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Infant Motor Assessment, Long-Term Clinical Outcome, Quantitative Cerebral MRI and Cognitive Training in Children Born Preterm with Very Low Birth Weight

Thesis for the degree of Philosophiae Doctor

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Faculty of Medicine
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If I can stop one heart from breaking,
I shall not live in vain:
If I can ease one life the aching,
Or cool one pain,
Or help one fainting robin
Unto his nest again,
I shall not live in vain.

Emily Dickinson

Tidlig bevegelses-analyse, langtids-oppfølging av klinisk utkomme, kvantitativ MRI av hjernen og kognitiv trening hos barn født prematurt med veldig lav fødselsvekt.

I løpet av de siste tiårene har insidensen av premature fødsler med overlevelse økt pga framskritt innenfor obstetrikken og innenfor nyfødtmedisinen. Prisen for dette er at mange av de overlevende barna utvikler alvorlige sekveler som cerebral parese (CP) og psykisk utviklingshemning, eller mindre alvorlige problemer innenfor kognisjon, konsentrasjon, atferd og i hverdagslivet. Perinatal hjerneskade omfatter diffus og fokal ødeleggelse (nekrose) av den hvite nervefibersubstansen, samt skader i den grå hjernesubstansen (hjernebark og dype kjerner) og er den mest vanlige årsaksmekanismen til varige nevrologiske skader og følgetilstander hos de for tidlig fødte barna. Uttrykket "Encephalopathy of prematurity" beskriver at hjerneskaden i den premature hjernen som er under utvikling, er en kompleks skade som kan ha sekundære effekter både med tanke på modningsprosessen og utviklingen av hele hjernen.

Flere studier viser at problemene til de prematurt fødte barna har innvirkning både på skoleprestasjoner, utdanning og også senere i arbeidslivet slik at det er meget viktig å diagnostisere problemene tidlig slik at man kan starte intervensjon så raskt som mulig. En metode som observerer småbarns spontane bevegelser ca 14 uker etter terminen, The General Movement Assessment (GMA), har vist seg å være en verdifull metode for å kunne predikere utvikling av nevrologiske sekveler og spesielt CP i høyrisiko-barn som enten er født til termin eller prematurt. Nylig antydet en gruppe forskere at en detaljert analyse av det motoriske repertoaret som er inkludert i GMA også kan predikere det kognitive utkommet hos barna. For å kunne undersøke den prediktive verdien av GMA metoden hos høyrisiko-barn som ikke utviklet CP og i tillegg undersøke langtids utkomme med spesielt fokus på barn med ekstremt lav fødselsvekt (ELBW = fødselsvekt under 1000 g), inkluderte vi 40 slike høyrisiko barn og en kontroll gruppe med 33 friske barn født i 1999-2001 i en oppfølgingsstudie. Ved 10 års alder ble barna undersøkt med et stort testbatteri hvor motorisk funksjon, kognisjon, eksekutiv funksjon, konsentrasjon og atferd ble undersøkt. Barna med ELBW og kontrollene ble i tillegg undersøkt med cerebral MRI. Film-opptakene av spontanmotorikk ved 14 ukers alder av alle høyrisiko-barna ble vurdert både mtp GMA og i tillegg ble en detaljert undersøkelse av motorisk repertoar gjort.

Vi fant at GMA og motorisk repertoar var prediktive for både CP og for sammensatte kognitive og motoriske vansker hos barna uten CP. Da vi sammenliknet ELBW barna uten CP med kontrollene, fant vi ingen forskjell i IQ og nevropsykologiske testresultater, men dårligere arbeidsminne og motorikk, mer konsentrasjonsvansker og mer atferdsproblemer hos ELBW barna uten CP. På MRI hadde ELBW barna mindre totalt hjernevolum, reduserte volumer av globus pallidus, hvit substans i lillehjernen og i corpus callosum (den midtre hjernebjelken), samt redusert overflate i visse områder av hjernebarken.
De lave kliniske testresultatene ble i hovedsak funnet hos de ELBW barna uten CP som hadde et unormalt tidlig motorisk repertoar. Dette kan indikere at en evaluering av spontanmotorikk som GMA i de første levemåneder, kan være en god metode for å predikere utkomme hos nevrologiske høyrisiko-barn. Dette gjelder også de barna som ikke utvikler CP, men som får mer sammensatte problemer innenfor motorikk, kognisjon, konsentrasjon, og atferd. Dersom man tidlig kan identifisere disse barna, kan man iverksette intervensjoner allerede i småbarnsalderen og kanskje dermed redusere risikoen for senere skolemessige og sosiale vansker.

Det andre målet med denne doktorgraden var å finne ut om et databasert treningsprogram av arbeidsminnet kunne ha positiv effekt hos prematurt fødte førskolebarn. Arbeidsminnet (Working memory) har blitt definert som vår evne til å holde på og manipulere informasjon «online» over en kort periode. Arbeidsminnet er ansett for å være en forutsetning for et barns evne til å lære, til å planlegge en handling, løse et problem, utvikle språk og å regne. Dersom arbeidsminnet er svekket, kan konsekvensen være lærevansker med vedvarende effekt langt inn i voksenlivet. Studier av barn med ADHD, Down syndrom, av barn som har fått kjemoterapi pga blodkreft (leukemi) og av ELBW ungdommer har vist at arbeidsminnet kan bedres gjennom et databasert treningsprogram utviklet av svenske forskere.

I vår studie inkluderte vi 20 premature barn med veldig lav fødselsvekt (VLBW = fødselsvekt under 1500 g). Barna trente med programmet 10-15 minutter hver dag, 5 dager pr uke over en 5 ukers periode. De ble testet kognitivt med IQ-test før trening og med et stort nevropsykologisk testbatteri før og 4 uker etter avsluttet trening. De premature VLBW førskolebarna viste seg å ha positiv korttidseffekt på trente og ikke trente arbeidsminneoppgaver. I tillegg fant vi en generalisert positiv effekt på auditiv konsentrasjon, fonologisk oppmerksomhet og visuell og verbal hukommelse.
For å kunne vurdere om treningsprogrammet også hadde en positiv langtidseffekt etter 7 måneder, inkluderte vi en ny gruppe ikke-trenende VLBW barn i samme aldersgruppe som de som hadde trent. Vi fant en vedvarende gevinst i ytelse etter 7 måneder blant VLBW barna som hadde trent, på ikke-trente visuelle arbeidsminne-oppgaver samt på visuell og verbal hukommelse og læring. Vi konkluderte derfor med at en slik intervensjon i form av databasert kognitiv trening kan være verdifull hos premature barn før de begynner på skolen, for på den måten å kunne redusere kognitive problemer som kan ha innvirkning på utdanning og også sosial omgang. Større studier må dog stadfeste eller avkrefte våre resultater før generaliserte anbefalinger om kognitiv trening av prematurt fødte førskolebarn kan gis.

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Contents

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List of papers

Paper 1

Toril Fjørtoft, Kristine Hermansen Grunewaldt, Gro C Christensen Løhaugen, Siv Mørkved, Jon Skranes, Kari Anne I. Evensen

Assessment of motor behaviour in high-risk-infants at 3 months predicts motor and cognitive outcome in 10 years old children.

Early Hum Dev. 2013;89(10):787-93. doi: 10.1016/j.earlhumdev.2013.06.007. Epub Jul 11.

Paper 2

Kristine Hermansen Grunewaldt, Toril Fjørtoft, Knut Jørgen Bjuland, Ann-Mari Brubakk, Live Eikenes, Asta K Håberg, Gro CC Løhaugen, Jon Skranes

Follow-up at age 10 years in ELBW children - Clinical outcome, brain morphology and results from motor assessments in infancy.

Early Hum Dev. 2014 Aug 4;90(10):571-578. doi: 10.1016/j.earlhumdev.2014.07.005.

Paper 3

Kristine Hermansen Grunewaldt, Gro Christine Christiansen Løhaugen, Dordi Austeng, Ann-Mari Brubakk, Jon Skranes

Working memory training improves cognitive function in VLBW preschoolers

Pediatrics. 2013;131(3):e747-54. doi: 10.1542/peds.2012-1965. Epub 2013 Feb 11

Paper 4

Kristine Hermansen Grunewaldt, Jon Skranes, Ann-Mari Brubakk, Gro Christine Christiansen Løhaugen

Computerized working memory training has positive long term effects in VLBW preschoolers

PLOS ONE (submitted May 2014)

Abbreviations

ADHD	Attention deficit hyperactivity disorders
AMR	Assessment of motor repertoire
BPD	Broncho Pulmonary Dysplasia
BRIEF	Behavioral Rating Inventory of Executive Function
BW	Birth weight
CP	Cerebral palsy
CUS	Cerebral ultrasound
ELBW	Extremely low birth weight
F	Fidgety movements
GA	Gestational age
GLM	General linear model
GMA	General Movement Assessment
IVH	Intraventricular hemorrhage
IQ	Intelligence quotient
MABC	Movement assessment battery for children
MRI	Magnetic resonance imaging
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit
PAS	Preschool Anxiety Scale
PDA	Patent Ductus Arteriosus
PVL	Periventricular leukomalacia
ROP	Retinopathy of prematurity
SES	Socioeconomic status
SGA	Small for gestational age
VABS	Vineland Adaptive Behavior Scale
VLBW	Very low birth weight
WISC	Wechsler Intelligence Scale for Children
WPPSI	Wechsler Preschool and Primary Scale of Intelligence;

Summary

The preterm birth incidence and survival rates have been increasing over the last few decades due to advances in obstetric care and neonatal treatment. Despite this, the number of preterm children that develop severe neuroimpairments or more subtle difficulties within cognition, attention, behavioral and every day skills are still high. Perinatal brain injury, including diffuse and focal white matter necrosis and grey matter injury is the most common cause of the neuroimpairments in preterm children. The suggested term "encephalopathy of prematurity" indicates that preterm brain injury is a complex injury in the developing brain that has secondary consequences regarding maturation and development, most likely of the whole brain.

Studies report that the difficulties preterm children have impact scholastic achievement and academic performance, and therefore early identification of impairments is essential in order to initiate early intervention strategies as soon as possible. An observational method of infant's spontaneous movements at 14 weeks post term age: The General Movement Assessment (GMA) has been shown to be a valuable predictor of development of later cerebral palsy (CP) in preterm and high-risk term-born children. Recently researchers suggested that a detailed analysis of the motor repertoire that is included in the general movement assessment also can identify non-CP children with motor and cognitive deficits. In order to examine the predictive value of the general movement assessment in high-risk children that do not develop CP and to examine long-term outcome with a special focus on the extremely low birth weight (ELBW) children without CP, we initiated a study including 40 high-risk term-born and preterm children at 10 year age and a control group consisting of 33 age matched healthy children. An extensive assessment of motor, cognition, executive function, attention and behavior was performed at 10 years follow-up. In addition to this we also performed a cerebral MRI in the ELBW children as well as in the controls. Videotapes of the high-risk children that had been filmed 10 years ago were assessed with the GMA and a detailed assessment of the infant motor repertoire shortly before the follow-up examination. We found that the assessment of GMA and motor repertoire was predictive for CP and a composite of cognitive and motor deficits in high-risk children without CP. When comparing non-CP ELBW children with controls we found similar IQ and neuropsychological test results but lower working memory skills, poorer motor skills, and more attention and behavioral problems in the non-CP ELBW children. On MRI we found smaller total brain volumes, reduced volumes of globus pallidus, cerebellar white matter, corpus callosum and regionally

reduced cortical surface area in the non-CP ELBW children. The inferior clinical test results and reduced brain volumes were mostly found in the non-CP ELBW children with abnormal early motor repertoire. This may indicate that the early motor assessment can be a valuable predictor in preterm children who do not develop CP but still are at a high risk of developing composite neuroimpairments. By successfully identifying these children, early intervention can be initiated and this might reduce the risk of later academic or social difficulties.

The second aim of this thesis was to investigate whether a computerized working memory training program could have positive effect in preterm-born preschoolers. Working memory has been defined as our ability to temporarily store and at the same time manipulate information "online" over short periods of time. Working memory is considered a prerequisite for other executive functions that are essential for a child's ability to learn, plan their actions, solve problems, and develop language as well as mathematical skills. When working memory skills are impaired, learning difficulties with lasting effects into adolescence and adulthood may result. Studies indicate that working memory can be trained and positive effects of a computerized working memory training program have been shown in children with ADHD, Downs syndrome, in children after chemotherapy, and in ELBW adolescents.
We included 20 very low birth weight (VLBW) children that trained with the Cogmed JM program designed for preschool aged children, 10-15 minutes a day, 5 days a week over a 5-week period. The children were examined with an extensive cognitive and neuropsychological test battery before and 4 weeks after training. We found that the VLBW preschoolers had positive short-term effects on trained and non-trained working memory tasks, and transfer effects were observed as improvement on auditory attention, phonological awareness, and visual as well as verbal memory. In order to examine whether the intervention had long-term positive effect after 7 months, we included a group of age-matched non training VLBW children. We found performance gain on non-trained visual working memory tasks and on tests of visual and verbal memory and learning, compared with VLBW controls who had not trained. We concluded that this intervention might be valuable in preterm children before they start school and that such interventions might prevent or at least reduce cognitive problems that impact educational achievement and social function. However, larger studies must be conducted to confirm our results before general recommendations can be made with regard to implementing such training in clinical practice.

INTRODUCTION

Topic of the thesis

During the last few decades, survival rates of preterm-born children with very low (VLBW, BW < 1500g) or extremely low birth weight (ELBW, BW<1000g) have been increasing (Saigal and Doyle 2008). This has primarily been attributed to improvements in pre- and postnatal treatment with increased use of antenatal steroids and postnatal surfactant treatment that was introduced in the mid-1980s (Ferrara, Hoekstra et al. 1994), but also due to prophylactic infection control, better modes of ventilation and nutritional supplements (Ehrenkranz, Dusick et al. 2006). Over the last several years, optimism regarding the long-term outcome of these high risk children has grown (Stjernqvist and Svenningsen 1993, Lorenz, Wooliever et al. 1998, Markestad, Kaaresen et al. 2005, Fawke 2007). However, studies examining long-term outcomes show that the number of children who develop neuromotor disabilities like cerebral palsy (CP) or more subtle difficulties with cognitive impairments, psychiatric and behavioral problems, still are very high (nearly 50%) when the extremely low birth weight children are compared to term-born peers (Baddeley 1992, Lorenz, Wooliever et al. 1998, Marlow, Wolke et al. 2005, Tyson and Saigal 2005, Larroque, Ancel et al. 2008, Nosarti, Giouroukou et al. 2008, Mulder, Pitchford et al. 2010, Johnson and Marlow 2011, Sullivan, Msall et al. 2012).

Imaging modalities like cerebral ultrasound (CUS) and structural cerebral magnetic resonance imaging (MRI) can identify macroscopic brain lesions and are used as early clinical diagnostic tools. However, studies have shown that both CUS and cerebral MRI have limited value as prognostic tools alone, especially for long-term neurological outcome.

During the last 30-40 years a qualitative general movement assessment (GMA) in infants based on the observation of spontaneous movements during the early post-term period (Prechtl, Einspieler et al. 1997) has been developed and is now increasingly performed in the clinics. Studies show that GMA is a good predictive tool for later CP (Prechtl, Einspieler et al. 1997) and recent studies suggest that this assessment also might be an early marker for later cognitive development in high risk children that do not develop CP (Butcher, van Braeckel et al. 2009, Bruggink, Van Braeckel et al. 2010). The first topic of this thesis was therefore to examine the long-term outcome in a group of 10-year old preterm children born after the introduction of antenatal steroids and surfactant treatment; assessing motor, cognitive, neuropsychological and behavioral outcome as well as performing cerebral MRI and comparing the outcome measures with the results of a GMA from infancy.

A recent Cochrane study (Spittle, Orton et al. 2012) demonstrated that early developmental interventions like high-quality parent-infant interaction, goal-directed physiotherapy and infant stimulation programs may have positive short-term effects on cognitive development and a small effect on motor outcome in infants and preschoolers. In recent years, there has been a growing interest in and understanding of the importance of early interventions in order to improve outcome in high-risk children at preschool and school age. However, cognitive intervention programs have been lacking. A research group at the Karolinska Institute in Stockholm, Sweden developed a computerized working memory training program primarily for children with ADHD. Over the last years this program has shown promising results in research studies of children with ADHD (Klingberg, Forssberg et al. 2002, Klingberg, Fernell et al. 2005), in children treated with chemotherapy (Hardy, Willard et al. 2013), in children with Downs syndrome (Bennett, Holmes et al. 2013) and in adults after acquired brain injury (Lundqvist, Grundstrom et al. 2010, Bjorkdahl, Akerlund et al. 2013). Our research group has reported promising results after working memory training with this program in a group of ELBW adolescents (Lohaugen, Antonsen et al. 2010) The second main topic of this thesis was therefore to perform a study in which we examined whether the same computerized working memory training program designed for preschool aged children could have positive effects on working memory and on non-trained cognitive tasks in a group of very low birth weight children. To our knowledge, no one has previously performed a cognitive intervention study in VLBW preschoolers.

Definitions

The World Health Organization (WHO) defines preterm birth as babies born alive before a full 37 weeks of pregnancy. Three subcategories based on gestational age (GA) have been defined: “extremely preterm” when born before 28 full weeks, “very preterm” when born between 28 and 32 full weeks and “moderate to late preterm” when born between 32 and 37 full weeks. Birth weight (BW) has also been used as a classification in preterm-born infants; those born with low birth weight (LBW: BW $\leq$ 2500 g), those with very low birth weight (VLBW: BW $\leq$ 1500 g) and those with extremely low birth weight (ELBW: BW $\leq$ 1000 g). It is important to notice that the weight classification is not equal to the classification based on GA. A neonate can have a lower birth weight than expected from its GA. When a child is born with BW < 10 percentile below mean birth weight for that specific GA, the baby is defined as small-for-gestational age (SGA). To be born SGA might be due to intrauterine

growth delay or intrauterine growth retardation (fetal growth restriction) and is associated with higher neonatal mortality, more neurological dysfunction and worse cognitive outcome compared to appropriate-for-gestational age (AGA) infants (Kok, den Ouden et al. 1998).

Every year an estimated 15 million babies (or more than one in ten babies) worldwide are born preterm with prevalence of 11.1% worldwide. The estimated rate of preterm birth ranges from 5% in several northern European countries to 18.1% in Southern Africa (Blencowe, Cousens et al. 2012). Of all living births in Norway in 2012, 287 children (0.5%) had ELBW, 616 (1.0%) had VLBW and 3000 children (4.9%) had LBW (data from Folkehelse instituttet, FHI 2012).

Each year around 1 million babies die worldwide due to complications of preterm birth. This means that preterm birth is the number one cause of newborn deaths and the second leading cause of deaths in children below five years of age (Liu, Johnson et al. 2012). The survival gap between preterm children born in low-income countries compared to high-income countries is dramatic, with 10% versus 90% surviving, respectively, when born < 28 weeks of GA. A recent study from the United Kingdom showed an increase in the survival rates for preterm children born between 22 and 25 weeks, from 36% in 1994 to 1999 to 47% between 2000 and 2005 (Field, Dorling et al. 2008).

Complications during the neonatal period

Very preterm-born children often face a number of partly interrelated complications following birth meaning that one complication can lead to another or increase the consequences for later outcome. This involves problems due to immaturity of the body systems including the lungs, cardiac and circulatory system, intestines, eyes and brain but also due to an increased risk of systemic infections. In the following sections, some of the most common complications will be described briefly. As the cerebral injuries and their relation to later functional outcome are the most relevant for this thesis, this topic will be described in greater detail.

Lungs

The immature lungs in preterm-born children increase the risk of developing acute respiratory problems with the need for respiratory support and also chronic problems like broncho pulmonary dysplasia (BPD). Studies have shown that the administration of the surface active lipoprotein complex surfactant in preterm-born children improves not only the immediate respiratory status, but also decreases the risk of BPD and mortality (Soll and Morley 2001, Halliday 2008, Farstad, Bratlid et al. 2011) in this group of children. In addition, a more recent Cochrane study indicates that the greater utilization of antenatal maternal steroids in combination with routine post-delivery stabilization on "Continuous positive airway pressure" (CPAP) which is used to maintain a continuous level of positive airway pressure in the spontaneously breathing neonate, "with a selective surfactant administration to those infants requiring intubation", is probably the most important contributor to the observed decreased risk of chronic lung disease and death in these immature babies (Rojas-Reyes, Morley et al. 2012).

Circulation

In-utero blood oxygenation occurs in the maternal placenta; hence the fetal lungs are bypassed through the ductus arteriosus connecting the pulmonary artery to the aorta. In most term-born infants the ductus arteriosus closes within few days after birth. In preterm-born children, this closure can be delayed or even fail to occur (Gersony, Peckham et al. 1983). A patent ductus arteriosus (PDA) leads to (reversed) shunting of blood from the aorta to the pulmonary circulation and causes a so-called "ductal steal" of blood that reduces the perfusion of other organs including the brain, kidneys and intestine. Preterm children with PDA are therefore at higher risk of developing adverse outcome like chronic lung disease (Rojas, Gonzalez et al. 1995), pulmonary hemorrhages (Kluckow and Evans 2000), renal hypo-perfusion

(Hammerman and Aramburo 1990), necrotizing enterocolitis (NEC) or death. In addition, the fluctuation in cerebral blood flow due to the PDA might cause cerebral hemorrhages. The treatment of PDA is still controversial (Closure or not? When? How?), with pharmacological treatment or surgical ductal ligation both associated with different complications.

Intestine

Due to immaturity of the intestinal system, the optimal administration and composition of nutrition in the preterm baby is challenging. The most severe intestinal complication in preterm children is the necrotizing enterocolitis (NEC), a syndrome of acute intestinal necrosis of unknown etiology (Obladen 2009). The most accepted hypothesis is that enteral feeding in the presence of abnormal bacterial colonization of the intestine provokes an overreaction of the immature immune system (Chen, Chung et al. 2014). The incidence of NEC in preterm children has been reported to range from 4% to 11.5% inversely proportional to birth weight (Sankaran, Puckett et al. 2004, Guillet, Stoll et al. 2006, Berrington, Hearn et al. 2012). The mortality rate by NEC range from 10-50% (Henry and Moss 2009, Christensen, Gordon et al. 2010, Berrington, Hearn et al. 2012). Studies show that preterm children that do survive NEC have significantly higher risk of developing long-term neurological disabilities like CP (Sonntag, Grimmer et al. 2000), visual impairment and also cognitive and psychomotor impairments (Rees, Pierro et al. 2007). This might be a consequence of the infection associated with NEC but also due to suboptimal nutrition during a very critical period of brain development (Westby Wold, Sommerfelt et al. 2009).

Eyes

Retinopathy of prematurity (ROP) is a vascular disease that is a major cause of blindness in very preterm-born children despite of the current cryo-treatment that can be performed in the late stage of the disease (Chen and Smith 2007). The major risk factors for ROP are oxygen supplement in the early and later postnatal period, low gestational age and low birth weight (Darlow, Hutchinson et al. 2005, Allvin, Hellstrom et al. 2014) early-postnatal low serum IGF-1 concentrations (Insulin-like Growth Factor-1) but also other risk factors like hyperglycemia, neonatal infections and genetic factors have been reported (Hellstrom, Smith et al. 2013).

Brain

Brain development

The development of the brain is a complex and amazing process that has been well documented in a multitude of international studies, though still many areas of interest and mechanisms of the brain development remain unexplored. Below, only a brief outline of the main mechanisms of brain development will be provided, as a more detailed description would exceed the scope of the thesis.

During the first half of gestation, neuronal progenitor cells are born (proliferation), differentiate and migrate to their final destination. The sites of the neuronal and glial cell proliferation are germinal matrix and ventricular- and subventricular zones (Volpe 2001, Volpe 2001, Volpe 2003, Volpe 2009). In the preterm brain the pre-myelinating-oligodendrocytes are the predominant cell of the differentiating oligodendroglial lineage in the white matter. These early progenitor cells are predominant in the white matter around 28 weeks of gestation (Back, Luo et al. 2001) and are vulnerable to ischemic insults. Loss of progenitor cells might lead to reduced myelination, or a maturational delay in myelination resulting in hypo-myelination and secondary axonal damage often found in the non-cystic PVL (Volpe, Kinney et al. 2011).
The migrating neurons are guided by radial glial cells that are located between the subventricular zone and the pial surface of the cortex/subplate (Kostovic and Jovanov-Milosevic 2006). At gestational age 22-24 weeks, the neuronal proliferation and migration process is mostly complete (Sidman and Rakic 1973), though the last part of the migration process continues until term age. In the second half of gestation, glial cell proliferation and programmed cell death is predominant. The neuronal cell death of approximately 50% of all neurons is essential in order to allow pruning and as hypothesized, to increase efficiency of the connectivity in the brain (Purves and Lichtman 1980).

The last third of gestation is characterized by development of axonal pathways (Judas, Rados et al. 2005) in the cerebral white matter from the region of the subplate at 20 weeks, to the cortex at 27 weeks and within the cortex at 37 weeks of GA (Mrzljak, Uylings et al. 1990, Volpe 2009).
The myelination of the peripheral nervous system has been shown to occur before 20 weeks (Yakolev and Lecours 1967) gestational age while studies of the central nervous system show

that the myelination processes begins a little later around gestational age 28 weeks in grey and white matter structures (Counsell, Maalouf et al. 2002, Melbourne, Eaton-Rosen et al. 2013) The main body of the myelination in the central nervous system is though a predominantly post-term process that continues through childhood, adolescence and early adulthood (Huppi, Schuknecht et al. 1996).

Due to the mechanisms of the brain development that is described briefly above, it is likely that the gestational age determines the regional brain vulnerability in combination with the characteristics of the insult, the brain tissue and cell vulnerability (Sannia, Natalizia et al. 2013).

Preterm brain injury

When a child is born preterm, the ongoing developmental changes of the immature brain are considerable. For instance, the cerebellar volume increases five-fold and the cerebellar surface area increases thirty-fold from 24 to 40 weeks gestational age. In addition, the germinal matrix increases in volume and reaches a maximum volume around 25 weeks gestational age.

