiology Reference Group of WHO and UNICEF 2012, "Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000", *Lancet (London, England),* vol. 379, no. 9832, pp. 2151-2161.

Maalouf, E.F., Duggan, P.J., Counsell, S.J., Rutherford, M.A., Cowan, F., Azzopardi, D. & Edwards, A.D. 2001, "Comparison of findings on cranial ultrasound and magnetic resonance imaging in preterm infants", *Pediatrics,* vol. 107, no. 4, pp. 719-727.

Maas, Y.G., Mirmiran, M., Hart, A.A., Koppe, J.G., Ariagno, R.L. & Spekreijse, H. 2000, "Predictive value of neonatal neurological tests for developmental outcome of preterm infants", *The Journal of pediatrics,* vol. 137, no. 1, pp. 100-106.

Markestad, T., Kaaresen, P.I., Ronnestad, A., Reigstad, H., Lossius, K., Medbo, S., Zanussi, G., Engelund, I.E., Skjaerven, R., Irgens, L.M. & Norwegian Extreme Prematurity Study Group 2005, "Early death, morbidity, and need of treatment among extremely premature infants", *Pediatrics,* vol. 115, no. 5, pp. 1289-1298.

Marlow, E.S., Hunt, L.P. & Marlow, N. 2000, "Sensorineural hearing loss and prematurity", *Archives of disease in childhood.Fetal and neonatal edition,* vol. 82, no. 2, pp. F141-4.

Marlow, N., Hennessy, E.M., Bracewell, M.A., Wolke, D. & EPICure Study Group 2007, "Motor and executive function at 6 years of age after extremely preterm birth", *Pediatrics,* vol. 120, no. 4, pp. 793-804.

Marlow, N., Wolke, D., Bracewell, M.A., Samara, M. & EPICure Study Group 2005, "Neurologic and developmental disability at six years of age after extremely preterm birth", *The New England journal of medicine,* vol. 352, no. 1, pp. 9-19.

Marret, S., Marchand-Martin, L., Picaud, J.C., Hascoet, J.M., Arnaud, C., Roze, J.C., Truffert, P., Larroque, B., Kaminski, M., Ancel, P.Y. & EPIPAGE Study Group 2013, "Brain injury in very preterm children and neurosensory and cognitive disabilities during childhood: the EPIPAGE cohort study", *PloS one,* vol. 8, no. 5, pp. e62683.

Maunu, J., Lehtonen, L., Lapinleimu, H., Matomaki, J., Munck, P., Rikalainen, H., Parkkola, R., Haataja, L. & PIPARI Study Group 2011, "Ventricular dilatation in relation to outcome at 2 years of age in very preterm infants: a prospective Finnish cohort study", *Developmental medicine and child neurology,* vol. 53, no. 1, pp. 48-54.

Maunu, J., Parkkola, R., Rikalainen, H., Lehtonen, L., Haataja, L., Lapinleimu, H. & PIPARI Group 2009, "Brain and ventricles in very low birth weight infants at term: a comparison among head circumference, ultrasound, and magnetic resonance imaging", *Pediatrics,* vol. 123, no. 2, pp. 617-626.

McArdle, C.B., Richardson, C.J., Nicholas, D.A., Mirfakhraee, M., Hayden, C.K. & Amparo, E.G. 1987, "Developmental features of the neonatal brain: MR imaging. Part II. Ventricular size and extracerebral space", *Radiology,* vol. 162, no. 1 Pt 1, pp. 230-234.

Mercuri, E., Guzzetta, A., Laroche, S., Ricci, D., vanhaastert, I., Simpson, A., Luciano, R., Bleakley, C., Frisone, M.F., Haataja, L., Tortorolo, G., Guzzetta, F., de Vries, L., Cowan, F. & Dubowitz, L. 2003, "Neurologic examination of preterm infants at term age: comparison with term infants", *The Journal of pediatrics,* vol. 142, no. 6, pp. 647-655.

Mikkola, K., Ritari, N., Tommiska, V., Salokorpi, T., Lehtonen, L., Tammela, O., Paakkonen, L., Olsen, P., Korkman, M. & Fellman, V. 2005, "Neurodevelopmental outcome at 5 years of age of a national cohort of extremely low birth weight infants who were born in 1996-1997", *Pediatrics,* vol. 116, no. 6, pp. 1391-1400.

Moore, T., Hennessy, E.M., Myles, J., Johnson, S.J., Draper, E.S., Costeloe, K.L. & Marlow, N. 2012, "Neurological and developmental outcome in extremely preterm children born in England in 1995 and 2006: the EPICure studies", *BMJ (Clinical research ed.),* vol. 345, pp. e7961.

Munck, P., Haataja, L., Maunu, J., Parkkola, R., Rikalainen, H., Lapinleimu, H., Lehtonen, L. & PIPARI Study Group 2010, "Cognitive outcome at 2 years of age in Finnish infants with very low birth weight born between 2001 and 2006", *Acta Paediatrica (Oslo, Norway : 1992),* vol. 99, no. 3, pp. 359-366.

Munck, P., Niemi, P., Lapinleimu, H., Lehtonen, L., Haataja, L. & PIPARI Study Group 2012, "Stability of cognitive outcome from 2 to 5 years of age in very low birth weight children", *Pediatrics,* vol. 129, no. 3, pp. 503-508.

Palisano, R., Rosenbaum, P., Walter, S., Russell, D., Wood, E. & Galuppi, B. 1997, "Development and reliability of a system to classify gross motor function in children with cerebral palsy", *Developmental medicine and child neurology,* vol. 39, no. 4, pp. 214-223.

Papile, L.A., Burstein, J., Burstein, R. & Koffler, H. 1978, "Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm", *The Journal of pediatrics,* vol. 92, no. 4, pp. 529-534.

Parikh, N.A., Lasky, R.E., Kennedy, K.A., McDavid, G. & Tyson, J.E. 2013, "Perinatal factors and regional brain volume abnormalities at term in a cohort of extremely low birth weight infants", *PloS one,* vol. 8, no. 5, pp. e62804.

Pearce, R. & Baardsnes, J. 2012, "Term MRI for small preterm babies: do parents really want to know and why has nobody asked them?", *Acta Paediatrica (Oslo, Norway : 1992),* vol. 101, no. 10, pp. 1013-1015.

Perivier, M., Roze, J.C., Gascoin, G., Hanf, M., Branger, B., Rouger, V., Berlie, I., Montcho, Y., Pereon, Y., Flamant, C. & Nguyen The Tich, S. 2015, "Neonatal EEG and neurodevelopmental outcome in preterm infants born before 32 weeks", *Archives of disease in childhood.Fetal and neonatal edition,* .

Peters, L.H., Maathuis, C.G. & Hadders-Algra, M. 2013, "Neural correlates of developmental coordination disorder", *Developmental medicine and child neurology,* vol. 55 Suppl 4, pp. 59-64.

Peters, L.H., Maathuis, C.G. & Hadders-Algra, M. 2011, "Limited motor performance and minor neurological dysfunction at school age", *Acta Paediatrica (Oslo, Norway : 1992),* vol. 100, no. 2, pp. 271-278.

Peters, L.H.J., Maathuis, K.G.B., Kouw, E., Hamming, M. & Hadders-Algra, M. 2008, "Test–retest, inter-assessor and intra-assessor reliability of the modified Touwen examination", *European Journal of Paediatric Neurology,* vol. 12, no. 4, pp. 328-333.

Plaisier, A., Govaert, P., Lequin, M.H. & Dudink, J. 2014, "Optimal timing of cerebral MRI in preterm infants to predict long-term neurodevelopmental outcome: a systematic review", *AJNR.American journal of neuroradiology,* vol. 35, no. 5, pp. 841-847.

Platt, M.J., Cans, C., Johnson, A., Surman, G., Topp, M., Torrioli, M.G. & Krageloh-Mann, I. 2007, "Trends in cerebral palsy among infants of very low birthweight (<1500 g) or born prematurely (<32 weeks) in 16 European centres: a database study", *Lancet,* vol. 369, no. 9555, pp. 43-50.

Prechtl, H.F. 1977, *The neurological examination of the full-term newborn infant,* 2nd edition edn, William Heinemann Medical Books Ltd, London.

Rademaker, K.J., Uiterwaal, C.S., Beek, F.J., van Haastert, I.C., Lieftink, A.F., Groenendaal, F., Grobbee, D.E. & de Vries, L.S. 2005, "Neonatal cranial ultrasound versus MRI and neurodevelopmental outcome at school age in children born preterm", *Archives of disease in childhood.Fetal and neonatal edition,* vol. 90, no. 6, pp. F489-93.

Ramenghi, L.A., Fumagalli, M., Righini, A., Bassi, L., Groppo, M., Parazzini, C., Bianchini, E., Triulzi, F. & Mosca, F. 2007, "Magnetic resonance imaging assessment of brain maturation in preterm neonates with punctate white matter lesions", *Neuroradiology,* vol. 49, no. 2, pp. 161-167.

Ramenghi, L.A., Ricci, D., Mercuri, E., Groppo, M., De Carli, A., Ometto, A., Fumagalli, M., Bassi, L., Pisoni, S., Cioni, G. & Mosca, F. 2010, "Visual performance and brain structures in the developing brain of pre-term infants", *Early human development,* vol. 86 Suppl 1, pp. 73-75.

Reiman, M., Kujari, H., Maunu, J., Parkkola, R., Rikalainen, H., Lapinleimu, H., Lehtonen, L., Haataja, L. & PIPARI Study Group 2008, "Does placental inflammation relate to brain lesions and volume in preterm infants?", *The Journal of pediatrics,* vol. 152, no. 5, pp. 642-7, 647.e1-2.

Ricci, D., Romeo, D.M., Haataja, L., van Haastert, I.C., Cesarini, L., Maunu, J., Pane, M., Gallini, F., Luciano, R., Romagnoli, C., de Vries, L.S., Cowan, F.M. & Mercuri, E. 2008, "Neurological examination of preterm infants at term equivalent age", *Early human development,* vol. 84, no. 11, pp. 751-761.

Rigoli, D., Piek, J.P. & Kane, R. 2012, "Motor coordination and psychosocial correlates in a normative adolescent sample", *Pediatrics,* vol. 129, no. 4, pp. e892-900.

Roberts, G., Anderson, P.J., Davis, N., De Luca, C., Cheong, J., Doyle, L.W. & Victorian Infant Collaborative Study Group 2011, "Developmental coordination disorder in geographic cohorts of 8-year-old children born extremely preterm or extremely low birthweight in the 1990s", *Developmental medicine and child neurology,* vol. 53, no. 1, pp. 55-60.

Roberts, G., Anderson, P.J., Doyle, L.W. & Victorian Infant Collaborative Study Group 2009, "Neurosensory disabilities at school age in geographic cohorts of extremely low birth weight children born between the 1970s and the 1990s", *The Journal of pediatrics,* vol. 154, no. 6, pp. 829-34.e1.

Romeo, D.M., Cioni, M., Scoto, M., Mazzone, L., Palermo, F. & Romeo, M.G. 2008a, "Neuromotor development in infants with cerebral palsy investigated by the Hammersmith Infant Neurological Examination during the first year of age", *European journal of paediatric neurology : EJPN : official journal of the European Paediatric Neurology Society,* vol. 12, no. 1, pp. 24-31.

Romeo, D.M., Cioni, M., Scoto, M., Pizzardi, A., Romeo, M.G. & Guzzetta, A. 2009, "Prognostic value of a scorable neurological examination from 3 to 12 months post-term age in very preterm infants: a longitudinal study", *Early human development,* vol. 85, no. 6, pp. 405-408.

Romeo, D.M., Guzzetta, A., Scoto, M., Cioni, M., Patusi, P., Mazzone, D. & Romeo, M.G. 2008b, "Early neurologic assessment in preterm-infants: integration of traditional neurologic examination and observation of general movements", *European journal of paediatric neurology : EJPN : official journal of the European Paediatric Neurology Society,* vol. 12, no. 3, pp. 183-189.

Roze, E., Benders, M.J., Kersbergen, K.J., van der Aa, N.E., Groenendaal, F., van Haastert, I.C., Leemans, A. & de Vries, L.S. 2015, "Neonatal DTI early after birth predicts motor outcome in preterm infants with periventricular hemorrhagic infarction", *Pediatric research,* vol. 78, no. 3, pp. 298-303.

Rysavy, M.A., Li, L., Bell, E.F., Das, A., Hintz, S.R., Stoll, B.J., Vohr, B.R., Carlo, W.A., Shankaran, S., Walsh, M.C., Tyson, J.E., Cotten, C.M., Smith, P.B., Murray, J.C., Colaizy, T.T., Brumbaugh, J.E., Higgins, R.D. & Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network 2015, "Between-hospital variation in treatment and outcomes in extremely preterm infants", *The New England journal of medicine,* vol. 372, no. 19, pp. 1801-1811.

Saigal, S. & Doyle, L.W. 2008, "An overview of mortality and sequelae of preterm birth from infancy to adulthood", *Lancet (London, England),* vol. 371, no. 9608, pp. 261-269.

Schneider, J., Vasung, L., Truttmann, A.C. & Huppi, P.S. 2014, "Cerebral brain injury in preterm infants and the role of neuroimaging in predicting neurodevelopmental outcomes", *Revue medicale suisse,* vol. 10, no. 418, pp. 442-449.

Schothorst, P.F., Swaab-Barneveld, H. & van Engeland, H. 2007, "Psychiatric disorders and MND in non-handicapped preterm children. Prevalence and stability from school age into adolescence", *European child & adolescent psychiatry,* vol. 16, no. 7, pp. 439-448.

Schulz, J., Henderson, S.E., Sugden, D.A. & Barnett, A.L. 2011, "Structural validity of the Movement ABC-2 test: factor structure comparisons across three age groups", *Research in developmental disabilities,* vol. 32, no. 4, pp. 1361-1369.

Sellier, E., Platt, M.J., Andersen, G.L., Krageloh-Mann, I., De La Cruz, J., Cans, C. & Surveillance of Cerebral Palsy Network 2015, "Decreasing prevalence in cerebral palsy: a multi-site European population-based study, 1980 to 2003", *Developmental medicine and child neurology,* .

Serenius, F., Kallen, K., Blennow, M., Ewald, U., Fellman, V., Holmstrom, G., Lindberg, E., Lundqvist, P., Marsal, K., Norman, M., Olhager, E., Stigson, L., Stjernqvist, K., Vollmer, B., Stromberg, B. & EXPRESS Group 2013, "Neurodevelopmental outcome in extremely preterm infants at 2.5 years after active perinatal care in Sweden", *Jama,* vol. 309, no. 17, pp. 1810-1820.

Sherlock, R.L., Anderson, P.J., Doyle, L.W. & Victorian Infant Collaborative Study Group 2005, "Neurodevelopmental sequelae of intraventricular haemorrhage at 8 years of age in a regional cohort of ELBW/very preterm infants", *Early human development,* vol. 81, no. 11, pp. 909-916.

Simard, M.N., Lambert, J., Lachance, C., Audibert, F. & Gosselin, J. 2011, "Prediction of developmental performance in preterm infants at two years of corrected age: contribution of the neurological assessment at term age", *Early human development,* vol. 87, no. 12, pp. 799-804.

Simmons, L.E., Rubens, C.E., Darmstadt, G.L. & Gravett, M.G. 2010, "Preventing preterm birth and neonatal mortality: exploring the epidemiology, causes, and interventions", *Seminars in perinatology,* vol. 34, no. 6, pp. 408-415.

Skiold, B., Eriksson, C., Eliasson, A.C., Aden, U. & Vollmer, B. 2013, "General movements and magnetic resonance imaging in the prediction of neuromotor outcome in children born extremely preterm", *Early human development,* vol. 89, no. 7, pp. 467-472.

Skiold, B., Vollmer, B., Bohm, B., Hallberg, B., Horsch, S., Mosskin, M., Lagercrantz, H., Aden, U. & Blennow, M. 2012, "Neonatal magnetic resonance imaging and outcome at age 30 months in extremely preterm infants", *The Journal of pediatrics,* vol. 160, no. 4, pp. 559-566.e1.

Smyser, C.D., Kidokoro, H. & Inder, T.E. 2012, "Magnetic resonance imaging of the brain at term equivalent age in extremely premature neonates: To scan or not to scan?", *Journal of paediatrics and child health,* vol. 48, no. 9, pp. 794-800.

Spittle, A.J., Cheong, J., Doyle, L.W., Roberts, G., Lee, K.J., Lim, J., Hunt, R.W., Inder, T.E. & Anderson, P.J. 2011, "Neonatal white matter abnormality predicts childhood motor impairment in very

preterm children", *Developmental medicine and child neurology,* vol. 53, no. 11, pp. 1000-1006.

Spittle, A.J., Doyle, L.W. & Boyd, R.N. 2008, "A systematic review of the clinimetric properties of neuromotor assessments for preterm infants during the first year of life", *Developmental medicine and child neurology,* vol. 50, no. 4, pp. 254-266.

Spittle, A.J. & Orton, J. 2014, "Cerebral palsy and developmental coordination disorder in children born preterm", *Seminars in fetal & neonatal medicine,* vol. 19, no. 2, pp. 84-89.

Stjerna, S., Sairanen, V., Grohn, R., Andersson, S., Metsaranta, M., Lano, A. & Vanhatalo, S. 2015, "Visual fixation in human newborns correlates with extensive white matter networks and predicts long-term neurocognitive development", *The Journal of neuroscience : the official journal of the Society for Neuroscience,* vol. 35, no. 12, pp. 4824-4829.

Stoll, B.J., Hansen, N.I., Bell, E.F., Walsh, M.C., Carlo, W.A., Shankaran, S., Laptook, A.R., Sanchez, P.J., Van Meurs, K.P., Wyckoff, M., Das, A., Hale, E.C., Ball, M.B., Newman, N.S., Schibler, K., Poindexter, B.B., Kennedy, K.A., Cotten, C.M., Watterberg, K.L., D'Angio, C.T., DeMauro, S.B., Truog, W.E., Devaskar, U., Higgins, R.D. & Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network 2015, "Trends in Care Practices, Morbidity, and Mortality of Extremely Preterm Neonates, 1993-2012", *Jama,* vol. 314, no. 10, pp. 1039-1051.

Synnes, A., Anderson, P.J., Grunau, R.E., Dewey, D., Moddemann, D., Tin, W., Davis, P.G., Doyle, L.W., Foster, G., Khairy, M., Nwaesei, C., Schmidt, B. & CAP Trial Investigator group 2015, "Predicting severe motor impairment in preterm children at age 5 years", *Archives of Disease in Childhood,* vol. 100, no. 8, pp. 748-753.

Valkama, A.M., Tolonen, E.U., Kerttul, L.I., Paakko, E.L., Vainionpaa, L.K. & Koivist, M.E. 2001, "Brainstem size and function at term age in relation to later neurosensory disability in high-risk, preterm infants", *Acta Paediatrica (Oslo, Norway : 1992),* vol. 90, no. 8, pp. 909-915.

van Haastert, I.C., Groenendaal, F., Uiterwaal, C.S., Termote, J.U., van der Heide-Jalving, M., Eijsermans, M.J., Gorter, J.W., Helders, P.J., Jongmans, M.J. & de Vries, L.S. 2011, "Decreasing incidence and severity of cerebral palsy in prematurely born children", *The Journal of pediatrics,* vol. 159, no. 1, pp. 86-91.e1.

Wechsler, D. 1995, Wechslerin älykkyystestistö esikouluikäisille, käsikirja. Psykologien kustannus, Helsinki.

Wilson, B.N., Crawford, S.G., Green, D., Roberts, G., Aylott, A. & Kaplan, B.J. 2009, "Psychometric properties of the revised Developmental Coordination Disorder Questionnaire", *Physical & Occupational Therapy in Pediatrics,* vol. 29, no. 2, pp. 182-202.

Wocadlo, C. & Rieger, I. 2008, "Motor impairment and low achievement in very preterm children at eight years of age", *Early human development,* vol. 84, no. 11, pp. 769-776.

Woodward, L.J., Anderson, P.J., Austin, N.C., Howard, K. & Inder, T.E. 2006, "Neonatal MRI to predict neurodevelopmental outcomes in preterm infants", *The New England journal of medicine,* vol. 355, no. 7, pp. 685-694.

Woodward, L.J., Mogridge, N., Wells, S.W. & Inder, T.E. 2004, "Can neurobehavioral examination predict the presence of cerebral injury in the very low birth weight infant?", *Journal of developmental and behavioral pediatrics : JDBP,* vol. 25, no. 5, pp. 326-334.

Zwicker, J.G., Missiuna, C., Harris, S.R. & Boyd, L.A. 2012, "Developmental coordination disorder: A review and update", *European journal of paediatric neurology : EJPN : official journal of the European Paediatric Neurology Society,* .

Zwicker, J.G., Yoon, S.W., Mackay, M., Petrie-Thomas, J., Rogers, M. & Synnes, A.R. 2013, "Perinatal and neonatal predictors of developmental coordination disorder in very low birthweight children", *Archives of Disease in Childhood,* vol. 98, no. 2, pp. 118-122.

