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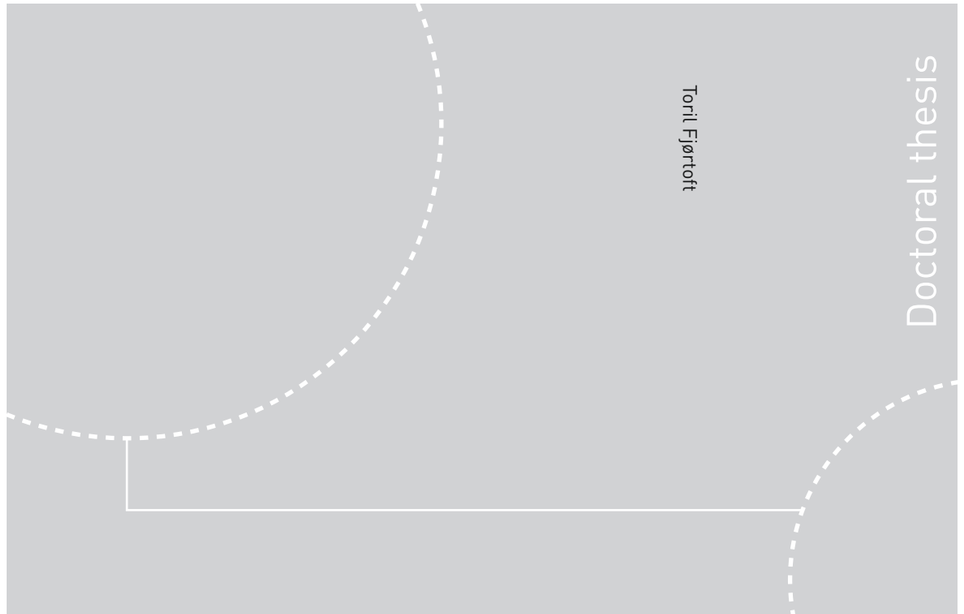

Doctoral theses at NTNU, 2016:21

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Norwegian University of Science and Technology
Thesis for the Degree of Philosophiae
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Thesis for the Degree of Philosophiae Doctor

Trondheim, February 2016

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Sammendrag

Tidlig motorisk repertoar og seinere motorisk, kognitiv og adaptiv funksjon hos barn med risiko for nevrologiske funksjonsforstyrrelser

Spedbarn med risiko for nevrologisk funksjonsforstyrrelse inkluderer både barn født premature (før uke 37 i svangerskapet) og barn født til termin med komplikasjoner i nyfødtperioden. I denne avhandlingen er hovedfokus på kvaliteten av spontanbevegelser i spedbarnsalder og seinere motorisk, kognitiv og adaptiv funksjon hos barn som er født premature med svært lav fødselsvekt (Very Low Birth Weight: VLBW; fødselsvekt <1500 gram) selv om studiepopulasjonen inkluderer også noen barn med neonatal encefalopati født til termin. Nyere studier har vist at barn som er født prematurt har motoriske og kognitive utfordringer, og behovet for støtte vedvarer gjennom barndommen, ungdomsårene og voksenlivet for mange av de premature barna som overlever. Det er behov for å utvikle og forbedre diagnostiske verktøy for tidlig identifisering av nevrologiske funksjonsforstyrrelser for å kunne starte intervensjon på et tidlig tidspunkt.

Studier av spontanbevegelser hos normale foster og spedbarn har ledet til en systematisk klassifisering av bevegelsene og definisjon av standardbevegelser for de ulike aldersgruppene. Noen av disse er beskrevet som general movements og en metode for evaluering av slike bevegelser er utviklet. «The Assessment of Motor Repertoire – 2 to 5 Months» (AMR) er en standardisert vurdering av fidgety-bevegelser som er general movements mellom 2-5 måneder. AMR beskriver også kvaliteten og kvantiteten til det motoriske repertoaret (concurrent movements), som er bevegelser som opptrer sammen med fidgety-bevegelser. Studier har vist at fravær av fidgety-bevegelser er en god prediktor for utvikling av cerebral parese (CP), og at kvaliteten av det motoriske repertoaret i fidgety-perioden hos VLBW-barn er assosiert med seinere motorisk og/eller kognitiv utvikling.

Denne avhandlingen inneholder både en oppfølgingsstudie og en multisenterstudie. Målet med oppfølgingsstudien i Artikkel I var å undersøke prediktiv verdi av kvaliteten av fidgety-bevegelser og det motoriske repertoaret for senere motorisk og kognitivt utkomme i ei gruppe høy-risiko barn. Vi viste at et unormalt motorisk repertoar, til tross for tilstedeværelse av fidgety-bevegelser, var assosiert med motoriske og kognitive utkomme ved 10-års alder, undersøkt med Movement Assessment Battery for Children-2 og Wechsler Intelligence Scale-III.

Målet med oppfølgingsstudien i Artikkel II var å beskrive foreldre-rapportert adaptiv og maladaptiv atferd hos 10-11 år gamle VLBW-barn med og uten CP sammenlignet med terminfødte kontrollbarn, ved hjelp av Vineland-II. I gruppa med VLBW-barn uten CP ønsket vi å beskrive mulige sammenhenger mellom adaptiv og maladaptiv atferd og neonatale faktorer samt kvaliteten på spedbarnas tidlige motoriske repertoar.

Vi fant at VLBW-barn, både med og uten CP, hadde dårligere adaptiv funksjon i skolealder enn sine jevnaldrende født til termin. Blant VLBW-barn uten CP var kvaliteten på det motoriske repertoaret assosiert med en lavere skår for adaptiv funksjon ved 10-11 år.

Målet med multisenterstudien i Artikkel III var å beskrive kvaliteten av general movements og det motoriske repertoaret i fidgety-perioden hos barn med svært lav gestasjonsalder (ELGAN: gestasjonsalder <28 uker) og/eller ekstrem lav fødselsvekt (ELBW: fødselsvekt

<1000 gram). Hos disse spedbarna fant vi dårligere kvalitet på det motoriske repertoaret ved 12 uker korrigert alder sammenlignet med ei representativ frisk kontrollgruppe. ELGAN/ELBW spedbarn med tilstedeværelse av fidgety-bevegelser hadde fire ganger så høy risiko for å ha et unormalt motorisk repertoar enn kontrollene.

Resultatene i denne avhandlingen tyder på at et unormalt motorisk repertoar hos høy-risiko spedbarn er hyppig forekommende, og at dette tidlige motoriske repertoaret er assosiert med senere utkomme for motorikk, kognisjon og adaptiv funksjon. Ettersom antallet overlevende barn som er ekstremt for tidlig født øker, er det viktig for helsevesenet og hjelpeetater å ha diagnoseverktøy med høy nok sensitivitet og spesifisitet med hensyn til framtidige behov. Like viktig er det å være i stand til å berolige foreldre så tidlig som mulig dersom deres spedbarn vil utvikle seg normalt og ikke ha risiko for funksjonsforstyrrelser forårsaket av problemer rundt fødselen. Studier av spontanbevegelser og det motoriske repertoaret i spedbarnsalder kan bidra til å møte disse utfordringene.

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Veiledere: Kari Anne Indredavik Evensen, Jon Skranes

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Paper I

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

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

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

Paper II

Adaptive behavior in 10-11 year old children born preterm with a very low birth weight (VLBW).

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

Eur J Paediatr Neurol. 2015 Mar;19(2):162-9. doi: 10.1016/j.ejpn.2014.11.006. Epub 2014 Nov 28.

Paper III

High Prevalence of Abnormal Motor Repertoire at 3 Months Corrected Age in Extremely Preterm Infants.

Toril Fjørtoft, Kari Anne I. Evensen, Gunn Kristin Øberg, Nils Thomas Songstad, Cathrine Labori, Inger Elisabeth Silberg, Marianne Loennecken, Unn Inger Møinichen, Randi Vågen, Ragnhild Støen and Lars Adde

Eur J Paediatr Neurol. 2016, doi: 10.1016/j.ejpn.2015.12.009.

Abbreviations

AMR	Assessment of Motor Repertoire
BPD	Broncho Pulmonary Dysplasia
BW	Birth weight
CI	Confidence interval
CNS	Central nervous system
CP	Cerebral palsy
GMFCS	Gross Motor Function Classification System
ICF	International Classification of Functioning, Disability and Health
ELBW	Extremely low birth weight
ELGAN	Extremely Low Gestational Age Newborns
F	Fidgety movements
GA	Gestational age
GLM	General linear model
GM	General Movements
GMA	General Movement Assessment
IVH	Intraventricular hemmorrhage
IQ	Intelligence quotient
MABC-2	Movement Assessment Battery for Children-2
MRI	Magnetic resonance imaging
OR	Odd ratio
NICU	Neonatal intensive care unit
PVL	Periventricular leukomalacia
SES	Socioeconomic status
SD	Standard deviation
VLBW	Very low birth weight
WISC	Wechsler Intelligence Scale for Children
WHO	World Health Organization

Summary

Early motor repertoire and long-term motor, cognitive and adaptive function in infants at risk for neurological impairment

Infants at risk for neurological impairments include both infants born preterm (before week 37 of gestation) and infants born at term with neonatal complications. In this thesis, the main focus is on the quality of spontaneous movements in infancy and long-term motor, cognitive and adaptive function in children born preterm with very low birth weight (VLBW: <1500 grams), even though the study population also includes some children born at term who have suffered neonatal encephalopathy. Recent studies have shown that preterm born children have motor and cognitive challenges, and the need for support persists through childhood, adolescence and into adulthood for many of these preterm born survivors. There is a need to develop and improve diagnostic tools for early identification of neurological impairment in order to start intervention at an early age.

The observation of spontaneous movements in normal fetuses and infants has led to a systematic classification of movements, thereby defining a set of standard movements for each respective age group. Some of these are described as general movements, and a method for the evaluation of such movements has been developed. The "Assessment of Motor Repertoire – 2 to 5 Months" (AMR) is a standardized assessment of fidgety movements, which are the general movements at 2-5 months of age. AMR also describes the quality and the quantity of the concurrent motor repertoire, which are movements occurring together with fidgety movements. Studies have shown that absence of fidgety movements is a good predictor of development of cerebral palsy (CP), and that the quality of the concurrent motor repertoire during the fidgety period in VLBW infants is associated with later motor and/or cognitive development.

This thesis includes both a follow-up study and a multicenter study. The aim of the follow-up study in Paper I was to determine the predictive value of the quality of fidgety movements and the concurrent motor repertoire for later motor and cognitive outcomes in a group of high-risk children. We showed that an abnormal concurrent motor repertoire, despite presence of fidgety movements, was associated with motor and cognitive problems at 10 years of age,

assessed by the Movement Assessment Battery for Children-2 and Wechsler Intelligence Scale-III.

The aim of the follow-up study in Paper II was to describe parent-reported adaptive and maladaptive behaviour in 10-11 year old VLBW children with and without CP compared with term-born controls, using Vineland-II. In the group of VLBW children without CP, we wanted to describe possible associations between adaptive and maladaptive behaviour and neonatal factors as well as the quality of the infants' early motor repertoire. We found that VLBW children, both with and without CP, had lower adaptive function at school age than their peers born at term. Among VLBW children without CP an abnormal infant motor repertoire at 14 weeks post-term age was associated with a lower score for adaptive behavior at 10-11 years of age.

The aim of the multicenter study in Paper III was to describe the quality of general movements and the additional concurrent motor repertoire during the fidgety movement period in infants with extremely low gestational age (ELGAN: <28weeks gestational age) and/or extremely low birth weight (ELBW: <1000 grams). In these infants, we found poorer quality of the early motor repertoire at 12 weeks corrected age compared with a matched control group of healthy term-born infants. ELGAN/ELBW infants with presence of fidgety movements had a four times higher risk of having an abnormal concurrent motor repertoire than control infants.

In conclusion, the results of the thesis suggest that abnormal concurrent motor repertoire is frequent in high-risk infants, and that this early motor repertoire is associated with later motor, cognitive and adaptive outcome. As the number of survivors of extreme birth is increasing, it is important for the healthcare and social system to have diagnostic tools with high enough sensitivity and specificity with respect to future needs. Just as important is to be able to reassure parents as early as possible that their children will develop normally and not suffer longstanding problems caused by their birth. Studies of general movements and the concurrent motor repertoire in infancy could contribute to meet these challenges.

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PAPER I, PAPER II, PAPER III

INTRODUCTION

Infants at risk for neurological impairments include in this thesis both infants born preterm and infants born at term with neonatal complications. While the study population includes some children who have suffered neonatal encephalopathy, the main focus is on motor and cognitive outcome (Paper I), adaptive behavior (Paper II) and the quality of general movements and the concurrent motor repertoire (Paper III) in children born preterm.

Even though preterm children as a group are at risk for later developmental problems, the clinical challenge is how to identify children in need of further follow-up, support and intervention. Physiotherapists are involved in the follow-up of these children, and I have for many years been working in a multidisciplinary follow-up team for infants born preterm at Trondheim University Hospital, Norway. Through my work I have observed differences between the extremely preterm and term-born infants with respect to general movements and the concurrent motor repertoire. Those observations combined with an increasing number of scientific reports on the topic made me curious to investigate whether certain elements of the quality of these movements could be used as early biomarkers for later function. We started to video-record these infants' spontaneous movements in 1999 and have subsequently been able to conduct follow-up studies of the children, assessing motor, cognitive and adaptive functions. As interesting results of outcome emerged, new questions regarding the variations in quality of the early motor repertoire in extremely premature children were raised.

Infant at risk for neurological impairment

High risk infants

According to Norwegian Directorate of Health's guidelines [1] high-risk infants defined as infants in need for a standardized follow-up program in specialist health care, include:

- Children born at gestational age <28 weeks (ELGAN) or with birth weight <1000 grams (ELBW)
- Premature infants (<37 weeks), regardless of birth weight, with: severe cerebral hemorrhage (Grade ≥III), periventricular leukomalacia, enlarged ventricles in the brain at discharge from the hospital, retinopathy of prematurity, suspected hearing loss or suspected injury to the brain or sensory organs, and infants with severe fetal growth restriction (birth weight below 2.5 percentile according to gestational age)
- Children with severe and prolonged lung disease requiring supplemental oxygen or breathing assistance at 36 weeks gestational age
- Children with major adjustment difficulties, for example in relation to feeding, sleep, behavioral disorders and interaction

High risk infants/children included in this thesis are:

- Infants/children with neonatal encephalopathy (NE) (Paper I)
- Very low birth weight children (VLBW: birth weight <1500g) (Paper I and II)
- Extremely low birth weight children (<1000g) born preterm (<28 gestational week) (ELBW/ELGAN) (Paper III)

Prematurity

The World Health Organization (WHO) defines preterm birth as infants born alive before a full 37 weeks of pregnancy. Gestational age (or postmenstrual age) is a measure of the length of a pregnancy from the first day of the last normal menstrual period, or the corresponding age as estimated by other methods. Such methods include adding 14 days to a known duration of pregnancy since fertilization (as is possible with *in vitro* fertilization), or by obstetric ultrasonography. Table 1 shows terms and definitions frequently used in scientific literature.

Table 1. Definition of gestational age and classification of prematurity according to gestational age and birth weight.

Full term infant	**Gestational age 37- 41 weeks**
Preterm infant	Gestational age < 37 weeks
Very preterm infant	Gestational age < 32 weeks
Extremely preterm infant	Gestational age < 28 weeks
Low birth weight	Birth weight < 2500 grams
Very low birth weight	Birth weight < 1500 grams
Extremely low birth weight	Birth weight < 1000 grams

The distribution of preterm birth according to gestational age in Norway is shown in Table 2. In Norway about 7.5 % (4300 children/year) of children are born preterm (Table 2).

Table 2. Distribution of preterm birth according to gestational age in Norway [1].

Gestational age	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**TOTAL**
Live newborns	26	34	37	50	65	82	96	127	162	234	351	569	875	1565	4273

Table 3 shows the distribution of newborn infants according to birth weight.

Table 3. Distribution of newborn infants according to birthweight (grams) in Norway [2].

Gestational weight	**≤ 499**	**500-999**	**1000-1499**	**1500-1999**	**2000-2499**	**2500-2999**	**3000-3499**	**3500-3999**	**4000-4499**	**4500-4999**	**5000-5499**	**5500+**	**TOTAL**
Live newborns	57	230	329	643	1741	7121	19667	21027	8749	1626	162	13	61368

Approximately 75% of children born preterm are born in gestational week 34, 35 and 36, and for these children prematurity represents a minor risk factor for later neurological development, in contrast to the infants born with very low or extremely low birth weight [3, 4]. The most common problems reported in children born very preterm are motor and

cognitive delay [5]. In spite of significant progress and improvement in neonatal intensive care, complications of extreme prematurity frequently occur in the neonatal period, which alone or in combination can influence the quality of general movements and the concurrent motor repertoire in infancy and/or later development.

Being born preterm is a well-known risk factor for impaired brain development, and the degree of prematurity and complicating perinatal factors are determining factors for later outcomes [6, 7]. While the survival of infants born at extremely low gestational ages increased in England between 1995 and 2006 [8], and high survival rates were reported in a Swedish population study [9], being born with weight below 1000 grams is a significant risk factor for abnormal neurological outcome [10, 11]. A 6.5% (95% CI: 2-11) decrease in moderate to severe impairment for each week of gestation between gestational age 22 to 25 weeks has been reported [3] , and the neurodevelopmental outcome of extremely low birth weight surviving infants has improved [12].

Prematurity is frequently accompanied by organ failure or injury. Periventricular leukomalacia (PVL) is a type of brain damage that involves the periventricular white matter and affects nerve tracts that traverse this region, including those primarily responsible for the transmission of nerve impulses that control motor function [13]. About 10% of very low birth weight infants develop cerebral palsy (CP), the cause of which in nearly 90% is periventricular leukomalacia [14]. Intraventricular hemorrhage (IVH) is a significant risk factor for aberrant neurodevelopmental outcome [15]. It is most common in premature infants; especially those who have experienced respiratory distress syndrome, collapsed lung (pneumothorax), or high blood pressure [16]. IVH is categorized into four grades (Grades I through IV) of increasing severity [17]. Grades I and II usually involve a small amount of bleeding contained in close proximity to (grade I) or in the ventricles without dilatation (grade II) and do not normally cause long-term problems. Grades III and IV entail more substantial bleeding which leads to ventricular dilatation (grade III) or periventricular involvement (grade IV, which is actually a hemorrhagic infarction). The incidence of IVH is directly correlated with the degree of prematurity. For infants with birth weight from 500 to 749 grams, the incidence of IVH is approximately 45% [16]. About 30% of extremely preterm infants with gestational age 23-24 weeks and diagnosed IVH grade III-IV in the neonatal period later develop CP [18]. The ventricular dilatation, in turn, can lead to post hemorrhagic

hydrocephalus which may cause raised intracranial pressure and may require surgical procedures to relieve [19, 20].

Respiratory failure because of immature lungs with respiratory distress syndrome is still one of the most threatening complications of prematurity, but the problem is decreasing as is the need for mechanical ventilation [21].

Bronchopulmonary dysplasia (BPD) (the need for supplementary oxygen after 36 weeks gestational age) [22] is still a common cause of morbidity among survivors of extreme preterm birth despite the widespread use of surfactant treatment, antenatal and postnatal glucocorticoids, and new and more gentle ventilatory strategies.

Neonatal encephalopathy

Neonatal encephalopathy (NE) is "a clinically defined syndrome of disturbed neurological function in the earliest days of life in the term infant, manifested by difficulty with initiating and maintaining respiration, depression of tone and reflexes, subnormal level of consciousness and often seizures" [23]*. NE occurs in approximately 3.5-6/1000 live births and usually affects the full term infant [24]. The term NE is preferred to hypoxic ischemic encephalopathy (HIE) as it is not always possible to document a significant hypoxic-ischemic insult [25], and there are several other potential etiologies [26, 27]. When hypoxia is the cause of NE, the timing and severity of the hypoxic insult will define its consequences. Before gestational week 35, hypoxia is likely to produce PVL. At term, the degree of hypoxia defines the area of the brain that is injured; mild hypoxia most often will affect the parasagittal white matter while severe hypoxia affects the deep grey matter nuclei like putamen and thalamus, and paracentral white matter. Consequently, the area of the brain that is affected will determine which symptoms the child later experiences [16]. Neurological impairments due to NE can include epilepsy, neurodevelopmental delay, and motor and cognitive impairments [28, 29]. NE was previously thought to be the leading cause of CP, but studies have shown that only 8% of CP cases are a direct result of NE [29]. Previous studies have shown significant associations between NE and qualities of general movements [30].

The first paper of this thesis includes eight infants with birth weight >1500 grams diagnosed with NE as well as one child with intracerebral abscess, as both conditions represent risk factors for later neurological development [31]. Five infants were born at term; 2 were born in

*page 1325 in ref.[23]

gestational week 36+3 and one infant in gestational week 42+1. We therefore classified these 9 children as “high-risk infants.”

Early motor repertoire

The General Movement Assessment (GMA)

Traditionally, neurological assessment of newborns and infants has been based on two different approaches: the systematic comparison of the children's developmental stages with those of the average population [32] and the identification of clinical symptoms of cerebral impairment such as changes in muscle tone and/or abnormal reflexes [33]. The observation of spontaneous movements in normal fetuses [34], neonates and infants has led to a systematic classification of movements, thereby defining a set of standard movements for each respective age group, some of which are described as general movements (GMs) [35]. The observation technique, General Movement Assessment (GMA), is based upon Gestalt perception [36]. The global Gestalt perception allows the assessment by all parts of the body and does not pay special attention to particular movement of specific body parts [37]. GMs have been found to be an effective reference for the functional assessment of the developing nervous system [38], and useful for discrimination and prediction [30]. Accordingly, a method for the evaluation of GMs has been developed, known by the term General Movements Assessment (GMA) [38-40]. The GMA has frequently been used in studies of the prognosis for neurological outcomes [30, 37, 41-43] and the assessment of GMs including fidgety movements (FMs) have been shown to be an important functional indicator of brain dysfunction [30]. Studies of preterm and term newborns as well as young infants have at an early stage shown that abnormal GMs and the concurrent motor repertoire can be related both to brain lesions and to an unfavorable neurological outcome [38, 44-46]. The absence of FMs was shown to be a valid predictor of later neurological impairment, especially CP [30, 37, 42, 47-49]. Studies of GMs as well as a detailed motor repertoire [39] in preterm and term infants during the last 10 years are presented in Appendix A. Most of these studies show that there is an association between GMs and outcomes as well as between motor repertoire and outcomes.

The GMs can be observed in fetuses as young as eight weeks postmenstrual age [34, 50] and are characterized by large variability in speed, amplitude, force, and intensity [51]. These movements have complex motor patterns involving all parts of the body. They last from several seconds to approximately a minute. The sequence of moving parts of the body is variable, and the infants’ movements have recognizable patterns of fluent, elegant and

complex movements. The speed and amplitude vary continuously, and their onset and end are gradual with waxing and waning of intensity during the course of a single movement [39]. In preterm born infants GMs continue to present the same movement pattern until the infant has reached term age [51]. The GMs of a preterm infant may occasionally have large amplitudes and are often of fast speed [39, 52]. In the first weeks after term, GMs are referred to as writhing GMs [42, 51-54]. These movements are of smaller amplitude and slower speed compared to the GMs of preterm infants. Fast and large elliptical movements may occasionally break through, particularly in the arms, which creates the impression of a writhing quality [51].

At 6 to 9 weeks after term, FMs gradually emerge and remain present until 15 to 20 weeks post-term age, around the time intentional and antigravity movements appear and start to dominate the repertoire [42, 51]. In normal infants the period around the end of their second month is a time of major transformation of the sensory-motor repertoire. The GMs change from a writhing character into a fidgety character consisting of a stream of small, circular movements of the limbs, head and trunk [42, 51, 52, 55]. The FMs constitute the characteristic general motor pattern. They are small movements of moderate speed and variable acceleration of neck, trunk and limbs in any direction, continual in the awake infant, except during fussing and crying [42]. Hadders-Algra et al. [56-58] have described characteristic age-dependent changes in the neonatal period using electromyography (EMG, an examination of the electrical activity of muscles) and found that the phasic bursts and the tonic background activity seen on EMG decreased during the transformation from writhing movements to fidgety movements.

According to Einspieler et al. [39, 48], temporal organization varies with age. Temporal organization describes how long the pauses are between sequences of fidgety movements. Einspieler et al. [48] defined sporadic FMs (F+/-) as movements which are interspersed with long pauses (up to 1 minute). Sporadic FMs may occur isolated in a few body parts and are of very short duration (1 to 3 seconds). These fidgety movements are usually present in the distal and proximal body parts. Some infants can have more activity in the wrists and ankles than in the trunk and proximal joints [48]. Dibiasi and Einspieler [48, 59] described continuous FMs (F++) as movements in the whole body more or less continuously and just interrupted with few short pauses; just 1 to 2 seconds [48]. FMs may be expressed differently in different body parts depending on the actual body posture. If the FMs are present for only half of the

observation time although FMs occur in all body parts they are called intermittent FMs (F+) [39, 48].

According to Prechtl's definition of spontaneous movements, the fetal, preterm, writhing and fidgety movements are all classified as GMs. The other movements which occur together with fidgety movements are classified as the concurrent motor repertoire (Figure 1).

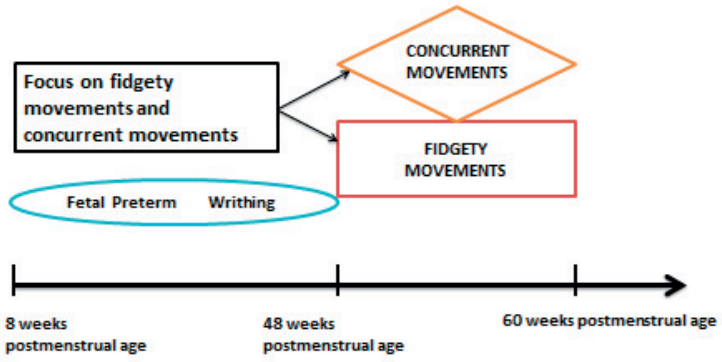


Figure 1. Timing of General Movements (GMs) and concurrent motor repertoire.

In other studies the quality of the concurrent motor repertoire has also been described as the quality of the movement character [39], and motor development is the same as motor repertoire [60]. The motor repertoire has often been used synonymously with GMs [61].

In this thesis the following terminology has been used:

- Motor repertoire is synonymous with motor behavior, motor development and general movements and the concurrent motor repertoire [60, 62]
- General movements which include fidgety movements [42]
- The concurrent motor repertoire which includes all the movements and postural patterns which occur together with fidgety movements [63]

In preterm, term and early post-term periods, abnormal GMs are described as poor repertoire. This means that the movements are monotonous and do not occur in the usual complex way [40, 55]. According to Prechtl et al. [42], the predictive value of the movements in the

writhing period with respect to neurological outcome is rather low. In the same age period, chaotic GMs also can occur. This means that the movements of the limbs are of large amplitude in a chaotic order, starting and stopping abruptly [40, 64].

In preterm, writhing and fidgety periods, the cramped-synchronized GMs are an abnormal pattern. Limb and trunk muscles contract and relax simultaneously [40, 55]. This abnormal pattern is of high predictive value for the development of cerebral palsy [30, 65].

Abnormal FMs (Fa) resemble FMs present but are exaggerated with regard to amplitude, speed and jerkiness. The predictive value is low [38] and these movements are rare. Sporadic FMs (F+/-) can be classified as both normal and abnormal. Absence of FMs (F-) is considered highly predictive for later development of both the spastic and dyskinetic types of CP [30, 42, 43, 65], while normal fidgety movements (F+ and F++) have been found predictive of normal neurological development [66].

Assessment of Motor Repertoire – 2 to 5 Months (AMR)

The scoring list which has been used in all 3 the papers of this thesis covers the motor behavior of 2 to 5 month old infants and introduces a more detailed movement analysis during the period of FMs (Figure 2). This assessment tool, Assessment of Motor Repertoire – 2 to 5 Months (AMR) [39] places emphasis on describing the best possible condition rather than classifying into normality, abnormality or pathology, and at the same time, focuses more on the details. Consequently the power of the global Gestalt perception is weakened except for the category "movement character" which is synonymous with category the quality of the concurrent motor repertoire where the global view is preserved [67]. A scoring list using different terminology, but which still describes the whole motor repertoire is published by Bruggink et al. [67]. The same terminology which is published by Bruggink et al. is used in Papers I, II and III (Appendix B).

