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Physiotherapy in infants born preterm

Measurement tools for assessing motor function in infancy and a randomised controlled trial of early intervention to optimise motor function

Thesis for the degree of Philosophiae Doctor

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Fysioterapi til for tidlig fødte barn

Måleredskap for vurdering av motorisk funksjon i spedbarnsalderen og en randomisert kontrollert studie av tidlig intervensjon for å optimalisere motorisk funksjon

Sammendrag

Barn som er født for tidlig er i risiko for en rekke senskader, for eksempel motoriske vansker og cerebral parese. I Norge blir barn som er født før 28. svangerskapsuke eller med fødselsvekt under 1000 gram rutinemessig henvist til fysioterapi. For å kunne skille mellom barn med normal motorisk utvikling og de som har motoriske vansker, og for å kunne rette oppfølgingen mot de med størst behov for tidlig intervensjon, trenger vi reliable og valide måleredskap. Målet med de to første artiklene i avhandlingen var å undersøke ulike egenskaper ved to måleredskap for barn under fem måneder. Den tredje artikkelen er fra en multisenter randomisert kontrollert studie, der foreldre gjennomførte intervensjon av sine barn før termin-alder. Målet var å undersøke effekten av intervensjonen ved å sammenligne endringen i motorisk funksjon etter en tre-ukers periode, mellom barn i en intervensjonsgruppe og en kontrollgruppe.

I den første artikkelen ble test-retest reliabilitet av testen "Test of Infant Motor Performance Screening Items" undersøkt. Testen ble gjentatt to ganger på barn i høy til moderat risiko for motoriske vansker og vi fant stor grad av samsvar mellom testresultatet på de to testtidspunktene.

Spedbarns spontane bevegelser, også kalt "general movements" (GMs), kan indikere normal eller avvikende utvikling. I den andre artikkelen ble validiteten mellom en detaljanalyse og en global analyse av GMs vurdert. Vi fant god korrelasjon ved termin-alder og de første ukene etter termin i en liten gruppe for tidlig fødte barn uten hjerneskade. Men detaljanalysen kunne ikke predikere om barnet hadde normal eller avvikende motorisk funksjon ved tre måneder korrigert alder.

Den tredje artikkelen omhandlet 150 barn født før 33. svangerskapsuke som ble randomisert til tidlig intervensjon eller til en kontrollgruppe. I intervensjonsgruppen var det foreldrene som gjennomførte intervensjonen, noe som anbefales når det gjelder tidlig intervensjon. Etter 3 uker var det en liten, men tydelig forskjell i endring i motorisk funksjon mellom barn som hadde fått intervensjon og barn i kontrollgruppen. Barna følges med motoriske vurderinger fram til de er to år korrigert alder. Vi kan da konkludere om intervensjonen har hatt en langtids effekt, og om mulig gi anbefalinger angående tidlig fysioterapi til barn i risiko for senskader.

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Contents

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List of papers

Paper I:

Test-retest reliability of the Test of Infant Motor Performance Screening Items in infants at risk for impaired functional motor performance

Tordis Ustad, Jorunn L. Helbostad, Suzann K. Campbell, Gay L. Girolami, Lone Jørgensen, Gunn Kristin Øberg, Kari Anne I. Evensen

Early Human Development 2016, Volum 93, page 43-46.

Paper II:

Validity of the general movement optimality list in very low birth weight infants without severe brain lesions

Tordis Ustad, Kari Anne I. Evensen, Natascia Bertoncelli, Rossella Frassoldati, Fabrizio Ferrari

Manuscript in preparation.

Paper III:

Early Parent-Administered Physiotherapy for Preterm Infants: A Randomized Controlled Trial

Tordis Ustad, Kari Anne I. Evensen, Suzann K. Campbell, Gay L. Girolami, Jorunn Helbostad, Lone Jørgensen, Per Ivar Kaaresen, Gunn Kristin Øberg

Pediatrics August 2016, Volum 138 / Issue 2.

Abbreviations

AUC	Area under the curve
BPD	Bronchopulmonary dysplasia
BSID-II	Bayley Scales of Infant Development II
BSITD-III	Bayley Scale of Infant and Toddler Development III
CA	Corrected age
CI	Confidence interval
COPCA	Coping with and Caring for Infants with Special Needs
CNS	Central nervous system
CP	Cerebral palsy
DCD	Developmental coordination disorder
GA	Gestational age
GMA	General movement assessments
GMs	General movements
GMOS	General movement optimality score
ICC	Intra-class correlation coefficient
ICF-CY	International Classification of Functioning, Disability and Health for Children and Youth
IQR	Interquartile range
IVH	Intra ventricular haemorrhage
MABC	Movement Assessment Battery for Children
MITP	Mother-Infant Transaction Program
MRI	Magnetic resonance imaging
NBAS	Neonatal Behavioural Assessment Scale
NDT	Neurodevelopmental treatment

NGST	Neuronal Group Selection Theory
NICU	Neonatal intensive care unit
NIDCAP	Newborn Individualized Development Care and Assessment Program
NOPPI	The Norwegian Physiotherapy Study in Preterm Infants
OS	Optimality score
PDMS	Peabody Development Motor Scale
PMA	Postmenstrual age
PT	Physiotherapy
PVL	Periventricular leukomalacia
RCT	Randomised controlled trial
ROC	Receiver operating characteristic
ROP	Retinopathy of prematurity
SD	Standard deviation
SGA	Small for gestational age
TIMP	Test of Infant Motor Performance
TIMPSI	Test of Infant Motor Performance Screening Items
VLBW	Very low birth weight
WHO	World Health Organization

Summary

Infants born preterm are at risk for a variety of neurodevelopmental difficulties, for example motor impairments, the most severe being cerebral palsy. In Norway, infants born before 28 weeks postmenstrual age (PMA) and/or infants with birth weight less than 1000 grams will be referred to early physiotherapy. To distinguish between infants with typical and atypical motor development, and to address the follow-up towards infants and parents who might gain most from early intervention, we need measurement tools that are reliable and valid. The aims of the two first papers in my thesis were to examine different aspects of reliability and validity in two measurement tools for use in infancy. The third paper was from a multi-centre randomised controlled trial (RCT) of early parent-administrated physiotherapy, before infants' term age. The aim was to investigate the short-term effect of early intervention and to compare the change in motor function from baseline to post-intervention between the intervention and the control group.

The first paper, the test-retest reliability study, showed that the Test of Infant Motor Performance Screening Items is a reliable test when performed on a group of infants with high to moderate risk for motor impairments.

The infants' spontaneous movements, the general movements (GMs), are indicators of neurodevelopment. In the second paper we found a good correlation between a detailed and a global assessment of GMs at term and early post-term age, in a small group of very low birth weight infants without severe brain lesions. However, the detailed assessment could not predict motor function at three months corrected age.

In the last paper, Paper III, 150 infants born before 33 weeks PMA were randomised either to an intervention or to a control group. The intervention was parent-administrated, which is the preferred and most recommended approach when conducting early intervention. We

documented a small but significant difference in motor function in favour of the intervention group as compared to controls after three weeks of intervention. The end-point of the RCT is motor function at two years corrected age. We will then assess the long-term outcome of the intervention, and may be able to give further recommendation concerning early physiotherapy for infant at risk for adverse development.

1. Introduction

The numbers of infants surviving preterm birth has increased in recent decades, due to advances in medicine.[1] But the long-term negative consequences of being born preterm increase with decreasing gestational age (GA).[1-4] Mild or severe motor impairments, such as cerebral palsy, are among long-term neurodevelopmental problems of being born at an early GA.[3, 5, 6] According to the national guidelines in Norway, all infants born before week 28 GA or with birth weight below 1000 grams should be included in multidisciplinary follow-up programs.[7] Many of these infants are referred to physiotherapy for assessment of motor development and early intervention. The most frequent used tools for assessing motor function during the preterm to early post-term age are the Test of Infant Motor Performance (TIMP) and the general movement assessments (GMA).[8, 9] But evidenced-based knowledge about early intervention is sparse.[10, 11] For instance, it is not known which of these infants would benefit most from early intervention, and it is not known at what age and what type of interventions are best suited to optimise motor development.

The topics of this thesis are examinations of the above mentioned measurement tools, and an early intervention program for infants born preterm. The thesis comprises one test-retest reliability study of the Test of Infant Motor Performance Screening Items (TIMPSI) and one study assessing the validity of a detailed versus a global GMA in infants born preterm. The TIMPSI and GMA will be described in the Background section. The third paper is from a multi-centre pragmatic randomised controlled trial (RCT) reporting outcome immediately after early parent-administrated physiotherapy in a group of infants born preterm.

2. Background

This chapter comprises a description of the theoretical framework, definitions, frequencies and aspects of preterm birth, description of development of the central nervous system, definition of motor development and motor function, theories of motor development and measurement tools for assessing motor function in infancy. Then, there is a short description of neonatal complications and the consequences of being born preterm, with focus on motor impairments. Finally, there is an overview of evidence-based knowledge about the effect of early intervention and the effect of early intervention on optimising motor development during the first year of life. The role of parents in administrating early intervention is also described.

2.1 Theoretical framework

The International Classification of Functioning, Disability and Health for Children and Youth (ICF-CY) of the World Health Organization (WHO) is a framework to describe health and health-related status in children and youth.[12] It is derived from, and compatible with, the International Classification of Functioning, Disability and Health (ICF) and is designed to record the characteristics of the developing child and the influence of the child's environment. Development in ICF-CY is described as a dynamic process in which the child's functioning is dependent on continuous interactions with the family or other caregivers in a close, social environment. Thus, the functioning of the child cannot be seen in isolation, but in the context of the family. The classification system is divided into two parts, each with two components.

1) Functioning and disability;

    a) body functions and structures; defined as physiological functions of body systems and anatomical parts of the body.

b) activities and participation; defined as execution of a task or action by an individual and involvement in a life situation.

2) Contextual factors;

c) environmental factors; the physical and social environment in which people live and conduct their lives.

d) personal factors; features of the individual that are not part of the health condition, for instance gender, age, lifestyle, race, social background, education, overall behavioural patterns etc.

The different components of ICF are seen in Figure 2. The bidirectional arrows indicate interactions and influences between the components of the model. The ICF-CY sets the framework for this thesis**.**

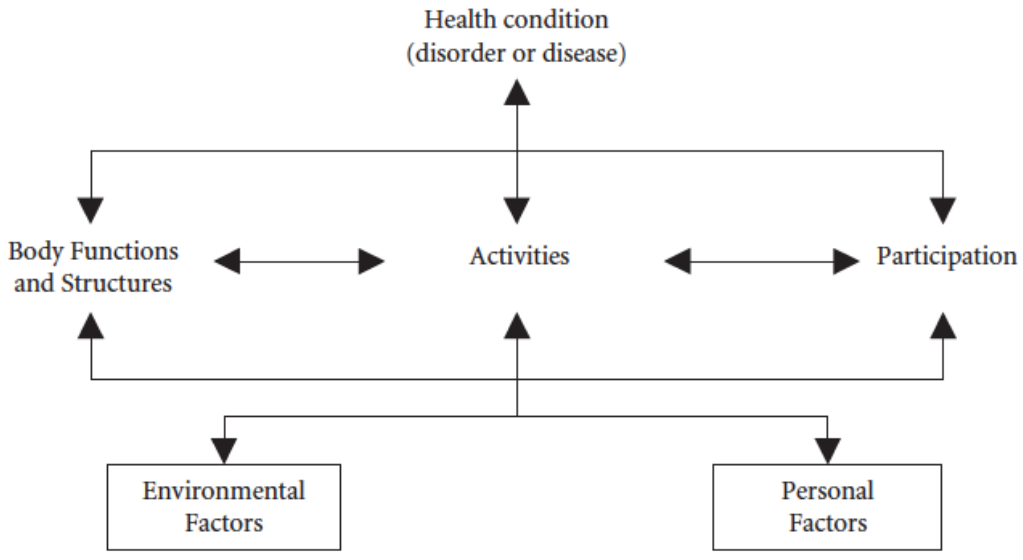

Figure 2. International classification of functioning, disability and health.[12]

2.2 Preterm birth

Preterm birth is defined as birth before week 37 GA.[13] Gestational age is calculated from the first day of the woman's last menstrual period.[13] Birth before week 32 GA is defined as very preterm birth and before week 28 GA as extremely preterm birth.[13] These sub classifications of preterm birth can be important because there is an increase in mortality and morbidity by decreasing GA.[13, 14] In this thesis I have also used the terms postmenstrual age (PMA: the age of the infant calculated from the first day of the woman's last menstrual period), corrected age (CA: the age of the infant calculated from estimated term age), very low birth weight (VLBW: birth weight ≤ 1500) and small for gestational age (SGA: birth weight below the 10th centile, adjusted for GA, sex and parity[15]). Table 1 gives the definition of preterm birth in weeks of pregnancy.