APPENDICES

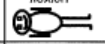
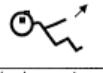
Appendix 1. The proforma of the Dubowitz neurologic examination

Hammersmith Neonatal Neurological Examination CODE_____ D.O.E._____

NAME _____ SEX___ RACE_____ D.O.B._____ AGE_____ G.A._____ BW _____

STATE ASYMM

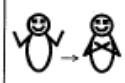
Posture and tone

POSTURE Infant supine. Look mainly at position of legs but also note arms. *Score predominant posture.*	arms & legs extended or very slightly flexed 	Legs slightly flexed 	legs well flexed but not adducted 	legs well flexed & adducted near abdomen 	abnormal posture: a) opisthotonus b) marked leg extension, strong arm flexion 		
ARM RECOIL Take both hands, quickly extend arms parallel to the body, Count to three. Release. Repeat 3 times.	arms do not flex 	arms flex slowly, not always; not completely 	arms flex slowly; more completely 	arms flex quickly and completely 	arms difficult to extend; snap back forcefully		
ARM TRACTION Hold wrist and pull arm upwards. Note flexion at elbow and resistance while shoulder lifts off table. *Test each side separately.*	arms remain straight; no resistance felt  R L	arms flex slightly or some resistance felt  R L	arms flex well till shoulder lifts, then straighten  R L	arms flex at approx 100° & maintained as shoulder lifts  R L	flexion of arms <100°; maintained when body lifts up  R L		
LEG RECOIL Take *both* ankles in one hand, flex hips + knees. Quickly extend. Release. Repeat 3 times.	No flexion 	incomplete or variable flexion 	complete but slow flexion 	complete fast flexion 	legs difficult to extend; snap back forcefully		
LEG TRACTION Grasp ankle and slowly pull leg upwards. Note flexion at knees and resistance as buttocks lift. *Test each side separately.*	legs straight - no resistance felt  R L	legs flex slightly or some resistance felt  R L	legs flex well till bottom lifts up  R L	knee flexes remains flexed when bottom up  R L	flexion stays when back+bottom up  R L		
POPLITEAL ANGLE Fix knee on abdomen, extend leg by gentle pressure with index finger behind the ankle. Note angle at knee. *Test each side separately.*	 180° R L	 ≈150° R L	 ≈110° R L	 ≈90° R L	 <90° R L		
HEAD CONTROL (1) ***(extensor tone)*** Infant sitting upright. Encircle chest with both hands holding shoulders. Let head drop forward.	no attempt to raise head 	infant tries: effort better felt than seen 	raises head but drops forward or back 	raises head: remains vertical; it may wobble 			
HEAD CONTROL (2) ***(flexor tone)*** Infant sitting upright. Encircle chest with both hands holding shoulders. Let head drop backward.	no attempt to raise head 	infant tries: effort better felt than seen 	raises head but drops forward or back 	raises head: remains vertical; it may wobble 	head upright or extended; cannot be passively flexed		
HEAD LAG Pull infant towards sitting posture by traction on both wrists & support head slightly. Also note arm flexion.	head drops & stays back 	tries to lift head but it drops back 	able to lift head slightly 	lifts head in line with body 	head in front of body		
VENTRAL SUSPENSION Hold infant in ventral suspension. Observe back, flexion of limbs, and relation of head to trunk. If it looks different, DRAW.	back curved, head & limbs hang straight	back curved, head ↓, limbs slightly flexed	back slightly curved, limbs flexed	back straight, head in line, limbs flexed	back straight, head above body		

Tone patterns

FLEXOR TONE (1) **(on traction: arm versus leg)** Compare scores of arm traction with leg traction.		score for arm flexion less than leg flexion	score for arm flexion equal to leg flexion	score for arm flexion more than leg flexion but difference 1 column or less	score for arm flexion more than leg flexion but difference more than 1 column		
FLEXOR TONE (2) **(arm versus leg)** Posture in supine.			arms and legs flexed	strong arm flexiqn with strong leg extension *intermittent*	strong arm flexion with strong leg extension *continuous*		
LEG EXTENSOR TONE Compare scores of leg traction and popliteal angle.		score for leg traction more than score for popliteal angle	score for leg traction equal to score for popliteal angle	score for leg traction less than score for popliteal angle, by 1 column only	score for leg traction less than score for popliteal angle, by more than 1 column		
NECK EXTENSOR TONE (SITTING) Compare scores of head control 1 and 2.		score for head extension less than head flexion	score for head extension equal to head flexion	score for head extension more than head flexion. but difference 1 column or less	score for head extension more than head flexion but difference more than 1 column		
INCREASED EXTENSOR TONE (HORIZONTAL) Compare scores of head lag and ventral suspension.		score for ventral suspension less than head lag	score for ventral suspension equal to head lag	score for ventral suspension more than head lag but difference 1 column or less	score for ventral suspension more than head lag but difference more than 1 column		

Reflexes

TENDON REFLEX Test biceps, knee, and ankle jerks.	absent	felt, not seen	seen	"exaggerated" (very brisk)	clonus		
SUCK / GAG Little finger into mouth with pulp of finger upwards.	no gag / no suck	weak irregular suck only No stripping	weak regular suck Some stripping	strong suck: (a) irregular (b) regular Good stripping	no suck but strong clenching		
PALMAR GRASP Put index finger into the hand and gently press palmar surface. Do not touch dorsal surface. *Test each side separately.*	no response R L	short, weak flexion of fingers R L	strong flexion of fingers R L	strong finger flexion, shoulder ↑ R L	very strong grasp; infant can be lifted off couch R L		
PLANTAR GRASP Press thumb on the sole below the toes. *Test each side separately.*	no response R L	partial plantar flexion of toes R L	toes curve around the examiner's finger R L				
PLACING Lift infant in an upright position and stroke the dorsum of the foot against a protruding edge of a flat surface. *Test each side separately.*	no response R L	dorsiflexion of ankle only R L	full placing response with flexion of hip and knee & placing sole on surface R L				
MORO REFLEX One hand supports infant's head in midline, the other the back. Raise infant to 45° and when infant is relaxed let head fall through 10°. Note if jerky. Repeat 3 times.	no response, or opening of hands only	full abduction at shoulder and extension of the arms; no adduction 	full abduction, but only delayed or partial adduction 	partial abduction at shoulder, and extension of arms followed by smooth adduction 	• minimal abduction or adduction • no abduction or adduction; only forward extension of arms • marked adduction only  or		

Movements

SPONTANEOUS MOVEMENT (quantity) Watch infant lying supine.	no movement	sporadic and short isolated movements	frequent isolated movements	frequent generalized movements	continuous exaggerated movements		
SPONTANEOUS MOVEMENT (quality) Watch infant lying supine.	only stretches	stretches and random abrupt movements; some smooth movements	fluent movements but monotonous	fluent alternating movements of arms + legs; good variability	• cramped, synchronized; • mouthing • jerky or other abnormal movements		
HEAD RAISING PRONE Infant in prone, head in midline.	no response	infant rolls head over, chin not raised	infant raises chin, rolls head over	infant brings head and chin up	infant brings head up and keeps it up		

Abnormal signs/patterns

ABNORMAL HAND OR TOE POSTURES		hands open, toes straight most of the time	intermittent fisting or thumb adduction	continuous fisting or thumb adduction; index finger flexion, thumb opposition	continuous big toe extension or flexion of all toes		
TREMOR		no tremor, or tremor only when crying or only after Moro reflex	tremor occasionally when awake	frequent tremors when awake	continuous tremors		
STARTLE	no startle even to sudden noise	no spontaneous startle but reacts to sudden noise	2-3 spontaneous startles	more than 3 spontaneous startles	continuous startles		

Orientation and behaviour

EYE APPEARANCES	does not open eyes		full conjugated eye movements	*transient* • nystagmus • strabismus • roving eye movements • sunset sign	*persistent* • nystagmus • strabismus • roving eye movements abnormal pupils		
AUDITORY ORIENTATION Infant awake. Wrap infant. Hold rattle 10 to 15 cm from ear.	no reaction	auditory startle; brightens and stills; no true orientation	shifting of eyes, head might turn towards source	prolonged head turn to stimulus; search with eyes; smooth	turns head (jerkily, abruptly) & eyes towards noise every time		
VISUAL ORIENTATION Wrap infant, wake up with rattle if needed or rock gently. Note if baby can see and follow red ball (B) or target (T).	does not follow or focus on stimuli B T	stills, focuses, follows briefly to the side but loses stimuli B T	follows horizontally and vertically; no head turn B T	follows horizontally and vertically; turns head B T	follows in a circle B T		
ALERTNESS *Tested as response to visual stimuli* (B or T).	will not respond to stimuli	when awake, looks only briefly	when awake, looks at stimuli but loses them	keeps interest in stimuli	does not tire (hyper-reactive)		
IRRITABILITY In response to stimuli.	quiet all the time, not irritable to any stimuli	awakes, cries sometimes when handled	cries often when handled	cries always when handled	cries even when not handled		
CONSOLABILITY Ease to quiet infant.	not crying; consoling not needed	cries briefly; consoling not needed	cries; becomes quiet when talked to	cries; needs picking up to be consoled	cries; cannot be consoled		
CRY	no cry at all	whimpering cry only	cries to stimuli but normal pitch		High-pitched cry; often continuous		

SUMMARY OF EXAMINATION:

HEAD AND TRUNK TONE:

LIMB TONE:

MOTILITY:

REFLEXES:

ORIENTATION AND ALERTNESS:

IRRITABILITY:

CONSOLABILITY:

LIST DEVIANT SIGNS:

Appendix 2. The proforma of the Hammersmith Infant Neurological Examination

HAMMERSMITH INFANT NEUROLOGICAL EXAMINATION

Name: **Date of birth:**

Gestational age: **Date of examination:**

SUMMARY OF EXAMINATION
No of asymmetries in section 1:
Neurological items score:
Behavioural score:

COMMENTS:

Cranial nerves functions

Posture

Movements

Tone

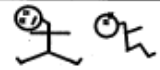
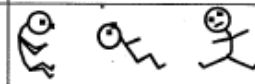
Reflexes and reactions

Behaviour

SECTION 1 : NEUROLOGICAL ITEMS

Assessment of cranial nerve function

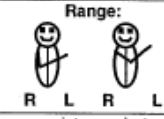
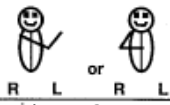
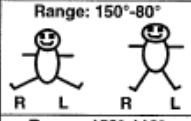
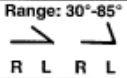
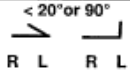
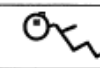
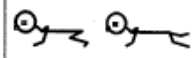
	column 1 (score 2)	c. 2 (sc. 1.5)	column 3 (score 1)	column 4 (score 0)	A	comment
Facial appearance (at rest and when crying or stimulated)	smiles or reacts to stimuli by closing eyes and grimacing		closes eyes but not tightly; poor facial expression	expressionless; does not react to stimuli		
Eye appearance	normal conjugated eye movements		**intermittent** deviation of eyes or abnormal movements	**continuous** deviation of eyes or abnormal movements		
Auditory response test the response to rattle or bell	reacts to stimuli on both sides		doubtful reaction to stimuli or asymmetrical	does not react to stimuli		
Visual response test the ability to follow a red ball or moving object	follows the object for a complete arc		follows the object for an incomplete arc, or asymmetry	does not follow the object		
Sucking/swallowing watch the infant suck on breast or bottle	good suck and swallowing		poor suck and/or swallowing	no sucking reflex, no swallowing		

	column 1 (score 2)	c 2 (sc.1.5)	column 3 (score 1)	column 4 (score 0)	A	
Head in sitting	 straight; in midline		 slightly to side *or* backward *or* forward	 markedly to side *or* backward *or* forward		
Trunk in sitting	 straight		 slightly curved or bent to side	 very rounded rocking back bent sideways		
Arms at rest	in neutral position: central, straight *or* slightly bent		**slight** internal rotation *or* external rotation	**marked** internal rotation *or* external rotation or dystonic posture hemiplegic posture		
Hands	hands open		**intermittent** adducted thumb *or* fisting	**persistent** adducted thumb *or* fisting		
Legs in sitting	able to sit with straight back, and legs straight or slightly bent (long sitting)		sit with straight back but knees bent at 15-20 °	unable to sit straight unless knees markedly bent (no long sitting)		
in supine and in standing	 legs in neutral position: straight *or* slightly bent	**slight** internal rotation or external rotation	 internal rotation *or* external rotation at hips	 **marked** internal rotation *or* external rotation *or* fixed extension or flexion or contractures at hips and knees		
Feet in supine and in standing	central; in neutral position toes straight midway between flexion and extension		**slight** internal rotation *or* external rotation **intermittent** tendency to stand on tiptoes; *or* toes up or curling under	**marked** internal rotation *or* external rotation at the ankle **persistent** tendency to stand on tiptoes *or* toes up or curling under		

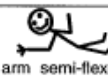
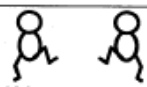
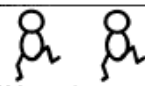
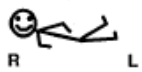
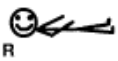
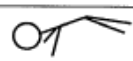
Movements

Quantity watch infant lying in the supine	normal		excessive or sluggish	minimal or none		
Quality	free, alternating, smooth		jerky, slight tremor	• cramped & synchronous • extensor spasms • athetoid • ataxic • very tremulous • myoclonic spasm • dystonic		

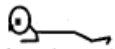
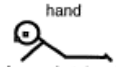
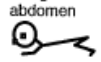
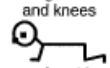
Tone

	column 1 (score 2)	c. 2 (sc.1.5)	column 3 (score 1)	column 4 (score 0)	A	
Scarf sign Take the infant's hand and pull the arm across the chest until there is resistance. Note the position of the elbow.	Range:  R L R L		 R L	 or R L R L		
Passive shoulder elevation Lift arm next to the infant's head. Note resistance at shoulder and elbow.	resistance, but overcome  R L		no resistance  R L	resistance,not overcome  R L		
Pronation/supination Steady upper arm while pronating and supinating forearm. Note resistance.	full pronation and supination, no resistance,		full pronation and supination but resistance to be overcome	full pronation and supination not possible, marked resistance		
Adductors With the infant's legs extended, open them as far as possible. The angle formed by the legs is noted.	Range: 150°-80°  R L R L	150°-160°  R L	>170°  R L	< 80°  R L		
Popliteal angle Legs are flexed at the hip simultaneously on to the side of the abdomen, then extended at the knee until there is resistance. Note angle between lower and upper leg.	Range: 150°-110°  R L R L	150°-160°  R L	~90° or > 170°  R L R L	<80°  R L		
Ankle dorsiflexion With knee extended, dorsiflex ankle. Note the angle between foot and leg.	Range: 30°-85°  R L R L	20°-30°  R L	< 20°or 90°  R L R L	> 90°  R L		
Pulled to sit Pull infant to sit by wrists.						
Ventral suspension Hold infant in ventral suspension; note position of back, limbs, and head.						

Reflexes and reactions

Tendon Reflexes	easily elicitable biceps knee ankle	mildly brisk bic knee ank	brisk biceps knee ankle	clonus or absent biceps knee ankle		
Arm protection Pull the infant by one arm from the supine position and note the reaction of the opposite side.	 arm & hand extend R L		 arm semi-flexed R L	 arm fully flexed R L		
Vertical suspension Hold infant under axilla. Make sure legs do not touch any surface.	 kicks symmetrically		 kicks one leg more, or poor kicking	 no kicking even if stimulated, or scissoring		
Lateral tilting (describe side up). Infant held vertically, tilt quickly to horizontal. Note spine, limbs, and head.	 R L	 R L	 R L	 R L		
Forward parachute Infant held vertically and suddenly tilted forward. Note reaction of the arms.	 (after 6 months)		 (after 6 months)			

SECTION 2: MOTOR MILESTONES

Head control	unable to maintain head upright (normal < 3 mo)	wobbles (normal at 4 mo)	all the time maintained upright (normal at 5 mo)			
Sitting	cannot sit	sits with support at hips  (normal at 4 mo)	props  (normal at 6 mo)	stable sit  (normal at 7-8 mo)	pivots (rotates)  (normal at 9 mo)	Observed: Reported (age):
Voluntary grasp	no grasp	uses whole hand	index finger and thumb but immature grasp	pincer grasp		Observed: Reported (age):
Ability to kick (in supine)	no kicking	kicks horizontally legs do not lift	upward (vertically)  (normal at 3 mo)	touches leg  (normal at 4-5 mo)	touches toes  (normal at 5-6 mo)	Observed: Reported (age):
Rolling	no rolling	rolling to side (normal at 4 mo)	prone to supine (normal at mo)	supine to prone (normal at mo)		Observed: Reported (age):
Crawling	does not lift head	on elbow  (normal at 3 mo)	on outstretched hand  (normal at 4 mo)	crawling flat on abdomen  (normal at 8 mo)	crawling on hands and knees  (normal at 10 mo)	Observed: Reported (age):
Standing	does not support weight	supports weight (normal at 4 mo)	stands with support (normal at 7 mo)	stands unaided (normal at 12 mo)		Observed: Reported (age):
Walking		bouncing (normal at 6 mo)	cruising (walks holding on) (normal at 12 mo)	walking independently (normal at 15 mo)		Observed: Reported (age):

SECTION 3: BEHAVIOUR

	1	2	3	4	5	6	Comment
State of consciousness	unrousable	drowsy	sleepy but wakes easily	awake but no interest	loses interest	maintains interest	
Emotional state	irritable, not consolable	irritable, mother can console	irritable when approached	neither happy or unhappy	happy, smiling		
Social orientation	avoiding, withdrawn	hesitant	accepts approach	friendly			

Score for behaviour:

Appendix 3. The proforma of the Touwen examination

EXAMINATION OF THE CHILD WITH MINOR NEUROLOGICAL DYSFUNCTION
(Hadders-Algra 2010)

Name of child: Sex:
Birth-date: Age:
Date of examination: Project:

General remarks: (note behavioral state and reactivity during examination!)

In case of asymmetry, enter score of worse side into computer scoring system.

ASSESSMENT DURING SITTING

Sitting:
0 = can without help of hands
1 = can, but needs help of hands
2 = cannot

PT[1] Posture during sitting:

Head:
0 = typical
1 = mildly abnormal R / L / R & L:
2 = definitely abnormal R / L / R & L:

Trunk:
0 = typical
1 = mildly abnormal R / L / R & L:
2 = definitely abnormal R / L / R & L:

Arms:
0 = typical
1 = mildly abnormal R / L / R & L:
2 = definitely abnormal R / L / R & L:

Legs:
0 = typical
1 = mildly abnormal R / L / R & L:
2 = definitely abnormal R / L / R & L:

Extended arms in pronation:
0 = typical
1 = mild unilateral deviation:
2 = mild bilateral deviation:
3 = marked unilateral deviation:
4 = marked bilateral deviation:

Extended arms in supination:
0 = typical
1 = mild unilateral pronation/flexion/deviation:
2 = mild bilateral pronation/flexion/deviation:
3 = marked unilateral pronation/flexion/deviation:
4 = marked bilateral pronation/flexion/deviation:

Involuntary movements:

I-Ath	athetotiform	0 = –	1 = +	2 = ++	3 = +++
I-Ch	choreiform	0 = –	1 = +	2 = ++	3 = +++
I-Tr	tremor	0 = –	1 = +	2 = ++	3 = +++

A Mouth opening finger spreading phenomenon:

		L				R			
Raw score:									
During mouth opening:	A	0	1	2	3	0	1	2	3
During closing eyes:	B	0	1	2	3	0	1	2	3
While sticking out tongue:	C	0	1	2	3	0	1	2	3

0 = no associated activity in rest of body
1 = age-adequate degree of associated activity
2 = excessive associated activity

Co Kicking :
0 = typical
1 = mildly abnormal R / L / R & L:
2 = definitely abnormal R / L / R & L:

---

[1] Abbreviations in first column refer to the domain of dysfunction to which the signs noted at a specific test might be attributed. A = associated movements, Ath = Athetoid movements, Ch = choreiform movements, CN = cranial nerves, Co = coordination, F = fine manipulation, PT = posture & muscle tone, R = reflexes, S = sensory function.

Co Response to being pushed:
0 = typical
1 = mildly abnormal R / L / R & L:
2 = definitely abnormal R / L / R & L:

Voluntary relaxation:
0 = easy 1 = difficult 2 = refuses

Muscle power:

Head:
0 = typical
1 = mildly abnormal:
2 = definitely abnormal:

Trunk:
0 = typical
1 = mildly abnormal:
2 = definitely abnormal:

Arms:
0 = typical to relatively high
1 = mildly abnormal R / L / R & L:
2 = definitely abnormal R / L / R & L:

Legs
0 = typical to relatively high
1 = mildly abnormal R / L / R & L:
2 = definitely abnormal R / L / R & L:

PT Resistance to passive movements: ↓ = hypotonia ↑ = hypertonia ↕ = variable muscle tone

Head:
0 = typical
1 = mildly abnormal: ↓ ↑ ↕
2 = definitely abnormal: ↓↓ ↑↑ ↕↕

Trunk:
0 = typical
1 = mildly abnormal: ↓ ↑ ↕
2 = definitely abnormal: ↓↓ ↑↑ ↕↕

Arms:
0 = typical
1 = mildly abnormal ↓ ↑ ↕ R / L / R & L:
2 = definitely abnormal ↓↓ ↑↑ ↕↕ R / L / R & L:

Legs:
0 = typical
1 = mildly abnormal ↓ ↑ ↕ R / L / R & L:
2 = definitely abnormal ↓↓ ↑↑ ↕↕ R / L / R & L:

Range of movements: ↓ = movement restriction ↑ = excessive range of movement
Head:
0 = typical
1 = mildly abnormal ↓ ↑
2 = definitely abnormal: ↓↓ ↑↑

Trunk:
0 = typical
1 = mildly abnormal: ↓ ↑
2 = definitely abnormal ↓↓ ↑↑

Arms:
0 = typical
1 = mildly abnormal ↓ ↑ R / L / R & L:
2 = definitely abnormal ↓↓ ↑↑ R / L / R & L:

Legs:
0 = typical
1 = mildly abnormal ↓ ↑ R / L / R & L:
2 = definitely abnormal ↓↓ ↑↑ R / L / R & L:

R Reflexes:

Arms: intensity	0 = typical	1 = abnormal	↓ ↑	R / L / R & L:
threshold	0 = typical	1 = abnormal	↑ ↓	R / L / R & L:
Legs:				
intensity	0 = typical	1 = abnormal	↓ ↑	R / L / R & L:
threshold	0 = typical	1 = abnormal	↑ ↓	R / L / R & L:

R Footsole response: 0 = typical: ↓ / –
1 = abnormal: ↑ R / L / R & L:

R Plantar grasp: 0 = bilaterally absent
1 = unilaterally present R / L
2 = bilaterally present

ASSESSMENT DURING STANDING

Standing: 0 = can without help of hands
1 = can, but needs help of hands
2 = cannot

PT Posture during standing:

Head:		Trunk:	
0 = typical		0 = typical	
1 = mildly abnormal	R / L / R & L:	1 = mildly abnormal	R / L / R & L:
2 = definitely abnormal	R / L / R & L:	2 = definitely abnormal	R / L / R & L:
Arms:		Legs:	
0 = typical		0 = typical	
1 = mildly abnormal	R / L / R & L:	1 = mildly abnormal	R / L / R & L:
2 = definitely abnormal	R / L / R & L:	2 = definitely abnormal	R / L / R & L:

R Abdominal skin reflex: 0 = symmetrically present
1 = unilaterally absent R / L
2 = bilaterally absent

Co Romberg: 0 = typical performance, stands still / only moves ankles or toes
1 = mildly abnormal, shows body and arm movements
2 = definitely abnormal, loses balance, falls to R / L / R & L:

Test for involuntary movements: (0 = absent → 3 = continuously and clearly present)

		L				R			
I-Ch	distal choreiform movements	0	1	2	3	0	1	2	3
I-Ch	proximal choreiform movements	0	1	2	3	0	1	2	3
I-Ath	athetotiform movements	0	1	2	3	0	1	2	3
I-Tr	tremor	0	1	2	3	0	1	2	3

Co Response to being pushed: 0 = typical performance, keeps balance
1 = mildly abnormal, steps too frequently aside R / L / R & L:
2 = definitely abnormal, loses balance R / L / R & L:

Co Diadochokinesis:

Performance: 0 = typical, age-adequate
1 = mildly abnormal R / L / R & L:
2 = definitely abnormal, serious dysdiadochokinesis R / L / R & L:

A associated movements: 0 = absent
(diadocho) 1 = present, age-adequate R / L / R & L:
2 = present, exceeding age-appropriate norms R / L / R & L:

Co Finger-nose test:
with eyes open: 0 = typical, age-adequate performance
1 = mildly abnormal R / L / R & L:
2 = definitely abnormal R / L / R & L:

with eyes closed:
0 = typical, age-adequate performance
1 = mildly abnormal R / L / R & L:
2 = definitely abnormal R / L / R & L:

Co Fingertip-touching test:
with eyes open:
0 = typical, age-adequate performance
1 = mildly abnormal R / L / R & L:
2 = definitely abnormal R / L / R & L:

with eyes closed:
0 = typical, age-adequate performance
1 = mildly abnormal R / L / R & L:
2 = definitely abnormal R / L / R & L:

Finger opposition test:
F smoothness:
0 = typical, age-adequate
1 = mildly abnormal R / L / R & L:
2 = definitely abnormal, serious difficulties in performing R / L / R & L:

F transition:
0 = typical, age-adequate
1 = mildly abnormal R / L / R & L:
2 = definitely abnormal, serious difficulties in performing R / L / R & L:

A associated movements:
0 = absent
1 = present, age-adequate R / L / R & L:
2 = present, exceeding age-appropriate norms R / L / R & L:

F Follow-a-finger test:
0 = typical, age-adequate
1 = mildly abnormal R / L / R & L:
2 = definitely abnormal, serious difficulties in performing R / L / R & L:

F Circle test :
opposite direction
0 = typical, age-adequate
1 = mildly abnormal R / L / R & L:
2 = definitely abnormal, serious difficulties in performing R / L / R & L:

same direction
0 = typical, age-adequate
1 = mildly abnormal R / L / R & L:
2 = definitely abnormal, serious difficulties in performing R / L / R & L:

transition
0 = immediately follows changes of direction
1 = has problems in the transition from one movement form into another

ASSESSMENT OF WALKING

Walking:
0 = can without help of hands
1 = can, but needs help of hands
2 = cannot

PT Posture during walking:

Head:
0 = typical
1 = mildly abnormal, R / L / R & L:
2 = definitely abnormal, R / L / R & L:

Trunk:
0 = typical
1 = mildly abnormal, R / L / R & L:
2 = definitely abnormal, R / L / R & L:

Arms:
0 = typical
1 = mildly abnormal, R / L / R & L:
2 = definitely abnormal, R / L / R & L:

Legs:
0 = typical
1 = mildly abnormal, R / L / R & L:
2 = definitely abnormal, R / L / R & L:

Feet:
0 = typical
1 = mildly abnormal, R / L / R & L:
2 = definitely abnormal, R / L / R & L:

Gait
width:
0 = typical
1 = abnormal: narrow / broad

Quality of gait:
0 = typical
1 = abnormal:

Heel-toe gait:
0 = adequate heel-toe gait
1 = mildly abnormal: does not adequately roll from heel to toe or walks occasionally on tiptoe, R / L / R & L:
2 = walks consistently on tiptoe R / L / R & L:

Co Walking on a straight line:
0 = typical, age-adequate
1 = mildly abnormal,
2 = definitely abnormal, cannot perform or frequently loses balance

Walking on tiptoe:
Performance
0 = typical, age-adequate
1 = mildly abnormal R / L / R & L:
2 = definitely abnormal, cannot perform R / L / R & L:

A associated movements:
0 = absent
1 = present, age-adequate R / L / R & L:
2 = present, exceeding age-appropriate norms R / L / R & L:

Walking on heels:
Performance:
0 = typical, age-adequate
1 = mildly abnormal R / L / R & L:
2 = definitely abnormal, cannot perform R / L / R & L:

A associated movements:
0 = absent
1 = present, age-adequate R / L / R & L:
2 = present, exceeding age-appropriate norms R / L / R & L:

Co Standing on one leg:

	L		R	
duration in seconds (test max 20 s)	.....		.....	
toe flexion	–	+	–	+
swaying	–	+	–	+

0 = typical, age-adequate
1 = mildly abnormal
2 = definitely abnormal, serious difficulties to perform

Co Hopping:

	L		R	
number of hops (at least 20)	.....		.....	
at same spot	–	+	–	+
on toes	–	+	–	+

0 = typical, age-adequate
1 = mildly abnormal
2 = definitely abnormal, serious difficulties to perform

Co Knee-heel test:
accurate placing:
0 = typical, age-adequate
1 = mildly abnormal R / L / R & L:
2 = definitely abnormal, serious difficulties to perform R / L / R & L:

sliding heel:
0 = typical, age-adequate
1 = mildly abnormal R / L / R & L:
2 = definitely abnormal, serious difficulties to perform R / L / R & L :

S Graphaesthesia:
0 = adequate
1 = inadequate R / L / R & L:

S Kinaesthesia:
0 = adequate
1 = inadequate hands: R / L / R & L: feet: R / L / R & L:

S Sense of position:
0 = adequate
1 = inadequate hands: R / L / R & L: feet: R / L / R & L:

ASSESSMENT OF HEAD AND CRANIAL NERVES

CN Facial motility:
0 = typical
1 = abnormal R / L / R & L:

S Spectacles:
0 = no
1 = pos. glasses, about .....D
2 = neg. glasses, about .....D

CN Position of the eyes:
0 = typical
1 = heterophoria: R / L / R & L
2 = convergent strabismus: R / L / R & L
3 = otherwise abnormal

CN Fixation:
0 = typical
1 = abnormal:

I-Ch during fixation choreiform movements eyes – + ++
choreiform movements face – + ++

CN Pupillary reactions:
0 = typical and symmetrical
1 = abnormal R / L / R & L:

CN Pursuit movements of the eyes:
0 = typical in all directions
1 = abnormal: movements in all directions, but jerky quality
2 = abnormal: imbalancement of the eyes
3 = abnormal: movements limited in specific directions:

I-Ch during pursuit choreiform movements eyes – + ++
choreiform movements face – + ++

CN Nystagmus:
0 = bilaterally absent
1 = unilaterally present R / L
2 = bilaterally present

S Visual fields:
0 = typical
1 = abnormal R / L / R & L:

S Hearing: indications for deficits
0 = no
1 = yes R / L / R & L:

Tongue:

CN motility
0 = typical
1 = abnormal:

I-Ch choreiform movements: – + ++

Speech:
0 = typical
1 = abnormal:

CN Pharyngeal arches:
0 = symmetrically typical
1 = asymmetrical:

BODY-SCHEME

Basic knowledge body parts
0 = age-adequate
1 = inadequate:

Knowledge of left-right
0 = age-adequate
1 = inadequate:

Crossing / Non crossing midline
0 = age-adequate
1 = inadequate:

ANTHROPOMETRIC DATA

Head circumference ..... cm

Weight: ..... kg

Length: ..... cm

GENERAL

Quantity of motility:
0 = typical
1 = abnormal: ↓ ↑

Quality of motility:
0 = typical, fluent
1 = abnormal, describe:

Hand-preference:
0 = R
1 = L
2 = ambidexter

SUMMARY

PT	POSTURE	0 = typical 1 = mildly abnormal: 2 = definitely abnormal:	
PT	TONUS ARMS	0 = normotonic 1 = hypotonic 2 = hypertonic	3= changing between hypo- and hypertonia 4 = asymmetry:
PT	TONUS LEGS	0 = normotonic 1 = hypotonic 2 = hypertonic	3= changing between hypo- and hypertonia 4 = asymmetry:
R	REFLEXES ARMS	intensity 0 = normal, medium 1 = low 2 = high 3 = asym: threshold 0 = normal, medium 1 = high 2 = low 3 = asym:	
R	REFLEXES LEGS	intensity 0 = normal, medium 1 = low 2 = high 3 = asym: threshold 0 = normal, medium 1 = high 2 = low 3 = asym:	
R	OTHER REFLEXES	footsole response 0 = normal 1 = Babinski sign: R / L / R&L plantar grasp reaction 0 = absent 1 = present: R / L / R&L abdominal skin reflex 0 = present 1 = absent: R / L / R&L	
I	INVOLUNTARY MOVEMENTS		
I-Ch	choreiform movements	0 = – 1 = + 2 = ++ 3 = asym:	
I-Ath	athetotiform movements	0 = – 1 = + 2 = ++ 3 = asym:	
I-Tr	tremor	0 = – 1 = + 2 = ++ 3 = asym:	
Co	COORDINATION PROBLEMS	0 = no problems 1 = some problems 2 = criteria for dysfunctional domain fulfilled	R / L / R & L R / L / R & L
F	FINE MANIPULATIVE DISABILITY	0 = no problems 1 = some problems 2 = criteria for dysfunctional domain fulfilled	R / L / R & L R / L / R & L
A	ASSOCIATED MOVEMENTS	0 = absent 1 = present, age-adequate 2 = present, exceeding age-appropriate norms	R / L / R & L R / L / R & L
S	SENSORY DEFICITS	0 = no 1 = some problems 2 = criteria for dysfunctional domain fulfilled	R / L / R & L R / L / R & L
CN	CRANIAL NERVE DYSFUNCTIONS	0 = no 1 = yes:	

CONCLUSION **0 = NORMAL** **In case of dysfunctional domain, note which:**
1 = SIMPLE MND:
2 = COMPLEX MND:
3 = CP:

Appendix 4. The free Finnish translation of the proforma of the Movement Assessment Battery for Children-2

MOVEMENT ABC (11-16v)

Nuppien kääntäminen

dominoiva käsi								ei-dominoiva käsi							
1		11,0-11,11	12,0-12,11	13,0-13,11	14,0-14,11	15,0-15,11	16,0-16,11	1		11,0-11,11	12,0-12,11	13,0-13,11	14,0-14,11	15,0-15,11	16,0-16,11
2		25sek	22sek	22sek	22sek	22sek	22sek	2		31sek	26sek	26sek	26sek	26sek	26sek

Kolmion kokoaminen ruuveilla ja muttereilla

1		11,0-11,11	12,0-12,11	13,0-13,11	14,0-14,11	15,0-15,11	16,0-16,11
2		55sek	48sek	48sek	48sek	48sek	48sek

Reitti-piirustustehtävä

	virheiden määrä
1	
2	

Yhdellä kädellä kiinniotto

oikea										yhteensä:
vasen										yhteensä:

Kohteeseen heittäminen

										yhteensä:

Tandemseisonta kahden tasapainolaudan päällä

	aika / sek
1	
2	

Tandemkävely viivaa pitkin takaperin

	askelten määrä	linja loppuun
1		K / E
2		K / E

Matoilla hyppiminen yhdellä jalalla

oikea jalka	hyppyjen määrä	vasen jalka	hyppyjen määrä
1		1	
2		2	

Muita huomioita:

Appendix 5. The free Finnish translation of the Developmental Coordination Disorder Questionnaire 2007

DCDQ

Nimi:_____ Syntymäaika: _____ID:_____

1. Lapsesi *heittää palloa* hallitusti ja tarkasti.

1 **2** **3** **4** **5**

2. Lapsesi *saa kiinni* pienen, n. tennispallon kokoisen *pallon*, joka on heitetty 1.8-2.4 metrin päästä. (2-2,5m?)

1 **2** **3** **4** **5**

3. Lapsesi *osuu* tarkasti *lähestyvään palloon tai sulkapalloon* mailalla.

1 **2** **3** **4** **5**

4. Lapsesi *hyppii* helposti puutarhassa tai leikkipuistossa olevien esteiden *yli*.

1 **2** **3** **4** **5**

5. Lapsesi *juoksee* yhtä nopeasti ja *samalla tavalla* kuin muut samanikäiset ja samaa sukupuolta olevat lapset.

1 **2** **3** **4** **5**

6. Jos lapsesi *suunnittelee* tekevänsä jonkin *motorisen liikkeen*, hän saa järjestettyä kehonsa niin, että onnistuu tämän liikkeen toteuttamisessa (esim. rakentaessaan pahvilaatikoista linnaketta tai siirtäessään välineitä leikkikentällä).

1 **2** **3** **4** **5**

7. Lapsesi kirjainten jäljentäminen, piirtäminen ja *kirjoittaminen* luokassa on riittävän *nopeaa*muiden luokkalaisten tahdissa pysymisen kannalta.

1 **2** **3** **4** **5**

8. Lapsesi jäljentämät tai *kirjoittamat* kirjaimet, numerot ja sanat ovat *luettavia*, huoliteltuja ja tarkkoja, tai jos lapsesi ei vielä jäljennä kirjaimia, hän *värittää* ja *piirtää*järjestelmällisellä tavalla ja tekee tunnistettavia kuvia.

1 **2** **3** **4** **5**

9. Lapsesi käyttää asianmukaisesti *voimaa*jäljentäessään/kirjoittaessaan/piirtäessään (*ei purista* liikaa kynää, kirjoitus ei ole liian tummaa/raskasta, eikä liian keveää).

1 **2** **3** **4** **5**

10. Lapsesi *leikkaa irti* kuvia ja *muotoja* tarkasti ja vaivatta.

1 **2** **3** **4** **5**

11. Lapsesi on innostunut ja *pitää urheilusta* tai *hyviä motorisia taitoja vaativista leikeistä*.

1 **2** **3** **4** **5**

12. Lapsesi oppii *uusia motorisia taitoja* (kuten uiminen ja rullaluistelu) helposti, eikä saman taitotason kehittyminen vaadi enemmän harjoitusta tai aikaa kuin muilla lapsilla.

1 **2** **3** **4** **5**

13. Lapsesi *osaava ja nopea*jälkiensä siistimisessä, kenkien jalkaan laittamisessa, kengännauhojen sitomisessa, pukeutumisessa, jne.

1 **2** **3** **4** **5**

14. Lastasi ei *koskaan* kuvattaisi sanonnalla "*kuin norsu posliinikaupassa*" (siis sellaisena, joka saattaa kömpelyytensä takia rikkoa jotakin särkyvää pienessä tilassa).

1 **2** **3** **4** **5**

15. Lapsesi *ei väsy helposti* tai vaikuta retkottavan tuolilla tai putoavan siltä, jos häntä vaaditaan istumaan pitkiä aikoja.

1 **2** **3** **4** **5**

1= ei lainkaan kuin lapsesi

2= hieman kuin lapsesi

3= jokseenkin kuin lapsesi

4= melkein kuin lapsesi

5= kuin lapsesi

	Hallinta liikkeen aikana (1-6)	Hienomotoriikka/Käsin kirjoitus (7-10)	Yleinen koordinaatio (11-15)
1. Heittää palloa			
2. Ottaa pallon kiinni			
3. Osuu palloon/sulkapalloon			
4. Hyppää yli			
5. Juoksee			
6. Suunnittelee liikkeen			
7. Kirjoittaa nopeasti			
8. Kirjoittaa luettavasti			
9. Yritys ja paine/voima			
10. Leikkaa			
11. Pitää urheilusta			
12. Oppii uusia taitoja			
13. Nopea ja osaava			
14. "Norsu posliinikaupassa"			
15. Ei väsy			

Summa _____/30 + _____/20 + _____/25 = _____/75

Lapset 5 v 0 kk – 7 v 11 kk

15-46 DCD:n indikaattori tai epäily

47-75 todennäköisesti ei DCD

Lapset 8 v 0 kk - 9 v 11 kk

15-55 DCD:n indikaattori tai epäily

56-75 todennäköisesti ei DCD

Lapset 10 v 0 kk – 15 v

15-57 DCD:n indikaattori tai epäily

58-75 todennäköisesti ei DCD

ORIGINAL PUBLICATIONS I–IV

ACTA PÆDIATRICA
NURTURING THE CHILD

Acta Pædiatrica ISSN 0803-5253

I

REGULAR ARTICLE

Predictive value of neonatal brain MRI on the neurodevelopmental outcome of preterm infants by 5 years of age

Sirkku Setänen (sirkku.a.setanen@utu.fi)[1,2], Leena Haataja[1,2], Riitta Parkkola[2,3,4], Annika Lind[5,6], Liisa Lehtonen[2,5] and the PIPARI Study Group

1.Department of Pediatric Neurology, Turku University Hospital, Turku, Finland
2.Department of Medicine, University of Turku, Turku, Finland
3.Department of Radiology, Turku University Hospital, Turku, Finland
4.Turku PET Center, Turku University Hospital, Turku, Finland
5.Department of Pediatrics, Turku University Hospital, Turku, Finland
6.Department of Psychology, University of Turku, Turku, Finland

Keywords
Cognitive Development, CP, Follow-up

Correspondence
S Setänen, Department of Pediatric Neurology, Turku University Hospital, Kiinamyllynkatu 5-8, Turku 20520, Finland.
Tel: +358 45 637 3420 |
Fax: +358 2 313 1460 |
Email: sirkku.a.setanen@utu.fi

Received
12 December 2012; revised 30 January 2013; accepted 4 February 2013.

DOI:10.1111/apa.12191

ABSTRACT

Aim: To study the prognostic value of MRI in preterm infants at term equivalent age for cognitive development at 5 years of age.

Methods: A total of 217 very low birth weight/very low gestational age infants who all received brain MRI at term equivalent age were categorized into 4 groups based on the brain MRI findings. Cognitive development was assessed at 5 years of chronological age by using a short form of Wechsler Preschool and Primary Scale of Intelligence – Revised. This information was combined with neurosensory diagnoses by 2 years of corrected age.

Results: Of all infants 31 (17.0%) had Full Scale Intelligence Quotient (FSIQ) <85, 14 (6.5%) had cerebral palsy and 4 (1.8%) had severe hearing impairment. A total of 41 (22.0%) infants had some neurodevelopmental impairment at 5 years of age. Considering cognitive outcome (FSIQ <85), the positive predictive value of several major MRI pathologies was 43.8%, and the negative predictive value of normal finding or minor pathologies was 92.0% and 85.7%, respectively.

Conclusion: The MRI of the brain at term equivalent age may be valuable in predicting neurodevelopmental outcome in preterm infants by 5 years of age. The findings should always be interpreted alongside the clinical information of the infant. Furthermore, MRI should not replace a long-term clinical follow-up for very preterm infants.

INTRODUCTION

There has been conflicting views of the routine use of brain magnetic resonance imaging (MRI) as a part of the assessment protocol in the care of a very preterm infant (1). The MRI can be helpful in identifying children for closer follow-up and in directing research for focused risk groups, in quality surveillance purposes of the neonatal care and in providing parents information of either decreased or increased developmental risks. Recently, for example, performing MRI at term without asking parental permission was questioned (2). Furthermore, there are situations when MRI increases rather than decreases parents' concerns and confusion, if the knowledge of the prognostic significance of the findings is not sufficient. To obtain more accurate information of the prognostic value of MRI findings, we need to differentiate between those findings that are associated with major consequences and those that do not cause significant clinical concern. This requires detailed information of long-term follow-up studies which have evaluated both neurosensory and cognitive outcomes of preterm infants with neonatal MRI (3). We have previously reported the positive (PPV) and negative (NPV) predictive values of abnormal MRI findings on

Abbreviations
CP, cerebral palsy; FSIQ, Full Scale Intelligence Quotient; MRI, magnetic resonance imaging; NDI, neurodevelopmental impairment; NPV, negative predictive value; PPV, positive predictive value; VLBW, very low birth weight; VLGA, very low gestational age; V/B, ventricular/brain.

Key notes

- The brain MRI in preterm infants at term equivalent age provides additional information aiding the clinician to identify those infants who are later at a high risk of neurodevelopmental impairment.
- The interpretations of MRI findings should always be carried out together with the clinical picture of the infant.
- A long-term follow-up of preterm infants is needed, irrespective of brain imaging findings.

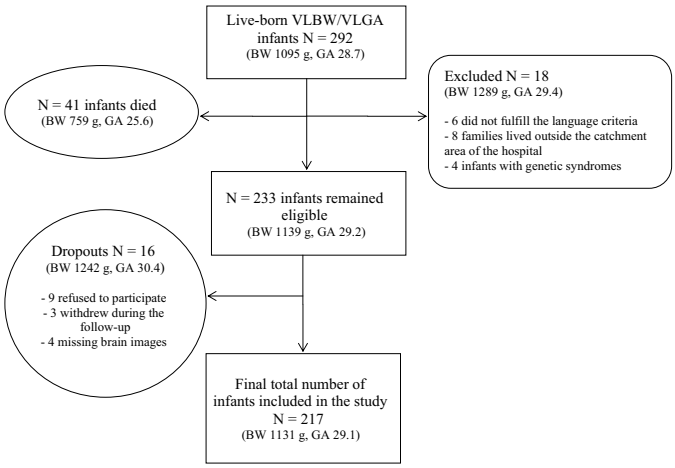


Figure 1 The flow chart of the participants, mean birth weights (BW) and gestational ages (GA) in weeks.

neurodevelopmental impairments (NDI) at the corrected age of 2 years in this cohort including 182 very low birth weight (VLBW) infants. A major pathological MRI finding at term had 33.3% PPV and normal MRI finding 98.1% NPV on NDI at 2 years of age (4). These findings are consistent with earlier studies showing that abnormal MRI findings at term equivalent age may predict an adverse neurodevelopmental outcome at 2 years of age (5).

Our aim was to study the prognostic value of MRI at term equivalent age in very preterm infants using cognitive test results at 5 years of age as an end point. We hypothesized that major brain pathologies in MRI in very preterm infants at term equivalent age predict neurodevelopmental impairments at 5 years of age.

PATIENTS AND METHODS

Participants

This prospective study is a part of the multidisciplinary PIPARI Study (The Development and functioning of Very Low Birth Weight Infants from Infancy to School Age). The PIPARI Study group consists of VLBW or very low gestational age (VLGA) infants born between 2001 and 2006, in the Turku University Central Hospital. The inclusion criteria from 2001 to the end of 2003 included birth weight $\leq$1500 grams in preterm infants (born <37 gestational weeks). From the beginning of 2004, the inclusion criteria were expanded to include all infants below the gestational age of 32 weeks at birth, even if the birth weight exceeded 1500 g. In addition, at least one of the parents had to speak either Finnish or Swedish. Fig. 1 shows the flow chart of the participants. All parents provided written consent after receiving oral and written information. The PIPARI Study protocol was approved by the Ethics Review Committee of the Hospital District of the South-West Finland in December 2000.

Magnetic resonance imaging of the brain

The MRI of the brain was performed at term. The imaging took place during postprandial sleep without any pharmacological sedation or anaesthesia. The infants were swaddled to calm them and to reduce movement artefacts in the imaging. A pulse oximeter was routinely used during MRI examinations. Ear protection was also used (3M Disposable Ear Plugs 1100; 3M, Brazil and Wurth Hearing protector, Art.-Nr. 899 300 232, Wurth, Austria). For 125 infants born between 2001 and 2003, the MRI equipment was an open 0.23-T Outlook GP (Philips Medical, INC, Vantaa, Finland) equipped with a multipurpose flexible coil fitting the head of the infant, until it was upgraded to the 1.5-T Philips Intera (Philips Medical Systems, Best Netherlands) for the remainder of the study infants (n = 73) born between 2004 and 2006 (6).

Axial T2-weighted images, coronal three-dimensional T1-weighted images and coronal T2-weighted images of the entire brain were obtained when using the 0.23-T equipment. With the 1.5-T equipment, axial T2-weighted, axial T1-weighted and sagittal T2-weighted images were obtained. All of the sequences were optimized for imaging of the term infant brain. The total imaging time was about 25 min. The extracerebral space was measured manually from the MRIs. A cut-off value of 4 mm was used according to the study by McArdle (7). The width of the extracerebral space was measured in front of the frontal lobe, where the extracerebral fluid space is widest. The group of infants with an extracerebral space of 5 mm was analysed separately, because accuracy of the measurement was 1 mm. V/B ratio refers to [the width of the frontal horns of the lateral

Table 1 The classification of MRI findings

Normal findings
Normal brain anatomy (cortex, basal ganglia and thalami, posterior limb of internal capsule, white matter, germinal matrix, corpus callosum and posterior fossa structures)
A width of extracerebral space <5 mm, ventricular/brain ratio <0.35
No ventriculitis
Minor pathologies
Consequences of intraventricular haemorrhages grade 1 and 2
Caudothalamic cysts
A width of the extracerebral space of 5 mm
A V/B ratio of 0.35
Major pathologies
Consequences of intraventricular haemorrhages grade 3 and 4
Injury in cortex, basal ganglia, thalamus or internal capsule, with injury of corpus callosum, cerebellar injury, white matter injury
An increased width of extracerebral space >5 mm
A V/B ratio >0.35, ventriculitis
Other major brain pathology (infarcts)

ventricles] divided by [the width of the brain tissue at the same plane of cerebral image] (6).

The brain MRI was evaluated by one neuroradiologist (R. Parkkola) blinded to both the clinical data and to the result of the brain ultrasound examinations.

Classification of the study groups

The brain MRI findings were categorized into normal findings, minor pathologies and major pathologies as described previously (6) (Table 1). To evaluate the relation between brain pathology and neurodevelopmental outcome, the infants were categorized into 4 groups, based on the MRI findings at term: (i) normal group, (ii) one or more minor brain pathologies, (iii) one major brain pathology and (iv) several major brain pathologies. If a patient had both minor and major findings, the classification was done according to the number of major pathologies: one major pathology (n = 33, 15.2%) and several major pathologies (n = 25, 11.5%).

Neurodevelopmental outcome

The children's cognitive level at 5 years of chronological age (+0–2 months) was evaluated by a psychologist using a short form of Wechsler Preschool and Primary Scale of Intelligence – Revised, Finnish translation (WPPSI-R) (8): subtests are information, sentences, arithmetic, block design, geometric design and picture completion, and Full Scale Intelligence Quotient (FSIQ) was estimated (normal M = 100, SD 15.0). A quotient of ≥ 85 (>−1.0 SD) was considered normal intelligence, a quotient of 70–84 (−2.0 SD to −1.0 SD) slightly below normal and a quotient of ≤ 69 (<−2.0 SD) significantly below normal (9).