Gross movements like kicking, hand-hand contact and hand-hand manipulation, foot-foot contact and foot-foot manipulation may occur together with fidgety movements. This suggests that FMs are superimposed on other movements or that other movements may occur during the pauses between FMs, or both [39, 48, 51]. Einspieler et al. [39] have presented an overview of these movements and the periods in which they usually occur. GMA is a reliable method to assess the quality of spontaneous motor repertoire and to evaluate the integrity of the central nervous system of young infants [38]. In the classical GMA the quality of three main periods of GMs is assessed based on video recordings: preterm GMs, writhing

movements and fidgety movements (Figure 1). The analysis is complex and requires clinical experience [38]. Inter-observer agreement of GMA has been studied in several groups of infants, with agreement being expressed as Cohen's kappa coefficient or percentage [38, 68-70].

When using this method the detailed movements' patterns are scored abnormal if the movements are predominant. For example, kicking is abnormal if monotonous, and head rotation is abnormal if repetitive, and the foot contact is abnormal if without small movements and mainly on the tibia side. Several studies show that the predictive value of the quality of fidgety movements and the concurrent movements is high with respect to outcome [63, 71].

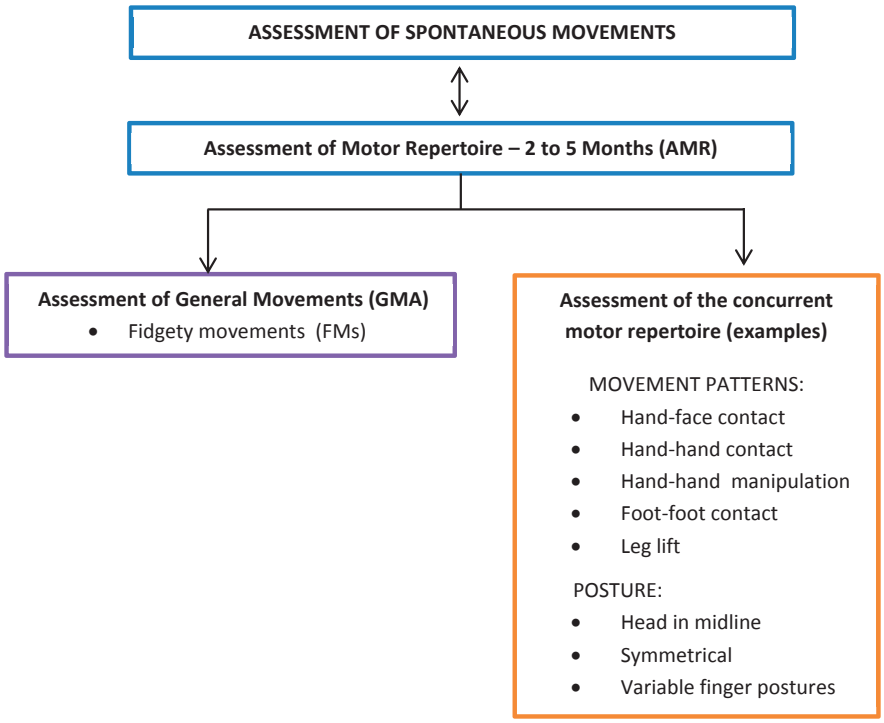


Figure 2. Description of the assessment of spontaneous movements.

AMR has been used to describe the GMs and the additional motor repertoire in healthy term-born infants, high-risk term-born infants, preterm born infants and in infants with NE. A detailed presentation of relevant studies is given in Appendix A.

After Prechtl and collaborators published the GMA method [42], discussion about the classification especially in the fidgety period has arisen, and another terminology has also been used when classifying fidgety movements. Hadders-Algra and collaborators classify the fidgety movements as normal/optimal GMs, normal/suboptimal GMs and mildly and definitely abnormal GMs [37]. These concepts may describe the same biological/behavioral phenomena and are shown in Figure 3.

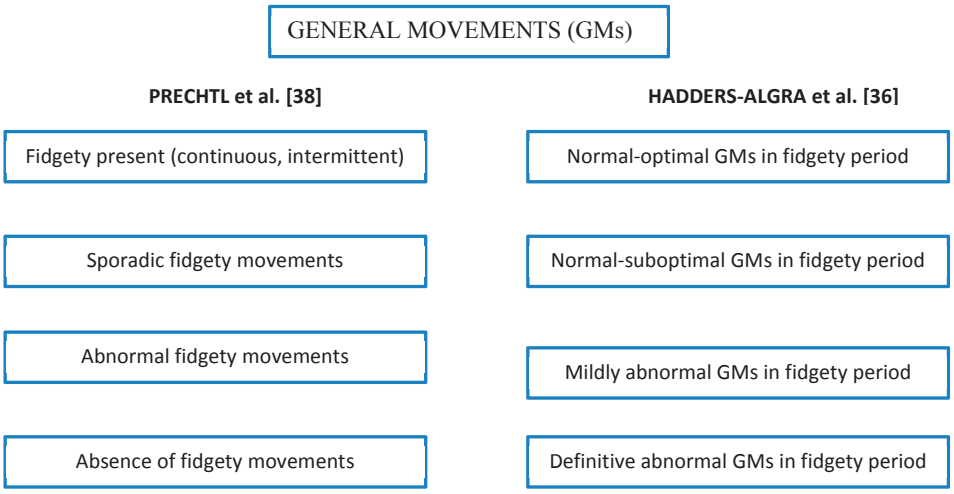


Figure 3. Terminology used when classifying general movements in the fidgety period.

The International Classification of Functioning, Disability and Health (ICF)

This thesis focuses on outcome and prediction of outcome in children with increased risk for neurological impairments, with prematurity and neonatal encephalopathy as the main risk factors. International Classification of Functioning, Disability and Health ICF is the World Health Organization (WHO) framework for measuring health and disability at both individual and population levels. The overall aim of the ICF classification is to provide a unified and standard language and framework for the description of health and health-related states [72]. ICF seeks to present a coherent view of health from a biological, individual and social perspective. The domains contained in ICF should, therefore, be seen both as health domains and health-related domains. These domains are described from the perspective of the body, the individual and society in two basic groups, which are body functions and structures, and activities and participation (Figure 4). As a classification, ICF systematically groups different domains for a person in a given health condition (e.g., what a person with a disease or disorder actually does or can do). Functioning is an umbrella term encompassing all body functions, activities and participation; similarly, disability serves as an umbrella term for impairments, activity limitations or participation restrictions. ICF also lists environmental factors that interact with all these constructs (Figure 4). In this way, it enables the user to record useful profiles of individuals' functioning, disability and health in various domains [72].

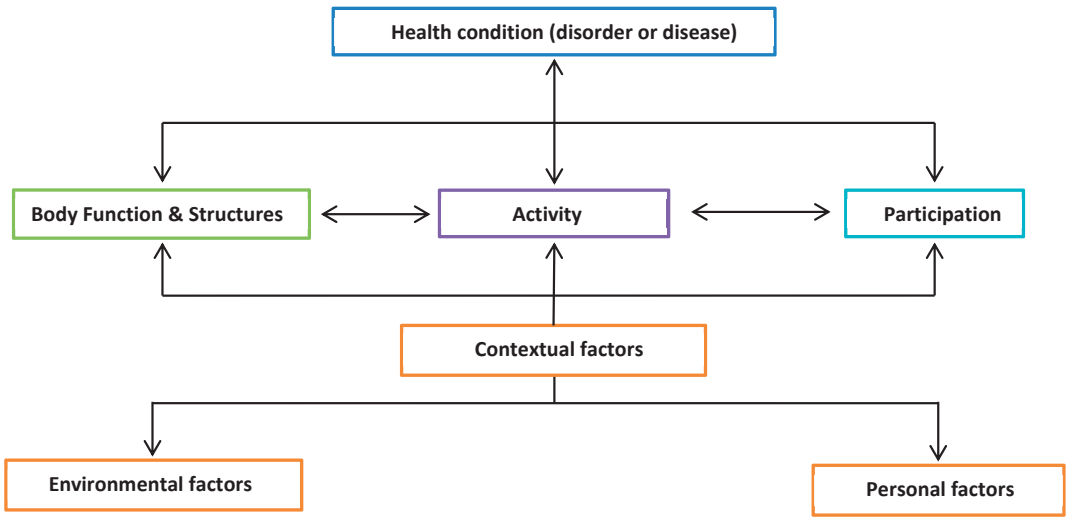


Figure 4. The International Classification of Functioning, Disability and Health [72].

In the ICF domain of body function and structures, preterm children are at risk for developing functional impairments due to complications of prematurity like PVL and intraventricular hemorrhage [18]. VLBW children have a higher risk of CP, epilepsy and sensory deficits [4]. In this thesis, general movement assessment (GMA) and Assessment of Motor Repertoire – 2 to 5 Months (AMR) [39] have been used to characterize aspects of body function and structures in these infants born at risk for neurological impairment, and also to predict later consequences for the two other ICF domains: activity and participation (Figure 4). However, these two approaches do not fully cover all aspects required for a complete functional evaluation according to the ICF (Figure 4). In the activity domain of ICF, VLBW children often experience learning difficulties [73], emotional/behavioral and motor problems [10, 74]. Regarding participation, a study has been done in adolescents born extremely preterm [75]. Lower gestational age was associated with greater participation in recreational activities. Male sex, higher maternal education and better motor competence were associated with involvement in physical activities. Preference was the strongest determinant of participation in all five leisure activities investigated in this study [75].

In this thesis, GMA and AMR results describe elements within the domain body functions and structures. In our follow-up study of 10-11 year old VLBW children, Movement ABC-2 was used to describe motor function, and WISC-III was used to elucidate cognitive and possible learning difficulties. In the participation domain of ICF, we used Vineland-II to describe possible consequences of prematurity for daily activity and social interaction.

Both environmental factors and personal factors may influence the actual ICF status of a child. However, in this thesis these factors will be just briefly discussed.

Quality of general movements and motor repertoire as predictor for later function

GMA has proven to be an important functional indicator of brain dysfunction. Absence of FMs, especially if associated with cramped-synchronized movements, has been shown to be a good predictor for CP [30, 43, 49, 65, 76]. Exaggerated FMs (also called abnormal FMs [39]) were found to be a marker of complex, minor neurological dysfunction (MND) at 7 to 11 years of age [63]. Normal FMs in conjunction with a normal concurrent motor repertoire are markers for normal outcome at school age [62, 63]. In addition to the qualitative assessment of GMs and FMs, other qualitative and quantitative aspects of the spontaneous motor repertoire have been demonstrated to be predictive with respect to motor outcome [60, 63, 67,

77]. Recently, studies have shown that the results of qualitative assessment of GMs/FMs combined with assessment of the quality of concurrent movements using the optimality score Assessment of Motor Repertoire – 2 to 5 Months may be predictors for later cognitive performance [71, 78] and behavioral [78, 79] and adaptive problems [80].

The quality of motor repertoire reflects stages of brain development and brain function at 3 months corrected age [30, 37]. Several studies confirm that these movements vary among individuals depending on neonatal risk factors like intracranial hemorrhages and perinatal hypoxia [30], and a clear association between lack of FMs and later CP has been described [42]. These observations raise a more general question of whether deviations from normal motor repertoire are transitory and without predictive value or an expression of aberrant brain development with later functional consequences. Abnormal imaging findings on routine neonatal ultrasound (US) and magnetic resonance imaging (MRI) have shown strong correlations with later neurological impairment [7]. However, especially among premature infants, it has been hard to find clinical tools sensitive and specific enough to predict later brain functioning [81].

Brain development

The connection between the quality of GMs and later neurological outcome can possibly be explained by events interfering with normal brain development.

The formation of the neural tube is the first stage of the development of the central nervous system. Neurons and glial cells found in the mature brain are all differentiated from neuroepithelial cells in the wall of the neural tube [16]. At 2 to 3 months of gestation, neurons in the ventricular and intermediate zone proliferate, followed by a migration of neurons to other parts of the nervous system at 3 to 4 months of gestation. Subplate neurons are among the first neurons that appear in the mammalian cerebral cortex [82] and are important in establishing the correct wiring and functional maturation of the cerebral cortex [83]. The subplate thus plays an important role in the migration process (Figure 5), as subplate neurons are involved in the establishment of pioneering cortical efferent axons and transient fetal circuitry [16]. Unfortunately, subplate neurons appear to be selectively sensitive to injury such as hypoxia, which in humans is associated with motor and cognitive defects [84]. Migrating neurons are guided by glial cells between the subventricular and intermediate zone and the pial surface of the cortex [85]. These glial cells derivate from the immature pre-myelinating oligodendrocytes in the white matter around 28 weeks of gestation [86] and are

also vulnerable to hypoxic-ischemic insults with risk of a reduced pool of maturating oligodendrocytes and hence reduced myelination [87]. Neuronal proliferation and the migrating process seem to be almost complete around 28 gestational weeks [88], and in the second half of the gestation glial cell proliferation and programmed cell death are most prominent [89].

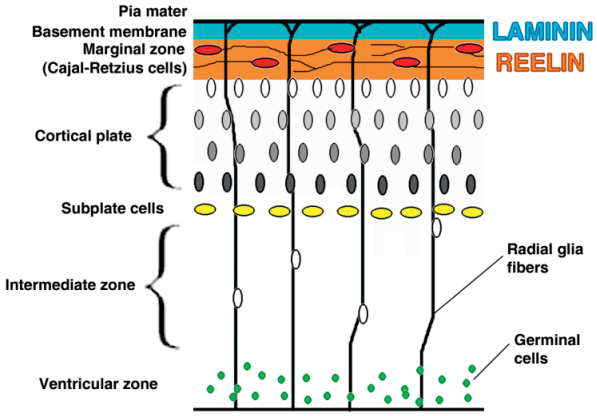


Figure 5. Development of the cerebral cortex (corticogenesis) in a mouse.
(https://en.wikipedia.org/wiki/Subplate)

Prematurity seems to be a disturbing event for several of these normal developmental processes. Luckily the incidence of the most severe focal brain injuries related to prematurity like hemorrhagic parenchymal infarction and cystic periventricular leukomalacia is decreasing [90]. The most common brain abnormalities found in preterm infants, as demonstrated by various MRI techniques, are non-cystic white matter disease, abnormal cortical development and enlargement of the ventricular system [91, 92]. These non-focal abnormalities are often subtle, but in follow-up studies several cognitive correlates have been described [91]. Structural MRI, however, is quite insensitive to minor abnormalities [93, 94] and neurodevelopmental impairment cannot be excluded without a long term follow-up, even in apparently healthy preterm children with normal findings on conventional MRI [95].

According to Hadders-Algra [96], the GMs' complexity and variation are possibly brought about by the presence of the transient cortical subplate. Abnormal GMs could be the result of damage or dysfunction of the subplate and its efferent motor connections in the

periventricular white matter. White matter damage occurring before term age leads to a loss of axons and subplate neurons thus impairing thalamo-cortical connections [97]. The notion that the quality of GMs is based in particular on the integrity of the subplate and its connections may also explain abnormal GMs occurring around 3 months post-term in some infants born prematurely.

If it is true that the quality of GMs in infancy mirrors the function and integrity of the subplate and its connections in fetal life, general motor assessment could add significant information to studies of morphometric abnormality with respect to neurodevelopmental outcome.

Theories of motor development

Discussions of theories explaining human movements have been going on for almost a century. A "reflex theory" has been the dominant basis for examination and treatment of children since the early 1900s [98]. In light of this theory, normal stepwise motor development in infants could be considered to be controlled by reflexes without the influence of the infant's environment.

Gradually "the program(s) theory" was introduced. Motor behavior has been regarded as the result of non-adjustable motor programs in the central nervous system [99]. This program theory partly disregards the environment's impact on the movement behavior and the effect of the context the person is in. In this theory, one is most concerned about how the movement is performed instead of which information is processed and its significance for development of movement skills. Put in a program theoretical perspective, infant movement patterns could be interpreted as pre-programmed during development and appear at a time and in an order that is predetermined. However, the program theoretical thinking has proved to be insufficient to explain the complexity and quality of infant movement.

A "system theory" called Dynamic Systems Theory involves ways of thinking that can better explain the complexity and quality of movements than the reflex theories. This theory recognizes that movements are influenced by external factors. The dynamic systems theories explain why people perform the same motor tasks differently, and every movement is a result of imperceptible interactions involving cognitive, sensory and motor aspects [100]. Common to the various dynamic systems theories is that they are based on the principle of self-organization of systems without specification of an overall control mechanism in the brain. These theories will be able to explain the infant's movements as a result of an interaction with

surroundings and environment [101], but pay little attention to the condition of central nervous system (CNS) [102].

Gerald Edelman combined the mentioned views to what he calls Neuronal Group Selection Theory (NGST) [103, 104]. According to this theory, the brain is dynamically organized into variable networks, the structure and function of which are influenced by development and behavior [102]. Motor development is characterized by two phases of variation; primary and secondary variability [105]. During the first phase, the variation in motor activity is not strictly tuned to environmental or external conditions, but in the second phase, variations are more function specific. For instance, the selection of a coordinated sucking pattern occurs before term age, while the selection of a more precise arm movement takes place during the second half of the first year [102]. AMR is a parameter to assess the condition of the young nervous system and can probably fit into the concepts of the NGST as AMR expresses the primary variability of the motor repertoire. The infants' motor repertoire can be influenced by environmental conditions [106]. If an infant has lesion in the brain it might lead to a reduction in the repertoire of primary cortical-subcortical neuronal networks responsible for the primary variability. The motor repertoire of these infants might consequently be affected [106].

Motor function in children born preterm

Preterm infants are susceptible to significant risk factors for abnormal neurological outcome, and perinatal complications can have an influence on the child neurological development [4].

Motor skills are important in mastering activities of daily life, and motor problems may have consequences in areas such as school performance, social skills and emotional life even among adults who were born prematurely [75, 107]. Children with extremely low birth weight (<1000 grams) have an increased level of motor problems compared to children with low birth weight (<2500 grams) and normal birth weight children. Different motor problems are frequent in prematurely born children [10, 15] and motor-perceptual difficulties are also reported in ELGAN children without other risk factors [108-110]. However, recent studies indicate a decrease in the incidence of CP and/or sensory impairments: only 10-12 % of school children born very preterm show severe neurological impairments [111]. Van Haastert et al. [90] reported that the CP incidence decreased from 6.5 % in period I (children born in 1990-1993), to 2.6 %, 2.9 % and 2.2 % (p <.001) in periods II-IV (1994-2005) together with a decrease in cystic periventricular leukomalacia (c-PVL). CP incidence and severity decreased from 1990-1993 onward, which could be attributed to a reduction of 93 % in severe c-PVL

[90]. Another study [8] found that a higher proportion of ELBW infants now survive without disability, due to better pre-and postnatal treatment. In spite of better treatment, recent long term follow-up studies have described that many of these children still end up with CP and motor impairments like balance and coordination problems [15]. Advances in obstetric and neonatal medical care and assisted reproductive technology during the last five decades have increased the rate of preterm births, decreased preterm mortality and lowered the limit of viability. However, morbidity in survivors, including neurodevelopmental disabilities, chronic lung disease, and retinopathy of prematurity (ROP) have increased for extremely preterm infant born ≤25 weeks gestation [112].

More subtle motor problems in children born prematurely include Developmental Coordination Disorder (DCD), also known as developmental dyspraxia, a type of motor learning difficulty [113, 114] and the motor and visual-motor problems associated with Attention Deficit/Hyperactivity Disorder (ADHD) [115, 116]. Recent studies of VLBW toddlers and young adults without obvious motor problems indicate aberrant motor development when using the Movement ABC-2 [107, 110, 117].

An important focus is therefore to identify these problems and to start intervention as early as possible [118, 119]. A group from the Netherlands [120] followed 86 premature children and 90 controls in an early intervention program called Infant Behavioral Assessment and Intervention Program. Five years after the early neurobehavioral intervention they found improvements on ball skills and visual-motor integration, and on performance IQ [120]. There is an urgent need to develop and improve diagnostic tools for an early detection of motor impairment in order to start intervention at an early stage [119, 121]. Despite the development and implementation of new, advanced imaging techniques, however, the information provided by clinical observation and clinical assessments is considered as important as ever. The general movement assessment (GMA) is not meant to be the only assessment tool in use, but should be used together with other assessments like cerebral ultrasound and MRI.

Cognitive function in children born preterm

An updated review from 2014 [81] concluded that children born very prematurely continue to be at risk of generalized cognitive and academic impairment and require close surveillance throughout development, and that most cognitive deficits observed in childhood are also present in adulthood. In a cohort study from 2015 [122], 228 adolescents born extremely preterm or with extremely low birth weight demonstrated generalized executive function

difficulties compared with controls. Information processing was similar in the two groups while attentional control, cognitive flexibility, goal setting and behavioral executive were significantly reduced in the preterm group. In a somewhat older review, a major risk for cognitive and behavioral problems among very premature children was reported, even in children without significant neuro-sensory impairments [123]. Preterm delivery has been associated with a 12-point reduction in IQ score [124], and this effect is sufficient to impact school performance and educational achievement. In the same meta-analysis, there was evidence of a linear dose-response relationship between degree of prematurity and IQ, with IQ falling steadily for each 1 week decrease in gestation [124]. Even if prematurity itself seems to be a significant risk factor for cognitive impairment, long neonatal intensive-care unit (NICU) admissions, postnatal steroids, necrotizing enterocolitis and abnormal findings on cerebral ultrasound can be independent predictors of cognitive outcome [125]. The EPIPAGE Cohort Study [126] showed that cognitive deficiencies without motor disorder were more frequent than either combined deficits or isolated motor deficiencies. Cognitive deficiencies without motor deficit were predominant among children with minor/moderate or no brain injury as identified by cerebral ultrasound, and provide evidence of impaired brain development in these children [126]. Løhaugen et al. [73] did a full scale IQ assessment with subtest analysis and found that about half of the VLBW young adults had impaired cognitive function. Less than half of the VLBW group achieved a full scale IQ score that reached or exceeded the mean value of the term born controls. About 9% of the young adults in the VLBW group and none in the comparison group had a cognitive disability, defined as IQ <70. All four IQ indices; verbal comprehension, working memory, processing speed and perceptual organization, were affected relative to controls. Interestingly, no correlation was found between cognition and perinatal variables in VLBW participants without CP, indicating, in accordance with Marret et al. [126] that the differences probably are more related to prematurity itself than to concomitant perinatal morbidity. In summary, cognitive difficulties highlighted in several cohort studies and reviews paint a relatively grim picture for families and health professionals of very preterm children.

However, the majority of preterm born children has relatively mild impairments or no problems at all and go on to live very productive lives. Outcomes are ultimately related to an interplay of genetic, medical, social and environmental factors [81, 127]. While it is still unclear whether the nature and severity of the different cognitive impairments persists, worsens or improves with age, sufficient long-term studies have reported that most cognitive

vulnerabilities observed in childhood and adolescence are also present in adulthood [81]. Early intervention programs for very preterm children are effective [119], but traditional modes of delivery of these programs are costly and inaccessible to many families. Cognitive training and other forms of intervention have also been conducted with VLBW children with positive and lasting effects on memory and learning [73, 128]. Grunewaldt et al. [129] found that a computerized working memory training program had long-term positive effects on memory and learning in 20 VLBW children at age 5 to 6 years. However, it is unlikely that any single program will fully resolve the breadth of cognitive challenges confronting the preterm born population. This can result in an intellectual disability or specific learning disorders [73]. Indredavik et al. [130] found higher prevalence of attention deficits and school problems among young adults born VLBW.

Motor and cognitive function in children with neonatal encephalopathy

Hypoxic-ischemic encephalopathy (HIE) or neonatal encephalopathy (NE) a significant risk factor of high mortality and later motor disability and impaired cognitive function among the survivors [31, 131-133]. A study by van Schie et al. [31] included 25 children with perinatal HIE, 8 of whom had CP. Of the 17 children without CP, 9 had impaired motor ability (of which 3 scored definitely abnormal), and 4 had behavioral problems. Two (of 4) children with normal motor ability and 7 (of 14) children with normal neurological examination at age 2 showed impaired motor ability at school age. Though the study group was small, these results indicate that HIE may have serious consequences for later development, and that even if the problems may not be obvious at an early age, later motor and cognitive impairment may appear. The results from a multicenter trial of whole-body hypothermia as treatment of HIE have indicated a favorable outcome in the treated group [134]. However, HIE is still a significant risk factor for impaired neurodevelopmental outcome. Subnormal IQ scores were identified in more than a quarter of the children in the treatment group, and 96% of survivors with CP had an IQ <70 [131].

Adaptive and maladaptive function in children born preterm

Studies describing the whole spectrum of adaptive behavior in school-aged children born preterm are still lacking even though adaptive behavior problems have been reported for other groups with established risks for impaired neurological outcome [135]. Adaptive behavior reflects a complex interaction of several elements of brain functioning and development

[136], and is here defined as the behavior necessary for an individual to function safely and appropriately in daily life, both at a personal and a social level. Consequences of prematurity for everyday practical and social skills in childhood have until now not been properly addressed, even if there have been many studies showing later mental health [137], motor [10] and cognitive [73] impairments among preterm born children. Consequences for social and behavioral adaption in preterm born adults have also been documented [11, 138]. In this thesis (Paper II) we also measure maladaptive behavior that consists of two subcategories: internalizing and externalizing behavior. Internalizing behavior expresses the child's feelings like anxiousness, while externalizing behavior expresses for example the child's temper. These categories have the opposite scoring as the adaptive behavior: the higher score, the more problems. In a literature search in 2013, we found 104 articles that used the Vineland Adaptive Behavior Scales, second edition, which measures the personal and social skills of individuals from birth through adulthood, and few studies included an age-matched control group. Most study groups were patients with specific medical diagnoses like autism, epilepsy or intellectual impairment. Only one study focused on prematurity, showing that extremely low birth weight children (ELBW) without any neurosensory impairments had lower social adaptive functioning than children born with normal birth weight at term (≥37 weeks) [139]. In a more recent study the Adaptive Behavior Composite was 92.7 (SD 16.22) in a group adolescents born extremely preterm which is very much in line with 92.2 (SD 12.3) in our study [75].

AIMS OF THE THESIS

This thesis focuses mainly on general movements and the concurrent motor repertoire at 3 months of age and a possible association with long term motor, cognitive and adaptive function.

- The main aim of Paper I was to determine the predictive value of the quality of fidgety movements and the concurrent motor repertoire for later motor and cognitive outcomes in a group of high-risk children. The hypothesis was that the presence of fidgety movements and a normal concurrent motor repertoire was predictive of a normal cognitive and motor outcome. An additional aim was to investigate if the presence of fidgety movements in combination with an abnormal concurrent motor repertoire was predictive of poor motor and cognitive outcomes.

- The aim of the study presented in Paper II was to compare parent-reported adaptive and maladaptive behavior in 10-11 year old VLBW children with and without CP with that of age-matched term born children. Secondly, in the group of VLBW children without CP, we examined associations between adaptive and maladaptive behaviors and neonatal factors as well as the quality of the infants' early general movements and the concurrent movements. We were particularly interested in the non-disabled group of preterm born children, as adaptive behavior problems are more easily overlooked among these children than in children with major disabilities like CP. We hypothesized that VLBW children with and without CP would have lower adaptive functioning than their term-born peers. Furthermore, we hypothesized that neonatal illness and abnormal infant motor repertoire at 14 weeks post-term age would be associated with lower adaptive functioning at school age in VLBW children without CP.

The results from Paper I and Paper II indicated that children born preterm as a group have minor motor, cognitive and adaptive problems in absence of major motor problems like CP or additional neonatal risk factors like IVH or PVL. There also seemed to be an association between the quality of the motor repertoire at 3 months and these later problems. The question therefore arose if impaired quality of the motor repertoire at 3 months and later motor, cognitive and adaptive problems are all consequences of prematurity per se. A comparison of

the quality of motor repertoire with a healthy term-born control group had not been examined previously.

- The aim of the study in Paper III was to compare the quality of general movements and the additional concurrent motor repertoire during the fidgety movements' period in extremely preterm infants with healthy, term-born infants at the same age. Additionally, we wanted to explore to which degree gestational age, birth weight and severe brain abnormalities like PVL and IVH would influence the quality of general movements and the concurrent movements at 3 months of age in the preterm group.

MATERIAL AND METHODS

Study design

The follow-up study at 10-11 years of age (Paper I and Paper II)

This hospital-based follow-up study included a group of high-risk infants treated during the years 1999, 2000 and the first part of 2001 in the Neonatal Intensive Care Unit (NICU) at Trondheim University Hospital, Norway, which is the referral hospital in this area. The children included had been referred to physiotherapy and had their spontaneous movements video-recorded in infancy, and they were invited to participate in the follow-up study at 10-11 years of age.