Table 1. Overview of definitions and variable cut-offs values for pregnancy and preterm birth, adapted from Blencowe.[13]

Pregnancy							
	Second trimester			Third trimester			Term
Gestational weeks	**16**	**20**	**24**	**28**	**32**	**36**	**40**
Preterm birth < 37 weeks gestation							
			Extremely preterm < 28 weeks gestation	Very preterm 28 - < 32 weeks	Moderate or late preterm 32 - < 37 weeks		Term 37 - < 42 weeks

Global percentage of preterm birth in 2010, based on 184 countries, was 11.1%, ranging from 5% in some European countries to 18% in some African countries.[13] Of these, 10.4% were classified as born very preterm and 5.2% as born extremely preterm. In Norway, 7.5% of the

infants born between 1999 to 2004 were born preterm (4400 infants yearly), of these 11% (467 infants) were born from week 28 to 32 GA and 5% (212 infants) below week 28 GA.[7]

An infant born preterm might suffer from various neonatal complications due to immaturity and exposure to stressors from the environment. The developing brain is especially vulnerable to lesion. Common lesions include intra ventricular haemorrhage (IVH), white matter damage (periventricular leucomalacia: PVL) and encephalopathy of prematurity (PVL accompanied by neuronal/axonal disease).[16, 17] The consequences might be combinations of destructive mechanisms and developmental delays.

In a national register study on neonatal data from the United States, comprising 9575 infants of extremely low GA and VLBW born between 2003 and 2007, 64% had normal cranial ultrasound within 28 days after birth. Sixteen per cent had grade 1 or 2 IVH and 16% grade 3 or 4, PVL was observed in 3% of the infants.[18] Rates of abnormal ultrasound findings decreased with increasing GA. Other frequent morbidities were infection, necrotizing enterocolitis, bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP) and sepsis. Infants at the lowest GA were at the highest risk for different morbidities. Overall, 93% of the infants experienced respiratory distress, of these 68% were in need of oxygen therapy for more than 28 days and thus received a diagnosis of BPD.[18]

Another factor that might influence development is the environment the infants born preterm experience the first weeks of life compared to term-born infants. In the Neonatal Intensive Care Units (NICUs) the infants are exposed to environmental stress, which might further influence the development negatively.[19] The infants are in danger of over-stimulation from a busy environment and from painful medical procedures. Non-optimal parent-infant interactions might also be a stressor, and the infant's poorly organised behaviour might suppress optimal parental responses necessary to facilitate infant recovery.[19]

Amongst the long-term consequences of being born preterm are motor disorders, cognitive difficulties, sensory impairments, epilepsy and behavioural, emotional or social problems.[1, 2, 4, 16, 20, 21] In the VLBW group the morbidity of any of these deficits listed above is reported to be from 25 to 50%, whereas 5 to 10% might be classified with cerebral palsy (CP).[16] In a population-based prospective cohort study of infants born extremely preterm in Sweden between 2004 and 2007, 27% had moderate to severe disabilities when assessed at two and a half years CA.[2] Furthermore, a cohort study from New Zealand of 105 infants born very preterm and 107 matched controls, found that only 40% of children born before week 33 GA were free of any impairments compared to 74% of full term children at four years.[20] In Norway, a large cohort study of infants born between 1967 and 1983, found increased likelihood of receiving disability pension or social security benefits, not completing high school, having low income and not finding a life partner with decreasing GA.[1]

To understand this vulnerability of infants born preterm the next chapter contain an overview of the development of the central nervous system (CNS).

2.3 Development of the central nervous system

Development of the CNS is characterised by age-dependent ontogenetic events continuing into adulthood, but the most important cerebral pathways are formed during the preterm- and neonatal periods.[22] In the thesis, I will primarily focus on CNS development from 24 to 37 weeks postmenstrual age (PMA) and the first year of life. In Figure 1 a timeline of major events in CNS development is given.

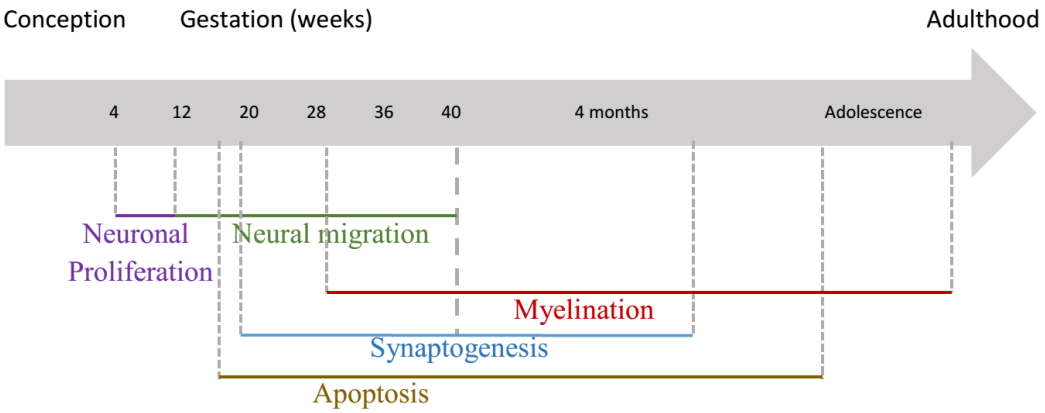

Figure 1. Timeline of major events in CNS development, adapted from Tau & Peterson.[23]

After the peak period of neuronal proliferation, millions of nerve cells move from their sites of origin in the ventricular and sub-ventricular zone to their permanent locations, a period of neuronal migration.[24]

The major site of formation of synapses (synaptogenesis) is in the temporary structure of the subplate zone, situated between the developing cortical plate and the periventricular white matter.[10, 22] The subplate zone also serves as a waiting area from which cortical afferent fibres relocate into the cortical plate, thus the subplate neurons play a role in the fine-tuning of cortical connectivity.[24, 25] From being four times thicker than the cortical plate, the subplate zone gradually disappears through a programmed cell death, apoptosis, during the perinatal and early postnatal periods.[10, 22, 26]

During the third prenatal trimester and the first year of life synaptic connections increase and there is an acceleration in dendritic development. Maximum dendrite density reaches its peak at different ages in different cortical regions.[27] The increase of dendrite density, the synaptogenesis and the apoptosis continue until term age in motor areas and in sensory areas until 44 weeks PMA.[28] Approximately 40% of synapses are subsequently eliminated.[24]

Experiments in rats indicate that being in an enriched environment during this period might reduce apoptosis.[28]

Also the growth and retractions of axons are assumed to be activity driven and use dependent as indicated in studies of children with congenital hemiplegia.[10, 29] During normal CNS development the corticospinal projections in the spinal cord are reorganised from bilateral to mainly contralateral.[10] In children having suffered a unilateral perinatal brain injury, increased ipsilateral corticospinal projection from non-infarcted areas and withdrawal of surviving contralateral projections from the damaged area, is seen.[30] Infants born preterm are especially vulnerable to damage of the CNS, especially in the periventricular area (the white matter area) because of the extensive synaptogenesis and axonal growth.[22]

Furthermore, myelination and glia cells production is important for the CNS development. Glia cell production comprises the development of the oligodendrocytes involved in myelination, which is the acquisition of myelin membrane around the axons.[10, 24] The myelination period begins in the second prenatal trimester and continues into adult life. The infant's most vulnerable period for myelination, caused by for example malnutrition or hypoxia, is from about the seventh intrauterine month to the first few months post-term age.[31]

The age for critical periods of cortical plasticity varies between different systems such as the visual, auditory, tactile, and motor systems.[27] Critical periods of cortical plasticity can be defined as periods in which development of a cortical function are strongly dependent and shaped by experience and environmental stimuli.[32] A sensitive period on the other hand is a period of time when the infants are more receptive to environmental stimuli than later in life.[27] Especially the last trimester of pregnancy and the first year of life is considered to be a sensitive period for motor development, as it is a period of rapid changes including neuronal proliferation

and migration, myelination, synapse formation and development of corticospinal fibres connections with spinal motor neurons.[16, 27, 33]

Many of the developmental events in CNS are activity dependent and the development of CNS should be considered the result of complex interaction between genes and social and physical environment.[32] From this, the parents play a key role in creating opportunities for the young infants to be active and interact with his environment. Since the first year of life is considered to be a sensitive period for motor development, early intervention should be especially efficient during this period.[27]

2.4 Motor development and motor function

Motor development can be described as change in a person's motor function as a result of growth, maturation and experience throughout the life-span, based on interaction between the person, the task and the environment.[34-36] In assessing infants' motor development, stages or milestones of development is the focus, for example movements up against gravity, upright head control, or sitting or standing. The infant's motor development is often assessed according to age norms.[37]

The term motor function is an umbrella term covering motor performance and motor capacity. Capacity describes the child's ability to execute a specific task, while motor performance is what the child does in daily life in his current environment, including a social context.[12] Motor performance belongs to the participation component of the ICF-CY model. Function is described as being goal directed and with a definite purpose.[37] Thus the motor function of a child cannot be seen in isolation but rather as a result of interaction between the child and his

environment.[12] Both the term motor function and the term motor performance are used in the thesis when describing measurement tools and intervention.

2.4.1 Theories of motor development

The Neural-Maturationist Theories were the prevailing theories of motor development up till 1980 – 1990.[38] These theories suggested that motor development was based on increasing cortical control over lower reflexes and that experience and environmental influence played a very small part. Maturation led to an unfolding of predetermined patterns, supported but not altered by the environment.[37] The assessment of developmental milestones was important in detecting delay.

The Dynamic Systems Theory, in which motor development is considered a product of interactions between many self-organising systems, followed the Neural-Maturationist Theories.[38] Some of these self-organising systems were body weight, muscle strength, joint configuration, the infant's mood, the CNS, and the environmental conditions. Thelen, in the 1990's, was among the first to apply the principles of dynamic systems to explain motor development and the influence of environmental conditions.[39] According to the Dynamic Systems Theory, motor progress can be modified by environmental manipulation, but the influence of the CNS is equally important as the other self-organising systems.

A third theory, the Neuronal Group Selection Theory (NGST) described by Edelmann in 1993, combines the 'nature' part of the Neural-Maturationist Theories with the 'nurture' part of the Dynamic Systems.[38, 40] According to this theory, development starts with primary neuronal repertoires determined by evolution, where each repertoire consists of multiple neuronal groups. On the basis of afferent information produced by behaviour and experience there are modifications in the strength of the synaptic connections within and between neuronal groups,

resulting in variable secondary repertoires allowing for situation-specific selections of neuronal groups. During the phase of primary neuronal repertoires motor activity is variable and not tuned into environmental conditions. The variable motor activities give rise to variable afferent information, which in turn is used to select a 'pragmatic' neuronal group. A variable movement repertoire is created for each specific situation. Mature movements are adapted exactly and efficiently to task-specific conditions, or a repertoire of motor solutions for a single motor task can be generated.[38]

Another theoretical model which explains a child's development through interaction between nature and nurture, is the transactional model.[41] This model highlights the plastic character of both the environment and the individual. Development is seen as a product of continuous bidirectional interactions between the individual and his environment over time provided by his social settings.