White matter injury

The most frequent injury in the preterm brain is cerebral white matter injury (Krageloh-Mann, Toft et al. 1999, Volpe 2003, Skranes, Martinussen et al. 2005) that consists of two basic components: focal and diffuse necrosis (Volpe 2001, Back 2006). The focal necrosis is characterized by loss of all cellular elements resulting in so-called cystic periventricular leukomalacia (PVL). The necrosis can be macroscopic in size and evolve into multiple cystic lesions. The cystic form of PVL is relatively rare today (found in <5% of the preterm-born VLBW infants) but is associated with the most severe disabilities like CP, blindness and mental retardation (Horbar, Badger et al. 1997, Larroque, Marret et al. 2003, Inder, Warfield et al. 2005).

In their diffuse form, white matter lesions are microscopic, resulting in glial scars that evolve over weeks. This form of PVL is called non-cystic PVL (Volpe 2009). In contrast to the cystic form, non-cystic PVL is a common pathological finding in the preterm brain, and it is possible that this form of white matter injury can to some extend explain the high incidence of mild to moderate neurological deficits (motor, cognitive, behavioral) reported in the preterm children.

PVL is often accompanied by neuronal/axonal disease that also affects cerebral grey matter like the thalamus, basal ganglia and cerebral cortex as well as structures like the brain stem and cerebellum. Joseph Volpe introduced the term "encephalopathy of prematurity" (Volpe 2009) suggesting that the injury of the preterm brain is "a complex amalgam of primary destructive disease and secondary maturational and trophic disturbances."

When a child is born preterm, the brain is also vulnerable to the immature cerebrovascular system where impaired auto-regulation can result in fluctuations in blood flow (Borch and Greisen 1998), blood pressure (Boylan, Young et al. 2000), hypocarbia and other parameters compromising cerebral perfusion and thereby endanger the brain. Moreover, perinatal hypoxia and/or infections can initiate a cascade of destructive processes (Leviton, Dammann et al. 2005) that exposure the brain to excitotoxicity (Matute, Alberdi et al. 2007), inflammation (Dammann, Phillips et al. 2001) and oxidative stress (Haynes, Baud et al. 2005) in its most vulnerable phase of development.

Intraventricular hemorrhages and periventricular hemorrhagic infarctions

Another frequent injury of the preterm brain is the intraventricular hemorrhage (IVH). During recent decades, the incidence of IVH in preterm-born children has declined from approximately 35-50% in the early 1980s (Ahmann, Lazzara et al. 1980) to 20-25% in the late 1990s (Horbar, Badger et al. 1997). The etiology of IVH is multifactorial with fluctuation in cerebral blood flow (hypo-perfusion following reperfusion) and hemostasis being preeminent (Volpe 1995, Volpe 2001). In preterm-born children, 80-90% of the IVHs are associated with germinal matrix hemorrhage (Guzzetta, Shackelford et al. 1986). The germinal matrix is an extremely vascular area located within the ventricular wall that reaches a maximum of volume around 25 weeks of GA and then gradually involutes around 32-34 weeks of GA. As earlier described the germinal matrix and the ventricular- and subventricular zones are sites of the neuronal and glial cell proliferation (Volpe 2009). As the germinal matrix capillaries are extremely sensitive to changes in cerebral blood flow and may easily rupture, especially during the first 2-3 days after birth, a germinal matrix hemorrhage can result in injury of the neuronal and glial cell proliferation (Inder and Volpe 2000). When the bleeding in the germinal matrix ruptures into the lateral ventricular system the blood in the cerebrospinal fluid might result in increased intraventricular pressure and hydrocephalus; in the most severe form of IVH, the hemorrhage can also penetrate into the brain parenchyma.

A severe germinal matrix hemorrhage might also lead to an obstruction of the terminal veins and subsequently the medullary veins, resulting in a periventricular hemorrhagic infarction

(Gould, Howard et al. 1987, Inder and Volpe 2000). The incidence of this injury has been relatively stable seen in 5-8% of ELBW neonates over the last few decades (Groenendaal, Termote et al. 2010). Periventricular hemorrhagic infarctions often occur as unilateral lesions and spread fan-shaped in the parenchyma of the white matter (Counsell, Maalouf et al. 1999). At follow-up the infarction might have caused a loss of white matter tissue resulting in a porencephalic cystic lesion (Volpe 2001, Volpe 2009, Soltirovska Salamon, Groenendaal et al. 2014). The clinical consequences of lesions like IVH and periventricular hemorrhagic infraction (depending on localization and size) include motor impairments like CP (spastic hemiplegia if unilateral lesion), visual problems and cognitive and behavioral disabilities (Bassan, Limperopoulos et al. 2007, Roze, Van Braeckel et al. 2009, Clark and Woodward 2010, Bolisetty, Dhawan et al. 2014, Soltirovska Salamon, Groenendaal et al. 2014).

Grey matter injury

Grey matter injury is commonly found in preterm infants, especially in the children with cystic PVL (Inder, Huppi et al. 1999) but also in children with diffuse non-cystic white matter abnormalities (Boardman, Counsell et al. 2006). Whether the grey matter injury occurs secondary to white matter injury or if there is a concomitant injury to both structures is not completely known but it has been suggested that white matter injury might impact the connectivity of the developing neuronal systems and therefore influence the development of basal ganglia and thalamus (Boardman, Counsell et al. 2006). In the preterm brain, grey matter injury can affect structures like thalamus, basal ganglia, cerebral and cerebellar cortex. Some of these injuries will be described briefly below.

Thalamus and basal ganglia

The thalamus receives its first neurons from the ventricular zone early in the second trimester (McConnell, Ghosh et al. 1989) and then in a second wave from the ventral telencephalic ganglionic eminence/germinal matrix (Letinic and Rakic 2001). Both the ventricular zone and germinal matrix are vulnerable to injury after preterm birth (Volpe 2009) and in addition to this diffuse white matter injury, may represent an attenuation of the second wave of neurons from the telencephalon (Boardman, Craven et al. 2010) affecting the thalamo-cortical circuits (Ball, Boardman et al. 2012, Ball, Boardman et al. 2013). The basal ganglia and especially the globus pallidus have been identified as contributing to the filtering of irrelevant information and through this can exert attentional control over access to working memory capacity

(McNab and Klingberg 2008). While the complete mechanisms have not yet been fully understood, there is a growing understanding that grey matter abnormalities comprise a number of structures that play a role within working memory and learning (Omizzolo, Scratch et al. 2013) and therefore contribute to the understanding of cognitive problems seen in preterm children (Inder, Warfield et al. 2005, Beauchamp, Thompson et al. 2008).

Cerebellum

The cerebellum grows exponentially from around 28 weeks until 42 weeks of gestation. This might explain the vulnerability of the cerebellum during this late gestation (Limperopoulos, Soul et al. 2005, Volpe 2009). Symmetrical cerebellar volume reduction is common in preterm children (Messerschmidt, Brugger et al. 2005) and these findings often occur in association with white matter lesions (Argyropoulou, Xydis et al. 2003, Shah, Anderson et al. 2006). It has been suggested that the symmetrical pattern indicates that reduced cerebellar volume is not due to a local event like hemorrhage or infarction in the preterm children, but that the cerebellar volume loss more likely is due to a destruction of immature structures and developmental arrest (Allin, Matsumoto et al. 2001, Messerschmidt, Brugger et al. 2005).
The cerebellum is known to be involved in coordination of movement, language (Leiner, Leiner et al. 1993), attention (Townsend, Courchesne et al. 1999) as well as in other cognitive processes (Riva and Giorgi 2000, Van Kooij, Benders et al. 2012) learning and behavior (Limperopoulos, Bassan et al. 2007, Baillieux, De Smet et al. 2008).

Surface area/Cerebral and cerebellar cortex

Studies have shown that preterm-born children have less cortical surface area and less complex cortices compared to healthy controls at term age (Ajayi-Obe, Saeed et al. 2000) and that the growth of surface area has been shown to be related to the degree of prematurity at birth (Kapellou, Counsell et al. 2006). Even in preterm children without PVL, regional thinning of the cortex has been found (Zubiaurre-Elorza, Soria-Pastor et al. 2012). Our research group has previously reported that areas of cortical thinning are associated with inferior IQ scores (Martinussen, Fischl et al. 2005, Skranes, Vangberg et al. 2007, Skranes, Lohaugen et al. 2013) and that these changes persist into adolescence and early adulthood (Bjuland, Lohaugen et al. 2013).

Term brain injury

Paper 1 included a small group of term-born high-risk children with neonatal encephalopathy. As the scope of this thesis was not to analyze the mechanisms for brain injury or cerebral findings in term-born children, only a brief overview of neonatal encephalopathy in term-born children will be presented.

Acquired brain injury in term-born children can be divided into two main groups: injury caused by perinatal stroke (cerebral arterial ischemic stroke, sinovenous stroke) and neonatal encephalopathy. The neonatal encephalopathy might occur following a hypoxic-ischemic event during the perinatal period (placental abruption, cord prolapse or uterine rupture), due to specific diagnoses in the neonatal period (meningitis, congenital infections, genetic syndromes) or more importantly events in the immediate perinatal period (birth asphyxia) (Cowan, Rutherford et al. 2003). In the majority of the children with neonatal encephalopathy though, the cause of the condition remains unknown.

When the blood flow to the brain is mildly or moderately reduced, the brain perfusion of the brain stem, cerebellum, basal ganglia and thalamus will be preferred over non-brain organs, and blood flow will be shunted from areas in the cerebral cortex and white matter of the inter-vascular boundary zones. These injuries are often referred to as "Watershed injuries." When the blood flow is severely reduced, deep grey matter, the posterior brain stem and the most active areas of the cerebral cortex will also be affected (Okereafor, Allsop et al. 2008, Inder, Tao et al. 2011).

In spite of the acute nature of the neonatal encephalopathy the brain injury evolves over time. In animal and human studies, it has been shown that the initial neuronal death is related to cellular hypoxia resulting in a primary energy failure of the cell and depletion of tissue energy reserves (Lorek, Takei et al. 1994). After a latent period of at least six hours, a delayed secondary neuronal death will occur, including cytotoxic oedema, mitochondrial dysfunction, anaerobic metabolism with lactate production (Groenendaal, Veenhoven et al. 1994), reduction of N-Acetyl aspartate (Peden, Rutherford et al. 1993) and necrotic as well as apoptotic cell death (Inder and Volpe 2000, Thornton, Rousset et al. 2012). The incidence of neonatal encephalopathy has been relatively stable over the last decades with 1-2/1000 term-born children (Levene, Sands et al. 1986, Pierrat, Haouari et al. 2005). Worldwide 10% - 60% of the affected children die (Vannucci 1990) and the survivors are at a high risk of adverse outcome like CP and mental retardation (Barnett, Mercuri et al. 2002) but also minor neurological disabilities and cognitive problems (Dilenge, Majnemer et al. 2001, Marlow,

Rose et al. 2005, Gonzalez and Miller 2006, Pin, Eldridge et al. 2009, Steinman, Gorno-Tempini et al. 2009). Due to the latent period between the primary injury and the secondary neuronal death, a "window of opportunity" for intervention exists. A recent Cochrane review concluded that the most effective therapy today is therapeutic hypothermia that reduces mortality and also the frequency of major disabilities and other neurodevelopmental disabilities in the surviving children (Jacobs, Berg et al. 2013).

The term-born children included in paper 1 were born before therapeutic hypothermia was introduced as a clinical practice at the NICU in Trondheim.

Magnetic resonance imaging

The very first magnetic resonance imaging (MRI) machine was developed by Dr. Raymond Damadian, a physician and scientist during the early 1970s (Damadian 1971). In the subsequent years, this scanning method was modernized and improved and today it is the predominant method for examining the whole body in the most minute detail in vivo (Sijbers, Scheunders et al. 1996). In modern medicine MRI is used among other techniques in the diagnostics of different tumors, cancer and multiple sclerosis. Further advancement has allowed us to perform functional MRI to create brain maps of the nerve cell activity, magnetic resonance angiography to create images of arteries and even of flowing blood and diffusion tensor imaging (DTI) to examine the connectivity of white matter axons in the central nervous system.

In our long-term follow-up study we performed structural MRI of preterm children and controls at the age of 10 years in order to assess morphometric analyses of the brain in the two groups. For the assessment we used a 1.5 Tesla MRI scanner, where Tesla describes the strength of the magnetic field. MRI is based on the magnetic moment and spin of the atomic nuclei of the hydrogen molecule in a magnetic field (Westbrook, Roth et al. 2011). When the head is positioned in the scanner between the poles of a large magnet, a high frequency radio impulse (Larmor frequency) is passed through the brain. This impulse will dislocate the hydrogen atoms' basic orientation of spins. When the radio pulse is turned off the excited hydrogen atoms will relax into their original position, and with this movement they emit energy that is registered by a computer and converted into an image.

T1-weighted images:

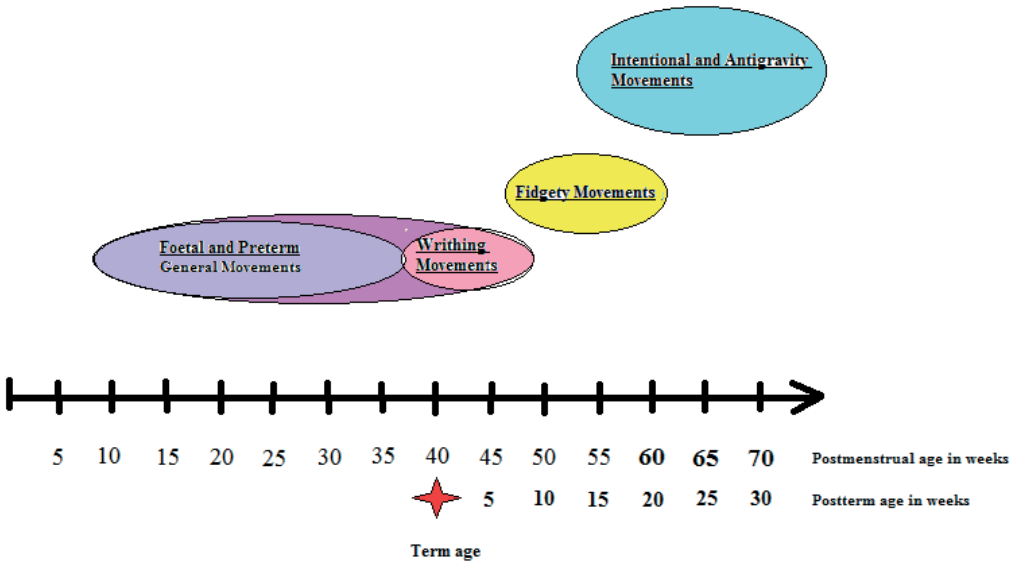
When the excited proton gives the energy it received through the radio frequency back to its surrounding lattice, it restores its equilibrium state. When performing a T1-weighted image, we therefore measure the relaxation time of protons in different tissues. This process is referred to as *spin-lattice relaxation.* MRI using T1-weighted images are useful when assessing for instance the cerebral cortex as the T1 weighted images differ significantly between grey and white matter. Further details of the MRI assessment performed in our study can be found in "Materials and Methods."

General Movement Assessment

General Movement Assessment (GMA) (Einspieler, Prechtl et al. 2004, Einspieler and Prechtl 2005) is based on the systematic observation and classification of spontaneous movements in infants. By assessing a child's spontaneous movements we can differentiate between the so-called "preterm general movements," "writhing movements" and the "fidgety movements".

The preterm general movements are the first fetal movements observed in utero or in the preterm baby (Cioni and Prechtl 1990). At term age and during the first two months post-term age, the movements are referred to as "writhing movements" (Prechtl, Einspieler et al. 1997). These movements are characterized by small to moderate amplitudes and with slow to moderate speed of the movements, often in an ellipsoid form. From 6 to 9 weeks post-term age the child's spontaneous movements change character and the so-called "fidgety movements" become predominant (Hadders-Algra and Prechtl 1992, Prechtl, Einspieler et al. 1997).

Fidgety movements are small, continuous movements of moderate speed and variable acceleration in the whole body in any direction. The fidgety movements are elegant, complex and can be present continuously when the child is in an optimal state (not crying, no hiccups, no dummy sucking). The fidgety movements are present until about 20 weeks post-term age, at which time intentional and antigravity movements become predominant. The figure below describes how the movements change character over time:



The assessment of GMA is a reliable, sensitive and non-intrusive predictive tool of later neurological development, especially as a predictor for later CP (Prechtl, Einspieler et al. 1997, Einspieler and Prechtl 2005). Studies show that absence of fidgety movements (F-) is predictive of later development of CP (Einspieler and Prechtl 2005, Darsaklis, Snider et al. 2011) while the presence of fidgety movements (F+) is predictive of a normal neurodevelopmental outcome (Prechtl, Einspieler et al. 1997, Darsaklis, Snider et al. 2011). Within the GMA a detailed analysis of the spontaneous movements has been developed (Einspieler and Prechtl 2005). This Assessment of Motor Repertoire (AMR) provides a motor optimality score consisting of the five parameters: fidgety movements, repertoire of co-existent movements, quality of other movements, posture and movement character (Fjortoft, Einspieler et al. 2009). The parameter "movement character" has also been described as "concurrent motor repertoire" (Bruggink, Einspieler et al. 2008). According to the AMR scoring procedure, a maximum score of 28 points (normal) and a minimum score of 5 points (abnormal) can be achieved. The AMR form has been attached in Appendix 1.

Recent studies suggests that the quality of the infant's movement character might be an early marker not only for CP but also for later cognitive and motor function in high-risk children who do not develop CP (Spittle, Brown et al. 2008, Butcher, van Braeckel et al. 2009, Bruggink, Van Braeckel et al. 2010). If this is correct the GMA could be an important additional clinical tool for the prediction of later neurodevelopmental outcome together with neonatal cerebral ultrasound, cerebral MRI at term age and perinatal morbidity.

Working memory

Preterm-born children perform more poorly on tests of attention and executive functions compared with term-born peers (Mulder, Pitchford et al. 2009, Aarnoudse-Moens, Duivenvoorden et al. 2012). These are all skills that are essential for a child's ability to learn, to plan their actions, to solve problems and to develop language (Melby-Lervag, Lyster et al. 2012) as well as mathematical skills (Krajewski and Schneider 2009). Working memory has been defined as our ability to temporarily store and at the same time manipulate information "online" over short periods of time (Baddeley 1986). Working memory is considered to be a prerequisite for other executive functions like reasoning and planning and is therefore essential for later academic success (Gathercole and Pickering 2000, Larroque, Ancel et al. 2008). Preterm children often have deficits within working memory and these deficits have been linked to learning difficulties in this group of children (Stewart, Rifkin et al. 1999, Larroque, Ancel et al. 2008, Alloway and Alloway 2010, Roberts, Quach et al. 2011) with lasting effect into adolescence and adulthood (Kulseng, Jennekens-Schinkel et al. 2006, Lund, Vik et al. 2012).

Working memory training

Over the last 20 years, Professor Klingberg and colleagues at the Karolinska Institute in Stockholm, Sweden, have developed a computerized working memory training program that continuously adjusts in difficulty as the skills of the training person increases. Studies have shown that the training program, designed for school aged children and adults, has positive effects on children with ADHD (Klingberg, Forssberg et al. 2002, Klingberg, Fernell et al. 2005), in adults after acquired brain injury (Lundqvist, Grundstrom et al. 2010), after stroke (Westerberg, Jacobaeus et al. 2007) and in children surviving childhood cancer (Hardy, Willard et al. 2010, Hardy, Willard et al. 2013). Our research group at NTNU has shown that a group of ELBW adolescents also had positive short- and long-term effects after finishing this intervention program (Lohaugen, Antonsen et al. 2010).

Early intervention strategies have been reported to have positive effects in children at high risk of neurodevelopmental disorders (Spittle, Orton et al. 2012) and therefore the research group in Sweden also developed a working memory training program designed for preschool aged children. The preschool version of the training program is based solely on visual-spatial stimuli and is less time-consuming than the original training program designed for school

aged children. Nevertheless a study with healthy preschoolers reported positive effects after 5 weeks of intensive training (Thorell, Lindqvist et al. 2009).

In recent years, several commercially available training programs have been developed, claiming to improve working memory capacity in children and adults. Some reviews of studies performed during the last few years report positive effects after such cognitive training (Morrison and Chein 2011, Chacko, Feirsen et al. 2013) while others are more skeptical about whether working memory capacity and cognition can be improved (Melby-Lervag and Hulme 2013). Taking into account how the brain is developing during childhood and adolescence and the neuroplasticity of the brain (Rabipour and Raz 2012), interventions like this certainly offer hope to children and parents, though more and larger studies must be performed before any recommendations can be given.

Outcome measures of the thesis

Motor outcome

Motor difficulties and impairments are the most frequently reported neurodevelopmental disorders in preterm survivors (Bracewell and Marlow 2002, de Kieviet, Piek et al. 2009, Spittle and Orton 2013). The severity of the motor impairments can vary from mild developmental delay to severe cerebral palsy (CP). CP has been described as "a group of disorders of the development of movement and posture, causing activity limitations, which are attributed to non-progressive disturbances that occurred within the developing fetal or infant brain" (Bax, Goldstein et al. 2005). The prevalence of CP in all live births has been reported to 0.1-0.2 % (Himpens, Van den Broeck et al. 2008). In preterm-born children, the risk of developing CP increases with decreasing gestational age, and a recent meta-analysis reported the prevalence of CP as 14.6% in infants born between 22 and 27 weeks gestational age, 6.2% for those born between 28 to 31 weeks and 0.7% for those born between 32 to 36 weeks gestational age (Himpens, Van den Broeck et al. 2008). Preterm-born children who do not develop CP still have a three to four times greater prevalence compared to the general population in developing motor impairments affecting coordination, balance, fine and gross motor function as well as visual-motor integration (Williams, Lee et al. 2010, Edwards, Berube et al. 2011, Bos, Van Braeckel et al. 2013).

The neural mechanisms involved in CP are varied, though in the preterm-born infants they are most often due to injury to the developing brain with an interruption of the genetically programmed brain genesis (Volpe 2001). The incidence of cystic PVL in preterm infants has been decreasing over recent decades (3-4% of surviving very preterm infants) (Inder, Wells et al. 2003, Volpe 2003), though it is still highly predictive for CP.

A meta-analyses reported that non-CP VLBW children at school age are six times more likely to have moderate motor impairments and almost nine times more likely to have mild motor impairments compared to term-born peers (de Kieviet, Piek et al. 2009, Edwards, Berube et al. 2011).

Motor impairments also called "developmental coordination disorders" influence the child's motor performance and everyday life but in addition to this there are also associations between the motor impairments and poorer cognitive function, ADHD, behavioral problems and lower academic performance (Davis, Ford et al. 2007, Marlow, Hennessy et al. 2007).

The neuronal mechanisms of motor impairments in preterm children without CP are not fully understood and MRI studies on this topic are still scarce. A study proposed that the dysfunctional motor pathways could include the corticospinal tract (Zwicker, Missiuna et al. 2012), and it has also been postulated that motor impairment might be associated with diffuse white matter abnormalities (Inder, Anderson et al. 2003) or caused by a mild dysfunction of multiple areas of the brain (Hadders-Algra 2002). Early diagnosis of CP and milder motor impairments are essential in order to prevent and compensate for deficits (Majnemer 1998) with specific and targeted intervention that might improve outcomes for these children.

Cognitive and behavioral outcome

IQ and neuropsychological outcome

The cognitive ability in children is traditionally measured with standardized assessments of intelligence quotient (IQ) like the Wechsler Preschool and Primary Scale of Intelligence third edition (Wechsler 2002) in children aged 4 to 7 years and with the Wechsler Intelligence Scale for Children third edition (Wechsler 2003) for children aged 6 to 16 years. The assessment of the full scale IQ is based on several tasks encompassing performance, verbal skills and processing speed in younger children and verbal comprehension, perceptual organization, working memory and processing speed for older children and adolescents. Many studies have previously estimated full IQ based on just a selection of subtests included in these IQ tools, though it has been shown that a full IQ assessment with subtest analyses is a more valuable tool (Lohaugen, Gramstad et al. 2010) for identifying specific problems in preterm children who may require special education or early intervention. In both studies included in this thesis we performed a full IQ assessment including all subtests.

In order to detect more subtle cognitive problems in preterm children neuropsychological assessments are performed. The neuropsychological assessment used in the clinical practice aims to give a detailed evaluation of the child's cognitive strength and weaknesses, helps in the planning of treatment strategies and evaluates the need of special education in school. Below is a brief description of the core functions tested with a neuropsychological assessment battery. A more detailed description of the assessments performed in the different studies of this thesis can be found in "Materials and Methods."

Attention and executive function

Executive functioning refers to a person's higher order cognitive functions in order to control and make decisions independently. Executive functioning also makes it possible for a person to use acquired information to adjust behavior according to the changing circumstances, to establish a goal and keep that goal in focus while planning actions to reach that goal, to think abstractly and to make inferences when necessary. Executive function also includes allocation of attention and working memory. Deficits within attention and executive function are among the most commonly reported problems in preterm-born children (Taylor, Klein et al. 2000, Taylor, Burant et al. 2002, Elgen, Lundervold et al. 2004, Bayless and Stevenson 2007, Mulder, Pitchford et al. 2009) with negative consequences for the ability to acquire new skills and knowledge and therefore comprise later academic achievement (Spira and Fischel 2005, Nosarti, Giouroukou et al. 2007, Moster, Lie et al. 2008, Strang-Karlsson, Andersson et al. 2010). Deficits within attention and executive function are often seen in children with ADHD (attention deficit hyperactivity disorder). The prevalence of ADHD in preterm-born children is 2-3 times higher than in term-born peers (Bhutta, Cleves et al. 2002), though in preterm-born children the hyperactivity component is not predominant hence attention deficit disorder (ADD) being more frequently reported (Strang-Karlsson, Raikkonen et al. 2008, Anderson, De Luca et al. 2011).

Attention and executive deficits are often associated with volumetric reduction of the brain (Bora, Pritchard et al. 2014) and white matter pathology, prefrontal cortical dysfunction and disruption of the fronto-subcortical neuronal network, pathological findings that are common in preterm-born children (Anderson, Jacobs et al. 2005, Chen and Desmond 2005, Edgin, Inder et al. 2008).