The regular clinical assessments of high-risk children according to our standardized follow-up program end when the children are 5 years, so the 10-11 year follow-up examinations for the studies in this thesis had to be an extra assessment.

The multicenter study of motor behavior in extremely preterm infants (Paper III)

The motor repertoire in infants with birth weight less than 1000 grams (ELBW) and/or a gestational age below 28 weeks (ELGAN) was described in a prospective multicenter cohort study of infants born at three hospitals in Norway between the years 2009 and 2013. Parents were invited to participate before discharge from the Neonatal Intensive Care Unit (NICU). For comparison, motor repertoire in a matched control group of healthy singleton, full-term infants with normal birth weight was also assessed.

Study population in the follow-up study

Early motor behavior and motor and cognitive functions at 10-11 years (Paper I)

Altogether, 148 VLBW children were admitted to the NICU at Trondheim University Hospital, during the years 1999, 2000 and partly 2001 (Figure 6). Of these, 74 had birth weight ≤1000 grams (ELBW) and 74 had birth weight between 1001-1500 grams. Of the 74 ELBW children, 9 died and 30 entered into follow-up programs at local hospitals. Thus, 35 ELBW children were eligible and were invited for the follow-up at 10-11 years.

During the 10 year follow-up period, unfortunately 9 video-recordings were lost as we did not have a standardized procedure for storage. One video-recording was not assessable. Paper I therefore included 25 infants ≤1000 grams and 6 infants with birth weight between 1001-1500 grams with video-recording for assessment of their spontaneous movements. In addition, 9 infants with a birth weight above 1500 grams were included in the study. Of these, 8 infants

had a probable or verified neonatal encephalopathy (NE) and 1 infant had an intracerebral abscess in the neonatal period (Paper I) (Figure 6). In sum, Paper I included 40 infants, whose clinical characteristics are shown in Table 4.

Table 4. Clinical characteristics of participants in Paper I.

	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)

[a]Bronchopulmonary dysplasia = Need for oxygen treatment at 36 weeks postmenstrual age
IVH = Intraventricular haemorrhage
SD = standard deviation

The infants' spontaneous movements were recorded at mean age 14 weeks post-term. The physiotherapists video-taped all infants with birth weight below 1000 grams and all infants who had suffered significant neonatal complications.

Adaptive and maladaptive behavior at 10-11 years (Paper II)

The primary study cohort (148 patients) included 74 ELBW children, of which 35 children were invited to participate (Figure 6). Four of these did not consent, 1 child was excluded due to severe autism and very low adaptive functioning, and another child was excluded because his mother did not know Norwegian or English well enough to perform the assessment.

In addition, 9 children with birth weight 1001-1500 g were included in the study; 7 with birth weight between 1001-1100 grams who had been on mechanical ventilator and 2 from a set of

triplets born in gestational week 29 (Figure 6). In sum, Paper II included 38 infants, whose clinical characteristics are shown in Table 5.

Table 5. Clinical characteristics of the very low birthweight group and the control group in Paper II.

	VLBW group without CP (n=28)		VLBW group with CP (n=10)		Control group (n=31)	
	Mean	(SD)	Mean	(SD)	Mean	(SD)
At birth:						
Gestational age (weeks)	26.8	(1.8)	26.4	(1.5)	40.2	(0.78)
Birth weight (g)	884	(217)	819	(213)	3599	(278)
Apgar 1 min	5	(3)	6	(2)	9	(1)
Apgar 5 min	7	(2)	7	(2)	10	(1)
Mechanical ventilator (days)	8.1	(11.5)	9.9	(13.2)	0	(0)
At follow-up:						
Age (years)	10.2	(0.8)	11.0	(0.7)	10.8	(0.7)
Socioeconomic status (SES)	3.3	(1.2)	3.6	(1.0)	3.9	(1.0)
Full scale IQ (WISC-III)[a)]	98	(17)	60	(21)	107	(18)
MABC-2[b)]	66.3	(17.5)	-	-	77.0	(12.8)
	n	(%)	n	(%)	n	(%)
Neonatal variables:						
Boys	9	(32.1)	8	(80.0)	13	(41.9)
Birth weight <1001g	22	(78.6)	7	(70.0)	-	-
IVH grade 1	7	(25.0)	2	(20.0)	-	-
IVH grade 2	4	(14.3)	0	(0)	-	-
IVH grade 4	0	(0)	4	(40.0)	-	-
PVL grade 1	0	(0)	1	(10.0)	-	-
Antenatal steroids	17	(60.7)	8	(80.0)	-	-
Postnatal steroids	7	(25.0)	3	(30.0)	-	-
Septicemia	8	(28.6)	3	(30.0)	-	-
Bronchopulmonary dysplasia	14	(50.0)	7	(70.0)	-	-
Surfactant	19	(67.9)	10	(100)	-	-
GMA at 14 weeks:						
Presence of fidgety and normal concurrent movements[c)]	12	(52.2)	0		-	-
Presence of fidgety and abnormal concurrent movements[c)]	10	(43.5)	3	(37.5)	-	-
Absence of fidgety and abnormal concurrent movements[c)]	1	(4.3)	5	(62.5)	-	-

WISC-III, Wechsler Intelligence Scale for Children-III; MABC-2, Movement Assessment Battery for Children-2; ELBW, Extremely low birth weight (<1000g); IVH, Intraventricular haemorrhage; PVL, Periventricular leukomalacia; GMA, General Movements Assessment

[a)] Data missing for 1 VLBW child with CP

[b)] Data not presented for the VLBW group with CP because only 3 children completed the test

[c)] Data missing for 2 VLBW children with CP and 7 VLBW children without CP

Ten of the VLBW children in Paper II had CP at follow-up; 9 had spastic CP (3 hemiplegic, 4 diplegic and 2 quadriplegic CP) and one ataxic CP. According to the Gross Motor Function Classification System (GMFCS) [140] , 5 children were classified with GMFCS level I, 2 children with GMFCS level II, 2 children with GMFCS level IV and 1 child with GMFCS

level V. None of the children were deaf or blind. Three children (including one child with CP) had hearing loss requiring a hearing device, and 8 children (including two children with CP) wore glasses.

Non-participants

There were no differences in gestational age or birth weight between participants included in Paper II and the 35 VLBW children followed in local hospitals (Table 6).

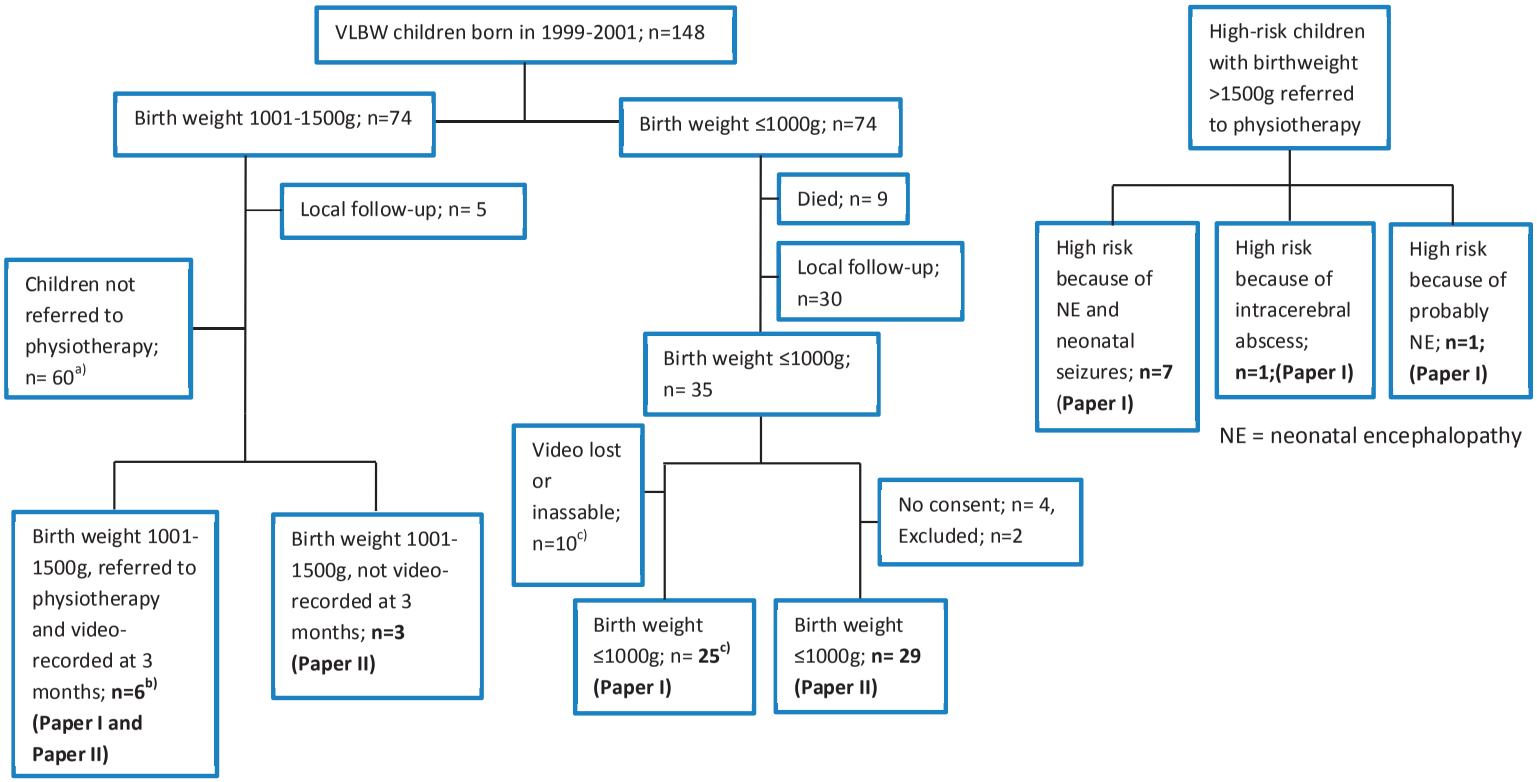
Table 6. Gestational age and birthweight of participants and non-participants in Paper II.

	Participants[a] (n=40)	Non-participants[b] (n=35)	*p-value*
Gestational age	26.5 (1.8)	27.2 (1.8)	0.145
Birth weight	857 (214.4)	875 (198.9)	0.696

[a] Including 2 infants who were excluded
[b] Gestational age missing for 11 non-participants

The control group

The term-born control children included in the study in Paper II were recruited from 4 schools in different areas of Trondheim. Teachers distributed letters of invitation to all pupils in the classroom. All pupils who accepted the invitation were included in the control group, approximately 10 children from each school. The controls were born at term in the same years as the study group, between 1999 and 2001.



a) The number of infants not referred to physiotherapy was 60, and not 62 as reported in Paper I
b) One of the 7 infants with birth weight 1001-1500 grams in Paper I only had video-recording in writhing period
c) One video was wrongly labelled as lost in Paper I, leaving 25 infants with birth weight ≤1000 grams in Paper I

Figure 6. Flow chart of participants in Paper I and Paper II.

Study population in the multicenter study

ELBW/ELGAN group

This study included 78 infants with a birth weight <1000 grams (ELBW) and/or a gestational age <28 weeks (ELGAN) born from Jan 1th, 2009 to Dec. 31st, 2012 from 3 hospitals in Norway. In addition, parents of 9 children in the same birthweight/gestational age group born in 2013 at Trondheim University Hospital were invited and consented to participate in the study. From the first university hospital 58 of a total of 86 infants where included. In the second hospital only 24 infants out of 135 could participate as most of their patients had their follow-up locally. From the third hospital 5 ELBW/ELGAN out of 40 infants were included, as most of the infants were included in other studies. Thus a total of 87 parents of ELBW/ELGAN infants consented to participate but 5 infants were excluded; 1 infant because of a plexus brachialis injury, one infant because of blindness, and the video recordings of 3 infants were not assessable because the infants were crying. Thus, 82 ELBW/ELGAN infants (35 girls and 47 boys) were assessed with the GMA and AMR at mean 12.3 weeks post term age. Gestational age was based on the second trimester routine ultrasound assessment. Information on birth weight, sex and any cerebral ultrasound abnormalities was collected prospectively in the multicenter cohort study.

Control group

A control group of healthy singleton, full-term infants with normal birth weight was recruited from local health centers and the maternity ward between 2010 and 2014. Only mothers with a normal pregnancy and delivery and infants with an uncomplicated neonatal period were invited to participate in the control group. Ninety-six healthy term-born infants were invited to participate in the study and consented. Two infants did not show up for the appointment, 5 appointments were cancelled because the infant was ill, and 2 video-recordings could not be assessed because the infants were not in the right state for assessment. Thus, 87 control infants (42 girls and 45 boys) were included whose clinical characteristics are shown in Table 7.

Table 7. Clinical characteristics of infants born extremely preterm and the control infants in Paper III.

	ELBW/ELGAN (n=82)		Control (n=87)	
	Mean	(SD)	Mean	(SD)
Gestational age (weeks)	26.6	(1.8)	39.6	(1.0)
Birth weight (g)	884	(217)	3689	(400.8)
	n	(%)	n	(%)
Boys	47	(58)	45	(52)
Birthweight ≤10th percentile	22	(33)	4	(5)
IVH grade ≥ 3	3	(4)	0	(0)
PVL	1	(1)	0	(0)
BPD	14	(17)	0	(0)
Treated ROP	4	(5)	0	(0)

SD= Standard deviation
ELBW= Extremely low birth weight
ELGAN= Extremely low gestational age newborn
IVH= Intraventricular hemorrhage
PVL= Periventricular leukomalacia (periventricular dilatation consistent with PVL on MRI)
BPD= Bronchopulmonal dysplasia (supplemental oxygen at discharge)
ROP= Retinopathy of prematurity

Summary of neonatal complications in the study populations

An overview of preterm born (VLBW or ELBW/ELGAN) participants with different neonatal complications is presented in Table 8.

Table 8. Number of children included in the papers and number and frequencies of bronchopulmonary dysplasia, periventricular leukomalacia (PVL) and intraventricular hemorrhage (IVH) grade 3-4.

	n	Born	BPD		PVL		IVH 3-4	
Paper 1	31	1999-2000	18	58%	3	8%	6	15%
Paper 2	38	1999-2000	21	55%	1	3%	4	11%
Paper 3	82	2009-2013	14	17%	1	1%	3	4%

BPD =Bronchopulmonary dysplasia
PVL = Periventricular leukomalacia
IVH = Intraventricular hemorrhage

Outcome measures at 3 months

Assessment of Motor Repertoire – 2 to 5 Months

In order to introduce a more detailed measuring approach for assessing motor repertoire during the age of fidgety movements, the Assessment of Motor Repertoire – 2 to 5 Months has been developed [39]. Based on the optimality concept [141], this assessment tool places emphasis on finding the best possible condition rather than finding normality, abnormality or pathology. It includes assessment of movements that co-occur with fidgety movements, for example wiggling-oscillating arm movements, swipes, hand-hand contact, hand-hand manipulation, fiddling with clothing, leg lifts, foot-foot contact, foot-foot manipulation, trunk rotation and axial rolling (Appendix B).

Procedure for video-recording for general movement assessment (GMA)

According to Prechtl, the infants should lay in supine position on a mattress without any disturbances from the caregiver or hospital staff [39]. Toys are removed as they will attract the infants' attention and therefore interfere with the spontaneous movements. The observer must be able to see the infant's face to make sure that possible rigid movements are not due to discomfort or crying. The room temperature should be comfortable, fitting the infant's age and clothing. The temperature can affect the infant's behavioral state and the movement quality. Most important for the assessment of GM quality is the correct behavioral state [40]. In infants older than 36 weeks recordings should preferably be performed during state 4 [40], which is characterized by an awake child with open eyes, irregular respiration, presence of movements, and absence of crying [142]. Einspieler et al. advise not to record the infant during the first three days after birth because physiological variables like respiration tend to fluctuate more in that period than they do later [39].

The duration of the recording depends on the age. From the FMs period onwards, 5 to t10 minutes of optimal recording is usually sufficient. Disturbances like soothing the infant with a dummy will result in a sucking posture; often with fingers in a fist, flexed arms and extended legs which will make it difficult to get the right picture of the infant's movement. The same happens if the infant is crying or during prolonged episodes of hiccups [39].

Six years ago, we did an examination of inter-observer reliability of the Assessment of Motor Repertoire – 2 to 5 Months (Appendix C) [70]. In the five subcategories, the degree of inter-observer agreement was identified by means of kappa statistics or expressed as percentage agreement if the κ (kappa) value could not be determined. [143]. The results were interpreted

according to guidelines adapted from Landis and Koch [144], [143]. For the Motor Optimality Score, ICC (2,1) statistics was applied to examine pairwise inter-observer agreement and agreement among all four observers. ICC (2,1) was chosen so the result could be generalized to other observers [145].

Inter-observer agreement for the total score was high (Appendix C). For pairwise agreement, ICC (2,1) values ranged between 0.80 and 0.95. Overall inter-observer agreement was 0.87. Variability among the observers was found to be high in case of children who scored in the middle range of the scale. The subcategory Fidgety Movements could only be expressed in terms of percent, 82%, 75% and 88% respectively. Moderate inter-observer reliability was achieved in the assessment of Repertoire of Co-Existent Other Movements, (κ values 0.48-0.69). Regarding the Quality of Other Movements, inter-observer reliability was moderate to high, with κ values ranging from 0.51 to 0.84. The assessment of Posture resulted in moderate κ values from 0.39 to 0.56. Movement Character appears to be the subcategory easiest to assess, since here the results were most consistent: κ values ranged between 0.54 and 0.84, with five values above 0.60.

In the follow-up study the assessments were carried out independently by one pediatrician and one child physiotherapist. They were blinded to the infants' medical histories. The assessments of the video-recordings were done 6 months before the examination of the 10 years old children. In the multicenter study the assessments were done by two experienced physiotherapists. First the classification of fidgety movements was done independently, followed by a detailed assessment of the concurrent motor repertoire for both of the studies. In case of disagreement, a consensus was reached, based on additional evaluations.

In Paper I and II FMs and the quality of the concurrent motor repertoire were classified according to Einspieler et al. [39] and the Assessment of Motor Repertoire – 2 to 5 months classification according to Bruggink et al. [63, 67, 78, 146]. However, in Paper III, we classified the FMs according to Figure 8 based on personal communication (C. Einspieler) and a recent paper where sporadic FMs were classified as abnormal [48].

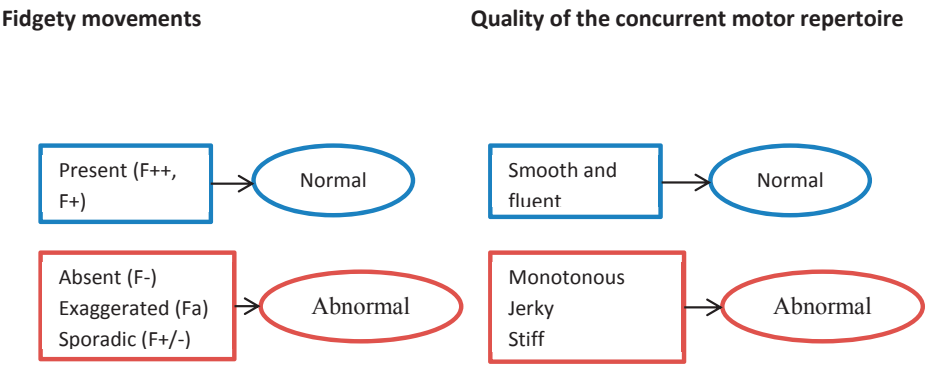


Figure 8. Classification of the fidgety movements and the concurrent motor repertoire.

Outcome measures at 10-11 years

Movement Assessment Battery for Children

Over the last two decades we have seen an increase in the knowledge of motor development, and we know more about the development and function of balance, postural control and eye-hand coordination than previously. The different strands of motor development are closely interwoven. Movement Assessment Battery for Children (Movement ABC) is a result from a long developmental process that started already in 1966. In 1972 the test was published as Test of Motor Impairment (TOMI). The purpose of the test was to discover and quantify motor problems in children at school age. Movement ABC is an improved version of TOMI. Although the test has not been standardized for Norwegian children, Mæland [147] concluded that the norms also are appropriate for Norwegian children, and the test is widely used in Norway.

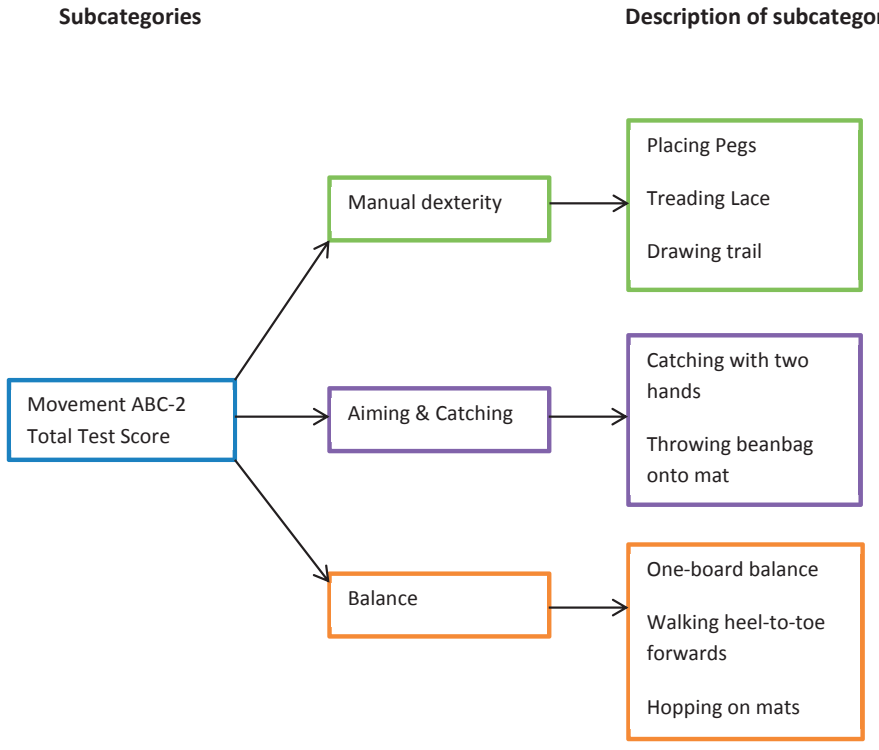


Figure 9. Internal structure of the Movement Assessment Battery for Children-2.

In the present study, the motor skills of the children at age 10 years were assessed by two physiotherapists according to the manual of the Movement Assessment Battery for Children-

Second edition (MABC-2) [148]. Both were blinded to the results of the early assessment of general movements and the concurrent motor repertoire. The MABC-2 consists of eight tasks grouped into three 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 $\leq 5^{th}$ percentile are indicative of definite motor problems, and were classified as poor motor outcome [148]. In the study group we had 10 children with cerebral palsy (CP), and two of them were able to complete MABC-2. The other 8 CP children were scored $\leq 5^{th}$ percentile and included as such in the statistical calculations for sensitivity and specificity.

For the MABC-2, which we used in our study, good inter-tester reliability has been shown among occupational therapists, physiotherapists, pediatricians, psychologists and human movement scientists. Chow and Henderson [149] examined MABC-2 inter-rater and test-retest reliability, employing two testers with quite different backgrounds of training, one an experienced educational psychologist, the other a relatively inexperienced occupational therapist. With the exception of a single item, ICCs for inter-tester reliability exceeded 0.95. Three studies have demonstrated the stability of children's scores on the Movement ABC test [149-151]. Croce and collaborators [150] reported good test-retest reliability across all four age bands of the original test. One hundred and six children between the ages of 5 and 12 years were tested twice by the same tester, one week apart. The ICC for total scores on the entire sample was 0.95, ranging across age bands from 0.92 up to 0.98. The Movement ABC-2 norms are derived from a validation sample representative of the UK population of children. A total of 1172 children participated in the study, and the tool has been standardized on children at age 3-16 years with norms for total score and subscores [148].

Evidence of the content validity of the Movement ABC test can be found in studies that correlate test scores with scores on motor tests that have a similar coverage including both gross and fine motor items; and studies that correlate test scores with scores on more narrowly focused tests involving, for example, only fine motor or gross motor items. Movement ABC relates well to other movement tests designed to measure a similar construct [148].

Comparing the test performance of two groups of individuals who would be expected to differ on the construct measured by a test is a common way of establishing test validity. Performance on Movement ABC by individuals belonging to different groups therefore provides important evidence on validity. Since the publication of Movement ABC in 1992,

more than 100 studies have been published that yield data relevant to this test's ability to distinguish between groups of children who might be expected to have movement difficulties and those whose motor development is typical for their age. Examples are children with or suspected of having Developmental Coordination Disorder (DCD), children with specific language impairments, children with Attention Deficit/Hyperactivity Disorder (ADHD), children with autism, with cognitive impairments or learning difficulties and children born at risk of motor impairment [148]. In Paper I and II, MABC-2 was used to measure motor performance both in the high-risk group and in the control group.

Wechsler Intelligence Scale for Children, third edition (WISC-III)

In this thesis the cognitive ability was measured using the Wechsler Intelligence Scale for Children, third edition (WISC-III) [152] (Figure10). The primary version of this test was developed by David Wechsler in 1991. WISC-III is an individually administered intelligence test for children between the ages of 6 and 16 years. The test can also be completed without reading or writing. Verbal IQ is based on ability to interpret and handle information, similarities, arithmetic, vocabulary and comprehension. Performance (non-verbal) IQ is based on the subtests picture completion, coding, picture arrangement, block design, and object assembly. Full scale IQ is based on all the ten subtests included in the verbal and performance (non-verbal) IQ scales [152].

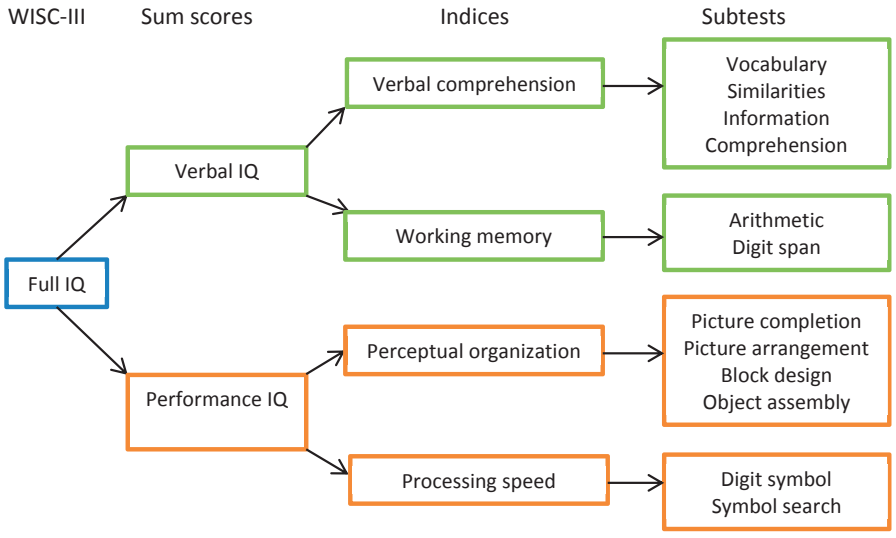


Figure 10. Internal structure of the Wechsler Intelligence Scale for Children, third edition (WISC-III).

Løhaugen et al. described [73] assessment of full scale IQ using WAIS (the adult version of the IQ test) among young adults born preterm with VLBW as a good screening method to identify cognitive problems in children born preterm who may need adapted education. On the WISC-III, the standard score scale has a mean of 100 and a standard deviation of 15. In Paper I in this thesis poor cognitive outcomes were defined as IQ <85, which corresponds to a score <-1 SD of the mean of a normative population [153] as some studies have shown this to be indicative of learning disabilities [154]. Data from more than 125 analyses on test validity of WISC indicate that test validity is strong and comparable when used both in medical and psychological conditions [155].

The cognitive assessment using WISC-III (Paper I and II) was performed by a pediatrician who was trained and supervised by an experienced neuropsychologist. Both were blinded to the general movement assessment results and group adherence.

Vineland Adaptive Behavior Scale, second edition (Vineland-II)

Adaptive behavior was assessed at 10-11 years using the Vineland-II parent/caregiver rating form [136]. The Vineland Adaptive Behavior Scales, second edition (Vineland-II) is an individually administered measure of adaptive behavior for ages from birth through 90 years and assesses abilities in the domains of communication, daily living skills and socialization (Figure 11).