Based on knowledge about CNS plasticity and development, many clinicians and researchers argue that it is important to make early detection of infants who might be in need of early intervention to optimise development.[27, 42] In addition to neurological examinations, ultrasonography and MRI, different tools to discriminate between infants with typical and atypical motor development have been developed.

2.4.2 Principles of measurement

A definition of measurement is "the process of assigning numerals to variables to represent quantities of characteristics according to certain rules".[43 p.63] Its purpose is to describe phenomena and relationships between phenomena or to demonstrate changes as precisely as possible.

Assessment based on measurement tools can either be used to discriminate between persons, to predict the relationship between variables, for decision making or for evaluating response to a treatment.[43] Therefore measurement tools for different purposes have been developed, for instance tools to discriminate between typically and atypically developing infants, tools to predict long-term adverse motor development or tools to evaluate changes with respect to intervention.

The usefulness of the measurement tools depends on their measurement properties; the tool should be reliable and valid for its purpose. Reliability is the extent to which a measurement is consistent and free from errors, whereas validity is whether the tool measures what it is intend to measure.[44] If the purpose of the measurement tool is to evaluate changes, the responsiveness, which is the ability to measure a meaningful or a clinically important change, is also essential.[44]

Some measurement tools are criterion-referenced where a minimum criteria or competence is set to pass an item.[45] Other tools are norm-referenced, designed to determine how an individual performs in comparison to a reference group, usually based on average scores.[43] The measurement tools need to be standardised, containing a documented set of procedures for administering and scoring, to be sure that all infants are assessed under the same conditions.[45]

There is a range of measurement tools for assessing different aspects of infants' and children's neuro-motor development. In the thesis I will focus on measurement tools developed for assessing motor development or motor function during the first year of life.[46, 47] Neurological examinations and tools designed for assessing the infant's behavioural state, social, attentional and autonomic responses are not included in the following overview.

2.4.3 Measurement tools for assessing motor function during the first years of life

The theoretical construct of measurement tools for assessing motor function varies. Some tools involve observation of the infant's posture and spontaneous movements and others include handling of the infant to elicit responses.[45, 47] Moreover, the clinical utility of the tools is important, for example if the tool is suitable for use in the NICU, for assessing fragile and unstable infants, or for use during the first months of life.[47] To target early interventions towards those at highest risk and to prevent unnecessary intervention for those who are unlikely to have motor impairments, it is important to discriminate between infants with typical and atypical motor function. For diagnostic purposes, the measurement tool also needs to be predictive of long-term outcome.[43] Furthermore, it is a strength if the tool can be used longitudinally, to build a trajectory of the infant's development. This will give information about maturation or in some cases, regression of development, recovery from injury as well as the possible effects of intervention.[45, 47] In Table 2 an overview of measurement tools for assessing motor function during the first year of life and at preschool- and school age is given.

Systematic reviews have found that the most reliable and valid instruments to discriminate between typically and atypically developing infants during the first months of life are the TIMP[8] and GMA.[9, 45, 47] The clinical utility of these tools is excellent and both tools, used at three months CA, are predictive of motor developmental impairments, especially if used longitudinally.[45-47] They are the only tools appropriate for use before term. Both TIMP and GMA are described in detail in the following chapters.

Table 2. Measurement tools for assessing motor function the first year of life and at preschool and school age.

Test	Short name	Age-span	Purpose	Type of test	Description of the test	Time to administer	ICF-CY component
First year of life							
Alberta Infant Motor Scale[48]	AIMS	0 month – independent walking	Discriminative, predictive	Norm – referenced	Observation of infant in prone, supine, sitting and standing	15 minutes	Activities and participation
Bayley Scale of Infant and Toddler Development 3rd ed[49]	BSITD-III	1 month – 3,5 years	Discriminative, evaluative	Norm – referenced	Motor scale (81 items, gross and fin motor behaviour) and mental and behavioural scale	15 – 20 minutes (motor scale)	Activities and participation
General Movement Assessment[9]	GMA	Preterm – 4 months CA	Discriminative, predictive	Criteria – referenced	Assessment of spontaneous movements scored from video-recording of infant in supine	10 – 30 minutes recording	Body functions and structures
Infant motor profile[50]	IMP	3 – 18 months	Discriminative	Criteria – referenced	Observed or elicited behaviour scored from video-recording	15 minutes video – recording	Activities and participation
Movement Assessment of Infants[51]	MAI	0 – 12 months	Discriminative, predictive evaluative	Criteria – referenced	Assessment of muscle tone, reflexes, automatic reactions, and volitional gross and fine motor.	30 – 60 minutes	Body functions and structures/ Activities and participation
Neuro Sensory Motor Development Assessment[52]	NSMDA	1 month – 6 years	Discriminative, predictive, evaluative	Criteria – referenced	Gross and fine motor and neurological assessment, primitive reflexes, postural reactions, and motor responses to sensory input	10 – 30 minutes	Body functions and structures/ Activities and participation
Peabody Development Motor Scale 2nd ed.[53]	PDMS-II	0 month – 5 years	Discriminative, predictive, evaluative	Norm – referenced	5 sub-scales; reflexes, stationary, locomotion, object manipulation, grasping and visual motor integration	45 – 60 minutes	Activities and participation
Test of Infant Motor Performance[8]	TIMP	34 weeks PMA – 5 months CA	Discriminative, predictive, evaluative	Norm – referenced	42 items of motor function grouped into observed and elicited items	25 – 35 minutes	Body functions and structures/ Activity and participation

Test	Short name	Age-span	Purpose	Type of test	Description of the test	Time to administer	ICF - component
First year of life							
Posture and Fine Motor Assessment of Infants[54]	PFMAI	2 – 12 months	Discriminative, evaluative	Criteria – referenced	Gross and fine motor assessment	25 – 30 minutes	Activities and participation
Structured Observation of Motor Performance in Infants[55]	SOMP-I	0 – 12 months	Discriminative	Norm and criteria – referenced	Level (progress) of motor development and quality of the motor performance.	15 – 30 minutes	Activities and participation
Toddler and Infant Motor Examination[56]	TIME	0 month – 3,5 years	Discriminative, evaluative	Norm – referenced	5 sub-scales; mobility, motor organization, stability, social/emotional and functional ability	15 – 45 minutes	Activities and participation
Preschool / school age							
Movement Assessment Battery for Children 2[57]	MABC-2	3 – 16 years	Discriminative	Norm – referenced	3 sub-scales; Manual dexterity, ball skills and static dynamic balance	20 – 40 minutes	Activities and participation
Bruininks-Oseretsky Test of Motor Proficiency[58]	BOT-2	4 - 21 years	Discriminative, evaluative	Norm – referenced	8 sub-scales; fine motor precision and integration, manual dexterity, bilateral coordination, balance, running speed and agility, upper limb coordination, strength	45 – 60 minutes	Activities and participation

2.4.4 Test of Infant Motor Performance and Test of Infant Motor Performance Screening Items

The Test of Infant Motor Performance is developed as a tool to assess posture and selective motor control needed for functional performance in infants below five months CA.[8] The test discriminates among infants with typical motor development and infants with motor developmental delay.[59] It is a useful tool when guiding parents in handling and stimulating their infants.[8, 59] Age-standards of the TIMP have been developed based on 990 low birth weight infants (birth weight < 2500 g) in the U.S. with different race/ethnicity and different risk for adverse development.[60] The TIMP can be used longitudinally and is useful for documenting developmental changes, but its responsiveness has not yet been assessed. Its predictive validity has been assessed within different age groups. At three months CA used with cut-off points -0.5 standard deviation (SD), the TIMP correctly identified 72% of the infants who later received scores below -2 SD on the Peabody Developmental Motor Scale-2 (PDMS-II) at four to five years. In comparison, 90% of infants who received scores above -0.5 SD on the TIMP, scored within normal on PDMS-II when assessed at preschool age.[61] Test-retest reliability and validity of the test is good.[59, 62-64]

It takes approximately 25 to 45 minutes to perform and score the TIMP if the infant is in a good behavioural state. For the youngest and for the most fragile infants this can be too demanding. Therefore, a short version of the test has been developed, the TIMPSI, containing half of the items from the TIMP.[8] Average time to complete the TIMPSI is 22 minutes. The correlation between the full version and the screening version of the test is high, 0.88 ($p<0.0001$).[8] Age standards for TIMPSI based on the motor performance of 990 U.S. infants are available in the TIMP manual.[8, 65] Its purpose is mainly discriminative and thereby, to identify infants for whom a full version of the test should be performed.

2.4.5 General movement assessments

General movement assessment, developed by Prechtl and co-workers, is an assessment of the infants' spontaneous movements.[9, 66-68] These spontaneous movements, the general movements (GMs), seen in foetuses and young infants have age-specific characteristics (Figure 3).

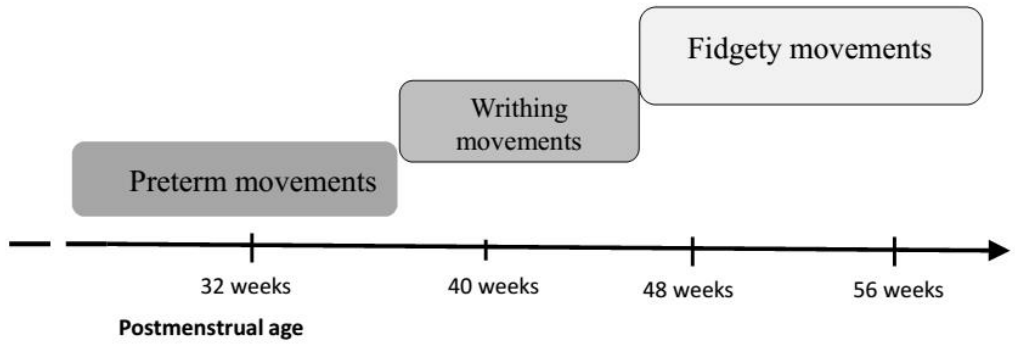

Figure 3. Age specific characteristics of general movements

Until approximately 37 weeks PMA the movements are described as preterm GMs, at term and early post-term as writhing movements, and at two to four months CA as fidgety movements.[9, 68] The assessment, based on a visual gestalt perception or a global view, is performed through observation of video-recording of the infants in supine lying, awake and without any interruptions.[9] The GMs are classified as either normal or abnormal, depending on their complexity, fluency and variability. In the period of preterm and writhing movements, which is the focus of this thesis, subgroup classifications of abnormal GMs are; chaotic, cramped-synchronized, or poor repertoire. GMA discriminates between typically and atypically developing infants. Lack of or abnormal fidgety movements is seen as an indicator of brain damage[66], and is highly predictive with respect to CP. [9, 42, 47, 66, 69, 70] During the period of preterm and writhing movements the predictive value of GMA is low. The sensitivity of

abnormal GMs is high across different ages, whereas the specificity is only reported to be high when the assessment is performed during the period of fidgety movements.[9, 71] It is found that the abnormal movement patterns of poor repertoire GMs gradually normalises.[72]

For a detailed analysis of the GMs, two different optimality lists has been developed, one for use at preterm to early post-term age, and one for use from two to four months CA.[9, 67, 73, 74] The first optimality list comprises the evaluation of detailed aspects of the GMs, whereas the second optimality list covers movements occurring together with fidgety movements.[9, 75] Low motor optimality score at two to four months CA is indicative of later impaired motor and cognitive function[75-77], but the consequences of low optimality score at preterm to early post-term age is less conclusive.[72, 73, 78]

GMA can be considered to be an assessment tool of the body functions and structures component according to the ICF-CY as general movements express brain maturation and function.[79]

2.4.6 Motor impairments in infants born preterm

The most severe motor impairment seen in infants born preterm is CP. Results from a meta-analysis from 2000, including 26 studies, found that the prevalence of CP was 14% for infants with GA from 22 to 27 weeks, 6% for infants with GA from 28 to 31 weeks and < 1% for infants with GA 32 to 36 weeks.[4, 80] In the United Kingdom and Ireland between March and December 1995 the prevalence of children with CP was 20% in infants born before 26 weeks PMA.[81] In Norway in a cohort study of children born from 1967 to 1983, the prevalence of CP was 9.1% in infants born before 28 weeks PMA versus 0.1% for infants born at term.[1] However, there has been a decline in this prevalence since 1980. A collaborative network of CP registers and surveys, Surveillance of Cerebral Palsy in Europe, has documented a significant reduction

in the prevalence of CP in infants with birth weight lower than 1575 grams from 60.6 (99% CI: 37.8 – 91.4) per 1000 live births in 1980 to 39.5 (99% CI: 28.6 – 53.0) in 1996 ($p < 0.0004$).[80, 82]

Other motor impairments linked with preterm birth have been described variously like developmental coordination disorder (DCD), minor neurological dysfunction or soft neurological signs.[3] These motor impairments might not be evident before the children reach school age and they often persist into adulthood.[83] The prevalence has been reported to vary from 47 to 64% for fine motor deficits and from 14 to 81% for gross motor deficits, depending on the child's age when assessed.[3] A review of preterm birth and neurological outcomes from 2010 found a prevalence of children having DCD varying from 9.5 to 51% compared to estimated 5 to 6% in the general population.[4] Motor impairment was in this review defined as < 5 centile on the Movement Assessment Battery for Children (MABC) or scores < -1SD on the MABC or on the Bruininks-Oseretsky Test of Motor Proficiency.