Behavior and everyday life skills

Even preterm-born children without apparent brain injury and also late preterm-born children (van Baar, Vermaas et al. 2009) are at high risk of developing behavioral problems, showing difficulties in social cognition (Farooqi, Hagglof et al. 2007) and performing worse at school than term-born peers (Anderson and Doyle 2003, Kirkegaard, Obel et al. 2006, Mathiasen, Hansen et al. 2010). A study reported a prevalence of 20% of clinically significant behavior problems that persisted in low birth weight children from 3 to 8 years of age (Gray, Indurkhya et al. 2004). As these difficulties have consequences for a child's life, education and health

(Larroque, Ancel et al. 2011) there is now a growing interest in research of mental health problems in preterm children (Indredavik, Vik et al. 2004).

For assessing behavior, everyday life skills and school performance in preterm-born children, a wide range of different tools have been used. Some of the tests are standardized while others are developed by the researchers themselves, which makes comparison of results across studies difficult.

In our studies, we administered several parental questionnaires assessing anxiety (PAS), Attention (ADHD rating scale IV), everyday life skills (VABS) and executive function (BRIEF). All of these tools are feasible and validated tools that have been used in several studies and in different patient groups.

AIMS OF THE THESIS

The aim of this thesis was twofold.

- The first aim was to investigate whether an observational method of spontaneous general movement assessment (GMA) in infancy was associated with long-term outcomes and whether this method could be a useful early diagnostic tool in high-risk children (paper 1). We further wanted to investigate possible relationships between a detailed early motor assessment and a comprehensive clinical assessment combined with quantitative MRI in non-CP ELBW school children (paper 2). Lastly we wanted to present a thorough evaluation of cognitive, neuropsychological, behavioral and motor outcome as well as cerebral MRI findings in a 3 year cohort of non-CP ELBW children at age 10 years and to compare the results with a healthy term-born control group (paper 2).

- The second aim of the thesis was to evaluate whether a computerized cognitive intervention program designed for preschool aged children could improve working memory and have positive short- (paper 3) and long-term (paper 4) generalizing effects on memory, learning, attention, behavior and anxiety in preterm-born preschoolers. This was the first study to evaluate cognitive training in preterm-born preschoolers.

Study hypothesis

For the GMA study of VLBW children and high-risk children at age 10 years, we hypothesized the following:

- The presence of fidgety movements and a normal concurrent motor repertoire is predictive of a normal cognitive and motor outcome.
- The presence of fidgety movements with an abnormal concurrent motor repertoire is predictive of impaired motor and cognitive outcomes, especially in VLBW infants.

For the non-CP ELBW children at age 10 years, we hypothesized the following:

- The presence of fidgety movements and abnormal concurrent motor repertoire associated with clinical outcome measures and MRI morphometry.
- Lower cognitive ability and increased prevalence of neuropsychological impairments more attention and more behavioral problems compared to controls.
- Poorer motor and poorer everyday life skills compared to controls.
- Smaller volumes of white and grey matter brain structures and reduced cortical surface area on MRI compared to controls.
- Poorer clinical test results and pathological MRI findings predominantly in the non-CP ELBW children with abnormal motor repertoire.

For the preschool aged VLBW children, we hypothesized the following:

- Persistently higher scores on neuropsychological tests, working memory tasks as well as generalizing positive effects following cognitive training compared with children who had not trained.

The hypotheses were tested in the papers as follows:

Aims of paper 1

To determine the predictive value of the quality of fidgety movements and concurrent motor repertoire for the later motor and cognitive outcomes in a group of high-risk children born preterm and/or with neonatal encephalopathy. We also aimed to examine the respective predictive values in a subgroup of infants born with VLBW.

Aims of paper 2

To examine the clinical outcome and brain pathology evaluated with MRI morphometry at 10 years of age in a cohort of ELBW children without CP compared with healthy term-born controls. In addition, we aimed to study whether early infant motor repertoire in the ELBW children who did not develop CP was associated with clinical outcome and cerebral MRI findings at age 10.

Aims of paper 3

To determine whether a group of preterm-born VLBW preschoolers would benefit from a computerized working memory training program and to evaluate if such training has (short-term) generalized beneficial effects on memory and learning as well as behavior, attention, and anxiety.

Aims of paper 4

To determine whether computerized working memory training in VLBW preschoolers had persisting positive effects on working memory as well as transfer effects on verbal and visual memory, behavior and anxiety in VLBW preschoolers 7 months after the completion of cognitive training. In addition to this we wanted to determine if the gains in performance observed during the follow-up period would have occurred in any case, as a natural part of the developmental process.

MATERIALS AND METHODS

Study design

Long-term follow-up study

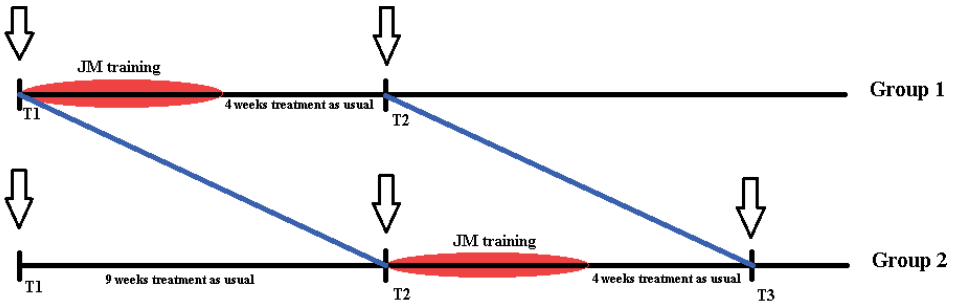
The long-term follow-up study was a hospital based prospective cohort-study including three year-cohorts of preterm-born VLBW children and a small group of term-born children with neonatal encephalopathy born at the Trondheim University Hospital in Norway during the years 1999-2001. All included children had been videotaped around 14 weeks post term age in order to perform a General Movement Assessment during regular follow-up. During the years 1999-2001, the GMA was introduced as a clinical routine assessment in all ELBW children, in VLBW children with additional medical complications and in neurologically high-risk term-born children. The follow-up examination that included cognitive, neuropsychological, behavioral and motor assessments as well as structural cerebral MRI was carried out between August 2010 and October 2011 when the children were between 10 and 11 years old. For the follow-up part of the study, test results and MRI findings of the included ELBW children were compared with a healthy, term-born control group that was included from 4 different schools in the Trondheim region. The controls that also were born between 1999 and 2001 were examined with the same test assessments and MRI as the preterm children at the same age.

Intervention study

The intervention study was a prospective hospital based study including preschool aged VLBW children born at the Trondheim University Hospital during the years 2005 - 2006 and a preschool aged VLBW control group born at the Trondheim University Hospital in 2007. The intervention study was carried out between May 2011 and June 2012, and the control group was examined from December 2012 to August 2013.

In the first part of the study we used a Stepped Wedge randomized trial design (Brown and Lilford 2006) where the participants were split randomly into 2 groups for sequential rollout of the intervention. Both groups were tested with cognitive and neuropsychological tests at two time points: just before intervention and 4 weeks after intervention. To be able to identify test-retest effects, nine children were assessed with the same test battery also 9 weeks before they started training. All tests with improvement in results just by repeated testing before training were excluded from further analyses. Owing to the small sample size, we combined

the results from pre- and post-training testing in both groups to look at training effects in the whole sample. The figure below describes the Stepped Wedge trial design.



The study population was divided into two groups, Group 1 and Group 2. The figure illustrates the time points of testing (white arrows) and JM training in the two groups (in red). The results from pre-and post-training testing in both groups combined were compared to investigate any training effects in the whole sample (blue lines)

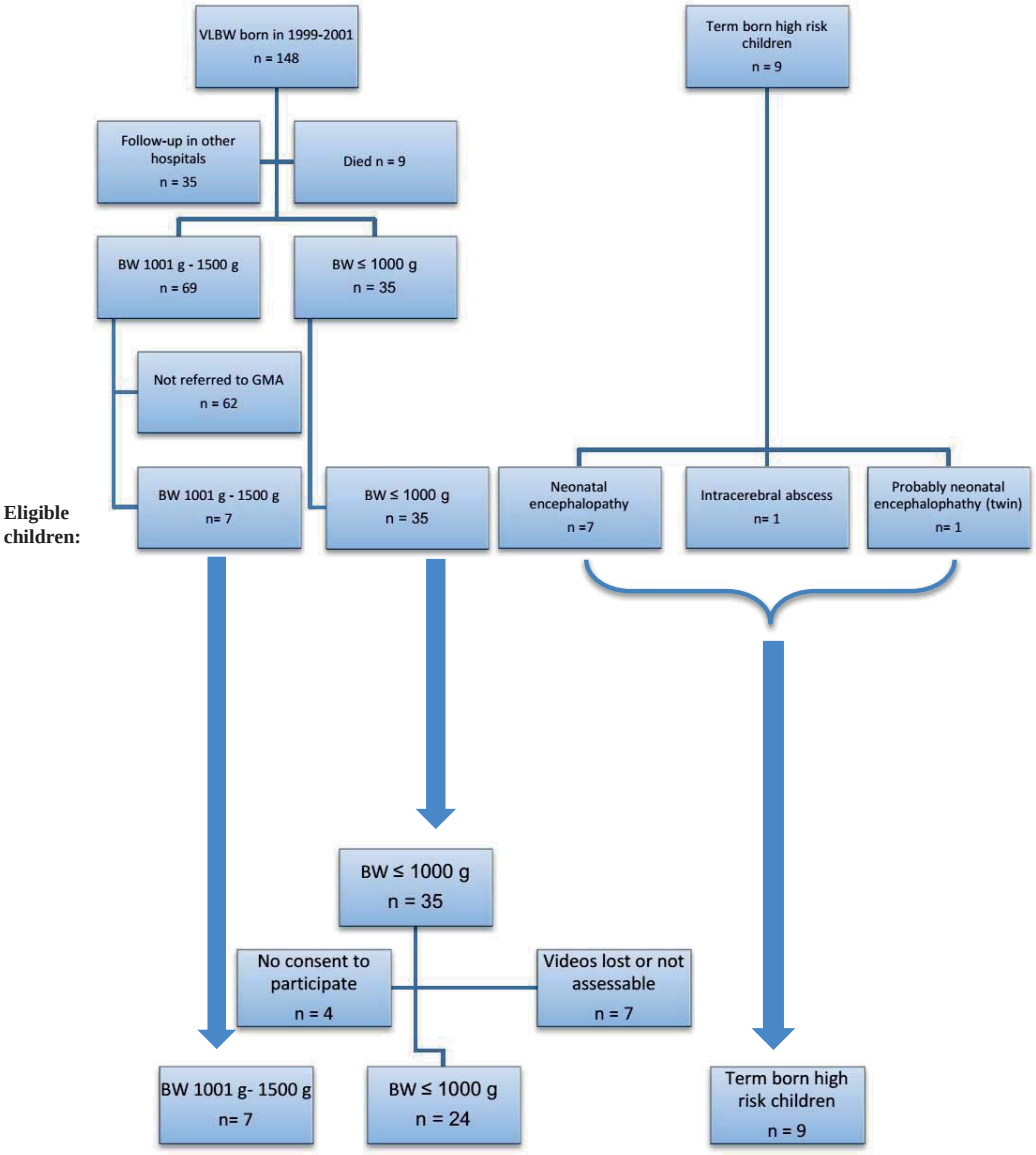
In the second part of the study we examined the long-term training effect 7 months after completion of training. To be able to determine if the gains in performance observed during the follow-up period would have occurred in any case as a natural part of the developmental process, we included a control group consisting of 17 age-matched VLBW children that did not train to compare performance gains with time across groups. All included children were assessed with neuropsychological tests and parental questionnaires at baseline and at follow-up seven months later.

Baseline for the intervention group in this long-term follow-up study represented four weeks after completed training.

Study population

Long-term follow-up study

Inclusion criteria for the original study selected for preterm-born VLBW children with BW < 1500g and term-born children at high risk of developing neurological impairments due to perinatal or neonatal history. An additional inclusion criterion was that all children included should have been videotaped at about 14 weeks post term age in order to perform a GMA. Exclusion criteria were congenital syndromes or children living outside the Trondheim region (>100 km). During the years 1999-2001 a total of 148 VLBW children were born and admitted to the Neonatal Intensive Care Unit (NICU), Trondheim University Hospital in Norway (see flow chart below). Nine children died (all ELBW children) and 35 lived outside the Trondheim region. Of the children with BW between 1001g and 1500g (n=69) only seven children were referred to physiotherapist and videotaped at 14 weeks post-term age. Of the children with BW ≤ 1000g, 35 children were eligible and included in the study. A small group of term-born high-risk children (n=9) was referred to physiotherapist and eligible for participation in the first part of the study. Seven of these children had neonatal encephalopathy and neonatal seizures, one baby had an intracranial abscess and one child that was the twin-sibling of a child with encephalopathy, was defined as "high-risk" and included in the study. Parents gave their written consent to participate in the study for 7 children with BW between 1001 g and 1500 g, 31 ELBW children and 9 term-born children.

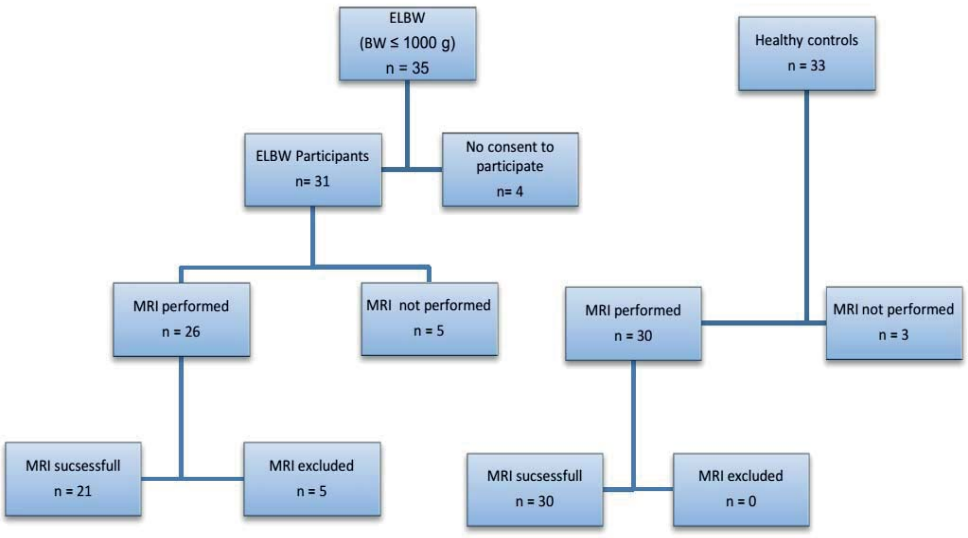


Flow chart of participants in study 1, paper 1

Non-Participating children: There were no significant differences in neonatal characteristics or risk factors in the participating and non-participating children.

Control group: For the second part of the study a term-born, age-matched control group (all born in 1999-2001) consisting of 33 healthy children was recruited from four different schools within the Trondheim area. All parents and children at age 10-11 in the respective schools received written information about the study and were asked to participate.

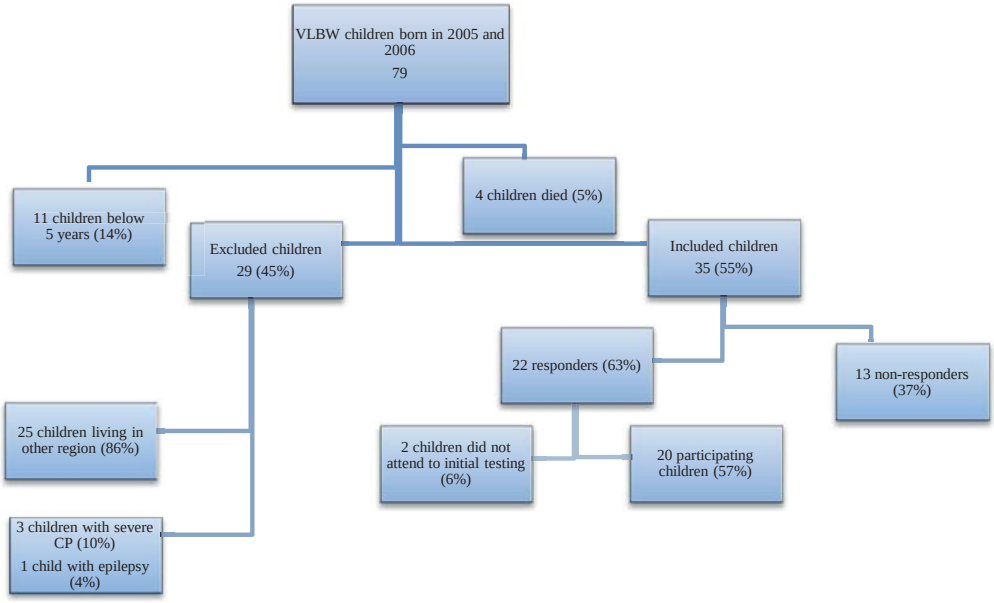
MRI participants: In the second part of the study (paper 2), all ELBW children and controls were asked to participate in MRI examination. In total, cerebral MRI was performed in 26 of the ELBW children, including four children with CP. In four ELBW children, MRI was not possible to perform due to severe CP with involuntary movements and in one ELBW child due to anxiety where sedation would have been needed. This was not permitted in the study. Five MRI examinations performed in the ELBW children had to be excluded because of movement artifacts. Four of these children had CP. Hence MRI was successfully performed in 21 ELBW children all without CP. In the control group two children did not consent to participate in the MRI examination and one child had braces that made MRI impossible to perform. Hence MRI was successfully completed in 30 control children.



Flow chart of participants in study 1, paper 2

Intervention study

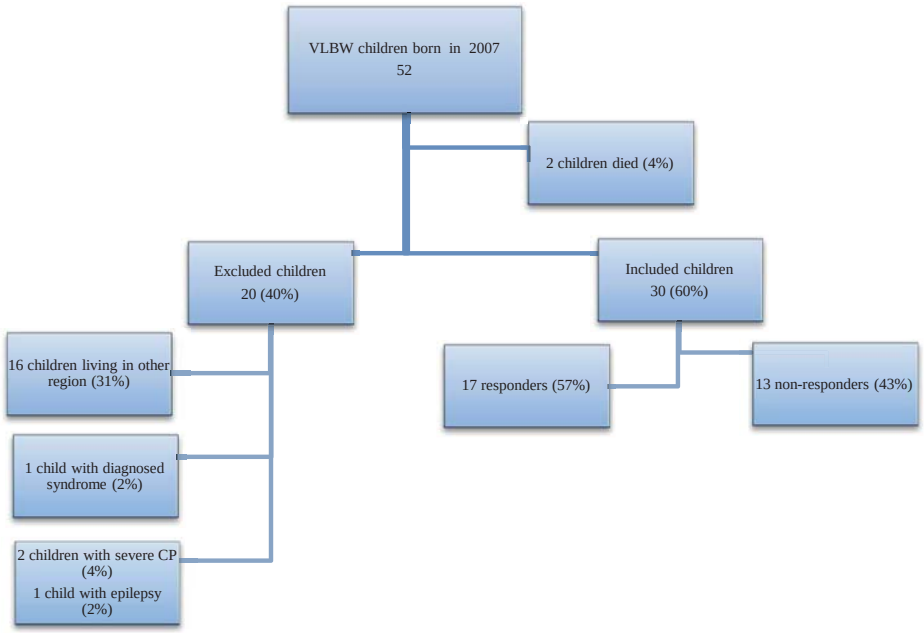
Inclusion criteria were applied to preterm-born children with very low birth weight (BW < 1500 g) that were born and admitted to the Neonatal Intensive Care Unit (NICU), Trondheim University Hospital in Norway during the years 2005-2007. All children had to be 5 years at intervention start. Exclusion criteria for the study were VLBW children with known epilepsy, those with severe cerebral palsy with grossly impaired bilateral hand function, children with blindness or congenital syndromes and children living outside the Trondheim region (> 100 km). The intervention group included 20 VLBW children born in 2005 and 2006. The figure below describes the recruitment procedure in the intervention group.



Flow chart of the recruitment procedure in the intervention group

Non-participants: There were no differences in neonatal data, risk factors or clinical characteristics in the group of responders and non-responders except for more use of antenatal steroids among the participants. Clinical characteristics of the non-responders were published in paper 3 (supplemental materials Table S1).

Control group: A non-training control group consisting of 17 age matched VLBW children born in 2007 was included for the second part of the study. In 2007 fifty-two VLBW children were admitted to the NICU in Trondheim. Two children died (4 %). Sixteen children (31 %) lived outside the region, one child (2 %) with a diagnosed syndrome, two children (4 %) with severe CP and one child (2 %) with epilepsy were excluded. Hence a total of 30 children were asked to participate as a non-training control group. Written consent to participate was received in seventeen children (57 %). The figure below describes the recruitment procedure in the control group.



Flow chart of the recruitment procedure in the control group

Assessments performed in the studies

General movement assessment

Long-term follow-up study

In our study the high-risk children were videotaped at mean age 14 post term weeks with a camera that was located over the infant. The infant was placed in supine position and recorded for 5 to 10 minutes. During the videotaping an optimal state of the infant was required; the child had to be fully awake without crying, fussing or hiccups. No sucking on dummies was allowed.

All videotapes were analysed before the first follow-up examination at age 10. A certified and experienced child physiotherapist (TF) and a pediatrician (KHG) analyzed all available video recordings independently and blinded to neonatal risk factors and later outcome of the children. In cases of disagreement, a second assessment was performed and a consensus was made.

In the first study (paper 1), ten tapes were lost during the ten-year follow-up period and one infant that was crying could not be assessed do to the child's state. Hence a total of 40 video recordings in the original study could be analyzed.

In the long-term follow-up study we performed analyses with emphasis on fidgety movements according to Prechtl and on AMR with particular focus of the infant movement character, which were characterized according to Bruggink et al (Bruggink, Van Braeckel et al. 2010).

- Fidgety movements were defined as;
    - normal "F+", when present continuously
    - abnormal "F-", when completely absent
    - "F+/-", when sporadic or not continuously present
- Movement character was defined as
    - "normal concurrent motor repertoire" when the movements were fluent, variable and smooth
    - "abnormal concurrent motor repertoire" when the movements were monotonous, jerky or stiff

Other motor tests

All motor function assessments were performed by two specialized physiotherapists who were blinded to neonatal characteristics of the children.

Long-term follow-up study

The Movement Assessment Battery for Children, second edition (MABC-2) (Henderson SE 2007) was used to assess general motor skills. The test consists of eight items grouped in three subscores; 1) Manual dexterity, 2) Ball skills and 3) Static/dynamic Balance. Each item is scored from 1 point which is the lowest performance and up to 19 points which represent the optimal result.

Cognitive assessment

All cognitive assessments in the *long-term follow-up study* were carried out by the same trained pediatrician (KHG) who was blinded to the neonatal history of the children at assessment.

In the first part of the *intervention study* a specialized neuropsychologist (GCCL) who was blinded to group adherence and neonatal risk factors of the participants carried out all cognitive assessments. In the second part of the intervention study including a VLBW control group the same neuropsychologist tested most of the children though some of the control children were tested by another specialized psychologist who was also blinded to neonatal risk factors.

General cognitive ability

Long-term follow-up study

The Wechsler Intelligence Scale for Children third edition (*WISC-III*) (Wechsler 2003) was administered in all children. A full IQ exam, considered the most representative measurement of global intellectual functioning was based on 12 subtests. In addition to the full IQ, the four indices — Verbal comprehension index, Perceptual organization index, Working memory index and Processing speed index — were conducted.

Intervention study

The Wechsler Preschool and Primary Scale of Intelligence third edition (WPPSI-III) (Wechsler 2002) was administered in all children: in the intervention group before training

and in the control group at baseline. A full IQ representing a measurement of global intellectual functioning was based on 8 subtests. In addition, the IQ indices; Performance index, Verbal index and Processing speed were computed.

Neuropsychological testing

Long-term follow-up study

Stroop Color Word (Delis 2001) is considered to measure the ability of a child to respond selectively to competing stimulus or selective attention. All 4 subtests must be completed as fast as possible: 1) Name the colors of the ink; 2) Read the words; 3) Inhibition: Name the color of the printed ink, do not read the words; 4) Inhibition/switching: Name the color of the ink or read the word according to a given instruction.

Tower of London (Culbertson 2005) is a task to measure planning and problem-solving ability. The child must rearrange a set of disks placed on rods to match a presented picture. The child must follow a number of rules and keep them in mind while solving the tasks. The task must be completed within a time limit.

The Trail-making test (TMT) (Delis 2001) is considered to measure attention and focused attention. The test contains 5 subtasks and all tasks must be completed as fast as possible. 1) Visual Scanning: the child must find and mark a given number; 2) Number Line: the child must connect circles of numbers in ascending order; 3) Letter Line: the child must connect circles of letters in ascending order; 4) Number and Letter Line: the child must connect circles of alternating numbers and letters in ascending order; 5) Motor Speed: the child must connect circles according to a given pattern.

Beery-VMI-IV (Beery 1997). The Beery-Buktenica Developmental Test of Visual-Motor Integration assesses visual perceptual and constructional abilities in children. The test consists of 27 two-dimensional geometric shapes of increasing complexity that the child must copy without time limit. The supplementary tasks "Test of Motor coordination" where the child must trace geometric designs with a pencil without leaving double-lined paths (time limit 5 minutes) and "Test of Visual perception" where the child must identify the correct geometric shapes that he/she has copied earlier and that decrease in size (time limit 3 minutes) were also performed.

Intervention study

To assess short- and long-term generalization effects after training we performed nine subtests from the NEPSYsecond edition (A developmental NEuroPSYchological assessment) (Korkman, Kirk et al. 1998).