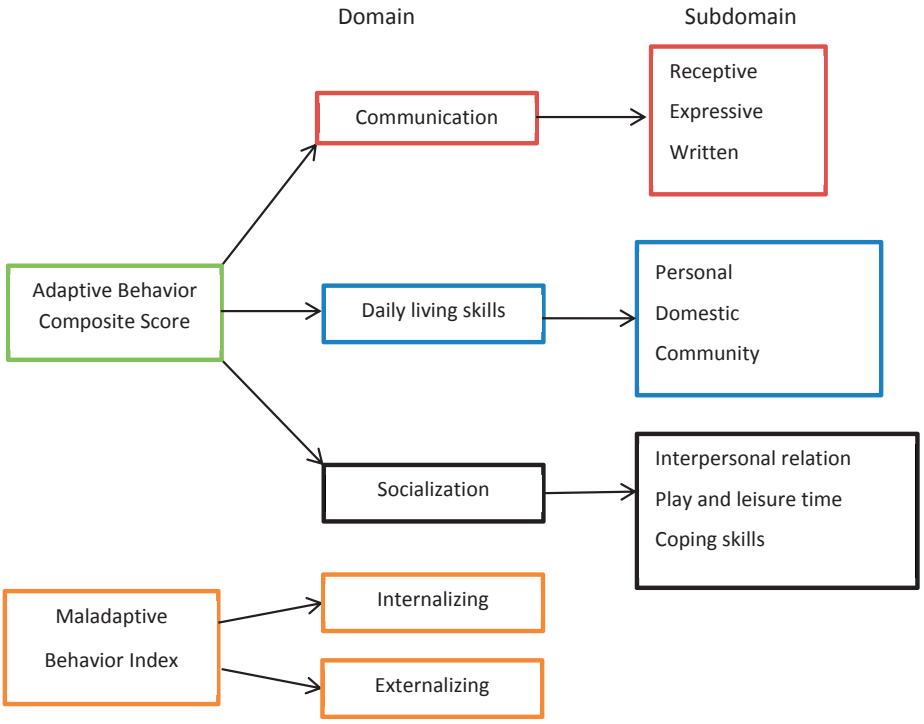
The communication domain consists of the subcategories of receptive, expressive and written communication, which reflect the child's ability to listen and understand, talk, read and write. Daily living skills consist of personal, domestic and community skills, expressing the child's ability to perform the activities of daily living. Socialization consists of the subcategories of interpersonal relation, play and leisure time as well as coping skills, all of which reflect the child's ability to interact with other people. These subcategories with 287 items in total add up to the Adaptive Behavior Composite score. A high score indicates better adaptive behavior. Vineland-II also contains a Maladaptive Behavior Index which reflects the children's internalizing and externalizing behaviors. Internalizing behavior represents the child's feelings, e.g. anxiousness or nervousness, sadness for no obvious reason, and their avoidance of social interaction. Externalizing behavior includes impulsive behavior, temper tantrums, etc. As opposed to the Adaptive Behavior Composite score, children with a high score on the Maladaptive Behavior Index have more problems.

The scales are available in two survey versions [136]: the Survey Interview Form and the Parent/Caregiver Rating Form, which assess adaptive behavior in the four domains of communication, daily living skills, socialization and motor skills, and also include a maladaptive behavior domain that assesses problem behavior. The two forms differ only in method of administration (interview versus rating scale for parents/caregivers).

The Expanded Interview Form offers a more comprehensive assessment of adaptive behavior within the four domains and provides a systematic basis for individual educational, habilitation, and treatment programs.

The Teacher Rating Form provides assessment of behaviors in the same four domains but focuses on readily observable behaviors exhibited in a classroom setting and includes items related to basic academic functioning.

In Paper II we used the Parent/Caregiver Rating Form, which is detailed in Figure 11.



A semi-structured interview with the children's parents, mostly mothers, provides information about the three different domains of adaptive behavior: Communication, Daily Living Skills and Social Skills. According to the manual, the domain Motor Skills is not included in the total Adaptive Behavior Composite when the child is 10-11 years of age. On the Vineland-II, as on almost all other individually administered assessment instruments, the standard score scale has a mean of 100 and a standard deviation of 15, and score distribution for the Adaptive Behavior Composite and domains have been normalized [136]. This measure is standardized based on extensive normative data.

Internal-consistency reliability of the domain and Adaptive Behavior Composite scores was computed on the basis of the subdomain internal-consistency reliability [136]. Reliability coefficients for domains are generally very high. The levels of consistency, with few exceptions, are clinically significant in the good to excellent range, by the criteria of Cicchetti [156]. To evaluate the test-retest reliability of the Vineland-II, a study was conducted using 414 respondents, ICC was used to estimate the test-retest reliability of the Vineland-II domains and subdomains [157]. Subdomain test-retest reliability coefficients were very high (0.85) and the Adaptive Behavior Composite retest reliability above 0.90. Inter-rater reliability measures the consistency of scores obtained from different respondents describing the same individual. 152 individuals participated in a reliability study where inter-rater reliability was measured to 0.81 for the Adaptive Behavior Composite score [136]. For the Maladaptive Behavior Index, the results of analyses of internal-consistency, test-retest, and inter-rater reliability were also high [136].

Validity refers to the degree to which test scores measure what they are supposed to measure, and many studies show clinical evidence of the Vineland-II as a reliable measure of adaptive functioning in patients with mental retardation, autism, Attention-Deficit/Hyperactivity Disorder (ADHD), Emotional/Behavioral Disturbance, learning disability, and visual and hearing impairments. Results from the Vineland-II document significant deficits in individuals with intellectual disability. The mean Adaptive Behavior Composite score and domain scores were at least two standard levels below the mean of the non-clinical group [136].

The controls in Paper II were examined using the same tests as the study group at the same age.

Socioeconomic status (SES)

SES was calculated using Hollingshead's Two-Factor Index of Social Position [158] which is based on education and occupation of one parent or the mean index of both.

Ethics

Both studies were approved by The Regional Ethics Committee (Study 1: 2010/121-9 and Study 2: 2011/1811). All parents gave their written informed consent. When invited to the follow-up study (Papers I and II), the children received a separate letter of information describing the nature, purpose and approximate duration of the tests. According to the recommendation from the Regional Ethics Committee, children determined to be in need of special health care based on their results from the follow-up testing were referred for further assessments. This was also the case for the children in the control group.

Statistics

SPSS Statistic version 19.0-21 (IBM SPSS Statistic, Chicago, IL, USA) was used for statistical analysis. Two-sided p-values less than 0.05 were considered statistically significant. Three-group comparisons were done by one-way ANOVA with Scheffe's post-hoc test for variables with normal distribution and two-group comparisons were done by Independent Samples *t*-test. Differences in non-parametric data were analyzed by the Mann-Whitney *U* test. Differences in proportions were analyzed using Pearson's chi-squared test or Fischer's exact test.

In Paper I, sensitivity, specificity and predictive values were calculated by cross tables and 95% confidence intervals (CI) were calculated using the Wilson method. In Paper II, univariate general linear models were used to investigate group differences in adaptive/maladaptive behavior with adjustment separately for sex, socioeconomic status (SES), and cognitive and motor functions, and to examine associations between adaptive/maladaptive behavior and neonatal variables and early motor repertoire in the non-CP VLBW group.

In Paper III, odds ratio with 95% CI was calculated as an estimate of the risk of having abnormal general movements and abnormal concurrent movements in the ELBW/ELGAN group as compared to the control group. Correlation coefficients between motor repertoire subcategories and gestational age and birth weight were calculated using Spearman's rho.

MAIN RESULTS

Results in papers included in thesis

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

In this this paper we used the Movement ABC-2 and WISC-III to identify motor and cognitive problems in a populated-based cohort of high-risk infants. In children with birth weight <1500 grams and the group of high-risk children with birth weight >1500 grams, 50% had a poor motor outcome defined as MABC-II score ≤5 percentile, and 40% had a poor cognitive outcome defined as IQ ≤85. In total, 58% had a pathological clinical outcome (motor and/or cognitive problems) at age 10 years. We also found that pathological outcome at 10 years of age was identified by the presence of fidgety movements and an abnormal concurrent motor repertoire at 14 weeks post-term age. 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 that most children with fidgety movements and a normal concurrent motor repertoire went on to have normal motor and cognitive outcomes at 10 years of age. In the children with presence of fidgety movements, the sensitivity of the quality of concurrent motor repertoire was approximately 0.90 both for motor and cognitive problems. The specificity, however, was lower; 0.65 (95% CI: 0.43-0.82) and 0.58 (95% CI: 0.39-0.76) for normal motor and cognitive scores, respectively. Normal clinical outcome at 10 years of age was found in most children with fidgety movements and a normal concurrent motor repertoire in infancy, but one third of children with a normal clinical outcome had had presence of fidgety movements and abnormal concurrent motor repertoire.

Paper II: Adaptive behavior in 10-11 year old children born preterm with a very low birth weight (VLBW).

In this this paper we used the Vineland-II to identify adaptive and maladaptive problems in a populated-based cohort of VLBW infants. Compared with the control group with Adaptive Behavior Composite score of mean 105.7 (SD 17.5) the VLBW group without CP had a lower Adaptive Behavior Composite score; mean 92.2 (SD12.3) and lower scores in the domains of daily living skills and socialization, but not in the fields of communication. Additionally, the scores for written communication, community, play and leisure, and coping skills were lower,

whereas the scores for internalizing and externalizing behavior and the Maladaptive Behavior Index score were higher than in the control group. The VLBW group with CP scored lower than the control group on the Adaptive Behavior Composite score and all its domains and subcategories. Compared with the control group, they also had higher scores for internalizing and externalizing behavior and on the Maladaptive Behavior Index.

The differences between the non-CP VLBW group and the control group were still significant after adjustment for sex, SES and the results of tests of motor and cognitive function. The differences between the VLBW group with CP and the control group were minor and mainly insignificant, except for the daily living skills after adjustment for IQ.

The presence of fidgety movements and an abnormal concurrent motor repertoire was significantly associated with a lower Adaptive Behavior Composite score and a higher Maladaptive Behavior Index in the VLBW group without CP, and explained 20% of the variance in adaptive behavior and 25% of the variance in maladaptive behavior at age 10 years. No significant associations were found between neonatal risk factors like gestational age, birth weight, Apgar scores at 5 minutes, presence of IVH, septicemia, bronchopulmonary dysplasia, the use of surfactant, and ante- or postnatal steroids and adaptive or maladaptive behavior in the VLBW group without CP.

Paper III: High Prevalence of Abnormal Motor Repertoire at 3 Months Corrected Age in Extremely Preterm Infants.

In this paper we used the General Movements Assessment and Assessment of Motor Repertoire –2 to 5 Months to investigate the motor repertoire in ELBW infants in a multicenter study. A higher proportion of infants in the ELBW/ELGAN group had exaggerated, sporadic or absent FMs when compared to the control group ($p<0.001$). Continual FMs were seen in 22 (25%) controls, while only 4 (5%) ELBW/ELGAN infants presented this finding ($p<0.001$). Almost all detailed aspects of the motor repertoire differed significantly between the groups. Hand–hand manipulation was twice as frequent in the control group as in the ELBW/ELGAN group and foot-foot manipulation was seen in 59% infants in the control group as opposed to in 38% in the ELBW/ELGAN group, – both differences significant (*p-values* 0.049 and 0.016 respectively). The quality of the concurrent movements was assessed as smooth and fluent twice as often in the control group as in the ELBW/ELGAN group.

The odds of having abnormal, absent or sporadic fidgety movements in the ELBW/ELGAN group was 12.0 (95% CI: 2.7-53.4) compared to the control group, and the odds of having an abnormal concurrent motor repertoire despite the presence of FMs were 4.1 (95% CI: 2.0-8.7).

Even after excluding ELBW/ELGAN infants with severe ultrasound abnormalities (IVH grade III-IV or PVL) in the analyses, differences in AMR remained statistically significant between the groups. No significant correlation between motor repertoire and gestational age within the ELBW/ELGAN group was found when the analysis was done with or without the 3 infants with severe IVH and/or PVL.

DISCUSSION

Main finding of the thesis

In a follow-up study of children at risk for developmental problems, we found that the quality of general movements and the quality of the detailed early motor repertoire in preterm-born children and a small group of infants with neonatal encephalopathy were predictive of motor and/or cognitive impairments at 10-11 years of age (Paper I). We found poorer adaptive behavior in VLBW children with and without CP at 10-11 years compared with a control group. There was an association between the early motor repertoire in VLBW infants without CP and their adaptive behavior at 10-11 years of age. These novel findings in the group without CP were still significant after adjustment for sex, socioeconomic status and cognitive and motor function scores, whereas the lower adaptive functioning in VLBW children with CP seemed mainly due to impaired cognitive function. Correspondingly, we also found increased maladaptive behavior in VLBW children with and without CP when compared with the controls (Paper II). In a multicenter study of ELBW/ELGAN infants, we found poorer quality of the early motor repertoire at 12 weeks corrected age compared with a matched control group of healthy term-born infants. Infants with presence of fidgety movements born extremely preterm had four times the risk of abnormal concurrent motor repertoire than controls (Paper III).

Validity of the thesis

In this chapter the following aspects concerning validity will be discussed: methodological considerations, the role of chance, bias and confounding as well as generalizability of the thesis/studies.

Methodological considerations

Inclusion criteria

The follow-up study (Paper I and II) was hospital-based and included mostly ELBW children, some VLBW children with additional risk of impaired neurological outcome and a few 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. As the primary aim of the study in Paper I was estimating sensitivity and specificity of GMA and the concurrent motor repertoire with respect to later neurological impairments, the heterogeneity of the study group was not regarded as a limitation.

In Paper II, we included only VLBW children; however 6 had birth weight between 1001 and 1100 grams and only 3 children had birth weight between 1100 and 1500 grams. Mean gestational age was 26.8 weeks (SD 1.8) and mean birth weight was 884 grams (SD 217) for the VLBW children without CP; mean gestational age was 26.4 weeks (SD 1.5) and mean birth weight was 819 grams (SD 213) for the VLBW children with CP. Consequently, from a clinical perspective this group could be regarded more as an ELGAN/ELBW group than a group of VLBW children. This should be taken into consideration when interpreting the results.

Paper III included a well-characterized group of ELBW/ELGAN and a group of term-born infants video-recorded at exactly the same age. The proportion of boys was almost similar in the ELBW/ELGAN group and the controls groups; 58% and 52% respectively. The patients constitute a non-selected cohort of ELBW/ELGAN infants from one university hospital and can be regarded as representative of this group of infants.

Outcome measures

GMA/AMR

In both the follow-up study and in the multicenter study, we classified fidgety movements according to Prechtl [38, 39]. These classifications were chosen since the observers had their training at and were certified by the General Movement Trust [39].

We have previously demonstrated moderate to high inter-observer reliability for the AMR [70]. Because of the paucity of outcome studies of sporadic FMs it is difficult to say for sure if to classify these movements as normal or abnormal. An association between sporadic FMs and impaired neurologic outcome has been described in recent studies [48, 62]. Sporadic FMs should possibly be classified along with absence of FMs as the outcome data shows association with later abnormal development [48]. In paper III [39, 48] we therefore classified sporadic fidgety movements as abnormal.

Movement ABC-2

Movement ABC-2 is a reliable and valid tool to identify motor problems [148]. In the follow-up study (Paper I and II), poor motor outcome were defined as Movement ABC-2 scores $\leq 5^{th}$ percentile. The 5^{th} percentile cut-off used in this thesis is in accordance with the manual and is widely used in clinics to identify the need for intervention in children with motor problems [148].

WISC-III

WISC-III is well-validated and widely used for assessing intellectual abilities [153] . Mental disability is usually defined as an IQ <70 (2 SD below the normative mean). However, an IQ below 85, corresponding to 1 SD below the normative mean, has been shown to be indicative of learning disabilities [154]. Thus, in the follow-up study we used an IQ <85 as a cut-off for poor cognitive outcome.

Vineland-II

The Vineland-II is a well-known, reliable and valid comprehensive rating form for parents of children born preterm to report their offspring's adaptive/maladaptive behavior [136]. It has often been used for assessing children with intellectual disability, autism and epilepsy, but only a few studies have used it in preterm populations [139]. At the time of data collection no standardized Norwegian translation of Vineland-II was available. Raw scores in the reports

were converted into standard and v-scale scores using American norms, which may not be optimal due to cultural and ethnic differences. To overcome this problem we used a local control group for comparison.

The role of chance

One of the major determinants of the degree to which chance affects the findings in any particular study is sample size [159]. As the sample size of the follow-up study was relatively small, as indicated by large SDs and wide confidence intervals, only large group differences and strong associations could reach significant levels (Paper I and II). Thus, negative findings in the follow-up study should be interpreted with caution due to the small simple size and the risk of a type II error.

In the multicenter study (Paper III), the sample size was larger, reducing the risk of underestimating differences and possibly increasing the risk of Type I errors. However, findings were consistent as almost all detailed aspects of the motor repertoire differed significantly between the groups, and the proportion of children with abnormal motor repertoire despite presence of fidgety movements was similar to that in Paper I.

In sum, the highly significant differences between groups on the Adaptive Behavior Composite score in the VLBW group and the controls (Paper II) ($p < 0.001$) and the ELBW/ELGAN and the controls with regard to the quality of fidgety movements and the concurrent motor repertoire (Paper III) ($p < 0.001$) indicate that these differences are unlikely to be due to chance.

The role of bias

Observation and information bias

In the follow-up study, the observers were blinded with respect to the infant's medical history. A strength of the thesis is that assessment of the video-recordings in all the studies was carried out according to standard procedures [39] by experienced professionals, blinded and time-independent from the outcome assessments. WISC-III was supervised and co-scored by a neuropsychologist, blinded to the clinical status of the children. In the multicenter-study one observer was blinded; however the second observer knew if the participants were controls or not without any knowledge about the medical conditions in the two groups. The fact that the observers were blinded reduced the risk of the judgement being affected by the knowledge of the infant's medical history.

Using parents as proxies in reporting outcomes for their children may have certain limitations. Parent-reports may be biased, as significant differences between self- and parent-reports have been described [160, 161]. For instance, it has been shown that VLBW adolescent girls report having more emotional and behavioral problems than observed by their parents [160]. However, using parent reporting is often the way of getting sufficient information about children in a follow-up study [162]. The fact that mostly mothers completed the questionnaires could potentially be a bias in Paper II. Nevertheless, no studies using Vineland-II have reported that mothers respond differently to the questions than fathers, and inter-rater reliability studies of the instrument show high agreement when two persons who know the child well answered the questions [136]. Additionally, the percentage of participating mothers was the same in the study group and control group, which makes comparison reliable.

Selection bias

Both the follow-up study and the multicenter study were population-based and prospective, which minimizes selection bias. Loss to follow-up is common in long-term follow-up studies [163], but in our follow-up study, all invited children who had video-recordings of their spontaneous movements in infancy, accepted. A weakness of the study in Paper I may be that it did not include all children admitted to the NICU in this period, as the GMA was not yet implemented as a routine assessment tool. As predictive values are dependent on the prevalence of the condition studied, it should therefore be kept in mind that we had a selection of high-risk patients referred to physiotherapy, not a whole cohort of children. Thus, one should probably focus more on sensitivity and specificity of the AMR than on the positive and negative predictive values. Furthermore, there were no differences in gestational age and birth weight between the survivors who were followed locally and those included in the follow-up study (Paper II).

In the multicenter study (Paper III), the cohort of ELBW/ELGAN infants consisted of 67 % of the total number of infants born at the first university hospital, and the study group could possibly be regarded as representative for the total cohort in that particular area. The selection in the second and third university hospitals was influenced by the routines for follow-up in local hospitals in those areas, and for the third university hospital also the involvement in other studies. The infants from the second university hospital were included because they for geographical reasons had their follow up at the hospital where they had had intensive care.

The infants who had their follow-up locally were hard to include for practical reasons. However, no calculations were done to prove similarities or differences between the patients included and who were followed-up locally.

Inclusion of infants in the studies was not influenced by the infants' medical history except for the inclusion criteria. The non-included infants were not included for practical, organizational or geographical reasons. Selection bias influencing generalizability is therefore not likely.

Confounding

When studying preterm children, CP and cognitive impairments could possibly affect the outcome. However, one can argue that these factors are mediators of the association between preterm birth and later developmental problems, and therefore need not be adjusted for. In Paper II, there were a higher proportion of boys in the control group. Socioeconomic status (SES) is known to be strongly associated with later outcome [164] and was higher in the control group. However, when we adjusted for sex, socioeconomic status, cognitive and motor function, the lower adaptive functioning was still significant for the group of VLBW children without CP, whereas in VLBW children with CP it was mainly due to low cognitive function. In the multicenter study we did not adjust for possible confounding factors, as there were no statistically significant sex differences and we did not have information on SES.

Generalizability

Even though the study population in the follow-up study (Paper I) is rather small and heterogeneous, it reflects the clinical challenges of high-risk infants, and we think therefore that results can be of relevance for other study populations of high-risk infants. The study group in the multicenter study (Paper III) was larger than in the follow-up study, and comprised a substantial part of ELBW/ELGAN infants born in that period. Thus, results are likely to be valid for other similar populations as well.

The follow-up study included children born 15 years ago, and one might question whether the results are applicable to infants born today. Nonetheless, they were all born in the post-surfactant period with advanced and improved neonatal care. As a result of this, more immature infants may survive, but morbidity has been shown to be stable [165]. The finding that the proportion of abnormal motor repertoire in preterm-born infants with normal fidgety movements was approximately the same in the follow up study (42%) as in the multicenter study (47%) indicate that this could be a general phenomenon in preterm infants. The two

study groups were born 13-14 years apart, and in that period neonatal intensive care improved even further, also supporting the assumption that abnormal motor repertoire is a consequence of prematurity and possibly impaired brain development.

Strength of the association

In the follow-up study (Paper I) we showed that 50% of the VLBW children had poor motor outcome and 40% had poor cognitive outcome at 10-11 years of age, numbers indicating a strong association between preterm birth and later developmental problems. In total, 58% had a pathological clinical outcome (motor and/or cognitive problems). The high sensitivity and negative predictive values indicate a strong relationship between quality of the concurrent motor repertoire and later motor and/or cognitive outcome, even though point estimates should be interpreted with caution due to limited sample size.

The VLBW group without CP had lower Adaptive Behavior Composite score and lower scores in the domains of daily living skills and socialization compared with the control group (Paper II). The group differences were approximately 10-15%, which we would argue reflects a clinically significant difference between the groups. The odds of having abnormal, absent or sporadic fidgety movements in the ELBW/ELGAN group was 12.0 (95% CI: 2.7–53.4) compared to the control group, and the odds of having an abnormal concurrent motor repertoire despite the presence of fidgety movements were 4.1 (95% CI: 2.0-8.7).

Biological credibility

In the follow-up study (Paper I) we found that the quality of the motor repertoire could predict later motor and/or cognitive impairments. This corresponds well with the cerebral MRI findings reported form the same group , showing a correlation between MRI at 10 years where cerebral white matter is reduced in children who had an abnormal motor repertoire at 3 months compared with those who had normal motor repertoire [166].

Another finding in the follow-up study (Paper II) was that there were no association between the total score of the Adaptive Behavior Composite score and the Maladaptive Behavior Index score at 10-11 years and the neonatal characteristics like degree of prematurity, need for ventilation support, presence of IVH or BPD. A possible biological negative effect of these neonatal factors seems to have vanished during the first 10 years of life. The only early marker identified in this paper of the difference between the preterm children and the controls except for the prematurity itself seems to be the quality of the motor repertoire at three months of age.

In Paper III, the presence of IVH grade III-IV and/or PVL in 3 infants, of whom only one lacked fidgety movements, did not explain the difference between the preterm and term group with respect to early motor repertoire. It could be that severe brain abnormalities seen on cerebral ultrasound mainly indicate later major handicaps like CP and intellectual disability, whereas the motor repertoire is a general expression of early brain development and associate better with milder motor and cognitive and behavioral outcomes [71]. The difference between the extremely premature and the controls could be explained simply by delayed brain maturation, but could also be explained by white matter injury not seen by ultrasound or conventional magnetic resonance imaging [7]. Ten percent of the infants in the ELBW/ELGAN group had absence of fidgety movements, but whether this reflects a 10% prevalence of CP in the extremely preterm population [8] remains to be verified. The significance of the temporal organization of fidgety movements is unclear except for the well-established relationship between absence of fidgety movements and CP [42]. Based on the findings in Paper III it could be tempting to suggest that prematurity itself is responsible for the differences between the two groups. However, alternative explanation could be that environmental conditions for preterm neonates both in the NICU and after discharge from the hospital are different from term-born infants, resulting in both impaired motor repertoire at 3 months and possible later impairments. None of these environmental factors, as well as additional effects of intrauterine alcohol or smoking exposure, have been investigated in this study.

When analyzing the subcategories of AMR in the ELBW group, it turned out that the preterm infants expressed the same number of normal (or abnormal) movement patterns as the term-born control infants. As this is one of two categories describing the quantity of concurrent movements, one may speculate that preterm birth affects the quality more than the quantity of movements.

Our findings of an association between preterm birth, abnormal concurrent motor repertoire and later outcome suggest brain injury because of preterm birth as a common cause.

Consistency with other investigations

Early motor behavior and motor and cognitive functions at 10-11 years of age (Paper I)

Our findings 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 (Paper I) is in line with studies by Bruggink et al. [63]. They 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. Bruggink et al. [78] 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. In a study by Butcher et al. [71] spontaneous movement quality was assessed at 11 to 16 weeks post term in 65 infants born at ≤33 weeks of gestation. Intelligence, behavior 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, attentional outcome.

As has been reported in several studies [42, 65], we confirmed that absence of fidgety movements is a strong predictor of later CP based on the findings that 9 out of 12 children with CP at 10 years of age showed no fidgety movements in infancy. Two of the remaining children with CP had sporadic fidgety movements, which in Paper I was classified as normal fidgety movements. If these had been classified as abnormal fidgety movements, as is now being advocated [48], GMA would have been able to identify almost all children who developed CP.

The proportion of VLBW children with poor motor and cognitive outcome of around 40-50% at 10-11 years of age (Paper I) is in line with other studies [10, 81, 107, 167]. Several studies have found an association between later cognitive impairments and the quality of fidgety movements and the concurrent motor repertoire [71, 78, 168]. In Paper I, cognitive and motor outcomes were highly correlated and only two children had an isolated poor cognitive outcome. Therefore, it could be that the relationship between early motor repertoire and cognition is mainly due to an association with the combination of motor and cognitive problems.

The follow-up study of adaptive behavior at 10-11 years of age (Paper II)

One of the main new findings of the follow-up study is the consequences for individuals' daily functioning (Paper II) within the ICF domain of participation, instead of just assessing motor and cognitive outcomes within the activity domain [148, 153]. This is the first follow-up study of adaptive behavior in a cohort of VLBW children with and without CP. However, as mentioned before, the results in this study probably apply best to children with birth weight

less than 1000 grams as the mean birth weight of the preterm group with and without CP was 854 grams (SD 214.4).

When Vineland-II has been used in follow-up studies of children born preterm, the main focus has been on consequences of medical complications of prematurity or specific treatment methods [169]. Hack et al. [139] found that ELBW children, including children with CP, differed significantly from children born at term with respect to social adaptive functioning. Even more interesting is that the findings remained significant when neurosensory-impaired children were excluded, indicating that prematurity itself could be a contributing factor.

The maladaptive behavior in preterm children has been reported in studies before, and the findings in our study (Paper II) are in line with other studies. Lund et al. [137] shows that being born preterm with VLBW may have a long-term negative influence on mental health, into adulthood. The VLBW group had predominantly internalizing problems on self-report and mental health scores were reduced when adjusting for IQ in this group.

However, an interesting and novel finding of this thesis is the association between adaptive and maladaptive behavior scores and the children's abnormal concurrent motor repertoire in infancy. Even if abnormal concurrent motor repertoire explained only 20% of the variation in the adaptive scores and 25% of the variation in maladaptive scores this could be a clinically important observation indicating an increased risk of developing adaption problems in children with presence of fidgety movements but an abnormal motor repertoire in infancy.