The spontaneous movements of infants born preterm often lack variation and complexity compared to the movements of full-term born infants[74], without this indicating adverse long-term neurological outcome.[72] In a study of postural behaviour in infants born preterm compared to full-term born infants at four to six months CA, the infants born preterm showed relatively immobile postural behaviour.[84] Furthermore, the immobile postural behaviour was related to reduced postural behaviour and scores on balance assessed by Movement ABC when the children were six years old.[85] Another study of postural control in 90 children born very preterm found impaired static and dynamic balance in the preterm group compared to term-born children assessed at four years CA.[86]

A meta-analysis of motor ability in infants born very preterm concluded that preterm birth is associated with significant motor impairments persisting throughout childhood.[5] These motor

impairments can be seen both in balance and in fine and gross motor function. A geographically based follow-up study of 36 VLBW young adults and matched controls describes overall poorer fine and gross motor skills in VLBW adults compared to controls, indicating that these children do not outgrow their motor problems when entering adulthood.[83]

2.5 Early intervention

The term "early intervention" covers a range of approaches aiming at preventing perinatal disabilities, ensuring neuroprotection and providing optimal environmental conditions.[87] A consensus on a definition of "early" is lacking but it usually comprises intervention conducted before term age and the first year of life.[27] The plasticity of an immature CNS provides rationale for early intervention strategies.[27]

A program designed to reduce stress and improve self-regulation in infants born preterm while in the NICU is the Newborn Individualized Developmental Care and Assessment Programs (NIDCAP), which involve caregivers, infants and parents.[87, 88] The NIDCAP is an extensive program consisting of individually tailored interventions to minimize possible stress on the young infants caused by the environment, for example noise, light or painful routines. It is found that the NIDCAP improves respiratory and nutritional disorders associated with preterm birth, improves weight gain and decreases hospital stay duration.[87] A RCT of 33 low-risk infants born preterm compared NIDCAP with care as usual, and it was found better outcomes in the group having received NIDCAP.[88] These differences were seen both in the neurological assessment and in behaviour functioning when the infants were assessed at two weeks CA. When assessed at nine months CA by the Bayley Scales of Infant Development II (BSID-II), the difference between the groups was still evident. The study also reported evidence of

enhanced brain function and structure in the NIDCAP group. A similar study was conducted in a group of SGA infants born preterm, demonstrating corresponding results.[89]

A program designed for use in transition from hospital to home is the Mother-Infant Transaction Program.[90, 91] This program aims to sensitize the parents to their infant's cues, especially to signals indicating stimulus overload, distress or readiness for interaction. The intervention starts with 1-hour daily sessions with the parents and infant one week before discharge from hospital, followed by four home visits; day 3, 14, 30, and 90 after discharge. A modified version of this program has been used in a RCT of 146 infants born preterm.[90, 92] The program seemed to sensitize the mothers to their infants temperament assessed when the infants were six months CA.[93] Furthermore, parents who had participated in the program scored significantly lower on stress parameters assessed by Parenting Stress Index when the infants were 6, 12 and 24 months CA.[90, 92] There were no significant differences between the infants in the two groups assessed at two years CA by BSID-II, but at five years the infants IQ scores were significantly higher in the intervention group compared to the control group.[92, 94]

Providing enriched environment has shown positive effect on brain development and behaviour in studies of animals and birds.[95, 96] Increased cortical weight and thickness and increased dendritic branching have been documented.[96] Enriched environment interventions encompass interventions that facilitate cognitive, motor, sensory, or social aspects to promote learning and require that the individuals actively explore the environments.[27, 97] Very young infants need support from parents or caregivers to be able to explore the environment.[97] A meta-analysis of enriched environments and motor outcomes in infants with or at high risk for CP reported promising results, but because of the high levels of heterogeneity of participants and type of interventions, a conclusion could not be drawn.[97]

Challenges in conducting meta-analysis of early intervention include the diversity of types of interventions, varying from interventions addressing maternal health, parent-infant relationship, infants' cognitive or motor development, or combinations of these.[27] The objective of the interventions, the content, and the persons conducting the interventions have also varied. The following sections focuses on early intervention to optimise motor development.

2.5.1 Early intervention to optimise motor function

A prerequisite in motor development and motor learning is that the child actively explores the environment.[27] The positioning of the infant defines the infant's possibility of exploring, for instance a certain level of experience and control in prone and in supine precedes independent sitting.[98] Environmental adaptation and postural support can provide new possibilities for the infant to be active. Thus, the parent or caregiver plays a crucial role in the infant's development by creating an environment that facilitates his possibilities for learning.

A study of head control in 22 infants born at term without known risk for impairments, comparing intervention with no intervention, documented more advanced head control and general motor development in the intervention group compared to the control group.[99] The intervention comprised four weeks of 20 minutes daily postural and movement activities provided by the caregivers, and an additional 20 minutes daily upright experience starting when the infants were one month old. All infants were tested every second week for three months.[99] Head control is crucial in different aspects of development, like for the use of vision, oro-motor function and trunk and arm development, all necessary for exploring the environment.

The role of experience was studied in a trial including 28 typically developing infants born at term.[98] At two months of age the infants were divided into two groups, both receiving 15 minutes daily intervention for three weeks. One group received face-to-face interactions in

prone (control group) and one group received handling and positioning activities and enriched perceptual- and motor environment. Motor function was assessed weekly for 12 months after the end of intervention. The infants who had received handling and positioning showed greater advances in motor development compared to the control group. The difference was seen immediately after the three-week period and continued throughout 12 months.

Both these aforementioned studies demonstrate the positive effect of early intervention in typically developing infants. We can assume that the effects of early interventions might also apply for atypically developing infants but there are many unanswered questions. For instance, at what age, what dosage and what type of intervention is the preferred in optimising motor development in infants at risk and in atypically developing infants. An overview of RCTs of early intervention to optimise motor development in infants born preterm during the first three years of life is given in Appendix 1.

A recent meta-analysis on the effect of early interventions post-hospital discharge to prevent motor and cognitive impairments in infants born preterm, and its update, found a small significant difference in motor outcome at zero to three years, favouring intervention groups.[11, 100] Furthermore, subgroup analysis comparing interventions that begun before discharge from hospital versus those that begun post discharge found slightly greater, but not significant, impact on motor outcome when the intervention was started before discharge from the hospital.

One of the studies included in this review, which was not appropriate for the meta-analysis due to the measurement tool being used, revealed greater improvements in motor function in the intervention group compared to controls.[11, 101] One hundred and eleven infants with GA < 37 weeks were included in this study. Infants who at term age received high score on the TIMP served as a not-at-risk control group. The other infants, defined as at-risk group, were randomly assigned to an intervention or to a comparative group. The parents performed the intervention

designed to facilitate motor development, when the infants were 40 weeks to 4 months CA.[101]

Another systematic review of early intervention with parents actively involved found more consistent effects in favour of the intervention groups on the mental scale of BSID/ BSID-II than on the psycho motoric scale, when assessed at 12, 24 and 36 months CA.[102] But by the age of five years there was no difference between groups.

2.5.2 Parent-infant relationship

Experiencing a preterm birth and caring for a baby while being in the NICU is for most parents a very stressful situation.[90, 103] Being a sensitive and responsive parent implies responding appropriately and in a timely way to the infant's cues.[104] Because of the infant's immaturity his capacity for attention and for interacting socially is reduced. Therefore, the infant's behavioural cues can be difficult for the parents to interpret, something that might have negative impact on the parent-infant relationship.[105, 106] Increasing the parents' sensitivity and responsiveness towards their infants could influence the infants' environment positively and subsequently improve the infants' development.[105, 107]

Interventions which include active involvement from the parents and which give support to the parents have a proven positive effect on maternal sensitivity and on maternal stress.[107] Interventions that provided information or parent education only seemed to be less effective.[107] Furthermore, interventions that included parent support were often associated with improved child outcome. Another systematic review demonstrated that mother-preterm infant relationships improved after having participated in intervention of their infant.[108] A sensitive parent gives the infant a secure base to explore the environment from, and thereby enhances the infant's development.[109]

2.5.3 The Norwegian Physiotherapy Study in Preterm Infants

The Norwegian Physiotherapy Study in Preterm Infants (NOPPI) is a multi-centre parallel-group pragmatic RCT of early parent-administrated physiotherapy (ClinicalTrials.gov NCT01089296).[110] Three university hospitals participated in recruiting the 153 participants randomised to receive intervention (carried out in week 34, 35, 36 PMA) or care as usual. The study consists of two parts; the aim of part one is to evaluate the effect of parent-administrated physiotherapy on infants' motor function, end-point two years CA. Part two is a qualitative observation and interview study to assess different aspects of the encounter between physiotherapist and parent, with focus on the physiotherapist. It aims to increase knowledge about parents' experiences of being actively involved in the intervention, as well as assessing the short- and long-term effects on the parent-child relationship. The study protocol, containing a detailed description of the intervention, was published in 2012 (Appendix 2). Paper III in the thesis reports the short-term outcome from this study.

3. Aim of the thesis

The overall aim of the thesis is to assess different aspects of two measurement tools used in infancy and to evaluate the effect of early parent-administrated physiotherapy conducted before term-equivalent age. The aims of the separate papers are:

Paper I: To examine the test-retest reliability of the TIMPSI in a group of infants in high to moderate risk for long-term motor developmental difficulties.

Paper II: To examine aspects of validity of the general movement optimality list at preterm, term and early post-term age in a group of VLBW infants without severe brain lesions.

Paper III: To investigate the short-term effect of parent-administered physiotherapy in the preterm period on motor function in medically stable infants. We wanted to assess whether infants in the intervention group demonstrated a different change in motor function from baseline to post-intervention as compared to infants in the control group.

4. Material and methods

The thesis comprises two methodological studies (Papers I and II), and one RCT of early intervention (Paper III). The study population was infants born preterm except for in Paper I where also six infants born at term were included.

4.1 Study design

The first study (Paper I) is a test-retest reliability study of the "Test of Infant Motor Performance Screening Items".

The second study (Paper II) is a validity study of the optimality list "Detailed Assessment of General Movements (GMs) During Preterm and Term Age" (Appendix 3).

The third study (Paper III) is a multi-centre parallel group pragmatic RCT of parent-administrated physiotherapy when the infants were 34, 35, 36 weeks PMA. The randomisation was performed by a web-based, computer-generated randomisation system developed and administered by the Unit for Applied Clinical Research, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway, with the infants stratified according to GA (< 28 week and ≥ 28 weeks) and hospitals. Twins were assigned to the same group.