The domain attention and executive function were assessed by:

- Visual attention. This test assesses the speed and accuracy with which a child is able to focus selectively on and maintain attention to visual targets within an array.
    - **Cats:** The child is presented with a response booklet with drawings of rabbits, cats, faces, cars, etc. The child must find and mark all the *cats* presented in the booklet as fast as possible.
    - **Faces:** The child is presented with a booklet with drawings of different faces. The child must identify two fixed faces correctly and as fast as possible.
- Auditory attention and response set. This test assesses the child's ability to be vigilant and to maintain selective auditory attention, as well as its ability to shift set, to maintain a complex mental set, and to regulate responses to contrasting and matching stimuli.
    - **Part A**: Auditory attention: The child is placed in front of a box with foam squares in different colors and gets clear instructions about the task. The child hears some recorded words. When he/she hears the word *"red"* he/she must place a red square in the box lid.
    - **Part B**: Auditory Response set: The child is now instructed to place a *yellow* square in the box lid at the word *red*, a *red* square in the box lid at the word *yellow*, and to place a *blue* square in the box lid at the word *blue.*
- Statue. This test assesses a child's inhibition and motor persistence.
    - The child is told to stand completely still over a time period of 75 seconds. When the administrator distracts the child, he/she is supposed to inhibit a response to the distraction (e.g., eyes opening, body movement, vocalization).

The domain language was assessed by:

- Phonological processing.
    - **Part A:** The first task assesses the child's ability to identify words from segments and to form an auditory gestalt. The child is presented with 3 pictures and must then identify a picture from an orally presented word segment.

    - **Part B:** The second task assesses phonological segmentation at the level of word segments and letter sounds. The child creates a new word by a) omitting a word segment, b) omitting a letter sound or c) by substituting one letter for another.
- Comprehension of instructions. The test assesses the child's ability to understand and respond to verbal instruction. In the beginning, the child is presented with simple tasks and then given more complex instructions.
- Repetition of nonsense words. This test assesses phonological encoding and decoding of a sound pattern and the ability of the child to articulate complex words without meaning. The child hears nonsense words on an audiotape and must then repeat the nonsense words.

The domain learning and memory was assessed by:

- Memory for faces. The test assesses memory for faces. The child is presented with a series of pictures of faces and must identify whether it is a boy or a girl. He/she is then presented a three-face array and must identify the faces previously seen. After a 30-minute delay, the child must identify the faces seen previously on a new three-face array.
- Narrative memory. The test assesses narrative memory. a) The child listens to a story and must recall it (free recall). b) The child must answer questions to the story (cued recall).
- Sentence repetition. The child must repeat sentences of increasing difficulty and length.

Digit span

To assess verbal working memory we used a subtest from The Wechsler Adult Intelligence Scale-III (WAIS-III) (Tulsky, Zhu et al. 2002); the Digit span subtest. The administrator reads numbers and the test subject must repeat the numbers in the same order. The test subject is required to remember an increasing number of digits. In the second part of the task the test subject must repeat the numbers backwards.

Spatial span

To assess visual working memory we used the Spatial Span test that is a part of the Wechsler memory scale-III (WMS-III) (Tulsky, Zhu et al. 2002). The test consists of a white board with ten blue blocks. The administrator points to the blocks in a certain order and the test subject

must point to the blocks in the same order. The test subject is required to remember an increasing number of blocks on the board. In the second part of the task the test subject must reverse the order of the sequence the administrator presented.

Parental Questionnaires

Long-term follow-up study and Intervention study

In both studies a number of questionnaires were completed by the parents, preferably the mother.

The *ADHD Rating Scale-IV (parents report)* (DuPaul, Power et al. 1998) is a reliable and easy-to-administer instrument for assessing hyperactivity and inattention in children. The questionnaire consists of nine questions regarding attention and nine questions regarding hyperactivity.

The *Preschool Anxiety Scale (PAS)* (Spence, Rapee et al. 2001) was completed to measure symptoms of anxiety disorders in young children. Five of the questions assessed obsessive-compulsive disorder, six questions assessed social anxiety, five questions assessed separation anxiety, seven questions assessed physical injury fear and five questions assessed generalization anxiety. A total preschool anxiety scale score consisting of 28 questions was also calculated.

Behavioral Rating Inventory of Executive Function, parent report (BRIEF) (Gioia, Isquith et al. 2000). Executive function was assessed based on the BRIEF, parent report. This is a 86-item questionnaire divided into 8 subscales regarding the child's ability to regulate behavior, including emotional control, working memory, inhibit, shift, initiate, planning and organizing. A cut-off score for reported executive problems have been defined as scores above 65 on each subtask.

Vineland Adaptive Behavior Scales, second edition, English version (VABS) (Sparrow 2005) is the leading instrument for supporting the diagnosis of intellectual and developmental disabilities in children was assessed to measure communication, daily living skills, socialization and problem behaviors.

Visual function

Intervention study

In order to rule out any reduced vision or pathology in visual function during the computerized training program, an experienced ophthalmologist assessed visual acuity in all children in the intervention group with Lea Symbols 15 Line Distance Chart. The test distance was 3 meters, and visual acuity was first tested binocularly before each eye was tested separately.

Cerebral MRI examination

Long-term follow-up study

In the second part of the long-term follow-up study, cerebral MRI was performed in ELBW children and controls. The same researcher (KHG) informed the parents and children about the assessment, obtained informed consent, organized the MRI appointments and accompanied and motivated the children during the MRI examination.

MRI – acquisition

Cerebral MRI was performed on a 1.5 Tesla Siemens Avanto scanner (Siemens, Erlangen, Germany) with Quantum gradients 40mT/m and a 12-channel head coil. A structural T1-weighted magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence was acquired with the following specifications: TR=2400 ms, TE=3.61 ms, TI=1000 ms, flip angle 8^{o}, FOV 240×240, slab thickness 160 mm, slice thickness 1.2 mm and matrix 192×192, giving a reconstructed voxel resolution of 1.25×1.25×1.2 mm^3.

MRI – image analysis:

Morphometric analyses of the brain volumes, cortical thickness and surface area were performed using the freely available FreeSurfer software package 5.1 (http://surfer.nmr.mgh.harvard.edu/). This program has been developed by researchers from USA and Norway from the mid-1990s until today and is a powerful tool to provide automated analyses of key structures of the human brain (Fischl 2012).

In order to perform a reconstruction of the cortical surface in each subject as well as cross-subjects statistics (Dale, Fischl et al. 1999, Fischl, Sereno et al. 1999), an MPRAGE sequence

was used. An automatic algorithm was then performed for motion correction of the T1 images (Reuter, Rosas et al. 2010) and for the removal of non-brain tissue (Segonne, Dale et al. 2004). White and grey matter was segmented using Talairach transformation and intensity normalization. Subcortical volumes were obtained from the automated segmentation procedure for volumetric measures of brain structures that are performed in Freesurfer (Fischl, Salat et al. 2002, Fischl, Salat et al. 2004). The gray and white matter boundary was tessellated and topological errors automatically corrected (Fischl, Liu et al. 2001, Segonne, Pacheco et al. 2007). Cortex was then segmented based on gyrus and sulcus information (Fischl, van der Kouwe et al. 2004), and the cortical thickness was calculated as described by Fischl et al (Fischl and Dale 2000).

Each subject was registered to a spherical atlas in FreeSurfer, based on individual cortical folding patterns and matched geometry across subjects with minimized metric distortions (Fischl, Sereno et al. 1999). The surfaces were then smoothed with a full-width-half-maximum Gaussian kernel of 30 mm (662 iterations) and vertex-wise estimates of relative areal expansion for each individual subject in atlas space were then computed. The surface area maps were then created.

When an automatic process within FreeSurfer is performed, it is important to identify and exclude segmentation errors. All images were therefore controlled with a specific script (http://surfer.nmr.mgh.harvard.edu/fswiki/QATools) and then visually inspected for errors and misalignments by two trained technicians and a medical doctor. All subjects with segmentation errors were not corrected manually, but rejected from further analysis. Images with low signal-to-noise-ratio (SNR) and with significant left-right differences of volumes of thalamus and hippocampus were checked carefully for segmentation errors.

Intervention program

The intervention study used a software-based computerized working memory training program designed for preschoolers as young as four years of age. The participating families received a computer link, and the web-based software program was downloaded at their home computer (www.cogmed.com). Every child had their own personal user name and password. The children trained 10-15 minutes, 5 days a week over a 5-week period, for a total of 25 sessions. The computer program consisted of seven different, partly rotating tasks based solely on visual-spatial stimuli. For a detailed description of the different tasks — Rollercoaster, Hotel, Animals, Twister, Pool, Bumper Cars, Ferris Wheel — see supplemental materials in paper 3.

Seven different tasks included in the Cogmed JM intervention program. Picture published with permission of Cogmed ©

Three tasks were administered to the child each day. The exercises became more difficult as the child's skills improved, and the difficulty level of the training was adjusted in real time by the Cogmed JM software based on the child's performance. After each training day, the parents uploaded the training results to a secure internet site. The parents were instructed to support and encourage the children whenever possible during the training period, for instance with praise and small gifts (stickers, pencils, etc.) or events (go to the cinema, to choose their favorite dinner, go swimming etc.) that was agreed upon with the child when a goal was achieved. Once a week, the principal investigator contacted the family to give advice about the further training based on the uploaded results received on the secure internet site. During the training period the principal investigator sent each child stickers and small presents in order to encourage them to keep on training. When the intervention was completed each child received a diploma and a small present for their efforts. All children completed all 25 training sessions within the time limit of 5-6 weeks as required.

Pictures published with permission of Cogmed ©

Statistics

PAPER 1

Data analyses were performed with Statistical Package for Social Sciences version 19.0 (IBM SPSS Statistics, Armonk, NY, USA). The sensitivity, specificity and predictive values were calculated by cross tables, and 95% confidence intervals (CI) were calculated according to the Wilson method.

PAPER 2

In this paper SPSS Statistics, version 21.0 (IBM SPSS Statistics, Armonk, NY, USA) was used for the statistical analyses. Student t-test, Mann-Whitney U-test and Chi-squared test were used for group comparisons. A General Linear Model (GLM) was performed to compare group differences in brain volumes, cortical thickness and brain surface area with SES, gender and age at MRI as covariates. The same model was used to compare group differences in clinical test results. We used the partial correlation analysis controlled for SES, gender and age at MRI to calculate the linear correlation between different test results and brain regions of interest based on MRI results. A two-tailed p-value $\leq .05$ was considered to be statistically significant, except when looking at group comparisons of brain volumes where a *p*-value $\leq .01$ was used as level of significance in order to adjust for multiple comparisons.

PAPER 3

SPSS Statistics, version 19.0 (IBM SPSS Statistics, Armonk, NY, USA) was used for the statistical analyses. Differences in group means for normally distributed variables were analyzed with the Student t tests, and not normally distributed outcome measures with the Mann-Whitney U test. χ^2 test was used as appropriate to compare differences in proportions between groups. Wilcoxon signed rank test for two related samples was used to compare scores at the different time points: T1 versus T2 (group 2) and pre-training versus post-training (groups 1 and 2). This test was also used to analyze changes in scores in separate group analysis before to after training. Correlation analyses with the use of the Pearson correlation coefficient were performed to describe the relationship between the improvement index and IQ and total anxiety score, respectively. Two-tailed p-values of $\leq .05$ were considered to be statistically significant.

PAPER 4

In paper 4 SPSS Statistics, version 21 (IBM SPSS statistics, Armonk, NY) was used for the statistical analyses. For normally distributed variables differences in group means were computed with the Student t-test, whereas not normally distributed variables were analyzed with the Mann-Whitney U-test. The Wilcoxon signed rank test for two related samples was performed to compare test result at the two time points for the intervention and control groups separately. A General Linear Model for repeated measures with Within-Subjects variables = time (baseline and follow-up) and Between-Subjects factors = intervention_vs_controls and age as covariates was performed to assess group differences in performance gains during the study period. Variables that were not normally distributed were log transformed in this model, while neuropsychological test scores were presented as raw scores for the ease of interpretation. To adjust for multiple testing we used the False-Discovery Rate (FDR) (Benjamini 1995) approach reporting statistically significant results at a two-tailed p-value $\leq$ .02.

Socioeconomic status

In both studies socioeconomic status (SES) was calculated according to Hollingshead's 2-factor index of social position based on mean educational levels and current employment of both or single parents.

Ethics

Long-term follow-up study

The Regional Committee of Medical Research Ethics approved the study protocol (REK number: 2010/121-9) and written informed consent was obtained from the parents. When the results of the follow-up testing yielded a need for specialized health care or pedagogical intervention, the children were referred to further assessments and/or treatment.

Intervention study

The Regional Committee of Medical Research Ethics approved the study protocol (REK number 2011/532-7). The study was also registered at *www.ClinicalTrials.gov* (identifier NCT01518452). Written informed parental consent was obtained and based on the result from the clinical assessments, VLBW children in need of specialized health care or pedagogical intervention were referred to further assessments and/or treatment.

RESULTS

This thesis consists of two clinical studies. The different aims are specified and addressed in each of the four papers and in the following section group characteristics of the two studies will be described and then a summary of the main results in each paper will be presented separately.

Group characteristics

Long-term follow-up study

In paper 1 high-risk children with birth weight < 1500 g as well as a small group of high-risk children with birth weight > 1500g were included. The table below with clinical characteristics is published in paper 1.

Table 1
Clinical characteristic of the whole study group, high-risk children with birth weight ≥1500 g and very-low-birth-weight (VLBW) children (birth weight <1500 g).

	Study group (n = 40)		High-risk children with birth weight ≥1500 g (n = 9)		VLBW children (n = 31)	
	Mean	(SD)	Mean	(SD)	Mean	(SD)
Gestational age (weeks)	29.3	(5.3)	38.3	(2.8)	26.8	(1.9)
Birth weight (g)	1373	(999)	3081	(672)	877	(219)
Days on mechanical ventilator	9	(13)	3	(4.1)	9	(12.1)
Socioeconomic status (SES)	3.2	(1.3)	2.7	(1.4)	3.4	(1.2)
	n	(%)	n	(%)	n	(%)
Boys	18	(45)	4	(44)	14	(45)
Septicaemia	11	(28)	3	(33)	8	(26)
Bronchopulmonary dysplasia[a]	19	(48)	1	(11)	18	(58)
Cerebral ultrasound						
- IVH, Grade 1	9	(22)	0		9	(29)
- IVH, Grade 2	3	(8)	0		3	(10)
- IVH, Grade 4	6	(15)	2	(22)	4	(13)
- Periventricular leukomalacia, grade 1	3	(8)	1	(11)	2	(6)
- Intracerebral abscess	1	(3)	1	(11)	0	
Apgar score ≤4 at 5 min	6	(15)	3	(33)	3	(10)

IVH = intraventricular haemorrhage.
SD = standard deviation.
[a] Bronchopulmonary dysplasia = need for oxygen treatment at 36 weeks postmenstrual age.

In paper 2 a group of ELBW children from the original study and healthy age matched controls were included. Clinical characteristics are described in the table below and published in paper 2:

TABLE 1: Clinical characteristics of the study population.

	ELBW n=31 Mean(SD)	Non-CP ELBW n=23 Mean(SD)	CP-ELBW n=8 Mean(SD)	Controls n=33 Mean(SD)
Gestational age, weeks	26.1 (1.8)**	26.3 (1.9)$^{\#\#}$	25.6 (1.7)	40.1 (0.9)
Birth weight, grams	773 (146)**	797 (145)$^{\#\#}$	706 (137)	3609 (329)
Male gender, n (%)	15 (48)	8 (35)	7 (88)	16 (49)
Socioeconomic status	3.3 (1.3)*	3.3 (1.3)$^{\#}$	3.4 (1.2)	3.9 (1.0)
Singletons, n (%)	16 (52)**	12 (52.2)$^{\#\#}$	4 (50)	33 (100)
Twin birth, n (%)	12 (39)**	8 (34.8)$^{\#\#}$	4 (50)	0
Triplet birth, n (%)	3 (9)**	3 (13.0)$^{\#\#}$	0	0
APGAR 1 minute	5 (2.4)**	5 (2.6)$^{\#\#}$	6 (1.6)	9 (1.0)
APGAR 5 minutes	7 (2.2)**	7 (2.3)$^{\#\#}$	7 (1.9)	10 (0.6)
Antenatal steroids, n (%)	18 (58)	13 (56.5)	5 (63)	0
Postnatal steroids, n (%)	12 (39)	8 (35)	5 (50)	0
Mechanical ventilation, days	13.4 (18.3)	13.2 (19.7)	14.4 (14.4)	0
Intraventricular hemorrhage				
• Grade 1, n (%)	8 (26)	7 (30)	1 (13)	0
• Grade 2, n (%)	4 (12)	4 (17)	0	0
• Grade 4, n (%)	3 (10)	0	3 (38)	0
Periventricular leukomalacia, cystic n (%)	1 (3)	0	1 (13)	0
Septicemia, n (%)	11 (36)	7 (30.4	5 (50)	0
Patent Ductus Arteriosus, n(%)	9 (29)	7 (30)	2 (25)	0
Surgery, n (%)	7 (78)	6 (26)	1 (50)	0
BPD/O_2 at GA 36 weeks, n (%)	19 (61)	13 (57)	6 (75)	0

Mann-Whitney U-test, Chi-square-test.
*$p \leq .05$, **$p \leq .001$ ELBW vs controls. $^{\#}p \leq .05$, $^{\#\#}p \leq .001$ non-CP ELBW vs controls
Abbreviations: ELBW: extremely low birth weight; SD: standard deviation; CP: Cerebral palsy; BPD: Bronchopulmonary dysplasia

Intervention study

The working memory intervention study consisted of a group of preterm-born VLBW preschoolers as well as a group of age matched VLBW children that did not train. The clinical characteristics are shown in the table below.

Clinical characteristics of the study population paper 3 and paper 4.

	Intervention group N=20 Mean(SD)	Controls N=17 Mean(SD)	P value
Gestational age, weeks	28.8 (2.8)	29.6 (2.6)	.388
Birth weight, grams	1099 (311)	1147 (351)	.666
Male gender, n (%)	6 (30)	6 (35)	.732
Socioeconomic status	3.8 (0.7)	3.8 (0.7)	.921
APGAR 1 minute	7 (2.7)	8 (1.3)	.062
APGAR 5 minutes	9 (1.5)	9 (0.9)	.155
Antenatal steroids, n (%)	17 (85)	15 (88)	.774
Surfactant n (%)	9 (45)	10 (59)	.402
Mechanical ventilation, days	10 (40)	8 (14)	.831
CPAP, days	31 (31)	26 (20)	.563
Intraventricular haemorrhage 1, n (%)	3 (15)	1 (6)	.373
Intraventricular haemorrhage 2, n (%)	2 (10)	0	.180
Intraventricular haemorrhage 3, n (%)	0	1 (6)	.272
Septicemia, n (%)	2 (10)	3 (18)	.498
Patent ductus arteriosus, n (%)	4 (20)	6 (35)	.297
Surgery, n (%)	2 (10)	1 (6)	.647
BPD/O_2 at GA 36 weeks, n (%)	6 (30)	6 (35)	.732
Cerebral palsy, n (%)	2 (10)	1 (6)	.647
Full IQ	93 (8)	98 (14)	.217
Verbal IQ index	96 (10)	91 (8)	.133
Performance IQ index	94 (8)	93 (14)	.919
Processing speed IQ index	101 (10)	104 (15)	.367
Age at baseline	**5.8 (0.49)**	**5.4 (0.29)**	**.002**

Mann-Whitney U-test, Chi-square-test.
Abbrevations: SD: standard deviation; CPAP: Continuous positive airway pressure; BPD: Bronchopulmonary dysplasia; IQ: Intelligence quotient

Summary of the results in the papers

PAPER 1:

Assessment of motor behavior in high-risk-infants at 3 months predicts motor and cognitive outcomes in 10 years old children.

Of the 40 high-risk children included in this study, 31 were VLBW children and 9 were term born high-risk children with birth weight > 1500g.

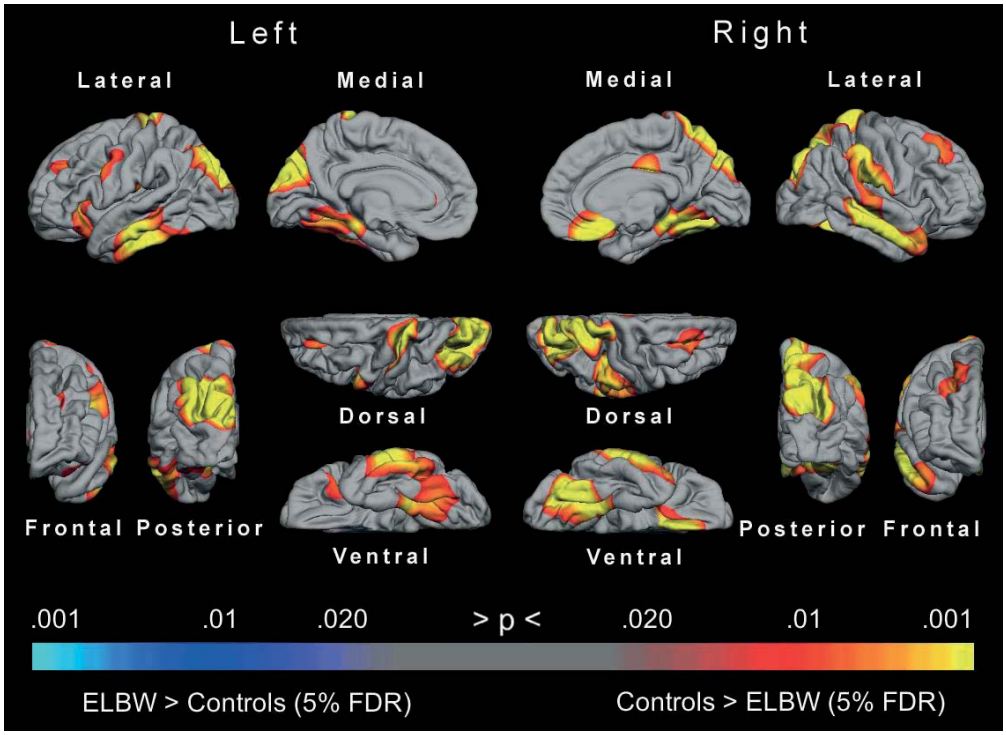
The children with presence of fidgety movements, poor motor and/or cognitive outcome at 10 years was identified by abnormal concurrent motor repertoire at 14 weeks post-term age in 86% (95% CI: 0.60–0.96) of the children. 71 percent (95% CI: 0.47–0.87) of the children with normal motor and cognitive outcomes were identified by presence of fidgety movements and normal motor repertoire. 14 (35%) infants had presence of fidgety movements and a normal concurrent motor repertoire, 17 (43%) infants had fidgety movements and abnormal concurrent motor repertoire, while 9 infants (23%) showed no fidgety movements combined with an abnormal concurrent motor repertoire. 12 infants comprising 10 VLBW infants and 2 term-born children with neonatal encephalopathy had CP at follow-up. 9 (75%) of these children had no fidgety movements, and all of them had an abnormal concurrent motor repertoire. In 2 children, who later developed hemiplegic CP, sporadic fidgety and abnormal concurrent motor repertoire was found while in 1 child with non-spastic ataxic CP fidgety movements and abnormal concurrent motor repertoire was present.

PAPER 2:

Follow-up at age 10 years in ELBW children - Clinical outcome, brain morphology and results from motor assessments in infancy.

In paper 2, 31 ELBW children with mean birth weight: 773g (SD 146) and mean gestational age 26.1 weeks (SD 1.8) and 33 term-born controls with mean birth weight: 3609g (SD329) and mean GA 40.1 (SD 0.9) were examined. At follow-up 8 ELBW children had CP. The non-CP ELBW children had similar full-IQ scores compared to controls (ELBW: 98 (95% CI: 90,106) versus controls: 105 (95% CI: 98,112), but lower working memory index (91 (95% CI: 84,98) versus 101 (95% CI: 96,107). The non-CP ELBW children had lower motor skills reflected on the MABC-2, more reported attention problems reflected on all ADHD rating scale scores and more behavioral problems evaluated by their parents on Brief. On cerebral MRI we found smaller total brain volume and reduced volumes of thalamus, putamen, globus pallidus, cerebellar grey and white matter as well as posterior corpus callosum in the non-CP ELBW children compared to controls. When adjusting for total brain volumes, SES, gender and age at MRI examination volumes of globus pallidus, cerebellar white matter as well as posterior corpus callosum remained significantly smaller. Cortical surface area was reduced in temporal, parietal and anterior-medial-frontal areas in the ELBW group. The cortical surface area findings are demonstrated in the figure below (published in paper 2)

FIGURE 1. Group differences in cortical surface area between non-CP ELBW children and controls.



The mapping of cortical surface areal reduction in non-CP ELBW children compared with controls is shown on the reconstructed cortical surface. Top panel shows lateral and medial views of left and right hemispheres and bottom panel shows frontal, posterior, dorsal and ventral views. Cortical areas with statistically significant difference between groups after False Discovery Rate (FDR) correction at $p < 0.05$ are shown in color, and the color scale indicates the dynamic range of the statistically significant changes (in p-values), red to yellow represents an increasing surface area reduction in the non-CP ELBW group compared with controls. Most significant areas of reduced surface area in the non-CP ELBW group were observed in the temporal and parietal lobes bilaterally, and in the right anterior-medial-frontal lobe. No areas with increased surface area (blue areas) were found in the non-CP ELBW group compared with controls.

The inferior clinical test-results and reduced brain volumes at age 10 were mostly found in the non-CP ELBW children who had fidgety movements but abnormal motor repertoire in infancy.

PAPER 3:

Working Memory Training Improves Cognitive Function in VLBW Preschoolers.

In paper 3, 20 VLBW preschool aged children were examined before and 4 weeks after training. The children improved significantly on trained working memory tasks measured by the Cogmed program. We measured a mean Start Index of 42.1 [SD 6.3] and a mean Max Index (best scores achieved during training) of 60.6 [SD 5.7], which gives a mean Improvement Index of 18 in all participating children. In addition, the VLBW preschoolers improved significantly on the following non-trained working memory tasks from the neuropsychological assessment battery:

Spatial span backward: 2.3 before to 3.6 after training [confidence interval (CI) -2.2 to -0.4].
Spatial span total score: 6.4 before to 8.3 after training [CI -3.7 to -0.1].