The multicenter study of motor behavior in extremely preterm infants (Paper III)

The study in paper III of this thesis is the first study to compare several aspects of the motor repertoire between a well-characterized group of ELBW/ELGAN infants and an age-matched term-born control group. Interestingly, we found significant group differences in almost all subcategories of the early motor repertoire. Several studies have reported abnormal general movements in preterms [30, 43]. However, fewer studies have assessed the motor repertoire in addition to the general movements (Appendix A). The risk of having abnormal quality of the concurrent movement repertoire along with normal fidgety movements was much higher in the ELBW/ELGAN group than in the control group, and all but one of the subcategories of AMR differed between the two groups. A new finding presented in paper III is that continual FMs were rarely seen in the preterm group, while intermittent FMs were equally frequent in the two groups. A recent study which does not distinguish between continual and intermittent FMs showed that 21 out of 29 infants born preterm (72%) had continual FMs, 6 infants had

sporadic FMs, and 2 infants had no FMs [68]. According to Einspieler et al., [39] this temporal organization of FMs varies with age in the fidgety period. It could therefore be that the rare occurrence of continual FMs in the extremely preterm group compared with term infants may reflect delayed maturation, but whether this would influence clinical outcome remains to be seen.

Hitzert et al. [60] found that as many as 58% of term-born infants showed an abnormal quality of concurrent movements in contrast to our study, where 20% of the control infants had an abnormal quality of concurrent movements. Even if the percentages are highly different, both studies show that abnormal quality of early motor repertoire, as identified by AMR, is quite frequent in a healthy population. Nevertheless, Hitzert et al. [60] reported that an abnormal quality of the concurrent motor repertoire was associated with behavior problems in early school age in healthy term-born children. Further studies should be performed to evaluate the long-term predictive value of the fidgety movements and abnormal quality of the concurrent motor repertoire in low-risk infants.

Given the predictive value of AMR for later motor and/or cognitive outcomes (Paper I), it may be surprising that we did not find a correlation between AMR and gestational age or birth weight (Paper III), as others have reported increased risk of adverse outcomes with lower gestational age [3]. However, our study group was probably too small with insufficient power to detect any possible week by week difference in AMR caused by differences in gestational age. The predictive value of AMR with respect to different aspects of neurodevelopmental outcome is still uncertain, and more follow-up studies are needed. As the incidence of severe IVH and PVL decreases, the need for early and accurate clinical tools to identify those with the highest risk of less severe yet still adverse outcomes is even more important. It is not known whether AMR alone is sensitive enough for that purpose, but it may in combination with quantitative MRI [166] or inflammatory biomarkers [170] be a valuable prognostic tool.

Function as an outcome measure

According to ICF, function is a complex concept involving body function and structure, activity and participation and is influenced by health conditions and environmental and personal factors. In this thesis, the main focus has been the influence of health conditions, first of all prematurity. Though control groups have been used in two papers, this cannot fully compensate for the concomitant influence of both environmental and personal factors. It is possible that the results presented in both Paper I and Paper II are additionally influenced by

environmental factors like follow-up programs, extra help in school and support from society and family. In Paper III, differences in motor repertoire were described when comparing a group of ELBW children with a group of infants born at term. It is however likely that these differences are not only due to health conditions (prematurity and related complications) but may also be influenced by very different care and environmental conditions in the first 3 months of life. Function as an outcome measure must therefore be interpreted in this rather complex context.

CONCLUSIONS

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 high-risk children who do not develop CP. Furthermore, most children with normal clinical outcome were identified by a normal concurrent motor repertoire in infancy. This finding could help to start individualized early intervention programs in those at risk and reassure parents whose children develop normally. VLBW children, both with and without CP meet greater adaptation challenges in preschool and school age than their peers born at term, even after adjustment for possible confounders like sex, socioeconomic status, and cognitive and motor skills. The presence of fidgety movements accompanied by an abnormal motor repertoire in infancy could therefore also be a valuable early clinical marker of an increased risk of maladaptive and impaired adaptive behavior in VLBW children without CP. The multicenter study (Paper III) describes poorer quality of the early motor repertoire at 12 weeks corrected age in a group of ELBW/ELGAN infants when compared with term-born infants. Preterm infants with presence of fidgety movements had an increased risk of abnormal concurrent motor repertoire that was four times higher than controls. The comprehensive consequences of these early abnormal movement patterns have to be evaluated in future larger follow-up studies. However the follow-up study suggests a strong association between an abnormal motor repertoire and later neurological impairment.

CLINICAL IMPLICATIONS AND FUTURE RESEARCH

The Norwegian Directorate of Health's guidelines for follow-up of preterm born ELBW/ELGAN babies and other high-risk neonates, which recommend multidisciplinary follow-up until 5 years of age, is currently applied at all hospitals in Norway [1]. However, the results from the long-term follow-up studies in this thesis indicate that problems present at 10-11 years of age may evolve during childhood and school age. This is also in accordance with our research group's other long-term follow-up studies on preterm children from year cohorts born in the late 80s [107, 117, 130]. It is of great importance to have good methods to reveal neurodevelopmental problems at an early stage and to start appropriate intervention as early as possible. Recent research indicates that early intervention can help the brain to reorganize aberrant signal patterns [171-173] and increased awareness and support from family, society and school is probably helpful [120]. However, this new knowledge makes it even more important to select the infants at risk who really need intervention programs instead of treating all as a group. For the purpose of discovering children with adaptive and maladaptive problems, the Vineland-II survey seems to be a promising and valuable tool used in routine follow-up programs for preterm born children.

Each year, approximately 700 children in Norway are born premature with birth weight below 1500 grams, and fortunately most of them survive [1]. However, a significant percentage of these children, even in the absence of major neuroimpairments like CP and intellectual disability, will need specific intervention or more general support from schools and communities [121]. It seems that the specific and general need for support and adaption persists through adolescence and into adulthood for many of these preterm born survivors [130]. To be able to handle these challenges, the healthcare and social system have two options: one is to design and run an ongoing follow-up program for these children all the way through school age and adolescence, and the second option is to develop diagnostic tools with high enough sensitivity and specificity with respect to future needs. Just as important is to be able to reassure parents as early as possible that their children will develop normally and not suffer any longstanding problems caused by their preterm birth. Until now no single instrument has been able to predict outcome for premature children with no or only minor neonatal risk factors. GMA and AMR seem to be valuable methods for predicting CP but also for identifying infants with very low risk of impaired motor, cognitive and adaptive functioning. Based on the results of this thesis, we would argue that GMA and AMR are very valuable instruments which could be applied to all infants neurologically at risk, in addition to

other clinical evaluations and imaging techniques. GMA and AMR require observers with specific skills and experience but are otherwise cheap and convenient to perform and involve no risk for the patient.

Future research calls for several approaches. First of all it is necessary to establish an international agreement on terminology to make sure that scientists describe the various fidgety and concurrent movement qualities uniformly, and new large-scale multi-center reliability studies have to be conducted using this unified terminology.

As present subjective analyses require human skills and experience, it is critical to establish standardized computer-based technology for movement analysis. This could increase both sensitivity and reliability of the method, and also make it possible to analyze longer sequences. When developing computer-based technology, emphasis should be put on studying the quality of the concurrent movements and not only the quality of the fidgety movements. Studies of sensitivity and specificity with respect to outcome have until now been conducted based on relatively small heterogeneous cohorts [62, 63, 71], and larger multi-center studies of well characterized groups of infants are therefore needed. Larger studies to characterize general movements and additional concurrent motor repertoire in premature children are also required as the quality of these movements seems to differ significantly from those in term-born infants. The implication of these findings needs to be clarified in longitudinal follow-up studies, as it is not obvious if an early pathologic motor repertoire is a temporal phenomenon or indicates a permanent disturbance leading to later neurological impairments, even if the relationship between lack of fidgety movements and later CP seems well-established [42]. The results presented in this thesis indicate that there are other qualities of the motor repertoire than fidgety movements which can give valuable information for predicting future neurological functioning. More studies of fidgety movements and additional concurrent motor repertoire, and preferably using automated techniques in larger cohorts, could hopefully uncover information of value for predicting neurodevelopment in children born preterm.

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Appendix A

Studies on general movements and a detailed assessment of the motor repertoire from the years 2005-2015.

Author	Aim	Sample	Born	Results
2015				
Einspieler et al. [174]	To explore the appropriateness of applying a detailed assessment GMs and characterize the relationship between global and detailed assessment in wrighting age.	783 video recordings of 233 infants (154 males, 79 females)	Infants from 1990	General movement optimality scores (GMOS) differentiated between normal general movements, poor repertoire general movements, and cramped-synchronized general movements. The optimality score for chaotic GMs was similar to those for cramped-synchronized general movements. Short-lasting tremulous movements occurred from very preterm age to post-term age across all GMs categories, including normal GMs. The detailed score at post-term age was slightly lower compared to the scores at preterm and term age for both normal ($p=0.02$) and poor repertoire GMs ($p<0.01$).
Hitzert et al. [175]	To determine whether preterm born infants reach mature levels of movement variety (the number of different movement patterns) and visual attention earlier than full-term. Second, to determine whether individual developmental trajectories of movement variety and visual attention were associated. Finally, comparing the associations of developmental trajectories between full-term and preterm infants.	20 term-born 9 preterm	2000-2002	During the first 6 months post-term, movement variety and visual attention developed independently. Temporarily, preterm exposure to the extra uterine environment led to shorter latencies of looks but it did not affect developmental trajectories of frequencies of looks and movement variety.
Fjørtoft et al. [80]	To compare adaptive behavior in 10-11 year old VLBW children with and without cerebral palsy (CP) to term-born children, and examine its relationship with neonatal factors and infant motor repertoire in VLBW children without CP	38 VLBW children and 31 term-born control children	1999-2001	Among VLBW children without CP, the quality of an abnormal infant motor repertoire at 14 weeks post-term age was significantly associated with a lower Adaptive Behavior Composite score at 10-11 years of age $r^2 = 0.20$, $p = 0.03$.
Einspieler et al. [48]	To determine whether infants who had developed CP and had sporadic fidgety movements have a better outcome than infants who did not have FMs.	61 infants who developed CP (46 male, 15 female; 29 infants born preterm)	2003-2010	There was no difference between children diagnosed with CP who had sporadic FMs at 9 to 16 weeks post-term age ($n = 9$) and those who never developed fidgety movements ($n = 50$) with regard to their functional mobility and activity limitation at 3 to 5 years of age. One infant had normal FMs and developed unilateral CP, GMFCS Level I; the remaining infant had abnormal FMs and developed bilateral CP, GMFCS Level II.
Marschik et al. [176]	To add to the knowledge of the abnormal early motor repertoire we analyzed prospectively collected video recordings of a boy clinically diagnosed with Cornelia de Lange syndrome.	Case report		The observed atypical GMs are a further step to disentangle early motor peculiarities in the light of the genetic impact on the developing brain.

2014				
Grunewaldt et al. [166]	To investigate functional outcome and cerebral MRI morphometry at 10 years in extremely low birth weight (ELBW) children without CP compared to healthy controls and to examine any relationship with the quality of infant-motor-repertoire included in the GMA.	31 ELBW infants	1999-2001	The non-CP ELBW children had similar full-IQ but poorer working memory, poorer motor skills, and 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. Poorer test-results and reduced brain volumes were mainly found in ELBW children with fidgety movements combined with the quality of an abnormal motor repertoire in infancy.
Hitzert et al. [177]	To determine the effect of HC and DXM therapy in preterm infants on neurological functioning as assessed by the quality of GMs until 3 months after term	17 preterm	2010 and 2012	GM/FM quality improved in 9 out of 13 initially abnormal infants (p = 0.004).Of the surviving infants, neurological functioning improved with the majority having normal neurodevelopment at the age of 12-36 months.
Hitzert et al. [60]	To determine whether motor development at 3 months of age is associated with cognitive, motor, and behavioral outcomes in healthy children at early school age.	74 full-term	2001-2002	Children with a monotonous motor repertoire experienced behavior problems. Detailed aspects of motor development at 3 months of age are associated with cognition and behavior, but not with motor outcome. An age-adequate motor repertoire, in particular the presence of antigravity, midline leg, and manipulation movements, was related to poorer cognition, whereas variable finger postures were related to better cognition. Children with a monotonous concurrent motor repertoire had better ball skills but experienced more behavioural problems. The presence of antigravity movements tended to be associated with abnormal recognition (odds ratio [OR] 4.4, 95% confidence interval [CI], 0.9-21; R(2) =0.17; p=0.070), where the absence of variable finger postures was associated with borderline and abnormal visual-spatial perception (OR 20, 95% CI, 1.7-238; R(2) =0.39; p=0.018).
Ploegstra et al. [178]	To assess the quality of GMs and to determine the motor optimality score (OS) in healthy full term infants during the first week after birth and to evaluate the influence of the mode of delivery on GM quality.	33 full-term infants in wrighting age	2009-2011	Abnormal GMs were observed mainly on the early recordings: 86% on the day of birth (day 0), 94% on day 1, and 68% on day 2. On days 5 to 7 (day 5-7) all GMs were normal (P<.001). The OSs increased significantly from median 12 on day 0 to 18 on day 5-7 (P<.001). Monotonously slow movements were frequently seen during the first days but not on day 5-7 (P<.001). GM quality and OS did not differ between infants born by vaginal delivery or after CS under spinal anesthesia.
2013				
Berghuis et al. [179]	To determine whether prenatal background exposure to PCBs and OH-PCBs was associated with the motor development of three-month-old infants.	97 mother-infant pairs	1998-2000	We found several associations between PCB and OH-PCB levels and motor optimality score (MOS), including detailed aspects of the early motor development. High 4-OH-PCB-107 levels were associated with a low MOS (P=.013). High PCB-187 levels were associated with reduced midline arm and leg movements (P=.047 and P=.043, respectively). High 4'-OH-PCB-172 levels were associated with more manipulation (P=.033).
Fjørtoft et al. [62]	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.	40 neurologically high-risk infants	1999-2001	Among the high-risk children with presence of FMs, 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.

2012				
Hitzert et al. [180]	To determine the effect of HC and DXM therapy in preterm infants on neurological functioning as assessed by the quality of GMs until 3 months after term.	56 preterm born <32 weeks 22 Controls	1992-2000	MOS decreased in DXM infants on the first day following treatment and at 3 months after term.
Hitzert et al. [181]	A report about the first case of an infant, prenatally diagnosed with MoCD type A, whom we started on treatment with cPMP 4 hours after birth.	Case report	2012	The most reliable method to evaluate neurologic functioning in early infancy is to assess the quality of GMs and FMs. After a brief period of seizures and cramped-synchronized GMs on the first day, our patient showed no further clinical signs of neurologic deterioration. Her quality of GMs was normal by the end of the first week. Rapid improvement of GM quality together with normal FMs at 3 months is highly predictive of normal neurologic outcome. We demonstrated that a daily cPMP dose of even 80 µg/kg in the first 12 days reduced the effects of neurodegenerative damage even when seizures and cramped-synchronized GMs were already present. We strongly recommend starting cPMP treatment as soon as possible after birth in infants diagnosed with MoCD type A.
Yang et al. [76]	To determine whether an association between the early motor repertoire and the GMFCS also holds true for children born at term	60 boys and 19 girls; 47 infants born at term	2003-2009	Motor optimality at age 3 to 5 months showed a significant correlation with functional mobility and activity limitation as classified on the GMFCS at age 2 to 5years in both children born at term and born preterm . Infants born preterm were more likely to show normal movement patterns than infants born at term. A normal posture and an abnormal, jerky (yet not monotonous) movement character resulted in better levels of function and mobility. With the exception of one, none of the infants showed FMs. A cramped-synchronized movement character, repetitive opening and closing of the mouth, and abnormal finger postures characterized children who would show a poor self-mobility later
2011				
De Vries et al. [61]	To assess the motor repertoire of extremely low-birthweight infants at term-equivalent age (TEA), in relation to their neurological outcome.	13 ELBW infants	2003-2004	Abnormal general movements at TEA are common in extremely low-birthweight infants. GMs often appear stiff and cramped with extended legs. At the age of 3 months after term, general movements are mostly normal, but concurrent movements are not. Nevertheless, these abnormalities do not imply an impaired neurological outcome such as cerebral palsy.
Yuge et al. [66]	To implement a more detailed assessment of GMs and co-existing movements and postural patterns in a rehabilitation clinic, and to examine to what extend is the optimality of movements and postures of infants aged 3 to 5 months related to perinatal events and the neurological outcome.	46 infants whereas 11 preterm were admitted to pediatric neurology and rehabilitation department	2003-2005	Motor optimality at age 3 to 5 months correlated positively with neonatal optimality ($r=0.48$, $p<0.01$), especially regarding factors associated with hypoxic events. A non-optimal motor performance (lowest possible scores) predicted cerebral palsy with 100% accuracy. Other adverse outcomes such as developmental delays, developmental coordination disorders, pervasive developmental disorder or attention deficit hyperactivity disorder turned out not to be associated with early motor performance. In 13% of cases absence of fidgety movements proved to be false positives, but their normal appearance along with a smooth concurrent motor performance was solely found in infants with a normal neurological development.
Cahed-Cheikh et al. [182]	To describe general movement in extremely premature infants and examine correlations with risk factors for antenatal, perinatal, and postnatal	19 preterm-born infants below 28 weeks	2008-2009	Infants' motor activity fluctuated during the WM period, especially in extremely premature infants where poor repertoire is often observed. No correlations were found between WMs and obstetric factors. Gestational age correlated with WMs' quality ($p=0.023$). WMs correlated with factors of

	morbidity.			postnatal morbidity such as chronic lung disease (CLD) (p=0.034) and nosocomial infections (p=0.05). At 3 months corrected age, the spontaneous movement quality are correlated with neurological explorations such as US brain (p=0.032), MRI (p=0.039), EEG (p=0.036), and neurological follow-up assessments (p=0.015).
Hamer et al. [183]	To determine whether specific movement characteristics can improve the predictive power of definitely abnormal GMs	46 preterm-born infants below 32 weeks (all with definitively abnormal GMs)	2003-2005	Of the 46 assessed infants, 10 developed spastic CP (Gross Motor Function Classification System levels I to V; eight bilateral spastic CP, two unilateral spastic CP). The absence of FMs and the presence of predominantly stiff movements were associated with CP and lower Infant Motor Profile scores; stiff and predominantly stiff movements were associated with lower Alberta Infant Motor Scales scores. Cramped synchronized movements and the asymmetrical tonic neck reflex pattern were not related to outcome. None of the movement characteristics were associated with Pediatric Evaluation of Disability Inventory scores or the Mental Developmental Index.
2010				
Bruggink et al. [78]	To determine whether the quality of GMs for preterm children had predictive value for cognitive development at school age.	60 preterm-born infants without CP	1992-1997	The median TIQ was 93 (range: 67-113), VIQ 96 (range: 68-117), and PIQ 92 (range: 65-119). Fifteen children (25%) had low TIQ scores (<85). When the quality of GMs normalized before 8 weeks after term, TIQ, VIQ, and PIQ scores were in the normal range. Consistently abnormal GMs to 8 weeks after term were associated with lower TIQ, VIQ, and PIQ scores. With correction for male gender and the educational levels of the parents, the likelihood ratio of consistently abnormal GMs for a low TIQ was 4.9 (95% confidence interval: 1.3-17.6). The model explained 22.4% of the variance.
De Vries et al. [184]	To assess the quality and evolution of GMs during the first ten days of life in preterm infants, and relating them to clinical factors and neurological outcome at 24 months' post-term.	45 preterm infants	2003-2004	Abnormal GMs were seen mostly in early recordings. A better GM trajectory correlated with a higher birthweight, a higher gestational age and a lower Nursery Neurobiologic Risk Score (NBRS). Predictive value for normal outcome of at least one normal GM was 94%. Predictive value for abnormal outcome of only abnormal GMs was 21%. ChF were seen mostly in early recordings. Occurrence of ChF on day 2 correlated with lower serum Calcium.
Guzzetta et al. [185]	To explore the predictive value of quantitative assessment of hand movements in 3 month old infants after neonatal stroke.	Thirteen infants born at term (five females, eight males with neonatal arterial ischemic cerebral infarction, and 13 healthy infants	2004-2007	Five of the 13 infants with neonatal stroke had normal neurological development, and eight had hemiplegia. Asymmetry of wrist segmental movements and the absolute frequency of independent digit movements were significantly different between infants with and without hemiplegia (p=0.006 and p=0.008, respectively). No differences were found in global hand movements.
Kodric et al. [186]	To analyze the results of the assessment of GMs in relation to the developmental outcome measured by the Bayley scales of infant development in a group of preterm infants.	Twenty-six preterm infants	2002-2004	Infants with normal writhing GMs achieved the highest scores on the mental and psychomotor developmental index, and those with cramped-synchronized general movements had the lowest scores. Infants with normal general movements during the fidgety period achieved the highest scores on both scales; those with an absence of FMs achieved the lowest scores. We found the sensitivity of GMs to predict cognitive impairments to be 1.00 during the writhing period and 0.83 during the fidgety period; and 0.85 and 0.54, respectively, to predict motor impairments. The differences in the

				mental developmental index score between the groups with different qualities of GMs were significant in the writhing period and approached significance in the fidgety period, while for the psychomotor developmental index the differences between the groups with different qualities of general movements were not significant
2009				
Fjørtoft et al. [70]	To determine inter-observer reliability of the "Assessment of Motor Repertoire 3 to 5 Months"	24 infants (gestational age from 24 weeks to 42 weeks)	1999-2005	The present study on inter-observer agreement in the "Assessment of Motor Repertoire — 3 to 5 Months" has produced satisfactory kappa values for the subcategories and high ICC values for the total score. The subcategory "Fidgety Movements" showed high to very high inter-observer agreement across the 6 pair-wise analyses, while there was less agreement in the other subcategories, ranging between moderate and high.
Bruggink et al. [187]	To investigate (1) the course of the spontaneous motor repertoire during the first months of age, and (2) its relationship to the later neurological and developmental findings in infants presenting with a severe IEM in the neonatal period.	5 infants with inborn error of metabolism	1999-2002	This study showed that the assessment of the quality of the early motor repertoire might be helpful to assess neurological outcome at 2 to 3 years of age in infants with a neonatal presentation of an (inborn errors of metabolism) IEM. Specifically the quality of FMs and concurrent motor repertoire between 11 and 16 weeks post term age were associated with neurological outcome.
Bruggink et al. [67]	To investigate whether quantitative aspects of the motor repertoire between 6 and 24 weeks post-term also have predictive value for neurological outcome at 7 to 11 years of age.	82 preterm <1500 grams	1992-1997	If FMs are normal at 11–16 weeks post-term, a smooth, variable concurrent motor repertoire is a marker for a normal outcome and the risk for developing MND is low (5%). If the concurrent motor repertoire is abnormal, the presence of a spontaneous obligatory ATN posture identifies the infants at high risk for developing MND (75%), whereas the absence of an obligatory ATN is associated with a relatively low risk for MND (15%).
Bruggink et al. [146]	To determine the predictive value of the early motor repertoire for the level of self-mobility in children CP at school age.	37 preterm infants (mean <1500 grams)	1999-2000	The absence of the age-adequate motor repertoire, a cramped motor repertoire, an abnormal kicking pattern, and a non-flat supine posture were associated with lower levels of self-mobility (chi (2) for trend test, $p<0.05$). Predictive for a low level of self-mobility was a cramped motor repertoire/non-flat supine posture (positive predictive values [PPV] 100%, negative predictive values [NPV] 54%). Predictive for a high level of self-mobility was a non-cramped repertoire/flat supine posture (PPV 80%, NPV 74%).
Butcher et al. [71]	To investigate associations between the quality of spontaneous movements between 11 and 16 weeks post-term and intelligence and behavior problems in childhood. Second goal to determine whether any associations between movement quality and intelligence and behavior problems were mediated by neurological status rather than directly associated with movement quality.	65 infants born at65 infants born ≤ 33 weeks	1993-1998	Spontaneous movement quality at 11 to 16 weeks post-term was significantly, positively associated with later intelligence. The number of normal postural patterns displayed contributed most strongly to the association, which was not mediated by neurological status. FMs, strong predictors of later neurological dysfunction, were not associated with intelligence. Spontaneous movement quality was not associated with internalising or externalising problems but showed a trend to an association with attention problems.
2008				
Bruggink et al. [63]	To investigate the predictive value of the quality of the early motor repertoire for the development of MND at school age.	82 preterm infants <1500 grams	1992-1997	The quality of FMs and the quality of the concurrent motor repertoire had independent prognostic value for MND at school age. Abnormal FMs evolved into MND in 64% of the children. Nine of the 28 children with normal FMs and an abnormal concurrent motor repertoire developed

				abnormally (32%). Only 1 child of the 21 children with normal FMs and a normal concurrent motor repertoire developed MND (5%).
Zuk et al. [188]	This study aims to examine the usefulness of spontaneous upper limb movements (ULM) as an early marker for predicting neurodevelopmental outcome in infants with intrauterine-growth retardation (IUGR).	32 intrauterine-growth retardation (IUGR) infants born between 31and 40 weeks. The control group comprised 32 appropriate for gestational age (AGA)	1995-1997	The mean ULM score was lower in the IUGR infants than the controls ($p< 0.05$) and in the IUGR group was lower in the infants with abnormal outcome ($p< 0.05$). Significant correlations were found between ULM and 2-year neurodevelopmental scores in the IUGR group. The ULM during late-fidgety period was most predictive for 2-year neurodevelopmental score. No difference was found in the mean ULM score between the pre-term and term IUGR infants.
De Vries et al. [189]	To assess the quality of GMs in the first fourteen days of life in relation to obstetric and postnatal risk factors and neurodevelopmental outcome in ELBW infants.	19 ELBW infants	2003-2004	GMs and OSs fluctuated substantially during the first fourteen days of life. Most infants had abnormal GMs, especially poor repertoire (PR) GMs. No relation was found between GMs and obstetric factors. Regarding postnatal factors, septicaemia correlated to hypokinesia (H) and artificial ventilation correlated to a lower OS
Pagava et al. [190]	To detect whether abnormalities in spontaneous motor activity can be observed already in the first months of life in infants with ASD.	20 children (male 17, female 3) later diagnosed as ASD and 20 controls	During the last 10 years from 2008	The optimality scores were lower in the ASD group. The reduced optimality scores were mainly due to a lack of variable sequences, amplitude and speed of writhing GMs and an altered quality of fidgety and other spontaneous movements in the ASD group.
2007				
Ferrari et al. [191]	To evaluate whether lying in a nest affects the posture and spontaneous movements of healthy preterm infants.	10 healthy preterm infants	1991-2001	When lying in the nest, the infants more often displayed a flexed posture with shoulder adduction and elbow, and hip and knee flexion, and the head was frequently in the midline. The nest was also associated with an increase in elegant wrist movements and movements towards and across the midline and a reduction in abrupt movements and frozen postures of the limbs. The nest did not affect the occurrence of asymmetrical tonic neck posture.
2006				
De Graaf Peters et al. [192]	To evaluated the effect of specific postural support on motor behaviour of infants with and without minor neurological dysfunction (MND) at age 1 to 5 months.	20 term born normal and 20 term born with MND.	2001	The presence of pillows did not affect the time spent in GMs, specific movements, or GM quality in either group. In neurologically normal infants the shoulder pillow with or without pelvic pillow induced an increase in the variation index ($p<0.01$), whereas in the infants with MND, all pillow conditions resulted in a substantial increase of the movement repertoire ($p<0.001$). Our results demonstrate that specific postural support promotes variation in motor behavior of young infants. This is particularly true for infants with MND.
Sival et al. [193]	To determine whether the transiently present leg movements caudal to the MMC indicate functional neural conduction through the MMC in neonates with spina bifida aperta (SBA)	Fetuses and neonates with SBA (n= 7 and n= 13)		Leg movements caudal to the MMC remained concurrently present with GMs in all five neonates available for follow-up after day 7. Comparing these leg movements between days 1 and 7 indicated a decreased duration

Nakajima et al.[194]	To find out whether a detailed scoring of poor repertoire GMs might lead to a better prediction of the neurological outcome	18 preterm infants (5 girls and 13 boys)	1992-1995	A detailed analysis of the different aspects and components of poor repertoire GMs could not improve the predictive value of this abnormal GM pattern.
2005				
Groen et al. [195]	To explore the value of GM assessment in predicting MND at 9 to 12 years of age.	28 low-risk full-term infants (11 females, 17 males) and 24 high-risk infants, born preterm (<37 weeks; 11 females, 13 males).	1988-1993	In children without CP, quality of GMs in the fidgety period was related to neurological condition (normal, simple MND, complex MND) at follow-up. Abnormal GMs at 'fidgety GM age' showed a specific relationship to the development of coordination problems and fine manipulative disability at 9 to 12 years. It was found that a refinement of GM assessment consisting of a 10-point Likert score to estimate the amount of variability and complexity of GMs did not enhance the predictive power of GM assessment.
Einspieler et al. [196]	An apparently normal early development was one of the initial criteria for classical Rett syndrome. Several investigators considered Rett syndrome to be a developmental disorder manifesting very soon after birth.	14 infants with Retts syndrome	1964-1997	A detailed analysis clearly demonstrated that none of the infants had normal GMs. However, a specific abnormal GM pattern could not be detected for Rett disorder. The abnormal GMs described here, and their individual developmental trajectories are different from the abnormal GMs described in infants with acquired brain lesion. Considered Rett syndrome to be a developmental disorder manifesting very soon after birth.
Einspieler et al. [197]	Videos of infants with Retts syndrome were assessed carefully for movements, posture, and behavior during the first 6 months of life.	22infants with Retts syndrom	1964-1997	A detailed analysis clearly demonstrated an abnormal quality of general movements (100%), tongue protrusion (62%), postural stiffness (58%), asymmetric eye opening and closing (56%), abnormal finger movements (52%), hand stereotypies (42%), bursts of abnormal facial expressions (42%), bizarre smile (32%), tremor (28%), and stereotyped body movements (15%).