4.2 Study population

Inclusion and exclusion criteria of all three studies are presented in Table 3 and clinical characteristics of the participants are given separately for each paper, Table 4 to 6.

The first study (Paper I) included a convenience sample of 51 infants recruited from the NICUs or from the follow-up program for high-risk infants at two University hospitals in Norway, from April 2013 to December 2014. The infants had to be available for testing twice within three days. The study was conducted as part of ordinary follow-up of infants at risk for adverse neurodevelopment and included two age groups only, either infants at 36 to 37 weeks PMA or infants at 12 to 13 weeks CA.

The second study (Paper II) included 20 VLBW infants born at Modena University Hospital, Italy, between November 2008 and November 2010. The infants were participating in another prospective study of low risk infants born preterm. They had no severe brain lesion on cranial ultrasonography, and video-recordings of their GMs at preterm, term, early post-term age and at three months CA had already been performed.

The third study (Paper III) included 150 infants born very preterm recruited from the NICUs at three University hospitals belonging to the National Health Service in Norway, from March 2010 to October 2014. Fifteen of the participants from the first study (Paper I) also participated in the RCT. As the intervention was parent-administrated, the parents had to speak and understand Norwegian to secure that they had learned and understood the different activities and could ask for guidance if necessary. The infants had to be medically stable due to the nature of the intervention.

Table 3. Inclusion and exclusion criteria in Paper I – III

	Inclusion criteria	Exclusion criteria
Paper I	Infants at high risk; - GA < 28 weeks - Birth weight < 1000 grams - Grade 3 or 4 intraventricular haemorrhage - Periventricular leukomalacia - Infants born at term with asphyxia treated with hypothermia Infants at moderate risk; - GA from 28 to 33 weeks. Parents understand Norwegian or English Available for assessment twice within 3 days	Malformations Syndromes Having undergone major surgery
Paper II	Infants with GA < 32 weeks, and infants with birth weight < 1500 grams Repeated ultra-sound scans had excluded moderate to severe brain lesions	Cerebral lesions (grade 3 or 4 intraventricular haemorrhage, cystic periventricular leukomalacia or cerebellar damage) Malformations, Genetically disorders Blindness
Paper III	Infants with GA ≤ 32 weeks Infants able to tolerate handling at 34 weeks PMA Parents speak and understand Norwegian. Follow-up in the same hospital	Triplets or higher pluralities Malformations Syndromes Having undergone major surgery

Table 4. Clinical characteristics of participants Paper I

	High risk (n=27)		**Moderate risk** (n=24)		**Total** (n=51)	
	mean	**SD**	**mean**	**SD**	**mean**	**SD**
Gestational age (weeks)	29.8	(6.2)	30.4	(1.7)	30.1	(4.4)
Birth weight (grams)	1499	(1158)	1546	(292)	1524	(814)
	n	**%**	**n**	**%**	**n**	**%**
Male	17	(63)	15	(63)	32	(63)
Bronchopulmonary dysplasia	12	(24)	0	(0)	12	(24)
Abnormal caput ultrasound	9	(18)	4	(8)	13	(25)
Intracranial bleed grade 3 or 4	2	(4)	0	(0)	2	(4)
Periventricular leukomalacia	3	(6)	2	(4)	5	(10)
Tested at 36 - 37 weeks PMA	6	(12)	21	(41)	27	(53)
Tested at 12 - 13 weeks CA	11	(22)	13	(25)	24	(47)

SD: Standard deviation

Table 5. Clinical characteristics of participants in Paper II

	Moderate risk (n=20)	
	n	**%**
Gestational age 24 - 27 weeks	11	(55)
Gestational age 28 - 31 weeks	9	(45)
Extremely low birth weight (< 1000 grams)	14	(70)
Very low birth weight (1000 - 1500 grams)	6	(30)
Male	8	(40)
Bronchopulmonary dysplasia	1	(5)
Intracranial bleed grade 1 or 2	3	(15)
Retinopathy of prematurity grade 1 or 2	1	(5)

Table 6. Perinatal and social background factors of participants in the intervention group and control group in Paper III

	Intervention n=71		**Control n=79**	
Perinatal factors	n	%	n	%
Gestational age below 28 weeks	10	(14)	17	(22)
Male	36	(51)	44	(55)
Twins	12	(17)	23	(29)
Not older siblings	41	(57)	54	(68)
Intraventricular haemorrhage grade 1 - 2	4	(6)	8	(10)
Intraventricular haemorrhage grade 3 - 4	2	(3)	2	(2)
Periventricular leukomalacia	6	(8)	4	(5)
Sepsis	7	(10)	12	(15)
Bronchopulmonary dysplasia	6	(8)	8	(10)
	mean	**SD**	**mean**	**SD**
Number of other diagnoses	2.3	(1.8)	2.8	(1.7)
Birth weight: grams	1417	(417)	1385	(368)
Days of ventilation	1.6	(4.2)	1.7	(4.4)
Days of CPAP	15.3	(19.9)	15.9	(17.7)
Days with oxygen	7.9	(16.9)	10.5	(19.3)
Social background factors	**mean**	**SD**	**mean**	**SD**
Mother's age, years	32.1	(5.5)	30.5	(4.9)
Mother's education, years	15.6	(2.7)	14.9	(2.8)
Father's education, years	14.5	(3.0)	14.6	(2.7)

CPAP: continuous positive airway pressure

Of 217 invited participants in Paper III, 153 consented to participate and 64 declined. Three families withdrew after the randomisation and declined to the already collected data being used, leaving 150 participants. The parents were informed about the study both verbally and by written information by a physiotherapist unknown to the parents. They were also informed that they could withdraw from the study at any time. No explanations for declining to participate or for withdrawing were asked for, but the participants were welcomed and encouraged to meet in the follow-up assessments. Figure 4 shows the flow chart from invitation through randomisation, participation in intervention, and post-intervention assessment.

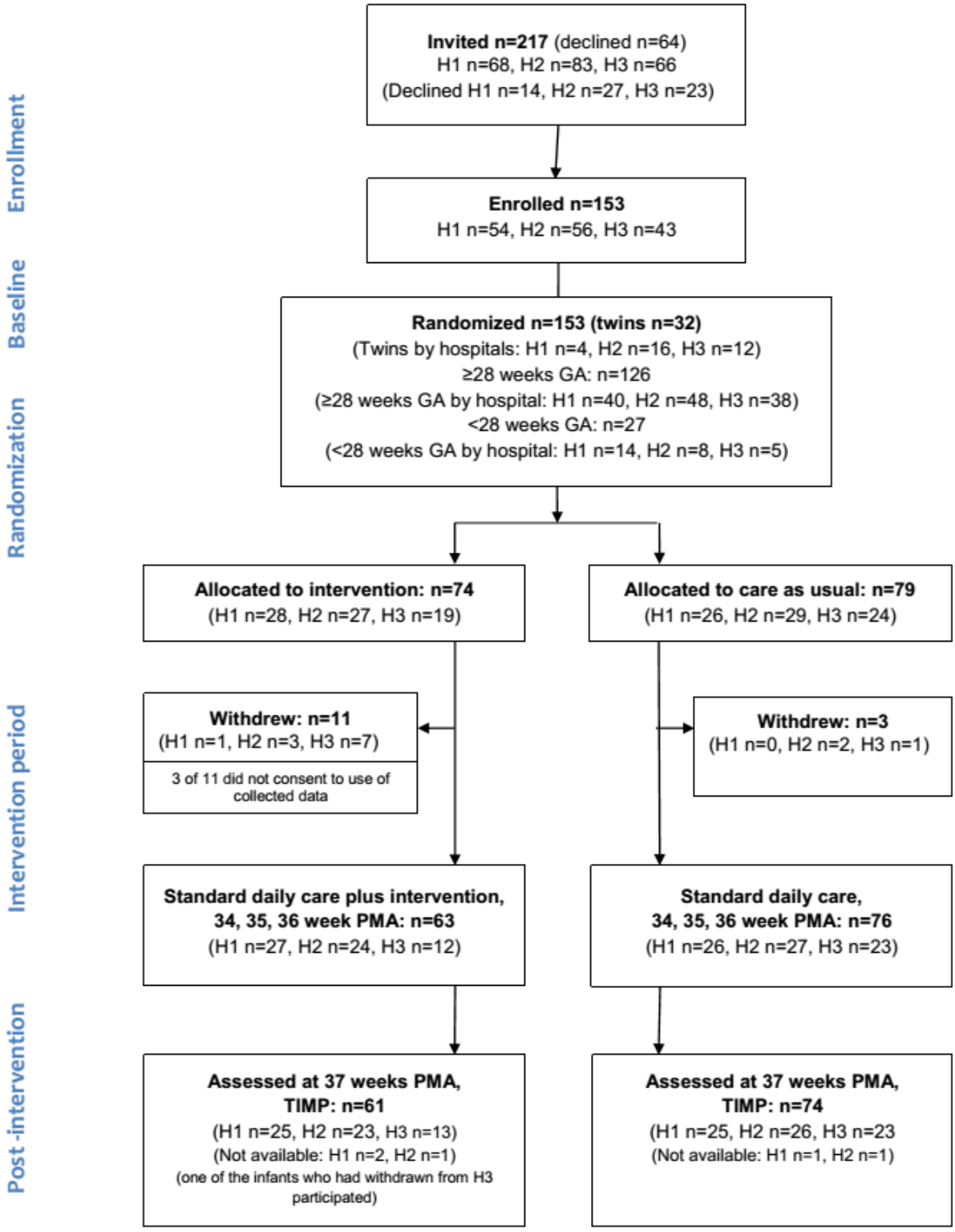

Figure 4. Participant flowchart from invited through randomisation, participation in intervention, and post-intervention assessment. H1: University hospital of North Norway, Tromsø University Hospital, H2: St. Olavs Hospital, Trondheim University Hospital, H3: Oslo University Hospital, Ullevål, PMA: ostmenstrual age, TIMP: Test of Infant Motor Performance.

4.3 Measurement tools

The measurement tools used in this thesis were the TIMPSI, TIMP and GMA.[8, 9]

The TIMPSI was used both in the test-retest reliability study (Paper I), and as a baseline measure in NOPPI (Paper III). The TIMP was used as an outcome measure in Paper III, at 37 weeks PMA. The TIMP consists of two subscales, one comprising 13 items observing the infants' spontaneous movements, scored dichotomously, and one comprising 28 items observing the infants' responses to handling and to visual and auditory stimuli, scored on a zero to three – six points rating scale. Maximum total score is 142. The TIMPSI is divided into the following three subsets: a "Screening Set", an "Easy Set", and a "Hard Set". The infants are first assessed with the Screening Set consisting of 11 items scored on a five- to seven-points rating scales, score range 0 – 51.[8] If the sum score of the "Screening Set" is below 18 the "Easy Set" will be performed. The "Easy Set" consists of four dichotomously scored items and six items scored on a five- or six-point rating scale, score range 0 – 31. If the sum score of the "Screening Set" is above 18 the "Hard Set" will be performed. The "Hard Set" consists of eight items: five dichotomously scored and three scored on a five-point rating scale, score range 0 – 17. The scores for the subsets are summed with higher scores indicating better motor performance. Maximum TIMPSI score is 99.

The optimality list for detailed GMA at preterm to early post-term age was developed by Prechtl et al.[67] and later modified by Einspieler et al.[9, 73, 74] We used the optimality list "Detailed Assessment of General Movements (GMs) during preterm and Term Age" later published in 2016 (Appendix 3).[74] It comprises a global assessment followed by a detailed scoring of the movements of neck, trunk, upper and lower limbs. In the detailed analyses of neck and trunk rotatory movements are scored, whereas in the upper and lower limbs nine different movement

components are scored; amplitude, speed, space, proximal and distal rotation, onset and offset of movements, tremulous movements, and cramped components. The items are scored on a zero- to two-points rating scale, with two indicating optimal score. Maximal general movement optimality score (GMOS) is 42 points. Optimality subscore (OS) for upper and lower limbs and neck and trunk are calculated separately, maximum score is 18 for upper or lower limbs and four for neck and trunk, respectively.