A generalization effect of training was found within the following tasks measured by NEPSY:
Auditory attention: 49.6 before training to 58.2 after training [CI -15.5 to -1.6].
Phonological awareness: 9.3 before training to 12.6 after training [CI -5.2 to -1.4].
Visual memory: 20.0 before training to 24.9 after training [CI -7.4 to -2.5].
Verbal memory: 12.9 before training to 17.5 after training [CI -7.1 to -2.0].
Sentence repetition: 15.7 before training to 17.7 after training [CI -3.3 to -0.7].

PAPER 4:

Computerized Working Memory Training has Positive Long Term Effect in VLBW Preschoolers.

In paper 4, we included 17 age-matched non-training VLBW preschoolers in addition to the 20 VLBW children in the intervention group (from paper 3). At follow-up, higher scores and increased performance gain were found in the intervention group compared with controls on the following tasks: Memory for faces, Narrative memory and Spatial span.

On the task Phonological processing, significant improvement was found in both groups. No group differences in performance gain were found on attention, anxiety and behaviour evaluated by parental questionnaires at long-term follow-up.

We concluded that the working memory training program in preschool VLBW children had positive and persisting positive effects on working memory, visual and verbal learning and memory at 7 months follow-up.

DISCUSSION

Summary of the main findings

- In a group of preterm-born and high-risk term born children, an early general movement assessment (GMA) including an assessment of spontaneous motor repertoire at 14 weeks post-term was predictive for motor outcome and for combinations of motor problems and cognitive impairments at age 10 years (paper 1). These findings will be discussed together with the GMA assessments in paper 2. In paper 2, ELBW children without cerebral palsy at age 10 had full IQ scores similar to healthy controls, but lower working memory index. Extensive neuropsychological test results did not differ between the two groups. The non-CP ELBW children had lower motor skills and more reported attention and behavioral problems. On MRI non-CP ELBW children had significantly smaller intracranial brain volumes, smaller volumes of globus pallidus, cerebellar white matter and posterior corpus callosum. Cortical surface area was reduced in temporal, parietal and anterior-medial-frontal areas.
  The non-CP ELBW children with presence of fidgety movements but abnormal concurrent motor repertoire on GMA in infancy had inferior clinical test results and smaller brain volumes compared to those with normal concurrent motor repertoire.

- In the intervention study VLBW children had positive short- as well as long-term effects on cognition and learning after computerized working memory training. The positive training effects were shown on trained and non-trained working memory tasks and as a generalization effect on tasks not directly trained in the program (paper 3 and 4).

Strengths and limitations

Strengths

Strength of the long-term follow-up study was that we were able to include almost three complete year cohorts of ELBW children born in 1999-2001 at the Trondheim University Hospital and that two experienced and certified researchers assessed the videotapes for GMA independent of each other. In the case of disagreement, a consensus was made based upon a second individual assessment. Strength was also the comprehensive cognitive and neuropsychological assessments performed in all participating children and that these were performed by only one trained pediatrician under supervision of a specialized neuropsychologist. Another strength was the cerebral MRI using an automated segmentation technique (FreeSurfer) for quantitative measures of cortical, white matter and deep nuclei brain structures.

In the intervention study a major strength was that all children participating in the intervention group completed all 25 training days within the prescribed time limit of 5-6 weeks. In addition, all participating children attended all follow-up examinations. The first part of the intervention study had a randomized stepped wedge design. With this design we were able to offer all participating children the training program.

Limitations

A limitation of this thesis is the rather small sample size of children included in both studies. This is mainly due to the small total number of preterm children born in the Trondheim area during the respective birth years. In addition, we had to exclude children that lived far away (> 100 km) from follow-up as the travel distance and the extra load on the children and parents would not be reasonable.

A limitation in the long-term follow-up study was the reduced sample size of eligible children who participated in MRI and that some MRI scans had to be rejected because of movement artefacts. Due to the small sample size, only large group differences in test results and MRI findings would reach significance, and this made it difficult to make general conclusions based on the results in the two studies and especially with regard to the subgroup analysis. The subgroup analysis including the early GMA results therefore has to be considered a pilot study.

Recently, intervention studies that are not randomized have been criticized, and doubt towards the working memory training effect has been expressed (Melby-Lervag and Hulme 2013). We did not choose a randomized design for the long-term follow-up of our intervention study. If we initially had had a larger sample size of VLBW children, we should ideally have performed a randomized prospective study design including three groups: a VLBW training group, a VLBW non-training group and a VLBW placebo-training (using a non-adaptive, i.e. fixed low level training version of the program) group. As we initially recruited only a limited sample size due to practical reasons, this was unfortunately not possible. In addition to this we had ethical considerations as we intended to offer the intervention program to all participating children, and it is likely that the preterm children that would have been randomized to a placebo program would have had major motivational problems.

Bias and confounders

A possible limitation in both studies is selection bias regarding the preterm and control children. It is possible that parents that experience problems or have expectations of disabilities in their child might be more interested in participating in intervention and follow-up studies (Castro, Yolton et al. 2004). However, we were not able to identify any significant differences in the responders versus non-responders in the preterm group, making it unlikely that the results could be explained by selection bias.

In the long-term follow-up study the socio-economic status in the preterm children without CP was slightly lower than in the healthy controls. Differences in SES could therefore confound the results; hence all statistical analyses were corrected for SES in this follow-up study.

The concept of the Cogmed training program is that the training must be intense, sustained and adaptive to the skills of the training person (Klingberg, Fernell et al. 2005, Holmes, Gathercole et al. 2009, Diamond and Lee 2011, Green, Long et al. 2012, Chacko, Feirsen et al. 2013, Dunning, Holmes et al. 2013) in order to work on the limit of the child's skills consistently. This can be very tiresome and demotivating for a child. Thus the success of the intervention might be dependent on the child's and his/her family's high motivation and willingness to complete the training. In our intervention study, the possible positive influence that highly motivated parents and children could have on the test results should not be ignored. It is also possible that the positive attention and focus that the children received from the parents and the researchers during the training and test situation could positively impact their results.

Long-term outcome in non-CP ELBW children

Cognitive and neuropsychological function

In our long-term follow-up study comparing non-CP ELBW children with controls, we did not find any significant differences in full IQ between the two groups. During the last few decades, improvements in pre- and postnatal treatment have increased the survival rates of the preterm-born children (Saigal and Doyle 2008), and over the last 10-15 years there has also been reported a trend towards better neurodevelopmental and cognitive outcomes (Markestad, Kaaresen et al. 2005, Baron and Rey-Casserly 2010). A meta-analysis of preterm children born between 1980 and 2001 (Bhutta, Cleves et al. 2002) showed that preterm children scored lower than term-born peers on IQ tests, and during the late 1990s only 44-62% of the preterm children had a full IQ > 84 (Saigal, den Ouden et al. 2003). Studies in extremely premature children born before 2000 reported an average of 10 to 12 points lower IQ in these children compared with term-born peers (Kerr-Wilson, Mackay et al. 2012). Studies in preterm children born after 2000 are still few, though more optimistic findings regarding cognitive function have been reported. For instance studies from Finland (Mikkola, Ritari et al. 2005) and Australia (Woodward, Clark et al. 2012) reported that preschool aged children born preterm and without considerable white matter injury were indistinguishable from term peers in cognitive functioning. These positive findings together with the results in our study are certainly reassuring for today's parents of preterm-born children.

Despite the normal full IQ in our study, the non-CP ELBW children had poorer working memory skills, more attention problems and more problems regarding inhibition, emotional control, planning and organizing. Deficits within these areas are often reported in preterm-born children (Taylor, Klein et al. 2000, Anderson and Doyle 2004, Elgen, Lundervold et al. 2004, Taylor, Minich et al. 2004, Mulder, Pitchford et al. 2009) and might have negative consequences for the ability to acquire new skills and knowledge and may therefore compromise school performance and later academic achievement (Nosarti, Giouroukou et al. 2007, Moster, Lie et al. 2008). Such executive and attention problems that might have serious consequences for the child's cognitive functioning should be diagnosed as early as possible in order to initiate early intervention strategies to reduce the negative effects that these deficits may have on school performance and the child's everyday life.

In our study we were surprised to find that the non-CP ELBW children scored similarly to the healthy controls on the neuropsychological tests TMT, Stroop and Beery VMI. This is in

contrast to a meta-analysis conducted by Mulder et al (Mulder, Pitchford et al. 2009). A possible explanation might be that the non-CP ELBW children included in our study had normal full IQ and did not have any signs of necrotizing enterocolitis (NEC) or severe cerebral brain injury on neonatal ultrasound, which were important predictors for adverse outcome in the referred studies (Sherlock, Anderson et al. 2005, Rees, Pierro et al. 2007, Mulder, Pitchford et al. 2009, Anderson, De Luca et al. 2011).

MRI findings in the long-term follow-up

In our long-term follow-up study we examined a group of 31 ELBW children, of which 23 children did not have CP. In the non-CP ELBW group less than 50% of the children (n= 11) had a IVH grade 1 or 2, and none of them had more severe brain damage like PVL or periventricular hemorrhagic infarction diagnosed on cerebral ultrasound during the neonatal period.

However, when we compared the non-CP ELBW children with healthy term-born controls we found that the preterm children had smaller total brain volumes and reduced volumes of globus pallidus, thalamus, putamen, cerebellar grey and white matter and posterior part of corpus callosum. Controlling for multiple comparisons, the globus pallidus, cerebellar white matter and corpus callosum remained significantly smaller. These findings are in agreement with other findings. Ball et al. found reduced thalamic volumes in preterm children and the reduced volumes in that study were related to deviations in the microstructure of the thalamic radiations and cortical volume (Ball, Boardman et al. 2012). In a large study including one year old preterm infants, Inder et al. found reduced cortical and deep gray matter volumes (Inder, Warfield et al. 2005), and such reductions in volumes seems to persist into adulthood (Peterson, Vohr et al. 2000, Bjuland, Rimol et al. 2014). Limperopolous et al. investigated the effect of prematurity on cerebellar growth and found that long-term neurodevelopmental disabilities were partly attributed to impaired cerebellar development (Limperopoulos, Soul et al. 2005). The authors argued that cerebellar hemorrhagic injuries might play an under-recognized role not only in reduced motor functioning but also in the cognitive and behavioral dysfunction observed in many preterm-born survivors (Limperopoulos, Bassan et al. 2007).

There is a male disadvantage with regard to perinatal morbidity (Drevenstedt, Crimmins et al. 2008), cerebral injuries and cognitive and behavioral outcomes in premature children (Wood, Costeloe et al. 2005, Skiold, Alexandrou et al. 2014). In our long-term follow-up study we did not find any significant gender differences regarding clinical outcome or brain imaging

findings. This may be due to the small sample size in our study and lack of power to show any gender differences in results for our non-CP ELBW children.

In our study the ELBW children without CP had reduced volumes of brain structures in white and grey matter and significantly reduced cortical surface area in temporal, parietal and anterior-medial-frontal areas. Previous studies report that preterm survivors have neuronal loss and/or gliosis within grey matter structures such as the thalamus (Constantinidis and Procyk 2004), hippocampus (Leutgeb, Leutgeb et al. 2005), basal ganglia (Monchi, Petrides et al. 2006) and cerebellum (Kalashnikova, Zueva et al. 2005) as well as structural abnormalities in white and grey matter (Inder, Warfield et al. 2005, Nosarti, Giouroukou et al. 2008, Eikenes, Lohaugen et al. 2011, Mullen, Vohr et al. 2011). In our study the non-CP ELBW children did not suffer any severe brain injury during the neonatal period, so our finding of reduced volumes of different brain structures may indicate that even premature children without signs of moderate to severe brain injuries on neonatal ultrasound probably have diffuse perinatal brain injury compromising the microstructure of white matter and the development of grey matter. Possible mechanisms may include fewer amounts of pre-oligodendrocytes, arrest in pre-oligodendrocyte maturation, deviations in myelination, abnormal neuronal migration and organization, reduced amount of axons and impaired axonal connections and gliosis (Pierson, Folkerth et al. 2007, Volpe 2009). Nosarti interpreted the preterm brain findings as a "neuroplastic" framework where an injury in one area might cause changes or injuries in many other areas as well (Nosarti 2013). Pierson et al concluded that due to the possible combination of white and grey matter injury in the preterm survivors, future treatment strategies to prevent neurological deficits should target both white and grey matter brain injury (Pierson, Folkerth et al. 2007).

General movement assessment

In paper 1, we were able to identify 9 of 12 children that later developed CP by GMA at 14 weeks post-term age, resulting in a sensitivity of the test of 75%. We assessed presence of fidgety in 31 children, and of these 28 had normal outcomes at 10 years, resulting in a specificity of the assessment in our high-risk children of 90%. The predictive value of GMA and fidgety movements for CP is well established (Prechtl, Einspieler et al. 1997, Einspieler, Prechtl et al. 2004, Yang, Einspieler et al. 2012). Two recent reviews reported a sensitivity of ≥92% and a specificity of ≥ 82% of the assessment for prediction of CP or severe neurodevelopmental outcome in infants aged 1-2 years (Burger and Louw 2009, Darsaklis, Snider et al. 2011). In older children up to 11 years sensitivity and specificity for the assessment to predict CP has been found to be between 55-100% (Darsaklis, Snider et al. 2011). The sensitivity in our study is slightly lower than many other studies, but this could be due to the dispersed composition of VLBW and term-born children in our study.

The majority of studies focusing on early motor assessment have examined the GMA and its predictive value regarding CP and adverse motor outcomes. Only a few studies have investigated the predictive value of the concurrent motor repertoire which is a part of the GMA assessment, showing that the risk of developing minor neurological dysfunctions (Bruggink, Einspieler et al. 2008), lower fine motor skills and coordination problems (Groen, de Blecourt et al. 2005) increases when a child presents with abnormal motor repertoire on GMA. In our study (paper 2), the non-CP ELBW children with present fidgety and abnormal concurrent motor repertoire had higher scores on all ADHD rating scale subscores, though we did not examine any additional psychiatric comorbidity. Interestingly, these children had a combination of inattention and hyperactivity as well as more behavioral problems, which could indicate the presence of psychiatric co-morbidity. Our findings are similar to a recent study from Holland in which the authors concluded that abnormal general movements in high-risk children without CP were associated with ADHD and psychiatric co-morbidity at 9-11 years of age (Hadders-Algra, Bouwstra et al. 2009).

Recent studies suggest that the quality of GM might be an early predictor also for cognitive function in very preterm-born children (Bruggink, Einspieler et al. 2009, Butcher, van Braeckel et al. 2009, Spittle, Spencer-Smith et al. 2013). However, none of these studies looked at the combination of motor and cognitive skills. In our study, we found that almost all the children with low IQ also had a combination of motor difficulties. Taking into account

that the brain injury especially in preterm-born children is complex and involves different parts of the cerebral network it is likely that injuries in preterm-born children affect several brain areas comprising a diversity of skills not only within the motor area (Nosarti 2013). When we published the first paper we therefore found it difficult to conclude that the early motor assessment can be used to predict cognitive outcome alone. We think that a more precise understanding of the GMA would be that when assessing lack of fidgety or presence of fidgety movements but with abnormal concurrent motor repertoire, this could represent different degrees of brain injury – the former reflecting more severe injury leading to CP, most often with additional disabilities, while the latter representing milder, but still probably widespread brain injury with an increased risk of neurodevelopmental disorders consisting of a combination of attention, behavioral, cognitive and motor impairments and deficits.

GMA and MRI findings

Our study is to our knowledge the first to investigate the relationship between GMA in infancy, clinical outcome and structural brain findings in 10 year old ELBW children (paper 2). When examining the correlations between MRI findings and clinical outcome at 10 years, we found that the non-CP ELBW children with abnormal concurrent motor repertoire had significantly smaller white matter, grey matter, thalamus, putamen and cerebellar white matter volumes compared to the ELBW children with normal concurrent motor repertoire. This is to some extend in accordance with a previous study showing that reduced cerebellar size at term-equivalent age was correlated with poor motor outcome in very preterm children (Spittle, Doyle et al. 2010) and that GMA and white matter abnormalities predicted motor outcome at 12 months of age (Spittle, Cheong et al. 2011).

In our study, the non-CP ELBW children with abnormal concurrent motor repertoire also scored lower on working memory, had more attention and behavioral problems and had lower motor skills compared to the children with normal concurrent motor repertoire. Unfortunately due to the small number of children, secondary subgroups correlation analyses between MRI findings and clinical outcome were not meaningful to perform, and larger studies are needed to look at this relationship.

An interesting finding was that the ELBW children with normal concurrent motor repertoire did not differ from controls on any motor, cognitive and neuropsychological test or on any brain structure measure. This support our speculation that GMA including the assessment of the movement repertoire in infancy can predict or help identify those children who are at increased risk of abnormal outcome, but also those that will develop normally and in this way

be able to reassure the parents (Fjortoft, Grunewaldt et al. 2013). Due to our findings we suggest that this observational and easy-to-perform method should be implemented as a valuable early biomarker to identify preterm children at high or low risk of developing neuroimpairments.

Working memory intervention

Our intervention study is the first to explore the effect of a computerized working memory training program in VLBW preschoolers. We were able to show that working memory training had short-term positive effects on trained and non-trained working memory tasks. In addition, we also found a generalizing positive effect on auditory attention, phonological awareness, visual and verbal memory and learning. These results are consistent with studies performed in healthy preschoolers (Thorell, Lindqvist et al. 2009) and similar to the results in a study of a group of ELBW adolescents who trained with a more advanced and extensive version (Cogmed RM) of the same working memory training program (Lohaugen, Antonsen et al. 2010). As auditory attention, phonological awareness and visual as well as verbal memory are tasks similar to what is presented in the school environment and keeping in mind that intervention strategies initiated as early as possible may have positive effects for preterm children (Spittle, Orton et al. 2012), this preschool training program could be beneficial for the preterm children regarding later school performance and academic achievement.

Several studies in school-aged children have shown positive effects on attention and hyperactivity after working memory training. A recent study in ELBW adolescents reported improvements in attention as well as hyperactivity (Lohaugen, Antonsen et al. 2010), and we expected this to be similar in our group of preschool aged preterm children. However, after training we did not find any reduction in ADHD scores. An explanation for this might be that none of the participating children had attention scores within clinical levels before training, which definitely would be a limitation of possible improvements. It is also possible that the training time in the preschool version of the program (Cogmed JM) is too short (10-15 minutes per day) to improve attention compared to the school version of the program. Surprisingly we found a reduction of separation anxiety and total anxiety scores after training, as measured by parental questionnaires. This could be due to chance or we could speculate that the children after intervention had a better perception of the surroundings they live in making them feel more secure and possibly that the interrelation and attention from the

parents and researchers could make them more secure and less anxious. Larger studies have to confirm or reject our findings with regard to reduced anxiety after this type of cognitive training.

In our intervention study we also wanted to investigate long-term training effects evaluated 7 months after completed training. Due to our initial stepped wedge design and small sample size, we did not have a non-training control group for the first part of this intervention study. To be able to determine whether any gains in performance observed after the 7-month follow-up period was a natural part of the developmental process, we included a non-training VLBW control group for the long-term evaluation of effect. This group of VLBW children was examined at two time points with a seven-month interval. In the long-term follow up we found that the intervention group had higher scores and increased performance gains on non-trained visual working memory tasks as well as on visual and verbal memory and learning compared to the non-training VLBW children. This indicated persistent effects of the training and could not be explained by normal development. The positive effects observed at seven months were not as comprehensive as those reported at the short-term follow-up; though it is important to keep in mind that the intervention program in preschoolers are relatively short and not as time consuming and intense as the program designed for school-aged children. Still we found performance gains after 7 months on tasks that are important for scholastic performance and later academic achievements. We therefore speculate that this kind of intervention could be positive in preterm children before they start in school with lasting effects also after starting school.

How does working memory training improve function? During the last several decades, areas of the brain related to working memory performance have been explored. Studies have shown that hippocampus (Beauchamp, Thompson et al. 2008), dorsolateral prefrontal cortex and also other cortical and subcortical structures (Woodward, Edgin et al. 2005) mediate executive skills such as working memory. As working memory training has shown positive results on working memory but also generalizing positive effects there is a growing interest in research projects that survey changes in the brain during or after intervention. Several neuroimaging studies report that working memory training increases brain activity measured in the parietal and prefrontal cortex (Klingberg and Roland 1998, Hautzel, Mottaghy et al. 2002, Curtis and D'Esposito 2003, Hempel, Giesel et al. 2004, Olesen, Westerberg et al. 2004, Moore, Cohen et al. 2006, Jolles, Grol et al. 2010). A study in healthy adults found increased fractional

anisotropy values within white matter tracts in the parietal lobe as well as in the anterior corpus callosum, suggesting that the intervention increases myelination of tracts in these brain areas (Takeuchi, Sekiguchi et al. 2010). Hoekzama et al found increased grey matter following working memory training in ADHD children (Hoekzema, Carmona et al. 2011). Working memory training has also been found to alter dopamine (D1) receptor density (McNab, Varrone et al. 2009) and a recent study indicates that a common neural system in the lateral prefrontal cortex is recruited to improve visual-spatial working memory and fluid intelligence in preschoolers (Kuwajima and Sawaguchi 2010).

All these findings support the theory that working memory emerges from the interaction between several brain regions to large scale network (Poch and Campo 2012) and that working memory can be trained with structural and functional changes in the brain. This might be an explanation for the positive effects on cognition by computer-based working memory training seen in our study. However, still many questions regarding the methods and effects of working memory training remain unanswered and more studies on different patient groups should be performed.

Clinical implications

In Norway, preterm-born children with birth weight < 1000 g and other high-risk children are included in multidisciplinary follow-up programs with extensive diagnostic and intervention when indicated from birth, until they are 5 years old. After this age, follow-up is transferred to local authorities or to a local rehabilitation institution for children with the most severe impairments. Comparable European countries (and the US) have similar multidisciplinary follow-up strategies, though many countries end their follow-up examinations at 2 years of age, while others do not have follow-up at all. The results from this thesis supported by the findings of several large international studies show that even very preterm children without signs of severe brain injuries in the neonatal period are at high risk of developing subtle problems within motor, cognition, attention and behavioral skills possibly due to a widespread and persisting influence on normal brain development. In Norway ELBW children are offered the last multidisciplinary follow-up examination shortly before they start in school. At the beginning of the 5th grade though, the scholastic demands change and the curriculum is more verbal and abstract. In addition, the load on working memory increases for instance when the child reads a text and must extract and remember the most important information. We therefore recommend, due to the more subtle cognitive, attention-related and behavioral impairments in the ELBW children that may be visible in school age, that a multidisciplinary examination should be performed before starting the 5th grade with emphasis on neuropsychological testing in order to initiate intervention or supportive strategies in forms of special education.

As more very preterm born children survive there will be more children in need of help and assistance in school. We believe that early general movement assessment (GMA) can be a suitable early predictive tool in order to identify high-risk children who will develop CP but also those children who will most likely develop normally and lastly those preterm children that are at high-risk of developing more subtle problems but not CP. Such an early prognostic tool together with neuroimaging could help clinicians focus on those preterm children who would benefit the most from early intervention programs.

This thesis shows that working memory training has positive effects in preterm preschoolers, and we speculate that such interventional programs might prevent or at least reduce cognitive problems that may impact the children's academic achievement and maybe also improve the social function in these high-risk children. As our study is small, larger studies must confirm

our findings before a general recommendation of pre-school cognitive training in preterm children can be given.

Future research

A limitation of this thesis was the rather small sample size in both studies which makes general conclusions difficult. As the number of birth in Norway is small only multicenter studies within Norway or as international collaboration studies would be able to include a large group of preterm born children. At present we collaborate with researchers at the Norwegian Institute of Public Health in the multicenter study: "The Norwegian Mother and Child Cohort Study" (MoBa) where pre- and postnatal data and long-term outcome of 100.000 children born between 1999 and 2008 are collected. In this study a relatively large group of premature children and also term-born children at different ages (5-11 years) have been included in an ongoing study at NTNU, Trondheim, and data on long-term outcome with repeated extensive neuropsychological testing and cerebral MRI is collected. A possible future research project would be to examine these data longitudinally to explore the relationship between trajectories of brain development and cognition in normal and at risk children.

Almost all extremely preterm children born in Trondheim after 1999 have been videotaped during the neonatal period for a general movement assessment. In collaboration with St. Olav's Hospital, a possible and very interesting future study would be to examine all available video-clips over the last 10-15 years and to compare them with long-term outcome, including quantitative MRI.

Our working memory intervention study was the first study to evaluate effects in preterm-born preschoolers. However, short and long-term positive effects of such training programs are debated in the recent literature due to bias and confounders. Future studies should therefore be randomized into training versus non-training groups. More research is also needed to explore the right time, dose and number of training sessions for such training or other type of cognitive training, especially in children. It is possible that repetition of the training program used in our study or a short booster session within some months after finished training could have an additional positive effect and increase the maintenance of the positive effect. No study has investigated such variations in the use of the program, and future

research should therefore focus on the effect of repeated training and try to identify whether there is a window of opportunity where intervention is most effective. As a continuation of our intervention study an interesting future study would also be to combine the Cogmed JM preschool program with the Cogmed RM program designed for school-aged children in the same child as the child gets older. Future studies of working memory training in preterm-born children should also include structural and functional MRI to explore plasticity-induced changes in the brain caused by training.

CONCLUSIONS

In our long-term follow-up study we found that ELBW children without CP and with full IQ within normal range at 10 years have signs of deviant brain development, reduced fine motor skills, deficits in working memory and more reported problems with attention and executive function when compared to term-born peers. We also showed that presence of fidgety movements together with an abnormal motor repertoire in infancy can be a valuable early clinical marker for high-risk children that do not develop CP but still are at an increased risk of developing a composite of motor, cognitive and behavioral impairments. We speculate that a non-intrusive observational method such as the GMA, which includes an assessment of the quality of the early motor repertoire, might serve as an early biomarker to identify high risk and preterm children at increased risk of neuroimpairments. By successfully identifying these children, early intervention programs can be initiated and the risk of later academic or social difficulties may be reduced.