CP: cerebral palsy
ELBW: Extremely low birthweight
VLBW: Very low birth weight
FM: Fidgety movement
GM: General Movement
MND: Minor developmental dysfunction

Appendix B

Appendix

Assessment of Motor Repertoire - 2 to 5 months

Christa Einspieler and Arie Bos, the GM Trust 2000

Name: .....

born: ..... PMA: ..... BW: .....

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

Observed movement patterns: ☐☐ normal ☐☐ abnormal

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

Observed postural patterns: ☐☐ normal ☐☐ abnormal

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

Movement character (global score):

- ☐ smooth and fluent
- ☐ jerky
- ☐ monotonous
- ☐ tremulous
- ☐ stiff
- ☐ cramped
- ☐ synchronous
- ☐ cramped-synchronized
- ☐ predominantly slow speed
- ☐ predominantly fast speed
- ☐ predomin. large amplitude
- ☐ predomin. small amplitude

Motor Optimality List:

1.	Fidgety Movements ± + ++ P D	normal abnormal absent	☐ 12 ☐ 4 ☐ 1
2.	Repertoire of co-existent other movements	age-adequate reduced absent	☐ 4 ☐ 2 ☐ 1
3.	Presence and normality of individual **movement** patterns	N > A N = A N < A	☐ 4 ☐ 2 ☐ 1
4.	Presence and normality of individual **postural** patterns	N > A N = A N < A	☐ 4 ☐ 2 ☐ 1
5.	Quality of the concurrent motor repertoire	smooth and fluent abnormal, not cramped-synchr. cramped-synchronized	☐ 4 ☐ 2 ☐ 1

Motor Optimality Score: from 28 to 5 ☐

Appendix C

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Inter-observer reliability of the "Assessment of Motor Repertoire — 3 to 5 Months" based on video recordings of infants

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ABSTRACT

Objective: A detailed analysis of infant motor behaviour can show up indicators for later neurological impairment. The "Assessment of Motor Repertoire — 3 to 5 Months", which is part of Prechtl's general movement assessment, could potentially be used for this purpose. The aim of the present study was to investigate inter-observer reliability in this instrument.
Method: Video recordings of 24 infants (corrected ages 3 to 5 months, gestational ages 24 to 42 weeks) were analysed by four observers. Kappa and ICC statistics were applied in the reliability analysis.
Results: High to very high inter-observer reliability was found in the assessment of "Fidgety Movements" (kappa 0.75–0.91). Agreement on the "Movement Character" was also high (kappa 0.54–0.84), while the assessment of the "Posture" showed the lowest inter-observer reliability (kappa 0.39–0.56). Moderate to high inter-observer reliability (kappa 0.51–0.84) was achieved in the field "Quality of Other Movements", and moderate in "Repertoire of Co-Existent Other Movements" (kappa 0.51–0.69).
Inter-observer reliability in the assessment of the total "Motor Optimality Score" was very high between all four observers as intraclass correlation coefficient (2,1) was 0.87, and ICCs for the pairwise analyses ranged between 0.80 and 0.94.
Conclusion: Inter-observer reliability in the "Assessment of Motor Repertoire — 3 to 5 Months" was satisfactory in respect of the subcategories and in case of high and low total optimality scores in pairwise assessments. In the total optimality scores, however, there was some inconsistency in the middle range of the scale.

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1. Introduction

Preterm infants are susceptible to significant risk factors for abnormal neurological outcome [1–3], and perinatal complications [2,4–8] can have a strong influence on a child's neurological development. There is an urgent need to develop and improve diagnostic tools for an early detection of neurological impairment in order to start intervention at an early stage [9–12]. Despite the development of new, advanced imaging techniques, however, the information provided by observation and clinical assessment is considered as important as ever. Both extremely preterm birth (at less than 27 completed weeks of pregnancy) [13] and complications related to treatment in the intensive care unit can result in later neurological complications. Survival after extremely preterm birth is estimated to range around 60% [13], with a significant number of preterm infants developing later neurological impairment. Data from the last two decades indicate that the neurological outcome in this particular group has not improved to the extent that it has in children born less preterm [14–16].

Traditionally, neurological assessment of newborns and infants has been based on two different approaches: the systematic comparison of the children's developmental stages with those of the average population [17]; and the identification of clinical symptoms of cerebral impairment such as changes in muscle tone or abnormal reflexes [18]. The observation of spontaneous movements in normal foetuses [19], neonates and infants has led to a systematic classification of movements, thereby defining a set of standard movements for each respective age group [20], some of which are described as general movements (GMs). GMs have been found an effective point of reference for the functional assessment of the developing nervous system [21]. Accordingly, a method for the evaluation of general movements has been developed, known by the term General Movement Assessment (GMA) [21–23]. The GMA has frequently been used in studies for the prognosis of neurological outcomes [24–27]. Studies of preterm and term newborns as well as young infants have shown

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that abnormal general movements in preterm infants, abnormal writhing movements and/or the absence of fidgety movements can be related both to brain lesions and to an unfavourable neurological outcome [8,21,27–30].

In the classical GMA the quality of three main periods of general movements is assessed by means of video recordings: preterm general movements, writhing movements and fidgety movements. The analysis is complex and requires a lot of clinical experience [21]. Inter-observer agreement in GMAs has been studied in several groups of infants, agreement being expressed in terms of kappa [21,31,32] or percent [21].

Fidgety movements constitute the characteristic general motor pattern in 3 to 5 month-old infants. They are small movements of moderate speed and variable acceleration of neck, trunk and limbs in any direction, continual in the awake infant, except during fussing and crying [27]. Absence of fidgety movements is considered predictive for later development of cerebral palsy [8,21,27,28,33,34] while normal fidgety movements have been found predictive of normal neurological development [27,29,35]. The GMA has been optimised to improve its predictive value for minor motor impairment and possible cognitive disturbances. Indication of a positive prediction of the GMA for complex minor neurological dysfunction has been reported in several studies [24,32,36–39]. In one study [35], however, the diagnosis of "poor repertoire" – the most frequently observed abnormal GM-pattern in preterm infants – failed to be predictive for the neurological outcome.

After a standardised basic course over five days, 800 observers performed 9000 GMAs in total. Correct agreement with the gold standard was achieved in 83% of the assessments — a result that was improved to 88% after an advanced course [40]. Repeated assessments of 20 GM recordings, carried out after a time interval of 2 years, resulted in a test–retest reliability of 100% for the global judgement [21] and 85% for a more detailed analysis of movement quality based on the same principle of optimality as the "Assessment of Motor Repertoire — 3 to 5 Months" [41].

The global GMA is not suitable for an evaluation of therapeutic effects, which necessitates a detailed assessment. In order to introduce a more detailed approach during the age of fidgety movements, the "Assessment of Motor Repertoire — 3 to 5 Months" [22] has been developed. Based on the optimality concept, this assessment tool [42] places emphasis on finding the best possible condition rather than finding normality, abnormality or pathology. It includes assessment of movements that co-occur with fidgety movements, namely wiggling–oscillating arm movements, swipes, mutual manipulation of fingers, fiddling with clothing, leg lifts, trunk rotation and axial rolling [22].

It takes sufficient inter-observer reliability in order for a different group of testers to use an instrument for scientific and clinical purposes. Before this study, the "Assessment of Motor Repertoire — 3 to 5 Months" had not been subjected to an examination of inter-observer reliability. The aim of this study, which was based on video-recordings of infants, was to determine inter-observer reliability of the above mentioned assessment tool.

2. Subjects and methods

2.1. Design

To determine the degree of inter-observer agreement, a cross-sectional study design was chosen. Four participants (observers A, B, C and D) analysed the same 24 videotapes of infants at the same time, applying the "Assessment of Motor Repertoire — 3 to 5 Months" and following a standardised assessment procedure [21].

2.2. Observers

Before the actual study, the four observers had participated in a four-day basic and a four-day advanced training course on the assessment of GMs [21]; they all had previously used GMA as a diagnostic tool in clinical practice. They were labelled by the characters A to D. Observer A, having accomplished the development of the "Assessment of Motor Repertoire — 3 to 5 Months" as a tool, was highly qualified in the assessment of general movements [22]. Observers B, C and D were highly qualified child physiotherapists. Since only observer A was conversant with the given scoring system, all four observers had completed a joint training workshop before commencing the study. The workshop had consisted of four theoretical lectures and one training session in which ten video recordings of infants had been analysed; one of the four observers had recorded and edited the 16 videos while another had recorded and edited 9 videos in accordance with Prechtl's method [21]. In the actual study, the observers were not familiar with the children's histories — except for observer D, who recognised five children from a previous clinical study [28].

2.3. Subjects

Prior to the study, video recordings of 25 infants aged 3 to 5 months post-term were arranged. The recordings had been carried out at the Department of Paediatrics, Trondheim University Hospital between 1999 and 2005. The Regional Ethics Committee approved the study, and all parents gave their written informed consent, allowing the video recordings to be used for research purposes. The intention was to select a diversified group of children both regarding gestational age and the risk for later neurological impairments. All 25 infants participated in a follow-up programme for children with significant risk factors. Sixteen of the infants had previously participated in a follow-up study [28]. Additional video recordings of 9 infants were selected for the present study from clinical files.

A broad spectrum of infants of various gestational ages and full term infants with various risk factors for later neurological impairments – 13 females and 12 males in total – participated in the study. Birth weight ranged from 680 to 4725 g. Gestational age was 24 to 28 weeks in 13 infants and 29 to 33 weeks in 5 infants; 6 infants had been born at term. Nine infants had shown abnormal ultrasound imaging or MRI findings during their first three months of life (intraventricular haemorrhages or infarcts). Moderate or severe asphyxia had been recorded in 8 infants; 5 infants had been treated for septicaemia during the first four weeks of life. All 25 infants showed peri- and/or neonatal risk factors for later development of neurological problems. One recording had to be discarded, because the child's motor behaviour did not meet the criteria for assessment [21].

2.4. Video recordings

In compliance with a procedure described by Einspieler et al., representative sequences of movements were selected from the video recordings [23]: The infants were always videoed in supine position for 5 to 10 min and had to be fully awake. Sequences that included crying and fussing were discarded. Accordingly, a total of 24 infants were included in the study; one was discarded, because the video recording did not meet the criteria for assessment.

The average time it took the observers to assess one video (out of 24) was 4.5 min, always ranging between 2 and 5.5 min. Twelve recordings were seen twice, the other 12 three times. In case of two infants, observer A regarded the subcategory "Fidgety Movements" as not assessable and chose not to valuate them. Consequently, only 22 recordings were included in the calculations of kappa values and ICCs for observer A, whereas the other three observers had analysed 24 recordings.

2.5. The assessment tool

"Assessment of Motor Repertoire — 3 to 5 Months" [22] is a tool designed for the assessment of video recordings of infants. It

consists of three main fields of observation: "Movement Patterns" (consisting of 33 items), "Postural Patterns" (13 items), and "Movement Character" (12 items). The overall result (58 items) is taken as a basis for the "Motor Optimality List", based on the scoring of five subcategories, the first of which rates "Fidgety Movements" as normal (12 points), abnormal (4 points) or absent (1 point); the second subcategory, "Repertoire of Co-Existent Other Movements", is classified as age-adequate (4 points), reduced (2 points) or absent (1 point); the third subcategory, "Quality of Other Movements" is evaluated by the number of normal or abnormal items within the field "Movement Patterns": a number of normal patterns (N) higher than that of abnormal patterns (A) scores 4 points; N = A scores 2 points; N<A scores 1 point. The fourth subcategory, "Posture", is assessed in the same way, based on the items of the second main field of observation, "Postural Pattern". The fifth subcategory, "Movement Character", describes the overall movement character observed in all movement categories: smooth and fluent (4 points); abnormal, but not cramped-synchronised (2 points); abnormal and cramped-synchronised (1 point). Finally, adding up the scores of each subcategory results in a total of 5 to 28 points — the "Motor Optimality Score".

The author has omitted two items from the assessment tool after its first publication [22]: "Saccadic Arm Movements" were not taken into consideration in the present study because their description was insufficient and they could have been confused with abnormal fidgety movements; the category "Mouth Movements" was withdrawn, because, if abnormal, they co-occur with abnormal "Tongue Movements". "Hand–Face Contact" and "Hand–Mouth Contact" were regarded as one item. These changes, however, did not affect the total optimality score. The subcategories "Fidgety Movements", "Repertoire of Co-Existent Other Movements", "Posture" and "Movement Character" were all given numeric values as a result of a sum of nominal values. These numeric values added up to a total "Motor Optimality Score".

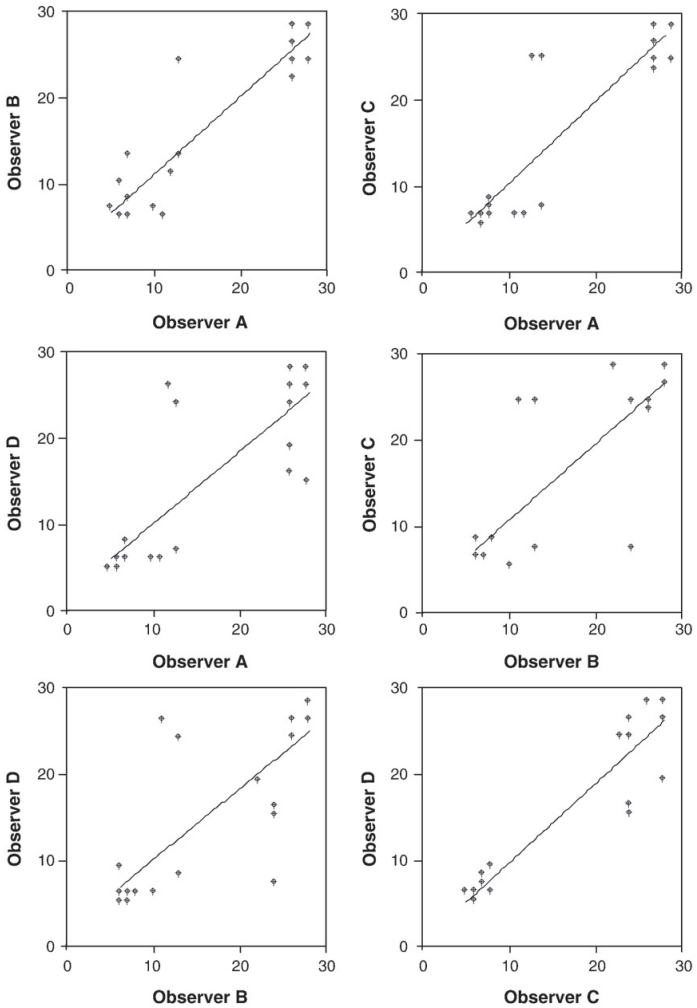

Fig. 1. Inter-tester reliability of the instrument "Assessment of Motor Repertoire — 3 to 5 Months": pair wise correlations of test results and linear regression lines for the total "Motor Optimality Score" by observer A, B, C and D.

2.6. Assessment procedure

The assessment of the 24 video recordings was performed in the same room by all observers, using a large video screen. There was no possibility for the observers to communicate. Upon request, they were allowed to view the video sequences repeatedly. Each observer saw each video recording the same number of times and for the same length of time. The time that was spent on each infant was recorded. The scoring sheets were numbered consecutively from 1 to 24 — in analogy to the infants.

2.7. Statistics

SPSS version 14.0 was used for statistical analyses. In the five subcategories of the assessment tool, the degree of inter-observer agreement was identified by means of kappa statistics or expressed in terms of percent agreement if the kappa value could not be determined, and it was arranged on an ordinal scale. Cohen's kappa is a statistical measure that is used to determine inter-observer agreement, taking into account agreement by chance [43]. The results were interpreted according to guidelines adapted from Landis and Koch [44], who classify a κ value of <0.20 as poor agreement, of 0.21–0.40 as fair, of 0.41–0.60 as moderate, of 0.61–0.80 as good, and of 0.81–1.00 as very good agreement.

Intraclass correlation coefficient (ICC) statistics was applied to examine pairwise agreement of sum scores among the observers. ICCs are correlation coefficients that allow comparison of two or more repeated measurements; the method is based on the repeated measures analysis of variance (ANOVA) [43]. For the "Motor Optimality Score", ICC (2,1) statistics was applied to examine pairwise inter-observer agreement (A–B, A–C, A–D, B–C, B–D, C–D), and agreement among all four observers (A–B–C–D). ICC (2,1) was chosen so the result could be generalised to other observers [45]. The measurement error was termed "Sw"; it was calculated as the square root of the mean within-subject variance. The difference between an observer's evaluation of an infant and the true value was expected to be less than 1.96 Sw in 95% of the observations [46].

3. Results

By tendency, the children that participated in the study either ranged at the lower end or at the head of the 5- to 28-point total "Motor Optimality Score" (Fig. 1). Inter-observer agreement for the total score – expressed in terms of ICC (2,1) values – was high, as is shown in Table 1. Regarding pairwise agreement, ICC (2,1) values ranged between 0.80 and 0.95. Pairwise correlations between the observers are shown in scatter plots (Fig. 1). Overall inter-observer agreement was 0.87.

The measurement error (Sw) between the various pairs of observers in the assessment of the "Motor Optimality Score" ranged from 2.42 to 4.25. Variability among the observers was found to be high in case of children who scored in the middle range of the scale. The overall Sw between the observers was 3.47, which implies that in 95% of the cases the measurement error will be within $\pm 3.47 \times 1.96$, which equals 13.6 points on the 5- to 28-point optimality score scale.

Table 1
Inter-tester reliability of the total "Motor Optimality Score" in pair wise between four observers (A–D) and for all observers, reporting Intra Class Correlation Coefficient (ICC) and within subject standard deviation (Sw).

Observers	ICC (2,1)	Sw
A–B	0.93	2.42
A–C	0.91	2.97
A–D	0.82	4.09
B–C	0.84	3.83
B–D	0.80	4.25
C–D	0.94	2.31
A–B–C–D	0.87	3.47

N = 24 observations for B, C, and D, and 22 for A.

Table 2
Inter-tester reliability of "Assessment of Motor Repertoire — 3 to 5 Months" subcategories.

Subcategories	Tester A–B	Tester A–C	Tester A–D	Tester B–C	Tester B–D	Tester C–D
	κ (se κ)[a]	κ (se κ)[a]	κ (se κ)[a] or %	κ (se κ)[a]	κ (se κ)[a] or %	κ (se κ)[a] or %
Fidgety	0.91 (0.09)[b]	0.82 (0.12)[b]	82%[b]	0.75 (0.14)	75%	88%
Repertoire	0.51 (0.13)	0.56 (0.14)	0.51 (0.14)	0.56 (0.13)	0.48 (0.15)	0.69 (0.12)
Quality	0.51 (0.14)	0.61 (0.12)	0.62 (0.12)	0.58 (0.15)	0.60 (0.15)	0.84 (0.10)
Posture	0.48 (0.16)	0.39 (0.13)	0.41 (0.13)	0.40 (0.14)	0.56 (0.13)	0.54 (0.13)
Character	0.54 (0.16)	0.62 (0.15)	0.56 (0.16)	0.75 (0.13)	0.84 (0.10)	0.61 (0.14)

Pair wise analysis between the observers (A–D) based on video recordings of 24 infants, expressed in kappa (κ)-values or percent (%) agreement.
[a] $se(\kappa)$ = standard error of κ.
[b] Fidgety movements observed in 22 infants by tester A.

In the subcategory "Fidgety Movements", kappa values could only be calculated for three pairs of observers: A–B = 0.91, A–C = 0.82 and B–C = 0.75 (Table 2): Since only observer D attested that children numbers 3 and 24 showed abnormal fidgety movements, no symmetric 2-way table could be constructed, and consequently no kappa value for fidgety movements could be calculated between observer D and the other observers. Therefore, agreement between observers A–D, B–D and C–D regarding the subcategory "Fidgety Movements" was expressed in terms of percent — 82%, 75% and 88% respectively. Observer A considered children 19 and 24 not to meet the criteria for an assessment of fidgety movements and therefore scored no fidgety movements for them.

In the other subcategories, data from all 24 infants were included in the analysis. Moderate inter-observer reliability was achieved in the assessment of "Repertoire of Co-Existent Other Movements", with kappa values ranging between 0.48 and 0.69 and one single value under 0.5. Regarding the "Quality of Other Movements", inter-observer reliability was moderate to high, with kappa values ranging from 0.51 to 0.84 and three out of six values higher than 0.6. The assessment of "Posture" resulted in moderate kappa values, ranging from 0.39 to 0.56 with only two values above 0.5. "Movement Character" appears to be the subcategory easiest to assess, since here the results were most consistent: Kappa values ranged between 0.54 and 0.84, with five values above 0.60 (Table 2).

Observer D may have recognised five video recordings from a previous study [28], but it must be added that none of observer D's present scores differed significantly from the other observers' scores for these videos.

4. Discussion

The objective of this study was to investigate inter-observer reliability in the "Assessment of Motor Repertoire — 3 to 5 Months". Four observers qualified and then participated in the assessment of video recordings of spontaneous movements in a large number of infants. ICCs between 0.80 and 0.93 for the "Total Optimality Score" indicate high to very high reliability according to Munro's descriptive terms of the intraclass correlation coefficient [40]. But regardless of the fact that ICCs were high, the great variance of the scores made it difficult to interpret the results. A look at the scatter plots (Fig. 1) reveals that most scores were located either at the upper or at the lower end of the 5- to 28-point scale. Such a broad range of scores may result in artificially high ICC values; but then the observers seemed to agree both on the respective high scores and on the low scores in the category "Total Optimality Score". Those few valuations in the middle range of the scale showed large variability, and the overall within-subject standard deviation was wide. Consequently, it was difficult to determine inter-observer reliability for the middle range of the "Total Optimality Score" on the basis of the present study.

It must be taken into consideration that, within the assessment of the "Motor Optimality Score", the subcategory "Fidgety Movements" accounted for as much as 12 out of 28 points. Thus, the assessment of "Fidgety Movements" – which itself showed good inter-observer agreement [21] – had a significant effect on the ICCs for the total "Motor Optimality Score".

The points achieved in the subcategories "Quality of Other Movements" and "Posture" were calculated on the basis of 33 or 13 items respectively. The observed patterns were described either as normal or as abnormal, with the total points achieved per subcategory being the sum of all respective normal and abnormal observations. Accordingly, the result was not simply based on the inter-observer agreement in each item. It is only the sum that counts. Therefore, there might be a certain degree of expected chance agreement involved in these subcategories, which was not examined further in this study. Even if inter-observer agreement on each item of these subcategories turned out to be low, the points achieved for "Quality of Other Movements" and "Posture" came out with high agreement, which again influenced the "Motor Optimality Score" and ultimately the ICC values of reliability.

In the subcategory "Fidgety Movements", observers A–B, A–C and B–C achieved high or very high agreement, expressed in terms of kappa values. These results corresponded with previous findings, which show that inter-observer agreement in the assessment of fidgety movements is rather high in general [40]. From a clinical point of view, these findings are of utmost importance as the presence or absence of fidgety movements has a high prognostic value [27]. Those three pairwise observations in which agreement was expressed in percent without taking into consideration agreement by chance are harder to interpret. A percentage of 75% to 88% would seem satisfactory as it clearly exceeds potential agreement by chance. Six pairwise assessments were carried out for the other subcategories, agreement being expressed by means of kappa values. In the subcategory "Repertoire of Co-Existent Other Movements", moderate inter-observer reliability was achieved in five pairwise observations and high interobserver reliability in one pairwise observation. Regarding "Quality of Other Movements" and "Movement Character", inter-observer agreement was also moderate to high in all pairwise observations. Yet in the assessment of the subcategory "Posture" it proved more difficult to achieve high inter-observer agreement than in the other categories, since here, four kappa values ranged between 0.39 and 0.48, the other two being 0.54 and 0.56. It has been argued, however, that in studies that apply observational methods, lower reliability values should be acceptable than in studies that use more objective methods of measurement [43]. Taking into consideration that the present study was based on visual observations and clinical judgement, the kappa value for "Posture" might be regarded satisfactory [43].

In the present study we preferred Cohen's kappa statistics to percent agreement in order to examine inter-observer agreement on ordinal data. This sort of analysis has also been used in a number of previous studies on general movements (for review see [21]). With kappa being a chance-corrected measure of agreement, the analysis not only calculates the observed agreement but also relates it to the agreement that is to be achieved by chance alone. Kappa thus expresses the chance-corrected proportional agreement — with "0" standing for total absence of agreement and "1" for 100% agreement. While there is no perfect agreement on how to interpret the values between 0 and 1, we followed Landis and Koch [44], since theirs are the guidelines that are commonly referred to in reliability studies of ordinal data. Out of the 30 pairwise calculations, no value appeared to be poor, and only two values indicated fair inter-observer reliability — namely those related to the observation of "Posture" between A and C and between B and C. All other values indicated moderate to high inter-tester reliability, which seems satisfactory.

The group of infants assessed in this study was certainly representative of the type of patients tested both in the global GMA and in another, more detailed assessment that applied the optimality score [22] in clinical practice. Most known perinatal risk factors for later neurological impairments were represented in the group of infants studied. Children with congenital cerebral malformations and children who were remarkably small for their gestational age, however, were not included in the sample. The number of infants studied – which was similar to samples of previous reliability studies of GMA [32,34] – should be sufficient to demonstrate variability in scores on the scale. Considering the fact that the children assessed had a broad range of ages and risk factors, it was surprising that the sample came to demonstrate scores clustered around the upper and lower ends of the optimality score scale.

The observers have had all the formal training required for the assessment of general movements in infants [21], but had different clinical backgrounds and research experience. The video recordings and the assessment procedure were performed according to the recommendations of the analysis of GMs [21]. Even if the group of infants studied was fairly representative of the group of infants that this instrument aimed at, the results should be interpreted with due care, since the observations do not cover the optimality scale sufficiently and the measurement error – 59% of the total score of all observers taken together (A–B–C–D) – was found to be rather high.

Those few children who ranged in the middle section of the scale contributed substantially to the variability in scores among the testers. Another survey of the characteristics of the children tested was conducted to examine possible reasons for the fact that the testers had scored so inconsistently. Five recordings with a total optimality score divergence of more than 12 points between two testers were identified and reanalysed. In all five recordings, the discrepancy was located in diverging scores for fidgety movements. In general, these children moved less and seemed to be partly distracted by staff and equipment — which in turn may have influenced the observers' judgements. Perhaps this indicates that the recording conditions were not always ideal for data acquisition. In order to obtain good video quality and high inter-observer agreement it is of paramount importance that the described procedure be followed carefully when selecting the recordings.

5. Conclusion

The present study on inter-observer agreement in the "Assessment of Motor Repertoire — 3 to 5 Months" has produced satisfactory kappa values for the subcategories and high ICC values for the total score. The subcategory "Fidgety Movements" showed high to very high inter-observer agreement across the 6 pair-wise analyses, while there was less agreement in the other subcategories, ranging between moderate and high. The reliability based on ICC values was hard to interpret since the scores were clustered mainly around the upper and lower ends of the optimality scale. Regarding the total scores, there was great variability in the middle range of the scale. Reanalyses of five of the recordings indicated that this variability was due to inconsistent judgement of fidgety movements. Further studies are needed to examine reliability of the scale — including scores along the whole scale.