The tools used reflect different aspects of the ICF-CY, GMA addresses the body functions and structures component whereas the TIMP and the TIMPSI also addresses the activities and participation component.

4.4 Procedures

In Paper I, one tester from each of the two hospitals participated in the assessment of the infants. Both were paediatric physiotherapists who were experienced in assessing very young infants and who had good knowledge of the TIMP. The infants were examined either before discharge or when the infants came to the first follow-up assessment at the hospitals. The infants should be in appropriate behavioural state for testing, awake and not crying or fussing. Test 2 was carried out within three days after Test 1. This period of time was chosen because no changes in infants' motor performance are expected within such a short period.[8, 62] In case of two tests carried out on the same day, pauses of several hours between the tests ensured that the infants were rested and that the testers did not remember the scoring details from the previous test.

In Paper II, the video-recordings of infants were anonymised by giving the infants random numbers. A physiotherapist, without knowledge of the infants' medical history and neurodevelopmental outcome, edited the video-clips into two-minute video-clips or video-clips

comprising three GMs. The observers were blinded for names and characteristics of the infants when assessing the video-recordings. Two observers, certified in the GMA, performed the assessments separately by replay of each video for a minimum of four times. First a global motor assessment was performed, then movements of the neck and trunk were assessed followed by detailed assessment of upper- and lower-extremities movements. In cases of disagreement with either the global assessment or a difference of more than five points in GMOS, a third observer were asked to assess the videos. The scores that two of the observers agreed upon were used.

In Paper III, the infants were assessed at baseline using the TIMPSI and GMA, before they were randomised to intervention or to a control group. The nature of the intervention made it impossible to withhold group assignment from the parent of the infants, the staff at the NICUs and the physiotherapists instructing the parents. Post-intervention, at 37 weeks PMA, all infants were assessed with the TIMP. If the physiotherapists administering post-intervention assessment knew group allocation, the test was video-recorded and later scored by a second physiotherapist unaware of group assignment. The physiotherapists that administrated the TIMPSI and the TIMP had all completed a two-day training workshop on administrating and scoring the test.

4.5 Early parent-administered physiotherapy (Paper III)

The main objectives of the intervention Paper III were to enhance the infants' postural control, head control and midline orientation during active participation from the infant. The intervention was developed based on the interventions in two previously published studies. The handling and motor stimulation was based on Girolami and Campbell[111] and the social

interaction between the parent and the infant on Kaaresen et al.[92] The intervention was performed by the parent, with the infant lying on the changing table or on the parents' lap. Postural support was given to facilitate the infant's midline orientation as a base for social interaction and for increasing the infant's variation of movements. To increase variation of movements each infant had at least one activity in each of the following positions; prone, side-lying, supine, supported sitting, and in transition between positions.

The intervention was individualized based on the infant's level of development and tolerance for movement. The parents were taught to give just sufficient postural support to facilitate activity and to adapt the support to the infants' responses. They learned to read their infants cues and to assess whether the infant was actively participating or not, in order to promote motor development and motor learning, in line with theories of motor development and motor learning.[37, 38] The intervention was carried out in dynamic interaction between the environment (social and physical) and personal factors in the infant. The infant, with help of the parent, was actively participating during the intervention as the intervention was to be terminated if the infant was not participating.

Two physiotherapists at each hospital were involved in teaching the intervention to one parent in each family. On day one the physiotherapist explained and demonstrated the activities. On day two, the parent demonstrated the intervention and hand-over-hand guidance was provided if necessary. The parent performed the intervention for a week and additional consultations were provided based on individual needs. The parents could ask for more consultations if in doubt or had difficulties performing the intervention. After a week, all parents received a new consultation with the physiotherapist before continuing with the intervention for another two weeks.

A booklet containing photos and written instructions of fifteen activities implemented in different positions was given to the parents during the first day of intervention. An example of a page from the booklet is given in Figure 5.

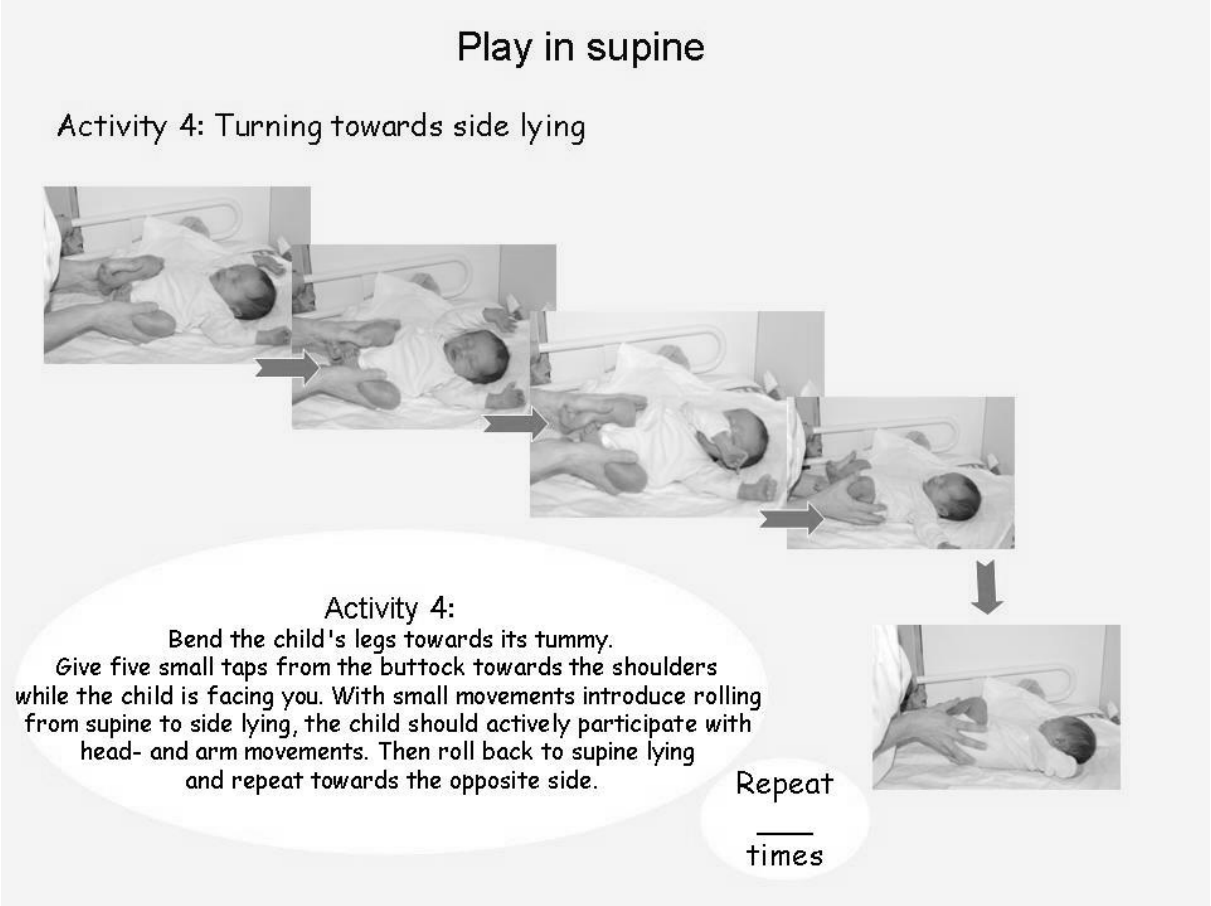

Figure 5. Page from the booklet given to the parents in the intervention group.

According to the protocol the intervention time was set to a maximum of 10 minutes twice a day for three weeks when the infant was 34, 35 and 36 weeks PMA. The intervention was to be stopped if the infant was not in a behavioural state for intervention: fussing, falling asleep, hungry, or showed signs of stress. The parent chose the time of the day for performing the interventions and they were asked to keep a daily log to record the time spent on intervention and report any reasons for terminating a session or for not performing the intervetion.[110] A

detailed description of the intervention is published in a previous paper of the study protocol (Appendix 1).

The control group received care as usual, which included general information from the physiotherapist to the parents about positioning and handling. No specific and structured stimulation program was given routinely to infants in the control group. In all three NICUs principles from NIDCAP[88] were applied to minimize possible stress on the young infants caused by, for example, noise, light or painful routines

4.6 Ethical approval

The Regional Committee for Medical and Health Research Ethics Central in Norway (REC Central) reviewed the study protocol, Paper I, in January 2012. It was concluded that the study did not require approval but only needed to be reported to the Data Protection Officer at the Hospital.

The validity study of the optimality list "Detailed Assessment of General Movements (GMs) During Preterm and Term Age" (Paper II), was part of a study of VLBW infants born preterm and developmental outcome at 24 months approved by the ethical committee in Modena (z 32/13).

The NOPPI (Paper III) was approved by the Regional Committee for Medical and Health Research Ethics North in Norway (REC North: 2009/916-7) and registered in Clinical Trials.gov NCT01089296.

4.7 Statistics and analyses

In the methodological studies (Paper I and II), the software IBM SPSS statistics version 22 (IBM SPSS Statistic, Chicago, IL, USA) was used to perform the statistical analyses. In Paper III Stata version 13.1 (StataCorp LP, USA) was used. Normality of the data was examined by by Q-Q plot.

Intra-class correlation coefficient (ICC) was used in Paper I and II. The ICC reflects both the degree of correspondence and agreement, as well as relative reliability between two ratings.[43] Values above 0.75 indicate good reliability, but for clinical measurements, the ICC should exceed 0.90.[43] In Paper I, $ICC_{1.1}$ was used to calculate relative reliability for within-subject differences. Absolute reliability was calculated as the square root of the mean within-subject variance (S_W).[112, 113] Low values express a small degree of measurement error. For graphical presentation of the differences between the two tests, a Bland Altman plot was constructed, where the differences of the two tests were plotted against the mean difference.[114] In Paper II, $ICC_{2.1}$ was used to assess agreements between the observers.

In Paper II, the Mann-Whitney *U* test was applied to compare GMOS between infants with normal and abnormal global GMA. Receiver-operating characteristics curves (ROC curves) were used to calculate area under the curve (AUC) as an estimate of diagnostic accuracy of the GMOS with respect to motor outcome at three months CA.[43]

Spearman's rho (r_s) was used in Paper II to assess concurrent validity between the optimality list and GMA, and in Paper III to explore the correlation between time in minutes spent on intervention and change in z scores.[43]

A linear mixed model for repeated measures was used in Paper III to analyse differences in change in motor function from 34 to 37 weeks PMA between the two groups.[115] Because of the age of the infants, different measurement tools were used at baseline and post-intervention.

TIMPSI and TIMP raw-scores were transformed to z scores for comparison of scores between the two time-points.[8, 43] Z scores are the number of standard deviations that a given value is above or below the mean of the distribution.[43] Because of the randomisation, all differences at baseline between the groups were expected to be due to chance,[116-119] therefore the only fixed effect variables were TIMPSI z scores and GA. GA was included because of its possible impact on long-term neurodevelopment.[2, 4, 6] Random effect variables were hospitals and individuals in families. The ICC of the random effect variables was also estimated to get information about within-cluster correlation. Effect size, Cohens *d*, was estimated based on comparison of scores for the two groups post-intervention. An effect size of 0.20 is regarded small, 0.50 moderate and 0.80 large.[43]

5. Main results

The main results of the studies are presented separately.