In our intervention study we showed that computerized working memory training in VLBW preschoolers has short-term and long-term positive effects on working memory, visual and verbal memory as well as learning. On several tests the working memory training seemed to give a booster effect in the first months after training, followed by less, but still positive performance gain with time. As our study is relatively small with no long-term follow up, we can only speculate that such working memory training in pre-school age may prevent or reduce cognitive problems that impact later educational achievement and potentially also social function in these children. However larger studies must confirm our findings before a general recommendation of working memory training as an interventional tool for preterm children before starting school should be given. Future studies are also needed in order to define in what way such cognitive training should be given and whether repeated training at defined intervals or a combination of preschool and school-aged working memory program would be most beneficial to provide the best performance gains and to further improve transfer effects on other cognitive domains and behavior.

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Appendix I

Assessment of Motor Repertoire - 3 to 5 Months

Christa Einspieler and Arie Bos, the GM Trust 2001

Name: .....

born: ..... Postmenstrual Age: ..... Birth weight: .....

Recording Date: ..... Postterm Age: .....

Number of movement patterns observed: ⌊⌊⌋ **normal (N)** ⌊⌊⌋ **abnormal (A)**

N	A	fidgety movements	N		hand-face contact	N	A	legs lift, flexion at knees
N	A	swiping movements	N		hand-mouth contact	N	A	legs lift extension at knees
N	A	wiggling-oscillating movem.	N		hand-hand contact	N		hand-knee contact
N	A	saccadic arm movements	N		hand-hand manipulation	N	A	arching
N	A	kicking	N	A	fiddling / clothes, blanket	N	A	trunk rotation
N	A	excitement bursts	N		reaching	N		axial rolling
	A	'cha-cha-cha movements'	N	A	foot-foot contact	N	A	visual scanning
N	A	smiles	N		foot-foot manipulation	N		hand regard
N	A	mouth movements	N	A	segmental movements arms	N		head anteflexion
N	A	tongue movements	N	A	segmental movements legs		A	arm movements in circles
N	A	head rotation		A	segm: discrepancy arm-leg		A	almost no leg movements

Number of postural patterns observed: ⌊⌊⌋ **normal (N)** ⌊⌊⌋ **abnormal (A)**

N	A	head in midline (20 °)	N		variable finger postures		A	hyperextension of the neck
N	A	symmetrical		A	predominant fisting		A	hyperextension of trunk
N	A	spontaneous ATNR absent or could be overcome		A	finger spreading		A	extended arms/ on / above surface are predominant
	A	body and limbs 'flat' on surface		A	few finger postures			
				A	synchronised opening and closing of the fingers		A	extended legs / on / above surface are predominant

Movement character (global score):

N		smooth and fluent		A	stiff		A	predominantly slow speed
	A	jerky		A	cramped		A	predominantly fast speed
	A	monotonous		A	synchronous		A	predomin. large amplitude
	A	tremulous		A	cramped-synchronised		A	predomin. small amplitude

Motor Optimality List:

1.	Fidgety Movements	normal	❑	12
		abnormal	❑	4
	± + ++ P D	absent	❑	1
2.	Repertoire of co-existent other movements	age-adequate	❑	4
		reduced	❑	2
		absent	❑	1
3.	Quality of other movements	N > A	❑	4
		N = A	❑	2
		N < A	❑	1
4.	Posture	N > A	❑	4
		N = A	❑	2
		N < A	❑	1
5.	Movement character	smooth and fluent	❑	4
		abnormal, not cramped-synchr.	❑	2
		cramped-synchronised	❑	1

Motor Optimality Score:
Maximum: 28; Minimum: 5

Paper I

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Assessment of motor behaviour in high-risk-infants at 3 months predicts motor and cognitive outcomes in 10 years old children

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ABSTRACT

Background: The general movement assessment has mainly been used to identify children with cerebral palsy (CP). A detailed assessment of quality of infant motor repertoire using parts of the "Assessment of Motor Repertoire — 3 to 5 Months" which is based on Prechtl's general movement assessment can possibly identify later motor and cognitive problems in children without CP.
Aims: This study aims to determine whether analysis of quality of infant motor repertoire has predictive value for motor and cognitive outcomes at age 10 in children at risk for later neurological impairment.
Study design: A longitudinal study design was used.
Subjects: Video-recordings of 40 "neurologically high-risk" infants at 14 weeks post-term age were analysed with respect to motor repertoire.
Outcome measures: Fidgety movements were classified as present or absent. Quality of concurrent motor repertoire was classified as normal if smooth and fluent and abnormal if jerky, monotonous or stiff. Poor motor outcome was defined as a score ≤5th centile on the Movement-Assessment-Battery-2, while poor cognitive outcome as total IQ <85 on Wechsler Intelligence Scale-III.
Results: Among the high-risk children with presence of fidgety movements, poor motor and/or cognitive outcome at 10 years was identified by abnormal concurrent motor repertoire at 14 weeks post-term age in 86% (95% CI: 0.60–0.96) of the children. On the other hand, 71% (95% CI: 0.47–0.87) of those with normal motor and cognitive outcomes were identified by presence of fidgety movements and normal motor repertoire.
Conclusions: Assessment of quality of infant motor repertoire may be a valuable early clinical marker for later impaired motor and cognitive outcomes in high-risk children who do not develop CP.

1. Introduction

Children born prematurely and/or with neonatal encephalopathy have an increased risk for impaired neurological outcomes [1]. Abnormal motor and cognitive outcomes have especially been reported in preterm-born children with a very low birth weight (VLBW: birth weight <1500 g) [2,3]. Studies have shown that early intervention can reduce motor and cognitive [4,5] impairments in early childhood. In order to intervene at an early stage and give parents the support they need, it should be a top priority to develop and improve assessment tools that reveal neurological problems at an early stage. Early resource-demanding intervention in children at risk of an impaired neurological outcome but without actual symptoms should not be initiated unless a relatively reliable prediction of outcome can be made. Several studies have described a method for such a purpose — the General Movement Assessment (GMA), developed by Prechtl et al. and based on a systematic observation and classification of spontaneous movement behaviour in infancy [6]. A set of normal general movements (GMs) was defined for the preterm, term and post-term periods. Fidgety movements (FMs) are characteristic of the spontaneous motor behaviour in 3- to 5-month-old infants. They are small movements of moderate speed and variable acceleration of the neck, trunk and limbs in any direction, and are continuous and present almost all the time [7]. The concurrent motor repertoire denotes general movements co-occurring with fidgety movements; together, they constitute the motor behaviour in 3- to 5-month-old infants. To

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assess the quality of these movements, the Prechtl group developed the "Assessment of Motor Repertoire" (AMR) [7]. AMR yields a motor optimality score, i.e. the sum of five parameters: fidgety movements, repertoire of co-existent other movements, quality of other movements, posture and movement character.

The GMA has mostly been used in studies to predict later development of cerebral palsy (CP) [6,8]. Absence of fidgety movements has been shown to be predictive of later development of CP [6,9], whereas the presence of fidgety movements has been found predictive of a normal neurological development [9,10]. So-called "mildly abnormal GMs" have been reported as a possible risk for minor neurological dysfunction (MND) in 4- to 12-year-old children [11–13]. Recently, an association has been proposed between the quality of the spontaneous motor repertoire in early infancy and the cognitive outcome later in childhood [14,15].

The objective of the present study was to determine the predictive value of the quality of fidgety movements and concurrent motor repertoire for the later motor and cognitive outcomes in a group of high-risk children born preterm and/or with neonatal encephalopathy. Furthermore, we aimed to examine the respective predictive values in a subgroup of infants born with VLBW. We hypothesised that the presence of fidgety movements and a normal concurrent motor repertoire were predictive of a normal cognitive and motor outcome, whereas the presence of fidgety movements with an abnormal concurrent motor repertoire was predictive of impaired motor and cognitive outcomes, especially in VLBW infants.

2. Methods

2.1. Design

The present study was a follow-up study of a group of high-risk infants treated at the Neonatal Intensive Care Unit (NICU) at St. Olav University Hospital, Trondheim, Norway. They were invited to participate in the study at 10 years of age. Data had been collected at birth and at 3 to 4 months' corrected age, and the motor and cognitive outcomes were assessed at 10 years of age.

2.2. Participants

During the years 1999, 2000, and partly in 2001, 148 VLBW children were admitted to the NICU at Trondheim University Hospital, which is the referral hospital in this area (Fig. 1). Nine died and 35 entered into follow-up programmes at local hospitals. One hundred and thirteen children, of whom 69 had a birth weight between 1000 and 1500 g, had their follow-up at the university hospital. Of these 69, 62 had an uncomplicated neonatal period; 7 were found to have additional risk factors due to diverse incidents during their stay at the NICU, and were subsequently referred to the Department of Physiotherapy. Thirty-five infants had a birth weight of less than 1000 g and were referred to the hospital as part of its follow-up strategy. Ten tapes were lost during the ten-year follow-up period; 1 infant was fussing and crying and could not be examined; and 9 infants with a birth weight above 1500 g were referred to the hospital due to other risk factors (Fig. 1). A total of 40 video recordings could be analysed. Clinical details of the 40 children are presented in Tables 1 and 5.

The infants' spontaneous movements were recorded at a mean age of 14 weeks post-term. The gestational age (GA), birth weight and classification of CP at 10 years of age were collected from the children's medical records. Of the 40 infants, 31 had been born very preterm (GA <32 weeks) and VLBW; 3 children moderately preterm (GA 32–37 weeks), with a birth weight above 1500 g. One of them developed periventricular leukomalacia (PVL); the two others were twins with neonatal encephalopathy. The study population also included 6 children born at term with clinical signs of moderate to severe neonatal encephalopathy. Eighteen children included in the study had an intraventricular haemorrhage (IVH) during the neonatal period; 3 of them developed PVL as well (Tables 1 and 5). Twelve children (8 boys) had CP and were classified according to the Gross Motor Function Classification System (GMFCS) [16].

The socioeconomic status (SES) was calculated using Hollingshead's Two-Factor Index of Social Position [17], which is based on education and occupation of one parent or the mean index of both.

2.3. Video recordings

Video recordings of all 40 infants were analysed as described by Einspieler and Prechtl [6]. The infants were recorded in supine position for 5 to 10 min and needed to be fully awake without crying or fussing. Assessments of the video recordings were carried out independently – by one paediatrician and one child physiotherapist, who were blinded to the infants' clinical histories – and 6 months before the follow-up examination. In case of disagreement, a

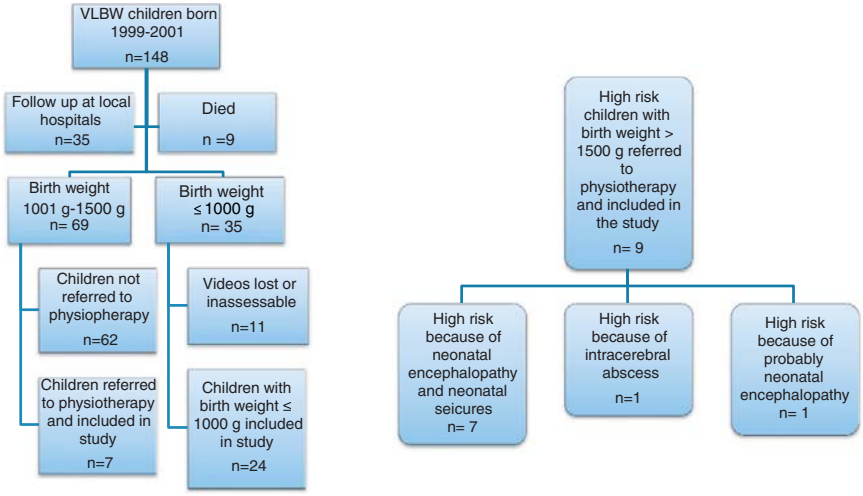

Fig. 1. Flow chart of participants in the study. VLBW = very low birth weight.

Table 1
Clinical characteristic of the whole study group, high-risk children with birth weight ≥1500 g and very-low-birth-weight (VLBW) children (birth weight <1500 g).

	Study group (n = 40)		High-risk children with birth weight ≥1500 g (n = 9)		VLBW children (n = 31)	
	Mean	(SD)	Mean	(SD)	Mean	(SD)
Gestational age (weeks)	29.3	(5.3)	38.3	(2.8)	26.8	(1.9)
Birth weight (g)	1373	(999)	3081	(672)	877	(219)
Days on mechanical ventilator	9	(13)	3	(4.1)	9	(12.1)
Socioeconomic status (SES)	3.2	(1.3)	2.7	(1.4)	3.4	(1.2)
	n	(%)	n	(%)	n	(%)
Boys	18	(45)	4	(44)	14	(45)
Septicaemia	11	(28)	3	(33)	8	(26)
Bronchopulmonary dysplasia[a]	19	(48)	1	(11)	18	(58)
Cerebral ultrasound						
- IVH, Grade 1	9	(22)	0		9	(29)
- IVH, Grade 2	3	(8)	0		3	(10)
- IVH, Grade 4	6	(15)	2	(22)	4	(13)
- Periventricular leukomalacia, grade 1	3	(8)	1	(11)	2	(6)
- Intracerebral abscess	1	(3)	1	(11)	0	
Apgar score ≤4 at 5 min	6	(15)	3	(33)	3	(10)

IVH = intraventricular haemorrhage.
SD = standard deviation.
[a] Bronchopulmonary dysplasia = need for oxygen treatment at 36 weeks postmenstrual age.

consensus was reached, based on an additional evaluation. If multiple recordings of the same infant had been performed, the one video made closest to the recommended age of 12 to 14 weeks post term was used in the assessment [7].

2.4. Assessment of the quality of fidgety movements and the concurrent motor repertoire

GMA was used to assess the video recordings with respect to the quality of fidgety movements and age-specific GMs for 14-week-old infants. Fidgety movements were classified as present when they were continuous, intermittent or sporadic; otherwise they were classified as absent [7]. The quality of the concurrent motor repertoire was determined using the parameter "movement character" of the AMR according to the scoring procedure [7]. "Movement character" describes the overall movement character observed in all movement parameters included in the AMR; smooth and fluent (4 points), abnormal, but not cramped-synchronised (2 points); and abnormal and cramped-synchronised (1 point) [7]. Classification of the movement character, also reported as the quality of concurrent movements [14] or the quality of the concurrent motor repertoire [18] as normal (4 points) or abnormal (2 points), was done based on global scores and the performance of all movements. The concurrent motor repertoire was scored as normal if it was fluent, smooth and variable, and as abnormal if it was monotonous, jerky or stiff [18,19].

The results of the assessments were categorised according to Bruggink et al. [15]: presence of FMs and normal concurrent motor repertoire; presence of FMs and abnormal concurrent motor repertoire; and absence of FMs and abnormal concurrent repertoire.

2.5. Outcome measures

At age 10, the motor skills were assessed by two physiotherapists according to the Movement Assessment Battery for Children-2 (MABC-2) [20]. The MABC-2 consists of 8 parameters grouped into 3 subcategories: manual dexterity, aiming and catching, and balance. Each child is given a component score for each subcategory and a total score for the sum of the 3 subcategories. According to the manual, scores ≤5th percentile are indicative of definite motor problems, and were classified as poor motor outcome [20]. In the study group, 28 children without CP and 2 children with mild CP completed the MABC-2. The 10 children with CP could not complete the MABC-2 due to their motor disability, and scored ≤5th percentile.

The Wechsler Intelligence Scale for Children-III (WISC-III) was performed by a trained paediatrician to assess the general cognitive ability [21]. The assessments were supervised and co-scored by a neuropsychologist, blinded to the clinical status of the children. The total, verbal and performance IQs were assessed in relation to age-appropriate standardised Scandinavian norms. A total IQ <85 was classified as a poor cognitive outcome (<−1 SD from the normative mean).

The term "pathological outcome" denotes a poor motor and/or cognitive outcome, whereas "normal clinical outcome" denotes normal motor and cognitive outcomes at 10 years of age.

2.6. Statistical analysis

Data was analysed with SPSS Statistics, version 19.0 (IBM SPSS Statistics, Chicago, IL, USA). The sensitivity, specificity and predictive values were calculated by cross tables; and 95% of confidence intervals (CI) were calculated using the Wilson method, as recommended by Altman [22].

2.7. Ethics

The study was approved by the Regional Ethics Committee (project number: 2010/121-9). All parents gave their written informed consent to participate. When invited to the follow-up study, the children got a separate letter with detailed information on the tests they would participate in, including the respective nature, purpose and approximate duration of the individual tests. As recommended by the Regional Ethics Committee, patients were referred for further investigation and follow-up treatment if the results of the follow-up test yielded a need for specialised health care.

3. Results

3.1. GMA classification at 14 weeks post-term age

Table 2 shows that 14 (34%) infants in the study group had presence of fidgety movements and a normal concurrent motor repertoire. Another 17 (43%) infants had fidgety movements and abnormal concurrent motor repertoire, whereof two infants had sporadic fidgety movements at 14 weeks post term age. Another 17 (43%) infants had fidgety movements and abnormal concurrent motor repertoire. Nine (23%) showed no fidgety movements and an abnormal concurrent motor repertoire. No infant in the study group had exaggerated fidgety movements. Table 2 also shows the proportion of children in the high-risk group with a birth weight ≥1500 g and those in the VLBW group.

At the follow-up, 10 children had spastic CP. Three of them were diagnosed with hemiplegic CP with GMFCS level I. Four children had diplegic CP, one with GMFCS level I, one with level II and two with GMFCS level IV. The remaining three had quadriplegic CP, each with GMFCS levels II, IV and V, respectively. One patient had dystonic CP with GMFCS level IV and one ataxic CP (GMFCS level I). All 12 children who later developed CP (9 with VLBW) had an abnormal concurrent motor repertoire, and 9 (75%) of them lacked fidgety movements. Two children, who later developed hemiplegic CP, had sporadic fidgety movements, while 1 child, who later developed non-spastic ataxic CP, had presence of fidgety movements; all of them classified as GMFCS level I. All 9 children with absent fidgety movements were later diagnosed with CP.

Table 2
Results of the General Movements Assessment at 14 weeks post-term in the whole study group, in high-risk children with birth weight ≥1500 g and in very-low-birth-weight (VLBW) children (birth weight <1500 g).

	Study group (n = 40)		High-risk children with birth weight ≥1500 g (n = 9)		VLBW children (n = 31)	
	n	(%)	n	(%)	n	(%)
Presence of fidgety movements and normal concurrent motor repertoire	14	(35)	2	(22)	12	(39)
Presence of fidgety movement and abnormal concurrent motor repertoire	17	(43)	4	(44)	13	(42)
Absence of fidgety movements and abnormal concurrent motor repertoire	9	(23)	3	(33)	6	(19)

3.2. Motor and cognitive outcomes at 10 years of age

Table 3 shows the numbers and proportions of children with low scores on the MABC-2 and WISC-III. Twenty children (50%) had a poor motor outcome, and 16 (40%) had a poor cognitive outcome. In total, 23 of 40 children (58%) had a pathological clinical outcome (motor and/or cognitive problems) at age 10.

Sixteen of 31 children (52%) with a birth weight <1500 g had a pathological clinical outcome at age 10. Fourteen (45%) children had a poor motor outcome, 11 (36%) had a poor cognitive outcome, and nine (29%) of them had poor motor and cognitive outcomes. Fifteen of 31 (48%) children with a birth weight <1500 g had a normal clinical outcome at age 10.

Of the 9 high-risk children with a birth weight ≥1500 g, 7 (78%) had a pathological clinical outcome at age 10. Six (67%) children had a poor motor outcome, 5 (57%) had a poor cognitive outcome, and 4 (44%) had poor motor and cognitive outcomes. Only 2 of 9 (22%) high-risk children with a birth weight ≥1500 g had normal motor and cognitive scores at age 10.

3.3. Predictive value of AMR for the later motor and cognitive outcomes

Table 4 presents the predictive values of the quality of concurrent motor repertoire in children with presence of fidgety movements at 14 weeks post-term age for the clinical outcome at 10 years of age.

In the children with presence of fidgety movements (n = 31), the sensitivity of the quality of concurrent motor repertoire was 0.91 (95% CI: 0.62–0.98) for motor problems and 0.90 (95% CI: 0.60–0.98) for cognitive problems at 10 years of age. The specificity was 0.65 (95% CI: 0.43–0.82) and 0.58 (95% CI: 0.39–0.76) for normal motor and cognitive scores, respectively. All children with balance problems (n = 7) and a verbal IQ <85 (n = 7, 4 of them with balance problems) were identified by the presence of fidgety movements, but an abnormal concurrent motor repertoire.

Pathological clinical outcome was identified by abnormal concurrent motor repertoire in 12 of 14 children with presence of fidgety movements. Furthermore, 12 of 17 children with a normal clinical outcome at 10 years of age had had fidgety movements and a normal concurrent motor repertoire at 14 weeks post-term age. Five of the 17 children with a normal clinical outcome had had presence of fidgety movements and abnormal concurrent motor repertoire. There were no significant differences in any of the IQ or MABC-2 scores between the group of 5 with an abnormal and the group of 12 with a normal concurrent motor repertoire.

Table 4 further shows that 59% (10/17) of the children with presence of fidgety movements and abnormal concurrent motor repertoire in infancy had a poor motor outcome, while 53% (9/17) had a poor cognitive outcome at age 10. In total, 71% (12/17) of the children with an abnormal concurrent motor repertoire had a pathological clinical outcome. Only 2 of 14 infants with presence of fidgety movements and a normal concurrent motor repertoire (14%) had a pathological clinical outcome later on.

The neonatal characteristics of children with normal and pathological clinical outcomes are presented in Table 5. There was no significant difference in the gestational age, birth weight, days on ventilator, or socioeconomic status between the children with a normal and those with a pathological outcome at 10 years of age. However, a higher proportion of boys (p = 0.003) and all 6 children with an IVH grade 4 (p = 0.03) and 1 child with leukomalacia were in the group with a pathological outcome, none of them in the group with a normal clinical outcome.

In the 25 VLBW children with presence of fidgety movements, the sensitivity was 1.0 (95% CI: 0.68–1.0) for a poor motor outcome, and 0.86 (95% CI: 0.49–0.97) for a poor cognitive outcome. The specificity was 0.71 (95% CI: 0.47–0.87) and 0.61 (95% CI: 0.39–0.80) for normal motor and cognitive outcomes, respectively. Also in this group, all children with balance problems (n = 5) and a verbal IQ <85 (n = 6) had presence of fidgety movements and abnormal motor repertoire. The sensitivity of an abnormal motor repertoire for a pathological outcome was 0.90 (95% CI: 0.60–0.98), and the specificity of a normal motor repertoire for a normal clinical outcome was 0.73 (95% CI: 0.48–0.89).

Table 3
Numbers and proportions of children with poor motor and/or cognitive outcome at 10 years of age in the whole study group, in high-risk children with birth weight ≥1500 g and in very-low-birth-weight (VLBW) children (birth weight <1500 g).

	Study group (n = 40)		High-risk children with birth weight ≥1500 g (n = 9)		VLBW children (n = 31)	
	n	%	n	%	n	%
Total MABC-2 score ≤5th centile	20	(50)	6	(67)	14	(45)
Manual dexterity ≤5th centile	22	(55)	6	(67)	16	(52)
Aiming and catching ≤5th centile	15	(38)	5	(56)	10	(32)
Balance ≤5th centile	15	(38)	5	(56)	10	(32)
Total IQ <85	16	(40)	5	(57)	11	(36)
Verbal IQ <85	13	(33)	3	(33)	10	(32)
Performance IQ <85	17	(43)	5	(56)	12	(39)
Pathologic clinical outcome[a]	23	(58)	7	(78)	16	(52)

MABC-2 = Movement Assessment Battery for Children-2.
WISC-III = Wechsler Intelligence Scale for Children-III.
[a] Poor motor and/or cognitive outcome.

4. Discussion

In high-risk children, we found that the pathological clinical outcome at 10 years of age was identified by presence of fidgety movements and an abnormal concurrent motor repertoire at 14 weeks post-term age. In line with the findings of Yang et al. [23], almost all children with CP had no fidgety movements, and all of them had an abnormal concurrent motor repertoire. None of the children with fidgety movements and a normal concurrent motor repertoire developed CP. The negative predictive values were high in general; in that most children (13 of 14 in our study) with fidgety movements and a normal concurrent motor repertoire went on to have normal motor and cognitive outcomes at 10 years of age.

Table 4
Predictive values of the quality of concurrent motor repertoire in high-risk children with presence of fidgety movements at 14 weeks post-term for clinical outcome at 10 years of age (n = 31).

	Sensitivity	(95% CI)	Specificity	(95% CI)	PPV	(95% CI)	NPV	(95% CI)
Total MABC-2 score <5th centile (n = 11)	0.91	(0.62–0.98)	0.65	(0.43–0.82)	0.59	(0.36–0.78)	0.93	(0.69–0.99)
Manual dexterity <5th centile (n = 13)	0.77	(0.50–0.92)	0.61	(0.39–0.80)	0.59	(0.36–0.78)	0.79	(0.52–0.92)
Aiming and catching <5th centile (n = 7)	0.86	(0.49–0.97)	0.54	(0.35–0.72)	0.35	(0.17–0.59)	0.93	(0.69–0.99)
Balance <5th centile (n = 7)	1.0	(0.65–1.0)	0.58	(0.39–0.76)	0.41	(0.22–0.64)	1.0	(0.78–1.0)
Total IQ <85 (n = 10)	0.90	(0.60–0.98)	0.58	(0.39–0.76)	0.53	(0.31–0.74)	0.93	(0.69–0.99)
Verbal IQ <85 (n = 7)	1.0	(0.65–1.0)	0.58	(0.39–0.76)	0.53	(0.31–0.74)	0.93	(0.69–0.99)
Performance IQ <85 (n = 10)	0.90	(0.60–0.98)	0.62	(0.41–0.79)	0.53	(0.31–0.74)	0.93	(0.69–0.99)
Pathologic clinical outcome[a] (n = 14)	0.86	(0.60–0.96)	0.71	(0.47–0.87)	0.71	(0.47–0.87)	0.86	(0.60–0.96)

CI = confidence interval.
IQ = intelligence quotient.
MABC-2 = Movement Assessment Battery for Children-2.
NPV = negative predictive value.
PPV = positive predictive value.
[a] Poor motor and/or cognitive outcome.