In addition, neurodevelopmental impairment (NDI) included at least one of the following findings: FSIQ score <85, cerebral palsy (CP), severe hearing impairment or severe visual impairment. We chose to use a cut-off of 85 for FSIQ, which is close to a −2.0 SD level in our control group, a regional cohort of full-term Finnish children (M = 111.7, SD 14.8) (9). A diagnosis of CP was determined during a systematic clinical follow-up by 2 years of corrected age. Severe hearing impairment was defined as hearing loss requiring amplification in at least one ear or hearing impairment with a cut-off of 40 dB. Hearing was systematically screened in early infancy (at 1 month of corrected age) by using brain stem auditory evoked potentials (BAEP). Severe visual impairment was categorized as a visual acuity <0.3, or blindness (10).

Statistical analysis

The NPV was defined as the percentage of children with no or minor brain pathology in the MRI, resulting in an average developmental outcome without NDI. The PPV was defined as the percentage of children with one or more major brain pathologies in the MRI, resulting in an abnormal developmental outcome with NDI.

RESULTS

The neonatal characteristics are shown according to the brain magnetic resonance imaging (MRI) group at term equivalent age in Table 2.

One hundred and twenty (55.3%) of the infants (n = 217) had normal MRI, 39 (18.0%) one or more minor, 23 (10.6%) one major, 9 (4.2%) several major and 27 (12.4%) minor and major findings in the MRI at term equivalent age.

One hundred and seventy-eight of 217 (82.0%) WPPSI-R assessments were completed. There were 4 (1.8%) children who were too severely handicapped to be assessed. They were included in the analysis as having a significant cognitive delay (FSIQ <70) at the age of 5 years. Of all the infants, 31 (17.0%) had FSIQ<85, 14 (6.5%) had CP, and 4 (1.8%) had severe hearing impairment. There were no children with severe visual impairment. A total of 41 (22.0%) infants had NDI at 5 years of age. (Table 3).

The most common major pathologies were white matter injury (n = 29, 13.4%), capsula interna injury (n = 21, 9.7%), ventriculitis (n = 21, 9.7%) and a ventricular/brain (V/B) ratio >0.35 (n = 21, 9.7%). There were 7 different single major findings (n = 33, 15.2%) (capsula interna injury, white matter injury, ventriculitis, corpus callosum injury, haemorrhage in posterior fossa structures, V/B ratio >0.35, extracerebral space >5 mm) associated with NDI in some children. The minor pathologies were consequences of intraventricular haemorrhages grade 1 (n = 49, 22.6%), an extracerebral space of 5 mm (n = 15, 6.9%) and a V/B ratio of 0.35 (n = 9, 4.1%).

Considering cognitive outcome (FSIQ <85), the PPV of several major findings was 43.8%, and the NPV of normal or minor findings was 92.0% and 85.7%, respectively (Table 3). The distribution of FSIQ at 5 years of age in MRI groups is shown in Table 4. Considering NDI, the PPV of several major findings was 75.0%, and the NPV of normal or minor findings was 91.0% and 85.7%, respectively (Table 3).

Table 2 Neonatal characteristics are shown according to the brain magnetic resonance imaging (MRI) group at term equivalent age

	Normal findings	One or more minor pathologies	One major pathology	Several major pathologies
Birth weight, mean (SD) [minimum, maximum], g	1195.8 (311.4) [580, 2120]	1106.5 (347.8) [400, 1940]	1012.9 (340.2) [525, 1730]	1014.6 (315.7) [560, 1675]
Gestational age at birth, mean (SD) [minimum, maximum], wk	29.7 (2.6) [24.0, 35.9]	28.5 (2.7) [24.0, 33.0]	28.3 (2.5) [23.0, 32.1]	28.2 (3.1) [23.4, 35.1]
Males, n (%)	63 (52.5)	22 (56.4)	24 (72.7)	13 (52.0)
Females, n (%)	57 (47.5)	17 (43.6)	9 (27.3)	12 (48.0)
Cesarean section, n (%)	79 (65.8)	25 (64.1)	21 (63.6)	9 (36.0)
Small for gestational age, n (%)	45 (37.5)	14 (35.9)	14 (42.4)	8 (32.0)
Bronchopulmonary dysplasia, n (%)	7 (5.8)	9 (23.1)	8 (24.2)	5 (20.0)
Sepsis, n (%)	18 (15.1)	7 (18.4)	7 (21.2)	3 (12.0)
Operated necrotizing enterocolitis, n (%)	4 (3.4)	1 (2.6)	4 (12.5)	1 (4.0)
Laser-treated retinopathy, n (%)	1 (0.9)	3 (7.9)	3 (9.4)	1 (4.0)

Table 3 The prevalence of Full Scale Intelligence Quotient (FSIQ) <85, cerebral palsy (CP), severe hearing impairment (use of hearing aid) and neurodevelopmental impairment (NDI) (one or more of the three above-mentioned outcomes) are shown according to the brain magnetic resonance imaging (MRI) group at term equivalent age

	FSIQ<85 (n = 31, 17.0%)	CP (n = 14, 6.5%)	Severe hearing impairment (n = 4, 1.8%)	NDI (n = 41, 22.0%)
Normal findings	NPV = 92.0% (n = 100, 55.0%)	NPV = 99,2% (n = 120, 55.3%)	NPV = 100% (n = 120, 55.3%)	NPV = 91.0% (n = 100, 53.8%)
One or more minor pathologies	NPV = 85,7% (n = 35, 19.2%)	NPV = 100% (n = 39, 18.0%)	NPV = 100% (n = 39, 18.0%)	NPV = 85.7% (n = 35, 18.8%)
One major pathology	PPV = 35.5% (n = 31, 17.0%)	PPV = 6.1% (n = 33, 15.2%)	PPV = 6.1% (n = 33, 15.2%)	PPV = 38.7% (n = 31, 16.7%)
Several major pathologies	PPV = 43.8% (n = 16, 8.8%)	PPV = 44.0% (n = 25, 11.5%)	PPV = 8.0% (n = 25, 11.5%)	PPV = 75.0% (n = 20, 10.8%)

Table 4 The mean values (SD, median and interquartile) of Full Scale Intelligence Quotient (FSIQ) at 5 years of age are shown by categories of MRI findings at term equivalent age

	Mean	SD	Median	Interquartile
Normal findings (n = 100)	104.2	15.0	104.5	93.5–113.0
One or more minor pathologies (n = 35)	102.4	15.6	105.0	92.0–116.0
One major pathology (n = 29)	94.6	18.8	93.0	82.0–107.0
Several major pathologies (n = 14)	86.8	23.4	87.5	70.0–104.0

DISCUSSION

This study shows that brain MRI of very preterm infants at term equivalent age provides additional information in predicting neurodevelopmental outcome at 5 years of age. This information was derived from a regional population of preterm infants with a very high coverage of both MRI and follow-up.

The major MRI pathologies aid clinicians in identifying those infants who are later at a high risk of developmental problems, even though good functional outcome can be achieved despite major lesions. Our findings are in agreement with previous studies with shorter follow-up times (11). The major lesions seen in the brain MRI indicate that the child needs to be followed by a child neurologist, and the possibilities for early interventions have to be evaluated.

Current practice in neonatal care includes brain ultrasound imaging. Therefore, MR imaging provides additional information to ultrasound images. Ultrasound is more sensitive in detecting transient early findings such as small intraventricular haemorrhages. Brain ultrasound examinations can also be used to identify patients requiring MRI, for example, ventriculomegaly indicates a high risk for additional pathologies seen by MRI (6). Although some significant parenchymal lesions can be detected by ultrasound (12), MRI is more sensitive in identifying small lesions in the white matter (13–15) which were shown in this study to be significant for the later development of the child. Our findings are supported by a previous study (16) showing an association between diffuse white matter injury and adverse neurodevelopmental outcome at 2 years of age. MRI is also more sensitive in finding cerebellar lesions (17), which can be difficult to discover in a routine neonatal ultrasound examination, although there are specialists who do master ultrasound scanning of the cerebellum. The value of ultrasound examinations increases if carried out repeatedly in short intervals by an experienced specialist. However,

not all units have the resources for weekly ultrasound examinations exceeding routine levels. Although the interpretation of MRI also requires an expert neuroradiologist, the readings can be centralized without moving the patient from the closest hospital with MRI capacity.

Normal findings or minor pathologies in MRI provide information for families of the good developmental capacity of their child. The NPV of normal MRI was close to 100%. The PPV for any major developmental problem by 5 years of age was also high (75.0%) when MRI findings were graded by severity. Considering only cognitive outcome, the PPV was lower. This is understandable as cognitive impairments have a multifactorial background. It must also be noted that normal FSIQ does not exclude specific neuropsychological impairments.

An MRI should be offered to families stating the good NPV and the PPV of 44%. From the perspective of the family, normal MRI is likely to be relieving. Major brain pathologies are often detected by ultrasound which increases parental anxiety for their child's future development. The combination of ultrasound imaging and brain MRI at term equivalent age provides better definition of the nature of the brain lesion, which may also be relieving from parental point of view. In our study, the predictive efficacy of the brain MRI was better compared with different available perinatal scoring systems of clinical data (18). However, the image of brain structures never equals brain function, and therefore, development can be normal despite major pathologies.

We agree that ultrasound and MRI are complementary techniques in neuroimaging for preterm infants (19). If brain MRI is used routinely, as a part of follow-up protocol (15), the findings have to be interpreted systematically by an experienced neuroradiologist including the most common minor and major pathologies. The clinical significance of the brain MRI should always be interpreted alongside information from ultrasounds, standardized neurological examinations and the medical history of the infant. More research is needed on interventions to optimize the development in those children with major structural brain lesions. Irrespective of brain imaging findings, very preterm infants and their families benefit from a long-term clinical follow-up.

ACKNOWLEDGEMENTS

This work was supported by a grant from the Foundation for Paediatric Research. The PIPARI Study Group: Mikael Ekblad, MD; Satu Ekblad, RN; Eeva Ekholm, MD, PhD; Leena Haataja, MD, PhD; Mira Huhtala, MD; Pentti Kero, MD, PhD; Hanna Kiiski-Mäki, PhD; Riikka Korja, PhD; Harry Kujari, MD; Helena Lapinleimu, MD, PhD; Liisa Lehtonen, MD, PhD; Tuomo Lehtonen, MD; Virva Lepomäki, MA; Marika Leppänen, MD; Annika Lind, PhD; Hanna Manninen, MD; Jaakko Matomäki, MSc; Jonna Maunu, MD, PhD; Petriina Munck, PhD; Sirkku Setänen, MD; Laura Määttänen, MD; Pekka Niemi, PhD; Anna Nyman, MA; Pertti Palo, MD, PhD; Riitta Parkkola, MD, PhD; Jorma Piha, MD, PhD; Liisi Rautava, MD, PhD; Päivi Rautava, MD, PhD; Milla Ylijoki, MD, PhD; Hellevi Rikalainen, MD, PhD; Katriina Saarinen, Physiotherapist; Elina Savonlahti, MD, Matti Sillanpää, MD, PhD; Suvi Stolt, PhD; Päivi Tuomikoski-Koiranen, RN; Timo Tuovinen, BA; Anniina Väliaho, MA, Tuula Äärimaa, MD,PhD.

References

1. Janvier A, Barrington K. Trying to predict the future of ex-preterm infants: who benefits from a brain MRI at term? *Acta Paediatr* 2012; 101: 1016–17.
2. Pearce R, Baardsnes J. Term MRI for small preterm babies: do parents really want to know and why has nobody asked them? *Acta Paediatr* 2012; 101: 1013–15.
3. Hintz SR, O'Shea M. Neuroimaging and neurodevelopmental outcomes in preterm infants. *Semin Perinatol* 2008; 32: 11–19.
4. Munck P, Haataja L, Maunu J, Parkkola R, Rikalainen H, Lapinleimu H, et al. Cognitive outcome at 2 years of age in Finnish infants with very low birth weight born between 2001 and 2006. *Acta Paediatr* 2010; 99: 359–66.
5. Woodward LJ, Anderson PJ, Austin NC, Howard K, Inder TE. Neonatal MRI to predict neurodevelopmental outcomes in preterm infants. *N Engl J Med* 2006; 355: 685–94.
6. Maunu J, Parkkola R, Rikalainen H, Lehtonen L, Haataja L, Lapinleimu H, et al. Brain and ventricles in very low birth weight infants at term: a comparison among head circumference, ultrasound, and magnetic resonance imaging. *Pediatrics* 2009; 123: 617–26.
7. McArdle CB, Richardson CJ, Nicholas DA, Mirfakhraee M, Hayden CK, Amparo EG. Developmental features of the neonatal brain: MR imaging. Part II. Ventricular size and extracerebral space. *Radiology* 1987; 162: 230–4.
8. Wechsler D. *Wechslerin älykkyystestistö esikouluikäisille, käsikirja*. Helsinki: Psykologien kustannus, 1995.
9. Lind A, Korkman M, Lehtonen L, Lapinleimu H, Parkkola R, Matomaki J, et al. Cognitive and neuropsychological outcomes at 5 years of age in preterm children born in the 2000s. *Dev Med Child Neurol* 2011; 53: 256–62.
10. Maunu J, Lehtonen L, Lapinleimu H, Matomaki J, Munck P, Rikalainen H, et al. Ventricular dilatation in relation to outcome at 2 years of age in very preterm infants: a prospective Finnish cohort study. *Dev Med Child Neurol* 2011; 53: 48–54.
11. Skiold B, Vollmer B, Bohm B, Hallberg B, Horsch S, Mosskin M, et al. Neonatal magnetic resonance imaging and outcome at age 30 months in extremely preterm infants. *J Pediatr* 2012; 160: 559–66e1.
12. Jary S, Kmita G, Wroblewska J, Whitelaw A. Quantitative cranial ultrasound prediction of severity of disability in premature infants with post-haemorrhagic ventricular dilatation. *Arch Dis Child* 2012; 97: 955–9.
13. Rademaker KJ, Uiterwaal CS, Beek FJ, van Haastert IC, Lieftink AF, Groenendaal F, et al. Neonatal cranial ultrasound versus MRI and neurodevelopmental outcome at school age in children born preterm. *Arch Dis Child Fetal Neonatal Ed* 2005; 90: F489–93.
14. Ramenghi LA, Fumagalli M, Righini A, Bassi L, Groppo M, Parazzini C, et al. Magnetic resonance imaging assessment of brain maturation in preterm neonates with punctate white matter lesions. *Neuroradiology* 2007; 49: 161–7.
15. Smyser CD, Kidokoro H, Inder TE. Magnetic resonance imaging of the brain at term equivalent age in extremely

premature neonates: to scan or not to scan? *J Paediatr Child Health* 2012; 48: 794–800.
16. Boardman JP, Craven C, Valappil S, Counsell SJ, Dyet LE, Rueckert D, et al. A common neonatal image phenotype predicts adverse neurodevelopmental outcome in children born preterm. *Neuroimage* 2010; 52: 409–14.
17. de Vries LS, van Haastert IC, Benders MJ, Groenendaal F. Myth: cerebral palsy cannot be predicted by neonatal brain imaging. *Semin Fetal Neonatal Med* 2011; 16: 279–87.
18. Zaramella P, Freato F, Milan A, Grisafi D, Vianello A, Chiandetti L. Comparison between the perinatal risk inventory and the nursery neurobiological risk score for predicting development in high-risk newborn infants. *Early Hum Dev* 2008; 84: 311–17.
19. de Vries LS, Cowan FM. Should cranial MRI screening of preterm infants become routine? *Nat Clin Pract Neurol* 2007; 3: 532–3.

Early Human Development 90 (2014) 851–856

Contents lists available at ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

Neurological examination combined with brain MRI or cranial US improves prediction of neurological outcome in preterm infants

Sirkku Setänen [a,*], Katri Lahti [b], Liisa Lehtonen [c], Riitta Parkkola [d], Jonna Maunu [e], Katriina Saarinen [f], Leena Haataja [a]

[a] Department of Pediatric Neurology, University of Turku, Turku University Hospital, Turku, Finland
[b] Department of Medicine, University of Turku, Turku, Finland
[c] Department of Pediatrics, University of Turku, Turku University Hospital, Turku, Finland
[d] Turku PET Center, Turku University Hospital, Turku, Finland
[e] Department of Pediatric Psychiatry, University of Turku, Turku University Hospital, Turku, Finland
[f] Department of Pediatrics, Turku University Hospital, Turku, Finland

ARTICLE INFO

Article history:
Received 22 April 2014
Received in revised form 17 September 2014
Accepted 18 September 2014

Keywords:
Cerebral palsy
The Dubowitz neurologic examination
The Hammersmith Infant Neurological Examination
Long-term development
Predictive value

ABSTRACT

Background: The predictive value of the combination of neurological examination and brain magnetic resonance imaging (MRI) or cranial ultrasound (cUS) in preterm infants is not known.
Aims: To study the prognostic value of the combination of neurological examination and brain MRI at term equivalent age (TEA) or serial neonatal cUS in very preterm infants for neurosensory outcome at 2 years of corrected age.
Study design: A prospective follow-up study.
Subjects: A total of 216 very preterm infants (birth weight 1132 g [SD 331 g]) born in Turku University Hospital, from 2001 to 2006, were included.
Outcome measures: The Dubowitz neurologic examination and brain MRI were done at TEA, and serial cUS examinations were performed until TEA. The Hammersmith Infant Neurological Examination (HINE) and neurosensory impairments (NSI) were assessed at 2 years of corrected age.
Results: Of all infants, 163 (76%) had one or more deviant neurological items at TEA, and 32 (15%) had the HINE total score below the 10th percentile at 2 years of corrected age. A total of 17 (8%) infants had NSI. Neurological examination at TEA improved the negative and positive predictive values of brain MRI for NSI from 99% to 100%, and from 28% to 35%, respectively, and the negative and positive predictive values of cUS from 97% to 100%, and from 61% to 79%, respectively.
Conclusions: The combination of the Dubowitz neurologic examination and the brain MRI at TEA or serial neonatal cUS provides a valuable clinical tool for predicting long-term neurosensory outcome in preterm infants.

1. Introduction

The prognostic value of neonatal brain magnetic resonance imaging (MRI) findings on the long-term developmental outcome of preterm infants has been debated. The current practice in neonatal care includes most commonly only cranial ultrasound (cUS) imaging. MRI has potentially better prognostic value compared to cUS providing more information especially on the white matter and cerebellum. We have previously reported the positive (PPV) and negative (NPV) predictive values of brain pathologies on MRI at term equivalent age (TEA) on neurodevelopmental impairments in a cohort of 217 very low birth weight (VLBW)/very low gestational age (VLGA) infants [1]. Normal MRI findings had NPV of 99.2% on cerebral palsy (CP), but the PPV of major brain pathologies remained low being 6.1% and 44.0% for one or several major pathologies, respectively. We emphasized that MRI findings should always be interpreted in parallel to the clinical information.

The Dubowitz neurologic examination [2,3] is widely used both clinically and in research. The assessment method and the most frequent findings in low-risk full term infants have been described in detail previously [3]. The intra and inter-observer reliabilities of the examination are also known [4]. The Dubowitz neurologic examination can also be used as a quantitative measure. However, the total optimality score (the sum of the optimality scores of individual test items) considered as normal for full-term infants [3] cannot be applied to VLBW preterm infants because the variation in neurological findings at TEA in low-risk preterm infants is much wider compared to term infants [5]. The norms for low-risk preterm infants at TEA have been published in a European multicentre study [6].

* Corresponding author at: Department of Pediatric Neurology, Turku University Hospital, Kiinamyllynkatu 5-8, 20520 Turku, Finland. Tel.: +358 45 637 3420; fax: +358 2 313 1460.
E-mail address: sirkku.a.setanen@utu.fi (S. Setänen).

http://dx.doi.org/10.1016/j.earlhumdev.2014.09.007
0378-3782/

II

The Hammersmith Infant Neurologic Examination (HINE) [7] is based on the same principles as the Dubowitz neurologic examination. The test has been standardized for full-term infants between 12 and 18 months of age [7] and has been shown to be a reliable prognostic assessment tool also for VLBW infants who have a high risk for developmental impairments [8,9].

Our aim was to study the combined prognostic value of neurological examination and brain MRI at TEA or serial neonatal cUS in very preterm infants using results of neurological examination and prevalence of neurosensory impairment (NSI) at 2 years of corrected age as endpoints. We hypothesized that adding the information of neurological examination to the information from brain MRI or cUS yields better PPV and NPV compared to either of these alone.

2. Material and methods

2.1. Participants

This study is part of the multidisciplinary PIPARI Study (the development and functioning of Very Low Birth Weight infants from infancy to school age), a prospective study of VLBW or VLGA infants born to Finnish- or Swedish-speaking families between 2001 and 2006, in the Turku University Hospital, Finland. The inclusion criterion was a birth weight ≤1500 g in preterm infants born <37 gestational weeks, from 2001 to the end of 2003. From the beginning of 2004, the inclusion criteria were broadened to include all infants born below the gestational age of 32 weeks, regardless of birth weight. The flow chart of the participants is shown in Fig. 1. All parents gave informed consent for the follow-up study. The PIPARI Study protocol was approved by the Ethics Review Committee of the Hospital District of the South-West Finland in December 2000.

2.2. Magnetic resonance imaging of the brain

The brain MRI was performed at TEA with an open 0.23-T Outlook GP (Philips Medical, INC, Vantaa Finland) (infants born between 2001 and 2003, n = 119) that was upgraded to the 1.5-T Philips Intera (Philips Medical Systems, Best Netherlands) (infants born between 2004 and 2006, n = 97). One neuroradiologist (R.P.) analyzed all the images and was blinded both to the clinical information and to the result of the cUS examinations of the infant. The MRI findings were categorized into three groups: normal findings consisted of normal brain anatomy (cortex, basal ganglia and thalami, posterior limb of internal capsule, white matter, germinal matrix, corpus callosum and posterior fossa structures), width of extracerebral space <5 mm, ventricular/brain (V/B) ratio <0.35 and no ventriculitis; minor pathologies consisted of consequences of intraventricular hemorrhage grades 1 and 2, caudothalamic cysts, width of the extracerebral space of 5 mm and V/B ratio of 0.35; major pathologies consisted of consequences of intraventricular hemorrhage grades 3 and 4, injury in cortex, basal ganglia, thalamus or internal capsule, with injury of corpus callosum, cerebellar injury, white matter injury, increased width of extracerebral space >5 mm, V/B ratio >0.35, ventriculitis or other major brain pathology (infarcts). [1] The infants were categorized into three groups (normal, minor brain pathologies, and major brain pathologies) based on the MRI findings at TEA [10] to evaluate the relation between brain pathology and neurosensory outcome.

2.3. Cranial ultrasound

cUS examinations were performed at 3 to 5 days, at 7 to 10 days, at 1 month of age, monthly thereafter until discharge from the hospital and at TEA. The cUS examinations were performed with a 7-MHz vector transducer (Sonos 5500 Hewlett-Packard, Andover, Mass). Intraventricular hemorrhages were classified from grades 1 to 4 [11]. The cUS examination at TEA was performed with a 7.5-MHz vector transducer (Aloka SSD 2000, Aloka Co., Ltd., Tokyo, Japan) from January 2001 to August 2002 and an 8-MHz vector transducer (General Electric Logic 9 [General Electric, Waukesha, WI]) from September 2002 to March 2007. The cUS examination at TEA was performed by a pediatric radiologist blinded both to the clinical information and to the result of the MRI examination of the infant. The infants were categorized into three groups (normal,

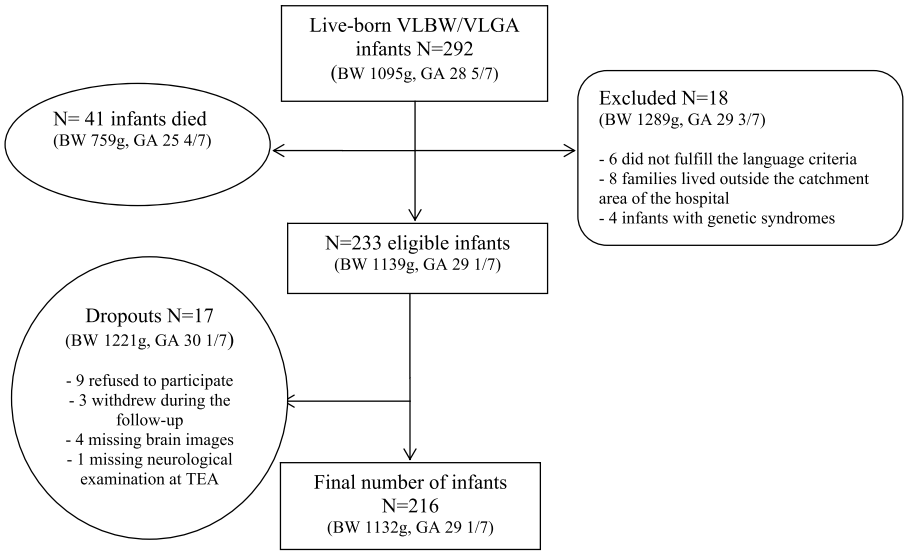


Fig. 1. The flow chart of the participants, mean birth weights (BW) and gestational ages (GA) in weeks.

minor brain pathologies, and major brain pathologies) according to the most serious findings on cUS examinations. [12] The division into these groups was done as previously described [13].