Paper I: Test-retest reliability of the Test of Infant Motor Performance Screening Items in infants at risk for impaired functional motor performance

In this paper, we examined test-retest reliability of the Test of Infant Motor Performance Screening Items. The intra-class correlation coefficient ($ICC_{1.1}$) was 0.99 (95% CI: 0.98 – 0.99), indicating very high relative reliability of the TIMPSI. Absolute reliability (S_W) for TIMPSI score of all infants was 3.1, implying that the measurement error will be within 3.1 x 1.96 = 6.07 points on the total TIMPSI score in 95% of the cases. Furthermore, the mean differences in TIMPSI scores of the two tests were close to zero, and in 94% of the cases the difference between the two tests fell within 1.96 SD of the mean difference. The TIMPSI showed strong test–retest reliability when performed on a group of infants with high to moderate risk for later motor developmental difficulties. We can recommend use of the TIMPSI to screen development of infants for whom the full version of the test is too demanding.

Paper II: Validity of general movement optimality list in very low birth weight infants without severe brain lesions

In this paper, we examined the concurrent and predictive validity of the optimality list "Detailed Assessment of General Movements (GMs) during preterm and Term Age".[74] We found the concurrent validity to be moderate to high between the general movement optimality list and GMA across all items at term and early post-term age ($r_s > 0.6$, $p < 0.05$), except for tremulous movements and cramped components. The only items correlating moderate to excellent with the global GMA across all three ages were amplitude and speed in upper and lower limbs, rotation in upper limbs, and involvement of the neck. There was no overlap in median GMOS

for normal and for poor repertoire GMA for any of the ages, and GMOS differed significantly between the two groups across all ages ($p < 0.035$). Thus, the GMOS distinguish between infants who had normal and poor repertoire GMs. The AUC for the optimality list used at the three different ages and outcome at three months CA was from 0.32 (95% CI: 0.03 – 0.61) to 0.53 (95% CI: 0.24 – 0.83), indicating low predictive validity of the optimality list. We concluded that the concurrent validity of the optimality list was moderate to high against the GMA across preterm, term and early post-term age, but the predictive validity of GMOS for motor function at three months CA was low.

Paper III: Early parent-administered physiotherapy for preterm infants: a randomised controlled trial

This paper reports the short-term results from an RCT examining effect of parent-administrated physiotherapy for infants born very preterm during three weeks in the preterm period. We found that the intervention group had higher improvement in motor function from baseline to post-intervention compared to the control group. The group difference in change of z score was 0.42 (95% CI: 0.13 – 0.72), $p = 0.005$. Most parents conducted the intervention at least once per day for three weeks. The analysis was performed according to the protocol[110] and the Consolidated Standards of Reporting Trials (CONSORT) guidelines.[120, 121] From this study, we concluded that the intervention optimised motor function on short-term in the intervention group, and that conducting the intervention once a day can be feasible for medically stable preterm infants and their parents from week 34 PMA.

Unpublished results of the RCT

In Paper III, the median number of diagnoses was borderline significantly higher in the control group than in the intervention group (p=0.059, see Table 1 in Paper III). As a number of diagnoses might influence motor development, additional analyses were performed for comparison. A linear mixed model for repeated measures including number of diagnoses as a fixed effect variable was applied. The results remained unchanged as shown in Table 7. Furthermore, because of more participants withdrawing from the study in the intervention group a linear mixed model for repeated measures complete cases, was applied for comparison, also indicating similar result (Table 7).

Table 7. Changes in z score from baseline to post-intervention.

	Change in z score intervention group		**Change in z score control group**		**Between-group differences**		***p***
	mean	(95% CI)	mean	(95% CI)	mean	(95% CI)	
1	0.25	(0.01 to 0.50)	-0.16	(-0.39 to 0.06)	0.42[1]	(0.13 to 0.72)	0.005
2	0.25	(0.01 to 0.50)	-0.15	(-0.38 to 0.07)	0.41[2]	(0.11 to 0.71)	0.006
3	0.29	(0.05 to 0.54)	-0.13	(-0.35 to 0.10)	0.42[3]	(0.13 to 0.71)	0.004

1. Intention to treat linear mixed model adjusted for clustering effects of twin pairs and hospitals, fixed effect variables GA and TIMPSI z scores.
2. Intention to treat linear mixed model adjusted for clustering effects of twin pairs and hospitals, fixed effect variables GA, TIMPSI z scores and number of diagnosis.
3. Intention to treat linear mixed model adjusted for clustering effects of twin pairs and hospitals, with fixed effect variables GA and TIMPSI z-score, complete cases only.

6. Discussion

6.1 Main findings

The first two papers of the thesis examined two measurement tools developed for assessing motor function in infancy. In Paper I, the test-retest reliability of the TIMPSI, was found to be excellent when performed twice within three days in a group of infants with high to moderate risk for later motor developmental difficulties. In Paper II, the concurrent validity between the general movements optimality list and GMA was moderate to high at term and early post-term age. The GMOS distinguished between infants with normal and poor repertoire GMA at all ages. But the predictive validity of the optimality list for motor outcome at 3 months CA was low.

In Paper III, we reported the short-term outcome from a multi-centre RCT, the NOPPI, where the parents performed the intervention with the supervision of physiotherapists. The TIMPSI and GMA were used for assessment at baseline and the TIMP was used as an outcome measure at week 37 PMA. A small, but highly significant group difference in change in motor function from baseline to post-intervention was found in favour of the intervention group, even though the number of intervention sessions was about half of that intended.

6.2 Validity of the studies

In this section I will discuss methodological aspects of the three studies concerning internal and external validity as well as strengths and limitations of the studies. The internal validity of studies lie in the degree to which conclusions drawn are correct based on data available.[43] The

internal validity might be compromised by for example the number and selection of participants, and how the data was collected and analysed. External validity refers to the extent to which the results can be generalised to other populations beyond the internal specification of a study sample.[43, 131]

6.2.1 Study design and study population

In study one, Paper I, we used an observational design to investigate the test-retest reliability of the TIMPSI within three days. The paper included a convenient sample of 51 infants at risk for adverse neurodevelopment, recruited from two different University hospitals in Norway. This sample size was estimated a priori to be sufficient to secure power of the study. However, only infants available for testing twice within three days were included. Therefore, the study population consisted of infants still staying in the hospitals, infants living close to the hospitals, or infants available for testing twice within the same day. Since the participants came from a convenient sample of infants, there might have been some selection bias, but because of two collaborating hospitals the possibility of selection bias might have been reduced.

Paper II is a validity study based on detailed scores of GMs by use of the general movement optimality list. Two to three observers assessed the 60 video-recordings of 20 VLBW infants without known severe brain lesions. As the infants were participating in another study, the inclusion criteria were already defined. Besides, only infants with four video-recordings of their GMs was eligible. This might have created some selection bias. The limitation of the study is the small and rather homogeneous sample of infants. Thus, our conclusion from this validity study can only be for this restricted sample, VLBW infants born preterm without severe brain lesions.

The NOPPI, which Paper III is based upon, is a parallel group, pragmatic, multi-centre RCT conducted very properly and according to CONSORT statements.[120] Randomised controlled trial is the "gold standard" for evaluating the effects of interventions and potential confounding factors are expected to be distributed randomly across the two groups.[120] The randomisation was performed by a web-based system, with infants stratified according to hospitals and GA. The sample size was 150, 71 in the intervention and 79 in the control group. A sample size of 63 in each group had been estimated a priori to be sufficient to secure power for the primary outcome of the NOPPI: motor function at two years CA.[110] All participants were infants born very to extremely preterm. They were recruited consecutively at 33 weeks PMA from the NICUs at three University hospitals from different regions of Norway. More than 70% of the invited families consented to participate. Because of the randomisation being performed very correctly, it is unlikely that the reported result is affected by selection bias influencing the internal validity of the study. However, a major limitation of Paper III is that it only reports short-term outcome immediately after intervention.[64]

6.2.2 Measurement tools and assessment procedures

The measurement tools used in this thesis were the TIMPSI, TIMP and GMA, all evaluated and found to be valid and reliable.[45, 47, 59, 62, 64, 122-125] They were developed for use in infants between 32 weeks PMA to 5 months CA, to discriminate between typically and atypically developing infants.[9, 62] The TIMP can also be used to evaluate changes over time.[45, 101, 111] Because of the good psychometric properties of the measurement tools used in the three papers, the possibility of information bias was reduced.

All observers had a thorough knowledge of the measurement tools through courses, workshops and long clinical experience in assessing very young infants.

In Paper I the same physiotherapist assessed the infants twice within two days. Cautions were made to not remember the scores from the first to the second assessment, but this could potentially have created systematic error and thereby a possibility of observer bias.

In Paper II, we found some disagreement between the observers, with the more experienced observers scoring more similar. This indicates that the qualifications of the observers when using the GMA are important for reducing observer bias. Thus the scores that two of the observers agreed upon were used in the statistical analyses.

The physiotherapists who assessed the video-recordings in Paper II and the infants at baseline and post-intervention in Paper III were blinded to the medical history of the infants and to group assignments. In Paper III, different physiotherapists assessed the infants at baseline and post-intervention, which further decreased the chance of observer bias.

6.2.3 Intervention

In Paper III the intervention was based on current recommendations for early interventions involving parents as the main practitioners.[32, 37, 100] Physiotherapy, with parents as the main practitioners of the intervention, was conducted as part of ordinary clinical practice. Due to the nature of the intervention, all parents knew their group allocation, as did the physiotherapist instructing the parents. The parents performed the intervention as part of time spent with their infants at the NICU. The infant, with help of the parent, was actively participating during the intervention as the intervention was to be terminated if the infant was not participating. Thus, the intervention can be described both as belonging to the activities and the participation component of the ICF-CY including both environmental and personal factors.[12]

The intended amount of intervention, according to the study protocol, was up to 10 minutes twice a day for three consecutive weeks.[110] Because of the infants' age and the short time during

a day of being awake and in proper "state" for intervention, 10 minutes was chosen as the maximum time of intervention. This dosage was similar to the intended dosage in a study of early PT by Cameron at al.[126] and the dosage in the study of Girolami and Campbell.[111] A recent published study by Dusing et al. of therapist-delivered intervention in the NICU, provided 20 minutes per session five times per week with opportunities for the infant to experience variable and self-directed movements and social interaction.[127] But the number of infants assessed post-intervention was very small, two in the intervention group and four in the control group, thus the conclusion of this study was only about the feasibility of the intervention program.

In Paper III the number of sessions during the intervention period varied largely, as reported by the families, but as a rule most families performed the intervention at least once a day, with a median duration time of nine minutes. Even though this was only half the intended number of sessions, the intervention group showed a significantly better improvement in motor function compared to controls following the three weeks' intervention. But increased sensitivity from the parents towards the infants' signals could have resulted in transfer to other situations, and thereby led to increased time spent on intervention other than reported in the parents' logs. Because of the large variation in the number of intervention sessions between infants, it was not possible to make conclusions about what amount of intervention was best in optimising motor function before term-equivalent age.

6.2.4 Statistical analyses

In Paper I, both relative and absolute reliability between Test 1 and Test 2 of the TIMPSI were calculated.[113, 128] The relative reliability, $ICC_{1.1,}$ was very high. However, the absolute reliability (S_W) was also quite high, which indicates that the difference between two measurements for the same subject needs to be rather high to be sure that there has been a real change in motor

function. This indicates that the TIMPSI is primarily a screening tool to discriminate between typically and atypically developing infants.[8, 65]

In Paper II, with a sample size of only 20, the number was small for calculating correlation. Even so, we found the correlation between the optimality list and the GMA to be good at term and early post-term age, but not at preterm age. Why the correlation at preterm age only was little to fair might be because the preterm GMs are slightly different from writhing movements, and the items of the optimality list might reflect more of the writhing movements. The predictive validity of the GMA has in previous studies been assessed to be low at preterm to early post-term age with respect to outcome at 24 months CA.[47] As expected, the diagnostic accuracy of the optimality list with respect to outcome at three months CA, was low in our study. For estimating the predictive validity of the optimality list, the number of subjects with normal and abnormal GMS at three months CA was too small to provide a probability > 80% for being correctly identified.[129]

In Paper III, missing data could have created selection bias and possibly led to overestimates or underestimates of treatment effects.[130] Possible bias due to missing data was reduced by the model used in the analyses. The assumption in this model was that data was missing at random. A complete case analysis for comparison was performed, but the result of the analyses remained unchanged. Potential confounders in Paper III were GA, twins and three different participating hospitals. Possible nesting effects of twins and hospitals were adjusted for in the analyses. Because of properly conducted randomisation, all differences at baseline between the intervention and the control group were expected to be due to chance and were not included as covariates in the analyses.[118, 120] But, since there was a higher number of other diagnoses in the neonatal period in the control group, we performed an analysis including the number of other diagnoses as a covariate, but the result remained the same.