4.1. Strength and limitations of the study

The present study was hospital-based and included children born preterm, most of them with VLBW, and term-born children with signs of neonatal encephalopathy. Even though the study group was diverse, all infants had a high risk of an impaired neurological outcome later on [1]. A weakness of the study may be that it did not include all children admitted to the NICU in this period, as the GMA was not yet a routine then. Yet even if the group of infants examined was not a complete cohort, we still found it to be representative with regards to risk factors for later impaired development. The study group was relatively small, as indicated by the wide confidence intervals. The point estimates must therefore be interpreted with caution. Furthermore, as predictive values are dependent on the prevalence of the condition studied, it should be kept in mind that we had a selection of high-risk patients referred to physiotherapy, not a whole cohort of children.

Assessment of the recordings was carried out according to standard procedures [6], blindly and time-independent from the outcome assessments. Motor problems were defined as MABC scores ≤5th percentile. A less strict cut-off for motor problems would possibly have resulted in reduced sensitivity and increased specificity. Still, the 5th percentile cut-off is in accordance with the manual [20] and is widely used in the clinics to identify the need for intervention in children with motor problems. However, distinguishing children with GMFCS level 1 from children with low MABC-2 scores without CP is not easy, as CP may represent the extreme on a continuum of motor functions. Poor cognitive outcomes were defined as IQ <85, which corresponds to a score <−1 SD of the normative population [21]. Studies have shown this to be indicative of learning disabilities [24].

Table 5
Neonatal characteristics of the children with normal clinical outcome and pathological outcome at 10 years of age in the whole study group (n = 40).

	"Normal clinical outcome" at 10 years (n = 17)		"Pathological outcome" at 10 years (n = 23)		p value
	Mean	(SD)	Mean	(SD)	
Gestational age (weeks)	28.0	(3.8)	30.3	(6.1)	0.14
Birth weight (g)	1103	(566)	1571	(250)	0.11
Days on mechanical ventilator	8	(12)	8	(11)	0.94
Socioeconomic status (SES)	3.4	(1.2)	3.0	(1.3)	0.45
	n	(%)	n	(%)	
Birth weight ≤1000 g	12	(70)	13	(57)	0.36
Birth weight 1001–1500 g	3	(18)	3	(13)	1.0
Birth weight >1500 g	2	(12)	7	(30)	0.26
Boys	3	(18)	15	(65)	0.003
Septicaemia	4	(24)	7	(30)	0.73
Bronchopulmonary dysplasia[a]	7	(41)	12	(52)	0.49
Cerebral ultrasound					
- IVH, Grade 1	5	(30)	4	(18)	0.46
- IVH, Grade 2	2	(12)	1	(4)	0.57
- IVH, Grade 4	0	(0)	6	(26)	0.03
- Cystic periventricular leukomalacia, grade 1	0	(0)	3	(13)	0.25
- Intracerebral abscess	0	(0)	1	(4)	1.0
Apgar score ≤4 at 5 min	3	(18)	3	(13)	1.0

IVH = intraventricular haemorrhage.
SD = standard deviation.
[a] Bronchopulmonary dysplasia = need for oxygen treatment at 36 weeks postmenstrual age.

4.2. Prediction of later outcome

The present study confirms previous observations that the absence of fidgety movements at around 3 months post-term age is a strong predictor for later development of CP [18,25]. In our study, 75% of the children who later developed CP lacked fidgety movements. In the remaining 3 children with CP, the fidgety movements were sporadic in 2 (i.e. those with hemiplegic CP) and present in 1 (i.e. the child with non-spastic ataxic CP), yet all children with CP had an abnormal concurrent motor repertoire. A recent study by de Vries and Bos [26] found that the presence of fidgety movements accompanied by abnormal concurrent movements at the age of 3 months after term did not result in CP in a small sample of children with an extremely low birth weight. This is in accordance with our study, where most children with fidgety movements and an abnormal concurrent repertoire did not develop CP.

Our study shows that presence of fidgety movements combined with an abnormal concurrent motor repertoire may be a valuable marker for later motor problems in children without CP. This is in line with a study by Bruggink et al. [18], who showed that the risk of minor neurologic dysfunction (MND), at 7 to 11 years of age was

increased by 30% in children with fidgety movements and an abnormal concurrent motor repertoire in infancy. Groen et al. [11] found that the quality of general movements was related to fine motor and coordination problems in high- and low-risk children without CP at 9 to 12 years of age. In our study, an abnormal motor repertoire seemed to be a better predictor for the impairment of balance than for the other two subcategories of the MABC-2. This discrepancy may be due to different assessment methods, although one could argue that balance is a prerequisite for all kinds of coordination.

Bruggink et al. [15] have also examined the predictive value of the GMA with respect to the cognitive outcome at school age, and have reported a sensitivity of 67% (95% CI: 43%–91%) and a specificity of 71% (95% CI: 23%–63%) of abnormal general movements at 8 weeks after term as a predictor for a later IQ <85. Our results suggest that the sensitivity increases when the children are assessed later in the "fidgety age".

In a study by Butcher et al. [14], spontaneous movement quality was assessed at 11 to 16 weeks post term in 65 infants born at ≤33 weeks of gestation. Intelligence, behaviour and the neurological status were assessed at 7 to 11 years of age. The findings suggested that early spontaneous movement quality has a prognostic value for the neurological and intellectual outcomes and, to a lesser extent, for attentional outcome. Unfortunately, neither Bruggink et al. [15] nor Butcher et al. [14] reported on the association between the cognitive and motor outcomes at school age. In our study, the cognitive and motor outcomes were highly correlated; in fact, only 2 children had an isolated poor cognitive outcome. Thus, the relationship between early motor repertoire and cognition is most probably associated with the combination of motor and cognitive problems.

4.3. Relationship between abnormal movements and the later outcome

The motor and cognitive problems identified at 10 years of age in the present study may be directly or indirectly related to the quality of motor behaviour at 3 to 4 months. A monotonous, stiff or jerky movement character could result in the child's reduced ability to interact with the environment and may affect the development of appropriate motor skills. However, it seems less likely that the cognitive impairments are a direct consequence of the poor movement quality. Rather, the quality of spontaneous movements could reflect global brain functioning. Consequently, an abnormal motor repertoire in early postnatal life might reflect an impairment not only of motor areas in the brain, but also of normal global brain development caused by pre- and/or perinatal brain injury, and might thus be an early clinical marker of later motor and cognitive deficits.

It is interesting in this respect that the quality of general movements in infancy has a good sensitivity and specificity for the motor and cognitive outcomes in an identified risk group of children, particularly in children with VLBW.

Our hospital's strategy for neurologically high-risk infants is to offer a non-selective follow-up and intervention programme. Using GMA and parts of AMR in infants at risk for neurological impairments could be a valuable screening tool to better identify infants in need of a more intensive and specific stimulation of their motor and cognitive development. Even more importantly, though, the GMA and parts of AMR provide an opportunity to identify children with a normal early motor repertoire who will most likely develop normally with respect to motor and cognitive skills, and to thereby reassure their parents. However, more comprehensive studies are needed to confirm these suggestions.

5. Conclusion

In conclusion, we found that the presence of fidgety movements accompanied by an abnormal motor repertoire in infancy could be a valuable early clinical marker for an increased risk of impaired motor and cognitive outcomes in neurologically high-risk children – particularly in VLBW children – who do not develop CP. Furthermore, most children with a normal clinical outcome were identified by a normal concurrent motor repertoire in infancy. This could help to start early intervention programmes and reassure parents whose child develops normally.

Conflict of interest

No disclosures.

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Paper II

Follow-up at age 10 years in ELBW children - clinical outcome, brain morphology and results from motor assessments in infancy

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Abstract:

Background: Extremely-low-birth-weight (ELBW) children without severe brain injury or CP are at high risk of developing deficits within cognition, attention, behavior and motor function. Assessing the quality of an infant's spontaneous motor-repertoire included in Prechtl's General-Movement-Assessment (GMA) has been shown to relate to later motor and cognitive functioning in preterm children without CP.

Aims: To investigate clinical outcome and cerebral MRI morphometry at 10 years in ELBW children without CP compared to healthy controls and to examine any relationship with the quality of infant-motor-repertoire included in the GMA.

Study design: A cohort-study-design.

Subjects: 31 ELBW children (mean birth-weight: 773g, SD 146, mean gestational age 26.1weeks, SD 1.8) and 33 term-born, age-matched controls.

Outcome measures: GMA was performed in ELBW children at 3 months corrected age. At 10 years the children underwent comprehensive motor, cognitive, behavioral assessments and cerebral MRI.

Results: The non-CP ELBW children had similar full-IQ but poorer working memory, inferior motor skills, more attentional and behavioral problems compared to controls. On cerebral MRI reduced volumes of globus pallidus, cerebellar white matter and posterior corpus callosum were found. Cortical surface-area was reduced in temporal, parietal and anterior-medial-frontal areas. Inferior test-results and reduced brain volumes were mainly found in ELBW children with fidgety movements combined with abnormal motor-repertoire in infancy.

Conclusion: Non-CP ELBW children have inferior clinical functions, reduced brain volumes and cortical surface-area compared with term-born controls at 10 years. ELBW children with abnormal infant motor-repertoire seem to be at increased risk of later clinical deficits and brain pathology.

Key Words: Preterm, brain pathology, cognition, neurodevelopment, General Movement Assessment

Abbreviations:

ELBW-extremely low birth weight, MRI-magnetic resonance imaging, CP-cerebral palsy, GMA-general movement assessment, WISC-Wechsler Intelligence Scale for Children, IQ-intelligence quotient, MABC-Movement assessment battery for children, ADHD-attention-deficit/hyperactivity disorders, BRIEF-Behavioral Rating Inventory of Executive Function, SGA-small-for-gestational-age

Introduction

The survival rates of children born with extremely-low-birth-weight (ELBW, BW<1000g) have been increasing during the last decades (1). However, the number of ELBW children who develop disabilities like cerebral palsy (CP), cognitive impairments, psychiatric and behavioral problems is still high compared with term-born peers (2). Increased incidence of perinatal brain injury is the most common cause of the neurologic morbidity reported in preterm born children (3). The brain injuries include focal periventricular white matter necrosis and diffuse white matter injury with widespread gliosis and axonal damage that may have secondary effects on development of the immature cerebral cortex, thalamus, cerebellum and basal ganglia (3, 4). A qualitative General Movement Assessment (GMA) in infants based on the observation of spontaneous movements during the early post-term period is a sensitive and non-intrusive method to predict motor disorders like CP in later childhood (5). A recent study suggested that the quality of general movements might be an early predictor also for cognitive function in very preterm born children (6) however, that study did not include motor or behavioral outcomes. We previously reported that the assessment of infant motor repertoire in a group of high risk neonates might be an early clinical marker for a composite of later motor dysfunction and cognitive impairments in non-CP children (7). As an extension of that study we now aimed to examine the clinical outcome and brain pathology evaluated with MRI morphometry at age 10 years in a cohort of ELBW children without CP compared with healthy term-born controls. In addition, we aimed to study whether early infant motor repertoire in the ELBW children that did not develop CP was associated with clinical outcome and cerebral MRI findings at age 10. We hypothesized that non-CP ELBW children would have inferior clinical test results and more brain pathology than controls and that pathological outcome would be related to abnormal early motor repertoire.

Methods

This geographically based follow-study included three year-cohorts of ELBW children born at the Trondheim University Hospital in Norway during the years 1999-2001. Inclusion criteria were children with birth-weight below 1000g who participated in the regular follow-up at the Trondheim University Hospital. Exclusion criteria were diagnosed congenital syndromes. A total of 74 ELBW

children were born and admitted to the Neonatal Intensive Care Unit (NICU) in Trondheim during the three year period. Nine children (12%) died during the neonatal period and 30 children had follow-up at other hospitals; hence 35 ELBW children were asked to participate in the study. Parents of 31 (88.6%) children gave their written consent. At follow-up the ELBW children were assessed at a mean age of 10 years and 2 months (SD 0.8). A term-born, age-matched control group of 33 healthy children were recruited from four different schools within the Trondheim area. Mean age at examination for controls was 10 years and 6 months (SD 0.7).

General movement assessment (GMA)

At 14 weeks (SD 1.6) post-term age, all the ELBW children were videotaped at the NICU as part of a standard follow-up program for general movement assessment (GMA) including an "Assessment of Motor Repertoire" (5). Assessment of Motor Repertoire is part of the GMA and provides a motor optimality score consisting of the parameters: fidgety movements, repertoire of co-existent movements, quality of other movements, quality of postural patterns and quality of infant motor repertoire. A certified child physiotherapist and a pediatrician reanalyzed all the video recordings at the 10-year follow-up, independently and blinded to neonatal medical history, earlier assessments and later outcome of the children. In case of disagreement of scoring (in two videos), a second evaluation was performed by each researcher independently and consensus was reached. In this study we focused on fidgety and motor repertoire. Fidgety movements seen as small, continuous movements of moderate speed and variable acceleration in the whole body in any direction from the age of 6 weeks to 20 weeks post-term, were classified as normal "F+" when present continuously. When the fidgety movements were completely absent, they were classified as "F-", and when they were sporadic or not continuously present they were classified as "F+/-". For the Assessment of Motor Repertoire a classification of concurrent motor repertoire based on the categories of Bruggink et al (8) was used. Concurrent motor repertoire was defined as "normal" when the movements were fluent, variable and smooth, and "abnormal" when the movements were monotonous, jerky or stiff. The videotapes of two infants were of too poor quality to be analyzed, and in three children the videotapes were lost to follow-up; hence videotapes from 26 of 31 ELBW infants (84%) were analyzed with GMA.

Clinical assessments

The Wechsler Intelligence Scale for Children, version-III (WISC-III) (9) was administered to all children and full intelligence quotient (IQ) and four IQ indices were calculated. The neuropsychological assessment included the Stroop Color Word (10) to assess the ability to respond selectively to competing stimulus and selective attention. The Tower of London test (11) was included to assess planning and problem-solving ability and The Trail-Making Test (10) for assessing attention and focused attention. The Beery-Buktenica Developmental Test of Visual-Motor Integration (Beery-VMI) (12) was used to assess visual, perceptual and constructional abilities. The Movement-Assessment-Battery for Children, second-edition (MABC-2) (13) was administered to assess motor skills.

Questionnaires

The ADHD rating scale (14) questionnaire was completed by all parents to assess hyperactivity and inattention. Executive function was evaluated by the parental reported Behavioral Rating Inventory of Executive Function (BRIEF) (15).

Cerebral MRI

Cerebral MRI was acquired on a 1.5 Tesla Siemens Avanto (Siemens, Erlangen, Germany) with Quantum gradients 40mT/m and a 12 channel head coil. A structural T1-weighted magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence was acquired. For the image analysis of brain morphology, we used the freely available FreeSurfer software version 5.1 (http://surfer.nmr.mgh.harvard.edu/). Further details about MRI acquisition and analysis can be found in Supplemental materials. MRI was not performed in four ELBW children without CP due to anxiety and in one child the performed MRI scan had to be excluded due to movement artifacts. Hence MRI was successfully performed in 21 ELBW children without CP. In the control group, one child had braces and two children did not consent to MRI scanning, hence MRI was successfully completed in 30 control children.

Socioeconomic status

Socioeconomic status (SES) was calculated according to Hollingshead's two-factor index of social position based on mean educational levels and current employment of both or single parents (16).

Statistics

IBM SPSS Statistics, version 21 (Armonk, NY) was used for the statistical analyses. Student t-test, Mann-Whitney U-test and Chi-squared test were used for group comparisons. A General Linear Model (GLM) was performed to compare group differences in brain volumes, cortical thickness and brain surface area with SES, gender and age at MRI as covariates. The same model was used to compare group differences in clinical test results between the two groups. We used the partial correlation analysis controlled for SES, gender and age at MRI to calculate the linear correlation between different test results and brain regions of interest based on MRI results. Two-tailed p value ≤ 0.05 was considered to be statistically significant, except when looking at group comparisons of brain volumes where a p-value ≤ 0.01 was used as level of significance to adjust for multiple comparisons.

Ethics

The Regional Committee of Medical Research Ethics approved the study protocol (REK number: 2010/121-9) and written informed consent was obtained from the parents.

Results

Clinical characteristics of the whole study population (including the CP children) are described in **TABLE 1**. At 10 years follow-up eight ELBW children (26%) were diagnosed with cerebral palsy (CP). Four of them had a spastic unilateral, three had diplegic and one child had quadriplegic CP. Four of the eight ELBW children with CP had intraventricular hemorrhage grade 4 or cystic periventricular leukomalacia diagnosed on neonatal cerebral ultrasonography. The children with CP were assessed clinically and with MRI, but not included in this paper since the focus was on non-CP children. Since socioeconomic status was lower for the non-CP ELBW children than controls all analyzes were corrected for SES in addition to gender and age.

GMA results and outcome within the whole ELBW group

The general movement assessment analyzed at 10 years follow-up revealed that twenty out of twenty-six ELBW children (77%) had continuous fidgety movements F+. None of these children developed CP. Four children had absence of fidgety movements, F- and all of them developed CP. Two children were assessed F+/- and both had a mild spastic unilateral CP at follow-up. Focusing on the 20 non-CP children, nine children had normal, while eleven children had abnormal concurrent early motor repertoire. All the children with CP had abnormal concurrent motor repertoire. Of the five children with missing GMA data, two children had CP.

Clinical outcomes in the non-CP ELBW children compared with controls

The 23 ELBW children without CP did not score significantly lower than controls on full IQ or any of the IQ indices except for the working memory index (**TABLE 2)**. However, their parents reported more inattention and hyperactivity on the ADHD rating scale and more behavioral problems on BRIEF compared to parents of controls. On the MABC-2 the ELBW children scored significantly poorer on manual dexterity and total motor skills compared to controls (**TABLE 2**). When looking at neuropsychological test-results no significant group differences were reported (**TABLE 3**).

MRI results in the non-CP ELBW children compared with controls

The non-CP ELBW children had significantly smaller volumes of thalamus, putamen, globus pallidus, and cerebellar grey and white matter as well as posterior part of corpus callosum compared to controls (**TABLE 4**). Total cortical surface area was not significantly reduced in the ELBW group compared with controls (ELBW: 178.00 cm^2 (95%CI: 170.43, 185.60) versus controls: 185.42 cm^2 (95%CI: 179.29, 191.54) p=0.17). However, the surface area was regionally reduced in temporal, parietal and right anterior-medial frontal areas in the ELBW group compared with controls (**FIGURE 1**). Mean cortical thickness was similar in the two groups (ELBW; 2.82 mm (95%CI: 2.77, 2.87) versus controls 2.81 mm (95%CI: 2.76, 2.85), p=0.74, except that the ELBW children had thicker mean occipital cortex compared to controls; 2.24 mm (95%CI: 2.19, 2.30) versus 2.13 mm (95% CI: 2.08, 2.17), p=0.003.

Structure-function relationships in the non-CP ELBW group

Associations between the clinical outcome variables and brain volumes in the ELBW children without CP are shown in **TABLE 5.** Only brain volumes that correlated significantly (p-value <0.05) with one or more of the clinical outcome measures are included in the table. We found positive correlations between full IQ and volumes of putamen and globus pallidus. The working memory index correlated with volumes of putamen and cerebellar white matter. Regarding motor skills we found a correlation between better MABC-2 total score and total brain volume, volumes of thalamus, caudate nucleus, putamen, globus pallidus and cerebellar white matter. Negative correlations were found between ADHD total score and volumes of putamen, cerebellar white matter and corpus callosum, and between BRIEF main indices and volumes of putamen, cerebellar white matter and corpus callosum.

Relationship between clinical outcomes and MRI findings at age 10 and motor repertoire in infancy

When comparing the non-CP ELBW children with normal versus abnormal motor repertoire in early infancy, no clinical characteristics or neonatal risk factors differed between the groups, except for more singletons and more small for gestational age children (birth weight $\leq 10^{th}$ percentile) in the group with abnormal early motor repertoire (Supplemental materials **TABLE S1**). The children with abnormal motor repertoire in infancy had lower scores on the working memory and processing speed indices, but not on full IQ at age 10 (**TABLE 6)**. In addition, they had poorer balance and total motor skills on MABC-2 and their parents reported more hyperactivity, inattention and behavioral problems (**TABLE 6**). Neuropsychological test results did not differ significantly between the two groups (Supplemental materials **TABLE S2**). On MRI, children with abnormal motor repertoire in general had smaller volumes of all brain structures than those with normal motor repertoire. However, when adjusting for multiple comparisons ($p \leq 0.01$) only cerebral white matter volume was significantly reduced (**TABLE 7**). While cortical thickness did not differ, smaller total cortical surface area was found in the children with abnormal early motor repertoire; 186.54cm^2 (95%CI: 176.17, 196.90) versus 168.02cm^2 (95%CI: 159.20, 176.83) for those with normal early motor repertoire (p=0.012).

Discussion

Compared with controls, the ELBW children without CP in this study had smaller brain volumes and regional reduction in cortical surface area, inferior working memory and motor skills and more parent-reported problems with attention, hyperactivity and executive function at 10 years. In addition, to our knowledge this is the first study to investigate the relationship between the quality of infant motor repertoire implemented in the general movement assessment and a morphometric MRI analysis at 10 years in ELBW children without CP. We found that normal fidgety combined with abnormal early motor repertoire on GMA was associated with poorer clinical outcome and more MRI pathology at 10 years when compared to those with normal early motor repertoire.

Strength and limitations of study

Strength of this study was the comprehensive assessments of cognition, motor function, attention and executive function that included both standardized testing and parents' reports and the quantitative MRI. We were able to include a nearly complete geographically based 3-year cohort of ELBW children which makes selection bias unlikely. Ten years ago all the ELBW children included in the study were videotaped at 14 weeks post-term age, with 84% of the recordings accessible for evaluation at 10 years follow-up. Clinical characteristics and test results at follow-up did not differ for those with and without early GMA. Socio-economic status was a bit lower in the preterm group than in controls; however, this was corrected for in the statistical analyses. A weakness of the study was the rather small total number of participating children, especially when subgroup analysis were performed and due to this, only large group differences and strong associations could reach significant levels and negative findings should be interpreted with caution. With regard of the subgroup analysis including the early GMA results, our study must be considered a pilot study and larger studies must confirm or reject our findings before general conclusions or recommendations regarding the clinical value of early GMA can be made.

Outcome in non-CP ELBW children versus controls

The main aim of this study was to examine the clinical and MRI findings at 10 years in ELBW children without CP compared with age-matched term-born controls. Our results are mainly in line with previous reports with regard to clinics and brain morphology. When focusing on the MRI findings, regional reduction of cortical surface area has to our knowledge not been reported before in non-CP ELBW children at school age (**FIGURE 1**). The reduced cortical surface, especially in the temporal and parietal lobes may indicate aberrant cortical development (3). This is consistent with earlier reports of ELBW neonates at term equivalent age (17) and has recently also been reported in very low birth weight (VLBW) young adults (18). In the latter study the areas with surface area reduction compared with controls were more extensive than in the present study, which may indicate less cortical pathology in ELBW children born in the 2000s versus VLBW children born in the late 1980ies. In our study the non-CP ELBW children did not differ from controls in mean cortical thickness except for a significantly thicker occipital cortex. We speculate that this might be explained by a delayed pruning of the occipital cortex in these pre-pubertal children or delayed intra-cortical myelination. A recent study in a cohort of preterm preschoolers that showed a trend of thicker cortex and decreased surface area (19) supports this speculation.

With regard to clinical outcome the non-CP ELBW children in our study had similar full IQ and scored similar to the controls on the neuropsychological tests assessing attention/executive function, which is very encouraging. However, parents of the ELBW children still reported more inattention, more hyperactivity and more executive function problems on ADHD-Rating scale and the BRIEF, respectively. The discrepancy between neuropsychological test results and parents' reports could imply that these measures assess different aspects of attention and executive functions (20). Studies have shown that neuropsychological tests do not necessarily tap executive problems in everyday life activities and that these are better uncovered by behavioral observations and parental reports (21). Possible structure-function relationships seemed to involve brain volumes that were significantly reduced in the ELBW group compared with controls, including deep nuclei like thalamus (motor function), putamen (motor, cognition and behavior), globus pallidus (motor and cognition), cerebellar white matter (motor, cognition and behavior) and corpus callosum (cognition and behavior) (**TABLE**

5). Cognitive and motor impairments in preterm born children are frequently reported and correlations have been found with reduced grey matter volumes (4), reduced cortical thickness (22) or thinning of the corpus callosum (23). Nosarti et al (23) reported that thinning of posterior and anterior corpus callosum was associated with learning difficulties in boys. Reduced volumes of corpus callosum are probably due to perinatal loss of commissural fibers that could influence the efficacy of cognitive networks connecting both hemispheres. In our study reduced volumes of putamen, cerebellar white matter and corpus callosum were correlated with higher ADHD scores. Nosarti et al demonstrated an association between smaller left caudate volumes and higher hyperactivity scores in preterm adolescents (24) which together with our findings are in line with a theory claiming that basal ganglia are involved in the pathogenesis of ADHD (25). To our knowledge no study has correlated parental BRIEF scores to cerebral MRI findings in preterm born children. We found a correlation between increasing scores on the BRIEF indices reflecting more executive function problems and reductions of the same volumes that correlated with the ADHD scores including cerebellar white matter and corpus callosum. This is to some extend in accordance with a diffusion tensor imaging study that shows that executive function/attention skills rely on white matter tract integrity within subcortical and cortical regions (26). It may also emphasize a role of cerebellar connectivity in higher order cognitive processes (27).