2.4. Neurosensory outcome

Neurological examination at TEA was performed by an experienced physician and physiotherapists, using a standardized proforma of the Dubowitz neurologic examination [4]. It includes 34 qualitative and quantitative items for preterm and term infants with measurement subscales of tone and posture (10 items), tone patterns (5 items), reflexes (6 items), spontaneous movements (3 items), abnormal signs (3 items), and behavior (7 items). The assessment proforma consists of 5 alternative findings for each of the items, and the examiner is supposed to circle the one that corresponds most closely to the infant's performance. The deviant items are defined according to the gestational age specific norms [6]. The two subgroups with the lowest gestational ages (infants born <25 weeks and between 25 0/7 and 27 6/7 weeks) were assessed according to same criteria as well as the two subgroups with the highest gestational ages (infants born between 33 0/7 and 34 6/7 weeks and ≥35 weeks). The cut-off value for a deviant result in the neurological examination was set at ≥1 because even a single deviation from the TEA norm reference [6] in the neurological examination indicated an increased risk for later impairment. Neurological development was reassessed at 2 years of corrected age by an experienced physician and physiotherapists, using the HINE [7]. It consists of 37 items that are further divided into three sections: cranial nerve function, posture, movements, tone and reflexes (first section of 26 items), description of motor development (second section of 8 items), and description of behavioral state of the infant during examination (third section of 3 items). All the item scores in the first section can be summed up yielding a maximum score of 78. The optimal total scores for full-term infants are ≥73 and ≥74 at 12 and 18 months of age, respectively [7]. A cut-off score of >70 was used for this preterm population. We defined the cut-off as the 90th percentile of the healthy preterm infants (i.e. brain MRI normal or with minor pathologies and no NSI), as there are no norms for preterm infants at 2 years of corrected age.

The diagnosis of CP including the grading of severity by Gross Motor Function Classification System (GMFCS) [14] was ascertained by one child neurologist (L.H.) at 2 years of corrected age after a systematic clinical follow-up. Severe hearing impairment was categorized as a hearing impairment with a cut-off of 40 dB or hearing loss requiring amplification in at least one ear, and severe visual impairment was determined as a visual acuity <0.3, or blindness [1,10]. NSI included at least one of the following findings: CP, severe hearing impairment or severe visual impairment.

2.5. Statistical analysis

Univariate associations between either brain MRI or cUS and continuous response variables were studied using a linear model. This linear model was also used to study the association between the Dubowitz neurologic examination at TEA and the HINE at 2 years of corrected age. The associations were further studied using either MRI or cUS and the Dubowitz neurologic examination as predictor variables of the HINE. The associations between the Dubowitz neurologic examination at TEA and NSI at 2 years of corrected age were studied using logistic regression analysis. The association was further studied controlling for either brain MRI or cUS. All statistical models were fitted using the scores of the Dubowitz neurologic examination and the HINE as continuous variables, but descriptive statistics are also shown for dichotomized values of the two variables. Univariate associations between the subscales of the Dubowitz neurologic examination and response variables were studied using Pearson correlation for the HINE and point biserial correlation for NSI. Statistical analyses were done using SAS for Windows version 9.3. p-Values below 0.05 were considered as statistically significant.

The NPV was defined as the percentage of children with no deviant findings in the Dubowitz neurologic examination and no or minor brain pathologies either in the brain MRI or cUS resulting in a developmental outcome without NSI at 2 years of corrected age. The PPV was defined as the percentage of children with one or more deviant findings in the Dubowitz neurologic examination and major brain pathologies either in the brain MRI or cUS resulting in an abnormal developmental outcome with NSI.

3. Results

The neonatal characteristics of the 216 preterm infants are shown in Table 1. All the infants were examined by brain MRI and serial cUS. The findings are shown in Table 2. All the infants were examined at TEA and 208 (96.3%) were examined at 2 years of corrected age. Of all the infants, 14 (6.5%) had CP and 4 (1.9%) had severe hearing impairment. There were no children with severe visual impairment.

3.1. The Dubowitz neurologic examination at term equivalent age

The gestational age subgroups are shown in Table 1. The mean postmenstrual age of the infants at the time of examination was 40 weeks (SD 2.5 days, [38 5/7, 42 1/7]). The mean number of deviant items in the Dubowitz neurologic examination was 2.0 (SD 2.1, [0.0, 13.0]). The number of deviant items was 1.8 (SD 1.8, [0.0, 9.0]) in the infants with normal MRI findings, 1.8 (SD 2.0, [0.0, 10.0]) in the infants with minor MRI pathologies, and 2.5 (SD 2.6, [0.0, 13.0]) in the infants with major MRI pathologies. The number of deviant items was 1.6 (SD 1.7, [0.0, 9.0]) in the infants with normal cUS findings, 2.4 (SD 2.4, [0.0, 13.0]) in the infants with minor cUS pathologies, and 2.3 (SD 2.0, [0.0, 6.0]) in the infants with major cUS pathologies.

Fifty-three (24.5%) of the infants had no deviant items. Of these infants, brain MRI was normal in 32 (60.4%), 9 (17.0%) had minor pathologies, and 12 (22.6%) major pathologies. cUS was normal in 35 (66.0%) of these infants, 14 (26.4%) had minor pathologies, and 4 (7.6%) had major pathologies, respectively.

There wasn't any single test item which alone correlated significantly with the HINE total scores or NSI at 2 years of corrected age. The subscales that correlated with the HINE total scores were tone patterns ($r = -0.25$, $p < 0.001$), posture and tone ($r = -0.18$, $p = 0.01$) and behavior ($r = -0.13$, $p = 0.07$). The same subscales correlated with NSI: tone patterns ($r = -0.18$, $p = 0.01$), posture and tone ($r = -0.13$, $p = 0.06$) and behavior ($r = -0.19$, $p = 0.01$).

Table 1
Neonatal characteristics of the VLBW or VLGA infants (n = 216).

Characteristics	Data
Birth weight, mean (SD) [minimum, maximum], g	1132 (331) [400, 2120]
Gestational age at birth, mean (SD) [minimum, maximum], week	29 1/7 (2 5/7) [23 0/7, 35 6/7]
Males, females, n (%)	121 (56.0), 95 (44.0)
Cesarean section, n (%)	133 (61.6)
Small for gestational age, n (%)	81 (37.5)
Bronchopulmonary dysplasia, n (%)	28 (13.0)
Sepsis, n (%)	35 (16.4)
Necrotizing enterocolitis, surgical, n (%)	10 (4.7)
Retinopathy of prematurity, laser treated, n (%)	8 (3.8)
Gestational age subgroups, n (%)	
<25 weeks	15 (6.9)
25 0/7–27 6/7 weeks	55 (25.5)
28 0/7–29 6/7 weeks	61 (28.2)
30 0/7–31 6/7 weeks	56 (25.9)
32 0/7–34 6/7 weeks	26 (12.0)
≥35 weeks	3 (1.4)

Table 2
Brain MRI and cUS findings, n (%).

	MRI	cUS
Normal findings	120 (55.6)	113 (52.3)
Minor pathologies	38 (17.6)	85 (39.4)
Major pathologies	58 (26.9)	18 (8.3)

3.2. The Hammersmith Infant Neurological Examination at 2 years of corrected age

Mean age at examination time was 2 years of corrected age (SD 9 days, [−71 days, +60 days]). The mean total score of the examinations was 72.9 (SD 5.6, [38.0, 78.0]).

The Dubowitz neurologic examination was significantly related to the variation in the HINE total scores ($R^2 = 0.04$, $b = -0.6$, $p = 0.003$). The NPV of no deviant items in the Dubowitz neurologic examination for HINE total score >70 was 88.5%, and the PPV of one or more deviant items for total score ≤70 was 16.7%.

Brain MRI explained 11.9% of the variation in the HINE total scores ($p < 0.0001$). Major brain pathologies on MRI reduced the HINE total scores compared to normal findings ($b = -0.7$ for minor pathologies and $b = -4.5$ for major pathologies, respectively). cUS explained 13.2% of the variation in the HINE total scores ($p < 0.0001$). Major brain pathologies on cUS reduced the HINE total scores compared to normal findings ($b = -1.4$ for minor pathologies and $b = -7.9$ for major pathologies, respectively).

One hundred and seventy-six (84.6%) of the children had HINE scores >70. Of these infants, brain MRI was normal in 108 (61.4%), 31 (17.6%) had minor pathologies, and 37 (21.0%) had major pathologies. cUS was normal in 97 (55.1%) of these infants, 71 (40.3%) had minor pathologies, and 8 (4.6%) had major pathologies, respectively.

The NPV of normal findings or minor pathologies on brain MRI for the HINE scores >70 was 90.3%, and the PPV of major pathologies for total score ≤70 was 31.5%. The NPV of normal findings or minor pathologies on cUS for the HINE scores >70 was 87.1%, and the PPV of major pathologies for total score ≤70 was 46.7%. Neurological examination and brain MRI at TEA together explained 14.9% of the variation in the neurological examination at 2 years of corrected age. Neurological examination and cUS together explained 17.2% of the variation in the neurological examination at 2 years of corrected age. Thus neurological examination at TEA improved the predictive value of MRI (R^2 change = 0.03, $p = 0.01$) and cUS (R^2 change = 0.04, $p = 0.002$). The PPV improved to 35.7% (MRI) and to 63.6% (cUS), and the NPV of 90.3% (MRI) and 87.1% (cUS) remained the same (Table 3).

3.3. Neurosensory impairment

A total of 17 (7.9%) infants had NSI at 2 years of corrected age. Brain MRI was normal in 1 (5.9%) of these infants, none had minor pathologies, and 16 (94.1%) had major pathologies. cUS was abnormal in all of these infants, 6 (35.3%) had minor pathologies, and 11 (64.7%) had major pathologies. All the children with NSI had abnormal result in the Dubowitz neurologic examination at TEA: five infants (29.4%) had 1 deviant item, two infants (11.8%) had 2 deviant items, three infants (17.7%) had 3 deviant items, two infants (11.8%) had 4 deviant items, one infant (5.9%) had 5 deviant items, three infants (17.7%) had 6 deviant items, and one infant (5.9%) had 13 deviant items. A higher number of deviant items increased the risk for NSI (OR = 1.4, CI 95% 1.1–1.6, $p = 0.002$), and the association remained when controlling for either brain MRI (OR = 1.3, CI 95% 1.0–1.7, $p = 0.03$) or cUS findings (OR = 1.4, CI 95% 1.1–1.9, $p = 0.005$). The NPV of no deviant items in the Dubowitz neurologic examination for development without NSI was 100%, and the PPV of one or more deviant items for NSI was 10.4%. Neurological examination improved the NPV and PPV of brain MRI from 99.4% to 100.0%, and from 27.6% to 34.8%, respectively (Table 3). Neurological examination improved the NPV and PPV of cUS from 97.0% to 100%, and from 61.1% to 78.6%, respectively (Table 3).

All infants with CP had at least one deviant item in the Dubowitz neurologic examination (Table 4). A higher number of deviant items increased the risk for CP (OR = 1.4, CI 95% 1.2–1.8, $p = 0.0006$). There were 4.1 (SD 3.1, [1.0, 13.0]) and 1.9 (SD 1.9, [0.0, 10.0]) deviant items in infants with and without CP, respectively. The mean total score in the HINE was 54.3 (SD 10.34, [38.0, 74.0]) and 73.9 (SD 2.6, [67.0, 78.0]) in infants with and without CP, respectively (Table 4).

4. Discussion

This prospective follow-up study of a regional cohort of very preterm infants showed that a systematical use of the Dubowitz neurologic examination at TEA is a valuable tool to predict neurological development in preterm infants. This neurological examination combined with either the brain MRI or cUS improves the predictive value of the brain MRI or cUS alone considering neurosensory outcome at 2 years of corrected age.

Table 3
The predictive values of the Dubowitz neurologic examination and brain MRI at term equivalent age and serial neonatal cUS for total score ≤70 of the Hammersmith Infant Neurologic Examination (HINE) and neurosensory impairment (NSI) at 2 years of corrected age.

	HINE ≤70 (n = 32, 15.4%)	NSI (n = 17, 7.9%)
The Dubowitz neurologic examination		
No deviant items, n = 53 (24.5%)	NPV = 88.5%	NPV = 100%
One or more deviant items, n = 163 (75.5%)	PPV = 16.7%	PPV = 10.4%
Brain MRI findings		
Normal findings or minor pathologies, n = 158 (73.2%)	NPV = 90.3%	NPV = 99.4%
Major pathologies, n = 58 (26.9%)	PPV = 31.5%	PPV = 27.6%
cUS findings		
Normal findings or minor pathologies, n = 198 (91.7%)	NPV = 87.1%	NPV = 97.0%
Major pathologies, n = 18 (8.3%)	PPV = 46.7%	PPV = 61.1%
The Dubowitz neurologic examination and brain MRI findings		
No deviant items and normal findings or minor pathologies, n = 41 (19.0%)	NPV = 90.0%	NPV = 100%
One or more deviant items or major pathologies, n = 129 (59.7%)	PPV = 10.3%	PPV = 0.78%
One or more deviant items and major pathologies, n = 46 (21.3%)	PPV = 35.7%	PPV = 34.8%
The Dubowitz neurologic examination and cUS findings		
No deviant items and normal findings or minor pathologies, n = 49 (22.7%)	NPV = 87.5%	NPV = 100%
One or more deviant items or major pathologies, n = 153 (70.8%)	PPV = 12.8%	PPV = 3.9%
One or more deviant items and major pathologies, n = 14 (6.5%)	PPV = 63.6%	PPV = 78.6%

Table 4
The characteristics of the infants with CP (n = 14).

Characteristics	Data
CP type, n (%)	
Spastic diplegia	7 (50.0)
Spastic hemiplegia	4 (28.6)
Spastic triplegia	2 (14.3)
Dystonic	1 (7.1)
Gross Motor Function Classification System (GMFCS), n (%)[a]	
I	2 (15.4)
II	6 (46.2)
III	3 (23.1)
IV	2 (15.4)
V	0 (0.0)
Gestational age at birth, mean (SD) [minimum, maximum], week	27 5/7 (22 4/7) [23 3/7, 35 1/7]
Number of deviant items in the Dubowitz neurologic examination at term equivalent age, n (%)	
0	0 (0)
1	3 (21.4)
2	1 (7.1)
3	3 (21.4)
4	2 (14.3)
5	1 (7.1)
6	3 (21.4)
7–12	0 (0)
13	1 (7.1)
Items that were more frequently outside the normative range in the Dubowitz neurologic examination at term equivalent age, n (%)	
Posture: opisthotonus or arms flexed and legs extended	6 (42.9), p = 0.002
Eye appearance: does not open eyes, persistent nystagmus, strabismus, roving eye movements or downward deviation	2 (14.3), p = 0.01
Visual orientation: does not follow or focus on stimuli, stills, focuses, follows briefly to the side but loses stimuli	5 (35.7), p = 0.004
Flexor tone (compare arm and leg traction): arm flexion > leg flexion: difference >1 column	4 (28.6), p = 0.01
Head control (sitting): neck extension > neck flexion: difference >1 column	2 (14.3), p = 0.04
Brain MRI findings, n (%)	
Normal findings	1 (7.1)
Minor pathologies	0 (0.0)
Major pathologies	13 (92.9)
cUS findings, n (%)	
Normal findings	0 (0.0)
Minor pathologies	5 (35.7)
Major pathologies	9 (64.3)
Total score of the Hammersmith Infant Neurologic Examination at 2 years of corrected age, mean (SD) [minimum, maximum]	54.3 (10.3) [38.0,74.0]

[a] Data missing for 1 (7.1%) child.

Our results support the validity of preterm norms of the Dubowitz neurologic examination [6]. None of the deviant items alone predicted abnormal outcome, but any single deviation increased the risk for later neurosensory impairment. Importantly, specific subscales (tone patterns, posture and tone, and behavior) correlated to developmental outcome. Our findings are in agreement with a previous study showing that the Dubowitz neurologic examination at TEA was related to concurrent cerebral abnormalities in MRI [15]. With regard to predicting CP, our results differed from a previous study including infants with major ultrasound pathologies showing often 7 or more deviant items in infants later developing CP [6]. In our study, only one infant with CP had 7 or more deviant items. This difference may be due to the differences in the populations as we included all preterm infants regardless of brain pathology. The items that were most commonly deviant in children with CP were posture, eye appearance, visual orientation, flexor tone, and head control. In addition, the children with CP had good functional level as the majority of children were independently mobile and only two of them needed assistive device. It is noteworthy also from this perspective that all children with even mild CP had at least one deviant item in the Dubowitz neurologic examination at TEA. On the other hand, there were seven infants with 7 or more deviant items without CP. Some of these infants might have performed suboptimally due to disturbances related to the examination situation, and some had neurological abnormalities other than CP.

It has been previously shown that Amiel-Tison Neurological Assessment at TEA predicts psychomotor and behavioral development at 2 years of corrected age [16]. A meta-analysis of neurological examination methods at TEA pointed out that neurological examination could reach as good sensitivity and specificity as brain MRI to predict CP [17]. The meta-analysis did not show sensitivity and specificity for the combined information of these methods. The sensitivity of prediction of combined brain MRI and neurobehavioral assessment has been evaluated using the general movement analysis and the neurobehavioral assessment of preterm infants [18]. A combination of the two methods increased sensitivity and specificity for CP. The HINE and general movement analysis at 3 months of age were shown more effective than either of the assessments alone or serial cUS in predicting neurologic outcome at 2 years of age [19].

The present study is the first showing the combined predictive value of the Dubowitz neurologic examination and either brain MRI or cUS in preterm infants. All these examinations were excellent in predicting normal neurological outcome at 2 years of corrected age. Normal findings in the Dubowitz neurologic examination provide valuable information for clinicians and families by predicting with a very high likelihood a good neurosensory development irrespective of the available imaging facilities. Obtaining a high PPV is challenging as many neurological deviations normalize during the development in early infancy due to the unique plasticity of the neonatal brain. Compared to either brain MRI or cUS alone, a combination of neurological examination and brain imaging improved the prediction for abnormal outcome. However, it should be emphasized that even though the Dubowitz neurologic examination together with either the brain MRI or cUS aid clinicians in identifying those infants who are later at a high risk of developmental problems, good functional outcome can be achieved despite several deviant items or major lesions. The significant proportion of normal development in the infants with either major MRI or cUS pathologies also supports the use of functional measures like the Dubowitz neurologic examination. The neurological examination is valuable also in follow-up as it can easily be repeated in order to see which of the abnormal findings normalize, worsen or remain stable.

MRI has a value for predicting also cognitive outcome as we showed in our previous study [1]. The PPV of one or several major pathologies in MRI was 39% and 75%, respectively, for neurodevelopmental impairments including also the cognitive development at 5 years of age. New imaging methods or combinations of neurological examinations and imaging techniques may be able to improve the PPV for abnormal outcome. For example, diffusion-weighted MRI has been shown to be associated with a poorer developmental performance in later childhood and may be of prognostic value for neurodevelopmental outcome in preterm infants with no abnormalities on conventional brain MRI [20]. Brain volumes also associate with later development [21].

The strengths of this study included a high coverage of the examinations at TEA and at 2 years of corrected age with very little variation in the age at the examinations. As there are no norms for preterm children for the HINE at 2 years of corrected age, the cut-off scores were defined according to this cohort. These data could be used in future as a reference when examining preterm infants.

A possible technical limitation of this study was the upgrading of the MRI equipment during the study period. Comparability was supported by our findings about the incidence of brain lesions, which did not increase after the MRI equipment upgrading in our study population.

In conclusion, this study showed that the combination of the neurological examination and either brain MRI or cUS provides an effective tool to estimate long-term neurosensory development in preterm

infants. The families need individualized information which is as accurate as possible about the neurodevelopmental prognosis of their child. It is important not to forget the great potential for compensation provided by the maturing brain in optimal growth environment.

Conflict of interest

The authors report no conflict of interest.

Financial support

This work was supported by grants from the Foundation for Paediatric Research, Arvo and Lea Ylppö Foundation and The Foundation of Märtha Donner.

Abbreviations

CP	cerebral palsy
cUS	cranial ultrasound
HINE	Hammersmith Infant Neurologic Examination
MRI	magnetic resonance imaging
NSI	neurosensory impairment
PPV	positive predictive value
NPV	negative predictive value
TEA	term equivalent age
VLBW	very low birth weight
VLGA	very low gestational age
V/B	ventricular/brain

Acknowledgments

The PIPARI Study Group: Karoliina Aho, BM; Mikael Ekblad, MD, PhD; Satu Ekblad, RN; Eeva Ekholm, MD, PhD; Annika Eurola, BM; Leena Haataja, MD, PhD; Mira Huhtala, MD; Pentti Kero, MD, PhD; Hanna Kiiski-Mäki, PhD; Riikka Korja, PhD; Katri Lahti, BM; Helena Lapinleimu, MD, PhD; Liisa Lehtonen, MD, PhD; Tuomo Lehtonen, MD; Marika Leppänen, MD; Annika Lind, PhD; Hanna Manninen, MD; Jaakko Matomäki, MSc; Jonna Maunu, MD, PhD; Petriina Munck PhD; Laura Määttänen, MD; Pekka Niemi, PhD; Anna Nyman, MA; Pertti Palo, MD, PhD; Riitta Parkkola, MD, PhD; Liisi Rautava, MD, PhD; Päivi Rautava, MD, PhD; Katriina Saarinen, Physiotherapist; Virva Saunavaara, MA; Sirkku Setänen, MD; Matti Sillanpää, MD, PhD; Suvi Stolt, PhD; Päivi Tuomikoski-Koiranen, RN; Timo Tuovinen, BA; Anniina Väliaho, MA; Milla Ylijoki, MD, PhD.