6.2.5 External validity

In Paper I, enough infants were included to secure the power of the study. Since the test-retest reliability was very high, and the study was conducted as "real time" scoring of the TIMPSI in order to reflect clinical use of the test, we can assume that the TIMPSI is applicable for screening motor function in infants born preterm and at risk for adverse neuro-development. The TIMPSI might also be applicable for use in other groups of infants for whom the full version of the test is too demanding.

The validity of the general movement optimality list, Paper II, was explored for three different ages. But because of the small sample size and the participants being a selected group of few infants, the generalisation of the findings to other group of infants must be done very carefully.

Since the NOPPI, Paper III, was a pragmatic trial, with the benefits of intervention assessed under real clinical conditions with a study population similar to the general populations of infants born preterm, we can expect the external validity to be high.[132] More than 70% of invited parents consented to participate, from the north, the middle and the south-east of Norway, which further strengthens the external validity. Only parents who understood and spoke Norwegian were included, to rule out misunderstanding about the content of the intervention and the handling of the infants. The intervention should be applicable to other infants and their parents as long as the therapist and parents are fluent in the same language. Because of both the internal and the external validity of Paper III is found to be good, our findings might be generalised to other groups of medically stable infants from similar NICUs. For example, infants born preterm from other regions and from other cultural backgrounds, and infants at risk for adverse development due to other pre- and neonatal factors.

6.3 Consistency with other studies

In this section I will discuss the results from each of the three papers with respect to consistency with other studies. Paper III will also be discussed against studies of CNS development and motor development.

6.3.1 Test-retest reliability of the TIMPSI (Paper I)

A test-retest study of the TIMPSI had previously only been performed in children with spinal muscular atrophy (n = 38) and the correlation was found to be high (r = 0.95)[125] However, a test-retest study of the full version of the test, the TIMP, had been performed in 106 infants 32 to 56 weeks PMA with varying ethnicity and varying risk for adverse neuro-development.[62] The correlation between scores on two different days was reported to be high (r = 0.89). In Paper I, we found the test-retest reliability of the TIMPSI to be high, which is in line with the two aforementioned studies.[62, 125] But a direct comparison of Pearson`s $r$ and ICC is not quite appropriate, since Pearson`s r is a measure of linear correlation between two values[133], and ICC is a measure of both association and agreement.[128] However, since both the correlation coefficients were high, we might argue that our finding is in line with the two previous studies.

6.3.2 Validity of the general movement optimality list in very low birth weight infants without severe brain lesions (Paper II)

In Paper II, we documented moderate to high concurrent validity for the optimality list versus GMA at term and early post-term age, which could be expected, since both are expressions of the same phenomenon.[9, 75] A previous study of the correlation between global and detailed GMs in 233 infants, GA 26 to 46 weeks, demonstrated that the detailed analyses distinguished between infants with normal and abnormal GMs.[74] They also found that there was no overlap of median GMOS for infants with normal or poor repertoire GMA, which also was our finding

in Paper II. The GMOS distinguished between infants with normal and poor repertoire GMs from preterm to early post-term age.

Furthermore, our finding of presence of tremulous movements and cramped components, both if normal and if poor repertoire GMA, is consistent with the high rate of these movements across different categories of GMA reported in the aforementioned study.[74] Cramped components across ages irrespective of neurological outcome have also been described in several previous studies.[72, 73] Thus, tremulous movements and cramped components can be seen across different categories of GMA. However, some items correlated moderately to excellently with the global GMA across all three ages and can therefore be of more importance in the detailed assessment of GMs. These items are amplitude and speed in upper and lower limbs, rotation in upper limbs, and involvement of neck movements. For distinguishing between typically and atypically developing infants at very early ages, these items can be useful supplements to the global score of normal and abnormal GMs.

The validity of GMA in predicting long-term adverse neuro-development has previously been assessed to be good at three months CA but not at preterm and term age.[124] Therefore, it was unlikely that the diagnostic accuracy of the optimality list used at preterm to early post-term age in Paper II, with respect to outcome at three months CA, should be very high. Until more studies of the predictive validity of the optimality list have been conducted, the optimality list is first and foremost useful as a tool to identify infants with typical or atypical general movements.

6.3.3 Early parent-administered physiotherapy (Paper III)

Few other RCTs have been conducted with infants before term age with focus specifically on motor outcome. The results of previous studies are inconclusive and the aims and the interventions have varied as reported in the following discussion.

The intervention in the NOPPI was based on a study of Girolami and Campbell.[111] The main differences between our study and the study of Girolami and Campbell were a much higher number of infants included in ours and that the intervention was parent-administrated. Assessment just after the end of the intervention demonstrated superior motor function in the intervention group as compared to the control group infants in both studies. We involved the parents as main practitioners, as in the study of Kaaresen et al.[92] who used a modified version of "The Mother–Infant Transaction Program" (MITP).[91] Kaaresen et al. reported that there was no difference between groups, measured by BSID-II mental and motor scale at two years. Since we only have short-term outcomes and the fact that there is only a weak association between TIMP scores before three months CA and motor development at 12 months[64], the group difference in the NOPPI might not be obtained for the end-point at 24 months.

Lekskulchai and Cole investigated the effect of a parent-administrated intervention in a RCT of early intervention in moderate preterm born infants.[101] The intervention was performed from term-equivalent age until four months CA. The short-term result measured by the TIMP demonstrated significantly greater improvement in motor function in the intervention group compared to the control group ($p < 0.001$), a result in line with our findings.

Hielkema et al.[134] could not demonstrate such a short-term effect of a new family-centred intervention program (COPCA) conducted in infants at very high risk for CP. But the study population and the intervention period was different from the NOPPI, as inclusion criteria were abnormal GMs at 10 weeks CA, and the intervention lasted from infants CA three to six months.

Another study of 30 infants also at high risk for CP, demonstrated advanced motor outcome in the intervention group as compared to controls.[135] In this study the infants were included at three to four months if abnormal GMs or other indications of high risk for CP were found. The

intervention was based on active motor learning, family-centred care, parent coaching, and environmental enrichment, and lasted from enrolment until 12 months CA.

The meta-analysis of 12 studies included in a recent systematic review by Spittle et al.[100] regarding motor outcome, concluded that there was a small significant effect of early intervention in infancy. Our short-term result is in line with this result.

The interventions in the NOPPI were performed during a sensitive period in the infants' development because of rapid changes in the brain's structure and function at this age.[16, 27, 33] The criteria for carrying out the intervention were that the infants actively participated, thus the intervention might have influenced CNS development and thereby optimised motor function which is in line with the description of part of the CNS development being activity-dependent.[10, 29, 30] Furthermore, the parents provided an enriched environment both socially and physically when performing the intervention, which also might have influenced CNS development positively.[32]

The intervention might have led to modifications in the strength of the synaptic connections through variable afferent information produced by the infants' behaviour and experience, in line with the Neuronal Group Selection Theory.[38, 40] Furthermore, the intervention might have influenced the infants' primary neuronal repertoires which over time might create a task-specific and variable movement repertoire. Thus, the intervention can also be described as belonging to the body functions and structures component according to the ICF-CY model.[12]

The fact that part of CNS development is considered to be activity-dependent[10, 29, 30] substantiates the possibility of the parent–administrated intervention in the NOPPI having optimised short-term motor function in the intervention group. However, whether the observed

differences of changes of scores between the groups is important for health or is biologically important is yet unknown.[136]

7. Conclusions

In this thesis I have demonstrated that the TIMPSI has high test-retest reliability (Paper I) when performed in a group of infants at high to moderate risk for later motor impairments. The test can be used to screen motor development of infants for whom the full version of the test is too demanding. In Paper II, in a small group of very low birth weight infants without severe brain lesions, the concurrent validity between "Detailed Assessment of General Movements (GMs) During Preterm and Term Age" against global GMA was moderate to high at term and early post-term age. Furthermore, the GMOS were able to distinguish between infants with normal and poor repertoire GMA at all three ages. However, the predictive validity of the detailed assessment for outcome at three months was low.

In Paper III we have demonstrated that implementing parent-administrated physiotherapy before term-equivalent age in medically stable infants resulted in improved short-term motor function in the intervention group as compared to the control group.

8. Clinical implications

Being the most valid and reliable measurement tools for assessing motor function in infants, the TIMPSI, the TIMP and the GMA should be the preferred tools used at preterm and term age. The clinical utility of TIMPSI for identifying infants in need of follow-up seems to be very good. The TIMPSI is less demanding for the infants, and performing the TIMPSI as compared to the TIMP is less time consuming for the therapist. However, for evaluative or predictive purposes the TIMP should be used.[8]

Many infants at preterm to early post-term age have poor repertoire GMs. A detailed assessment of the GMs by use of the optimality list the "Detailed Assessment of General Movements (GMs) during preterm and Term Age" can distinguish between infants with normal or poor repertoire GMA and can also possibly identify subtle spontaneous movements which the global assessment of GMs does not cover. Its usefulness seems to be best during term and early post-term age. Since the same video-recording is used for both the detailed and the global GMA, the assessment does not involve more stress for the infants. But it is more time consuming for the observers as the video-recordings need to be replayed more times. Furthermore, the observers need to be certified in the method. The optimality list, until more studies have been conducted, is not a tool for predicting long-term motor outcome.

Implementing parent-administrated intervention in NICU to optimise short-term motor function in medically stable infants seems to be useful and feasible for the parents to perform once a day when the infants are > 34 weeks PMA. Due to the nature of the intervention the physiotherapists and the parents need to speak the same language and the physiotherapists need to be available if more than three encounters are needed. The use of a booklet with pictures and written explanations seems to reinforce learning of the activities. If offered routinely, this intervention might reduce the need of physiotherapy after discharge from hospital. Hence, the results from

this RCT could possibly influence the physiotherapy service offered to infants born preterm and their parents during the preterm period.

9. Future research

During my doctoral work I have identified new research questions. Inter-tester reliability of the TIMPSI in infants at different ages and risk for adverse development has not been assessed. Minimal clinical important change documented by TIMP has not yet been established and can be a topic for future research. The predictive validity of the "Detailed Assessment of General Movements (GMs) during preterm and Term Age" should have been explored in larger scale studies with larger and more heterogeneous sample sizes. One question to be addressed, as also suggested by Einspieler et al.[74], is if this detailed assessment can be used to evaluate subtle changes of GMs over time or subtle changes caused by early intervention. The spontaneous movements of the infants in the NOPPI have been video-recorded at week 34, 36 and 52 PMA, and these data could be used in performing such a study.

The primary outcome of the NOPPI is motor function at two years CA assessed by PDMS-II. This end-point could preferably have been set at an older age for several reasons. Firstly, two-year-old infants might have difficulties in taking instruction and in cooperating, making the assessments less reliable. Secondly evaluating the long-term effect at two years CA can be too early, as minor motor difficulties often do not appear before preschool or school age.[6] It has been suggested that four years of age is the minimum age required to enable investigators to distinguish between children with typical and atypical motor development.[6] A topic for future research could be assessment of motor function of the participants in the NOPPI, at for example seven to eight years CA. This would give more information about the long-term effect of early intervention.

Another question that has emerged is if similar intervention as in the NOPPI could be useful for other groups of infants at risk for adverse motor development, for example for infants having

been exposed to alcohol or drugs during pregnancy. Conducting a study for this group of infants would add knowledge to the effect of early physiotherapy.

10. References

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