Early general movement assessment and later outcome

Another aim of this study was to analyze whether the quality of the early motor repertoire assessed with GMA was associated with clinical outcome measures and MRI findings at 10 years in the ELBW children that did not develop CP. Few studies have investigated the association between early motor assessment and composite outcome in school aged preterm children. A recent study suggested that the quality of general movements is an early predictor for cognition (6); however, that study did not include motor or behavioral outcomes. We previously reported that in a group of neurologically high-risk children with presence of fidgety movements, poor outcome at 10 years was identified by abnormal concurrent motor repertoire in 86% of the children (7). In the present study, non-CP ELBW children with fidgety movements and abnormal motor repertoire showed signs of more composite

clinical deficits and more extensive brain pathology at age 10 compared to those with normal early motor repertoire. When comparing the two groups for any differences in clinical characteristics and perinatal risk factors the only significant group difference that we could identify was more singleton small-for-gestational-age ELBW children within the abnormal motor repertoire group. We speculate that the tendency of smaller brain volumes and reduced cortical surface area in this group and the reduced functioning at 10 years may therefore be a consequence of fetal growth restriction with compromised normal brain growth. This is in line with studies indicating that children born small-for-gestational-age have increased risk of developmental deficits (28) and reduced brain volumes and cortical surface area (29).

Clinical implications

Compared to term born peers ELBW children without CP and with full IQ within normal range at 10 years, have signs of deviant brain development, reduced fine motor skills, deficits in working memory and more reported problems with attention and executive function, which may have negative influence on scholastic performance and later academic achievement in these children. Based on our subgroup analysis we speculate that an easy to perform, non-intrusive observational method as the GMA including an assessment of the quality of the early motor repertoire might contribute as an early biomarker to identify preterm children at increased risk of neuroimpairments. By successfully identifying these children, early intervention programs can be initiated and the risk of later academic or social difficulties may be reduced. However, larger studies must be performed to confirm our findings.

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TABLE 1: Clinical characteristics of the study population.

	ELBW n=31 Mean(SD)	**Non-CP ELBW n=23 Mean(SD)**	**CP-ELBW n=8 Mean(SD)**	**Controls n=33 Mean(SD)**
Gestational age, weeks	26.1 (1.8)**	26.3 (1.9)##	25.6 (1.7)	40.1 (0.9)
Birth weight, grams	773 (146)**	797 (145)##	706 (137)	3609 (329)
Male gender, n (%)	15 (48)	8 (35)	7 (88)	16 (49)
Socioeconomic status	3.3 (1.3)*	3.3 (1.3)#	3.4 (1.2)	3.9 (1.0)
Singletons, n (%)	16 (52)**	12 (52.2)##	4 (50)	33 (100)
Twin birth, n (%)	12 (39)**	8 (34.8)##	4 (50)	0
Triplet birth, n (%)	3 (9)**	3 (13.0)##	0	0
APGAR 1 minute	5 (2.4)**	5 (2,6)##	6 (1.6)	9 (1.0)
APGAR 5 minutes	7 (2.2)**	7 (2.3)##	7 (1.9)	10 (0.6)
Antenatal steroids, n (%)	18 (58)	13 (56.5)	5 (63)	0
Postnatal steroids, n (%)	12 (39)	8 (35)	5 (50)	0
Mechanical ventilation, days	13.4 (18.3)	13.2 (19.7)	14.4 (14.4)	0
Intraventricular hemorrhage				
• Grade 1, n (%)	8 (26)	7 (30)	1 (13)	0
• Grade 2, n (%)	4 (12)	4 (17)	0	0
• Grade 4, n (%)	3 (10)	0	3 (38)	0
Periventricular leukomalacia, cystic n (%)	1 (3)	0	1 (13)	0
Septicemia, n (%)	11 (36)	7 (30.4	5 (50)	0
Patent Ductus Arteriosus , n(%)	9 (29)	7 (30)	2 (25)	0
PDA Surgery, n (%)	7 (78)	6 (86)	1 (50)	0
BPD/O_2 at GA 36 weeks, n (%)	19 (61)	13 (57)	6 (75)	0

Mann-Whitney U-test, Chi-square-test.

**p≤.05, **p ≤ .001 ELBW vs controls. #p ≤.05, ##p ≤ .001 non-CP ELBW vs controls*

Abbreviations: ELBW: extremely low birth weight; SD: standard deviation; CP: Cerebral palsy; PDA: Patent Ductus Arteriosus; BPD: Bronchopulmonary dysplasia

TABLE 2: Clinical test results in ELBW children without CP compared with controls at 10 years

	ELBW n=23 mean(95%CI)	**Controls n=33 mean(95%CI)**	**p value**
WISC-III			
• Full IQ	98 (90,106)	105 (98,112)	0.208
• Verbal comprehension index	102 (95,109)	106 (101,112)	0.374
• Perceptual organization index	98 (90,105)	104 (98,110)	0.227
• Working memory index	91 (84,98)	101 (96,107)	**0.038**
• Processing speed index	97 (88,106)	103 (96,111)	0.301
ADHD rating scale:			
• Inattention	8.0 (5.5,10.5)	3.0 (0.9,5.0)	**0.005**
• Hyperactivity	5.0 (3.3,6.7)	1.9 (0.5,3.3)	**0.011**
• Total scale	13.0 (9.1,16.9)	4.9 (1.7,8.1)	**0.004**
BRIEF:			
• Behavioral Regulation	49.0 (44.9,53.2)	41.2 (37.8,44.5)	**0.006**
• Metacognition Index	49.3 (45.1,53.5)	43.4 (40.0,46.7)	**0.033**
• Global Executive Composite	49.1 (44.9,53.3)	42.1 (38.7,45.5)	**0.013**
MABC-2:			
• Manual dexterity	20.2 (16.7,23.8)	27,9 (25.0,30.8)	**0.003**
• Aiming and catching	17.3 (14.9,19.7)	18.4 (16.5,20.3)	0.497
• Balance	26.1 (22.3,29.9)	31.2 (28.2,34.3)	0.056
• Total score	63.8 (55.8,71.8)	77.1 (70.6,83.6)	**0.019**

A General linear model was used to compare groups with SES, gender and age at testing as covariates. For the BRIEF inventory gender and SES were used as covariates. Significant p-values ($p \leq 0.05$) are shown in bold font.

Abbreviations; CI: confidence interval, ELBW: Extremely low birth weight; CP: Cerebral palsy; IQ: Intelligence quotient; WISC-III: The Wechsler Intelligence Scale for Children III; BRIEF: Behavioral Rating Inventory of Executive Function; MABC-2: Movement Assessment Battery for Children

TABLE 3: Neuropsychological test results in ELBW children without CP compared to controls

	ELBW n=23 mean(95%CI)	Controls n=33 mean(95%CI)	P value
Stroop color word:			
• Naming colors	45.0 (40.5,49.5)	39.5 (33.1,45.9)	0.140
• Reading colors	30.7 (27.5,33.9)	29.0 (22.6,35.5)	0.761
• Inhibition	87.7 (78.5,97.0)	78.7 (68.8,88.5)	0.205
• Inhibition and switching	84.2 (75.1,93.4)	86.1 (74.3,98.0)	0.559
• Total errors	13.8 (9.4,18.2)	13.5 (10.1,17.0)	0.943
The Trail Making Test:			
• Visual scanning	28.1 (24.8,31.4)	26.4 (23.3,29.6)	0.592
• Number line	51.3 (42.5,60.0)	45.0 (30.7,59.4)	0.531
• Letter line	50.1 (38.8,61.4)	47.4 (33.1,61.6)	0.860
• Number and letter line	126.4 (107.2,145.6)	108.2 (90.6,125.8)	0.191
• Motor speed	32.3 (27.0,37.5)	28.0 (22.2,33.9)	0.349
• Total errors	3.1 (2.2,4.1)	1.8 (0.5,3.0)	0.071
Tower:			
• Time to first move	24.4 (15.9,32.9)	27.6 (19.5,35.8)	0.450
• Rule breaking	2.2 (1.4,3.0)	1.3 (0.6,2.0)	0.154
• Total completion time	552.9 (481.4,624.3)	471.3 (409.1,533.5)	0.100
• Total achievement	15.5 (13.8,17.1)	16.8 (15.2,18.3)	0.373
Beery-VMI:			
• Visual perception	97.8 (92.3,103.4)	103.3 (97.9,108.8)	0.158
• Motor coordination	78.1 (71.5,84.6)	84.6 (79.0,90.2)	0.148
• Full form	87.8 (83.1,92.6)	87.1 (82.4,91.7)	0.758

A General linear model was used to compare groups with SES, gender and age at testing as covariates.

Abbreviations: CI: Confidence Interval; ELBW: Extremely Low Birth Weight; CP: Cerebral Palsy; VMI: Visual Motor Integration

All scores are raw scores, except for the VMI that are standard scores.

TABLE 4: Absolute brain volumes in ELBW children without CP compared to controls at 10 years

Volumes (cm^3)	ELBW n= 21 mean (95%CI)	Controls n=30 mean (95%CI)	p value
Total brain volume	1487.95 (1428.81,1547.09)	1572.81 (1524.95,1620.65)	0.045
Cerebral Gray Matter	743.69 (712.51,774.89)	787.15 (761.92,812.39)	0.051
Cerebral White matter	446.81 (424.87,468.76)	472.74 (454.98,490.50)	0.096
Cerebral Cortex	564.31 (539.66,589.00)	585.44 (565.50,605.39)	0.223
Hippocampus	7.95 (7.62,8.29)	8.39 (8.10,8.67)	0.076
Amygdala	2.96 (2.79,3.13)	3.07 (2.93,3.21)	0.367
Thalamus	13.66 (12.99,14.32)	14.92 (14.38,15.45)	**0.009**
Lateral ventricle	16.54 (12.52,20.57)	12.28 (9.02,15.53)	0.134
Caudate nucleus	7.57 (7.06,8.07)	8.40 (7.99,8.81)	0.022
Putamen	11.38 (10.85,11.90)	12.36 (11.93,12.78)	**0.010**
Globus Pallidus	3.13 (2.96,3.30)	3.65 (3.52,3.79)	**0.000**
Cerebellar White Matter	22.64 (21.0,24.29)	26.90 (25.60,28.20)	**0.000**
Cerebellar Cortex	108.05 (100.41,115.69)	121.92 (116.10,127.74)	**0.010**
Corpus Callosum			
• **Anterior**	1.14 (1.04,1.23)	1.25 (1.18,1.33)	0.084
• **Central**	0.33 (0.29,0.37)	0.40 (0.36,0.43)	0.019
• **Posterior**	0.99 (0.89,1.08)	1.21 (1.13,1.28)	**0.002**

A General linear model was used to compare groups with SES, gender and age at MRI as covariates.

Significant p-values ($p \leq 0.01$) are shown in bold font.

Abbreviations: CI: Confidence Interval; ELBW: Extremely low birth weight; CP: Cerebral palsy

TABLE 5: Partial correlations between clinical findings and absolute brain volumes in ELBW children without CP at 10 years (n=21).

Absolute brain volumes	Full IQ	WMI	MABC 2 total score	ADHD total score	BRI	MCI	GEC
Total brain volume	n.s	n.s	.562*	n.s	n.s	n.s	n.s
Thalamus	n.s	n.s	.504*	n.s	n.s	n.s	n.s
Caudate nucleus	n.s	n.s	.500*	n.s	n.s	n.s	n.s
Putamen	.751**	.604**	.688**	-.696**	-.645**	-.645**	-.695**
Globus pallidus	.594*	n.s	.540*	n.s	n.s	n.s	n.s
Cerebellar white matter	n.s	.502*	.593*	-531*	-.512*	n.s	-.539*
Central corpus callosum	n.s	n.s	n.s	-.563*	-.529*	n.s	n.s
Posterior corpus callosum	n.s	n.s	n.s	-.484*	n.s	n.s	n.s

$*p \leq .05$, $**p \leq .01$.

Partial correlations controlled for SES, gender and age at MRI.

Abbreviations: ELBW: extremely low birth weight; IQ: Intelligence Quotient; VCI: Verbal comprehension index; POI: Perceptual organization index; WMI: Working memory index; PSI: Processing speed index; MFNA: Motor Function Neurological Assessment; MABC-2: Movement Assessment Battery for Children-2; BRI: Behavioral Regulation Index; MCI: Meta Cognition Index; GEI: Global Executive Index

TABLE 6: Clinical test result at 10 years in ELBW children without CP with normal versus abnormal motor repertoire in early infancy.

	Normal motor repertoire (n=9) mean (95%CI)	Abnormal motor repertoire (n=11) mean (95%CI)	p value
WISC-III:			
• Full IQ	107 (95,119)	94 (83,105)	0.105
• Verbal comprehension index	109 (98,119)	97 (88,107)	0.113
• Perceptual organization index	104 (92,116)	97 (87,108)	0.378
• Working memory index	103 (91,114)	84 (74,95)	**0.024**
• Processing speed index	112 (100,125)	89 (77,100)	**0.012**
ADHD rating scale:			
• Inattention	2.0 (-2.3,6.3)	10.7 (6.8,14.6)	**0.007**
• Hyperactivity	2.0 (-1.1,5.0)	6.6 (3.8,9.3)	**0.034**
• Total score	4.0 (-2.9,10.9)	17.3 (11.1,23.5)	**0.009**
BRIEF:			
• Behavioral Regulation index	42.3 (33.3,51.2)	54.1 (46.0,62.2)	0.058
• Metacognition Index	43.0 (35.8,50.2)	56.3 (49.8,62.7)	**0.011**
• Global Executive Composite	42.4 (34.8,50.0)	55.7 (48.8,62.6)	**0.016**
MABC-2:			
• Manual dexterity	24.6 (18.5,30.7)	19.7 (14.2,25.2)	0.231
• Aiming and catching	19.5 (16.0,23.0)	16.8 (13.7,20.0)	0.253
• Balance	34.0 (28.4,39.7)	22.2 (17.1,27.3)	**0.005**
• Total score	78.1 (65.0,91.3)	58.6 (46.8,70.5)	**0.035**

A General linear model was used to compare groups with SES, gender and age at testing as covariates. Significant p-values ($p \leq 0.05$) are shown in bold font

Abbreviations: CI: Confidence Interval; ELBW: Extremely low birth weight; CP: Cerebral palsy; WISC-III: The Wechsler Intelligence Scale for Children III; IQ: Intelligence quotient; BRIEF: Behavioral Rating Inventory of Executive Function; MABC-2: Movement Assessment Battery for Children-2

TABLE 7: Absolute brain volumes at 10 years in ELBW children without CP with normal versus abnormal concurrent motor repertoire in early infancy.

Brain volumes (cm^3)	Normal motor repertoire n=9 mean(95%CI)	Abnormal motor repertoire n=11 mean(95%CI)	P value
Total brain volume	1548.74 (1472.22,1625.26)	1424.21 (1359.17,1489.26)	0.020
Cerebral Gray Matter	771.61 (730.93,812.30)	708.60 (674.01,743.19)	0.025
Cerebral White Matter	478.07 (447.98,508.16)	417.69 (392.11,443.27)	**0.006**
Cerebral Cortex	581.48 (547.59,615.37)	538.77 (510.00,567.57)	0.061
Hippocampus	8.14 (7.64,8.64)	7.54 (7.09,8.00)	0.078
Amygdala	3.14 (2.84,3.44)	2.78 (2.53,3.04)	0.076
Thalamus	14.28 (13.50,15.07)	13.07 (12.40,13.74)	0.025
Lateral ventricle	19.19 (14.11,24.27)	16.06 (11.74,20.37)	0.335
Caudate nucleus	8.00 (7.21,8.70)	7.38 (6.75,8.01)	0.233
Putamen	12.07 (11.28,12.86)	10.92 (10.25,11.59)	0.033
Globus pallidum	3.35 (3.07,3.63)	3.03 (2.79,3.27)	0.088
Cerebellar White Matter	24.76 (22.69,26.83)	21.86 (20.02,23.71)	0.044
Cerebellar Cortex	114.11 (103.45,124.77)	100.87 (90.84,110.90)	0.077
Corpus Callosum			
• **Anterior**	1.28 (1.14,1.42)	1.09 (0.97,1.21)	0.050
• **Central**	0.35 (0.29,0.40)	0.33 (0.29,0.38)	0.676
• **Posterior**	1.07 (0.91,1.23)	0.95 (0.82,1.08)	0.253

A General linear model was used to compare groups with SES, gender and age at MRI as covariates. Significant p-values ($p \leq 0.01$) are shown in bold font.

Abbreviations: CI: Confidence Interval; ELBW: Extremely low birth weight; CP: Cerebral palsy

FIGURE 1

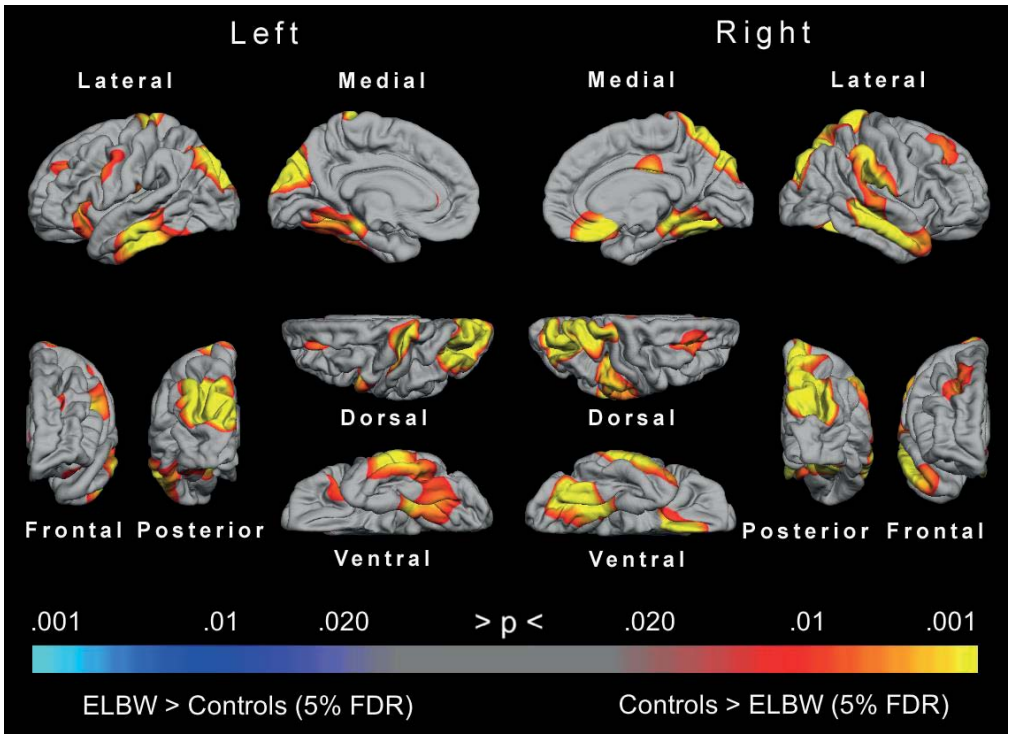

FIGURE 1. Group differences in cortical surface area between ELBW children without CP and term born controls at 10 years.

The mapping of cortical surface areal reduction in non-CP ELBW children compared with controls is shown on the reconstructed cortical surface. Top panel shows lateral and medial views of left and right hemispheres and bottom panel shows frontal, posterior, dorsal and ventral views. Cortical areas with statistically significant difference between groups after False Discovery Rate (FDR) correction at $p < 0.05$ are shown in color, and the color scale indicates the dynamic range of the statistically significant changes (in p-values), red to yellow represents an increasing surface area reduction in the non-CP ELBW group compared with controls. Most significant areas of reduced surface area in the non-CP ELBW group were observed in the temporal and parietal lobes bilaterally, and in the right anterior-medial-frontal lobe. No areas with increased surface area (blue areas) were found in the non-CP ELBW group compared with controls.

SUPPLEMENTAL MATERIAL:

Cerebral MRI – acquisition and analysis:

Cerebral MRI was performed on a 1.5 Tesla Siemens Avanto (Siemens, Erlangen, Germany) with Quantum gradients 40mT/m and a 12 channel head coil. A structural T1-weighted magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence was acquired with the following specifications: TR=2400 ms, TE=3.61 ms, TI=1000 ms, flip angle 8^{o}, FOV 240×240, slab thickness 160 mm, slice thickness 1.2 mm and matrix 192×192, giving a reconstructed voxel resolution of 1.25×1.25×1.2 mm^3. For the image analysis, we used the freely available FreeSurfer software package 5.1 (http://surfer.nmr.mgh.harvard.edu/). The MPRAGE sequences were used to perform a reconstruction of the cortical surface in each subject and cross-subjects statistics [1-3]. An automatic algorithm was used for motion correction of T1 image [4] and removal of non-brain tissue [5]. The brain was segmented into white and grey matter after a Talairach transformation and intensity normalization. Subcortical volumes were obtained from the automated segmentation procedure for volumetric measures of brain structures implemented in Freesurfer [6, 7]. The gray matter/white matter boundary was tessellated and topological errors were automatically corrected [8, 9]. Furthermore, the cortex was segmented based on gyrus and sulcus information [10, 11], and the cortical thickness was calculated as described by Fischl et al [12]. Group differences in total surface area were calculated as described in prior publications [13, 14]. We used the surface based method in FreeSurfer where each subject is registered to a spherical atlas based on individual cortical folding patterns, and matched geometry across subjects with minimized metric distortions [3]. The surfaces were smoothed with a full-width-half-maximum Gaussian kernel of 30 mm (662 iterations). Vertex-wise estimates of relative areal expansion for each individual subject in atlas space were then computed by assigning one third of the area of each triangle to each of its vertices. The surface area maps were created using spatial intensity gradients across tissue classes and are therefore not simply reliant on absolute signal intensity. The maps produced are not restricted to the voxel resolution of the original data thus are capable of detecting submillimeter differences between groups.

To avoid segmentation errors in the automated process, all processed images were controlled with a specific script (http://surfer.nmr.mgh.harvard.edu/fswiki/QATools) and visually inspected for errors and misalignments by two trained technicians and a medical doctor, and subjects with obvious errors during the automated process were disregarded. Images with low signal-to-noise-ratio (SNR) and with significant left-right differences of volumes of thalamus and hippocampus were especially checked carefully for segmentation errors. Volumes with segmentation errors were not manually corrected, but rejected from further analyses.

TABLE S1: Clinical characteristics of ELBW children without CP with normal versus abnormal motor repertoire in early infancy.

	Normal motor repertoire n=9 mean (SD)	**Abnormal motor repertoire n=11 mean (SD)**	**P value**
Gestational age, weeks	26.1 (1.8)	27.0 (1.9)	0.274
Birth weight, grams	831 (157)	803 (144)	0.686
Birth weight $\leq 10^{th}$ percentile, n (%)	0 (0)	5 (45)	**0.038**
Male gender, n (%)	3 (33.3)	4 (36.4)	1.0
Singletons, n (%)	1 (11.1)	8 (72.7)	**0.01**
Twin birth, n (%)	6 (66.7)	2 (18.2)	0.065
Triplet birth, n (%)	2 (22.2)	1 (9.1)	0.566
APGAR 1 minute	4.9 (2.5)	5.1 (3.1)	0.875
APGAR 5 minutes	6.6 (2.6)	7.3 (2.4)	0.532
Antenatal steroids, n (%)	7 (78)	5 (45.5)	0.197
Mechanical ventilation, days	11.3 (13.4)	9.6 (12.9)	0.778
Intraventricular hemorrhage			
• Grade 1, n (%)	4 (44.4)	3 (27.3)	0.642
• Grade 2, n (%)	2 (22.2)	1 (9.1)	0.566
• Grade 4, n (%)	0	0	1.0
Periventricular leukomalacia, cystic, n (%)	0	0	1.0
Septicemia, n (%)	3 (33.3)	3 (27.3)	1.0
Patent Ductus Arteriosus, n (%)	3 (33.3)	3 (27.3)	1.0
Surgery, n (%)	2 (22.2)	3 (27.3)	1.0
BPD/O_2 at GA 36 weeks, n (%)	6 (66.7)	5 (45.5)	0.406
Socioeconomic status	3.8 (1.3)	3.18 (1.2)	0.302

Mann-Whitney U-test, Chi-square-test.

Significant p-values ($p \leq 0.05$) are shown in bold font.

Abbreviations: SD: standard deviation; ELBW: Extremely Low Birth Weight; CP: Cerebral Palsy; F: Fidgety movements; BPD: Bronchopulmonary dysplasia; GA: gestational age.

TABLE S2: Neuropsychological test results at age 10 years in ELBW children without CP with normal versus abnormal motor repertoire in infancy.

	Normal motor repertoire n=8 mean(95%CI)	Abnormal motor repertoire n=11 mean(95%CI)	P value
Stroop:			
• Naming colors	42.3 (35.0,49.6)	48.0 (41.4,54.6)	0.244
• Reading colors	29.2 (23.1,35.3)	34.2 (28.7,39.7)	0.223
• Inhibition	85.3 (64.9,105.7)	92.7 (74.3,111.1)	0.580
• Inhibition and switching	78.2 (63.9,92.5)	89.5 (76.6,102.4)	0.237
• Total errors	9.6 (1.3,17.9)	16.7 (9.2,24.2)	0.199
The Trail Making Test:			
• Visual scanning	26.2 (21.1,31.4)	33.2 (28.5,37.8)	0.052
• Number Line	49.6 (32.2,67.0)	54.8 (39.1,70.4)	0.651
• Letter Line	52.8 (33.1,70.6)	52.2 (35.3,69.1)	0.975
• Number and letter line	120.4 (84.8,155.9)	133.1 (101.1,165.2)	0.584
• Motor speed	29.6 (22.6,36.5)	34.1 (27.8,40.4)	0.326
• Total errors	2.8 (1.1,4.5)	2.9 (1.3,4.4)	0.971
Tower:			
• Time to first move	34.3 (23.2,45.5)	21.7 (11.7,31.8)	0.099
• Rule breaking	1.4 (0.0,2.8)	2.8 (1.5,4.0)	0.150
• Total completion time	594.7 (489.6,699.9)	529.0 (434.3,623.8)	0.346
• Correct	15.6 (12.6,18.5)	14.9 (12.3,17.6)	0.732
BEERY-VMI:			
• Visual perception	100.7 (90.9,110.4)	95.7 (86.9,104.5)	0.445
• Motor coordination	84.7 (73.3,96.0)	74.4 (64.1,84.6)	0.179
• Full form	91.1 (84.2,98.1)	85.1 (78.8,91.4)	0.198

A General linear Model was used to compare groups with SES, gender and age at testing as covariates.

Abbreviations: ELBW: Extremely Low Birth Weight, VMI: Visual Motor Integration. All scores are raw scores, except for the VMI that were standard scores.

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