References

[1] Setanen S, Haataja L, Parkkola R, Lind A, Lehtonen L. Predictive value of neonatal brain MRI on the neurodevelopmental outcome of preterm infants by 5 years of age. Acta Paediatr May 2013;102(5):492–7.
[2] Dubowitz LM, Levene MI, Morante A, Palmer P, Dubowitz V. Neurologic signs in neonatal intraventricular hemorrhage: a correlation with real-time ultrasound. J Pediatr Jul. 1981;99(1):127–33.
[3] Dubowitz L, Mercuri E, Dubowitz V. An optimality score for the neurologic examination of the term newborn. J Pediatr 1998 Sep;133(3):406–16.
[4] Dubowitz LMS, Dubowitz V, Mercuri E. The neurological assessment of the preterm and full-term newborn infant. 2nd ed. London: Mc Keith Press; 1999.
[5] Mercuri E, Guzzetta A, Laroche S, Ricci D, vanhaastert I, Simpson A, et al. Neurologic examination of preterm infants at term age: comparison with term infants. J Pediatr Jun. 2003;142(6):647–55.
[6] Ricci D, Romeo DM, Haataja L, van Haastert IC, Cesarini L, Maunu J, et al. Neurological examination of preterm infants at term equivalent age. Early Hum Dev Nov. 2008; 84(11):751–61.
[7] Haataja L, Mercuri E, Regev R, Cowan F, Rutherford M, Dubowitz V, et al. Optimality score for the neurologic examination of the infant at 12 and 18 months of age. J Pediatr Aug. 1999;135(2 Pt 1):153–61.
[8] Frisone MF, Mercuri E, Laroche S, Foglia C, Maalouf EF, Haataja L, et al. Prognostic value of the neurologic optimality score at 9 and 18 months in preterm infants born before 31 weeks' gestation. J Pediatr 2002 Jan;140(1):57–60.
[9] Romeo DM, Cioni M, Scoto M, Pizzardi A, Romeo MG, Guzzetta A. Prognostic value of a scorable neurological examination from 3 to 12 months post-term age in very preterm infants: a longitudinal study. Early Hum Dev Jun. 2009;85(6):405–8.
[10] Maunu J, Parkkola R, Rikalainen H, Lehtonen L, Haataja L, Lapinleimu H, et al. Brain and ventricles in very low birth weight infants at term: a comparison among head circumference, ultrasound, and magnetic resonance imaging. Pediatrics Feb. 2009; 123(2):617–26.
[11] Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. J Pediatr Apr. 1978;92(4):529–34.
[12] Reiman M, Kujari H, Maunu J, Parkkola R, Rikalainen H, Lapinleimu H, et al. Does placental inflammation relate to brain lesions and volume in preterm infants? J Pediatr May 2008;152(5):642–7 [647.e1-2].
[13] Rademaker KJ, Uiterwaal CS, Beek FJ, van Haastert IC, Lieftink AF, Groenendaal F, et al. Neonatal cranial ultrasound versus MRI and neurodevelopmental outcome at school age in children born preterm. Arch Dis Child Fetal Neonatal Ed Nov. 2005; 90(6):F489–93.
[14] Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. Dev Med Child Neurol Apr. 1997;39(4):214–23.
[15] Brown NC, Inder TE, Bear MJ, Hunt RW, Anderson PJ, Doyle LW. Neurobehavior at term and white and gray matter abnormalities in very preterm infants. J Pediatr Jul. 2009;155(1):32–8 [38.e1].
[16] Simard MN, Lambert J, Lachance C, Audibert F, Gosselin J. Prediction of developmental performance in preterm infants at two years of corrected age: contribution of the neurological assessment at term age. Early Hum Dev Dec. 2011;87(12):799–804.
[17] Bosanquet M, Copeland L, Ware R, Boyd R. A systematic review of tests to predict cerebral palsy in young children. Dev Med Child Neurol May 2013;55(5):418–26.
[18] Constantinou JC, Adamson-Macedo EN, Mirmiran M, Fleisher BE. Movement, imaging and neurobehavioral assessment as predictors of cerebral palsy in preterm infants. J Perinatol Apr. 2007;27(4):225–9.
[19] Romeo DM, Guzzetta A, Scoto M, Cioni M, Patusi P, Mazzone D, et al. Early neurologic assessment in preterm-infants: integration of traditional neurologic examination and observation of general movements. Eur J Paediatr Neurol May 2008;12(3): 183–9.
[20] Krishnan ML, Dyet LE, Boardman JP, Kapellou O, Allsop JM, Cowan F, et al. Relationship between white matter apparent diffusion coefficients in preterm infants at term-equivalent age and developmental outcome at 2 years. Pediatrics Sep. 2007; 120(3):e604–9.
[21] Lind A, Parkkola R, Lehtonen L, Munck P, Maunu J, Lapinleimu H, et al. Associations between regional brain volumes at term-equivalent age and development at 2 years of age in preterm children. Pediatr Radiol Aug. 2011;41(8):953–61.

DEVELOPMENTAL MEDICINE & CHILD NEUROLOGY ORIGINAL ARTICLE

Prediction of neuromotor outcome in infants born preterm at 11 years of age using volumetric neonatal magnetic resonance imaging and neurological examinations

SIRKKU SETÄNEN[1] | LIISA LEHTONEN[2] | RIITTA PARKKOLA[3] | KAROLIINA AHO[4] | LEENA HAATAJA[5] | ON BEHALF OF THE PIPARI STUDY GROUP

1 Department of Pediatric Neurology, University of Turku and Turku University Hospital, Turku; **2** Department of Pediatrics, University of Turku and Turku University Hospital, Turku; **3** Department of Radiology, Turku PET Center, University of Turku and Turku University Hospital, Turku; **4** Department of Medicine, University of Turku, Turku; **5** Department of Pediatric Neurology, University of Helsinki and Helsinki University Hospital, Children's Hospital, Helsinki, Finland.

Correspondence to Sirkku Setänen at Department of Pediatric Neurology, Turku University Hospital, Kiinamyllynkatu 5–8, 20520 Turku, Finland. E-mail: sirkku.a.setanen@utu.fi

PUBLICATION DATA
Accepted for publication 22nd October 2015.
Published online

ABBREVIATIONS

cMND	Complex minor neurological dysfunction
HINE	Hammersmith Infant Neurological Examination
MND	Minor neurological dysfunction
PPV	Positive predictive value
sMND	Simple minor neurological dysfunction
TEA	Term equivalent age

AIM To study the prognostic value of volumetric brain magnetic resonance imaging (MRI) at term equivalent age (TEA) and neurological examinations at TEA and at 2 years of corrected age for long-term neuromotor outcome in infants born very preterm.
METHOD A total of 98 infants born very preterm were included. Structural and volumetric brain MRI and the Dubowitz neurologic examination were done at TEA. The Hammersmith Infant Neurological Examination (HINE) was performed at 2 years of corrected age. The Touwen examination was used for the assessment of minor neurological dysfunction (MND) at the age of 11 years.
RESULTS Of all children (median birthweight 1083g [quartiles 820, 1300]; gestational age 28 5/7wks [26 4/7, 30 2/7]), 41 had simple MND, 11 had complex MND (cMND), and eight had cerebral palsy (CP). The negative and positive predictive value of structural brain MRI for cMND or CP was 88% and 50% respectively. Reduced volumes of total brain tissue, frontal lobes, basal ganglia and thalami, and cerebellum associated with cMND or CP. The results of the Dubowitz neurologic examination and the HINE correlated with the Touwen examination.
INTERPRETATION Structural and volumetric MRI at TEA and structured neurological examinations predict long-term neuromotor outcome in infants born preterm.

Severe neurological impairments such as cerebral palsy (CP) have decreased in children born preterm.[1,2] However, the rate of milder forms of motor dysfunction continues to be significantly high, from 25% to 50%.[3] The modified Touwen examination is a standardized neurological examination, which has been designed to detect minor neurological dysfunction (MND).[4] It is primarily a tool for clinical practice, but it is also applied in research, especially in evaluating the association between neurological conditions and preterm birth. Simple MND (sMND) represents typical but non-optimal brain function, whereas complex MND (cMND) may be considered a borderline form of CP. MND increases risk for learning difficulties and behavioural problems.[5,6]

We have previously reported the positive (PPV) and negative predictive values of different brain pathologies seen in magnetic resonance imaging (MRI) at term equivalent age (TEA) on neurosensory and neurodevelopmental impairments in a cohort of 217 very low birthweight/very low gestational age infants at 2 years and 5 years of age.[7,8] The Dubowitz neurologic examination[9] at TEA has also been shown to predict later neurological outcome in infants born preterm at 2 years of corrected age.[8] In addition, structured neurological examinations have been shown to improve the prediction of neurosensory outcome at 2 years of corrected age when combined with either brain MRI or cranial ultrasound at TEA.[8] Regional brain volumes at TEA have also been shown to associate with neurodevelopment at 2 years of corrected age.[10] There are no long-term data available on the associations between structural pathologies or volumetric alterations in the brain tissue at TEA and neuromotor development in infants born preterm. Moreover, it is not known how structured neurological examinations predict long-term outcome in infants born preterm.

Our aim was to study the prognostic value of volumetric brain MRI at TEA, and structured neurological examinations for MND in infants born very preterm at 11 years of age. We hypothesized that regional brain volumes provide additional value in predicting long-term neuromotor outcome in infants born preterm. We also hypothesized that structured neurological examinations of neonates and infants correlate with neuromotor outcome at 11 years of age.

III

METHOD

Participants

This study is part of the multidisciplinary PIPARI Study (The Development and Functioning of Very Low Birth Weight Infants from Infancy to School Age), a prospective study of very low birthweight or very low gestational age infants born between 2001 and 2006, at Turku University Hospital, Finland. All infants born preterm (<37 gestational wks) born below 1500g from 2001 to 2003 were included. From the beginning of 2004, the inclusion criteria were broadened to include all infants born below the gestational age of 32 weeks, regardless of birthweight.[7,8,11] Only the infants born before April 2004 were included in this study, because the MRI equipment was upgraded thereafter. The flow chart of the participants is shown in Figure 1. All parents and children gave informed consent for the follow-up study. The PIPARI Study protocol was approved by the Ethics Review Committee of the Hospital District of South-West Finland in December 2000 and January 2012.

Magnetic resonance imaging of the brain

The brain MRI was performed at TEA with an open 0.23-T Outlook GP (Philips Medical, Inc., Vantaa, Finland).[7,8,11] The infants were categorized into three groups according the structural MRI findings (normal findings, minor pathologies, and major pathologies)[7,8] to evaluate the relationship between the brain pathology and the neuromotor outcome. The details about the brain MRI classification are shown in the Appendix.

Volume measurements were manually performed by one observer (RP) who visually separated the cerebrospinal fluid from the brain tissue image by image. The anatomical differentiation of the brain was based both on anatomical landmarks and signal intensity differences of the brain structures. The volumes of the total brain tissue (total brain volume minus ventricle volumes), the cerebrum, the cerebellum, the frontal lobes, the brain stem (medulla oblongata together with pons), the basal ganglia together with the thalami, and ventricles (lateral ventricles, third and fourth ventricles) were measured. A T1-weighted 2FE (field echo) sequence with a 3TR (time of repetition) of 30ms, a 4TE (time of echo) of 10ms, a flip angle of 45°, a slice thickness of 5mm, a field of view of 220 × 220mm^2, and a matrix of 256 × 256 in the coronal plane were obtained.[11]

What this paper adds

- Structural brain magnetic resonance imaging (MRI) at term equivalent age predicts long-term neuromotor outcome in infants born preterm up to 11 years of age.
- Volumetric brain MRI provides an additional tool for prediction of long-term neuromotor outcome in infants born preterm.
- Structured neurological examinations of neonates and infants correlate with long-term neuromotor outcome.

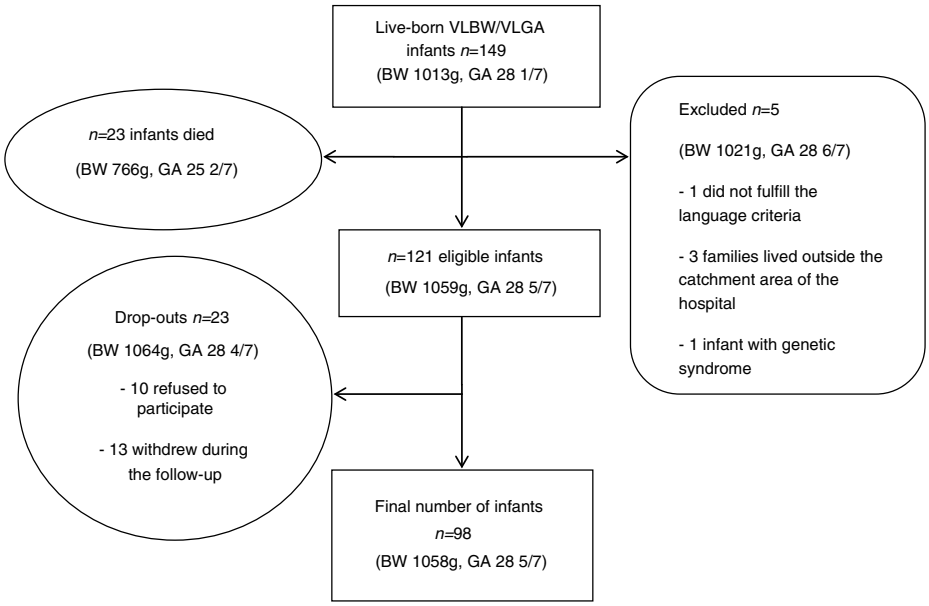


Figure 1: The flow chart of the participants, mean birthweights, and gestational ages in weeks. BW, birthweights; GA, gestational ages; VLBW, very low birthweight; VLGA, very low gestational age.

Neuromotor outcome

Neurological examination at TEA was performed by an experienced physician and physiotherapists, using a standardized proforma of the Dubowitz neurologic examination.[9] Neurological development was reassessed at 2 years of corrected age by an experienced physician and physiotherapists, using the Hammersmith Infant Neurological Examination (HINE).[12] These methods have been previously described in detail.[8]

Neurological examination at 11 years of age was performed by the first author (SS) using the latest version of the Touwen examination.[4] This examination included eight domains: posture and muscle tone; reflexes; involuntary movements (athetotiform movements, choreiform movements, and tremor); coordination and balance; fine manipulation; associated movements; sensory function; and cranial nerve function. Hand preference, head circumference, weight, and length were also recorded. The domains were classified as dysfunctional according to the criteria of the manual using computerized scoring.[4] sMND was defined as the presence of one or two dysfunctional domains, and cMND as the presence of more than two dysfunctional domains. The presence of an isolated dysfunctional domain in reflexes did not qualify for the classification of sMND. All the examinations were videotaped (KA) and classified together with an experienced child neurologist (LH) in order to ensure a consensus regarding the details of the assessments.

The diagnosis of CP, including the grading of functional severity by the Gross Motor Function Classification System,[13] was ascertained by a child neurologist (LH) at 2 years of corrected age after a systematic clinical follow-up.

Statistical analysis

The negative predictive value was defined as the percentage of children with normal findings or minor brain pathologies in the structural brain MRI at TEA resulting in a normal neuromotor outcome (without MND) at 11 years of age. The PPV was defined as the percentage of children with major brain pathologies in the structural brain MRI resulting in an abnormal neuromotor outcome with cMND or CP. Multinomial logistic regression models were used to study the associations between brain volumes and the results of Touwen examinations controlling for brain pathology. As the data distribution of ventricular volume was right skewed, the variable was log transformed before further analysis. Because the results of the neurological examinations were not normally distributed, the following bivariate analyses were done using non-parametric methods. Associations between continuous (the Dubowitz neurologic examination and the HINE) and ordinal variables (the Touwen examination) were studied using Spearman's correlation coefficient. Continuous variables were compared between study infants and drop-outs using the Mann–Whitney *U* test and comparisons between two categorical variables were done using the χ^2 test or Fisher's exact test, as appropriate. Continuous variables are presented with the median (lower quartile, upper quartile). Statistical analyses were done using SAS (Version 9.3 for Windows; SAS Institute Inc., Cary, NC, USA), and *p*-values below 0.05 were considered as statistically significant.

RESULTS

The characteristics of the 98 infants born preterm are shown in Table I. Of all infants, 96 (98%) were examined by brain MRI at TEA. All the infants were examined by the Dubowitz neurologic examination at TEA and by the HINE at 2 years of corrected age. Of all children, 97 (99%) were examined by the Touwen examination. One child with CP was not examined at the age of 11 years. All the background characteristics (Table I) of the study infants and drop-outs (Fig. 1) were compared. The only

Table I: Characteristics of the very low birthweight or very low gestational age study infants and drop-outs

Characteristics	Study infants (*n*=98)	Drop-outs (*n*=23)	*p*
Birthweight, median (lower quartile, upper quartile), g	1083 (820, 1300)	1115 (795, 1330)	0.94
Gestational age at birth, median (lower quartile, upper quartile), wks	28 5/7 (26 4/7, 30 2/7)	28 3/7 (26 4/7, 29 6/7)	0.59
Males, females, *n* (%)	47 (48), 51 (52)	13 (57), 10 (43)	0.46
Cesarean section, *n* (%)	57 (58)	20 (87)	0.0098
Small for gestational age, *n* (%)	37 (38)	9 (39)	0.91
Bronchopulmonary dysplasia, *n* (%)	15 (15)	4 (17)	0.80
Sepsis, *n* (%)	23 (23)	5 (22)	0.86
Necrotizing enterocolitis, surgical, *n* (%)	4 (4)	2 (9)	0.36
Retinopathy of prematurity, laser treated, *n* (%)	2 (2)	2 (9)	0.11
The Dubowitz neurologic examination at term equivalent age			
Median number of deviant items (lower quartile, upper quartile)	2.0 (1.0, 3.0)	2.0 (1.0, 5.0)	0.46
No deviant items, *n* (%)	18 (18)	2 (9)	0.36
One or more deviant items, *n* (%)	80 (82)	21 (91)	
The Hammersmith Infant Neurological Examination at 2y of corrected age			
Median total score (lower quartile, upper quartile)	74.0 (71.0, 76.0)	74.0 (72.0, 76.0)	0.96
Total score >70, *n* (%)	82 (84)	16 (76)	0.53
Total score ≤70, *n* (%)	16 (16)	5 (24)	

Continuous variables were compared between study infants and drop-outs using Mann–Whitney *U* test and comparisons between two categorical variables were done using χ^2 test or Fisher's exact test.

Table II: The prevalence of normal neurological outcome, simple minor neurological dysfunction (sMND), complex minor neurological dysfunction (cMND), and cerebral palsy (CP) at 11 years of age according to brain magnetic resonance imaging (MRI) categories at term equivalent age

Structural brain MRI findings (MRI for two infants)	Motor outcome			
	Normal *n*=38 (39%)	sMND *n*=41 (42%)	cMND *n*=11 (11%)	CP *n*=8 (8%)
Normal findings, *n*=56 (58%)	*n*=25 (69%)	*n*=25 (61%)	*n*=5 (45%)	*n*=1 (13%)
Minor pathologies, *n*=20 (21%)	*n*=10 (28%)	*n*=7 (17%)	*n*=3 (27%)	*n*=0 (0%)
Major pathologies, *n*=20 (20%)	*n*=1 (3%)	*n*=9 (22%)	*n*=3 (27%)	*n*=7 (88%)

Table III: The associations between brain volumetric findings at term equivalent age, simple minor neurological dysfunction (sMND), and complex minor neurological dysfunction (cMND) or cerebral palsy (CP) in infants born preterm at 11 years of age. The analysis of the multinomial logistic regression models were adjusted for structural brain magnetic resonance imaging categories

	sMND OR (95% CI)	*p*	cMND or CP OR (95% CI)	*p*
Total brain tissue	0.99 (0.98–1.00)	0.18	0.99 (0.97–1.00)	0.04
Ventricles	0.50 (0.23–1.06)	0.08	0.59 (0.23–1.50)	0.27
Cerebrum	0.99 (0.98–1.01)	0.28	0.99 (0.97–1.00)	0.07
Frontal lobes	0.98 (0.96–1.00)	0.10	0.96 (0.93–0.99)	0.01
Basal ganglia and thalami	0.93 (0.84–1.02)	0.12	0.87 (0.76–0.98)	0.03
Cerebellum	0.89 (0.79–0.99)	0.04	0.83 (0.71–0.96)	0.02
Brain stem	0.89 (0.75–1.05)	0.17	0.82 (0.64–1.03)	0.10

OR, odds ratio; CI, confidence interval.

Table IV: The results of Spearman correlations between the domains of the Dubowitz neurologic examination at term equivalent age, the Hammersmith Infant Neurological Examination (HINE) at 2 years of corrected age, and the results of the Touwen examination at 11 years of age in all children born preterm and children born preterm without cerebral palsy (CP)

	All preterm children (*n*=98)	Preterm children without CP (*n*=90)
The Dubowitz neurologic examination		
Orientation and behaviour	(*r*=0.32, *p*=0.001)	(*r*=0.39, *p*=0.001)
Tone and posture	(*r*=0.02, *p*=0.85)	(*r*=−0.04, *p*=0.73)
Tone patterns	(*r*=0.11, *p*=0.30)	(*r*=0.06, *p*=0.58)
Reflexes	(*r*=−0.02, *p*=0.86)	(*r*=−0.08, *p*=0.47)
Spontaneous movements	(*r*=0.12, *p*=0.22)	(*r*=0.17, *p*=0.11)
Abnormal signs	(*r*=0.11, *p*=0.28)	(*r*=0.12, *p*=0.26)
The HINE		
Posture	(*r*=−0.46, *p*<0.001)	(*r*=−0.3, *p*=0.004)
Cranial nerve function	(*r*=−0.16, *p*=0.11)	(*r*=−0.18, *p*=0.08)
Movements	(*r*=−0.42, *p*<0.001)	(*r*=−0.09, *p*=0.40)
Tone	(*r*=−0.25, *p*=0.01)	(*r*=−0.08, *p*=0.46)
Reflexes and reactions	(*r*=−0.25, *p*=0.01)	(*r*=−0.06, *p*=0.55)

statistically significant finding was that the children lost to follow-up were more likely to have been born by caesarean section than the study infants (p=0.01).

The results of the Dubowitz neurologic examination at TEA and the results of the HINE at 2 years of corrected age are shown in Table I. The median age at the time of the Touwen examination was 11 years and 2 months (lower quartile 11y; upper quartile 11y 9mo). Of all children, 41 (42%) had sMND, 11 (11%) had cMND, and eight (8%) had CP. The results according to structural brain MRI categories are shown in Table II. The negative predictive value and PPV of brain MRI for cMND or CP were 88% and 50%. The multinomial logistic regression models showed that decreasing volume of cerebellum increased the risk for sMND as shown in Table III. Decreasing volumes of total brain tissue, frontal lobes, basal ganglia and thalami, and cerebellum increased the risk for cMND or CP.

The Touwen examination revealed deviant findings in different domains as follows: posture and muscle tone (n=16, 17%); reflexes (n=28, 29%); involuntary movements (n=1, 1%); coordination and balance (n=93, 96%); fine manipulation (n=73, 75%); associated movements (n=86, 89%); sensory function (n=6, 6%); and cranial nerve function (n=10, 10%). The proportions of dysfunctional domains were respectively: posture and muscle tone (n=7, 7%); reflexes (n=24, 25%); involuntary movements (n=1, 1%); coordination and balance (n=34, 35%); fine manipulation (n=23, 24%); associated movements (n=34, 35%); sensory function (n=0, 0%); and cranial nerve function (n=10, 10%).

The median head circumference (cm), weight (kg), and length (cm) of the children were 53.3 (lower quartile 52.1, upper quartile 54.2), 35.3 (lower quartile 31.1, upper quartile 39.9), 143.8 (lower quartile 138.9, upper quartile 149.3) respectively. The hand preference was right in 86 (88%) children, left in eight (8%) children, and ambidextrous in three (3%) children. Females performed marginally better in the Touwen examination than males (p=0.04). There were no statistically significant correlations between gestational age or small for gestational status and the results of the Touwen examination.

The results of Spearman correlations showed that the number of deviant items in the Dubowitz neurologic examination at TEA correlated with the results of the Touwen examination at 11 years of age (r=0.22, p=0.03). The total score of the HINE at 2 years of corrected age correlated with the results of the Touwen examination at 11 years of age (r=−0.39, p=0.001). The correlations between the domains of the Dubowitz neurologic examination and the Touwen examination, and the domains of the HINE and the Touwen examination are shown in Table IV. The probability of having cMND increased as

the total test score of the HINE decreased, as shown in Figure 2.

DISCUSSION

This prospective follow-up study of a regional cohort of infants born very preterm showed for the first time that structural brain MRI at TEA, including volume measurements and structured neurological examination at TEA and at 2 years of corrected age, predicts the neuromotor outcome even at 11 years of age.