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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.
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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

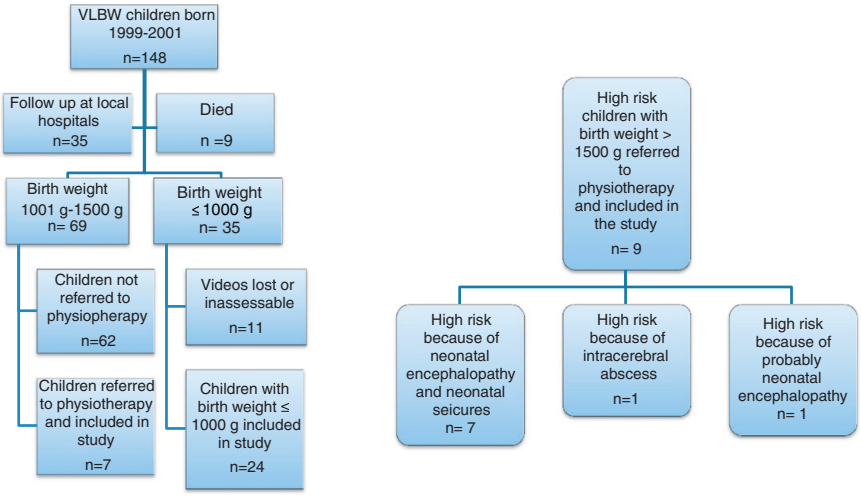

Fig. 1. Flow chart of participants in the study. VLBW = very low birth weight.

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

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Original article

Adaptive behavior in 10–11 year old children born preterm with a very low birth weight (VLBW)

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ABSTRACT

Aims: The aims were to compare adaptive behavior in 10–11 year old VLBW children with and without cerebral palsy (CP) to term-born children, and examine its relationship with neonatal factors and infant motor repertoire in VLBW children without CP.
Methods: Twenty-eight VLBW children without CP, 10 VLBW children with CP and 31 term-born control children were examined at 10–11 years using the parent-reported Vineland Adaptive Behavior Scales-II. The Adaptive Behavior Composite Score, based on communication, daily living skills and socialization, was adjusted for sex, socioeconomic status (SES), cognitive (WISC-III) and motor function (MABC-2). Associations with neonatal variables and infant motor repertoire were also examined.
Results: Adaptive Behavior Composite scores were significantly lower in the two VLBW groups (with CP: 72.5 ± 15.9; without CP: 92.2 ± 12.3) than in the control group (105.7 ± 17.5). The latter difference was still significant after adjustment for sex, SES, WISC-III and MABC-2. Among VLBW children without CP, an abnormal infant motor repertoire at 14 weeks post-term age was significantly associated with a lower Adaptive Behavior Composite score at 10–11 years of age ($r^2 = 0.20$, $p = 0.03$).
Conclusion: VLBW children have challenges regarding adaptive behavior. Specific attention may be needed to reveal such problems in VLBW children without major disabilities like CP, as these children had impaired adaptive function that could not be explained by their SES, cognitive or motor functions.

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1. Introduction

Preterm infants are exposed to significant risk for abnormal neurological outcome.[1,2] The consequences of prematurity for everyday practical and social skills in childhood have so far been poorly addressed, even though studies report mental health,[3] motor[2] and cognitive[4] impairments in preterm-born children, as well as consequences for social and adaptive behavior in adults.[5,6] Adaptive behavior is the behavior necessary for an individual to function safely and appropriately in daily life, both at a personal and a social level. Problems related to adaptive behavior have been described for children with intellectual disability, autism and epilepsy.[7,8] Among preterm-born infants, studies have reported on adaptive behavior after periventricular hemorrhagic infarction[9] or as effect of different treatment methods in the neonatal period,[10–13] but very few have used a term-born control group. Hack et al.[14] found that extremely low birth weight children (ELBW) had significantly lower social adaptive functioning than children born at term. Adaptive behavior may be more modifiable than for instance cognition and has been shown to improve depending on interventions.[15] The use of standardized assessment tools to reveal and describe adaptive behavior in follow-up programs may be important, as facilitation at home and at school may reduce later problems in daily life.[16]

Several studies report worse outcome for the smallest, sickest and most vulnerable preterm survivors,[1,2] and an association between the infants' early motor behavior and later motor and cognitive functions has been reported.[17,18] The aim of this study was to compare parent-reported adaptive and maladaptive behavior in 10–11 year old very low birth weight (VLBW) children with and without cerebral palsy (CP) to term-born children. Secondly, in the group of VLBW children without CP, we examined associations between adaptive and maladaptive behaviors and neonatal factors as well as the quality of the infants' early general movements. We were particularly interested in the non-disabled group of preterm-born children, as adaptive behavior problems is more easily overlooked among these children than in children with major disabilities like CP.

We hypothesized that VLBW children with and without CP would have lower adaptive functioning than their term-born peers and more internalizing and externalizing problems. Further, we hypothesized that neonatal illness and abnormal infant motor repertoire at 14 weeks post-term age would be associated with lower adaptive functioning at school age in VLBW children without CP.

2. Material and methods

2.1. Design

The present study is a hospital-based follow-up study of a group of children aged 10–11 years from two Middle Norwegian counties. The children had been born at St. Olavs University Hospital in Trondheim between 1999 and 2001. All ELBW infants, i.e. with a birth weight below 1001 g, were routinely enrolled in a follow-up program including referral to physiotherapy for assessment of their general movements and motor repertoire at 14 weeks post-term age. Additionally, children with birth weight between 1001 and 1500 g with additional risk factors were referred. A term-born control group of children aged 10–11 was recruited from four Trondheim schools. The follow-up examination involved motor and cognitive assessments and parental questionnaires assessing adaptive functioning. The results of the motor and cognitive assessments have been published before.[18]

2.2. Study population

2.2.1. VLBW group

The primary hospital cohort consisted of 74 ELBW children. Nine died, and 30 children had their follow-up at local hospitals because of the distance from the University Hospital. There were no statistically significant differences in gestational age and birth weight between the survivors who were followed locally and those included in the present study. Thirty-five children were invited to participate and four did not consent. The remaining 31 were included in the study. One of them was excluded because of severe autism and very low adaptive functioning; another child was excluded because his mother did not command Norwegian or English well enough to perform the assessment. In addition, nine children with a birth weight between 1001 and 1500 g were included in the study. Six of them had a birth weight between 1001 and 1100 g and had been on mechanical ventilator, and three were triplets born in gestational week 29. Thus, the study group comprised 38 VLBW children in total. Ten of them had CP at follow-up; nine had spastic CP (three hemiplegic, four diplegic and two quadriplegic CP) and one ataxic CP. According to the Gross Motor Function Classification System (GMFCS),[19] five children were classified with GMFCS level I, two children with GMFCS level II, two children with GMFCS level IV and one child with GMFCS level V. None of the children were deaf or blind. Three children had hearing loss requiring a hearing device (one with CP) and eight children used glasses (two with CP).

2.2.2. Control group

An age-matched control group of healthy children born at term were recruited from four schools in the Trondheim area. Thirty-one children consented to participate in this study.

2.3. Main outcome

2.3.1. Vineland adaptive behavior assessment Scale-II (Vineland-II)

Adaptive behavior was assessed at 10–11 years using the Vineland-II parent/caregiver rating form.[15] Vineland-II assesses abilities in the domains of communication, daily living skills and socialization (Fig. 1). The communication domain consists of the subcategories of receptive, expressive and written communication, which reflect the child's ability to listen and understand, talk, read and write. Daily living skills consist of personal, domestic and community skills, expressing the child's ability to perform the activities of daily living. Socialization consists of the subcategories of

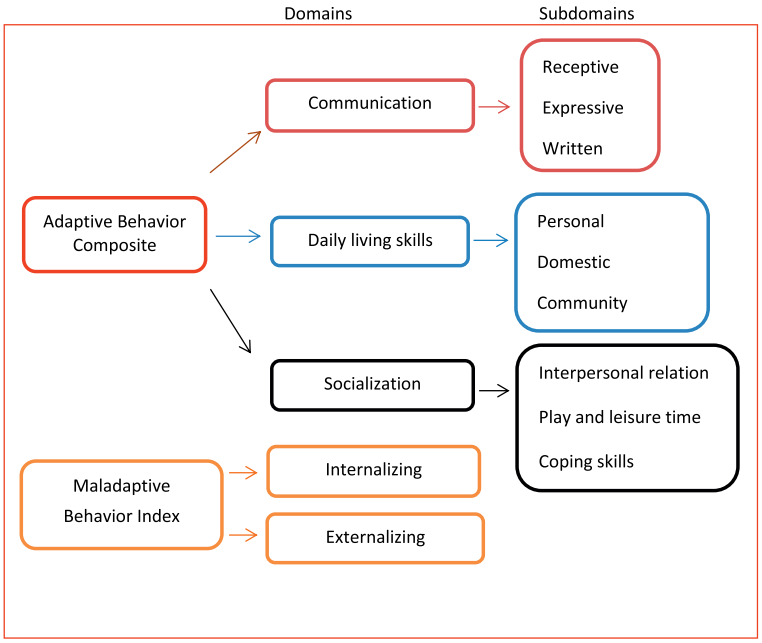

Fig. 1 – Internal structure of the Vineland-II parent/caregiver rating form.

interpersonal relation, play and leisure time as well as coping skills, all of which reflect the child's ability to interact with other people. These subcategories with 287 items in total add up to the Adaptive Behavior Composite. A high score indicates better adaptive behavior.

Vineland-II also contains a Maladaptive Behavior Index which reflects the children's internalizing and externalizing behaviors. Internalizing behavior represents the child's feelings, e.g. anxiousness or nervousness, sadness for no obvious reason, and their avoidance of social interaction. Externalizing behavior includes impulsive behavior, temper tantrums, etc. As opposed to the Adaptive Behavior Composite, children with a high score on the Maladaptive Behavior Index have more problems. Vineland-II has been thoroughly tested with respect to reliability and validity.[15] The Norwegian translation and Scandinavian norms were not available at the time of data collection. Therefore, in the present study, the American norms were used. In the VLBW group, Vineland-II was answered by 34 mothers and four fathers. In the control group, 28 mothers and three fathers completed the questionnaires. All caregivers both in the study group and the control group had the same basic education in English, and their English was good enough for completing the questionnaires. Whenever there was an uncertainty regarding language or understanding of the questions, TF was present for assistance.

We used the "Vineland II Survey Forms ASSIST™" computer program, which has been specifically designed for Vineland-II. This program calculates scores and allows for entry of domain and subcategory raw scores as well as individual item scores, and converts raw scores into standard scores and v-scale scores.[15] The standard Adaptive Behavior Composite and the domain scores have a mean of 100 and a standard deviation of 15, and describe an individual's overall functioning as well as their level of functioning in each adaptive behavior domain. The v-scale scores have a mean of 15 and a standard deviation of 3, and describe an individual's relative level of functioning in the subcategories as well as on the Maladaptive Behavior Index, compared with other children of the same age. All scores are automatically adjusted for age by the "Vineland II Survey Forms ASSIST™".

2.4. *Other variables*

2.4.1. *Socioeconomic status (SES)*

SES was calculated using Hollingshead's Two-Factor Index of Social Position,[20] which is based on education and occupation of one parent or the mean index of both.

2.4.2. *Wechsler intelligence scale for children-III (WISC-III)*

The children's cognitive function was assessed by a pediatrician (KHG) using the WISC-III[21] and applying age-appropriate standardized Scandinavian norms. The WISC-III gives a total IQ score based on a verbal and a performance IQ, with a mean of 100 and a standard deviation of ±15.

2.4.3. *Movement assessment battery for children-2 (MABC-2)*

The children's motor skills were assessed by a physiotherapist (TF) using the MABC-2.[22] The MABC-2 gives an age-adjusted total score based on three subcategories of manual dexterity,

Table 1 – Clinical characteristics of the study population.

	VLBW group without CP ($n = 28$)		VLBW group with CP ($n = 10$)		Control group ($n = 31$)	
	Mean	(SD)	Mean	(SD)	Mean	(SD)
At birth						
Gestational age (weeks)	26.8	(1.8)	26.4	(1.5)	40.2	(0.78)
Birth weight (g)	884	(217)	819	(213)	3599	(278)
Apgar score 1 min	5	(3)	6	(2)	9	(1)
Apgar score 5 min	7	(2)	7	(2)	10	(1)
Mechanical ventilator (days)	8.1	(11.5)	9.9	(13.2)	0	(0)
At follow-up						
Age (years)	10.2	(0.8)	11.0	(0.7)	10.8	(0.7)
Socioeconomic status	3.3	(1.2)	3.6	(1.0)	3.9	(1.0)
Full scale IQ (WISC-III)[a]	98	(17)	60	(21)	107	(18)
MABC-2[b]	66.3	(17.5)	–	–	77.0	(12.8)
	n	(%)	*n*	(%)	*n*	(%)
Neonatal variables						
Boys	9	(32.1)	8	(80.0)	13	(41.9)
Birth weight <1001 g	22	(78.6)	7	(70.0)	–	–
IVH grade 1	7	(25.0)	2	(20.0)	–	–
IVH grade 2	4	(14.3)	0	(0)	–	–
IVH grade 4	0	(0)	4	(40.0)	–	–
PVL grade 1	0	(0)	1	(10.0)	–	–
Antenatal steroids	17	(60.7)	8	(80.0)	–	–
Postnatal steroids	7	(25.0)	3	(30.0)	–	–
Septicemia	8	(28.6)	3	(30.0)	–	–
Bronchopulmonal dysplasia	14	(50.0)	7	(70.0)	–	–
Surfactant	19	(67.9)	10	(100)	–	–
GMA at 14 weeks						
Presence of fidgety and normal concurrent motor repertoire[c]	12	(52.2)	0		–	–
Presence of fidgety and abnormal concurrent motor repertoire[c]	10	(43.5)	3	(37.5)	–	–
Absence of fidgety and abnormal concurrent motor repertoire[c]	1	(4.3)	5	(62.5)	–	–

SES, socioeconomic status; WISC-III, Wechsler intelligence scale for children-III; MABC-2, movement assessment battery for children-2; ELBW, extremely low birth weight (<1000 g); IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; GMA, general movements assessment.

[a] Data missing for 1 VLBW child with CP.

[b] Data not presented for the VLBW group with CP because only 3 children completed the test.

[c] Data missing for 2 VLBW children with CP and 5 VLBW children without CP.

aiming and catching, and balance. The total MABC-2 standard score has a mean of 10 and a standard deviation of ±3.

2.4.4. *Neonatal variables*

Neonatal data on gestational age, birth weight, Apgar scores, days on mechanical ventilator, intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), septicemia, bronchopulmonal dysplasia (defined as oxygen required >28 days) and use of surfactant, ante- and postnatal steroids were retrieved from the medical journals with the parents' permission.

2.4.5. *General movements assessment (GMA)*

At 14 weeks post-term age, the VLBW infants had their spontaneous movements videotaped. In the present follow-up study, the infants' motor repertoire was assessed by a physiotherapist (TF) and a pediatrician (KHG) using the GMA and the "Assessment of Motor Repertoire 3–5 Months".[18,23,24] Infants were classified as having present, sporadic or absent so-called fidgety movements and a normal or abnormal concurrent motor repertoire according to Bruggink.[23,25]

2.5. *Statistical analysis*

Data were analyzed using IBM SPSS Statistics version 19.0 (Chicago, IL, USA). Two-sided *p*-values lower than 0.05 were considered statistically significant. Three-group comparisons were made by one-way ANOVA with Scheffe's post-hoc test for variables with normal distribution. Comparisons of proportions were made by Pearson's chi-squared test or Fischer's exact test. Univariate general linear models were used to adjust separately for sex, SES, cognitive and motor functions for all groups, and to examine associations between adaptive/maladaptive behaviors and neonatal variables and early motor repertoire in the VLBW group without CP.

2.6. *Ethics*

The study was approved by The Regional Ethics Committee (project number: 2010/121-9). All parents gave their written informed consent. When invited to the follow-up study, the children received a separate letter of information describing the nature, purpose and approximate duration of the tests.

According to the recommendation from The Regional Ethics Committee, children in need of special health care based on the results from the follow-up examination were referred for further assessments.

3. Results

Clinical characteristics of the study population are shown in Table 1.

3.1. *Adaptive and maladaptive behavior at 10–11 years*

The results of the Vineland-II are shown in Table 2. Compared with the control group, the VLBW group without CP had a lower Adaptive Behavior Composite score and lower scores in the domains of daily living skills and socialization, but not in the fields of communication. Additionally, the scores for written communication, community, play and leisure, and coping skills were lower, whereas the scores for internalizing and externalizing behaviors and the Maladaptive Behavior Index were higher than in the control group (Table 2).

The VLBW group with CP scored lower than the control group on the Adaptive Behavior Composite and all its domains and subcategories (Table 2). Compared with the control group, they had borderline higher scores for internalizing and externalizing behaviors and Maladaptive Behavior Index.

The differences between the VLBW group without CP and the control group were still significant after adjustment for sex, SES and the results of WISC-III and MABC-2 (Table 3). The differences between the VLBW group with CP and the control group were minor and mainly insignificant, except for daily living skills, after adjustment for the results of WISC-III (Table 3).

3.2. *Associations between adaptive behavior at 10–11 years and neonatal variables and early motor repertoire in the VLBW group without CP*

The presence of fidgety movements and an abnormal concurrent motor repertoire was significantly associated with a lower Adaptive Behavior Composite score and a higher Maladaptive Behavior Index in the VLBW group without CP, and explained 20% of the variance in adaptive behavior and 25% of the variance in maladaptive behavior (Table 4). No significant associations were found between the gestational age, birth weight, Apgar score at 5 min, presence of IVH, septicemia, bronchopulmonal dysplasia, use of surfactant, ante- or postnatal steroids and adaptive or maladaptive behaviors in the VLBW group without CP (Table 4).

4. Discussion

We found a significant difference between the adaptive behavior of VLBW children with and without CP at 10–11 years of age and that of the control group. The findings were still significant for the group of VLBW children without CP after adjustment for sex, socioeconomic status, cognitive and motor function, whereas the lower adaptive functioning in

Table 2 – Results of Vineland-II in two groups of very low birth weight children (VLBW) and a control group at 10 years of age.

	VLBW group without CP ($n = 28$)		p vs control	VLBW with CP ($n = 10$)		p vs control	Control ($n = 31$)	
	Mean	(SD)		Mean	(SD)		Mean	(SD)
Adaptive Behavior Composite*,[a]	92.2	(12.3)	0.005	72.5	(15.9)	<0.001	105.7	(17.5)
Communication*	93.5	(13.5)	0.071	76.2	(16.2)	<0.001	102.5	(15.8)
Receptive†	15.1	(2.7)	0.285	12.1	(3.1)	<0.001	16.1	(1.8)
Expressive†	13.5	(2.7)	0.763	9.8	(3.4)	0.001	14.1	(3.4)
Written†	12.8	(2.8)	0.013	10.4	(3.7)	<0.001	15.4	(3.6)
Daily living skills*	89.2	(13.0)	0.009	69.0	(15.8)	<0.001	102.4	(19.2)
Personal†	13.1	(3.5)	0.170	8.1	(4.0)	<0.001	14.8	(2.8)
Domestic†	13.7	(2.8)	0.177	9.7	(4.1)	<0.001	15.1	(3.0)
Community†	12.9	(3.0)	0.004	11.4	(4.1)	0.003	16.1	(4.2)
Socialization*,[a]	96.0	(14.2)	0.012	77.8	(17.3)	<0.001	109.3	(18.0)
Interpersonal relations†	14.0	(3.0)	0.144	10.4	(3.4)	<0.001	15.6	(3.3)
Play and leisure†	13.2	(3.9)	0.041	9.3	(3.8)	<0.001	15.7	(3.5)
Coping skills†,[b]	14.8	(2.7)	0.014	13.0	(3.1)	0.001	17.1	(2.9)
Maladaptive behavior index†,[c]	17.0	(2.4)	<0.001	16.4	(2.7)	0.057	14.4	(1.8)
Internalizing†,[c]	17.5	(3.3)	0.008	17.4	(3.2)	0.089	15.0	(2.2)
Externalizing†,[c]	15.7	(1.9)	<0.001	15.2	(2.2)	0.053	13.5	(1.6)

*Standard score.
†v-scale score.
One-way ANOVA for three-group comparisons: $p < 0.001$ for all scores.
[a] Data missing for 1 VLBW child without CP and 1 control child.
[b] Data missing for 1 control child.
[c] Data missing for 1 VLBW child with CP and 1 VLBW child without CP.

Table 3 – Unadjusted Vineland-II scores and scores adjusted for sex, socioeconomic status (SES), cognitive (WISC-III) and motor (MABC-2) function in two very low birth weight groups compared with the control group at 10–11 years of age.

	VLBW without CP ($n = 28$)			VLBW with CP ($n = 10$)		
	B	95% CI	p	B	95% CI	p
Adaptive Behavior Composite[a]						
Unadjusted	−13.6	−21.7 to −5.4	0.001	−33.2	−44.3 to −22.0	<0.001
Adjusted for sex	−14.3	−22.3 to −6.2	0.001	−30.7	−42.1 to −19.3	<0.001
Adjusted for SES	−13.9	−22.4 to −5.3	0.002	−33.4	−44.8 to −22.0	<0.001
Adjusted for WISC-III	−9.8	−17.1 to −2.4	0.010	−12.3	−26.0 to −1.3	0.076
Adjusted for MABC-2	−9.8	−17.1 to −2.4	0.010	–	–	–
Communication						
Unadjusted	−8.9	−16.7 to −1.2	0.025	−26.3	−36.1 to −15.4	<0.001
Adjusted for sex	−9.3	−17.1 to −1.4	0.021	−25.1	−36.4 to −13.8	<0.001
Adjusted for SES	−7.6	−15.6 to −0.5	0.065	−25.6	−36.4 to −14.7	<0.001
Adjusted for WISC-III	−5.1	−12.1 to 1.9	0.151	−5.0	−18.2 to 8.2	0.450
Adjusted for MABC-2	−4.4	−11.4 to 2.5	0.207	–	–	–
Daily living skills						
Unadjusted	−13.2	−21.8 to −4.6	0.003	−33.4	−45.3 to −21.4	<0.001
Adjusted for sex	−14.4	−22.5 to −6.2	0.001	−29.0	−40.6 to −17.2	<0.001
Adjusted for SES	−14.5	−23.4 to −6.0	0.002	−34.1	−46.1 to −22.0	<0.001
Adjusted for WISC-III	−10.0	−18.2 to −1.7	0.019	−15.5	−31.1 to 0.014	0.050
Adjusted for MABC-2	−9.2	−17.3 to −1.2	0.026	–	–	–
Socialization[a]						
Unadjusted	−13.3	−22.0 to −4.6	0.003	−31.5	−43.5 to −19.5	<0.001
Adjusted for sex	−13.6	−22.4 to −4.8	0.003	−30.5	−42.9 to −18.1	<0.001
Adjusted for SES	−14.0	−23.2 to −5.0	0.003	−31.9	−44.0 to −19.8	<0.001
Adjusted for WISC-III	−9.8	−18.0 to −1.6	0.020	−13.0	−28.1 to 2.2	0.093
Adjusted for MABC-2	−10.1	−18.2 to −2.0	0.016	–	–	–
Maladaptive Behavior Index[b]						
Unadjusted	2.5	1.4 to 3.7	<0.001	2.0	0.4 to 3.7	0.017
Adjusted for sex	2.6	1.4 to 3.7	<0.001	1.9	0.2 to 3.6	0.031
Adjusted for SES	2.1	1.0 to 3.3	<0.001	1.9	0.3 to 3.5	0.018
Adjusted for WISC-III	2.2	1.1 to 3.3	<0.001	0.1	−2.0 to 2.2	0.926
Adjusted for MABC-2	2.2	1.0 to 3.3	<0.001	–	–	–
Internalizing[b]						
Unadjusted	2.4	1.0 to 3.9	0.002	2.4	0.3 to 4.6	0.028
Adjusted for sex	2.5	1.0 to 4.0	0.001	2.1	−0.1 to 4.3	0.061
Adjusted for SES	2.0	0.5 to 3.5	0.010	2.3	0.2 to 4.4	0.031
Adjusted for WISC-III	2.0	0.6 to 3.5	0.008	0.3	−2.5 to 3.1	0.836
Adjusted for MABC-2	2.0	0.5 to 3.5	0.011	–	–	–
Externalizing[b]						
Unadjusted	2.2	1.3 to 3.2	<0.001	1.7	0.3 to 3.1	0.016
Adjusted for sex	2.2	1.2 to 3.2	<0.001	1.8	0.4 to 3.2	0.013
Adjusted for SES	2.1	1.1 to 3.1	<0.001	1.7	0.3 to 3.0	0.018
Adjusted for WISC-III	2.0	1.1 to 3.0	<0.001	0.8	−1.0 to 2.6	0.4
Adjusted for MABC-2	2.0	1.0 to 3.0	<0.001	–	–	–

SES, socioeconomic status; WISC-III, Wechsler intelligence scale for children-III; MABC-2, movement assessment battery for children-2.
[a] Data missing for 1 VLBW child without CP.
[b] Data missing for 1 VLBW child with CP and 1 VLBW child without CP.

VLBW children with CP was mainly due to low cognitive function. We also found increased maladaptive behavior in VLBW children with and without CP compared with the controls. The association between infant motor repertoire and later adaption problems in VLBW children without CP found in this study has not been reported before.

The present study was hospital-based and included three almost complete geographically based year cohorts of ELBW children and some VLBW children with additional risk of impaired neurological outcome. Thus, the full cohort reflects the clinical challenges of prematurity, and selection bias seems unlikely, especially for the ELBW children. However, the cohort is relatively small and only large group differences and strong associations would reach significant levels. In this study, the VLBW group without CP had 10–15% poorer scores on the Vineland-II than the control group, which we believe reflects a clinically significant difference between the groups. Furthermore, negative findings should be interpreted with caution due to the small simple size and risk of a type II-error.

Most follow-up studies of children born preterm and/or with a low birth weight have focused on tests and questionnaires for assessing motor and cognitive capacity,[21,22] but have addressed the consequences for the individuals' daily functioning only to a limited extent.[13,26] In the present study we used a comprehensive rating form for parents to report their offspring's adaptive behavior. Unfortunately, no

Table 4 – Associations between the adaptive behavior composite and the maladaptive behavior index at 10–11 years and neonatal variables and early motor repertoire in the VLBW group without CP ($n = 28$).

	Adaptive Behavior Composite[a]				Maladaptive Behavior Index[a]			
	B	95% CI	p	R^2	B	95% CI	p	R^2
Gestational age	0.3	−2.5 to 3.1	0.826	0.002	0.2	−0.3 to 0.7	0.397	0.029
Birth weight (grams)	0.004	−0.02 to 0.03	0.748	0.004	0.001	−0.004 to 0.01	0.712	0.006
Apgar score 5 min	−0.3	−2.7 to 2.0	0.761	0.004	−0.05	−0.5 to 0.4	0.833	0.002
Mechanical ventilator (days)	−0.1	−0.6 to 0.3	0.541	0.015	−0.01	−0.1 to 0.1	0.783	0.003
Presence of IVH	−2.7	−12.8 to 7.4	0.585	0.012	−1.3	−3.2 to 0.5	0.158	0.078
Antenatal steroids	7.4	−2.5 to 17.2	0.135	0.087	−0.9	−2.8 to 1.1	0.375	0.032
Postnatal steroids	−2.9	−14.2 to 8.4	0.602	0.011	−0.9	−3.1 to 1.2	0.388	0.030
Septicemia	4.4	−6.3 to 15.2	0.406	0.028	0.8	−1.3 to 2.8	0.454	0.023
Broncopulmonal dysplasia	−5.4	−15.1 to 4.4	0.267	0.049	0.2	−1.7 to 2.1	0.810	0.002
Surfactant	−0.9	−11.5 to 9.6	0.855	0.001	0.6	−1.4 to 2.6	0.537	0.015
Presence of fidgety and abnormal concurrent motor repertoire[b]	−11.3	−21.5 to −1.1	0.032	0.200	2.1	0.4 to 3.8	0.016	0.248

[a] Data missing for 1 child.
[b] Data missing for 5 children.

standardized Norwegian translation was available at the time of data collection. As the raw scores were converted into standard and v-scale scores using American norms, which may not be adequate due to cultural and ethnic differences, we used a local control group for comparison. Parent-reported outcomes may be biased but are often the only means of getting sufficient information on the subject of a follow-up study.[27] It could be a bias that mostly mothers completed the questionnaires in the present study. However, the proportion of mothers completing the questionnaires were the same in the study group and control group, and there are no studies using Vineland-II indicating that mothers respond to the questions differently than fathers. Inter-rater reliability studies of Vineland-II show high agreement when two persons knowing the child well answer the questions.[15]

Vineland-II has often been used for assessing children with intellectual disability and autism[7] and epilepsy.[8] When Vineland–II has been used in follow-up studies of children born preterm main focus has been on complications of prematurity[9] or treatment methods in infancy, and these studies have not included a control group born at term.[10–13] However, among studies including a term-born control group, Hack et al.[14] found that ELBW children, including children with CP, differed significantly from children born at term with respect to social adaptive functioning, and the findings remained significant when neurosensory-impaired children were excluded. This is the first follow-up study of adaptive behavior in a population-based cohort of preterm-born VLBW children without CP as yet.