A systematic review has previously suggested that white matter injury and intraventricular haemorrhages in addition to perinatal risk factors such as postnatal corticosteroid therapy, intrauterine growth retardation, and chronic lung disease are frequently associated with regional brain volume changes in infants born preterm.[14] Data concerning associations between volumetric alterations at TEA and long-term neurodevelopment are scarce. We have previously shown that a decrease in regional brain volumes associates with poorer neurodevelopmental outcomes in infants born preterm at 2 years and 5 years of age.[10,14,15] In the present study, the decrease in volumes of total brain tissue, frontal lobes, basal ganglia and thalami, and cerebellum at TEA is still associated with abnormal neuromotor outcome at 11 years of age.

The domains that were most often deviant in the Touwen examination were coordination and balance, associated movements, and fine manipulation. These abnormal findings in the neurological examination were associated with decreased volumes of cerebellum, and basal ganglia and thalami which have an essential role in controlling coordination and balance.[4] In addition to brain MRI findings, only sex correlated marginally with the results of the Touwen examination. This is in line with previous findings showing that male sex is a risk factor for MND.[5,6] No effect of gestational age or small for gestational age status on the long-term neuromotor performance was found in the present study. This is consistent with our previous results showing that small for gestational age infants have similar developmental outcomes compared to other infants born preterm in this study population.[10,16,17]

To our knowledge, general movements assessment is the only clinical method evaluated for its predictive value for later neurodevelopmental outcomes up to 11 years of age. General movements assessment has been shown to have high sensitivity and specificity in high-risk neonates. Sensitivity and specificity for adverse neurodevelopmental outcomes have ranged from 38% to 100% and 35% to 99% at 12 to 24 months respectively; 54% to 100% and 23% to 73% at 2 to 3 years; and 85% to 100% and 48% to 89%

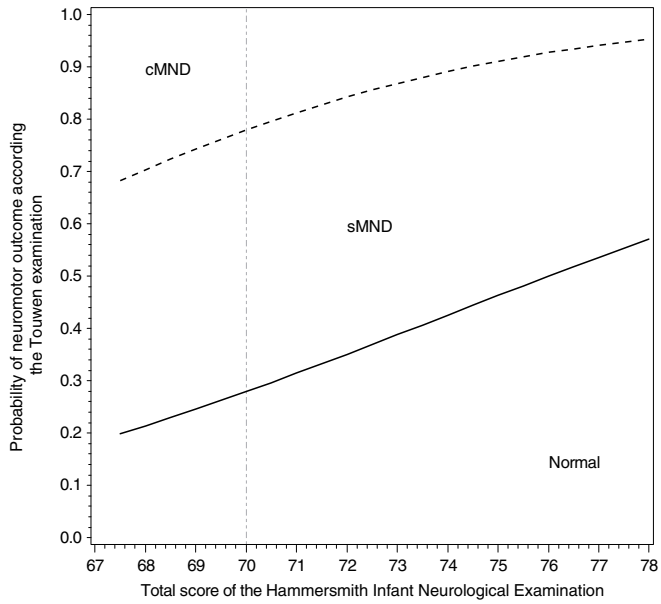


Figure 2: The association according to the logistic regression between the total score of the Hammersmith Infant Neurological Examination (HINE) at 2 years of corrected age and the outcome according to the Touwen examination at 11 years of age. For example, with a total score of 70 according to the HINE, the probability of normal neurological outcome is 28% (0.28), the probability of simple minor neurological dysfunction (sMND) (solid line) is 50% (0.78–0.28), and the probability of complex minor neurological dysfunction (cMND) (dashed line) is 22% (1–0.78).

at 4 to 11 years.[18] The quality of fidgety movements in early infancy has been shown to predict neuromotor development up to later school-age.[19,20] Based on the available evidence, this noninvasive though time-consuming method is the best single method in predicting CP. Combining general movements with brain MRI findings at TEA has been shown to increase the prediction of CP up to 100%.[21] The integrated use of a scorable neurological examination and general movements has also been shown to improve prediction of neurodevelopmental outcome in infants born preterm at 2 years of corrected age.[22]

The Dubowitz neurologic examination has been found to identify infants with significant MRI abnormalities with good negative predictive value (92%) but low PPV (34%).[23] The predictive value of the Dubowitz neurologic examination at TEA for neuromotor and neurosensory development at 2 years of corrected age has been previously studied using the number of abnormal items.[8] Combining this structured neurological examination with brain imaging has been found to significantly improve the PPV up to 79%.[8] This is the first time when the predictive value of the Dubowitz neurologic examination for the neuromotor outcome is evaluated in school-age children. Even though many abnormalities in neonatal neurological examination are known to resolve, the correlation between the results of the Dubowitz neurologic examination at TEA and Touwen examination at 11 years of age was 0.2. The domain that best predicted the neurological status at 11 years of age was orientation and behaviour (eye appearances, auditory orientation, visual orientation, alertness, irritability, consolability, and cry). Interestingly, visual behaviour in human newborns has recently been proposed to reflect the maturation of white matter networks.[24]

It is known that the HINE can give additional information about neuromotor development in children with CP.[25] This study showed the predictive value of the HINE for long-term neuromotor development also in children without CP. The correlation between the results of the HINE at 2 years of corrected age and Touwen examination at 11 years of age was −0.4. The domains which best predicted the neurological status at 11 years of age were posture, movements, tone, and reflexes and reactions. When excluding children with CP, the best predictive domain was posture.

Our study is consistent with previous findings showing that a high proportion of children born very preterm had sMND at the age of 5 years.[6] However, we found a significantly higher prevalence of cMND using the complete protocol of the Touwen examination. cMND was found in 11% of our study participants compared to 3% in the EPIPAGE cohort using the short version of the Touwen examination. The use of different versions can partly explain this discrepancy. The modified short form of the Touwen examination is not validated and may inaccurately indicate sMND and cMND.[4] Despite these differences, children born preterm continue to have significantly more difficulties in motor performance compared to children born full term. Therefore, it is of clinical importance to focus on prevention and prediction of cMND and its negative consequences on daily activities.

The strengths of this study included examinations at several age-points and a low attrition. The complete protocol of the Touwen examination was performed to obtain detailed and reliable information. The examination was video-recorded and re-evaluated together with an experienced child neurologist to ensure the reliability of the ratings. The children lost to follow-up did not significantly differ from the study population as only statistically significant difference was the mode of delivery.

This study shows the additional benefit of volume measurements for prediction of long-term neurodevelopment. The limitation is, however, that there is no normative data available for different regional brain volumes at TEA. Validation of volumetric brain MRI is needed to translate this knowledge into a practical clinical tool. Another limitation is the MRI equipment of the study period. More advanced and accurate imaging techniques including diffusion-weighted data and automated segmentation, different imaging classification systems, and combinations of neurological examinations and imaging techniques are plausible in improving the prediction for abnormal outcome. However, long-term follow-up data considering these methods are still needed.

In conclusion, our study showed that volumetric and structural brain MRI at TEA and structured neurological examination at TEA and at 2 years of corrected age are valuable in predicting the neuromotor outcome of infants born preterm up to later school-age. Especially, normal findings strongly predict normal outcome.

ACKNOWLEDGEMENTS

All phases of this study were supported by a grant from the Foundation for Paediatric Research, Finnish Cultural Foundation, and Arvo and Lea Ylppö Foundation. The PIPARI Study Group: Karoliina Aho, BM; Annarilla Ahtola, PhD; Mikael Ekblad, MD, PhD; Satu Ekblad, RN; Eeva Ekholm, MD, PhD; Annika Eurola, BM; Leena Haataja, MD, PhD; Mira Huhtala, MD; Pentti Kero, MD, PhD; Hanna Kiiski-Mäki, PhD; Riikka Korja, PhD; Katri Lahti, BM; Helena Lapinleimu, MD, PhD; Liisa Lehtonen, MD, PhD; Tuomo Lehtonen, MD; Marika Leppänen, MD, PhD; Annika Lind, PhD; Hanna Manninen, MD; Jaakko Matomäki, MSc; Jonna Maunu, MD, PhD; Petriina Munck PhD; Laura Määttänen, MD; Pekka Niemi, PhD; Anna Nyman, MA; Pertti Palo, MD, PhD; Riitta Parkkola, MD, PhD; Liisi Rautava, MD, PhD; Päivi Rautava, MD, PhD; Katriina Saarinen, physiotherapist; Virva Saunavaara, PhD; Sirkku Setänen, MD; Matti Sillanpää, MD, PhD; Suvi Stolt, PhD; Sanna Sutinen, BM; Päivi Tuomikoski-Koiranen, RN; Timo Tuovinen, BA; Anniina Väliaho, MA; Milla Ylijoki, MD, PhD. The authors have stated that they had no interests which might be perceived as posing a conflict or bias.

REFERENCES

1. Platt MJ, Cans C, Johnson A, et al. Trends in cerebral palsy among infants of very low birthweight (<1500 g) or born prematurely (<32 weeks) in 16 European centres: a database study. *Lancet* 2007; **369**: 43–50.
2. Fawke J. Neurological outcomes following preterm birth. *Semin Fetal Neonatal Med* 2007; **12**: 374–82.
3. Ferrari F, Gallo C, Pugliese M, et al. Preterm birth and developmental problems in the preschool age. Part I: minor motor problems. *J Matern Fetal Neonatal Med* 2012; **25**: 2154–59.
4. Hadders-Algra M. Neurological Examination of the Child with Minor Neurological Dysfunction. London: Mac Keith Press, 2010.
5. Hadders-Algra M. Two distinct forms of minor neurological dysfunction: perspectives emerging from a review of data of the Groningen Perinatal Project. *Dev Med Child Neurol* 2002; **44**: 561–71.
6. Arnaud C, Daubisse-Marliac L, White-Koning M, et al. Prevalence and associated factors of minor neuromotor dysfunctions at age 5 years in prematurely born children: the EPIPAGE Study. *Arch Pediatr Adolesc Med* 2007; **161**: 1053–61.
7. Setanen S, Haataja L, Parkkola R, Lind A, Lehtonen L. Predictive value of neonatal brain MRI on the neurodevelopmental outcome of preterm infants by 5 years of age. *Acta Paediatr* 2013; **102**: 492–97.
8. Setanen S, Lahti K, Lehtonen L, et al. Neurological examination combined with brain MRI or cranial US improves prediction of neurological outcome in preterm infants. *Early Hum Dev* 2014; **90**: 851–56.
9. Ricci D, Romeo DM, Haataja L, et al. Neurological examination of preterm infants at term equivalent age. *Early Hum Dev* 2008; **84**: 751–61.
10. Lind A, Parkkola R, Lehtonen L, et al. Associations between regional brain volumes at term-equivalent age and development at 2 years of age in preterm children. *Pediatr Radiol* 2011; **41**: 953–61.
11. Maunu J, Parkkola R, Rikalainen H, et al. Brain and ventricles in very low birth weight infants at term: a comparison among head circumference, ultrasound, and magnetic resonance imaging. *Pediatrics* 2009; **123**: 617–26.
12. Haataja L, Mercuri E, Regev R, et al. Optimality score for the neurologic examination of the infant at 12 and 18 months of age. *J Pediatr* 1999; **135**: 153–61.
13. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol* 1997; **39**: 214–23.
14. Keunen K, Kersbergen KJ, Groenendaal F, Isgum I, de Vries LS, Benders MJ. Brain tissue volumes in preterm infants: prematurity, perinatal risk factors and neurodevelopmental outcome: a systematic review. *J Matern Fetal Neonatal Med* 2012; **25** (Suppl. 1): 89–100.
15. Lind A, Haataja L, Rautava L, et al. Relations between brain volumes, neuropsychological assessment and parental questionnaire in prematurely born children. *Eur Child Adolesc Psychiatry* 2010; **19**: 407–17.
16. Maunu J, Lehtonen L, Lapinleimu H, et al. Ventricular dilatation in relation to outcome at 2 years of age in very preterm infants: a prospective Finnish cohort study. *Dev Med Child Neurol* 2011; **53**: 48–54.
17. Leppanen M, Lapinleimu H, Lind A, et al. Antenatal and postnatal growth and 5-year cognitive outcome in very preterm infants. *Pediatrics* 2014; **133**: 63–70.
18. Darsaklis V, Snider LM, Majnemer A, Mazer B. Predictive validity of Prechtl's method on the qualitative assessment of general movements: a systematic review of the evidence. *Dev Med Child Neurol* 2011; **53**: 896–906.
19. Groen SE, de Blecourt AC, Postema K, Hadders-Algra M. General movements in early infancy predict neuromotor development at 9 to 12 years of age. *Dev Med Child Neurol* 2005; **47**: 731–38.
20. Einspieler C, Marschik PB, Milioti S, Nakajima Y, Bos AF, Prechtl HF. Are abnormal fidgety movements an early marker for complex minor neurological dysfunction at puberty? *Early Hum Dev* 2007; **83**: 521–25.
21. Skiold B, Eriksson C, Eliasson AC, Aden U, Vollmer B. General movements and magnetic resonance imaging in the prediction of neuromotor outcome in children born extremely preterm. *Early Hum Dev* 2013; **89**: 467–72.
22. Romeo DM, Guzzetta A, Scoto M, et al. Early neurologic assessment in preterm-infants: integration of traditional neurologic examination and observation of general movements. *Eur J Paediatr Neurol* 2008; **12**: 183–89.
23. Woodward LJ, Mogridge N, Wells SW, Inder TE. Can neurobehavioral examination predict the presence of cerebral injury in the very low birth weight infant? *J Dev Behav Pediatr* 2004; **25**: 326–34.
24. Stjerna S, Sairanen V, Grohn R, et al. Visual fixation in human newborns correlates with extensive white matter networks and predicts long-term neurocognitive development. *J Neurosci* 2015; **35**: 4824–29.
25. Romeo DM, Cioni M, Scoto M, Mazzone L, Palermo F, Romeo MG. Neuromotor development in infants with cerebral palsy investigated by the Hammersmith Infant Neurological Examination during the first year of age. *Eur J Paediatr Neurol* 2008; **12**: 24–31.

APPENDIX
The Classification of the Brain Magnetic Resonance Imaging Findings

1 Normal findings: normal brain anatomy (cortex, basal ganglia and thalami, posterior limb of internal capsule, white matter, germinal matrix, corpus callosum, and posterior fossa structures), width of extracerebral space <5mm, ventricular/brain ratio <0.35, and no ventriculitis.

2 Minor pathologies: consequences of intraventricular haemorrhages grade 1 and 2, caudothalamic cysts, width of the extracerebral space of 5mm, and ventricular/brain ratio of 0.35.

3 Major pathologies: consequences of intraventricular haemorrhages grade 3 and 4, injury in cortex, basal ganglia, thalamus, or internal capsule, with injury of corpus callosum, cerebellar injury, white matter injury, increased width of extracerebral space >5mm, ventricular/brain ratio >0.35, ventriculitis or other major brain pathology (infarcts).

Pediatr Res. 2016; DOI:10.1038/pr.2016.90

The motor profile of preterm infants at 11 years of age

Motor profile of preterm infants

*Sirkku Setänen[1], Liisa Lehtonen[2], Riitta Parkkola[3], Jaakko Matomäki[4], Leena Haataja[5], on behalf of the PIPARI Study Group

[1]Department of Pediatric Neurology, University of Turku and Turku University Hospital, Turku, Finland

[2]Department of Pediatrics, University of Turku and Turku University Hospital, Turku, Finland

[3]Department of Radiology, and Turku PET Center, University of Turku, and Turku University Hospital, Turku, Finland

[4]Turku University Hospital, Clinical Research Centre, Turku, Finland

[5]Department of Pediatric Neurology, Children's Hospital, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

*Sirkku Setänen, Department of Pediatric Neurology, Turku University Hospital, Kiinamyllynkatu 5-8, 20520 Turku, Finland. Tel: +358 45 637 3420. E-mail: sirkku.setanen@utu.fi

All phases of this study were supported by a grant from Arvo and Lea Ylppö Foundation, the Finnish Cultural Foundation, the Finnish Medical Society Duodecim, Turunmaa Duodecim Society, the South-Western Finnish Foundation of Neonatal Research, and The Turku University Hospital Foundation.

Clinical study.

The authors have no financial relationships relevant to this article to disclose. The authors report no conflict of interest to disclose.

ABSTRACT

Background: Preterm infants are at a higher risk for poor motor outcome than term infants. This study aimed to describe the long-term motor profile in very preterm born children.

Methods: A total of 98 very preterm infants were included. Volumetric brain MRI was performed at term age, and the Movement Assessment Battery for Children – Second Edition (The Movement ABC-2) was employed at 11 years of age. The diagnosis of Developmental Coordination Disorder (DCD) was determined at 11 years of age according to International Classification of Diseases.

Results: Eighty-two of 98 (84%) very preterm infants had normal motor development at 11 years of age. In these children, the mean percentile for the total test score in the Movement ABC-2 examinations was 42 (SD 20). Eight (8%) children had DCD. The mean percentile in these children was 4 (SD 2). Eight (8%) children had CP. Their mean percentile was 6 (SD 14). Decreased volumes in all brain regions associated with lower Movement ABC-2 total scores.

Conclusions: The majority of the very preterm infants had normal motor development at 11 years of age. Volumetric brain MRI at term age provides a potential tool to identify risk groups for later neuromotor impairment.

INTRODUCTION

Preterm infants are at a higher risk for poor motor outcome than term infants (1-5). While the incidence of CP has slightly decreased due to vast advances in perinatal and neonatal care over the past decades (6), the rate of milder motor problems is reported to be significantly high in prematurely born children (7). Furthermore, these problems seem to continue when entering adulthood (8). The Developmental Coordination Disorder (DCD) is defined as a motor impairment that appears in the absence of any obvious neurological and structural abnormality or intellectual disability that would interfere with activities of daily living or academic performance (9). The prevalence of DCD in school-aged children is 5-6%, the reported prevalence being higher in children born at very low birth weight or very preterm, from 9.5% to 51% (4,7,9,10).

Table 1. Neonatal characteristics of the very preterm infants (n=98).

Characteristics	Children with normal motor outcome (n=82)	Children with DCD (n=8)	Children with CP (n=8)
Birth weight, mean (SD) [minimum, maximum], g	1087 (258) [580, 1500]	792 (338) [400, 1490]	1031 (306) [560,1500]
Gestational age at birth, mean (SD) [minimum, maximum], wk	29 0/7 (2 5/7) [24 0/7, 35 6/7]	26 3/7 (2 1/7) [23 0/7, 30 1/7]	28 0/7 (3 1/7) [25 5/7, 35 1/7]
Males, n (%)	34 (41)	8 (100)	5 (63)
Cesarean section, n (%)	48 (59)	4 (50)	5 (63)
Small for gestational age, n (%)	32 (39)	3 (38)	2 (25)
Bronchopulmonary dysplasia, n (%)	9 (11)	3 (38)	3 (38)
Sepsis, n (%)	17 (21)	3 (38)	3 (38)
Necrotizing enterocolitis, surgical, n (%)	1 (1)	1 (13)	2 (25)
Retinopathy of prematurity, laser treated, n (%)	1 (1)	1 (13)	0 (0)
Structural brain MRI findings at term age (data missing for 2 infants)			
Normal findings	52 (65)	3 (38)	1 (13)
Minor pathologies	18 (23)	2 (25)	0 (0)
Major pathologies	10 (13)	3 (38)	7 (88)

The Movement Assessment Battery for Children is the most commonly used and best validated tool for detecting DCD (9), also in a high-risk population of very preterm infants (11). The structural validity of its revised version (The Movement Assessment Battery for Children – Second Edition, The Movement ABC-2) has recently been established (12). The Developmental Coordination Disorder Questionnaire 2007 (DCDQ'07) is a parent report developed to assist in the identification of DCD. The sensitivity and the specificity of this revised questionnaire are 89% and 76%, respectively, in the age group of 10 to 15 years (13).

Even though the predictive value of MRI for short-term outcome is established (14), there is little data on the predictive value of MRI on long-term outcome. The existing data suggest that motor impairment in children with perinatal adversities is especially related to white matter abnormalities MRI (15). We have previously shown the predictive value of structural brain MRI at term age for neurosensory, cognitive and neurological outcome in very preterm born children at 2, 5 and 11 years of age (16-18). A recent study did not find correlations between brain volumes at term age and the Movement ABC-2 scores at age 5.5 years (19). We have recently published the associations between brain volumes at term age and neurological performance at 11 years of age in very preterm born children (18).

The objective of this study was to describe the long-term motor profile of very preterm infants at 11 years of age. The motor assessment was completed by using the Movement ABC-2 to identify children with movement difficulties. An additional aim was to study the associations between volumetric neonatal brain MRI and long-term motor outcome in very preterm infants.

RESULTS

The neonatal characteristics of the 98 very preterm infants are shown in Table 1. Of all infants, 96 (98%) were examined by brain MRI at term age. The mean age at the time of MRI examination was $40^{0/7}$ (SD 2.6 days, [minimum $39^{1/7}$, maximum $41^{3/7}$]). All the children without CP (n=90) were examined using the Movement ABC-2 at 11 years of age, and all their parents were interviewed according to the DCDQ'07. Seven (88%) of the eight children with CP could be examined. The mean age at the time of examination was 11 years and 2 months (SD 4 months, [10 years and 6 months, 11 years and 9 months]). All the neonatal characteristics (Table 1) of the study infants and drop-outs (n=23) (Fig. 1) were compared. The only statistically significant finding was that children lost to follow-up were more often born by cesarean section than the study children (p=0.01).

The number of children with normal motor outcome was 82 (84%). Of these children, 79 (96%) had a total test score >67 (>15th percentile), and 3 (4%) had a total test score of 57-67 (>5th-15th percentile) in the Movement ABC-2. The mean total score of the parental questionnaire DCDQ'07 for these children was 67 (SD 7, [46, 75]), and 7 (9%) children had a total score ≤57 indicating risk for DCD. Fifty-two (63%) of the children with normal motor outcome participated regularly in after-school sporting activities. Eight (8%) children had scores ≤56 (≤5th percentile) in the Movement ABC-2 and were diagnosed with DCD. The mean total score of the DCDQ'07 for these children was 52 (SD 14, [35, 74]), and 4 (50%) had a total score ≤57, indicating risk for DCD. Two (25%) of the children with DCD participated regularly in after-school sporting activities. There were 8 (8%) children with CP. The mean total

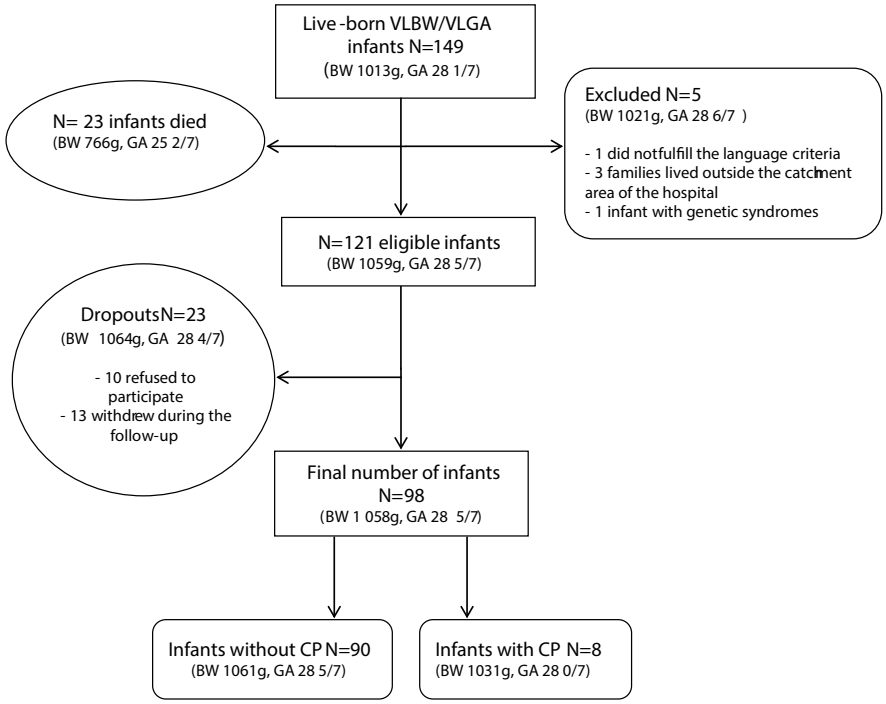


Figure 1 The flow chart of the participants, mean birth weights (BW) and gestational ages (GA) in weeks.

score of the DCDQ'07 for these children was 49 (SD 10, [37, 68]), and 6 (86%) had a total score ≤57. One (14%) of the children with CP participated regularly in after-school sporting activities. The mean values of the three domains and the total test score of the Movement ABC-2 in all children are shown in Table 2. The distribution

Table 2. The mean values (SD, median, and interquartile range) of the three domains and the total test score of the Movement ABC-2 in percentiles in very preterm born children with normal motor outcome (n=82), developmental coordination disorder (DCD) (n=8), CP (n=8), and all children (n=97).

Domain	Mean	SD	Median	Interquartile range
Manual dexterity				
Children with normal motor outcome	41	22	37	25-50
Children with DCD	11	16	7	1-13
Children with CP*	13	15	5	0-25
All children*	36	23	37	16-50
Aiming and catching				
Children with normal motor outcome	36	26	37	16-50
Children with DCD	10	10	5	2-21
Children with CP*	3	3	2	1-5
All children*	32	26	25	9-50
Balance				
Children with normal motor outcome	59	27	50	37-91
Children with DCD	11	12	9	4-13
Children with CP*	13	34	0	0-1
All children*	52	32	50	25-91
Total test score				
Children with normal motor outcome	42	20	37	25-63
Children with DCD	4	2	5	4-5
Children with CP*	6	14	1	0-2
All children*	36	23	37	16-50

*Data missing for one child

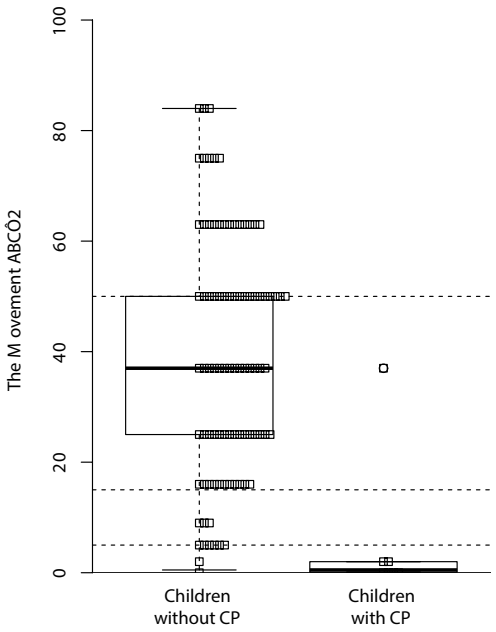


Figure 2 Combined dotplot and boxplot of the percentiles for the total test scores of the Movement ABC-2 examinations in very preterm born children with CP (n=8) and without CP (n=90). Horizontal dashed lines of the percentiles 5, 15, and 50 show the cut-offs of significant movement difficulty, risk of having a movement difficulty, and the mean of the norm population, respectively.

of the total test scores in children with and without CP is shown in Fig.2.

Brain MRI explained 17.8% of the variation in the Movement ABC-2 total scores (p<0.001) in all children and 7.8% in children without CP (p=0.03). Major brain pathologies on MRI reduced the Movement ABC-2 total scores compared to normal findings (b=-3.5 for minor pathologies and b=-25.2 for major pathologies in all children, and b=-3.6 for minor pathologies and b=-17.9 for major pathologies in children without CP). The negative predictive value (NPV) of normal findings or minor pathologies in brain MRI and positive predictive value (PPV) of major pathologies for DCD was 93.3% and 23.1%.

Table 3. The associations between brain volumetric findings at term age and the Movement ABC-2 total scores in very preterm born children at 11 years of age. The analysis was adjusted for gestational age, small for gestational age status, gender, and MRI categories.

	The Movement ABC-2	
	b (95% CI)	p
Total brain tissue	0.20 (0.10-0.30)	<0.001
Ventricles	-0.23 (-6.80-6.33)	0.94
Cerebrum	0.20 (0.10-0.30)	<0.001
Frontal lobes	0.32 (0.12-0.51)	0.002
Basal ganglia and thalami	1.65 (0.85-2.45)	<0.001
Cerebellum	1.16 (0.21-2.11)	0.02
Brain stem	2.13 (0.53-3.73)	0.01

The NPV and PPV of brain MRI for CP was 98.7% and 35.0%. Decreasing volumes in all brain regions associated with lower Movement ABC-2 total scores as shown in Table 3. All the associations remained statistically significant when excluding the children with CP. The mean values of brain volumes at term age in very preterm born children with normal motor outcome, DCD, and CP are shown in Table 4.

Of the other background characteristics shown in Table 1, gestational age (r=0.26, p=0.01), birth weight (r=0.25, p=0.01), and bronchopulmonary dysplasia (R^2=0.07, p=0.009) were significantly associated with the Movement ABC-2 total scores. The DCDQ'07 total scores correlated with the Movement ABC-2 total scores (r=0.43, p<0.001).

DISCUSSION

This prospective follow-up study of a regional cohort of very preterm infants showed that the majority of children performed within the lower range of normal variation considering motor outcome at 11 years of age. Decreasing regional brain volumes at term age associated with poorer motor outcome even when excluding children with CP.

The skills to aim and catch a tennis ball were the most commonly impaired in very preterm born children. Interestingly, others have found the most prominent problems to be in balance skills (2), whereas

Table 4. The mean values (SD) of brain volumes (ml) at term age in very preterm born children with normal motor outcome (n=82), DCD (n=8), and CP (n=8) at 11 years of age.

	Normal motor outcome	DCD	CP
Total brain tissue	399.2 (44.7)	374.3 (62.7)	359.1 (36.8)
Ventricles	16.1 (9.2)	14.4 (10.4)	44.1 (48.4)
Cerebrum	366.0 (43.0)	346.8 (58.4)	330.5 (33.4)
Frontal lobes	136.9 (22.2)	125.5 (17.0)	113.9 (19.2)
Basal ganglia and thalami	26.7 (5.2)	23.5 (4.0)	22.4 (3.4)
Cerebellum	25.4 (4.6)	21.1 (7.0)	21.4 (2.8)
Brain stem	7.7 (2.9)	6.4 (2.2)	7.2 (2.7)

the present study found also manual dexterity skills to be impaired more often than balance skills. This difference may partly be explained by the use of a previous version of the Movement ABC examination and the inclusion of only extremely low birth weight or very preterm infants. In addition, it would be interesting to know the regional brain volumes in different populations of very preterm infants. Different care practices may have different effects especially on the vulnerability of the basal ganglia and cerebellum, which modify the profile/quality of movement in motor performance. Another difference compared to previous literature was that no effect of gender or small for gestational age status on the motor performance was found (4,9,10). This is consistent with our previous results of similar outcomes in small for gestational age infants (20-22).

The neonatal characteristics that associated with poorer motor outcome were gestational age, birthweight, and bronchopulmonary dysplasia. A previous study of perinatal and neonatal predictors for DCD in very low birthweight children has shown that male sex, lower gestational age, lower birthweight, postnatal steroid exposure, longer duration of ventilation, more days of oxygen, retinopathy of prematurity, and hyponatremia were associated with poorer motor outcome. Of these variables, only male sex, low birthweight and postnatal steroid exposure remained significant with the addition of neonatal factors (10).

Interestingly, children with DCD seemed to have even lower gestational age and lower birthweight than children with CP in this study. Also the structural brain MRI findings differentiated the children with DCD and the children with CP. The majority of children with CP had major pathologies, whereas of the children with DCD, fewer had major pathologies compared to children with CP. According to volumetric findings, children with CP had significantly larger ventricles than children with DCD. Even though all children with DCD in the present study were boys, the small number of children with DCD and CP did not enable reliable statistical analysis.

We found increased prevalence of DCD in children born preterm as shown earlier. However, our prevalence was lower compared to previous studies (4,7,9,10). The possible reasons for these differences include different patient populations with different inclusion and exclusion criteria, and different age point at testing, as the present study is unique in having such a long follow-up time. There are also studies using different cut-off levels in the Movement ABC examination, and studies using the DCDQ as the only diagnostic instrument, which is in disagreement with the latest diagnostic recommendations (9).

It is noteworthy that more than half of the very preterm infants with normal motor development participated regularly in organized after-school sports, which might potentially have supported normal motor development. Having regular after-school sporting activities indicates sufficient motor outcome for participating in peer-group physical activities and, potentially, supports not only motor but also social development. It is also known that sporting activities are associated with higher quality of life (23). As for the children with DCD, only a quarter of them had after-school sport activities, which is in agreement with a previous study showing that fewer children with motor impairment participate in organized sporting activities outside school compared to children with normal motor development (24).

The present study showed that decreased volumes in all brain regions at term age associated with poorer Movement ABC-2 total scores at 11 years of age. In contrast to our results, a recent study with shorter follow-up time of 5.5 years found no correlations between automatically segmented brain volumes at term age and motor outcome in very preterm born children (19). The difference might be explained by the fact that our study included more major brain pathologies and also more children with CP. Our study also had higher follow-up rate. It is possible that motor problems manifest more clearly with increasing age. In addition, the brain volumes were measured manually in our study. We have previously shown an association between reduced volumes of total brain tissue, frontal lobes, basal ganglia and thalami, and cerebellum and poor neurological outcome at the age of 11 years (18). The present study strengthens these previous results suggesting that brain volumes are potentially valuable in finding the risk groups for later neuromotor impairment. However, clear cut-off values would require large normative samples.

A possible technical limitation is the MRI equipment of the study period. More advanced and accurate imaging techniques are plausible to improve the prediction of abnormal outcome. In addition, T2-weighted images were obtained, but they were not used for the volume measurements, since there was a gap in the T2-weighted images between slices. Accordingly, the continuous T1-weighted images were used. Although the slice thickness was rather thick (5mm) on T1-weighted images, this, however, allowed sufficient signal to noise ratio for interpretation. It is possible that partial volume effect may have caused some error on the volume measurements; however, the error would be similar in all infants. Another limitation is the lack of a control group.

The strengths of this study included a high coverage of the examinations at term age and at 11 years of age.

Furthermore, the latest versions of the Movement ABC and the DCDQ were used. The results of the DCDQ'07 were only used to support the results of the MABC-2 as the DCDQ'07 is not designed to be used alone to identify DCD. Instead, the diagnosis also requires valid clinical measures (13). The presence of DCD was defined according to International Classification of Diseases (ICD-10), which is used in many countries. These criteria are also comparable with Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV).

This study, showing normal motor outcome in the majority of very preterm infants, supports recent research on the improving outcome of preterm infants. Brain growth seems to play a pivotal role, since smaller regional brain volumes predict a poorer motor outcome.

METHODS

This study is part of the multidisciplinary PIPARI Study (The Development and Functioning of Very Low Birth Weight Infants from Infancy to School Age), a prospective study of very low birth weight or very low gestational age infants born to Finnish- or Swedish-speaking families between 2001 and 2006, at Turku University Hospital, Finland. The inclusion criteria was a birth weight ≤1500 grams in preterm infants born <37 gestational weeks, from 2001 to the end of 2003. From the beginning of 2004, the inclusion criteria were broadened to include all infants born below the gestational age of 32 weeks, regardless of birth weight. Only the infants born between January 2001 and April 2004 were included in this study because the MRI equipment was upgraded thereafter. The flow chart of the participants is shown in Fig. 1. Written informed consent was obtained from all children and parents for the follow-up study. The PIPARI Study protocol was approved by the Ethics Review Committee of the Hospital District of South-West Finland in December 2000 and in January 2012.

Magnetic resonance imaging of the brain

The brain MRI was performed at term age. One neuroradiologist (R.P.) analyzed the images and manually performed volume measurements blinded to the clinical information of the infant. Axial T2-weighted images, coronal three-dimensional T1-weighted images and coronal T2-weighted images of the entire brain were obtained using the MRI equipment of an open 0.23 Tesla Outlook GP (Philips Medical, INC, Vantaa, Finland) equipped with a multipurpose flexible coil fitting the head of the infant. All of the sequences were optimized for the imaging of a term infant brain. To evaluate the relationship between the brain pathology and the motor outcome, the infants were categorized into three groups based on the structural MRI findings: 1) Normal findings consisted of normal brain anatomy (cortex, basal ganglia and thalami, posterior limb of internal capsule, white matter, germinal matrix, corpus callosum and posterior fossa structures), width of extracerebral space <5 mm, ventricular/brain (V/B) ratio <0.35, 2) Minor pathologies consisted of consequences of intraventricular hemorrhages grade 1 and 2, caudothalamic cysts, width of the extracerebral space of 5 mm and V/B ratio of 0.35, and 3) major pathologies consisted of consequences of intraventricular hemorrhages grade 3 and 4, injury in cortex, basal ganglia, thalamus or internal capsule, with injury of corpus callosum, cerebellar injury, white matter injury, increased width of extracerebral space >5 mm, V/B ratio >0.35, ventriculitis or other major brain pathology (infarcts).-

Volume measurement was performed on T1-weighted images by visually separating the cerebrospinal fluid from the brain tissue image by image. The anatomical differentiation of the brain was based both on anatomical landmarks and signal intensity differences of the brain structures. The volumes of the total brain tissue (total brain volume minus ventricle volumes), the cerebrum, the cerebellum, the frontal lobes, the brain stem (medulla oblongata together with pons), the basal ganglia together with the thalami, and ventricles (lateral ventricles, third and fourth ventricles) were measured. The reproducibility of these measurements was assessed by repeated volume measurement of 20 children, performed by another neuroradiologist, who was blinded for the results of the first measurement. These methods have been previously described in detail (16-18,20,25).

Outcome classification

For this study, normal motor outcome was defined as a total test score ≥57 (>5th percentile). The diagnosis of DCD was defined as a total test score ≤56 (≤5th percentile) according to ICD-10. A further requirement was that the diagnosis was not solely explicable in terms of general intellectual disability or of any specific congenital or acquired neurological disorder (9). The diagnosis of CP, including the grading of functional severity by Gross Motor Function Classification System (GMFCS) (26), was ascertained by a child neurologist (L.H.) at 2 years of corrected age after a systematic clinical follow-up. Data concerning the children's regular participation in after-school sporting activities was acquired during the follow-up visit at 11 years of age.

The Movement Assessment Battery for Children - 2

The motor assessment was completed at 11 years of age by using the Movement ABC-2 to identify children with movement difficulties (27). The clinical examination was performed by the author (S.S.). The Movement ABC-2 included 3 domains: manual dexterity (3 items), aiming and catching (3 items), and balance (3 items). All the items were scored according to best attempt to receive raw scores. These were then further calculated to standard scores equating to percentiles of each domain and total test score, accordingly. A total test score ≤56 (≤5th percentile) denoted a significant movement difficulty. A total test score of 57-67 (>5th to 15th percentile) suggested the child was at risk of having a movement difficulty (monitoring required). Any total test score >67 (>15th percentile) indicated that there was no movement difficulty. The age band 3 (11 to 16 years) was used and the test was scored according to the norms for 11-year-old children as we wanted to use identical test tasks and references for all children even if some children had not yet turned 11 years at the time of the examination.

The Developmental Coordination Disorder Questionnaire 2007

Parents were asked to compare their child's motor performance to that of his/her peers to support the diagnosis of the DCD concerning the interference of motor difficulties in everyday functional activities. The DCDQ'07 consisted of 15 items, which were further grouped into 3 distinct factors: control during movement, fine motor and handwriting, and general coordination (13). The questionnaire was completed by interview (author S.S). All the items were scored using a 5-point Likert scale. Total scores were calculated by summing up item scores. The total score varied from 15 to 75. Scores from 15 to 57 indicated DCD.

Data analysis

Pearson's correlation was used to study the univariate associations between two continuous variables. Univariate associations between continuous Movement ABC-2 percentile and categorical predictor variables were studied using regression analysis. Associations between brain volumes and continuous Movement ABC-2 percentile were studied using regression analysis controlling for brain pathology, gender, small for gestational age status and gestational age. The regression equation for the associations between the total scores of the Movement ABC-2 and background characteristics was 3.88+0.19*gestational age in days-22.36*major pathologies in brain MRI-2.27*minor pathologies in MRI-0.19*small for gestational age status-2.52*male gender. All the results of regression analyses remained the same when controlling for the age at the time of brain MRI examination. Continuous variables are presented with mean (SD) [minimum, maximum]. Main results were analyzed both in all children and excluding children with CP. Continuous variables were compared between study infants and drop-outs using the Mann–Whitney U test and comparisons between two categorical variables were done using the v2 test or Fisher's exact test, as appropriate. Statistical analyses were performed using SAS for Windows version 9.3. and p-values below 0.05 were considered as statistically significant.

ACKNOWLEDGEMENTS

The PIPARI Study Group: Karoliina Aho, BM; Annarilla Ahtola, PhD; Mikael Ekblad, MD, PhD; Satu Ekblad, RN; Eeva Ekholm, MD, PhD; Annika Eurola, BM; Leena Haataja, MD, PhD; Mira Huhtala, MD, PhD; Jere Jaakkola, BM; Pentti Kero, MD, PhD; Riikka Korja, PhD; Katri Lahti, BM; Helena Lapinleimu, MD, PhD; Liisa Lehtonen, MD, PhD; Tuomo Lehtonen, MD; Marika Leppänen, MD, PhD; Annika Lind, PhD; Hanna Manninen, MD; Jaakko Matomäki, MSc; Jonna Maunu, MD, PhD; Petriina Munck PhD; Laura Määttänen, MD; Pekka Niemi, PhD; Anna Nyman, MA; Pertti Palo, MD, PhD; Riitta Parkkola, MD, PhD; Liisi Rautava, MD, PhD; Päivi Rautava, MD, PhD; Katriina Saarinen, Physiotherapist; Virva Saunavaara, PhD; Sirkku Setänen, MD; Matti Sillanpää, MD, PhD; Suvi Stolt, PhD; Sanna Sutinen, BM; Päivi Tuomikoski-Koiranen, RN; Timo Tuovinen, BA; Anniina Väliaho, MA; Milla Ylijoki, MD, PhD.

REFERENCES

1. Evensen KA, Vik T, Helbostad J, Indredavik MS, Kulseng S, Brubakk AM. Motor skills in adolescents with low birth weight. Arch Dis Child Fetal Neonatal Ed 2004;89:F451-5.

2. de Kieviet JF, Piek JP, Aarnoudse-Moens CS, Oosterlaan J. Motor development in very preterm and very low-birth-weight children from birth to adolescence: a meta-analysis. JAMA 2009;302:2235-42.

3. Edwards J, Berube M, Erlandson K, et al. Developmental coordination disorder in school-aged children born very preterm and/or at very low birth weight: a systematic review. J Dev Behav Pediatr 2011;32:678-87.

4. Zwicker JG, Missiuna C, Harris SR, Boyd LA. Developmental coordination disorder: A review and update. Eur J Paediatr Neurol 2012;16:573-81.

5. Synnes A, Anderson PJ, Grunau RE, et al. Predicting severe motor impairment in preterm children at age 5 years. Arch Dis Child 2015;100:748-53.

6. Sellier E, Platt MJ, Andersen GL, et al. Decreasing prevalence in cerebral palsy: a multi-site European popula-

tion-based study, 1980 to 2003. Dev Med Child Neurol 2015;58:85-92.

7. Ferrari F, Gallo C, Pugliese M, et al. Preterm birth and developmental problems in the preschool age. Part I: minor motor problems. J Matern Fetal Neonatal Med 2012;25:2154-9.
8. Husby IM, Skranes J, Olsen A, Brubakk AM, Evensen KA. Motor skills at 23 years of age in young adults born preterm with very low birth weight. Early Hum Dev 2013;89:747-54.
9. Blank R, Smits-Engelsman B, Polatajko H, Wilson P, European Academy for Childhood Disability. European Academy for Childhood Disability (EACD): recommendations on the definition, diagnosis and intervention of developmental coordination disorder (long version). Dev Med Child Neurol 2012;54:54-93.
10. Zwicker JG, Yoon SW, Mackay M, Petrie-Thomas J, Rogers M, Synnes AR. Perinatal and neonatal predictors of developmental coordination disorder in very low birthweight children. Arch Dis Child 2013;98:118-22.
11. Dewey D, Creighton DE, Heath JA, et al. Assessment of developmental coordination disorder in children born with extremely low birth weights. Dev Neuropsychol 2011;36:42-56.
12. Schulz J, Henderson SE, Sugden DA, Barnett AL. Structural validity of the Movement ABC-2 test: factor structure comparisons across three age groups. Res Dev Disabil 2011;32:1361-9.
13. Wilson BN, Crawford SG, Green D, Roberts G, Aylott A, Kaplan BJ. Psychometric properties of the revised Developmental Coordination Disorder Questionnaire. Phys Occup Ther Pediatr 2009;29:182-202.
14. Hintz SR, Barnes PD, Bulas D, et al. Neuroimaging and neurodevelopmental outcome in extremely preterm infants. Pediatrics 2015;135:e32-42.
15. Peters LH, Maathuis CG, Hadders-Algra M. Neural correlates of developmental coordination disorder. Dev Med Child Neurol 2013;55 Suppl 4:59-64.
16. Setänen S, Haataja L, Parkkola R, Lind A, Lehtonen L. Predictive value of neonatal brain MRI on the neurodevelopmental outcome of preterm infants by 5 years of age. Acta Paediatr 2013;102:492-7.
17. Setänen S, Lahti K, Lehtonen L, et al. Neurological examination combined with brain MRI or cranial US improves prediction of neurological outcome in preterm infants. Early Hum Dev 2014;90:851-6.
18. Setänen S, Lehtonen L, Parkkola R, Aho K, Haataja L, PIPARI Study Group. Prediction of neuromotor outcome in infants born preterm at 11 years of age using volumetric neonatal magnetic imaging and neurological examinations. Dev.Med.Child Neurol. 2016;DOI: 10.1111
19. Keunen K, Isgum I, van Kooij BJ, et al. Brain Volumes at Term-Equivalent Age in Preterm Infants: Imaging Biomarkers for Neurodevelopmental Outcome through Early School Age. J Pediatr 2016;DOI:10.1016
20. Lind A, Parkkola R, Lehtonen L, et al. Associations between regional brain volumes at term-equivalent age and development at 2 years of age in preterm children. Pediatr Radiol 2011;41:953-61.
21. Leppanen M, Lapinleimu H, Lind A, et al. Antenatal and postnatal growth and 5-year cognitive outcome in very preterm infants. Pediatrics 2014;133:63-70.
22. Maunu J, Lehtonen L, Lapinleimu H, et al. Ventricular dilatation in relation to outcome at 2 years of age in very preterm infants: a prospective Finnish cohort study. Dev Med Child Neurol 2011;53:48-54.
23. Gopinath B, Hardy LL, Baur LA, Burlutsky G, Mitchell P. Physical activity and sedentary behaviors and health-related quality of life in adolescents. Pediatrics 2012;130:e167-74.
24. Wocadlo C, Rieger I. Motor impairment and low achievement in very preterm children at eight years of age. Early Hum Dev 2008;84:769-76.
25. Maunu J, Parkkola R, Rikalainen H, et al. Brain and ventricles in very low birth weight infants at term: a comparison among head circumference, ultrasound, and magnetic resonance imaging. Pediatrics 2009;123:617-26.
26. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. Dev Med Child Neurol 1997;39:214-23.
27. Henderson SE, Sugden DA, Barnett AL. Movement assessment battery for children (examiner's manual). London: Pearson Assessment, 2007.