In our study, the VLBW children without CP had lower adaptive functioning in terms of daily living skills and socialization, independent of their sex, SES, cognitive and motor functions. Interestingly, this group did not differ from the control group when it came to receptive or expressive language. This might be related to their relatively high cognitive function. Likewise, these children scored similar to the control group on personal and domestic items like personal hygiene, dressing, and helping with simple household chores. The higher scores of this group for internalizing, externalizing and maladaptive behaviors are in line with other studies that have found that young adults born VLBW have more internalizing and externalizing problems than their respective controls.[1,3]

In almost all subcategories, the relatively small group of preterm-born children with CP had significantly more difficulties in their adaptive functioning than the control group, and the same goes for the three main domains of communication, daily living skills and socialization. This was, however, mainly due to their lower cognitive functioning. The higher scores in Maladaptive Behavior Index, internalizing and externalizing behavior did not reach statistical significance compared with controls, even though scores were similar to the VLBW group without CP. Thus, the lack of significance in maladaptive behavior is likely due to poor statistical power with only 10 children in the VLBW group with CP.

Unlike studies reporting a particularly poor outcome for the smallest, sickest and most vulnerable preterm survivors, we found no association between neonatal characteristics and the adaptive and maladaptive scores. The neonatal risk events may have been modified by environmental conditions over the relatively long observation period of 10 years. However, what we did find was that the presence of fidgety movements and abnormal concurrent motor repertoire at 3 months was associated with reduced adaptive and increased maladaptive behavior scores at 10–11 years old. We have previously reported that the combination of poor motor and cognitive functions at 10–11 years in this same group of children could be identified by abnormal concurrent motor repertoire at 14 weeks post-term age in 86% of the children.[18] An abnormal motor repertoire in infancy may thus reflect an impairment of normal global brain development caused by pre- and/or perinatal brain injury. We therefore believe that assessment of the motor behavior at 3–4 months may function as an early clinical marker to predict adaptive and maladaptive behavior at school age.

5. Conclusions

The findings of this study indicate that VLBW children with and without CP have to meet greater adaptation challenges

than their peers born at term. In VLBW children without major disabilities like CP, the results persisted after adjustment for possible confounders; however the lower adaptive functioning in VLBW children with CP was mainly due to low cognitive function. These problems are not necessarily picked up in routine follow-up programs using standardized tests, but may need specific attention to be revealed. We also found that the presence of fidgety movements accompanied by an abnormal motor repertoire in infancy could be a valuable early clinical marker of an increased risk of maladaptive and impaired adaptive behavior in VLBW children without CP.

Conflict of interest

None declared.

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Paper III

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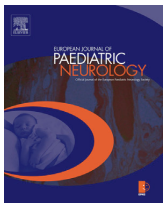

Original article

High prevalence of abnormal motor repertoire at 3 months corrected age in extremely preterm infants

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ABSTRACT

Aims: To compare early motor repertoire between extremely preterm and term-born infants. An association between the motor repertoire and gestational age and birth weight was explored in extremely preterm infants without severe ultrasound abnormalities.
Methods: In a multicentre study, the early motor repertoire of 82 infants born extremely preterm (ELGAN:<28 weeks) and/or with extremely low birth weight (ELBW:<1000 g) and 87 term-born infants were assessed by the "Assessment of Motor Repertoire – 2 to 5 Months" (AMR) which is part of Prechtl's "General Movement Assessment", at 12 weeks post-term age. Fidgety movements were classified as normal if present and abnormal if absent, sporadic or exaggerated. Concurrent motor repertoire was classified as normal if smooth and fluent and abnormal if monotonous, stiff, jerky and/or predominantly fast or slow.
Results: Eight-teen ELBW/ELGAN infants had abnormal fidgety movements (8 absent, 7 sporadic and 3 exaggerated fidgety movements) compared with 2 control infants (OR:12.0; 95%CI:2.7–53.4) and 46 ELBW/ELGAN infants had abnormal concurrent motor repertoire compared with 17 control infants (OR:5.3; 95%CI:2.6–10.5). Almost all detailed aspects of the AMR differed between the groups. Results were the same when three infants with severe ultrasound abnormalities were excluded. In the remaining ELBW/ELGAN infants, there was no association between motor repertoire and gestational age or birth weight.

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Conclusion: ELBW/ELGAN infants had poorer quality of early motor repertoire than term-born infants.The findings were not explained by severe abnormalities on neonatal ultrasound scans and were not correlated to the degree of prematurity. The consequences of these abnormal movement patterns remain to be seen in future follow-up studies.

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1. Introduction

Recent advances in perinatal medicine perinatal care have increased survival rates among the most immature infants, but the risk of impaired cognitive and motor outcome remains significant.[1,2] Early prediction of outcome in these infants remains a challenge, and the assessment of general movements developed by Prechtl et al.[3,4] has been shown to be one of the most promising tools to predict cerebral palsy (CP) or normal development in survivors.[3] Abnormal general movements in young infants is also associated with poor cognitive and motor outcome in children born preterm without CP.[5] In order to start early intervention for those with the highest risk of disability, there is a need to develop and improve diagnostic tools.[6]

The General Movements Assessment (GMA) is based on observations of spontaneous movements in normal fetuses,[7] neonates and infants, and has led to a systematic classification defining a set of normal movements for each respective age group.[8] Part of the GMA is the classification of presence or absence of fidgety movements at 9–18 weeks post-term age, which can predict later CP with a high degree of accuracy.[4,9] The "Assessment of Motor Repertoire – 2 to 5 Months" (AMR) is a standardised assessment of general movements,[8,10] also describing the quality and the quantity of the concurrent motor repertoire.[10,11] The concurrent motor repertoire refers to movements which co-occur with fidgety movements and include, among other things: kicking, hand–face contact, hand–hand manipulation, leg lift and fingers fiddling with clothing. The inter-observer reliability of the AMR instrument has been shown to be good.[12]

We have previously shown that an abnormal concurrent motor repertoire, despite present fidgety movements, is associated with an impaired cognitive and motor outcome at 10 years of age in very low birth weight (VLBW) children who did not develop CP.[5] This is in accordance with other studies showing that specific aspects of the concurrent motor repertoire during the fidgety movements period in extremely preterm infants is associated with later adverse motor and cognitive development.[11,13] In addition, as many as half of VLBW children showing the presence of fidgety movements also presented an abnormal concurrent motor repertoire in infancy.[5] However, the distribution of the different items of the AMR in term infants has not been established. In order to improve the diagnostic properties of the AMR for high-risk infants, it is necessary to establish normative data in healthy, term-born infants, and describe possible differences with preterm infants.

The aim of this study was to compare detailed aspects of the early motor repertoire during the fidgety movements' period between extremely preterm infants and healthy, term-born infants. Additionally, we wanted to explore associations between the motor repertoire, gestational age and birth weight in extremely preterm infants without severe abnormalities on neonatal imaging.

2. Material and methods

2.1. Design

The present study was a prospective multicentre cohort study including infants born between Jan. 1st, 2009 and Dec. 31st 2013 at Trondheim University Hospital (hospital 1), and between Jan. 1st, 2009 and Dec. 31st, 2012 at Oslo University Hospital (hospital 2) and at University Hospital of North Norway (hospital 3) in Norway. Inclusion criteria were extremely premature born infants with gestational age <28 weeks (ELGAN) and/or a birth weight <1000 g (ELBW) who had their follow-up at one of the participating university hospitals or a collaborating local hospital. The infants were invited to participate before discharge from their respective Neonatal Intensive Care Units (NICU). All parents that were asked for participation gave their written consent. Infants with syndromes, malformations, major surgery or with other problems which could affect spontaneous movements were excluded from the study. Infants participating in early intervention studies aimed to influence motor and/or cognitive development could not be included in this study.

Table 1 – Clinical characteristics of the study population.

	ELBW/ ELGAN (n = 82)		Control (n = 87)	
	Mean	**(SD)**	**Mean**	**(SD)**
Gestational age (weeks)	26.6	(1.8)	39.6	(1.0)
Birth weight (g)	884	(217)	3689	(400.8)
	n	**(%)**	**n**	**(%)**
Boys	47	(58)	45	(52)
Birthweight ≤10th percentile	22	(33)	4	(5)
Intraventricular hemorrhage grade 1	17	(21)	0	(0)
Intraventricular hemorrhage grade 2	4	(5)	0	(0)
Intraventricular hemorrhage grade ≥ 3[a]	3	(4)	0	(0)
Periventricular leukomalacia grade 1	1	(1)	0	(0)
Bronchopulmonal dysplasia	14	(17)	0	(0)
Treated retinopathy of prematurity	4	(5)	0	(0)

SD = Standard deviation.
ELBW = Extremely low birth weight; <1000 g.
ELGAN = Extremely low gestational age newborn; <28 week.
[a] One infant had intraventricular hemorrhage grade 3 and a cystic periventricular leukomalacia.

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Table 2 – Results of the assessment of early motor development in the ELBW/ELGAN group and the control group.

Motor optimality list	Score	ELBW/ ELGAN n = 82		Control n = 87		P value
		n	(%)	n	(%)	
1. Fidgety movements	12 = normal	64	(78)	85	(98)	<0.001
	4 = abnormal (exaggerated)	3	(4)	0	(0)	
	1 = absent or sporadic	15	(19)	2	(2)	
Temporal organisation of fidgety movements	F++	4	(5)	22	(25)	<0.001
	F+	63	(77)	63	(72)	
	F+/–	7	(9)	2	(2)	
	F–	8	(10)	0	(0)	
2. Repertoire of co-existent other movements	4 = age–adequate	73	(89)	87	(100)	0.006
	2 = reduced (5 or 6 movement patterns)	3	(4)	0	(0)	
	1 = absent (less than 5)	6	(7)	0	(0)	
3. Presence and normality of individual movement patterns	4 = N > A	79	(96)	87	(100)	0.198
	2 = N = A	1	(1)	0	(0)	
	1 = N < A	2	(2)	0	(0)	
4. Presence and normality of individual postural patterns	4 = N > A	68	(83)	82	(94)	0.039
	2 = N = A	7	(9)	4	(5)	
	1 = N < A	7	(9)	1	(1)	
5. Quality of the concurrent motor repertoire	4 = smooth and fluent	36	(44)	70	(81)	<0.001
	2 = abnormal, not cramped–synchronized	46	(56)	17	(20)	
	1 = cramped–synchronized	0	(0)	0	(0)	

Motor optimality score	Median	IQR	Median	IQR	0.001
	26	(23–28)	28	(28-28)	
	n	(%)	n	(%)	
Detailed aspects of motor repertoire					
Hand–hand contact	23	(28)	37	(43)	0.049
Foot–foot contact	56	(69)	75	(86)	0.016
Hand–hand manipulation	14	(17)	33	(38)	0.002
Foot–foot manipulation	31	(38)	51	(59)	0.007
Fiddling	22	(27)	43	(49)	0.003
Leg lifts, flexion at knees	70	(85)	85	(98)	0.013
Leg lifts, extension at knees	46	(56)	52	(60)	0.194
Movement character					
Smooth and fluent	36	(44)	70	(81)	<0.001
Jerky	4	(5)	3	(3)	0.641
Monotonous	41	(50)	13	(15)	<0.001
Tremulous	1	(1)	0	(0)	0.302
Stiff	7	(9)	0	(0)	0.005
Cramped	0	(0)	0	(0)	–
Synchronuous	0	(0)	0	(0)	–
Cramped-synchronised	0	(0)	0	(0)	–
Predominantly slow speed	1	(1)	0	(0)	0.302
Predominantly fast speed	10	(12)	2	(2)	0.012
Predominantly large amplitude	5	(6)	0	(0)	0.019
Predominantly small amplitude	0	(0)	0	(0)	–
Postures					
Variable finger postures	46	(56)	61	(70)	0.059
Few finger postures	36	(44)	23	(26)	0.017
Predominant fisting	17	(21)	9	(10)	0.061
Finger spreading	1	(1)	1	(2)	0.966

Chi-square test.
IQR = Interquartil range.
ELBW = Extremely low birth weight.
ELGAN = Extremely low gestational age newborn.
N = Normal.
A = Abnormal.
F++ = Fidgety movements continual.
F+ = Fidgety movements intermittent.
F+/– = Fidgety movements sporadic.
F– = Fidgety movements absent.

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A control group of healthy singleton, full-term infants with normal birth weight was recruited from local health centres and the maternity ward between 2010 and 2014. Only mothers with an uncomplicated pregnancy and delivery and infants with an uncomplicated neonatal period were invited to participate in the control group.

2.2. Clinical data

Gestational age was based on the second trimester routine ultrasound assessment. For ELBW/ELGAN infants, information on birth weight, sex and cerebral ultrasound (US) abnormalities was collected from the Norwegian Neonatal Network's registry, in which data from the NICUs is registered prospectively on a daily basis. Cerebral MRI of preterm infants was not routine practice in any of the participating units. Cerebral US was done according to each unit's routine practice, but included at least one examination during the first, and second week in addition to a later scan during week 3, 4 and/or before discharge.

2.3. Video recordings and the "Assessment of Motor Repertoire – 2 to 5 months"

All videos were recorded in compliance with a procedure described by Einspieler et al.[8] Infants were fully awake without crying or fussing and were lying supine on a mattress at a standardised distance (1.62 m) from the video camera. If multiple recordings of the same infant had been performed, the video closest to 12 weeks post-term age was used for the assessment and analysis.[8] Assessments of the video-recordings were carried out by two GMA certified and experienced paediatric physiotherapists blinded to the infants' clinical histories. First the FMs were assessed independently by each observer. The concurrent motor repertoire was then assessed by the same observers by replaying the videos. In cases of disagreements, a consensus was reached, based on additional evaluations.

According to Bruggink et al.,[10] the AMR is based on the scoring of five subcategories (Table 2). The first three subcategories are "Fidgety movements" (max. 12 points), "Repertoire of co-existent other movements" (max. 4 points), and "Presence and normality of individual movement patterns" (max. 4 points). The fourth subcategory, "Presence and normality of individual postural patterns" (max. 4 points) is based on the observation of items in the section "Postural pattern". The fifth subcategory is "Quality of the concurrent motor repertoire"[11] or "Quality of concurrent movements"[13] (also reported as "Movement character"[8]), which classifies the overall movement character as smooth and fluent (4 points); abnormal, but not cramped-synchronised (2 points) or abnormal and cramped-synchronised (1 point). Finally, the sum of scores from five subcategories results in a total of 5–28 points, the Motor Optimality Score (MOS).

Fidgety movements, if present, are interspersed with pauses. According to the duration of these pauses, the temporal organisation of fidgety movements can be classified as continual (F++), intermittent (F+) or sporadic (F+/–).[8] Continual and intermittent fidgety movements are given 12 points, exaggerated movements are given 4 points, and sporadic or absent fidgety movements are given 1 point in the AMR subcategory "Fidgety movements". In this study, fidgety movements (FMs) were classified as normal if continual or intermittent, and as abnormal if exaggerated, sporadic or absent. Two items of the original AMR were taken out in the present study: "Saccadic arm movements", because these can easily be confused with exaggerated fidgety movements; and abnormal "Mouth movements" because these co-occur with abnormal "Tongue movements". "Hand–face contact" and "Hand–mouth contact" were regarded as one item. The same modifications were used in a previous MOS study.[12]

2.4. Statistical analyses

Data was analysed using SPSS Statistic, version 21 (IBM SPSS Statistic, Chicago, IL, USA). Differences in motor repertoire items between groups were analysed using the chi-square test, and differences in non-parametric data were analysed by means of the Mann–Whitney U test. An odds ratio of 95% CI was calculated as an estimate of the risk of having abnormal general movements in the ELBW/ELGAN group as compared to the control group. Correlation coefficients between motor repertoire subcategories and gestational age and birth weight were calculated using Spearman's rho.

2.5. Ethics

The study was approved by The Regional Ethics Committee (project number: 2011/1811). All parents gave their written informed consent.

3. Results

3.1. Demographic and clinical characteristics

The primary study cohort included 87 ELBW/ELGAN infants born from 2009 to 2013. Of 87 ELBW/ELGAN infants born at hospital 1, 57 (66%) infants were invited to participate and consented, the rest were followed up at local hospitals. Of the 57 infants included in the study, 4 infants were excluded; one infant because of a plexus brachialis injury and the video recordings of 3 infants were not assessable because the infants were crying. At hospital 2, 25 (18%) of a total of 135 patients consented to participate; a majority of patients were not included because they had follow-up at other hospitals. One infant was excluded because of blindness. At hospital 3, 5 (13%) of a total of 40 ELBW/ELGAN infants were included because the majority of these infants participated in an early intervention study. Thus, a total of 82 ELBW/ELGAN infants (35 girls and 47 boys) were assessed with the GMA and AMR at mean 12.3 weeks post term age.

Ninety-six healthy term-born infants were invited to participate in the study. Two infants did not show up for the appointment, five appointments were cancelled because the infant was ill, and two video-recordings could not be assessed because the infant was in the wrong state for assessment. Thus, 87 infants (42 girls and 45 boys) were included.

Infants in the ELBW/ELGAN group had a mean birth weight of 884 (SD 217) grams and a mean gestational age of 26.6 (SD 1.8) weeks, compared with 3689 (SD 401) grams and 39.6 (SD

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1.0) weeks, in the control group, respectively. Seven-teen ELBW/ELGAN infants (21%) had intraventricular haemorrhage (IVH) grade 1, 4 infants (5%) had grade 2, 2 infants (3%) had grade 3 and 1 (1%) infant IVH grade 4. One of the infants with IVH grade 3 also developed cystic periventricular leukomalacia (Table 1).

3.2. *Motor repertoire at 3 months post-term age*

The infants' motor repertoire were video-recorded at mean 12.3 (SD1.1) weeks post-term age in the ELBW/ELGAN group and mean 12.2 (SD 1.8) weeks post-term age in the control group. The mean length of the video recordings was 4.2 min (SD1.0) in the ELBW/ELGAN group and 4.5 min (SD1.0) in the control group. Each video recording was assessed by the observers 2.1 (SD 0.8) times.

Table 2 shows the result of the assessment of early motor repertoire in the ELBW/ELGAN and the control groups at 12 weeks post-term age. A higher proportion of infants in the ELBW/ELGAN group had absent (n = 8), sporadic (n = 7) or exaggerated (n = 3) FMs compared to the control group ($p < 0.001$). Continual FMs were seen in 4 (5%) ELBW/ELGAN infants in contrast to 22 (25%) controls ($p < 0.001$). Almost all detailed aspects of the motor repertoire described in Table 2 differed significantly between the groups. Hand–hand manipulation was twice as frequent in the control group as in the ELBW/ELGAN group (33 [38%] versus 14 [17%]; $p = 0.002$), and foot–foot manipulation was seen in 51 (59%) infants in the control group as opposed to 31 (38%) in the ELBW/ELGAN group ($p < 0.007$). The quality of the concurrent movements was assessed as smooth and fluent twice as often in the control group as in the ELBW/ELGAN group (70 [81%] versus 36 [44%]; $p < 0.001$). Median MOS was 26 points (interquartile range 23–28) in the ELBW/ELGAN group and 28 points (interquartile range 28–28) in the control group ($p = 0.001$) (Table 2). There were no significant differences in the third subcategory, "Presence and normality of individual movement patterns".

The odds of having abnormal, absent or sporadic fidgety movements in the ELBW/ELGAN group were 12.0 (95% CI: 2.7–53.4) (Table 3) compared to the control group. Forty-six (56%) ELBW/ELGAN infants had an abnormal quality of the concurrent motor repertoire compared to 17 (20%) control infants (OR: 5.3; 95% CI: 2.6–10.5). The odds of having an abnormal concurrent motor repertoire despite the presence of FMs were 4.1 (95% CI: 2.0–8.7) (Table 3).

When 3 infants with severe ultrasound abnormalities (IVH grade 3–4 and/or PVL) were excluded from the ELBW/ELGAN group, differences in AMR remained significant between the groups. There was no significant correlations between motor repertoire and gestational age ($r_s = -0.11$ to 0.16, $p = 0.17–0.97$) or birth weight ($r_s = -0.20$ to 0.09, $p = 0.09–0.99$) within the ELBW/ELGAN group, both with and without infants with severe IVH and PVL.

Table 3 – Odds ratio (OR) with 95% confidence intervals (95% CI) as an estimate of the relative risk of having abnormal fidgety movements, abnormal quality of the concurrent motor repertoire and presence of fidgety movements and abnormal concurrent movements in the ELBW/ELGAN group compared with the control group.

	Abnormal	Normal	OR	(95% CI)
	n (%)	n (%)		
Quality of fidgety movements				
ELBW/ELGAN	18 (22)	64 (78)	12.0	(2.7–53.4)
Control	2 (2)	85 (98)	1.0	
Quality of the concurrent motor repertoire				
ELBW/ELGAN	46 (56)	36 (44)	5.3	(2.6–10.5)
Control	17 (20)	70 (81)	1.0	
Combination of fidgety movements and concurrent motor repertoire				
ELBW/ELGAN	30 (47)	34 (53)	4.1	(2.0–8.7)
Control	15 (18)	70 (82)	1.0	

ELBW = Extremely low birth weight.
ELGAN = Extremely low gestational age newborn.

4. Discussion

In this study, we found significant differences in almost all subcategories of the early motor repertoire between ELBW/ELGAN infants and a control group of healthy term-born infants. The odds of having abnormal quality of the concurrent movement repertoire along with normal fidgety movements were four times higher in the ELBW/ELGAN group compared to controls. These findings were not influenced by the exclusion of infants with severe abnormalities on neonatal cerebral ultrasound, and no associations between early motor repertoire and gestational age or birth weight were found within the group of preterm infants.

A limitation of the current study is that it was not population-based and only a proportion of all ELBW/ELGAN infants born at the 3 participating hospitals during the study period were included. Non-inclusion was mainly due to participation in other studies or follow-up taking place at other hospitals without selection based on the infants' medical history. Thus, the results are likely to be valid for other similar populations as well.

This is the first study to compare several aspects of the motor repertoire between a well-characterised group of ELBW/ELGAN and term-born infants. Two experienced observers conducted the video recording and analyses of the motor repertoire without knowledge of the infants' medical history and on video recordings with a standardised set-up. "Assessment of Motor Repertoire – 2 to 5 Months" has proven to be a valuable tool for systematically describing general movements and its association with the long-term neurological outcome.[10]

However, the motor optimality score used in "Assessment of Motor Repertoire – 2 to 5 Months" has some limitations. In this study, however statistically significant, the apparently minor difference in MOS of two points between the groups illustrates that this score depends very much on the score given for FMs, which alone accounts for 12 out of a total of 28 points. Clinically important characteristics like the quality of the concurrent motor repertoire account for a maximum of 4 points.[14] Each of the five subcategories should be analysed and interpreted individually, as has been done in this study.

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We found that all but one of the subcategories of "Assessment of Motor Repertoire – 2 to 5 Months" differed between the two groups. An interesting finding is that 10% of the infants in the ELBW/ELGAN group had an absence of FMs. Whether this reflects a 10% prevalence of CP in the extremely preterm population[15] remains to be verified in follow-up studies. A new finding is that continual FMs were rarely seen in the preterm group, while intermittent FMs were equally frequent in the two groups. The significance of the temporal organisation of FMs is unclear except for the well-established relationship between absence of FMs and CP.[3] A recent study of 29 infants born preterm showed that 21 infants were scored as having continual FMs, six infants showed sporadic FMs, and two infants were scored as having no FMs. However, this study does not distinguish between continual and intermittent FMs.[16] According to Einspieler et al.,[8] the temporal organisation of FMs varies with age in the fidgety period. It could therefore be that the rare occurrence of continual FMs in the extremely preterm group compared with term infants may reflects delayed maturation in this group. The question as to whether these findings influence the outcome should continue to be examined.

The only subcategory with similar results for extremely preterm and control infants was "Presence and normality of individual movement patterns". This means that the preterm infants expressed the same number of normal (or abnormal) movement patterns as the infants in the control group. This is one of two categories describing the quantity of concurrent movements. Even though the other quantitative category "Presence and normality of individual postural patterns" differed between the groups, one may speculate that preterm birth affects the quality more than the quantity of movements.

Few studies have published results on the quality of the motor repertoire in healthy term-born infants. Recently, Hitzert et al.[17] found that as many as 58% of term-born infants showed an abnormal quality of concurrent movements. This stands in contrast to our study, where 20% of the control infants had an abnormal quality of concurrent movements, even though both studies show that abnormal quality of early motor repertoire is frequent in a healthy population of term-born infants. The AMR classifies early motor repertoire as normal versus abnormal. However, given the high prevalence of so-called abnormal movements in healthy infants, it may be more pertinent to use the terms "optimal" and "suboptimal" movements.[18] Nevertheless, Hitzert et al.[17] reported that an abnormal quality of the concurrent motor repertoire was associated with behaviour problems in early school age. Whether our findings of abnormal movements in 20% of the control group have the same implications is a subject for future studies.

IVH and PVL are independent risk factors for adverse outcome in preterm infants.[19,20] However, in our study, only 3 of 82 infants had IVH grade 3–4 and/or PVL, and the presence of these brain abnormalities did not explain the difference between the preterm group and controls with respect to early motor repertoire. The reason for this may be that severe cerebral ultrasound abnormalities mainly indicate CP, whereas the motor repertoire is a general expression of early motor development and associate not only with CP but also with the cognitive and behavioural outcomes.[13] In addition, few infants had severe ultrasound abnormalities in the present study.

Furthermore, we found no correlation between AMR and gestational age or birth weight. This finding may be due to the relatively small range of gestational ages with only the most immature infants included. If AMR predicts cognitive and/or motor outcomes, this finding is not in accordance with findings of increasing risk of adverse outcomes with decreased gestational age.[19] As the incidence of severe IVH and PVL decreases, the need for early and accurate tools to identify those with the highest risk of adverse outcomes is even more important. Based on this and previous studies[5,11,13] it is likely that AMR could be sensitive enough for that purpose. It is of great importance to have appropriate methods to reveal neurodevelopmental problems to be able to start intervention as early as possible. Recent research indicates that early intervention can help the brain to reorganize aberrant signal patterns[21–23] and increased awareness and support from family, society and school is probably helpful.[24]

The quality of general movements could reflect brain function.[25] In fetal life, cortical subplate neurons are important in establishing the correct wiring and functional maturation of the cerebral cortex.[4,26] As Volpe[26] suggests, periventricular white matter injury would affect both white matter axons and their originating neurons in the cerebral cortex and thalamus, as well as the developing cerebral cortical neurons. Thus, damage to the white motor tracts is likely to be expressed as poor quality of motor behaviour. Consequently, an abnormal motor repertoire in early postnatal life may reflect an impairment of normal brain development and could possibly explain the later appearance of both motor and cognitive problems.[5,13,27,28] A monotonous, stiff or jerky movement character can also be a consequence of impaired postural control; as previously described in preterm infants, these show less mobile postural behaviour than term-born infants.[29] However, an abnormal motor repertoire can also result from an infant's reduced ability to interact with the environment and influence the further development of appropriate motor skills. This could at least partly explain the aforementioned association between the quality of general movements and later motor and cognitive outcome.[28]

5. Conclusions

We found poorer quality of the early motor repertoire in a group of ELBW/ELGAN infants compared with a control group of term-born infants at 12 weeks corrected age. Infants born extremely preterm had a risk of abnormal concurrent motor repertoire that was 4 times higher than controls, despite the presence of fidgety movements. The findings could not be explained by severe US abnormalities, as this was found in only three infants. Furthermore, findings were not correlated to the degree of prematurity within this ELBW/ELGAN group. The consequences of these abnormal movement patterns remain to be seen in future follow-up studies.

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Conflict of interest

None declared.

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